ROBERT BURNS WOODWARD 1917–1979

R. B. WOODWARD REMEMBERED

A Collection of Papers in Honour of
Robert Burns Woodward 1917 - 1979

Editor-in-Chief

SIR DEREK BARTON, FRS

Institut de Chimie des Substances Naturelles, CNRS, Gif-sur-Yvette, France

Editors

H. H. WASSERMAN, J. E. BALDWIN, FRS, A. R. KATRITZKY, FRS
P. POTIER and T. STEPHEN

PERGAMON PRESS

OXFORD · NEW YORK · TORONTO · SYDNEY · PARIS · FRANKFURT

U.K.	Pergamon Press Ltd., Headington Hill Hall, Oxford OX3 0BW, England
U.S.A.	Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, New York 10523, U.S.A.
CANADA	Pergamon Press Canada Ltd., Suite 104, 150 Consumers Rd., Willowdale, Ontario M2J 1P9, Canada
AUSTRALIA	Pergamon Press (Aust.) Pty. Ltd., P.O. Box 544, Potts Point, N.S.W. 2011, Australia
FRANCE	Pergamon Press SARL, 24 rue des Ecoles, 75240 Paris, Cedex 05, France
FEDERAL REPUBLIC OF GERMANY	Pergamon Press GmbH, 6242 Kronberg-Taunus, Hammerweg 6, Federal Republic of Germany

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First edition 1982

All papers in this volume have been previously published in *Tetrahedron*, Volume 37, and supplied to subscribers as part of their subscription.

ISBN 0 08 029238 0

Printed in Great Britain by A. Wheaton & Co. Ltd., Exeter

OBITUARY

ROBERT BURNS WOODWARD 1917–1979

R. B. Woodward, Donner Professor of Science at Harvard University, died July 8th of a heart attack in his home in Cambridge, Massachusetts. He was 62 years old. Considered to be the greatest organic chemist of modern times, he was awarded the 1965 Nobel prize for Chemistry.

Woodward was the father of a major school of organic chemistry in which the theory of reaction mechanisms and the latest physical methods were utilized to their fullest capability as guides through the complex stages of natural products synthesis. Few scientists have had such widespread influence in developing the careers of so many investigators. More than 400 graduate and postdoctoral students were associated with him at Harvard and at the Woodward Research Institute in Basel. These chemists, many of whom occupy important positions thoughout the world, include some of the most distinguished investigators in the field of organic chemistry.

Among his accomplishments in total synthesis are quinine (1944); patulin (1950); cholesterol (1951); cortisone (1951); lanosterol (1954); strychnine (1954); lysergic acid (1954); reserpine (1956); chlorophyll (1960); colchicine (1963); cephalosporin C (1965); vitamin B_{12} (1972, with A. E. Eschenmoser); prostaglandin F_{2a} (1973). At the time of his death, he was working on the synthesis of the antibiotic erythromycin.

At a time when X-ray crystallography was not yet fully developed, Woodward performed some masterly feats of structural deduction. He was the first, during the wartime programme on penicillin, to argue with logic and clarity for the correct β-lactam structure. His derivation of the correct constitution for the tetracycline antibiotics from a mass of conflicting evidence is probably the greatest feat of integration of correct (and of misleading!) facts ever accomplished.

Woodward also contributed heavily to the field of theoretical organic chemistry, as for example in the postulation of the Woodward-Hoffman rules for the conservation of orbital symmetry — certainly one of the most important advances in the entire history of organic chemistry.

He was born April 10, 1917 in Boston, the son of Arthur C. and Margaret Burns Woodward. As a very young man be became interested in organic chemistry and amused himself by devising syntheses for natural products. He liked to say that his synthesis of quinine was planned when he was 12 years old. By the time he graduated from high school, it is said that he possessed a knowledge of chemical reactions that easily surpassed that of college graduates majoring in organic chemistry and indeed of many professors.

At the Massachusetts Institute of Technology, the faculty recognized that he was a unique student and they bent the rules by arranging a special program for him whereby at age 20 he received both Bachelor's and Doctorate degrees. After an instructorship at the University of Illinois for the summer of 1937, he returned to Cambridge as research assistant to E. P. Kohler just before the latter's death. One year later he became a junior fellow of the Society of Fellows at Harvard, and in January 1941 became an instructor in Harvard's Chemistry Department. This was followed by an assistant professorship in 1944, an associate professorship in 1946 and then full professorship in 1950. In 1953 he became Morris Loeb Professor of Chemistry and, in 1960, Donner Professor of Science.

In 1958, with Sir Robert Robinson, he helped in the founding of *Tetrahedron* and *Tetrahedron Letters*, and he served as Co-Chairman of the Editorial Advisory Boards until his death. His concern for these journals, particularly for their international influence, was of immense importance in establishing them as major publications in the world of organic chemistry.

Besides the Nobel Prize, Woodward was awarded the National Medal of Science in 1964 by President Johnson. He has also received a long list of awards and honorary doctorates from universities all over the world, a partial listing of such honours being included at the front of this issue (p. iii).

Those of us who were privileged to know this great man personally will testify that Woodward was indeed unique. He had a mind like a computer which retained an enormous amount of factual information stored in an instantly integratable form. It was this, and his impeccable capacity for logical thought, that led him first to deductions of structure and secondly to long, brilliant and meticulously planned syntheses of natural products.

DEREK BARTON HARRY H. WASSERMAN

ROBERT BURNS WOODWARD 1917–1979

HONORARY DOCTORATES

Wesleyan University, 1945; University of Manchester (England), 1954; Bucknell University, 1955; University of New Brunswick (Canada), 1956; Yale University, 1956; Harvard University, 1957; University of Southern California, 1959; University of Chicago, 1961; New England College of Pharmacy, 1961; Colby College, 1963; University of Cambridge (England), 1964; Brandeis University, 1965; University of Glasgow (Scotland), 1966; Stonehill College, 1966; University of Sheffield (England), 1966; Israel Institute of Technology (Haifa), 1966; Polytechnic Institute of Brooklyn, 1967; Eidgenössische Technische Hochschule (Switzerland), 1967; University of Western Ontario (Canada), 1968; Columbia University, 1969; Université de Louvain (Belgium), 1970; Université Pierre et Marie Curie de Paris, 1975; University of St. Andrews (Scotland), 1976; The University of London (England), 1976.

AWARDS

John Stott Medal [Franklin Institute and City of Philadelphia], 1945; Baekeland Medal [North Jersey Section of the American Chemical Society], 1955; Ledlie Prize [Harvard University], 1955; Research Corporation Award, 1955; Nichols Medal [New York Section of the American Chemical Society], 1956; Synthetic Organic Chemistry Award [American Chemical Society], 1957; Richards Medal [Northeastern Section of the American Chemical Society], 1958; Davy Medal [Royal Society], 1959; Roger Adams Medal [American Chemical Society], 1961; Pius XI Gold Medal [Pontifical Academy of Sciences], 1961; Scientific Achievement Medal [City College Chemistry Alumni Association], 1961; Priestley Medallion [Dickinson College], 1962; Stas Medal [Société Chimique de Belgique], 1962; Gold Medal for Creative Research in Synthetic Organic Chemistry [Synthetic Organic Manufacturers Association], 1962; National Medal of Science [United States of American], 1964; Kirkwood Medal [Yale Department of Chemistry and New Haven Section of the American Chemical Society], 1965; Nobel Prize in Chemistry [Royal Swedish Academy of Sciences], 1965; Willard Gibbs Medal [Chicago Section of the American Chemical Society], 1967; Lavoisier Medal [Société Chimique de France], 1968; The Order of the Rising Sun, Second Class [His Majesty the Emperor of Japan], 1970; Hanbury Memorial Medal [The Pharmaceutical Society of Great Britain], 1970; Pierre Bruylants Medal [Université de Louvain], 1970; Scientific Achievement Award [American Medical Association], 1971; Dr. B. C. Law Gold Medal [Indian Association for the Cultivation of Science], 1972; Arthur C. Cope Award [American Chemical Society], 1973.

OTHER APPOINTMENTS

Member of the National Academy of Sciences; Fellow of the American Academy of Arts and Sciences; Honorary Member of the German Chemical Society; Honorary Fellow of the Chemical Society; Foreign Member of The Royal Society; Honorary Member of the Royal Irish Academy; Corresponding Member of the Austrian Academy of Sciences; Member of the American Philosophical Society; Honorary Member of the Belgian Chemical Society; Honorary Member of the Harvard Society of New York; Honorary Fellow of the Indian Academy of Sciences; Honorary Member of the Swiss Chemical Society; Member of the Deutsche Academie der Naturforscher (Leopoldina); Foreign Member of the Accademia Nazionale dei Lincei; Honorary Fellow of the Weizmann Institute of Science; Honorary Member of the Pharmaceutical Society of Japan; Honorary Member of the Pharmaceutical Society of Great Britain; Honorary Fellow of the Indian Chemical Society; Honorary Life Member of the New York Academy of Sciences; Foreign Fellow of the Indian National Science Academy; Honorary Member of the Royal Institution of Great Britain; Foreign Member of the Academy of Sciences of the U.S.S.R.

SELECTED SCIENTIFIC CONTRIBUTIONS OF R. B. WOODWARD

Syntheses

Quinine 1944
Patulin 1950
Cholesterol 1951
Cortisone 1951
Lanosterol 1954
Lysergic acid 1954
Strychnine 1954
Reserpine 1956
Chlorophyll 1960
Colchicine 1963
Cephalosporin C 1965
Vitamin B_{12} 1972
Prostaglandin F_{2a} 1973

Structures

Penicillin 1945
Strychnine 1948
Patulin 1949
Terramycin 1952
Aureomycin 1952
Cevine 1954
Magnamycin 1956
Gliotoxin 1958
Oleandomycin 1960
Streptonigrin 1963
Tetrodotoxin 1964

Synthetic Methods

Polypeptides 1947
Peptides 1961

Biogenetic Theory

Indole Alkaloids 1948
Steroids 1953
Macrolides 1956

General

Structure and ultraviolet spectra of ketones 1941
Structure and aromaticity of ferrocene and other metallocenes 1952
Structure and rotatory dispersion of ketones (the octant rule) 1961
Conservation of orbital symmetry 1965

SELECTED PUBLICATIONS

The total synthesis of quinine. RBW, and W. E. Doering, *J. Am. Chem. Soc.* **66**, 849 (1944).
The total synthesis of cholesterol. RBW, F. Sondheimer, and D. Taub, *Ibid.* **73**, 3548 (1951).
The total synthesis of cortisone. RBW, F. Sondheimer, and D. Taub, *Ibid.* **73**. 4057 (1951).
The synthesis of lanosterol. RBW, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *Ibid.* **76**, 2752 (1954).
The total synthesis of strychnine. RBW, Michael P. Cava, W. D. Ollis, A. Hunger, H. U. Däniker, K. Schenker, *Ibid.* **76**, 4749 (1954).
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The total synthesis of chlorophyll. RBW, W. A. Ayer, J. M. Beaton, F. Bickelhaupt, R. Bonnett, P. Buchschacher, G. L. Closs, H. Dutler, J. Hannah, F. P. Hauck, S. Ito, A. Langemann, E. Le Goff, W. Leimgruber, W. Lwowski, J. Sauer, Z. Valenta, and H. Volz, *Ibid.* **82**, 3800 (1960).
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Veratrum Alkaloids 9. Absolute Konfiguration des Kohlenstoffatoms 10 in Cevin and verwandten Alkaloiden. F. Gautschi, O. Jeger, V. Prelog, and RBW, *Ibid.* **XXXVIII**, 296 (1955).
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Tetrahedron, Vol. 37, Supplement No. 1, pp. 1 to 7
Printed in Great Britain.

0040-4020/81/Suppl. 1-0001-07 $02.00/0
Pergamon Press Ltd.

PRÉNYLATION EN MILEU ACIDE DU (−)- ET DU (+)-LIMONÈNE

SYNTHÈSE DES (−)- ET (+)-α-BISABOLOLS ET DES (−)- ET (+)-ÉPI-8-α-BISABOLOLS

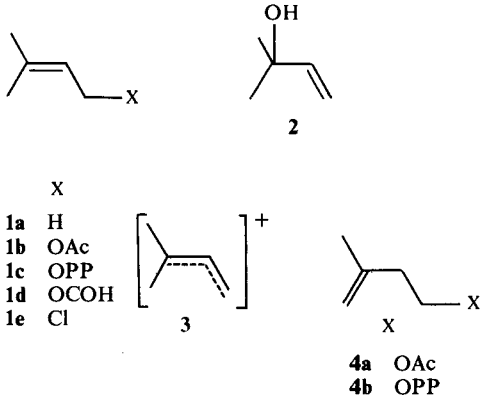
DIDIER BABIN, JEAN-DOMINIQUE FOURNERON et MARC JULIA*
Laboratoire de Chimie de l'Ecole Normale Supérieure, associé au C.N.R.S. N° 32, 24, rue Lhomond, 75231 Paris, Cedex 05, France

(*Received in the UK* 13 *March* 1980)

Abstract—In formic acid-dichloromethane solution optically active limonene and α,α-dimethylallyl alcohol give a mixture of C_{15} products from which optically active α-bisabolol and epi 8-α-bisabolol can be isolated.

Résumé—En milieu formique le limonène optiquement actif et le diméthylvinylcarbinol fournissent un mélange de produits de prénylation d'où l'on sépare l'α-bisabolol optiquement actif et son épimère en 8.

Il a été montré précédemment que dans des conditions appropriées l'acétate de méthyl-3 butène-2 ol-1 (acétate de prényle) **1b** ou le méthyl-2 butène-3 ol-2 (diméthyvinylcarbinol, DMVC) **2** donnaient naissance à des espéces électrophiles schématisées par **3**, (que nous appelerons cations prényles pour simplifier, sans préciser leur structure) capables d'attaquer la double liaison de l'acétate de méthyl-3 butène-3 ol-1 (acétate d'isopentényle IPA) **4a**, sur le carbone terminal pour donner l'enchainement iso-prénique des monoterpènes.[1–4] On sait que les organismes vivants réalisent cette synthèse par attachement des pyrophosphates de prényle et isopentényle **1c** et **4b**.[5,6] La possibilité de greffer un synthon prénylique primaire sur une double liason carbone-carbone, ouvrait une voie vers des terpènes supérieurs. Les premiers résultats sont décrits ici.



Le greffage d'un tel synthon sur la double liaison exocyclique du limonène **5**, devait en effet conduire au cation **6**, qui est considéré comme intermédiaire dans la biosynthèse et la synthèse[7] des bisabolènes **7** et de l'α-bisabolol **8** (R = H) à partir du nèrolidol **9**.[8,9,10] Les résultats obtenus dans les réactions $C_5 + C_5$ rendaient vraisemblable la formation des bisabolènes **7** en opérant dans des conditions peu nucléophiles,[(1)] ou d'α-bisabolol **8**, en opérant en présence de nucléophiles.[3,4] Il se posait de toutes façons la question de la compétition entre les deux doubles liaisons du limonène **5**.

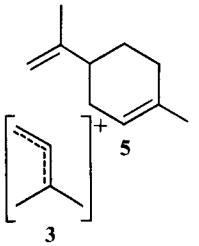
Les cinq isomères des bisabolènes **7**, ont été synthétisés sélectivement.[11] Nous avons préparé le mélange des 5 isomères par déshydratation de l'α-bisabolol **8** commercial (Dragosantol) et leur présence dans des mélanges réactionnels pouvait donc être détectée facilement. Pour l'α-bisabolol **8** les travaux antérieurs ont abouti à une situation confuse. La structure **8** (désignée par la suite sous le nom d'α-bisabolol), présente en effet quatre diastéréoisomères, épimères deux à deux sur les C4 et C8,† **10** (4R, 8R); **11** (4R, 8S); **12** (4S, 8S) et **13** (4S, 8R).

Les cyclisations du nérolidol **9**, ou de certains de ses esters donnent le mélange des quatre diastéréoisomeres.[8,9,10] D'autres voies de synthèse conduisent également à ce mélange.[18] La configuration S proposée[14] pour le carbone 4 du (−)-α-bisabolol naturel, a été confirmée[15c] par corrélation avec le (−)-β-bisabolène **7** de configuration connue[11c]. Par contre deux synthèses récentes [13,15a,b] attribuent au carbone 8 des configurations absolues opposées, avec des arguments sérieux.

Les deux couples d'énantiomères **10**, **12** et **11**, **13** donnent par chromatographie en phase vapeur (CPV par la suite) sur colonne capillaire enduite d'une phase polaire (Carbowax)[15a] les deux pics A et B (par ordre d'élution). Ils montrent en ^{1}H RMN, des signaux différents à 1,11 ± 0,01 ppm et 1,14 ± 0,01 ppm respectivement[13,14,15] pour le méthyle en C8.

Nouse avons isolé selon[15a] le (−)-α-bisabolol de l'huile essentielle de camomille allemande (Matricaria chamomilla) et le professeur Kergomard[13] nous a fourni un échantillon de (+)-α-bisabolol naturel, qu'il tenait lui-même du professeur Paknikar.[16] Nous avons groupé dans le Tableau 1 les caractéristiques physiques: $[\alpha]_D$, CPV, RMN, des produits naturels et des produits obtenus par synthèse.

†Cette numérotation est la plus généralement employée, l'α-bisabolol **8** étant considéré comme un sesquimenthane.[12,11,13]



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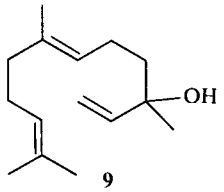

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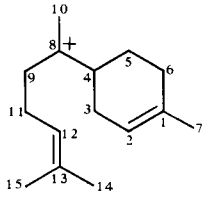

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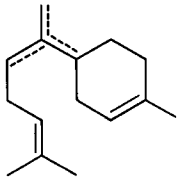
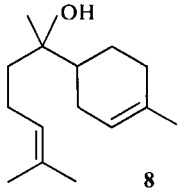


7 Δ8,9: isomères α(E,Z).
Δ8,10: isomère (β)
Δ4,8 : isomère γ(E,Z)



8

Pour connaître avec certitude la configuration relative, nous avons préparé selon,[17] le *p*-phénylazophényluréthane **12a** du (−)-α-bisabolol naturel. Une étude par rayons X,[18] indique sans ambiguité la configuration 4S,8S ou 4R,8R de cette substance.

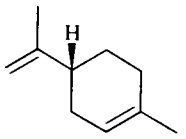
Dans le première technique de prénylation utilisée précédemment[1] l'IPA (**4a**) était traité par l'acétate de prényle dans le cyclohexane contenant du perchlorate de lithium et un peu d'acide acétique. Des acétates diéniques en C_{10} étaient obtenus. Dans les mêmes conditions le (+)-limonène, traité par l'acétate de prényle n'a pas fourni de composé en C_{15} mais un peu d'hydrocarbures en C_{10} et un acétate en C_{10} ayant en CPV le même temps de rétention que l'acétate d'α-terpinéol **14b**. L'acétate de prényle reste pratiquement inchangé. Lorsque l'acétate d'isopentényle était traité par le DMVC dans le dichlorométhane en présence d'acide trifluoracétique, le monoacétate d'un diol C_{10} était obtenu.[3] Le même traitement appliqué au (+)-limonène n'a fourni qu'une trace d'alcools en C_{15} (après saponification du mélange réactionnel) à coté de beaucoup d'α-terpinéol **14a**. Il semble que la protonation du limonène dans ces conditions soit plus rapide que la réaction désirée.

Les acides de Lewis tels que $SnCl_4$ et BF_3–Et_2O qui donnent parfois de bons résultats dans des cyclisations

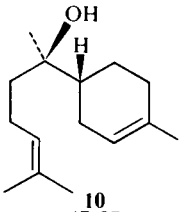
Tableau 1. Caractéristiques physiques des α-bisabolols naturels et synthétiques

Origine	$[\alpha]_D$ t, c, solvant	CPV	RMN ($CDCl_3$)	Référence
camomille allemande	23°, 1.06, $CHCl_3$; −66,3°	A	1,11 (250 MHz)	ce travail
camomille allemande	24°, 1,16, EtOH−; −68,4°	A	1,10 (270 MHz)	(15a)
Atalanta monophylla corréa*	23°, 2,6; $CHCl_3$; +53,8°	A	1,11 (250 MHz)	ce travail
6Z-farnesal	—	A	1,10 (270 MHz) 1,04**	(15a, 15b)
6E-farnesal	—	B	1,13 (270 MHz) 1,06**	(15a, 15b)
commerciale (Dragoco)	—	AB	1,11; 1,14 (250 MHz)	ce travail
(+)-limonène	23°, 1, 1, $CHCl_3$; +63,7° (60 MHz)	—	1,12; 1,15	(14)
(−)-limonène	24°, 0,8, $CHCl_3$; −60,2°	—	1,12; 1,15 (60 MHz)	(14)
(+)-limonène	25°, 1,2, EtOH; +55,4°	—	1,10 (60 MHz)	(13)
(+)-limonène	25°, 1, EtOH; +57,5°***	—	1,12 (60 MHz)	(13)

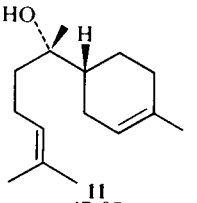
*Isolé par le professeur Paknikar,[16] et obtenu du professeur Kergomard.
**Dans CCl_4.
***$[\alpha]_{570}$.



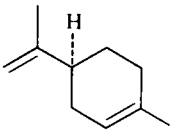
(+)-(4R)-**5**



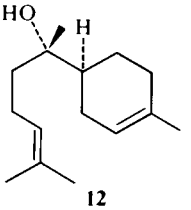
10
4R,8R



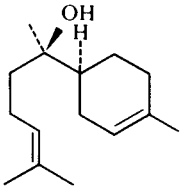
11
4R,8S



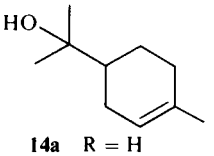
(−)-(4S)-**5**



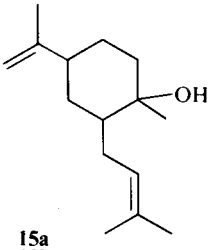
12
4S,8S



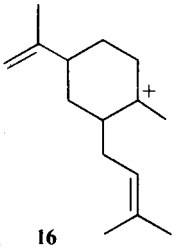
13
4S,8R



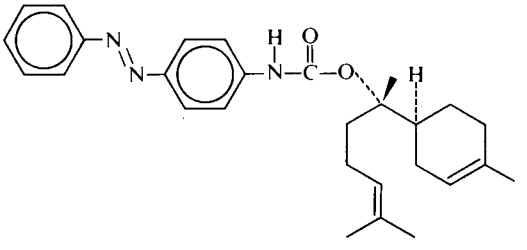
14a R = H
14b R = Ac



15a
15b
2 isomères



16



12a

d'alcools polyéniques,[19] n'ont pas permis de condenser le DMVC et le limonène. Le remplacement du DMVC par le chlorydrate d'isoprène **1e**, qui avait pu être additionné sur l'IPA,[20] ne nous a pas davantage permis d'obtenir des composés en C_{15}.

Une troisième technique utilisée pour attacher les synthons en C_5, était le traitement par l'acide formique seul ou dans le chlorure de méthylène.[4] La réaction du DMVC et du (+)-limonène dans ces conditions a montré la formation d'alcools en C_{15} en quantité appréciable. Après quelques essais on a pris pour 1 mole de (+)-(R)-limonène, 2 moles de DMVC et 20 moles d'acide formique† et la quantité suffisante de chlorure de méthylène pour avoir un milieu homogène (en son absence le milieu est biphasique et la réaction n'a pas lieu) Après 30 mn à 20° ou 2 h à 0°, on observe la transformation totale du DMVC.

La CPV sur colonne ordinaire montre un pic correspondant aux 4 diastéréoisomères de l'α-bisabolol **8** et deux autres composés isomères **15a** et **15b** dans les proportions 45, 40 et 15 respectivement. La CPV sur colonne capillaire permet de dédoubler le pic correspondant à l'α-bisabolol, en deux pics A et B de même intensité. Les pics correspondants à **15a** et **15b** restent uniques.

Le traitement appliqué à 0,2 moles de (+)-limonène a permis d'isoler les produits volatils: formiate de prényle **1d** (60% sur le DMVC initial) et le (+)-limonène inchangé (55%). Après méthanolyse ou saponification, on isole par distillation simple l'α-

†Nous avons utilisé avec le même succès de l'acide formique commercial (98–100%) ou anhydre après distillation sur acide borique (21).

terpinéol **14a** et le mélange des alcools, **10** et **11**; **15a** et **15b**.

Une distillation avec une colonne à bande tournante permet de séparer une fraction contenant seulement **15a** et **15b**, une fraction intermédiaire contenant 85% de **10** + **11** et 15% de **15a** + **15b**, puis une fraction contenant le mélange **10** + **11** pur à 95%. Les rendements calculés sur le (+)-limonène consommé sont 15% en **10** + **11** et 20% en **15a** + **15b**. Les composés **15a** et **15b**, sont séparés par chromatographie sur silice. Les structures proposés sont en accord avec les propriétés spectrales et le mode de formation: l'attaque du cation prényle **3** sur la double liaison endocyclique. Il semble que sur les quatre isomères possibles, deux seulement soient formés. Les stéréochimies précises n'ont pas pu être déterminées par l'analyse des spectres. L'étude de ces produits est en cours.

Pour séparer l'α-bisabolol de son épimère en -8, nous avons transformé le mélange **10** + **11** obtenu ci-dessus en p-nitrobenzoates (PNB par la suite). Le mélange d'esters, obtenu sous forme d'huile, a pu être résolu par chromatographie liquide à haute pression (HPLC). Les échantillons ainsi isolés sous forme d'huiles ont été réduits par l'hydrure de lithium et d'aluminium et purifiés par chromatographie sur silice.

Les propriétés des deux composés obtenus, groupées dans le Tableau 2 montrent bien qu'il s'agit de deux diastéréoisomères et que l'un d'entre eux d'identifie (Tableau 1) au (+)-(α)-bisabolol naturel. Les opérations analogues effectuées avec l'(−)-(S)-limonène ont fourni les produits antipodes optiques des précédents (Tableau 2).

Comme la substance synthétique identique au (−)-α-bisabolol naturel provient du (−)-(4S)-limonène, ceci confirme la configuration S pour le carbone 4 et par suite la configuration absolute 4S,8S **12** du (−)-α-bisabolol.[18]

L'avantage principal de cette synthèse est sa grande simplicité. Elle fournit en effet en une seule opération simple, suivie d'une méthanolyse et d'une distillation à la bande tournante, un mélange de deux des diastéréoisomères qui avait précedémment été obtenu en quatre étapes[14] avec un rendement inférieur. Grâce au pouvoir séparateur de la HPLC, on a pu isoler chacun des quatre diastéréoisomères de l'α-bisabolol, dont deux sont identiques aux produits naturels, (+) et (−). Le mécanisme de cette réaction est à l'étude. Il faut rappeler ici que la cation bisabolyle **6**, est proposé comme intermédiaire dans la synthèse d'autres sesquiterpènes polycycliques. Ces transformations ont pu être réalisées en laboratoire.[7] Si l'on rappelle que la déshydratation de l'α-bisabolol et de l'épi-α-bisabolol par l'oxychlorure de phosphore dans la pyridine donne un mélange des stéréoisomères de bisabolène **7**, et que ce mélange peut être isomérisé en γ-bisabolène et cyclisé efficacement en cedrènes (α et épi-α),[7] on a donc réalisé du même coup une synthèse simple de ces substances.

PARTIE EXPERIMENTALE

Les (+)- et (−)-limonènes sont des produits commerciaux Fluka. Leur pureté optique est mentionnée dans le texte. Le DMVC (98%) provient de chez Aldrich. Ils sont utilisées tels quels. Le CH_2Cl_2 est distillé avant usage.

Les analyses par CPV sont faites avec: un appareil Vârian 1740, sur colonne A: Carbowax 20M, 3 m, 5% sur support Gas. Chrom Q et B: DC 550 (silicone), 5 m, 15% sur le même support. Les dosages sont effectués à l'aide d'un appareil Intersmat Minigrator. Les analyses fines sont réalisées avec un appareil Girdel sur colonnes capillaires en verre, enduites de phase Carbowax 20M (dimensions 45 × 0,4 mm) C et SE 52 (25 m × 0,6 mm) D. Les temps de rétention et les pourcentages sont obtenus à l'aide d'un appareil Spectra. Physic Système 1.

Les spectres de masse sont obtenus avec un appareil Varian Mat CH7. Les spectres de RMN sont enregistrés dans $CDCl_3$ avec le TMS comme référence interne avec un appareil CAMECA à 250 MHz pour le ^1H, et Brucker WH 90 pour le ^{13}C. Les déplacements chimiques sont exprimés en ppm. Les pouvoirs rotatoires sont mesurés avec un appareil Perkin–Elmer 141 dans le chloroforme, et les spectres infrarouge sont obtenus en film avec un appareil Perkin–Elmer 599.

Les analyses par HPLC ont été effectuées avec un appareil Waters sur une colonne de silice Zorbaxsil, les produits sont détectés par U.V. à 254 mm.

Isolement du (−)-α-bisabolol méthyl-6(méthyl-4-cyclohexène-3-yl)-2 heptène-5 ol-2 **12**

Le produit est isolé de l'essence de camomille selon.[15a] Après plusieurs chromatographies sur silice, et deux distillations $Eb_{0,2} = 92°$ (bain d'huile), on obtient le (−)-α-bisabolol légèrement contaminé par du guaïazulène (présent en grande quantité dans l'essence de départ) qui donne une coloration bleu-vert et une odeur caractéristique au produit. L'analyse par CPV sur colonne C 165° ne permet pas de mettre en évidence une impureté.

$[\alpha]_D^{23} = -66{,}3°$, (1,16,) (litt.[15a] $[\alpha]_D^{23} = -68{,}4°$(EtOH)).

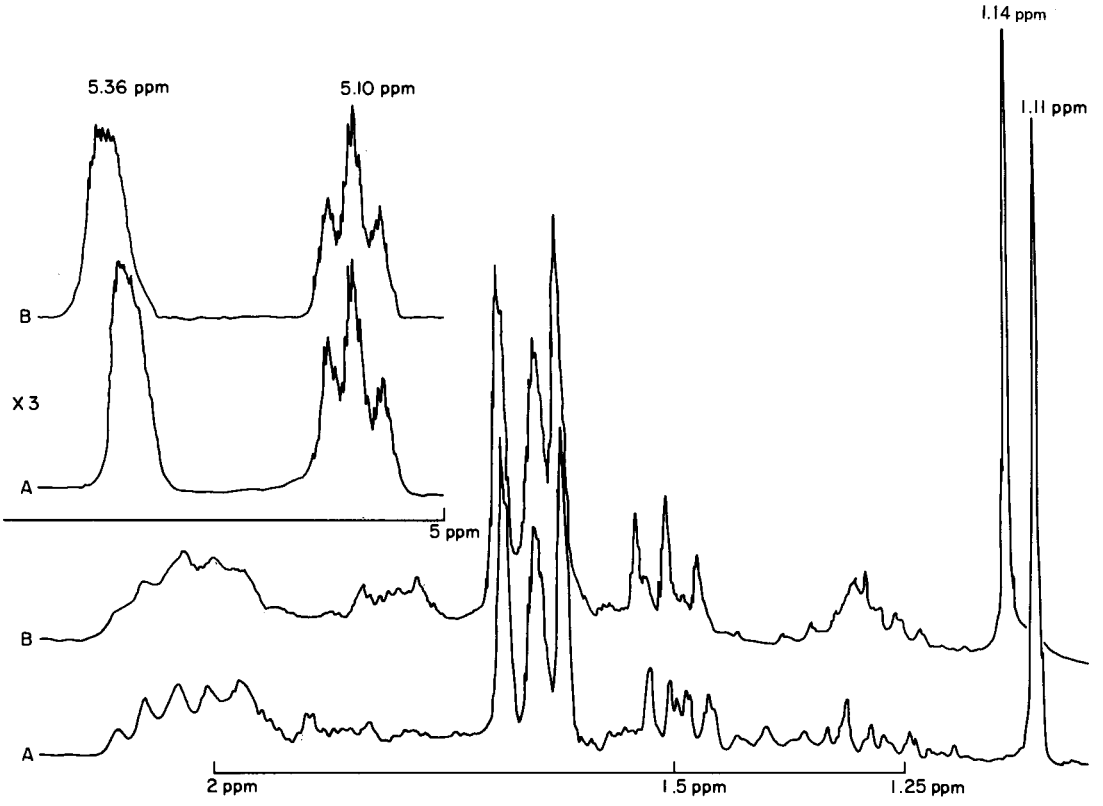
RMN.–^1H. Le spectre est reproduit sur la Figure 1 Courbe A.

RMN.–^{13}C: 133,7 (s), 131,24 (s), 124,31 (d), 120,3 (d); 74,21 (s); 43,01 (d); 40,16 (t); 31,1 (t); 27,02 (t); 25,73 (q); 23,4 (3 signaux superposés) (q et t); 22,17 (t); 17,77 (q).

Tableau 2. Constantes des quatre diastéréoisomères synthétiques

Diastéréoisomères	Origine	$[\alpha]_D^{23}$, C, $CHCl_3$	CPV	RMN
(+)-α-bisabolol (**10**)	(+)-limonène	(1,36), 51, 5° (62°)*	A	1,11
(+)-épi-α-bisabolol (**11**)	(+)-limonène	(2,8), 45,3° (54,5°)*	B	1,14
(−)-α-bisabolol (**12**)	(−)-limonène	(0,5), −59°C (66,4°)*	A	1,11
(−)-épi(8)-α-bisabolol (**13**)	(−)-limonène	(1,65), −44,7° (58,7°)*	B	1,14

* La valeur entre parenthèse est le pouvoir rotatoire corrigé compte tenu de fait que le (+)-limonène utilisé avait un $[\alpha]_D^{23} = 104°$. Comme la valeur la plus élevée mesurée est de 125,6°,[11a] la pureté optique de notre produit de départ est de 83%. Pour le (−)-limonène utilisé, la pureté optique était plus faible: 76% en prenant en compte la valeur la plus élevée—122,1°–.[11a]



Spectres de ^{1}H RMN des (±)-α-bisabolols (courbe A) et des (±)-épi (8)-α-bisabolols (courbe B).

Masse[15a] *m/e* (intensité): 222 (1); 204 (15); 161 (8); 121 (21); 119 (60); 109 (60); 109 (72); 95 (24); 93 (43); 79 (28); 69 (100).

P-Phénylazo-phényluréthane du (−)-α-bisabolol **12a**

Le p-phénylazo-phényl isocyanate est préparé d'après ref. 22 et 23. L'uréthane est préparé selon **17**, à partir de 300 mg (1,2 mmole) d'isocyanate et de 111 mg de **12** (0,5 mmole). On obtient 210 mg (95%) de cristaux oranges. La cristallisation dans le pentane fournit des aiguilles fines F = 103–104° (Litt.[17]) F: 103–103,5° de l'éther de pétrole). Par recristallisation dans le méthanol on obtient des aiguilles plus grandes F = 103,5°–104° qui sont utilisées pour l'étude par rayons X.[18]

$[\alpha]_D^{21°} = +7{,}7°$ (0,83, $CHCl_3$).

RMN–^{1}H: 1,48 (s, 3H); 1,60 (s, 3H); 1,66 (s, 6H); 5,1 (t, 7Hz, 1H); 5,36 (s, 1H); 6,74 (s, 1H); 7,4 à 7,56 (m, 5H); 7,8 à 7,94 (m, 4H).

Masse *m/e* (intensité): 445 (1); 306 (1); 241 (19); 204 (19); 93 (67); 77 (56); 69 (100).

Préparation des 5 isomères du bisabolène **7**

On traite 2,85 g de "Dragosantol" commercial (qui contient 85% soit 10 mmoles d'α-bisabolol) par $POCl_3$ dans la pyridine d'après (ref. 24). Après chromatographie sur silice (éluant: pentane) on obtient 1,6 g (82%) d'un mélange des isomères du bisabolène **7**.

CPV, colonne **D**, 140°, 5 pics: temps de rétention en s (proportions). 1392 (9,8); 1445 (25,8); 1494 (10,6); 1602 (12,9); 1692 (41).

RMN: 1,62 à 1,7 (méthyles allyliques); 2,7 (t); 4,74 (s); 5,12 (m); 5,38 (m); 5,38 (m).

Le signal à 2,7 ppm est caractéristique de protons bisallyliques en C_{11} et C_3 des isomères **7**α Δ, 8,9 et **7**γ Δ, 4,8.[11a,11c]

Le signal à 4,74 ppm est attribuable aux protons en C_{10} de l'isomère **7** β Δ, 8,10.[11c] Le signal à 5,12 ppm correspond au proton vinylique en C_{12} (présent dans tous les isomères)[11a,b,c] et au proton en C_9 de l'isomère **7**α.[11a]

Prénylation du limonène

Dans les essais préliminaires on dissolvait 1,36 g (10 mmoles) de (+)-limonène, et la quantité voulue de DMVC dans le volume désiré de CH_2Cl_2 à 0° ou 20°.

On ajoutait rapidement l'acide formique. Au temps choisi on versait dans l'eau et extrayait avec du pentane. A la phase organique, lavée et séchée sur $MgSO_4$, on ajoutait une quantité connue de n-décane et dosait le formiate de prényle **1d** et le (+)-limonène sur colonne **B** à 120°. On ajoutait ensuite à la solution, une quantité connue de n-dodécanol, filtrait, évaporait le pentane, reprenait à l'éther sec et traitait la solution par $LiAlH_4$ en excès pendant 2 h. à 20°. Après traitements usuels, les alcools étaient dosés sur colonne **A** à 200°. Les étalons choisis avaient une réponse en CPV, pratiquement égale à celles des produits à doser.

Dans les essais préparatifs on dissout 34,4 g de DMVC (0,4 mole) et 27,2 g (0,2 mole) de (+)-limonène dans 120 cm^3 de CH_2Cl_2 et ajoute rapidement 200 cm^3 d'acide formique. Après 25 mn à 20°, on verse dans 500 cm^3 d'eau et extrait au pentane. On lave à l'eau et sèche sur $MgSO_4$. Le pentane est distillé. Si la distillation est trop rapide un peu de formiate de prényle **1d** peut être entraîné. On distille ensuite sous 17 mm sur colonne Vigreux de 20 cm et obtient deux fractions.

I. Eb_{17} = 42-44°, 27,2 g **1d** Rdt/DMVC = 60%.
II. Eb_{17} = 60–64°, 14 g (+)-limonène: récupération 55%.

Le résidu (22 g) est dissous dans 250 cm^3 de méthanol. On ajoute 10 gouttes de HCl concentré et agite une nuit à 20°. Après évaporation sous vide des $\frac{2}{3}$ du méthanol, on ajoute de l'eau salée et extrait avec de l'éther. Après lavage et séchage, l'évaporation du solvant laisse 19,5 g de mélange brut qui est

distillé sur une colonne Vigreux de 20 cm. On obtient deux fractions:

III. $Eb_3 \leq 120°$, 8 g (26%) **14a** pur à 90% CPV colonne A 150°.
IV. $120° \leq Eb_3 \leq 140°$ 9,5 g (39%) de **10** et **11**, **15a**, **15b** cpv colonne A 200° (**10** et **11** donnent 1 pic).

Résidu 2g: ne contient pas les alcools en C_{15} ci-dessus. La fraction IV est redistillée sur une colonne à bande tournante métallique Nester-Faust semi-micro. On obtient trois fractions:

IV_1 $Eb_{0.2} < 82°$ 4,5 g (18,4%) **15a** + **15b**.
IV_2 $82° \leq Eb_{0.2} \leq 84°$ 2,5 g (10,2%) **15a** + **15b** (20%); **10** + **11**. 80%
IV_3 $Eb_{0.2}$ 84,85° 2 g (8,2%) **10** + **11** (95%); **15a** + **15b** (5%).
Résidu 0,5.

Ces trois fractions sont analysées par CPV sur colonne A à 200°. 2 g de la fraction IV_1, chromatographiés sur silice (éluant: éther de pétrole 85; éther 15), fournissent des échantillons purs de **15a**; (200 mg) et **15b** (450 mg).

Méthyl (méthyl-3, butène-2) yl-2, (méthyl-1, éthène-1 yl)-4, cyclohexanol: **15**.

Isomère **15a** $C_{15}H_{26}O$. $[\alpha]_D^{23} = -0{,}16°$ (C = 18, $CHCl_3$).

IR/3450, 1635, 1375, 895 cm^{-1}.

Masse. *m/e* (intensité): 222 (20), 204 (100); 189 (21); 161 (35); 153 (30); 139 (38); 107 (48); 93 (49).

RMN–^{1}H: 1,25 (s, 3H); 1,63 (s, 3H); 1,70 (s, 3H); 1,74 (s, 3H); 4,70-(d, 5,5 Hz, 2H); 5,36 (t, 7 Hz, 1H).

RMN–^{13}C: 150,08 (s); 132,08 (s); 123,21 (d); 108,13 (t); 70,91 (s); 46,44 (d); 45,41 (d); 40,81 (t); 32,59 (t); 28,84 (q); 28,45 (t); 27,22 (t); 25,91 (q); 20,94 (q); 17,96 (q).

Isomère **15b**: $C_{15}H_{26}O$ $[\alpha]_D^{23} = +16°$ (C=13, $CHCl_3$).

I.R.: identique à **15a**.

Masse: *m/e* (intensité): 222 (36); 204 (40); 189 (19); 161 (33); 135 (40); 107 (39); 93 (100).

RMN–^{1}H: 1,2 (s, 3H); 1,64 (s, 3H); 1,72 (s, 6H); 4,71 (s, 2H); 5,09 (t, J = 7 Hz, 1H).

RMN–^{13}C: 146,36 (s); 131,76 (s); 123,47 (d); 108,58 (t); 72,08 (s); 45,47 (d); 38,29 (d); 35,31 (t); 29,87 (t); 28,06 (q), 27,67 (t); 26,64 (q); 25,92 (t); 21,26 (q); 18,03 (q).

En CPV sur colonne C 165°; chacun dex deux isomères donne 1 pic **15a**, 2258 s; **15b**, 2617 s.

Mélange **10** et **11**.

I.R. = 3490, 1445, 1380, 1120 cm^{-1}.

Masse identique au (−)-α, bisabolol naturel **12**.

RMN ^{1}H: Superposition des deux spectres de la Figure 1.

Analyse par CPV colonne C 165°.

2 pics d'égale intensité A 3836 s et **B** 3865 s.

Paranitrobenzoates **10** *et* **11**

On procède comme décrit dans ref 25. Sur 1,4 g de mélange **10**, **11**. On obtient après purification sur silice (éluant: pentane: 95; éther: 5) 1,6 g (68%) d'une huile légèrement jaune.

$C_{22}H_{29}O_4N$. $[\alpha]_D^{23} = +15°$ (C=8, $CHCl_3$).

I.R. 1710, 1600, 1525, 1350, 1290, 735 cm^{-1}.

Masse *m/e* (intensité): 204 (26); 189 (3); 161 (12); 150 (24); 119 (100).

RMN–^{1}H: 1,55 (s); 1,56 (s); 1,58 (s); 1,62 (s); 1,66 (s); 5,0 (s, 1H); 5,4 (s, 1H); 8,12 (d, 9 Hz, 2H); 8,24 (d, 9 Hz, 2H).

Analyse par HPLC. Eluant Hexane-éther 95,5, 0.5 débit 2 cm^3/mn. 2 pics d'égale intensité: 18 mn et 19,2 mn.

Les deux épimères **10PNB** et **11PNB** sont séparés à l'aide d'un appareil de HPLC Dupont Instrument, sur une colonne Zorbaxsil (25 × 1 cm) (éluant: cyclohexane avec 0,5% AcOEt).

Les produits sont détectés par UV. à 254 nm.

A chaque injection de 30 mg maximum, on recueille 3 fractions, les deux pics étant mal résolus. Après évaporation du solvant, réduction par $LiAlH_4$ dans l'éther et purification sur colonne de silice, on obtient chacun des diastéréoisomères **10** et **11** purs et un mélange enrichi (80% de **10**; 20% de **11** déterminée par RMN).

Il est à noter que **10PNB** est élué sur silice après **11PNB**.

Les rendements en **10** et **11**, à partir du mélange des PNB, sont évalués à 30 et 15%; 50% pour la fraction intermédiaire.

Des opérations analogues réalisées avec le (−)-limonène, fournissent, les antipodes de **15a** et **15b**, et les composés **12** et **13**.

Les caractéristiques des 4 diastéréoisomères sont indiquées dans le texte. Les spectres de masses et IR sont identiques entre eux. Les spectres de RMN–^{1}H sont identiques deux à deux et sont reproduits sur la Figure 1.

Par CPV sur colonne *C* à 165°, ils donnent 1 pic unique A ou B.

Remerciements—Nous remercions très vivement le Dr. Brian J. Willis qui nous a gracieusement fourni un échantillon d'essence de camomille allemande "German Extra", de Fritzsche, Dodge and Olcott Inc., la Société Dragoco S.A., pour les dons généreux et répétés de "Dragosantol", et enfin les Professeurs Kergomard et Veschambre qui ont eu l'amabilité de nous fournir un échantillon de (+)-α-bisabolol, qu'ils tenaient eux-mêmes du Professeur Paknikar.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 9 to 12, 1981
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0040-4020/81/Suppl. 1-0009-04 $02.00/0
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STEREOSPECIFIC SYNTHESIS OF METHYL 2,6-DIACETAMIDO-2,3,6-TRIDEOXY-α-D-RIBO-HEXOFURANOSIDE AND HEXOPYRANOSIDE, DERIVATIVES OF TOBROSAMINE

JEAN-CLAUDE FLORENT and CLAUDE MONNERET*

Institut de Chimie des Substances Naturelles, 91190 Gif-sur-Yvette, France

(*Received in France* 9 *January* 1980)

Abstract—Title derivatives of 2,6-diamino-2,3,6-trideoxy-D-ribo-hexose (tobrosamine), the amino-sugar component of the antibiotic nebramycin factor 6, have been prepared in a stereospecific manner, based on the Tischenko rearrangement of methyl 3,6-dideoxy-α-arabino-hexopyranoside in the presence of benzaldehyde and Lewis acids.

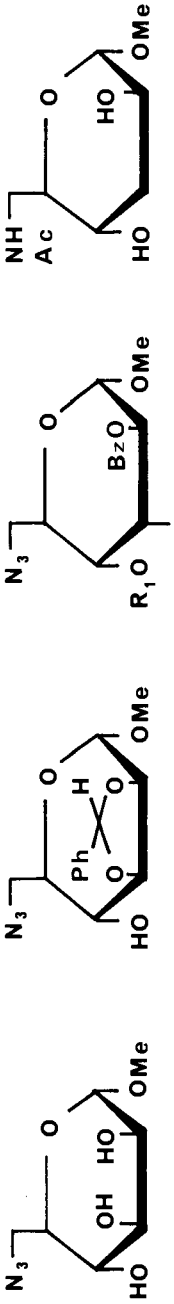
The highly successful clinical applications of aminoglycoside antibiotics has stimulated numerous investigations[1] in order to establish structure-activity relationships and to prepare more active compounds. At the same time an understanding of the mechanism of aminoglycosidic antibiotics resistance[2] has opened the way to the synthesis of new and improved compounds. For example, as one of the most frequently encountered means of inactivation of these antibiotics is phosphorylation at C-3′,[3] gentamycin, sisomicin and tobramycin having a 3′-deoxy-sugar unit are among the most active derivatives of this class.[4] Following from these observations a large number of 3′-O-methyl and 3′-deoxy or 3′,4′-dideoxy derivatives have been synthesized and in particular 3′-deoxy-kanamycin B or tobramycin.[5]

Derivatives of the sugar component of tobramycin, tobrosamine (2,6-diamino-2,3,6-trideoxy-D-*ribo-hexose*) **13** have already been described by Guthrie *et al.*[6] (methyl 2,6-diacetamido-4-*O*-mesyl tobrosaminide) and Gero *et al.*[7] (ethyl 2,6-diacetamido tobrosaminide). In a report of our laboratory[8] we have already described a new route to its methyl diacetamido derivative **12** by azidolysis at the allylic position of an enol ether sugar prepared from mannose.

We now wish to report a new higher yielding and stereoselective synthesis of the hexoside **12** based upon a Tischenko type rearrangement[9] of the key intermediate **6**, methyl 6-acetamido-3,6-dideoxy-α-D-arabino-hexopyranoside.[10] As previously published,[8] the starting materials for this synthesis, methyl 6-azido-α-D-mannopyranoside **1** and its 2,3-*O*-benzylidene acetal **2** were prepared respectively in 90% and 72% overall yield from methyl α-D-mannoside. As observed for other 2,3-*O*-benzylidene acetals of hexose of manno configuration[8,11] and for the corresponding 4-*O*-methyl ether[8] treatment of **2** with NBS led regio- and stereospecifically to the bromo-sugar **3**. This latter was converted by lithium aluminium hydride reduction followed by N-acetylation into the crystalline intermediate **6**.

A more direct route from **1** to **6** was also explored. Barton *et al.*[12] have shown that treatment of 1,2-diols at room temperature with imidoyl chloride derived from dimethylbenzamide led to the regiospecific formation of the chlorhydrin benzoate in excellent yields. Under similar conditions but in presence of ten molar equivalents of imidoyl chloride, the azido-sugar **1** gave a mixture of the 3-chloro-sugars **4** and **5** (80% yield, ratio 4/5 = 0.75/1). The formation of **5** can be explained by esterification of the OH-4 due to the excess of reagent. If lower concentration of imidoyl chloride are used, the ratio 4/5 increases but unfortunately the total yield drops, a part of the reagent being probably consumed by the free OH on C-4. In fact the formation of **5** is not inconvenient since the next step is the $LiAlH_4$ reduction of the mixture followed by acetylation which gave exclusively the acetamido-sugar **6** with an overall yield of 40% from **1**.

In contrast with the results obtained for methyl 3,6-dideoxy-α-D or L-arabino-hexopyranosides,[9] treatment of a benzaldehyde solution of **6** with different acids ($ZnCl_2$, $AlCl_3$ or $TiCl_4$) did not give any of the expected Tischenko type rearrangement product but led to a degradation of the starting material. Fortunately we found after many experiments that in the presence of an equal amount of $AlCl_3$ and $ZnCl_2$, **6** rearranged to **7** in rather good yield (65–70%). The structure of **7** was established from its spectroscopic data to be a furanoside derivative with a benzoic ester on C-2 and a benzyl ether on C-5. Catalytic transesterification of **7** gave **8** and subsequent treatment of **8** in a dichloromethane solution with triflic anhydride according to the procedure of Hall *et al.*[13] gave the sulfonate **9**. Azidolysis of **9** in HMPT at room temperature led to the azido-sugar **10** as the exclusive product (65% after purification). Hydrogenolysis of **10** in the presence of palladium-on-charcoal followed by acetylation in methanol of the crude product afforded the methyl furanoside of *N,N′*-acetyl tobrosamine **11**. Finally methyl 2,6-diacetamido-2,3,6-trideoxy-α-D-ribo-hexopyranoside (methyl 2,6-diacetamido-tobrosaminide) **12**[8] was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4 R1 = H ; R2 = Cl
5 R1 = Bz ; R2 = Cl
NH
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6
PhCH2O
H
NHAc
O
RO
OMe
7 R = Bz
8 R = H
9 R = Tf
R1O
H
NHAc
O
R2
OMe
10 R1 = CH2Ph ; R2 = N3
11 R1 = H ; R2 = NHAc
NH
R1
O
HO
OR2
NHR1
12 R1 = Ac R2 = Me
13 R1 = R2 = H Tobrosamine

isolated after acid hydrolysis and glycosidation with methanolic solution of hydrochloric acid.

EXPERIMENTAL

General. All m.ps were determined on a Büchi apparatus and are uncorrected. IR spectra (film or Nujol suspension) were registered on a Perkin–Elmer Model 257. ^{1}H NMR spectra were recorded at 90 or 240 MHz with TMS as internal standard, the chemical shifts being expressed in ppm. Optical rotations were measured on a Perkin–Elmer Model 141 MC polarimeter and 1-dm tubes were used. TLC used Merck silica gel GF_{254} plates. Column chromatography was conducted using Merck silica gel type H. Microanalysis were performed by the Service Central de Microanalyse du CNRS. Extraction in usual manner means that the organic layer is washed with dil HCl or aq $NaHCO_3$, dried, and concentrated *in vacuo*.

Methyl 6-azido-2-O-benzoyl-3-bromo-3,6-dideoxy-α-D-altropyranoside **3**

To a solution of **2**[8] (10.9 g, 35 mmol) in carbon tetrachloride (500 ml) was added *N*-bromosuccinimide (8 g) and barium carbonate (10 g). The suspension was heated with stirring under reflux for 3 h. After cooling and filtration, the filtrate was extracted with dichloromethane in the usual manner. The solvent was removed *in vacuo* giving pure **3** (12.3 g, 90 %) as a syrup, $[\alpha]_D^{20}$ + 18° ($CHCl_3$). IR (film): 2100 (N_3) 1725, 1265 and 1105 cm^{-1} (ester). NMR ($CDCl_3$, 60 MHz): δ = 5.52 (d, J = 2.5, H-2), 4.81 (s, H-1), 4.57 (dd, J=J′=2.5, H-3), 4.03 (m, H-4, H-5), 3.6 (m, H-6, H-6′), 3.47 (s, OMe). Calc. for $C_{14}H_{16}O_5N_3Br$ (386.21). C,H,N,Br.

Methyl 6-azido-2-O-benzoyl-3-chloro-3,6-dideoxy-α-D-altropyranoside **4** *and methyl 6-azido-2,4-di-O-benzoyl-3-chloro-3,6-dideoxy-α-D-altropyranoside* **5**

Reaction of the mannose derivative **1**[8] (236 mg, 1.08 mmol) with pyridine (0.5 ml) and *N,N*-dimethyl-α-chlorobenzylidene ammonium chloride (prepared as described[12] from N,N-dimethylbenzamide (2.5 g)) for 16h at reflux gave, on evaporation, a syrup. TLC (hexane–ethyl acetate–dichloro-methane, 5:1:1, v/v) showed two spots. Column chromatography on silica gel (same solvent as for TLC) gave **5** (197 mg) and in the later fractions **4** (146 mg): total yield 80 %. **4**: syrup, $[\alpha]_D^{20}$ + 70° ($CHCl_3$). IR (film): 2100 (N_3), 1725, 1250 and 1105 cm^{-1} (ester). NMR ($CDCl_3$, 250 MHz): δ = 5.42 (dd, J = 0.7, J′ = 3, H-2), 4.79 (s, H-1), 4.49 (dd, J = 3.5, J′ = 3, H-3), 4.11 (m, H-4, H-5), 3.63 (m, H-6), 3.55 (m, H-6′), 3.47 (s, OMe). Calc. for $C_{14}H_{16}N_3O_5Cl$ (341.70). C,H,N. **5**: syrup, $[\alpha]_D^{20}$ + 34.5° ($CHCl_3$), NMR ($CDCl_3$, 250 MHz): δ = 5.48 (dd, J = 9, J′ = 4, H-4), 5.46 (dd, J = 1, J′ = 4, H-2), 4.87 (s, H-1), 4.71 (t, J = J′ = 4, H-3), 4.56 (q, J = 9, J′ = 5, J″ = 4, H-5), 3.55 (m, H-6 and H-6′), 3.51 (s, OMe). Calc. for $C_{21}H_{20}N_3O_6Cl$ (445.80). C,H,O.

Methyl 6-acetamido-3,6-dideoxy-α-D-arabino-hexopyranoside **6**

To a solution of **3** (13g, 35 mmol) in a mixture of tetrahydrofuran (150 ml) and ether (150 ml) was slowly added lithium aluminium hydride (5 g). After stirring under reflux for 4h, the excess of hydride reagent was destroyed by addition of a saturated solution of ammonium sulfate. The mixture was filtered and the solids washed with a mixture of chloroform and methanol (1:1, 2 × 100 ml). The combined filtrates were evaporated to dryness to give a syrup. This syrup was dissolved in anhydrous pyridine (75 ml) and acetic anhydride (25 ml) and stirred overnight. Water was then added (100 ml) and then aqueous bicarbonate and extraction was carried out with dichloromethane. The organic layer was washed with aqueous solution of hydrochloric acid 1 N, water and then with aqueous bicarbonate. After evaporation to dryness, the syrup (5g) was dissolved in a methanolic solution of sodium methanolate (0.2N, 100 ml) and stirred for 2h. Neutralisation was effectued with Amberlite IR 50(H^+) and after filtration the solvent was removed under reduce pressure. The residue (3.5 g) was chromatographed on silica gel (solvent: dichloromethane-methanol, 9:1, v/v) to give **6** (3.1 g, 42 %): m.p. 141–142° (methanol-ether), $[\alpha]_D^{20}$ + 93° (MeOH, c 2). IR (Nujol): 1650, 1570 cm^{-1} (amide). NMR (pyridine-d_5, 250 MHz): δ = 4.9 (s, H-1), 3.35 (s, OMe), 2.6–2.25 (m, H-3 and H-3′), 2.07 (s, OAc). Calc. for $C_9H_{17}O_5N$ (219.23). C,H,N.

Methyl 6-acetamido-2-O-benzoyl-5-O-benzyl-3,6-dideoxy-α-D-arabino-hexofuranoside **7**

Zinc chloride (1 g, 7 mmol) and aluminium chloride (0.9 g 7 mmol) were added to a solution of **6** (493 mg, 2.2 mmol) in benzaldehyde (15 ml). The suspension was stirred for 3 h and then the excess of reagent was destroyed by addition of methanol (2 ml) and prolonged stirring for 5 min. Extraction with dichloromethane in usual manner and purification by preparative chromatography (solvent: hexane-dichloromethane-ethylacetate, 1:1:1, v/v) gave **7** as a syrup: $[\alpha]_D^{20}$ + 16° (MeOH). IR: (film): 1725, 1275 and 1100 cm^{-1} (ester), 1610 and 1495 (acetamide). NMR ($CDCl_3$, 60 MHz): δ = 7.4–8 (m, Ph), 7.32 (s, $\underline{Ph}CH_2$), 5.30 (m, H-2), 5.05 (s, H-1), 4.68 (wide s, $\underline{CH_2}Ph$), 3.40 (s, OMe), 1.87 (s, Ac). Calc. for $C_{23}H_{27}O_6N$ (413.45). C,H,N.

Methyl 6-acetamido-5-O-benzyl-3,6-dideoxy-α-D-arabino-hexofuranoside **8**

A solution of **7** (1.06 g, 2.6 mmol) in ethanolic KOH (4 %, 50 ml) was stirred at room temperature for 3 h. Extraction with dichloromethane afforded pure **8** (TLC dichloromethane-methanol, 7:1, v/v) (595 mg, 75 %) as a syrup, $[\alpha]_D^{20}$ + 58° (MeOH, c 1.75). IR (film): 1655 and 1540 cm^{-1} (amide). NMR ($CDCl_3$, 90 MHz): δ = 7.36 (m, Ph), 4.70–4.75 (m, 3 H, CH_2Ph and H-1) 3.25 (s, OMe), 1.87 (s, Ac). Calc. for $C_{16}H_{23}O_5N$ (309.35). C,H,N.

Methyl 6-acetamido-5-O-benzyl-3,6-dideoxy-2-O-trifluoromethanesulfonyl-α-D-arabino-hexofuranoside **9**

Pyridine (1.13 ml) and then a solution of triflic anhydride (1.13 g, 4 mmol) in dichloromethane (5 ml) were added dropwise to a solution of **8** (515 mg, 1.67 mmol) in dichloromethane (25 ml) chilled at −15°C. The mixture was kept at this temperature until TLC (solvent: dichloromethane-methanol, 7:1, v/v) showed complete disappearance of the starting material (3 h). The mixture was then poured into a chilled saturated solution of sodium bicarbonate and then extracted in the usual manner with dichloromethane. After concentration *in vacuo*, the residue (795 mg) was chromatographed on silica gel (dichloromethane-methanol, 33:1, v/v) to give **9** (569 mg, 90 %) unstable, immediately converted into **10**.

Methyl 6-acetamido-2-azido-5-O-benzyl-2,3,6-trideoxy-α-D-ribo-hexofuranoside **10**

Sodium azide (100 mg) was added over 15 mn to a cooled (0°) solution of **9** (480 mg, 1.2 mmol) in HMPT (15 ml). Stirring was then continued for 2 h at room temperature. Extraction with benzene–ether (1:1, v/v) gave a syrup which showed a single spot in TLC (dichloromethane-methanol 95:5, v/v). Purification by preparative TLC afforded **10** (234 mg, 60 %) as a syrup: $[\alpha]_D^{20}$ + 115° ($CHCl_3$). IR: 2100 cm^{-1} (N_3). NMR ($CDCl_3$, 240 (MHz): δ = 4.92 (d, J = 4, H-1), 4.80 (m, CH_2Ph), 3.43 (s, OMe), 1.6–2.3 (m, H-3 and H-3′), 1.84 (s, OAc). Calc. for $C_{16}H_{22}N_4O_4$ (334.37). CHN.

Methyl 2,6-diacetamido-2,3,6-trideoxy-α-D-ribo-hexofuranoside **11**

A solution of **10** (141 mg, 0.42 mmol) in methanol (20 ml) and acetic anhydride (1 ml) was stirred for 2 h under hydrogen in the presence of palladium-on-charcoal (10 %, 150 mg). The catalyst was then removed by filtration and the filtrate evaporated under reduced pressure, and evaporation repeated thrice after addition of toluene (10 ml).

Chromatography of the residue on silica gel (dichloromethane-methanol, 14:1, *v/v*) gave **11** (64 mg, 65%): mp 176–177° (acetone), $[\alpha]_D^{20}$ + 120° (c 2, methanol). IR (Nujol): 1635 and 1555 cm^{-1} (amide). NMR (240 MHz, pyridine-d_5): δ 5.07 (broad s, H-1), 3.30 (s, OMe), 2.09 (s, Ac). Calc. for $C_{11}H_{20}O_5$ (232.27). C,H,O.

Methyl 2,6-diacetamido-2,3,6-trideoxy-α-D-ribo-hexopyranoside **12**

A solution of **11** (50 mg) in a methanolic solution of hydrochloric acid (7 ml, 3%, v/v) was heated under reflux overnight. After cooling and neutralisation with Amberlite IR 45 (OH^-), the filtrate was evaporated *in vacuo*. TLC (dichloromethane-methanol, 12.5:1, v/v) showed two principal spots. Chromatography on silica gel gave starting material **11** (15 mg) and **12** (25 mg) whose constants are in agreement with those previously described in the literature.[8] mp, 207° (acetone-methanol); $[\alpha]_D^{20}$ + 90° ($CHCl_3$).

Acknowledgements—We thank Prof. D. H. R. Barton for his kind suggestion to use imidoyl chloride and Dr. P. Potier for his continuous interest and encouragement.

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Tetrahedron Vol. 37, Supplement No., 1, pp. 13 to 24
Printed in Great Britain

0040-4020/81/Suppl. 1-0013-12 $02.00/0
Pergamon Press Ltd.

THE CHEMISTRY OF AN ALLYLSILANE: THE SYNTHESIS OF A PROSTAGLANDIN INTERMEDIATE AND OF LOGANIN†

IAN FLEMING* and BOON-WAI AU-YEUNG

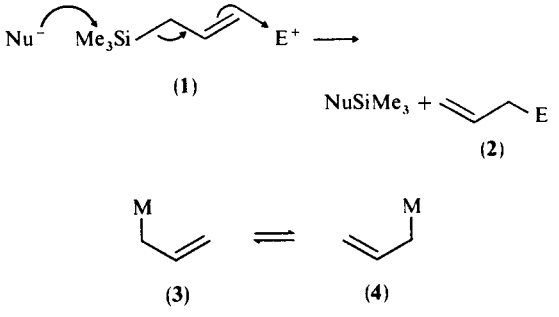
University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England

(*Received in the U.K.* 18 *April* 1980)

Abstract—The allylsilane 7,7-dichloro-4-*exo*-trimethylsilyl-bicyclo[3.2.0]hept-2-en-6-one (**6**) reacts regioselectively with a variety of electrophiles, and the product (**28**) of methoxymethylation can be converted into prostaglandins. Elaboration of the cyclobutanone ring of **6** in seven steps gives the allylsilane (**43**), which reacts regioselectively with chlorosulphonyl isocyanate. The product of this reaction can be converted into loganin aglucone acetate (**48**), a known intermediate in the synthesis of loganin (**49**).

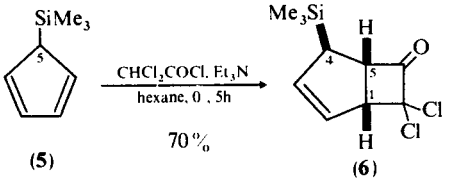
In a brief paper in 1948, Sommer, Tyler and Whitmore[1] proposed that allyltrimethylsilane reacts with electrophiles in the general sense (**1** → **2**). At about the same time, it was being established that allyl-metal compounds, such as the crotyl Grignard reagent, also react in this sense,[2] but that they appeared to be allylically unstable (**3** ⇌ **4**). In the intervening years, the allylic instability of metals has been well established, and many allyl-metal compounds even adopt, as their stable arrangement, a π-allyl structure which is related to the transition state for the allylic rearrangement. Because of this allylic instability, unsymmetrical allyl–metal compounds cannot be relied upon to give a single product, and there is little control over which product they will give. However, almost uniquely among metal compounds, allylsilanes are comparatively stable with respect to allylic rearrangement.[3] If, then, they can be relied upon to react in the sense (**1** → **2**), they should be useful synthetic intermediates. Furthermore, since they are comparatively unreactive, they might be expected to possess a second useful property: unlike other allyl–metal compounds, they should be able to survive a wide range of reaction conditions before their reactivity in the sense (**1** → **2**) is put to use. In this paper, we describe in full how these ideas have been combined in highly controlled syntheses of loganin (**49**) and of a well-known intermediate (**29**) in prostaglandin synthesis.[4]

Before we began this work, and during it, we and others established that unsymmetrical allylsilanes did react in the sense (**1** → **2**) with such electrophiles as the proton,[5–8] and, in the presence of Lewis acids, acetyl chloride,[6,8] acetone,[9] acetals,[10] and t-alkyl halides.[8] However, although unsymmetrical allylsilanes are evidently as regiochemically well-behaved as one could have hoped, there is a severe shortage of ways in which they can be synthesised regioselectively.[11] When they can be made easily, as here, they work well.



THE GENERAL CHEMISTRY OF THE ALLYLSILANE (6)

The crystalline allylsilane (**6**) used in this work was prepared in 70% yield by cycloaddition of dichloroketene to trimethylsilylcyclopentadiene (**5**),[12] which is known[13] to be largely (>90% at room temperature) the 5-isomer, as shown. The stereochemistry of the silyl group in the product (**6**) was judged to be *exo* because the PMR signal of the C-4 hydrogen is a narrow multiplet. The C-4 *exo* hydrogens in bicyclo[3.2.0]hepten-6-ones are usually[14] coupled by 6–9 Hz with the hydrogen on C-5. The similarity in chemical shift for the C-1 and C-5 hydrogens established that the regioisomer produced was the same as that for cyclopentadiene itself.[15] This was confirmed by protodesilylation (**6** → **7**) followed by dechlorination, which gave the known bicyclo[3.2.0]hept-2-en-7-one (**8**) much more conveniently than by the earlier syntheses.[16] The alternative order of events—dechlorination (**6** → **31**) followed by protodesilyation—failed in the second step. Although sulphuric acid in methanol was the best method for protodesilyation in this case, toluene-*p*-sulphonic acid also worked, and we used the latter to investigate the stereochemistry of the reaction. Using deuterated acid, we got a product (**9**) in which the PMR signal of the *exo* proton on C-4 was much diminished in intensity (*ca.* 70% d_1), and the signal of the *endo* proton was at full intensity. The reaction was therefore *syn*. Because of the *exo* bias in the bicyclic system, we are unable to say whether this is the inherently preferred stereochemistry for this type of S_E2' reaction, but Wetter *et*



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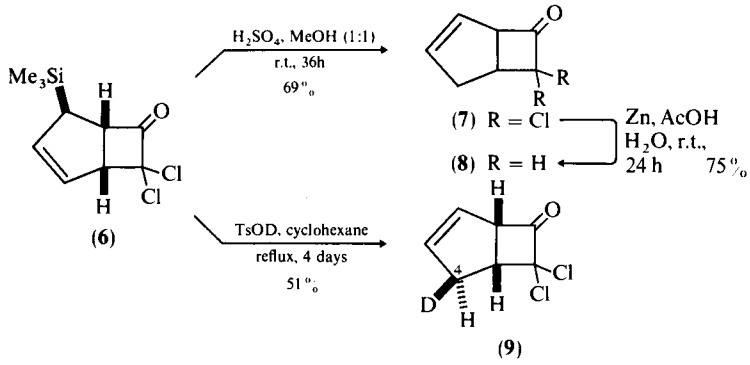
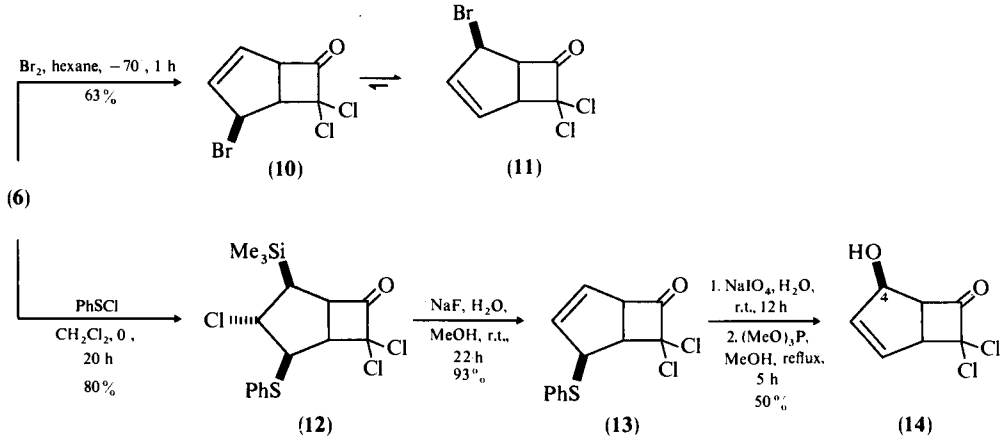


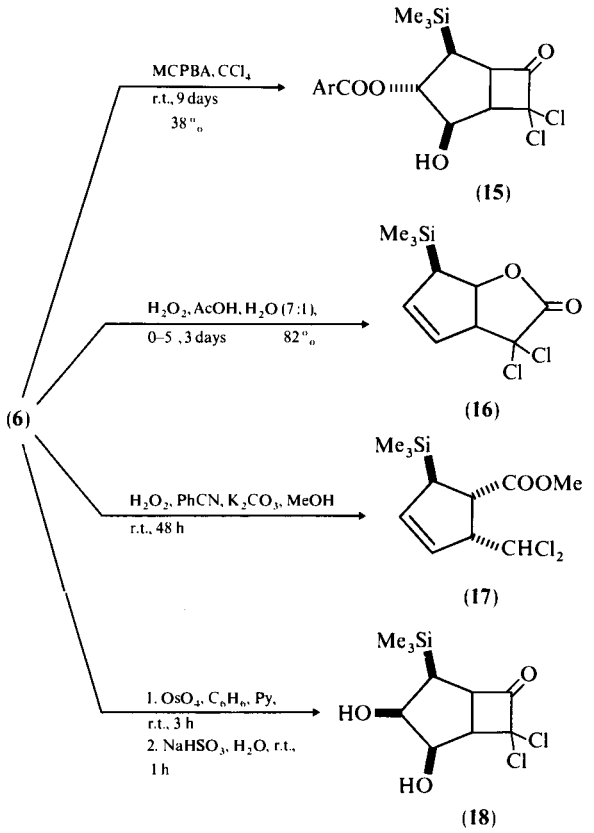
al. have recently shown that acylative desilyation in an open-chain allylsilane is also *syn.*[17]

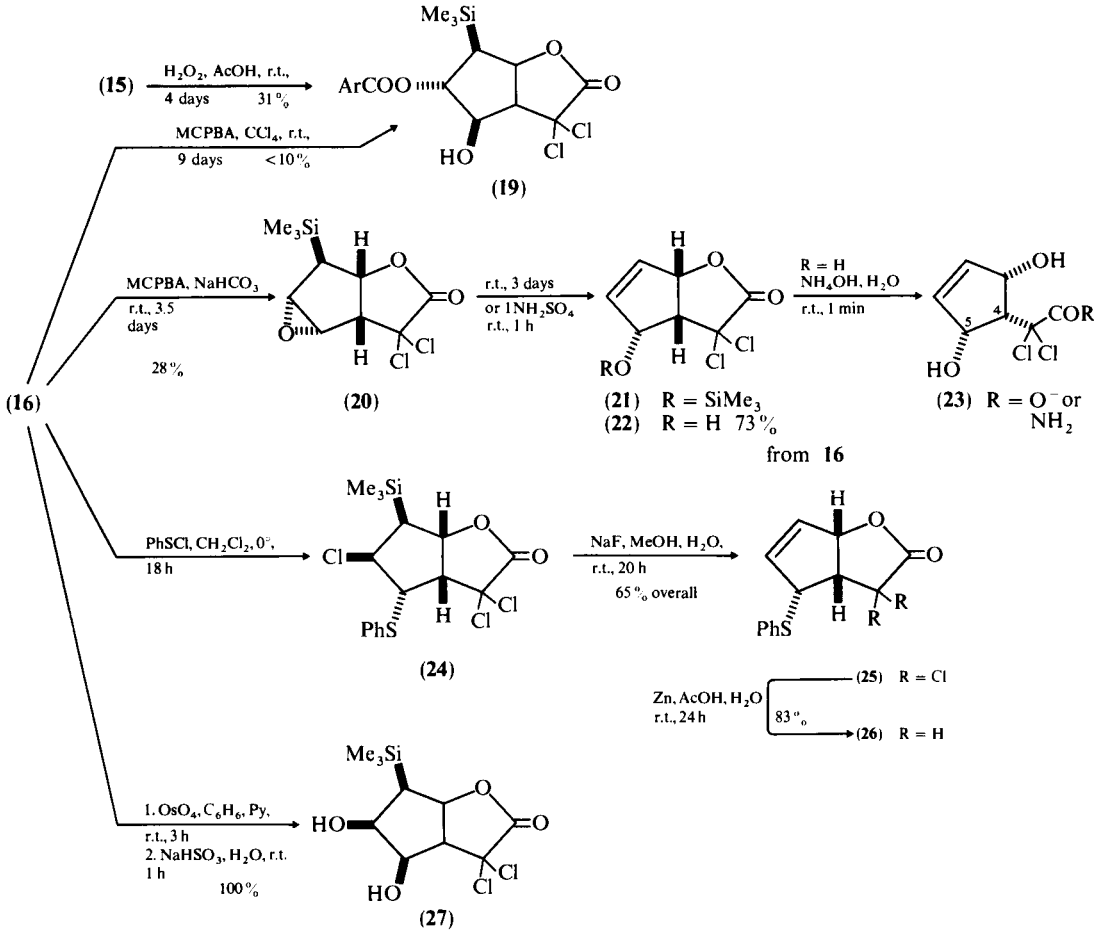
Careful, low temperature bromination of the allylsilane (**6**) gave the known[18] bromide (**10**) in 63% yield, but equilibration to its allylic isomer (**11**) was rapid and sometimes hard to avoid. Benzenesulphenylation of the allylsilane (**6**) gave the addition product (**12**) (80%), which reacted with fluoride ion to give the allylsulphide (**13**) (93%). The allylsulphide could be converted by the Mislow-Evans procedure to the allyl alcohol (**14**) (50%), the stereochemistry of which was evident from the PMR spectrum, which showed a *narrow* multiplet from the hydrogen on C-4.

The reactions of these three electrophiles were therefore uneventful. Our results with oxygen electrophiles were not so straightforward. Although we were able, eventually, in this series, and in our earlier work,[7] to convert an allylsilane to an allylically rearranged allyl alcohol, this deceptively simple transformation should not always be expected to work easily. In the first place, *m*-chloroperbenzoic acid (MCPBA) alone gave, as the only isolable compound, the addition product (**15**) (30–38%). The addition of a peracid to an olefin is, of course, known,[19] but was somewhat surprising in this case in view of the ease with which a silyl group is usually lost. Presumably the elimination step is not easy because of the *syn* relationship of the silyl and epoxy groups, and because they are present in a 5-membered ring. Other peracids were no better. Buffered peracids gave, as expected, the Baeyer–Villiger product (**16**), which was most easily made, in 82% yield, using hydrogen peroxide in acetic acid. Hydrogen peroxide and benzonitrile[20] in methanolic potassium carbonate also gave a small amount of the lactone (**16**), but the major product this time was the ring-cleaved[21] ester (**17**). Our last attempt with the ketone (**6**) was to oxidise it with osmium tetroxide. The PMR spectrum of the product showed that it was the diol (**18**), but neither acid[22] nor base[23] was effective in converting **18** into an allylic alcohol. In view of the difficulties caused by the presence of a ketone group in **6**, we turned to the lactone (**16**),

This lactone also reacted with MCPBA alone to give, as a minor component of a complex mixture, the addition product (**19**), which could also be prepared by Baeyer–Villiger oxidation of the ketone (**15**). Finally, buffered MCPBA converted the lactone (**16**) into a very sensitive epoxide (**20**). Merely on standing, it rearranged to the silyl ether (**21**), which was easily hydrolysed to the alcohol (**22**). By avoiding the isolation of the epoxide, we found that we could convert the allylsilane (**16**) to the allylic alcohol (**22**) in 73% yield. *Endo* epoxidation was reasonable, since the lactone (**33**), which lacks both the silyl group and the chlorines, was known to give largely the *endo* oxide.[24] The stereochemistry was suggested by the PMR spectrum of the alcohol (**22**), and was confirmed by dissolving it in aqueous ammonia and evaporating off the solvent. The PMR spectrum of the residue (**23**) in DMSO-d_6 showed a sharp singlet (2 H, δ 5.91), a sharp doublet (2 H, δ 4.46, $J = 6$ Hz), and a sharp triplet (1 H, δ 3.12, $J = 6$ Hz), ascribable to the olefinic, allylic, and C-4 hydrogens, respectively. The simplicity of this spectrum is a result of the plane of symmetry present in the salt (or possibly amide) (**23**). To get a spectrum as simple as this from the diastereoisomer with the C-5 hydroxyl β would need no fewer than *four* coincidences, two of chemical shift and two of coupling constants. The lactone (**16**) also reacted with benzene–sulphenyl chloride on what appears, from the PMR spectrum described below, to be the *endo* face, in contrast to the corresponding reaction of the ketone (**6**). The allyl-sulphide (**25**), produced by desilylchlorination of the first-formed adduct (**24**),




MCPBA, CCl_4
r.t., 9 days
38 %
(15)
H_2O_2, AcOH, H_2O (7:1),
0–5 , 3 days 82 %
(16)
H_2O_2, PhCN, K_2CO_3, MeOH
r.t., 48 h
(17)
1. OsO_4, C_6H_6, Py,
r.t., 3 h
2. $NaHSO_3$, H_2O, r.t.,
1 h
(18)
(6)


(15)
H_2O_2, AcOH, r.t.,
4 days 31 %
MCPBA, CCl_4, r.t.,
9 days <10 %
(19)
MCPBA, $NaHCO_3$
r.t., 3.5
days
28 %
(20)
r.t., 3 days
or 1 NH_2SO_4
r.t., 1 h
(21) R = $SiMe_3$
(22) R = H 73 %
from 16
R = H
NH_4OH, H_2O
r.t., 1 min
(23) R = O^- or
NH_2
(16)
PhSCl, CH_2Cl_2, 0°,
18 h
(24)
NaF, MeOH, H_2O,
r.t., 20 h
65 % overall
Zn, AcOH, H_2O
r.t., 24 h
83 %
(25) R = Cl
(26) R = H
1. OsO_4, C_6H_6, Py,
r.t., 3 h
2. $NaHSO_3$, H_2O, r.t.
1 h
100 %
(27)

showed in its PMR spectrum a large (6 Hz) coupling between the hydrogen α to the sulphur and the bridgehead hydrogen, and there was a similarly large coupling (7 Hz) in the PMR spectrum of the dechlorinated lactone (**26**). Unlike the *endo* selectivity shown in the epoxidation, the *endo* sulphenylation cannot have been caused by hydrogen-bonding of the electrophile to the lactone group. It seems likely, therefore, that the *endo* selectivity is electronic in origin, implying either that the silyl group encourages attack *anti* to itself or that the oxygen atom encourages attack *syn* to itself. In contrast, the lactone (**16**) gave the *exo* diol (**27**) with osmium tetroxide, but we were again unable to convert this product, either with acid or base (or with fluoride ion on the derived diacetate), into an allylic alcohol. In conclusion, in this section on oxygen electrophiles, we note that the successful epoxidation of an allylsilane and the subsequent formation of an allylic alcohol (**16** → **20** → **22**) took place only under *acidic* conditions, as was the case with our other example of this type of reaction.[7] It seems likely that this will prove to be a general requirement, especially in view of the entirely different course taken in a reaction observed by Hudrlik *et al.*,[25] where an allylsilane epoxide was a likely intermediate in a base-promoted reaction. Hudrlik also draws attention in this paper to the unsatisfactory level of characterization of those βγ-epoxysilanes which have been reported in the past. Except for those derived from 3-silacyclopentenes,[26] **20** is the first well-characterized βγ-epoxysilane.

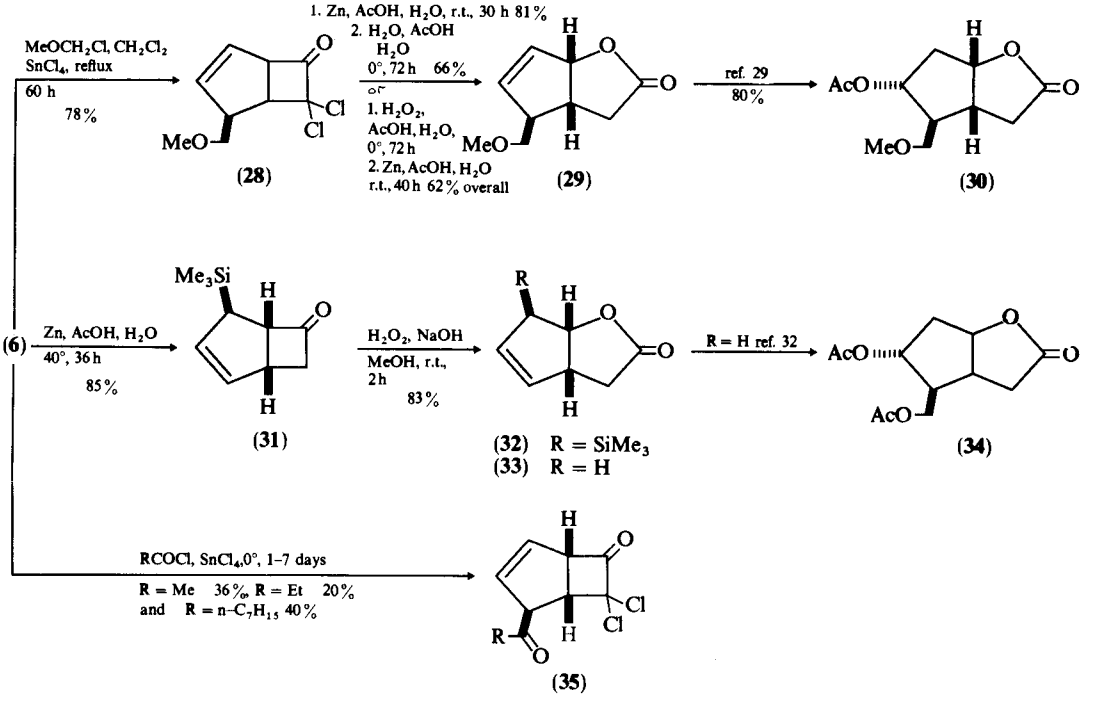
THE SYNTHESIS OF THE PROSTAGLANDIN INTERMEDIATE (29)

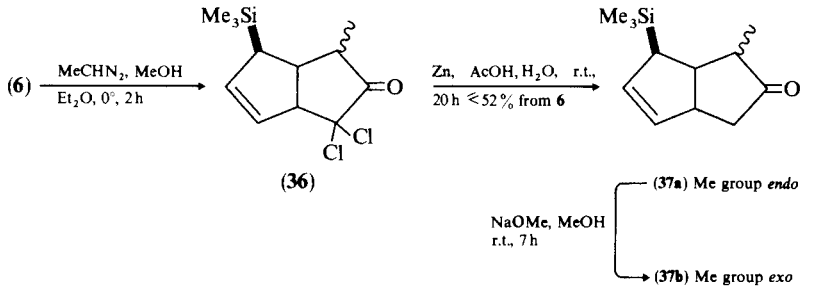
Having established that a proton and various heteroatom electrophiles reacted cleanly with our allylsilane, we turned to carbon electrophiles, of which the most interesting was chloromethyl methyl ether. It was known that alkenes react with chloromethyl methyl ether in the presence of Lewis acids to give addition, but that vinylsilanes give substitution.[27] We found that the allysilane (**6**) reacted cleanly with choromethyl methyl ether and stannic chloride to give the ether (**28**) in 78% yield. Other Lewis acids, such as aluminium chloride, boron trifluoride and titanium tetrachloride, gave, in this case at least, inferior yields and mixtures of unidentified products. The ether (**28**) was converted in two steps into the known[28,29] lactone (**29**), which was identical with an authentic sample.[28] The conversion by oxidation followed by reduction without isolation (62% overall) was better than the alternative, reduction (81%) followed by oxidation (66%). Other variations in the order of events, such as methoxy-methylation of **16** or **31** or **32** were unsuccessful.[30] The overall yield of the lactone (**29**) from cyclopentadiene was 25%. This lactone has been converted[29] to the Corey lactone (**30**)[31] in 80% yield, and hence into A and F prostaglandins. The overall yield of the Corey lactone (**30**) by our route is 20%, bv Ranganathan's route[29] 45%, and by Corey's,[31] 40%. Plainly ours is inferior in this respect. Its strength, however, is that none of our intermediates is so delicate that it demands immediate use after preparation. Scaling up should therefore be easier in our case. As it happens, a Prins reaction on the readily available lactone (**33**) has been reported[32] to give the derivative (**34**) stereo- and regioselectivity, thus doing away altogether with the need for the silyl group.

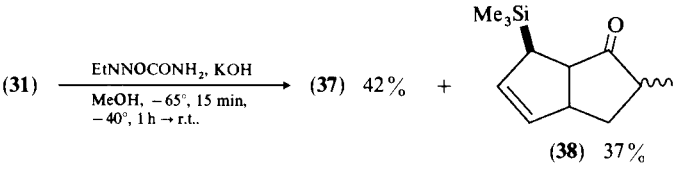
We tried to extend our route to prepare analogues of prostaglandins by using other electrophiles on the allylsilanes (**6**, **16**, **31**, and **32**). Except for acylation of **6**, which gave the appropriate ketones (**35**) in yields up to 40%, none of the usual carbon electrophiles which react with allylsilanes[11] gave identifiable products[30] (we tried acetals, methyl orthoformate, aldehydes and enones, with a variety of Lewis acids).

THE SYNTHESIS OF LOGANIN

Most of the reactions discussed above are reactions directly on the allylsilane group in **6**. However, this group should be stable to many reaction conditions which would allow elaboration of the cyclobutanone ring. For the synthesis of loganin we wanted to expand this ring regioselectively by one carbon atom, using diazoalkanes, and we hoped that the α-halogen atoms



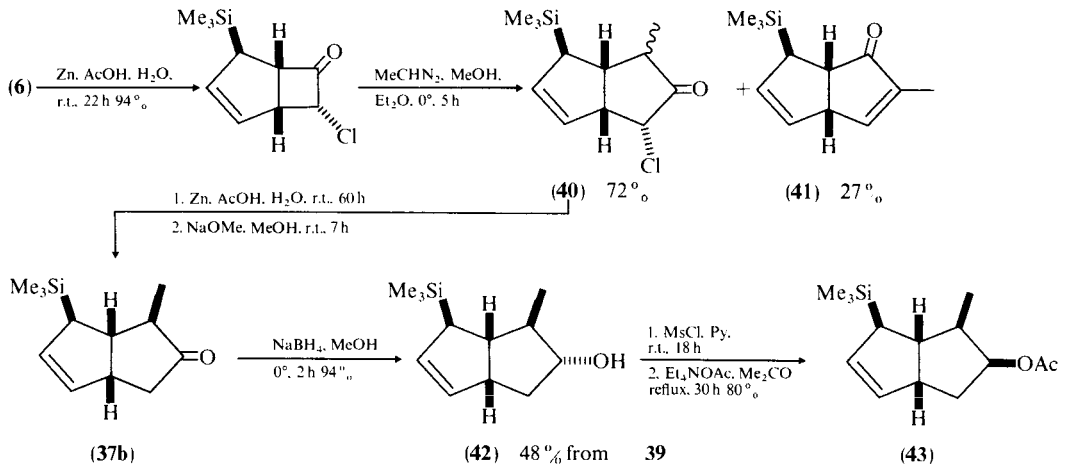


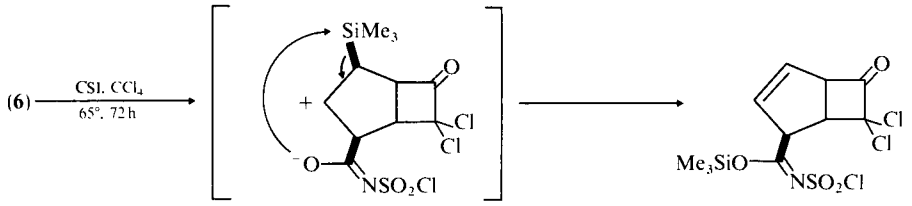


would give us the regioselectivity we wanted. This feature of our work has since been taken up and exploited in other ways.[33] The best order of events in our case took some working out. When we used the dichloroketone (**6**) itself and diazoethane in a mixture of ether and methanol, the first-formed product (**36**) was unstable. We therefore dehalogenated the crude mixture of products immediately and got the mixture of ketones (**37**) in, at best, 52% yield. However, we also got variable amounts of the dehalogenated starting material (**31**), and we could discover no convenient and reliable way of monitoring the reaction to make sure that all the starting material has been used up. The reaction was also troublesome, because the diazoethane polymerized faster than it attacked the ketone, and it had to be added in excess in batches throughout the reaction period. It was no use avoiding this problem by generating the diazoethane *in situ*, because the base used to generate the diazoethane would have opened the cyclobutanone ring (**6** → **17**). We therefore turned to the dehalogenated ketone (**31**), where we could generate the diazoethane *in situ* in methanol without trouble. The reaction with the ketone was now faster, and yields were good, but the ring expansion showed little regioselectivity, giving the mixture of ketones (**37**) in 42% yield and the mixture of ketones (**38**) in 37% yield. The preference for migration by the more-substituted carbon, slight though it was, was agreeable, and unexpected, in view of several reports[34] of higher proportions of migration by primary than by secondary alkyl groups. Although this route gave us material to work with, it was hardly satisfactory. Fortunately, the monochloroketone (**39**), easily prepared in 94% yield from the dichloroketone (**6**) by reduction with one equivalent of zinc, reacted fast enough with preformed diazoethane in ether and methanol so that only one equivalent of diazoethane was needed. The regioselectivity was reasonably high: the required ketones (**40**) were formed in 72% yield, and the by-product (**41**), from migration of the α-chloromethylene carbon, was formed in 27% yield. This was slightly disappointing in view of the report[35] that 2-chlorocyclohexanone and diazomethane gave only 2-chlorocycloheptanone.

Zinc removed the chlorine from the mixture of ketones (**40**), and the product (**37**) could then be separated chromatographically from **41**. Treatment of the mixture of stereoisomers (**37**) with sodium methoxide in methanol converted the minor isomer (**37a**), which had an *endo* methyl group, into the major (**37b**), in which the methyl group was *exo*. Sodium borohydride attacked the ketone group from the *exo* direction to give the *endo* alcohol (**42**), and the mesylate of this alcohol reacted with acetate ion to give the *exo* acetate (**43**). This reaction sequence was closely modelled on that used by Büchi in his synthesis of loganin.[36]

The right hand side of the molecule was now complete; the allylsilane function had dutifully survived seven steps, and it was time for it to perform





to order. We needed a carbon electrophile which would act overall as a methoxycarbonyl cation synthon, because we wanted the product to be the ester (**47**). Chlorosulphonyl isocyanate (CSI) appeared to have the right properties: it was known to react with alkenes; and, although the major products are usually β-lactams (70% with isobutene, for example),[37] substitution products are also formed. The presence of the silyl group ought, therefore, to tip the balance in favour of substitution, because of the ease with which the silyl group will be displaced in the zwitterionic intermediate (**44**, arrows). The model allylsilane (**6**) reacted with CSI cleanly, and the PMR spectrum of the product was entirely compatible with the structure (**45**), but we were unable to find hydrolytic conditions which gave a clean or recognisable product. With the allylsilane (**43**), the reaction with CSI was again clean, as judged by PMR, and, this time, with a lot of effort, we found conditions for the hydrolysis which were reasonably high-yielding. Simple treatment with dilute hydrochloric acid gave the amide (**46**) in 55% yield, and the amide could be converted to the ester (**47**) in 69% yield by nitrosation, hydrolysis and esterification with diazomethane. By not isolating any of the intermediates between the allylsilane (**43**) and the ester (**47**), we got an overall yield of 61%. Dunoguès *et al.*[38] have also found that allylsilanes react with CSI, and they used a pyridine work-up to get $\beta\gamma$-unsaturated nitriles. This did not work in the case of **45**; nor did the procedure just described.[30]

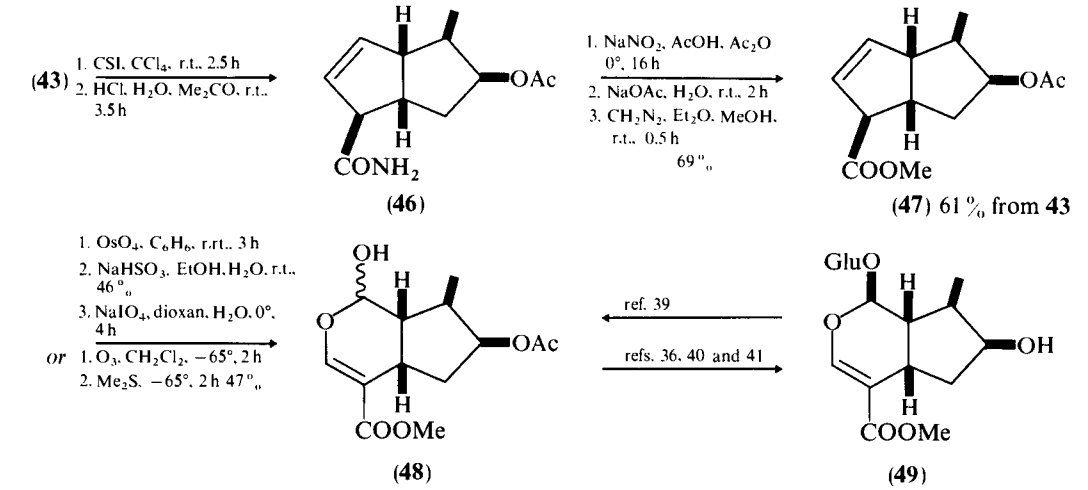
The oxidative cleavage of the double bond of **47** could be done by ozonolysis or by osmium tetroxide followed by periodate. The dialdehyde was not observed, but the hemiacetal (**48**) was isolated in 47% and 46% yields respectively. Our racemic sample was identical with an authentic, optically active sample of loganin aglucone acetate[39] prepared from loganin (**49**) itself.

This product was an intermediate in Büchi's[36] and in Uskokovic's[40] syntheses; the glycosidation step has since been improved by Tietze.[41] We have therefore completed a total synthesis of loganin; the overall yield of the intermediate (**48**) based on cyclopentadiene is 5.3%, double that of Büchi's synthesis,[36] and slightly higher† than Uskokovic's[40] (4%), both of which also began with cyclopentadiene. Our route, however, is principally interesting not for the overall yield, but for the control which the allylsilane chemistry has introduced.

EXPERIMENTAL

7,7-*Dichloro*-4-exo-*trimethylsilylbicyclo*-[3.2.0]*hept*-2-*en*-6-*one* (**6**). A solution of dichloroacetyl chloride (29.5 g, 0.2 mol) in dry hexane was added dropwise over 2 hr to a stirred mixture of 5-trimethylsilylcyclopentadiene[12] (20.6 g, 0.15 mol) and triethylamine (20.2 g, 0.2 mol) in dry hexane (300 ml) at 0°C under nitrogen. After stirring at 0–5° for an additional 3 hr, the mixture was poured into water (500 ml). The hexane layer was separated, dried ($MgSO_4$) and the solvent evaporated. Distillation gave the adduct (**6**) (26.1 g; 70%), b.p. 71–3°/0.3 mm Hg (Found: C, 48.0; H, 5.7. $C_{10}H_{14}Cl_2OSi$ requires: C, 48.2; H, 5.7%), ν_{max} (film) 1804s and 1594w cm^{-1}, δ (CCl_4) 0.02 (9 H, s, $SiMe_3$), 2.46 (1, H, m, $Me_3Si\underline{C}H$), 4.0 (2 H, m, bridgehead H's), and 5.65 and 5.96 (each 1 H, m, CH=CH).

6,6-*Dichlorobicyclo*[3.2.0]*hept*-2-*en*-7-*one* (**7**). A solution of the silane (**6**) (3.5 g) in a mixture of sulphuric acid (50 ml) and methanol (50 ml) was kept at room temperature for 36 hr. The mixture was poured into cold water (300 ml) and extracted with chloroform (3 × 40 ml) to give the ketone (**7**) (1.7 g, 69%), b.p. 55–6°/0.65 mm Hg (Found: C, 47.35; H, 3.6.



†This synthesis, however, was of optically active loganin aglucone acetate.

$C_7H_6Cl_2O$ requires: C, 47.5; H, 3.4%), ν_{max} (film) 1800s and 1604w cm^{-1}, δ (CCl_4) 2.62–2.88 (1 H, ddm, *J* 19 and 8 Hz, C-4 *exo* H), 2.95–3.16 (1 H, dm, *J* 19 Hz, *endo* C-4 H), 3.48 (1 H, *dt*, *J* 8 and 2 Hz, C-5 H), 4.54 (1 H, m, C-1 H), and 5.63 and 5.90 (each 1 H, m, CH=CH).

Bicyclo[3.2.0]*hept-2-en-7-one* (**8**). The ketone (**7**) (1.7 g) was stirred with zinc powder (7 g, excess) in a mixture of acetic acid (40 ml) and water (5 ml) at room temperature for 24 hr. The inorganic solids were filtered off and washed with chloroform (50 ml). The combined filtrate and washings were washed with water (3 × 150 ml) and then with sodium hydrogen carbonate solution. The chloroform layer was separated, dried ($MgSO_4$), and evaporated, and the residue distilled to give the ketone (**8**) (0.8 g, 75%), b.p. 56°/15 mm Hg (Found: C, 77.5; H, 7.4. Calc. for C_7H_8O: C, 77.75; H, 7.5%), ν_{max} (film) 1775s and 1602w cm^{-1} (lit.[16] 1780 cm^{-1}), δ (CCl_4) 2.2–3.5 (5 H, m), 4.2 (1 H, m, C–1 H), and 5.6 and 5.85 (each 1 H, m, CH=CH), λ_{max} (cyclohexane) 296, 306, and 317 nm (ε 128, 142, and 100), [lit.[16] 297, 306, and 317 nm (ε 142, 160, and 112)], *m/z* 108 (M^+) and 66 (base; M^+–CH_2CO) (lit.[16], same observations) 2,4-dinitrophenylhydrazone, needles (from ethanol), m.p. 149–150° (lit.[16] 149–151°).

6,6-*Dichloro-4-exo-deuteriobicyclo*[3.2.0]*hept-2-en-7-one* (**9**). The water of crystallisation of toluene-*p*-sulphonic acid monohydrate (0.8 g, 4 mmol) was first removed by azeotropic distillation with dry cyclohexane. Deuterium oxide (2 g) was added to the dry mixture and stirred for 5 min. The acid was dried again by azeotropic removal of water using dry cyclohexane. Another 2 g of deuterium oxide was again added and the removal of water repeated, until about 10 ml of cyclohexane finally remained. The silane (**6**) (0.15 g, 0.6 mmol) was added and the mixture heated under reflux with stirring for 4 days. The charred substances and excess acid were filtered off. The filtrate was washed with water and then evaporated. The residue, after purification by tlc on silica gel (benzene, $\underline{R}_F$ 0.4), gave an oil (54 mg, 51%) in which the PMR signal at δ 2.62–2.88 was much reduced in intensity, indicating a composition of about 70% of (**9**) and 30% of (**7**).

4-exo-*Bromo-6,6-dichlorobicyclo*[3.2.0]*hept-2-en-7-one* (**10**). Bromine (1.6 g, 10 mmol) in dry hexane (4 ml) was added dropwise over 0.5 hr to a solution of the silane (**6**) (2.5 g, 10 mmol) in hexane (11 ml) at −70°, and the mixture stirred for an additional 0.5 hr at −70°. The precipitate was quickly separated from the cold solution and washed with 5 ml of cold hexane (−70°) to give pure bromide (**10**) (1.6 g; 63%). A sample was recrystallised to give prisms, m.p. 71–2° (from hexane) (Found: C, 32.8; H, 2.3. $C_7H_5BrCl_2O$ requires: C, 32.9; H, 2.0%), ν_{max} (KBr) 1805s and 1594w cm^{-1}, δ (CCl_4) 3.88 (1 H, d, *J* 6.5 Hz, C–5 H), 4.80 (1 H, m, C–1 H), 5.33 (1 H, m, BrCH), and 5.92 and 6.18 (each 1 H, m, CH=CH).

2-exo-*Phenylthio*-3-endo-7,7-*trichloro*-4-exo-*trimethylsilylbicyclo*-[3.2.0]*heptan-6-one* (**12**). Phenylsulphenyl chloride (1.50 g, 10 mmol) was added to a solution of the silane (**6**) (2.50 g, 10 mmol) in dry dichloromethane (40 ml), and the mixture kept at 0–3° for 20 hr. After evaporation of solvent, the residue was crystallised from light petroleum (b.p. 40–60°) to give the adduct (**12**) (3.2 g, 80%) as needles, m.p. 85–6° (Found: C, 48.7; H, 4.7. $C_{16}H_{19}Cl_3OSSi$ requires: C, 48.8; H, 4.9%), ν_{max} (KBr) 1804s cm^{-1}, δ (CCl_4) 0.10 (9 H, s, $SiMe_3$), 1.74 (1 H, m, $Me_3SiC\underline{H}$), 3.18 (1 H, m), 3.65 (3 H, m), and 7.32 and 7.53 (3 H + 2 H, m, ArH).

6,6-*Dichloro-4-exo-phenylthiobicyclo*-[3.2.0]*hept-2-en-7-one* (**13**). Sodium fluoride (800 mg) in water (15 ml) was added to a solution of the adduct (**12**) (1.36 g) in methanol (50 ml) and the mixture stirred at room temperature for 22 hr. After evaporating off most of the methanol, the residue was extracted with ether (40 ml), the ether dried (Na_2SO_4), and evaporated to give the sulphide (**13**) (0.90 g, 93%) as prisms, m.p. 56–7° (light petroleum, b.p. 40–60°) (Found: C, 54.5; H, 3.4; Cl, 24.9; S, 11.0. $C_{13}H_{10}Cl_2OS$ requires: C, 54.75; H, 3.5; Cl, 24.9; S, 11.2%), ν_{max} (KBr) 1800s and 1602w cm^{-1}, δ (CCl_4) 3.58 (1 H, d, *J* 7 Hz, C–5 H), 4.28 (1 H, m, C–1 H), 4.62 (1 H, m, $PhSC\underline{H}$), 5.70 and 5.96 (each 1 H, m, CH=CH), and 7.30 (5 H, m, ArH).

7,7-*Dichloro*-4-exo-*hydroxybicyclo*[3.2.0]*hept-2-en-6-one* (**14**). Sodium metaperiodate (0.71 g, 3.3 mmol) in water (10 ml) was added dropwise to an ice-cold solution of the sulphide (**13**) (0.9 g, 3.2 mmol) in methanol (40 ml). The mixture was stirred at 0° for 2 hr and then at room temperature overnight. Methanol was evaporated off and the aqueous residue extracted with ether (20 ml). The extract was washed with water, dried (Na_2SO_4), evaporated, and the residue purified through a column (SiO_2; 30 g) eluting with dichloromethane-ether (1:1) to give a mixture of two diastereoisomers of the sulphoxide [0.86 g, 90%; R_f (ether) 0.33], ν_{max} (CCl_4) 1814s and 1058s cm^{-1}, δ ($CDCl_3$) 3.80 (1 H, m), 4.2–4.7 (2 H, m), 5.60, 6.04 (total 2 H, m, CH=CH), and 7.56, 7.64 (total 5 H, s, ArH), *m/z* 304, 302, 300 (M^+). The sulphoxide (0.58 g, 1.9 mmol) was heated with trimethyl phosphite (0.28 g, 2.2 mmol) in methanol (10 ml) under reflux for 5 hr. After evaporation of solvent, the residue was purified by tlc (SiO_2; ether; R_f 0.7) to give the alcohol (**14**) (0.19 g, 50%), liquid, ν_{max} (CCl_4) 3590m, 3400br, and 1810 cm^{-1}, δ (CCl_4) 2.80 (1 H, br, OH), 4.12 (2 H, m, bridge-head H's), 4.93 (1 H, m, $HOC\underline{H}$), and 6.13 (2 H, m, CH=CH). The alcohol (14) was characterised as its dimethyl(trityl)silyl ether,[42] prisms (hexane), m.p. 140–1°. (Found: C, 68.0; H, 5.3; Cl, 14.1. $C_{28}H_{26}Cl_2O_2Si$ requires: C, 68.2; H, 5.3; Cl, 14.4%), ν_{max} (CCl_4) 1808s and 1595m cm^{-1}, δ (CCl_4) 0.26 (6 H, sm, $SiMe_2$), 3.35 (1 H, d, *J* 6.5 Hz, C–5 H), 3.94 (1 H, m, C–1 H), 4.64 (1 H, m, $SiOC\underline{H}$), 5.55 and 5.82 (each 1 H, m, CH=CH), and 7.12 (15 H, m, ArH).

7,7-*Dichloro*-2-exo-*hydroxy*-6-*oxo*-4-exo-*trimethylsilylbicyclo*[3.2.0]*hept*-3-endo-*yl*-3-*chlorobenzoate* (**15**). A solution of **6** (250 mg, 1 mmol) and *m*-chloroperbenzoic acid (300 mg) in carbon tetrachloride (20 ml) was stirred at room temperature for 9 days. The resultant mixture was washed with 5% sodium hydroxide solution and water. The organic layer was separated, dried (Na_2SO_4) and evaporated, and the residue separated by tlc on silica gel (CH_2Cl_2). Besides 36 mg recovery of the starting silane, the only identified product was the benzoate (**15**) (137 mg, 38% based on consumed starting silane), prisms, m.p. 126–7° [from light petroleum (60–80°)] (Found: C, 48.4; H, 4.5; Cl, 25.2. $C_{17}H_{19}Cl_3O_4Si$ requires: C, 48.4; H, 4.5; Cl, 25.2%), ν_{max} (KBr) 3490s, 1810s, and 1692s cm^{-1} δ (CCl_4) 0.15 (9 H, s, $SiMe_3$), 1.98 (1 H, dd, *J* 3 and 2 Hz, $Me_3SiC\underline{H}$), 3.38 (1 H, d, *J* 8.5 Hz, C–1 H), 3.65 (1 H, d, *J* 3 Hz, OH), 4.03 (1 H, dd, *J* 8.5 and 3 Hz, C–5 H), 4.62 (1 H, m, C–2 H), 5.26 (1 H, t, *J* 3 Hz, C–3 H), and 7.1–7.7 (4 H, m, aromatic).

8,8-*Dichloro-6-oxa*-4-exo-*trimethylsilylbicyclo*[3.3.0]*oct-2-en-7-one* (**16**). A mixture of **6** (5 g, 20 mmol), hydrogen peroxide (4.5 ml, 100 vols) and water (10 ml) in acetic acid (70 ml) was kept at 0–5° for 3 days, then poured into water (800 ml), and extracted with ether (100 ml). The ethereal extract was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated to give the lactone (**16**) (4.38 g, 82%) as prisms, m.p. 69–70° (from light petroleum, b.p. 60–80°) (Found: C, 45.5; H, 5.4. $C_{10}H_{14}Cl_2O_2Si$ requires: C, 45.3; H, 5.3%), ν_{max} (CCl_4) 1805s cm^{-1}, δ (CCl_4) 0.03 (9 H, s, $SiMe_3$), 2.42 (1 H, m, $Me_3SiC\underline{H}$), 3.85 (1 H, m, CCl_2CH), 5.02 (1 H, d, *J* 4.5 Hz, CO_2CH), and 5.55 and 5.94 (each 1 H, m, CH=CH).

Methyl 2-(*Dichloromethyl*)-5-*trimethylsilylcyclopent*-3-*enecarboxylate* (**17**). A mixture of **6** (0.25 g, 1 mmol), benzonitrile (103 mg, 1 mmol), hydrogen peroxide (30 mg, 100 vols) and potassium hydrogen carbonate (20 mg) in methanol (5 ml) was stirred under nitrogen at room temperature for 48 h. The inorganic solid was filtered off and the filtrate evaporated. The residue (0.20 g) was purified by tlc on silica gel (CH_2Cl_2) to give, among other products, the ester to which we ascribe, by analogy,[21] the structure **17**, ν_{max} (CCl_4) 1736s cm^{-1}, δ (CCl_4) −0.4 (9 H, s, $SiMe_3$), 2.26 (1 H, m, $Me_3SiC\underline{H}$), 3.08 (1 H, dd, *J* 9 and 5 Hz), *ca.* 3.4 (1 H, m), 3.58 (3 H, s, CO_2Me), 5.58 and 5.80 (each 1 H, m, CH=CH), and 6.01 (1 H, d, *J* 8 Hz, $CHCl_2$).

7,7-*Dichloro*-2,3-exo-*dihydroxy*-4-exo-*trimethylsilylbicyclo*[3.2.0]*heptan-6-one* (**18**). The silane (0.20 g, 0.8 mmol)

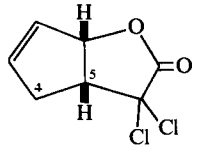
and osmium tetroxide (0.20 g, 0.8 mmol) in benzene (10 ml) were mixed with a catalytic amount of pyridine and stirred at room temperature for 3 hr. The benzene was evaporated off and the residue was taken up in ethanol (10 ml). A solution of sodium metabisulphite (1.5 g) in water (10 ml) was added and the mixture stirred at room temperature for 1 hr, diluted with water (100 ml) and extracted with ether (3 × 40 ml). The residue from the extracts was purified by tlc on silica gel (ether) to give the diol (**18**), ν_{max} (film) 3700–3050 br and 1805s cm^{-1}, δ (CCl_4) 0.10 (9 H, s, $SiMe_3$), 1.38 (1 H, dd, *J* 8 and 3 Hz, $Me_3SiC\underline{H}$), 3.36 (3 H, br m, OH, C–1 H), 3.98 (1 H, t, *J* 8 Hz, C–3 H), and 4.27 (2 H, m, C–2 and C–5 H), *m/z* 283 (M^+, not detectable), 265 (M^+–H_2O).

Reaction of the m-*chlorobenzoate* (**15**) *with hydrogen peroxide.* A solution of **15** (69 mg)and hydrogen peroxide (0.2 ml, 100 vols) in acetic acid (2 ml) was kept at room temperature for 4 days. The mixture was taken up in ether and washed with water. The ether layer was separated and purified by tlc on silica gel (CH_2Cl_2) to obtain a product (23 mg, 32%) which was assigned structure (**19**), ν_{max} (KBr) 3640–3300br, 1805s, and 1715s cm^{-1}, δ (CCl_4) 0.20 (9 H, s, $SiMe_3$), 1.94 (1 H, m, $Me_3SiC\underline{H}$), 3.25 (1 H, t, *J* 6 Hz, CCl_2CH), 3.35 (1 H, br, OH), 4.35 (1 H, m), 4.94 (1 H, dm, *J* 6 Hz), 5.18 *J* 1 H, t, *J* 5 Hz), 7.3–7.9 (4 H, m, aromatic), *m/z* 440, 438, 436 (M^+, weak), 425, 423, 421 (M^+–CH_3). The same product was obtained in <10% yield from the reaction of **16** with MCPBA alone.

8,8-*Dichloro*-2,3-*endo-epoxy*-6-*oxa*-4-exo-*trimethylsilyl-bicyclo*[3.3.0]*octan*-7-*one* (**20**). The lactone (**16**) (500 mg, 1.9 mmol) and *m*-chloroperbenzoic acid (650 mg) in dry dichloromethane (20 ml) were stirred with sodium hydrogen carbonate (8 g, large excess) at room temperature for 3.5 days. The salts were filtered off and washed thoroughly with dry dichloromethane (stirred with sodium hydrogen carbonate before use). The filtrates were evaporated and purified by tlc on silica gel (benzene) (R_f 0.22; 0.15 g, 28%). An analytical sample was obtained by recrystallization from ether-hexane at room temperature, to give the epoxide (**20**) as leaflets, m.p. 70–1° (Found: C, 42.7; H, 4.8. $C_{10}H_{14}Cl_2O_3Si$ requires: C, 42.7; H, 5.0%), ν_{max} (KBr) 1798s cm^{-1}, δ (CCl_4) 0.12 (9 H, s, $SiMe_3$), 2.08 (1 H, s, $Me_3SiC\underline{H}$), 3.38 (1 H, dd, *J* 5.5 and 2 Hz, CCl_2CH), 3.56 and 3.70 (each 1 H, m, OCH), and 4.82 (1 H, d, *J* 5.5 Hz, CO_2CH). The mother liquor was composed mainly of two components. After separation by tlc on silica gel (CH_2Cl_2), the slower running component (R_f about 0.15) was identified by PMR as the alcohol (**22**); the fastest running one (R_f about 0.6) was the trimethylsilyl ether (**21**), a liquid, ν_{max} (film) 1805s cm^{-1}, δ (CCl_4) 0.12 (9 H, s, $SiMe_3$), 3.14 (1 H, t, *J* 5.5 Hz, CCl_2CH), 4.78 (1 H, dd, *J* 5.5 and 2 Hz, $Me_3SiOC\underline{H}$), 5.18 (1 H, dd, *J* 5 and 2 Hz, CO_2CH), and 6.27 (2 H, m, CH=CH).

6,6-*Dichloro*-4-endo-*hydroxy*-8-*oxabicyclo*[3.3.0]*oct*-2-*en*-7-*one* (**22**). The lactone (**16**) (530 mg, 2 mmol) was treated with *m*-chloroperbenzoic acid (680 mg) in dry dichloromethane (20 ml) in the presence of sodium hydrogen carbonate (8 g), as in the preparation of the epoxide (**20**) above. The epoxide was not separated but the crude residue was stirred with dilute sulphuric acid at room temperature for 1 hr. The resultant mixture was extracted with dichloromethane (50 ml), washed rapidly with sodium hydrogen carbonate solution, quickly separated, dried (Na_2SO_4), and evaporated. The residue was stirred in sodium hydrogen carbonate solution (30 ml) for 2 hr and the insoluble substances were filtered off. The aqueous filtrate was acidified and then extracted with ether (2 × 20 ml). The ether layer was separated, dried (Na_2SO_4), evaporated and distilled (0.05 mm; bath temp 80–90°) to give the alcohol (**22**) as an oil (306 mg, 73%) (Found: C, 40.0; H, 3.1; Cl, 34.1 $C_7H_5Cl_2O_3$ requires: C, 40.2; H, 2.9; Cl, 33.9%), ν_{max} (film) 36–3100br and 1806s cm^{-1}, δ ($CDCl_3$) 2.48 (1 H, br, OH), 3.29 (1 H, t, *J* 5 Hz, CCl_2CH), 4.94 (1 H, dd, *J* 5.5 and 2.5 Hz, $HOC\underline{H}$), 5.32 (1 H, dd, *J* 5 and 2.5 Hz, CO_2CH), 6.35 (1 H, dm, J 5.5 Hz, $C\underline{H}$=CH), and 6.72 (1 H, dd, J 5.5 and 2.5 Hz, CH=$C\underline{H}$). The lactone (**22**) was dissolved in aqueous ammonia and the solvent evaporated. The residue of the ammonium salt (**23**) (or possibly the corresponding amide) showed δ (DMSO-d_6) 3.12 (1 H, t, *J* 6 Hz, $CHCCl_2$), 4.46 (2 H, d, *J* 6 Hz, $C\underline{H}OH$) and 5.91 (2 H, s, CH=CH).

6,6-*Dichloro*-8-*oxabicyclo*[3.3.0]*oct*-2-*en*-7-*one* (**50**). This lactone was prepared from **7** (107 mg) in the same way that **16** was prepared from **6**. The product (85 mg, 72%) was distilled (0.05 mm; bath temp 45–50°) to give the *lactone* (**50**) (Found: C, 43.4; H, 3.25; Cl, 36.6. $C_7H_6Cl_2O_2$ requires: C, 43.55; H 3.1; Cl, 36.7%), ν_{max} (film) 1890s and 1615w cm^{-1}, δ (CCl_4, 2.68 and 2.82 (each 1 H, m, CH_2), 3.61 (1 H, dt, *J* 8, 8, and 6 Hz, CCl_2CH), 5.42 (1 H, dm, *J* 6 Hz, CO_2CH), and 5.98 and 6.22 (each 1 H, m, CH=CH). It was prepared as a model compound, to give us coupling constants from the bridgehead proton on C-5 to each of the protons on C-4. We hoped to use these values in the assignment of configuration at C-4 of **22**, where the coupling constant between the protons on C-4 and C-5 was about 5.5 Hz. However, the PMR spectrum of **50**, as reported above, shows a remarkable example of *virtual* coupling, giving the impression that the coupling constant both to the *exo* and the *endo* protons on C-4 is 8 Hz.



(**50**)

6,6-*Dichloro*-8-*oxa*-4-exo-*phenylthiobicyclo*[3.3.0]*oct*-2-*en*-7-*one* (**25**). Phenylsulphenyl chloride (300 mg, 2 mmols) was added to a solution of the silane (**16**) (530 mg, 2 mmols) in dichloromethane (5 ml) and the mixture kept at 0–3° for 18 hr. The resultant solution was evaporated to give the adduct (**24**), δ (CCl_4), 0.32 (9 H, s, $SiMe_3$), 2.38 (1 H, m, $Me_3SiC\underline{H}$), 3.85 (1 H, d, *J* 7 Hz)m 4.15 (1 H, t, *J* 7 Hz), 4.8–5.2 (2 H, m), and 7.42 (5 H, m, ArH). The adduct was kept in methanol (30 ml) and water (10 ml) with sodium fluoride (400 mg) at room temperature for 20 hr. After removal of most of the methanol, the residue was extracted with ether. The ether layer was dried (Na_2SO_4) and evaporated, and the residue was purified by tlc (SiO_2; benzene; R_f 0.3) to give the sulphide (**25**) (0.39 g, 65%), ν_{max} (CCl_4) 1805 cm^{-1}, and 1585w cm^{-1}, δ (CCl_4) 3.70 (1 H, dd, *J* 7.5 and 6 Hz, C–5 H), 4.36 (1 H, dm, *J* 6 Hz, $PhSC\underline{H}$), 5.30 (1 H, dm, *J* 6 Hz, CO_2CH), 5.9 (1 H, dm, *J* 6 Hz, $C\underline{H}$=CH), 6.24 (1 H, dd, *J* 5.5 and 2 Hz, CH=$C\underline{H}$), and 7.3 (5 H, m, ArH), *m/z* 304, 302, 300 (M^+).

8-*Oxa*-4-exo-*phenylthiobicyclo*[3.3.0]*oct*-2-*en*-7-*one* (**26**). The sulphide (**25**) (300 mg, 1 mmol) was stirred with zinc powder (2 g) in a mixture of acetic acid (10 ml) and water (0.5 ml) at room temperature for 24 hr. The inorganic solid was removed by filtration and washed with ether (30 ml). The combined filtrate and washings were washed with water (2 × 70 ml), dried (Na_2SO_4) and evaporated to give the sulphide (**26**) (190 mg, 83%) as leaflets, m.p. 63–5° (CH_2Cl_2–hexane) (Found: C, 67.0; H, 5.3; S, 13.7. $C_{13}H_{12}O_2S$ requires: C, 67.2; H, 5.2; S, 13.8%), ν_{max} ($CHCl_3$) 1780s cm^{-1}, δ (CCl_4) 2.45 (1 H, dd, *J* 10.5 and 18 Hz, $C\underline{H}_AH_BCO$), and 2.86 (1 H, dd, *J* 7 and 18 Hz, $CH_A\underline{H}_BCO$), 3.38 (1 H, m, C–5 H), 4.42 (1 H, dm, *J* 7 Hz, SCH), 5.32 (1 H, dm, *J* 7.5 Hz, CO_2CH), 6.00 (2 H, s, CH=CH), and 7.26 (5 H, m, ArH).

8,8-*Dichloro*-2,3-exo-*dihydroxy*-6-*oxa*-4-exo-*trimethylsilyl-bicyclo*[3.3.0]*octan*-7-*one* (**27**). The procedure was the same as that in the preparation of the diol (**18**). The lactone (**16**) (100 mg) reacted with osmium tetroxide (100 mg) to give the diol (**27**) (100 mg, 100%) as leaflets, m.p. 155° (from CCl_4 or ether–hexane) (Found: C, 40.4; H, 5.3; Cl, 23.8. $C_{10}H_{16}Cl_2O_4Si$ requires: C, 40.14; H, 5.4; Cl, 23.7%), ν_{max} (KBr) 3650–3250br and 1798s cm^{-1}, δ ($CDCl_3$) 0.17 (9 H, s, $SiMe_3$), 1.64 (1 H, dd, *J* 10 and 3.5 Hz, $Me_3SiC\underline{H}$), 3.07 (1 H, dd, *J* 5 and 3.5 Hz, CCl_2CH), 3.23 (2 H, s, $O\underline{H}$), 4.07 (1 H, dd, *J* 10 and 3.5 Hz, C–2 H), 4.28 (1 H, t, *J* 3.5 Hz, C–3 H), and 4.76

(1 H, dd, *J* 5 and 3.5 Hz, CO_2CH). The diol was further characterised as its diacetate, 2,3-exo-diacetoxy-7,7-dichloro-4-exo-trimethylsilyl[3.2.0]heptan-6-one (90%) as plates, m.p. 124–6° (hexane) (Found: C, 45.55; H, 5.4; Cl, 19.5. $C_{14}H_{20}Cl_2O_5Si$ requires: C, 45.8; H, 5.5; Cl, 19.3%), ν_{max} (CCl_4) 1804s and 1746s cm^{-1}, δ (CCl_4) 0.0 (9 H, s, $SiMe_3$), 1.57 (1 H, dd, *J* 8 and 4 Hz, $Me_3SiC\underline{H}$), 1.88 and 1.92 (each 3 H, s, OAc), 3.30 (1 H, dd, *J* 9.5 and 7.5 Hz, C–1 H), 3,96 (1 H, t, *J* 9.5 Hz, C–5 H), 5.18 (1 H, dd, *J* 7.5 and 4 Hz, C–2 H), and 5.44 (1 H, t, *J* 4 Hz, C–3 H).

6,6-*Dichloro*-4-exo-*methoxymethylbicyclo*[3.2.0]*hept*-2-*en*-7-*one* (**28**). A mixture of **6** (5.0 g, 20 mmol), chloromethyl methyl ether (2.0 g, 25 mmol), and stannic chloride (10 ml, excess) in dry dichloromethane (70 ml) was heated under reflux under nitrogen for 60 hr. The mixture was poured into a mixture of crushed ice and conc. hydrochloric acid and the organic layer dried (Na_2SO_4) and evaporated. The residue was taken up in carbon tetrachloride, filtered and the filtrate distilled to give the ether (**28**) (3.45 g, 78%), b.p. 65–8°/0.03 mm (Found: C, 48.6; H, 4.6; Cl, 32.45. $C_9H_{10}Cl_2O_2$ requires: C, 48.9; H, 4.6; Cl, 32.1%), ν_{max} (film) 1805s and 1604w cm^{-1}, δ (CCl_4) 3.15–3.60 (7 H, m, with a singlet at 3.35), 4.55 (1 H, m, C–1 H), and 5.82 (2 H, m, CH=CH). The use of the harmless dimethoxymethane in place of chloromethyl methyl ether gave the same product but in only 15% yield (R. V. Williams).

4-exo-*Methoxymethylbicyclo*[3,2.0]*hept*-2-*en*-7-*one*. The ether (**28**) (2.50 g) was stirred with zinc powder (10 g) in an acetic acid-water mixture (30 ml: 2 ml) at room temperature for 30 hr. The inorganic solids were filtered off and washed with ether. The combined filtrate and washings were washed with water (2 × 200 ml) then with sodium hydrogen carbonate solution. The ether layer was dried (Na_2SO_4), and evaporated, and the residue distilled to give the ether (1.40 g, 81%), b.p. 45–8°/0.25 mm (Found: C, 71.0; H, 8.0. $C_9H_{12}O_2$ requires: C, 71.0; H, 8.0%), ν_{max} (film) 1775s and 1600w cm^{-1}, δ (CCl_4) 2.50–3.45 (9 H, m, with a singlet at 3.26), 4.18 (1 H, m, C–1 H) and 5.74 (2 H, m, CH=CH).

4-exo-*Methoxymethyl*-8-*oxabicyclo*[3.3.0]*oct*-2-*en*-7-*one* (**29**). *Method A*. The ketone described immediately above (880 mg, 5.8 mmol), hydrogen peroxide (1 ml, 100 vols), and water (2 ml) were kept in acetic acid (15 ml) at 0–3° for 72 hr. The mixture was taken up in ether (30 ml) and the solution washed with water (3 × 100 ml). The residue from the dried (Na_2SO_4) ether layer was crystallised to give the lactone (**29**) (640 mg, 66%) as plates, m.p. 29–30° (cold hexane) (Found: C, 64.1; H, 7.2. Calc. for $C_9H_{12}O_3$: C, 64.3; H, 7.2%), ν_{max} ($CHCl_3$) 1770s cm^{-1}, δ (CCl_4) 2.40 (1 H, m), 2.90 (3 H, m), 3.36 (5 H, m, with a singlet at 3.36, $MeOCH_2$), 5.55 (1 H, m, CO_2CH) and 6.02 (2 H, m, CH=CH), *m/z* 168 (M^+). This compound was identical (PMR, solution IR, tlc) with an authentic sample[28] of optically active lactone.

Method B. The ketone (**28**) (470 mg, 2.1 mmol), hydrogen peroxide (0.9 ml, 100 vols), and water (2 ml) in acetic acid (15 ml) were kept at 0–3° for 3 days. The mixture was taken up in ether (20 ml) and the solution washed with water (3 × 70 ml). The ether layer was dried (Na_2SO_4), and evaporated to give the lactone, ν_{max} (film) 1800s and 1620w cm^{-1}, δ (CCl_4) 3.05–3.65 (7 H, m, with a singlet at 3.40), 5.50 (1 H, m, CO_2CH), and 6.00 and 6.20 (each 1 H, m, CH=CH), which was then stirred with zinc powder (6 g) in an acetic acid–water mixture (15 ml: 0.5 ml) at room temperature for 40 h. The inorganic solids were filtered off and washed with ether. The combined filtrate and washings were washed with water (3 × 70 ml), dried (Na_2SO_4), and evaporated. The residue was crystallised from cold hexane to give the lactone (**29**) (220 mg, 62%), identical with the sample prepared by method A. A distillation of the crude product (0.02 mm, bath temp 70–85°) was found to be helpful when crystallisation was difficult.

4-exo-*Trimethylsilylbicyclo*[3.2.0]*hept*-2-*en*-6-*one* (**31**). The ketone (**6**) (10.0 g, 0.04 mol) was stirred with zinc powder (20 g) in a mixture of acetic acid (100 ml) and water (5 ml) at 40° for 36 hr. The inorganic solids were filtered off, and washed with ether (200 ml). The combined filtrate and washings were washed with water (3 × 250 ml) and with sodium hydrogen carbonate solution. The ether layer was dried (Na_2SO_4) and evaporated and the residue distilled to give the ketone (**31**), (6.1 g, 85%), b.p. 43–5°/0.05 mm, 72–3°/3 mm (Found: C, 66.9; H, 9.1. $C_{10}H_{16}OSi$ requires: C, 66.6; H, 9.0%), ν_{max} (film) 1776s and 1592w cm^{-1}, δ (CCl_4) −0.04 (9 H, s, $SiMe_3$), 2.30 (1 H, m, $Me_3SiC\underline{H}$), 2.5–2.85 (1 H, m, C–1 H), 3.15–3.45 (2 H, m), 3.64 (1 H, m), and 5.68 (2 H, m, CH=CH). The ketone was also characterised as its ethylene glycol acetal, 4-exo-*trimethylsilylbicyclo*[3.2.0]*hept*-2-*en*-6-*one ethyleneglycol acetal*: the ketone (**31**) (3.24 g, 18 mmol), triethyl orthoformate (2.7 g, 18 mmol) and toluene-*p*-sulphonic acid (0.1 g) in dry ethylene glycol (35 g) were kept at room temperature for 24 hr; potassium hydroxide was added and the mixture poured into water (150 ml) and extracted with chloroform (3 × 40 ml) to give the acetal (3.3 g, 82%), b.p. 64–6°/0.7 mm (Found: C, 64.5; H, 8.8. $C_{12}H_{20}O_2Si$ requires: C, 64.2; H, 9.0%), ν_{max} (film) 1596w cm^{-1}, δ (CCl_4) −0.10 (9 H, s, $SiMe_3$), 1.95–2.15 (2 H, m), 2.4–2.7 (1 H, m), 2.92 (2 H, m), 3.72 (4 H, m, OCH_2), and 5.58 (2 H, m, CH=CH).

6-*Oxa*-4-exo-*trimethylsilylbicyclo*[3.3.0]*oct*-2-*en*-7-*one* (**32**). The ketone (**31**) (1.35 g, 7.5 mmol), hydrogen peroxide (15 ml, 20 vols) and sodium hydroxide (0.4 g, 10 mmol) in methanol (50 ml) were kept at room temperature for 2 hr. The mixture was acidified and most of the solvent was evaporated. The residue was taken up in ether, washed with water and evaporated to give the lactone (**32**) (1.31 g, 83%), as plates, m.p. 52–3° (from hexane) (Found: C, 61.1; H, 8.2. $C_{10}H_{16}O_2Si$ requires: C, 61.2; H, 8.2%), ν_{max} (KBr) 1775s and 1596w cm^{-1}, δ (CCl_4) −0.07 (9 H, s, $SiMe_3$), 2.20 (1 H, m, $Me_3SiC\underline{H}$), 2.16–2.33 (1 H, dm, *J* 18 Hz, $C\underline{H}_AH_BCO$), 2.47–2.73 (1 H, dd, *J* 18 and 8 Hz, $CH_A\underline{H}_BCO$), 3.26 (1 H, m, C–1 H), 4.82 (1 H, d, *J* 5.5 Hz, CO_2CH), 5.34 (1 H, dt, *J* 5 and 2 Hz, $C\underline{H}$=CH), 5.68 (1 H, m, CH=$C\underline{H}$).

4-exo-*Acetyl*-6,6-*dichlorobicyclo*[3.2.0]*hept*-2-*en*-7-*one* (**35**, R=Me). Stannic chloride (7 ml) was added dropwise to a solution of the silane (**6**) (5.0 g) in acetyl chloride (20 ml) at room temperature and kept at 0–3° for 24 hr. The mixture was then poured into an ice–water mixture and extracted with light petroleum (60–80°). Column chromatography on silica gel eluting with light petroleum (40–60°)-dichloromethane (3:1) removed a mixture of by-products, and elution with light petroleum (40–60°)-dichloromethane (1:1) then gave the ketone (**35**, R=Me) (1.6 g, 36%) as prisms, m.p. 66–7° (cold hexane) (Found: C, 49.4; H, 3.7; Cl, 32.5. $C_9H_8Cl_2O_2$ requires: C, 49.35; H, 3.7; Cl, 32.4%), ν_{max} (KBr) 1805s, 1712s, and 1605w cm^{-1}, δ (CCl_4) 2.27 (3 H, s, COMe), 4.05 (2 H, m, $MeCOC\underline{H}$ and C–5 H), 4.60 (1 H, m, C–1 H), and 5.08 and 6.08 (each 1 H, m, CH=CH).

6,6-*Dichloro*-4-exo-*propanoylbicyclo*[3.2.0]*hept*-2-*en*-7-*one* (**35**, R=Et). In a similar preparation (by R. V. Williams), the allylsilane (**6**) (0.25 g), propanoyl chloride (0.5 ml) and stannic chloride (0.5 ml) were kept at 0° for 1 week to give the ketone (**35**, R=Et) (0.48 g, 20%), ν_{max} (CCl_4) 1815 and 1725 cm^{-1}, δ (CCl_4) 1.05 (3 H, t, *J* 6 Hz, CH_3), 2.55 (2 H, q, *J* 6 Hz, $CH_3C\underline{H}_2CO$), 4.0 (2 H, m, other ring protons), 4.55 (1 H, m, $C\underline{H}COEt$), 5.80 and 6.15 (each 1 H, m, HC=CH). (Found: $\underline{M}^+$, 232.0047, $C_{10}H_{10}O_2{}^{35}Cl_2$ requires $\underline{M}$, 232.0058), *m/z* 232 (7.5%, $\underline{M}^+$), 203 (10, $\underline{M}$–Et), 175 (73, M–EtCO) and 57 (100, M–$C_7H_5OCl_2$).

6,6-*Dichloro*-4-exo-*octanoylbicyclo*[3.2.0]*hept*-2-*en*-7-*one* (**35**, R=n-C_7H_{15}). In a similar preparation (by R. V. Williams), the allylsilane (**6**) gave the ketone (**35**, R=n-C_7H_{15}) (40%), ν_{max} (CCl_4) 1820 and 1725 cm^{-1}, δ 0.5 (3 H, t, CH_3), 1.15–1.80 (10 H, m, remaining CH_2's), 2.5 (2 H, t, $-CH_2CO-$), 3.9–4.1 (2 H, m remaining ring protons), 4.6 (1 H, m, $-C\underline{H}COCH_2-$), 5.78 and 6.04 (each 1 H, m, HC=CH) (Found: $\underline{M}^+$, 302.0842. $C_{15}H_{20}O_2{}^{35}Cl_2$ requires $\underline{M}$ 302.0840) *m/z* 302 ($\underline{M}^+$, 12%), 175 (16, $\underline{M}$-octanoyl) and 127 (100, M–$C_7H_5OCl_2$).

6-exo-*Methyl*-4-exo-*trimethylsilylbicyclo*[3.3.0]*oct*-2-*en*-7-*one* (**37**). *Method A*. An ethereal solution of diazoethane

(50 ml, prepared from 4.5 g of N-ethyl-N-nitrosourea, washed with water before use) was added to an ice-cold solution of **6** (1.0 g, 4 mmol) in methanol (10 ml) and kept at 0° for 1 hr. Most of the solvent was evaporated off, the residue was dissolved in methanol (10 ml) and ethereal diazoethane (40 ml, from 4 g of N-ethyl-N-nitrosourea) was again added and the mixture kept at 0° for 1 hr. The solvents were evaporated and the residue taken up in light petroleum (40–60°) and the insoluble polymers filtered off. The residue from the filtrate, [**36**, ν_{max} (film) 1780 cm^{-1}] was stirred with zinc powder (3 g) and water (1 ml) in acetic acid (20 ml) at room temperature for 20 h. Similar work-up as in previous dechlorinations and chromatography on a silica gel column gave the mixture of diastereoisomers (**37**) (430 mg, 52%). After equilibration with sodium methoxide, this mixture gave **37b**, identical with a sample prepared by Method B.

Method B. Aqueous potassium hydroxide (50 ml, 30%) was added to a mixture of N-ethyl-N-nitrousourea (18 g) and the ketone (**31**) (5.6 g, 31 mmol) in methanol (300 ml) at −65°. The mixture was stirred at −65° for 15 min, then at −40° to −45° for 1 hr, and finally allowed to warm to room temperature. Most of the solvent was evaporated off, the residue partitioned between ether and water, the ether layer dried (Na_2SO_4), evaporated, and the residue chromatographed on a column (silica gel, 180 g), eluting with light petroleum (40–60°)-dichloromethane (5:1) to give the mixture of diastereoisomers of 7-methyl-4-exo-trimethylsilylbicyclo[3.3.0]oct-2-en-6-one (**38**) (2.4 g, 37%), b.p. 52–5°/0.02 mm (Found: C, 69.4; H, 9.96. $C_{12}H_{20}OSi$ requires: C, 69.2; H, 9.7%), ν_{max} 1740s and 1600w cm^{-1}, δ (CCl_4) −0.04 (9 H, s, $SiMe_3$), 1.0 (3 H, d, *J* 6.5 Hz, Me), 1.4–2.6 (5 H, m), 3.26 (1 H, m, C–1 H), and 5.4 and 5.6 (each 1 H, m, CH=CH). Further elution with light petroleum (40–60°)-dichloromethane (3:1) gave the mixture of diastereoisomers (**37**), which was stirred under nitrogen in a solution of sodium methoxide in methanol (0.7 M, 100 ml) at room temperature for 7 hr. The mixture was neutralised under nitrogen at 0° with dilute hydrochloric acid and the solvent evaporated. The residue was taken up in ether, washed with water, dried (Na_2SO_4), and evaporated. Distillation of the residue gave the ketone (**37b**) (2.7 g, 42%), b.p. 55–8°/0.02 mm (Found: C, 69.3; H, 9.9. $C_{12}H_{20}OSi$ requires C, 69.2; H, 9.7%), ν_{max} 1740s and 1600w cm^{-1}, δ (CCl_4) −0.12 (9 H, s, $SiMe_3$), 0.96 (3 H, d, *J* 7 Hz, Me), 1.85 (2 H, m), 2.24 (3 H, m), 3.18 (1 H, m, C–1 H), and 5.50 and 6.65 (each 1 H, m, CH=CH).

7-endo-*Chloro*-4-exo-*trimethylsilylbicyclo*[3.2.0]*hept*-2-*en*-6-*one* (**39**). The ketone (**6**) (10.0 g, 40 mmol), zinc powder (2.9 g, 44 mmol), and water (2 ml) in acetic acid (50 ml) were stirred at room temperature for 22 hr. The inorganic salts were filtered off and washed with ether (50 ml). The combined filtrate and washings were washed with water (3 × 250 ml) and then with sodium hydrogen carbonate solution. Distillation gave the ketone (**39**) (8.0 g, 94%), b.p. 60–3°/0.01 mm (Found: C, 56.47; H, 6.95. $C_{10}H_{15}OClSi$ requires: C, 55.93; H, 7.04%), ν_{max} (film) 1800s and 1600w cm^{-1}, δ (CCl_4) −0.05 (9 H, s, $SiMe_3$), 2.35 (1 H, m, $Me_3SiC\underline{H}$), 3.5–3.9 (2 H, m, bridgehead H's), 4.98 (1 H, dd, *J* 8, 3.5 Hz, C-7 H), and 5.60 and 5.80 (each 1 H, m, CH=CH).

6-exo-*Methyl*-4-exo-*trimethylsilylbicyclo*[3.3.0]*oct*-2-*en*-7-endo-*ol* (**42**). *Method A.* Sodium borohydride (450 mg, 12 mmol) was added to a solution of the ketone (**37b**) (2.40 g, 11.5 mmol) in methanol (100 ml) at 0°. After stirring at 0° for 2 hr, the mixture was acidified with acetic acid. The solvent was evaporated off and the residue taken up in ether. The solution was washed with water, dried (Na_2SO_4), and evaporated. The residue was crystallised from cold aqueous methanol to give the alcohol (**42**) (2.1 g, 88%), needles, m.p. 74–6° (Found: C, 68.4; H, 10.8. $C_{12}H_{22}OSi$ requires: C, 68.5; H, 10.5%), ν_{max} (nujol) 3300br cm^{-1}, δ (CCl_4) −0.05 (9 H, s, $SiMe_3$), 0.97 (3 H, d, *J* 6.5 Hz, Me), 1.1–1.5 (2 H, m), 1.6–2.35 (3 H, m), 2.83 (1 H, m, C–1 H), 3.42 (2 H, m, CHOH), and 5.51 (2 H, s, CH=CH). A further 120 mg (4%) was obtained from the mother liquor after preparative tlc (SiO_2, CH_2Cl_2, R_f 0.15).

Method B. Ethereal diazoethane (0.04 M, 150 ml) was added to an ice-cooled solution of the ketone (**39**) (1.08 g, 5 mmol) in methanol (20 ml) and the mixture kept at 0° for 5 hr. Excess diazoethane was decomposed with acetic acid and the solvent was evaporated. The residue was dissolved in light petroleum (40–60°), filtered, and washed with water. After evaporation of solvent, the residue was stirred with zinc powder (1.5 g) and water (1 ml) in acetic acid (20 ml) at room temperature for 60 hr. The inorganic solids were filtered off and washed with ether (25 ml). The combined filtrate and washings were washed with water (3 × 70 ml) and sodium hydrogen carbonate solution, and then evaporated. The residue was purified by column chromatography on silica gel. Elution with light petroleum (40–60°)-dichloromethane (6:1) gave a compound assigned as **41** (280 mg, 27%), ν_{max} (film) 1712s, 1640w, and 1608w cm^{-1}, δ (CCl_4) 0.08 (9 H, s, $SiMe_3$), 1.74 (3 H, t, *J* 1.5 Hz, Me), 2.05 (1 H, m, $Me_3SiC\underline{H}$), 2.75 (1 H, ddm, *J* 6.5 and 4 Hz, HCCO), 3.71 (1 H, m, allylic H), 5.56 (2 H, m, CH=CH), and 7.24 (1 H, m, CMe=C$\underline{H}$), *m/z* 206 (M^+). Further elution with light-petroleum (40–60°)-dichloromethane (3:1) gave the mixture of ketones (**37**) (760 mg, 72%), which was equilibrated with sodium methoxide (1.2 g) in methanol (40 ml) at room temperature to give the ketone (**37b**). The crude **37b** was reduced with sodium borohydride (150 mg) in methanol (30 ml) at 0° as described under Method A, above, and the product crystallised from cold aqueous methanol to give the *endo* alcohol (500 mg, 48% based on **39**) identical to the sample prepared above.

6-exo-*Methyl*-4-*trimethylsilylbicyclo*[3.3.0]*oct*-2-*en*-7-exo-*yl Acetate* (**43**). Methanesulphonyl chloride (1.6 g) was added dropwise to a solution of the alcohol (**42**) (2.58 g, 12.3 mmol) in dry pyridine (20 ml). The mixture was stirred at room temperature for 18 hr and then diluted with dry ether (40 ml). The salts were removed by filtration and washed with dry ether. The combined filtrates were evaporated and the residue was filtered through a silica gel column (30 g) with dichloromethane to give the methanesulphonate, ν_{max} (film) 1602w, 1350s, and 1165s cm^{-1}, δ (CCl_4) −0.1 (9 H, s, $SiMe_3$), 1.0 (3 H, d, *J* 5.5 Hz, Me), 1.3–3.0 (6 H, m), 2.8 (3 H, s, O_3SMe), 4.3 (1 H, m, SO_3CH), and 5.5 (2 H, m, CH=CH). The methanesulphonate was heated with tetraethylammonium acetate (23 g) in dry acetone under reflux under a dry atmosphere for 30 hr. The solvent was evaporated and the residue taken up in dichloromethane. The solution was washed twice with water (200 ml) containing a few ml of acetic acid, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica gel column. After the separation of a small amount of a by-product (R_f 0.9, CH_2Cl_2) by elution with light petroleum (40–60°), a major fraction was eluted with dichloromethane and distilled to give the acetate (**43**) (2.46 g, 80%), b.p. 65–8°/0.01 mm (Found: C, 66.8; H, 9.65. $C_{14}H_{24}O_2Si$ requires: C, 66.6; H, 9.6%), ν_{max}(film) 1742s and 1605w cm^{-1}, δ (CCl_4) −0.04 (9 H, s, $SiMe_3$), 0.90 (3 H, d, *J* 7 Hz, Me), 1.6 (3 H, m), 1.88–2.26 (4 H, m, with a singlet at 2.00), 3.12 (1 H, m, C–1 H), 5.06 (1 H, m, AcOC$\underline{H}$), and 5.42 (2 H, m, CH=CH).

Reaction of chlorosulphonyl isocyanate with the allylsilane (**6**). (R. V. Williams) CSI (0.1 ml) was added to the allylsilane (**6**) (0.25 g) in dry carbon tetrachloride (0.5 ml) under nitrogen and the mixture kept at 65° for 72 hr. The PMR spectrum of the mixture now indicated the clean formation of **45**: δ 0.35 (9 H, s, $SiMe_3$), 3.55–4.25 (2 H, m, remaining ring protons), 4.50 (1 H, m, –CHCO–), and 5.90 (2 H, m, HC=CH).

2-exo-*Carbamoyl*-6-exo-*methylbicyclo*[3.3.0]*oct*-3-*en*-7-exo-*yl Acetate* (**46**). Chlorosulphonyl isocyanate (1 ml, 11 mmol) was added dropwise to a solution of the allylsilane (**43**) (2.34 g, 9.3 mmol) in dry carbon tetrachloride (5 ml) at 0°. The mixture was kept at 0° for 15 min and then at room temperature for 2.5 hr. The reaction was observed (PMR) to give the analogous adduct, δ 0.3 (9 H, s, $SiMe_3$), 1.0 (3 H, d, *J* 7 Hz), 1.2–3.0 (8 H, m, with a singlet at 1.9), 4.3 (1 H, m), 4.65 (1 H, m), 5.5 and 6.0 (each 1 H, m, CH=CH). The solvent was

evaporated off, the residue dissolved in a mixture of acetone (25 ml), water (10 ml) and 3N hydrochloric acid (2 ml), kept at room temperature for 3.5 h, and then extracted with dichloromethane (6 × 15 ml). The residue from the extracts was crystallised from diisopropyl ether, to give the amide (**46**) (1.14 g, 55%), m.p. 130–6°. (Found: C, 64.25; H, 7.65; N, 6.05. $C_{12}H_{17}NO_3$ requires: C, 64.55; H, 7,68; N, 6.27%), ν_{max} ($CHCl_3$) 3525, 3410, 1725s, and 1680s cm^{-1}, δ ($CDCl_3$) 1.0 (3 H, d, *J* 7 Hz, Me), 1.45–2.35 (7 H, m, with a singlet at 2.02), 3.02 and 3.15 (each 1 H, m, allylic H), 5.12 (1 H, q, *J* 8 Hz, 4.5 Hz, AcOC$\underline{H}$), 5.60, 5.85 (each 1 H, m, CH=CH), and 6.05 (2 H, broad, NH_2), *m/z*, 223 (M^+, weak) and 206 (M^+–NH_3).

2-exo-*Carbomethoxy*-6-exo-*methylbicyclo*[3.3.0]*oct*-3-*en*-7-exo-*yl acetate* (**47**). *Method A.* Sodium nitrite (4 g) was added in small portions over 1.5 h to the amide (**46**) (560 mg) in acetic acid (2.5 ml) and acetic anhydride (12 ml) at 0° and the mixture kept at 0–3° for 16 hr. Cold saturated aqueous sodium acetate solution (20 ml) was added to the precipitated solid and the mixture stirred in an ice bath for 0.5 hr, and then at room temperature for 2 hr. The mixture was extracted with dichloromethane (5 × 20 ml), and the extracts evaporated. The residue was dissolved in methanol and excess ethereal diazomethane added. After 0.5 hr at room temperature, the excess diazomethane was decomposed with acetic acid, the mixture was washed with water, dried (Na_2SO_4), and evaporated. The carbon tetrachloride-soluble part of the residue was purified by tlc (SiO_2, ether, R_f 0.6) followed by distillation (bath temperature (130–140°, 0.07 mm) to give the ester (**47**) (410 mg, 69%) (Found: C, 65.44; H, 7.85. $C_{13}H_{18}O_4$ requires: C, 65.5; H, 7.6%), ν_{max} (film) 1740s cm^{-1} δ (CCl_4) 0.96 (3 H, d, *J* 7 Hz, Me), 1.38–2.24 (7 H, m, with a singlet at 1.96), 2.95, 3.08 (each 1 H, m, allylic H), 3.60 (3 H, s, OMe), 5.03 (1 H, q, *J* 8 and 4 Hz, AcOC$\underline{H}$), 5.52 and 5.75 (each 1 H, m, CH=CH).

Method B. Chlorosulphonyl isocyanate (500 mg, 3.5 mmol) was added dropwise to the silane (**43**) (715 mg, 2.8 mmol) in carbon tetrachloride (1.2 ml) at 0°. After keeping at 0° for 10 min and then at room temperature for 2.5 hr, the solvent was evaporated off. The residue was stirred at 0° with acetic acid (3 ml) in acetic anhydride (15 ml), and sodium nitrite (4.5 g) added in portions over 1 hr. The mixture was kept under nitrogen at 0–3° for 16 hr, and the precipitate separated. Sodium acetate (10 g) in water (25 ml) was added at 0° to the precipitate; the mixture was stirred at 0° for 2 hr, then at room temperature for 3 hr, and then extracted with dichloromethane (5 × 25 ml), and the residue treated with diazomethane and purified as above to give the ester (**47**) (410 mg, 61%).

Methyl 6α-*Acetoxy*-7α-*methyl*-1-*hydroxy*-1,4aα,5,6,7,7aα-*hexahydrocyclopenta*[c]*pyran*-4-*carboxylate* (**48**). *Method A.* The diester (**47**) (4 mg, 0.04 mmol) was stirred with osmium tetroxide (100 mg, 0.4 mmol) in benzene (4 ml) at room temperature for 3 hr. After evaporation of solvent, the residue was taken up in 95% ethanol (10 ml). Sodium metabisulphite (1.5 g) in water (5 ml) was added and the mixture was stirred at room temperature for 3 hr. The mixture was extracted with ether (6 × 15 ml) and the extracts were dried and evaporated to give the crude diol, ν_{max} (film) 3440br and 1730s cm^{-1}, δ ($CDCl_3$) 1.04 (3 H, d, *J* 6 Hz, Me), 1.4–2.7 (7 H, m, with a singlet at 2.04), 3.22 (1 H, m), 3.70 (3 H, s, CO_2Me); 3.80 (1 H, m), 4.37 (1 H, m), 5.18 (4 H, m, CHOH). The diol was dissolved in 70% aqueous dioxan, (6 ml) and this solution added dropwise over 10 min to an ice-cold solution of sodium metaperiodate (95 mg, 0.44 mmol) in 50% aqueous dioxan (6 ml), and stirred at 0° for 4 hr. The solvent was evaporated and the residue dissolved in chloroform (10 ml), washed with water (5 ml), dried (Na_2SO_4), and evaporated. The residue was purified by tlc [SiO_2, EtOAc–benzene (1:2)] to give loganin aglucone acetate (**48**) (50 mg, 46%), a viscous liquid, ν_{max} ($CHCl_3$) 3600m, 3495br, 1735s, 1710s, and 1640s cm^{-1}, δ ($CDCl_3$ 1.07 (3 H, d, *J* 6.5 Hz, Me), 1–2.5 (4 H, m), 2.06 (3 H, s, OAc), 3.12 (1 H, m), 3.71 (3 H, s, CO_2Me), 4.4 (1 H, br, OH), 5.00 (1 H, d, *J* 5 Hz), 5.20 (1 H, m), and 7.41 (1 H, dm, *J* 1 Hz, C=CH). This compound was identical (tlc, solution IR, and PMR) with loganin aglucone monoacetate,[39] which we prepared from loganin.

Method B. The diester (**47**) (120 mg, 0.5 mmol) in dry dichloromethane (20 ml) was cooled to −65°C. Dry ozone was bubbled through this solution at a flow rate of *ca.* 10 l/hr until the solution became faintly blue. Dry oxygen was then passed through the solution to flush off any excess ozone. Dimethyl sulphide (1 ml) was then added dropwise and the mixture kept at −65° for 2 hr, then at 0° for 1 hr, and room temperature for 1 hr. The solvent and excess reagent were evaporated and the residue purified by tlc to give **48** (79 mg, 47%).

Acknowledgements—We thank Dr. Gandolfi for sending us a sample of the lactone (**29**), Dr. M. Thompson and Prof. Battersby for giving us the loganin, Christ's College, Cambridge for a studentship to B.-W. A.-Y., and R. V. Williams for several experiments identified in the experimental section with his name.

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Tetrahedron Vol. 37, Supplement No. 1, pp. 25–30, 1981
Printed in Great Britain

0040-4020/81/Suppl. 1-0025-06 $02.00/0
Pergamon Press Ltd.

CARBON-ALKYLATION OF SIMPLE NITRONATE ANIONS BY N-SUBSTITUTED PYRIDINIUMS

ALAN R. KATRITZKY,* GEORGE DE VILLE and RANJAN C. PATEL

School of Chemical Sciences, University of East Anglia, Norwich, NR4 7TJ, England

(*Received in U.K.* 1 *May* 1980)

Abstract—N-Primary and -secondary alkyl and N-(substituted benzyl) groups are transferred at $\leq 100°$ from N-substituted 2,4,6-triphenylpyridiniums to give carbon alkylation of the anions of nitro-methane and ethane and 2-nitropropane in preparatively useful yields (24 examples). Non-chain radical substitution processes are probably involved.

According to a recent review[1] there existed until recently only two examples of simple C-alkylation† of nitronate anions, both[2,3] intramolecular cyclisations. C-Alkylation by radical-chain processes described by Kornblum[4] had usually required additional activation in the form of a nitro or *p*-nitrophenyl group at the reaction centre.‡ After our preliminary communication[5] was submitted, a preliminary communication by Russell and co-workers[6] became available which reported that primary and secondary alkyl mercury halides participate with nitronate anions in $S_{RN}1$ processes when irradiated in nitrogen-purged dimethylformamide $RHgX + R'_2C{:}NO_2^- \rightarrow RR'_2CNO_2 + X^- + Hg^0$. Previously, Seebach and co-workers[7] had shown that dilithio derivatives of nitroalkanes are smoothly *C*-alkylated by primary alkyl and benzyl halides.

Despite these recent advances, and in view of the great potential of nitroaliphatics as synthetic intermediates,[1] the need clearly exists for a general C-alkylation technique of simple nitronate anions. We believe that the presently reported alkylation with 1-substituted-2,4,6-triphenylpyridiniums fills this gap in synthetic methodology.

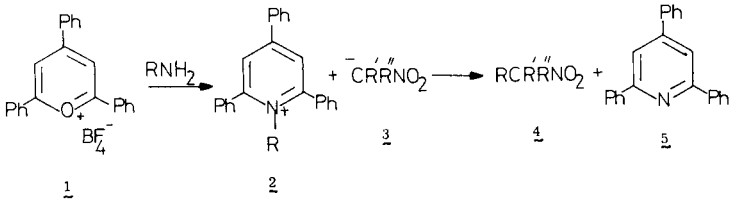
We have shown that 1-substituted pyridiniums (**2**) [themselves now available from primary amines and pyrylium **1** under very mild conditions[8] (Table 1)] transfer their N-substituent to a wide variety of nucleophiles.[9] We now report conditions under which they C-alkylate nitronate anions (**3**) to nitro compounds (**4**) in moderate to high yield.

N-Benzyl and N-(substituted benzyl) groups are transferred to nitronate anions in refluxing ethanol (Table 2): to optimise yields with respect to the alkylating agent it was found best to use 3 moles of the nitronate anion. Yields were 55–78% (average 65%) for reactions with the anion of nitromethane, somewhat lower (35–57%, average 51%) for the anion of nitroethane, and lowest for reactions with 2-nitropropane anions (41–44%, average 42%) (see later).

The reaction proceeds much faster in dimethyl sulphoxide: lower temperatures and shorter times being required than for comparable cases in ethanol. Heating at 100° was required for alkylation while 50° sufficed for benzylation (Table 3). However, we now find that yields are high for reactions with 2-nitropropane anion (44–75%, average 62%), moderate for nitroethane anion (33–52%, average 43%), and low for the nitromethane anion: we believe the reason for this to be the easy further reaction of the products for the last two anions with further alkylating agent, causing the formation of mixtures.

Noteworthy are the useful yields achieved using secondary alkyl (isopropyl, cyclohexyl) and 2- and 3-picolyl groups. Furthermore, benzyls other than *p*-nitrobenzyl may be used successfully in the reactions reported here (whereas the para nitro group is necessary in the Kornblum reaction[4a]).

The ^{1}H NMR spectra of the compounds prepared here are reported in Table 4. All have been satisfactorily analysed, and products were pure by glc



†Carbon-acylations are somewhat more common, see e.g. the use of acylimidazoles [D. C. Baker and S. R. Putt, *Synthesis* 478 (1978)].

‡Kornblum has recently shown that a *p*-cyanophenyl group also facilitates $S_{RN}1$ processes: N. Kornblum and M. J. Fifolt, *J. Org. Chem.* 360 (1980).

Table 1. Preparation of 1-alkyl-2,4,6-triphenylpyridinium tetrafluoroborates[a]

1-Substituent	Yield (%)	M.p. (°C)	Lit. m.p. (°C)	Ref.
$PhCH_2$	81	193-195	196-197	b
$ClC_6H_4CH_2$(o)	76	197-199	200	c
$Cl_2C_6H_4CH_2$(o,p)	65	233-235	239	c
$ClC_6H_4CH_2$(p)	83	141-142	144	c
$MeC_6H_4CH_2$(p)	79	118-120[d]	134	e
$PhCH_2CH_2$	75	265-270	274	f
n-C_4H_9	69	196-198	201-202	b
n-C_6H_{13}	57	240-242	236-238	e
Cyclohexyl	52	180-182	180-182	f
Pr^i	51	168-170	171-173	e
2-Picolyl	68	215-216	218-219	f
3-Picolyl	63	159-163	166-168	f

Footnotes

[a]Reaction time: 2 hr. Crystal form: white needles. [b] U. Gruntz, A.R. Katritzky, D.H. Kenny, M.C. Rezende and H. Sheikh, J. Chem. Soc. Chem. Comm. 701 (1977). [c] A.R. Katritzky, U. Gruntz, A.A. Ikizler, D.H. Kenny and B.P. Leddy, J. Chem. Soc. Perkin I 436 (1979). [d] New polymorphic form: plates (Found: C, 74.3; H, 5.1; N, 2.7. requires C, 74.5; H, 5.2; N, 2.8%). [e] A.R. Katritzky, G. Liso, E. Lunt, R.C. Patel, S.S. Thind and A. Zia, J. Chem. Soc. Perkin I in the press, paper 9/820. [f] A.R. Katritzky, U. Gruntz, D.H. Kenny, M.C. Rezende and H. Sheikh, J. Chem. Soc. Perkin I 430 (1979).

(Carbowax 220m) (as reported in Tables 1 and 2). For further details see Ref. 10].

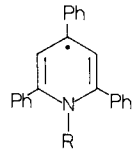
The mechanism of the reaction of nitronate anions with pyridinium

Previous nitroalkane syntheses involving the displacement of a leaving group by nitronate anion have been shown to involve a radical chain mechanism (eqns 1 and 2),[11] termed $S_{RN}1$ by Bunnett.[12] Many substrates are known to participate in $S_{RN}1$ reactions and interest in this area continues to be considerable: e.g. recent extension to primary or secondary alkyl mercury chlorides or bromides.[6]

$$RX \xrightarrow{e^-} RX^- \rightarrow R^\cdot + X^- \qquad (1)$$

$$R^\cdot + Nu^- \rightarrow RNu^- \rightarrow RNu + e^-. \qquad (2)$$

Although we observed no light acceleration, dark inhibition, or rate retardation in the presence of *m*-dinitrobenzene [usual criteria for establishing electron transfer processes[4a]] of the reaction of 1-benzyl-2,4,6-triphenylpyridinium BF_4^- with sodium 2-nitropropanide, we nevertheless believe that the ease of reaction under mild conditions indicates a radical reaction mechanism. Typical S_N2 reactions of these pyridiniums with hundredfold excess of nucleophile require a reaction time of 1 hr at 100° in chlorobenzene.[13]



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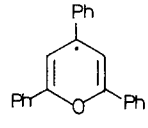

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We believe that our reactions involve charge transfer complexes between **2** and **3** and/or intermediates of type **6**; the latter is similar to stabilised cyano and carbethoxy substituted pyridinyls previously found.[14] Furthermore, (a) 2,4,6-triphenylpyrylium has itself been reduced to its radical (**7**) with Zn in acetonitrile[15] and (b) N-(*p*-nitrobenzyl)-pyridinium chloride[16] reacts with the anion of 2-nitropropane *via* an electron-transfer mechanism.

Quantitative kinetic measurements on this reaction are under way to define the precise mechanism, order of reaction, solvent dependence, *etc.*[17]

Table 2. Preparation of nitroalkanes in ethanol: $R^1R^2R^3CNO_2$

R^1	R^2	R^3	React. time (hr)	Yield (%)	b.p./mm	Lit. b.p./mm	Found C	Found H	Found N	Found Cl	Formula	Required C	Required H	Required N	Required Cl
$PhCH_2$	H	H	1	78[a]	120-130/15	125-135/1[b]	63.4	6.0	9.3	-	$C_8H_9NO_2$	63.6	6.0	9.3	-
$PhCH_2$	Me	H	2	53[a]	87-89/1	67-69/0.2[c]	65.9	6.9	8.4	-	$C_9H_{11}NO_2$	65.5	7.0	8.5	-
$PhCH_2$	Me	Me	6	41[a]	88-92/1	Oil[d]	66.8	7.3	8.2	-	$C_{10}H_{13}NO_2$	67.0	7.3	7.8	-
$ClC_6H_4CH_2$(o)	H	H	1	61	95-98/2	-	51.6	4.4	7.4	19.1	$C_8H_8ClNO_2$	51.8	4.3	7.6	19.1
$ClC_6H_4CH_2$(o)	Me	H	2	52	84-86/0.5	-	54.1	5.4	6.8	18.0	$C_9H_{10}ClNO_2$	54.1	5.0	7.0	17.8
$ClC_6H_4CH_2$(o)	Me	Me	6	44	91-92/1	-	56.4	5.7	6.3	16.6	$C_{10}H_{12}ClNO_2$	56.2	5.6	6.6	16.6
$Cl_2C_6H_3CH_2$(o,p)	H	H	1	55	85-87/2	-	43.5	3.5	6.2	32.5	$C_8H_7Cl_2NO_2$	43.6	3.2	6.4	32.3
$Cl_2C_6H_3CH_2$(o,p)	Me	H	2	35	61-63/0.5	-	46.3	4.0	5.9	30.1	$C_9H_9Cl_2NO_2$	46.2	3.9	6.0	30.3
$ClC_6H_4CH_2$ (p)	H	H	1	62	82-84/1	Oil[e]	52.0	4.0	7.7	19.4	$C_8H_8ClNO_2$	51.8	4.3	7.6	19.1
$ClC_6H_4CH_2$(p)	Me	H	2	57	106-109/2	Oil[f]	54.2	5.2	6.8	17.6	$C_9H_{10}ClNO_2$	54.1	5.0	7.0	17.8
$MeC_6H_4CH_2$(p)	H	H	1/2	68	63-64/1	-	65.7	7.1	8.6	-	$C_9H_{11}NO_2$	65.5	7.0	8.5	-
$MeC_6H_4CH_2$(p)	Me	H	1	54	65-67/0.5	Oil[f]	67.0	7.3	7.4	-	$C_{10}H_{13}NO_2$	67.0	7.3	7.8	-
$MeC_6H_4CH_2$(p)	Me	Me	1	42	88-90/0.5	-	68.0	7.8	7.4	-	$C_{11}H_{15}NO_2$	68.4	7.8	7.3	-

Footnotes

[a] Single pure compound by g.l.c. (Carbowax 220m, 200 °C). [b] J.W. Baker and I.S. Wilson, J. Chem. Soc. 842 (1927). [c] G.B. Bachmann and R.J. Maleski, J. Org. Chem. 37, 2810 (1972). [d] J.F. Brown, Jr. J. Am. Chem. Soc. 77, 6341 (1955). [e] R. Henning, F. Lehr and D. Seebach, Helv. Chim. Acta 59, 2213 (1976). [f] F.G. Bordwell, W.J. Boyle and K.C. Yee, J. Am. Chem. Soc. 92, 5926 (1970).

Table 3. Preparation of nitroalkanes in dimethyl sulphoxide: $R^1R^2CMeNO_2$

R^1	R^2	React. time (hr)	Yield (%)	B.p. (°C/mm)	Lit. b.p. (°C/mm)	Ref.	Found C	Found H	Found N	Found Cl	Formula	Required C	Required H	Required N	Required Cl
$PhCH_2$	Me	1	75	99-102/2	Oil	b	67.2	7.1	8.0	-	$C_{10}H_{13}NO_2$	67.0	7.3	7.8	-
$PhCH_2$	H	1	52	94-96/2	67-69/0.2	c	65.4	6.9	8.6	-	$C_9H_{11}NO_2$	65.5	7.0	8.5	-
$ClC_6H_4CH_2$(o)	Me	1	65	88-91/1			56.0	5.9	6.6	16.9	$C_{10}H_{12}ClNO_2$	56.2	5.6	6.6	16.6
$ClC_6H_4CH_2$(o)	H	1	47	93-97/1			53.9	4.8	7.2	17.5	$C_9H_{10}ClNO_2$	54.1	5.0	7.0	17.8
$MeC_6H_4CH_2$(p)	Me	1	69	97-100/1			68.1	8.1	7.1	-	$C_{11}H_{15}NO_2$	68.4	7.8	7.3	-
$MeC_6H_4CH_2$(p)	H	1	43	78-80/1	Oil	d	67.3	7.2	7.7	-	$C_{10}H_{13}NO_2$	67.0	7.3	7.8	-
n-C_4H_9	Me[a]	2	73	55-60/2	-	-	57.8	10.5	10.0	-	$C_7H_{15}NO_2$	57.9	10.3	9.7	-
n-C_4H_9	H[a]	2	46	64-66/20	176/760	e	54.9	10.0	10.9	-	$C_6H_{13}NO_2$	55.0	9.9	10.7	
n-C_6H_{13}	Me[a]	2	62	95-98/0.5	-		62.0	10.9	8.0	-	$C_9H_{19}NO_2$	62.4	11.0	8.1	-
n-C_6H_{13}	H[a]	2	38	81-83/4	102-105/23	f	60.3	10.4	8.9	-	$C_8H_{17}NO_2$	60.4	10.7	8.8	-
$PhCH_2CH_2$	Me	2	68	104-106/0.5			68.6	7.8	7.4	-	$C_{11}H_{15}NO_2$	68.4	7.8	7.3	-
Cyclohexyl	Me	5	48	82-84/0.8			63.3	10.0	8.0	-	$C_9H_{17}NO_2$	63.2	9.9	8.2	-
Cyclohexyl	H	5	33	67-69/0.8			61.3	9.5	9.0	-	$C_8H_{15}NO2$	61.2	9.6	8.9	-
Pr^i	Me	4	52	42-43/5			54.8	9.5	10.6	-	$C_6H_{13}NO_2$	55.0	9.9	10.7	-
2-Picolyl	Me	1	61	109-110/2			59.9	6.7	15.6	-	$C_9H_{12}N_2O_2$	60.0	6.7	15.6	-
3-Picolyl	Me	1	44	122-126/2			60.1	6.7	15.6	-	$C_9H_{12}N_2O_2$	60.0	6.7	15.6	-

Footnotes

[a] Single pure compound by g.l.c. (Carbowax 220m, 200 °C). [b] J.F. Brown, Jr., J. Am. Chem. Soc. 77, 6341 (1955). [c] G.B. Bachmann and R.J. Maleski, J. Org. Chem. 37, 2810 (1972). [d] F.G. Bordwell, W.J. Boyle and K.C. Yee, J. Am. Chem. Soc. 92, 5926 (1970). [e] Dictionary of Organic Compounds', Eyre & Spottiswoode, London 1965, Vol. 4, 2457. [f] Footnote e, p. 2473.

Table 4. ^{1}H NMR spectra[a] of nitroalkanes $R^1R^2R^3CNO_2$

Substituents R^1	R^2	R^3	δ (ppm) R^1 CH_2	Ph	Alkyl	R^2	R^3
$PhCH_2$	H	H	3.45(t)	7.50(s)	-	4.75(t)	4.75(t)
$PhCH_2$	Me	H	3.40(t)	7.45(s)	-	1.60(d)	4.95(m)
$PhCH_2$	Me	Me	3.25(s)	7.30(s)	-	1.60(s)	1.60(s)
$ClC_6H_4CH_2$(o)	H	H	3.35(t)	7.30(s)	-	4.65(t)	4.65(t)
$ClC_6H_4CH_2$(o)	Me	H	3.30(t)	7.20(m)	-	1.55(d)	4.90(m)
$ClC_6H_4CH_2$(o)	Me	Me	3.35(s)	7.1-7.4(m)	-	1.55(s)	1.55(s)
$Cl_2C_6H_3CH_2$(o, p)	H	H	3.30(t)	7.15(s, 2H) 7.30(s, 1H)	-	4.50(t)	4.50(t)
$Cl_2C_6H_3CH_2$(o, p)	Me	H	3.20(t)	7.15(s, 2H) 7.30(s, 1H)	-	1.50(d)	4.85(m)
$ClC_6H_4CH_2$(p)	H	H	3.25(t)	7.20(d)	-	4.55(t)	4.55(t)
$ClC_6H_4CH_2$(p)	Me	H	2.95(t)	7.15(d)	-	1.40(d)	4.50(m)
$MeC_6H_4CH_2$(p)	H	H	3.20(t)	7.10(s)	2.30(s)	4.50(t)	4.50(t)
	Me	H	3.10(t)	7.10(s)	2.30(s)	1.50(d)	4.75(m)
	Me	Me	3.10(s)	7.00(s)	2.30(s)	1.50(s)	1.50(s)
2-Picolyl	Me	Me	3.34(s)	7.15(t) 7.55(m) 8.5 old		1.60(s)	1.60(s)
3-Picolyl	Me	Me	3.15(s)	7.1-7.6(m, 2H) 8.2-8.6(m, 2H)	-	1.56(s)	1.56(s)
n-C_4H_9	Me	H	-	-	0.7-2.0(m)	1.50(d)	4.45(m)
n-C_4H_9	Me	Me	0.8(t)	-	1.0-2.0(m)	1.45(s)	1.45(s)
n-C_6H_{13}	Me	H	-	-	0.55-2.2(m)	1.55(d)	4.65(m)
n-C_6H_{13}	Me	Me	-	-	0.8-2.0(m)	1.65(s)	1.65(s)
$PhCH_2CH_2$	Me	Me	-	7.2(s)	2.0-2.7(m)	1.60(s)	1.60(s)
Cyclohexyl	Me	H	-	-	1.0-2.5(m)	1.50(d)	4.30(m)
	Me	Me	-	-	1.6-2.1(m)	1.45(s)	1.45(s)
Pr^i	Me	Me	-	-	0.8-2.5(m)	1.45(s)	1.45(s)

Footnote: [a] $CDCl_3$ solutions: ca.50 mg/0.5 ml.

EXPERIMENTAL

M.ps were obtained on a Kofler hot stage apparatus and are uncorrected. IR spectra were run using NaCl plates on a Perkin–Elmer 257 grating infrared spectrophotometer, neat in the case of the nitroalkanes and in Nujol mull elsewhere unless otherwise stated. ^{1}H NMR spectra were run on a Perkin–Elmer 60 MHz R12 permanent magnet spectrometer in deuteriochloroform, unless otherwise stated, with tetramethylsilane as the internal standard.

2,4,6-*Triphenylpyrylium tetrafluoroborate* was prepared by the method of Lombard and Stephan[18] (45%), m.p. 253° (lit.[18] 253–255°).

N-*Substituted* 2,4,6-*triphenylpyridinium tetrafluoroborates.* For a typical preparation, 2,4,6-triphenylpyrylium tetrafluoroborate (12 g, 0.03 mole) and benzylamine (2.8 g, 0.03 mole) were stirred in abs. EtOH (50 ml) with Et_3N (0.3 g, 0.003 mole) for 2 hr. The crude product was filtered off, washed with ether (25 ml) and recrystallised as white needles from abs. EtOH (15 ml). The same procedure was adopted for the other pyridinium salts, except isopropyl and cyclohexyl, which were instead stirred in ether.

Reaction of 1 *alkyl*-2,4,6-*triphenylpyridinium tetrafluoroborates with nitronate anions in ethanol.* In a typical experiment, NaH (0.72 g, 0.03 mole) was dissolved in EtOH (30 ml). Nitromethane (1.83 g, 0.03 mole) was added with stirring, followed by 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate (4.85 g, 0.01 mole). The soln was refluxed with stirring for 1 hr: the reaction was followed by tlc (silica; $CHCl_3$). When no further pyridinium remained, the soln was cooled; the resulting crystalline by-product 2,4,6-triphenylpyridine was filtered off. The filtrate was added to water (50 ml), extracted with ether (3 × 25 ml) and the extract dried over $MgSO_4$. Dry HCl was passed to remove residual 2,4,6-triphenylpyridine and the solution was evaporated under reduced pressure (25°/15 mmHg). The crude product was distilled *in vacuo* (1 mmHg) yielding 2-phenyl-nitroethane.

Reaction of 1-*alkyl*-2,4,6-*triphenylpyridinium tetrafluoroborates with nitronate anions in dimethylsulphoxide.* In a typical experiment, NaH (0.72 g, 0.03 mole) was dissolved in MeOH (10 ml), and 2-nitropropane (2.67 g, 0.03 mole) was added with stirring. After removal of the MeOH *in vacuo* (25°/0.5 mmHg), the resulting white product was mixed with 1-hexyl-2,4,6-triphenylpyridinium tetrafluoroborate (4.79 g, 0.01 mole) and dissolved in dimethylsulphoxide (30 ml). The soln was heated at 80° for 2 hr and again followed by tlc (silica; $CHCl_3$). An identical isolation procedure to the above was followed, yielding 2-methyl-2-nitrooctane.

Acknowledgement—We thank the S.R.C. for support of this work.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 31 to 40, 1981
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0040-4020/81/Suppl. 1-0031-10 $02.00/0
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REACTIONS DE PROXIMITE: ACYLATION INTRACOMPLEXE ENTRE UN ALCOOL ET UN ANHYDRIDE MIXTE COORDINES AU PLATINE(II)

J. C. CHOTTARD,* E. MULLIEZ, J. SOULIÉ et D. MANSUY

Laboratoire de Chimie de l'Ecole Normale Supérieure, 24, rue Lhomond, 75231 Paris Cedex 05, France

et

J. GUILHEM

Institut de Chimie des Substances Naturelles, CNRS, 91190 Gif-sur-Yvette, France

(*Received in France* 25 *February* 1980)

Abstract—Several proximity acylations of a pyridinic alcohol by an enoïc-acetic mixed anhydride have been performed with the two reactants coordinated in *trans* positions of a platinum (II) complex and studied as a function of their chain lengths. For the best case corresponding to the formation of a 13 elements metallamacrolactone, whose X-ray structure has been determined, the effective molarity of the alcohol within the complex is 0.4 M, which is of the order of ten times those observed for comparable large rings cyclizations. However this proximity within the complex is not sufficient to allow the selective acylation of the secondary hydroxyl of a primary-secondary diol.

Résumé—Plusieurs acylations de proximité d'un alcool pyridinique par un anhydride mixte énoïque-acétique, tous deux coordinés en positions *trans* dans un complexe du platine (II), ont été étudiées en fonction de la taille des ligands. Dans le meilleur cas, qui conduit à la formation d'une métallamacrolactone à treize éléments, dont la structure a été déterminée par diffraction des RX, la molarité effective de l'alcool au sein du complexe est 0,4 M, de l'ordre de dix fois celles observées pour des cyclisations comparables. La proximité ainsi obtenue est cependant insuffisante pour permettre l'acylation sélective de l'hydroxyle secondaire d'un diol primaire-secondaire.

Le but de ce travail était d'éprouver l'effet de proximité entre deux fonctions portées par deux ligands d'un même métal, mais non directement coordinées, et d'apprécier la valeur de cet effet pour la réalisation de réactions sélectives.

Nous pouvons citer quatre exemples de réactions, décrites dans la littérature qui sont considérées comme des réactions de proximité de ce type, au sein d'un complexe mixte: métal-réactif-substrat, sans que ce complexe intermédiaire ait pu être caractérisé. Il s'agit de la formation d'une Δ^2-isoxazoline entre la cyano-2 pyridine et le tris-(hydroxyméthyl) amino méthane en présence de Ni^{2+} ou Cu^{2+}, réaction 10^2 fois plus rapide que l'hydrolyse du nitrile;[1] de la phosphorylation de la pyridyl-2 méthanaldoxime par le *N*-phosphoryl-imidazole en présence de Zn^{2+}, réaction 10^3 fois plus rapide que l'hydrolyse du phosphate;[2] de la transestérification du pyridyl-2 carboxylate de p. nitrophényle par la N-(hydroxy-2 éthyl)-éthylène diamine, 16 fois plus rapide en présence de Zn^{2+};[3] et récemment de la catalyse de la décomposition de l'acétylphosphate par des amines liées à un groupe amino terminal d'un ligand polydentate soit triéthylène-tétramine, soit triamide-oxime en présence de Cu^{2+} (la catalyse est très modeste dans le premier cas avec une accélération de l'ordre de 3, ce qui pose le problème de la concentration du complexe mixte; elle est plus élevée dans le second avec une accélération de 17 fois mais le rôle du métal n'a pu être clairement établi).[4]

Les premiers résultats de notre étude concernant la formation privilégiée d'une métallamacrolactone **2** lors de l'acylation intracomplexe d'un alcool pyridinique (L'ni) par un anhydride mixte énoïque-acétique (Lm) (Fig. 1) avaient mis en évidence l'influence des valeurs de m et n, c'est-à-dire de la taille du cycle du complexe **2**, sur la sélectivité de l'acylation intracomplexe **1**[5] (Fig. 1).

Les meilleurs résultats obtenus correspondaient au couple (m = 4, n = 2) donc à la formation d'un cycle à 13 éléments (la double liaison étant comptée pour un élément). La poursuite de ce travail[6] nous a permis de préciser les conditions dans lesquelles les anhydrides mixtes énoïques-acétiques utilisés sont stables vis-à-vis de leur réaction de dismutation; de sélectionner le couple (m, n) le plus favorable à la réaction de proximité **1** → **2** (Fig. 1); de déterminer dans ce cas la molarité effective[7] de l'alcool au sein du complexe **1**; enfin, d'éprouver la possibilité de réaliser dans ces conditions l'acylation sélective de l'hydroxyle secondaire d'un diol primaire-secondaire.

RÉSULTATS ET DISCUSSION

Stabilité des anhydrides mixtes et préparation des complexes **1**

Les anhydrides mixtes énoïques-acétiques ont été choisis comme réactifs d'acylation parce que leur faible réactivité permet de réaliser leur coordination au platine (II), déjà porteur d'un alcool pyridinique, en

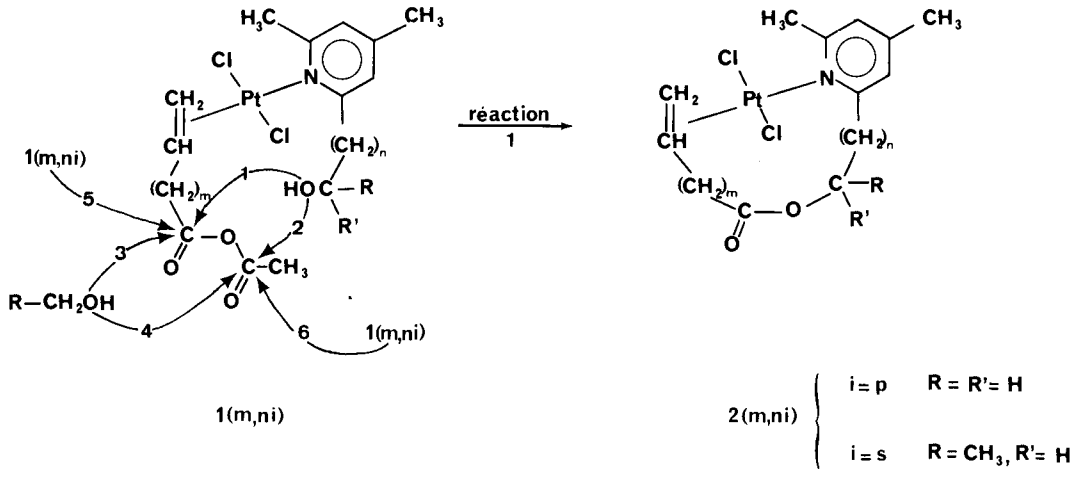


Fig. 1. Schéma des réactions d'acylation compétitives (1–6) pour les complexes **1** (m, ni) en présence de décanol-1.

absence de toute acylation parasite.[5] Les anhydrides mixtes énoïques-acétiques ont été très peu utilisés en synthèse à cause de la compétition entre les deux carbonyles, dont la sélectivité n'est prévisible que dans des cas particuliers.[5] De plus, ils donnent lieu à une réaction de dismutation, difficile à déceler dans notre cas:

$$2\,CH_2{=}CH{-}(CH_2)_m{-}CO{-}O{-}COCH_3 \rightleftharpoons [CH_2{=}CH{-}(CH_2)_m{-}CO]_2O + (CH_3CO)_2O.$$

En RMN ^{1}H à 90 MHz dans C_6D_6 (TMS) la dismutation est révélée par l'apparition du singulet du méthyle de l'anhydride acétique, déplacé de 4,5 Hz vers les champs forts par rapport au singulet à 1,60 ppm du méthyle de l'anhydride mixte; cet écart dans $CDCl_3$ n'est que de 0,5 Hz à 250 MHz.

L'équilibre de dismutation à 34°C correspond à 50% d'anhydride mixte. La réaction des acides éthyléniques avec un excès de cétène dans le benzène à 23°,[8] suivie d'une distillation sous pression réduite permet d'obtenir les anhydrides mixtes purs. Ceux-ci sont stables plusieurs mois en solution $3{,}5 \times 10^{-3}$ M dans CCl_4 ou CH_2Cl_2 à 0–5°. A température ambiante, en solution 0,2–0,5 M dans C_6H_6, l'anhydride mixte L3 est dismuté à environ 10% après deux heures. A 70°, en solution $6{,}5 \times 10^{-2}$ M dans CCl_4, il atteint l'équilibre de dismutation en 40 heures. A la même température, en solution $3{,}5 \times 10^{-3}$ M dans CCl_4, il est dismuté à moins de 5% après 48 h. Ces dernières conditions sont celles qui ont été choisies pour les réactions **1** → **2**.

Les complexes **1** (m, ni) sont préparés aisément à partir du complexe éthylénique correspondant par échange du vinyle terminal de l'anhydride énoïque-acétique avec l'éthylène coordiné. La réaction d'échange est réalisée en concentration environ 0,1 M, en général dans C_6H_6 à température ambiante et est complète en une heure. Les complexes **1** ne sont pas isolés et sont caractérisés par IR et par RMN ^{1}H dans C_6H_6 qui permet de contrôler la dismutation. Celle-ci est toujours inférieure à 5%, sauf dans les cas où $m \leq 2$ pour lesquels il semble que la coordination favorise la dismutation (environ 30% pour m = 2).

Cyclisation des complexes **1** *(m, ni) en métallamacrolactones* **2** *(m, ni)—meilleur couple (m, n)*

La cyclisation est effectuée en solution $3{,}5 \times 10^{-3}$ M dans CCl_4 à 70° jusqu'à conversion totale de l'anhydride mixte (~45 h) et les produits sont analysés après décoordination par la triphénylphosphine, comme décrit précédemment.[5] Nous ne comparerons ici que les trois meilleurs couples (3, 2), (3, 3) et (4, 2) pour les alcools primaires (L'np) et secondaires (L'ns). Dans tous les cas la réaction de cyclisation est conduite en compétition avec les acylations d'un alcool primaire extérieur, le décanol-1 en proportion stoechiométrique (réactions 3 et 4, Fig. 1). Cette compétition avait pour but de permettre d'évaluer dans le cas des complexes **1** (m, np) la contribution des réactions intercomplexes (5 et 6, Fig. 1). Dans le cas des complexes **1** (m, ns) elle permet de comparer les réactivités relatives d'un alcool secondaire coordiné et d'un alcool primaire extérieur. Les résultats sont présentés dans le Tableau 1.

Pour les deux types d'alcool, compte tenu de la précision des mesures, les trois couples (m, n) donnent des résultats très proches. Le couple (3, 3) apparait comme le couple optimum pour la réaction intracomplexe 1, qui conduit à la formation d'une métallamacrolactone à treize éléments (la double liaison comptant pour un élément).

Ainsi dans le cas du complexe **1** (3, 3p) si on assimile le rendement de la réaction intercomplexe 5, à celui de l'acylation du décanol, 3, on peut estimer à 91% le rendement de la réaction de cyclisation intracomplexe, 1, en l'absence de décanol, et à 95% le pourcentage de cette réaction parmi celles affectant le carbonyle-4 en présence de décanol-1. Par contre il ressort des résultats que l'acétylation du décanol-1 (réaction 4) est en fait plus importante que les acétylations intra et intercomplexes 2 et 6 de l'alcool coordiné et ne peut donc permettre d'évaluer le rendement de cette derniére, 6. Cela implique qu'il n'y a pas d'effet de proximité favorable à la réaction 2 et que les acylations du décanol-1 représentent une limite supérieure pour les réactions intercomplexes 5 et 6. La réaction témoin, sans, métal, entre l'anhydride mixte L3 et le décanol-1 ($3{,}5 \times 10^{-3}$ M dans CCl_4) conduit à 60 ± 5% de

Tableau 1. Acylations d'alcools primaires (L'np) et secondaires (L'ns) dans les complexes **1** (m, np) et **1** (m, ns), en compétition avec le décanol-1.[a]

	Couples (m,n)		
Rendements des réactions[b,c]	Complexes d'alcools primaires (**1** m,np)		
	3,2	3,3	4,2
1 + 5	80	85	72
2 + 6	4	6	13
3	3	2	4
4	13	7	11
% 1 dans 1 + 3 + 5 (avec 3 = 5)	93	95	89
Rendements des réactions[c]	Complexes d'alcools secondaires (**1** m,ns)		
	3,2	3,3	4,2
1[d]	70	73	65
2[d]	1	8	3
3	14	7	12
4	15	12	20
% 1 dans 1 + 3	83	91	84

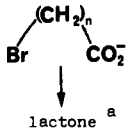
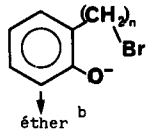
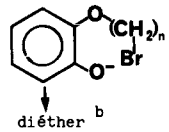
a) complexe **1** et décanol-1 3,5 X 10^{-3} M dans CCl_4 à 70°C.
b) réactions 1-6 schématisées sur la figure 1.
c) erreur relative ± 10%
d) dans ce cas, l'alcool du complexe étant secondaire, les réactions 5 et 6 sont négligeables (voir texte).

réaction d'acylation sur le carbonyle-4. Dans tous les cas de réactions compétitives entre les complexes **1** (m, np) et le décanol-1 il apparait que la proximite induite par la coordination favorise très nettement l'acylation 1 sur le carbonyle-4 pour l'alcool coordiné (au minimum 93 % en négligeant 6 pour le complexe **1** (3, 3p). Avec les alcools secondaires les réactions intercomplexes 5 et 6 peuvent être négligées devant les réactions de l'alcool extérieur primaire. Dans le cas du complexe **1** (3, 3s) l'acylation 1 de l'alcool secondaire est obtenue avec un rendement de 73 % contre 7 % pour l'acylation du décanol-1 soit une sélectivité de 91 %. En absence de métal, dans les mêmes conditions de concentration, la compétition entre le phényl-4 butanol-2 et l'heptanol-1 pour l'acylation par l'anhydride mixte L3 donne respectivement 20 et 80 % (± 5 %) des deux esters secondaire et primaire d'acylation sur le carbonyle-4. La proximité dans le complexe permet donc de multiplier par un facteur de l'ordre de 40 la réactivité de l'alcool secondaire par rapport à un alcool primaire extérieur. Pour les réactions intracomplexes on observe encore une très forte sélectivité en faveur de l'acylation 1 par rapport à l'acylation 2. Toutes les réactions étudiées, réalisées en l'absence de décanol-1, permettent de préparer les complexes **2** avec des rendements de 50 à 65 %, (Tableau 5) en évitant de les manipuler en solution concentrée ce qui conduirait à leur lente polymérisation.[5] La structure des complexes **2** a été établie principalement par RMN ^1H[5,9] et par RMN ^{13}C (tableaux 5 et 6, partie expérimentale). Elle a été confirmée par l'étude par diffraction des RX du complexe **2** (3, 3p) présentée à la fin de cet article.

Molarité effective de l'alcool au sein du complexe **1** (3, 3*s*)

Pour évaluer quantitativement la proximité induite par la coordination au platine (II) des deux réactifs, alcool et anhydride mixte, nous avons déterminé la molarité effective[7] de l'alcool vis-à-vis de la réaction 1 au sein du complexe **1** (3, 3s). Ce complexe correspond au meilleur couple (m, n) sélectionné précédemment (Tableau 1, et résultats antérieurs[5]) et le choix de l'alcool secondaire permet de négliger les réactions intercomplexes (5 et 6). La réaction de référence a été réalisée entre l'anhydride mixte L3 pur et le phényl-4 butanol-2, en proportions stoechiométriques, en solution 3,5 × 10^{-2} M dans CCl_4 à 70°. La constante de vitesse de cette réaction est $k_{inter} = (4,75 \pm 0,5) \times 10^{-3} M^{-1}.mn^{-1}$ ($r^2 = 0,977$). La réaction de cyclisation **1** → **2** a été suivie en solution 3,5 × 10^{-3} M dans CCl_4 à 70°, jusqu'à 30 % de conversion, conditions dans lesquelles la réaction d'acétylation 2 est négligeable. La constante de vitesse pour la réaction 1 est $k_{intra} = (2,05 \pm 0,1) \times 10^{-3} mn^{-1}$ ($r^2 = 0,990$). La molécularité effective de l'alcool au sein de **1** (3, 3s) est donc $k_{intra}/k_{inter} = (0,43 \pm 0,06)M$. Dans le Tableau 2, nous comparons ce résultat aux molarités effectives déterminées pour d'autres

Tableau 2. Molarités effectives pour diverses réactions de cyclisation.

Nombre d'éléments du cycle	 lactone [a]	 éther [b]	 diéther [b]	**1** (3,3s) → **2** (3,3s) [c]
5	$1,60 \times 10^{3}$	$1,31 \times 10^{5}$		
6	$1,45 \times 10$	$6,56 \times 10^{3}$	$3,88 \times 10^{3}$	
12	$6,02 \times 10^{-3}$		$5,69 \times 10^{-2}$	
13	$1,82 \times 10^{-2}$		$3,76 \times 10^{-2}$	
				$4,3 \times 10^{-1}$ [d]
14	$2,37 \times 10^{-2}$	$1,14 \times 10^{-2}$	$2,23 \times 10^{-2}$	

[a] réf. (10), sel de potassium $2-6 \times 10^{-4}$ M à 50°C dans DMSO/H_2O 99/1 [b] réf. (11), alcool $1-2 \times 10^{-4}$ M à 50°C dans C_2H_5OH/H_2O 75/25, en présence de K_2CO_3 0,01 M. [c] ce travail- CCl_4 à 70°C. [d] complexe **2**(3,3s), cycle à 13 éléments si la double liaison est comptée pour un élément.

réactions de cyclisation conduisant à des cycles à 12, 13 et 14 éléments.

La comparaison de ces réactions de cyclisation montre qu'à partir de 12 éléments les molarités effectives sont toutes de l'ordre de 0,01 M et Illuminati et coll. ont conclu que la facilité de formation des grands cycles est essentiellement indépendante de la nature des groupes fonctionnels, de la longueur de la chaîne et de la présence de motifs structuraux autres que des groupes méthylènes.[11]

Dans notre cas, nous avons vérifié que l'existence éventuelle d'une liaison hydrogène entre les fonctions anhydride et hydroxyle des deux réactifs au sein du complexe **1**, ne perturbait pas la libre rotation du ligand éthylénique.[12] Une étude en RMN ^{1}H, à basse température dans l'acétone deutériée, a montré que ces vitesses de rotation étaient très voisines dans les complexes trans-{$PtCl_2$ (décène-1) [(diméthyl-2,4 pyridyl-6)-4 méthyl-2 butanol-2]}, trans-[$PtCl_2$ (acide hexène-5 oïque) (triméthyl-2,4,6 pyridine)] et trans-[$PtCl_2$(L3)(L'3p)]. Dans ce dernier cas la vitesse de rotation de L3 est de l'ordre de $10\,s^{-1}$ à $-58°$ donc très rapide vis à vis de la réaction de cyclisation à 70°. Donc seule la diminution du nombre de degrés de liberté résultant de la géométrie plan-carré du complexe, donne pour la réaction 1 au sein du complexe **1** (3, 3s) une molarité effective de l'alcool de dix à trente fois supérieure à celles obtenues pour des réactions de cyclisation comparables. Ceci rend compte de la proximité induite par la coordination des deux réactifs en positions trans sur le platine (II).

Essai d'acylation sélective d'un diol primaire-secondaire coordiné

Afin d'éprouver la validité pratique de la sélectivité induite par l'association réactif-substrat présente dans le complexe **1**, nous avons étudié l'acylation du (diméthyl-2,4-pyridyl-6)-8 hydroxy-5 octanol-1, **3** (L'3s,7p). Le but était de voir si la proximité, correspondant à priori à celle du complexe **1** (3, 3s), permettrait l'acylation préférentielle de l'hydroxyle secondaire par rapport à l'hydroxyle primaire.

Pour des raisons de solubilité la réaction a dû être effectuée en solution $3,5 \times 10^{-3}$ M dans le dichloro-1,2 éthane à 70°, conditions dans lesquelles une lente décomposition a été observée (évaluée à 5–10% par RMN ^{1}H). L'analyse des produits formés a été réalisée après décoordination,[5] principalement par RMN ^{13}C et par RMN ^{1}H à l'aide d'esters du diol de départ et en particulier de l'ester authentique correspondant à l'acylation intracomplexe recherchée de l'hydroxyle secondaire (Tableau 4,). En considérant comme négligeable l'acétylation de l'hydroxyle secondaire, on peut évaluer celle de l'hydroxyle primaire à environ 25% de la réaction totale. Dans ces conditions, le rapport entre les réactions d'acylation 1, pour les hydroxyles secondaire et primaire peut être évalué à 40/60. La proportion d'acylation de l'hydroxyle secondaire est inférieure à celle que l'on aurait pu attendre d'après les résultats obtenus pour la compétition entre l'alcool secondaire coordiné et le décanol-1 dans le cas du complexe **1** (3, 3s), et d'après l'absence de sélectivité en faveur de la réaction 1 précédemment observée avec le complexe **1** (8, 2p).[5] Il n'est pas exclu que dans le cas du diol choisi les diverses conformations de la chaîne portant les hydroxyles soient moins favorables à la réaction de proximité 1 que dans les cas des complexes **1** (3, 3p) et **1** (3, 3s). Ce résultat ne justifiait cependant pas l'étude relativement délicate d'autres diols.

En conclusion, un effet de proximité a été mis en évidence pour la réaction d'acylation 1 dans les complexes **1** (m, n). Dans le meilleur cas, m=n=3, cette proximité conduit à la formation d'un cycle à 13 éléments avec une molarité effective ($\sim 4 \times 10^{-1}$ M) au sein du complexe, dix à trente fois supérieure à celle observée pour des cyclisations comparables. Cependant cette proximité ne permet pas l'acylation

sélective de l'hydroxyle secondaire "bien placé" d'un diol secondaire—primaire.

Structure aux Rayons X du complexe **2** (3, 3*p*)

Une vue perspective du complexe **2** (3,3p) est représentée Figure 2. Les principales distances interatomiques et angles de liaisons sont donnés, et comparés à ceux du complexe trans-$[PtCl_2(C_2H_4)$ (diméthyle-2,6-pyridine)],[13] dans le Tableau 3.

Plusieurs caractéristiques geométriques peuvent être remarquées qui témoignent de la déformation du complexe due à la présence du ligand chélate. Si M est le milieu de la liaison éthylénique, l'angle dièdre autour de l'axe Pt-M du plan Cl_1–Pt–M avec le plan Pt–C_9–C_{10} est différent de 90° (Fig. 3). Il en est de même des angles Cl_1–Pt–M(100°) et Pt–M–C_{10} (95°). Par ailleurs, le plan C_8–C_9–C_{10} a subi une rotation de l'ordre de 22° autour de l'axe C_9–C_{10} par rapport au plan perpendiculaire à l'axe Pt–M, éloignant la chaîne du platine.

PARTIE EXPERIMENTALE

Les points de fusion F (solvant de recristallisation) ont été mesurés sur un appareil Büchi et ne sont pas corrigés. Les spectres RMN ^{1}H ont été enregistrés sur un spectrographe Varian EM 390, en solution environ 10% en poids dans $CDCl_3$; abréviations utilisées: s, (singulet); d, (doublet); t, (triplet); m, (multiplet). Les spectres RMN ^{13}C ont été enregistrés sur un spectrographe Bruker WH 90 en solution environ 20% en poids dans $CDCl_3$. Les spectres de masse (SM) ont été enregistrés à 70 eV sur un appareil Varian CH 7. Les spectres infra-rouge (IR) ont été enregistrés sur un appareil Perkin–Elmer 599 en film liquide (liq.) ou en pastille de KBr (KBr); abréviations utilisées: F (forte), f (faible), m (moyenne). Les dosages par chromatographie en phase vapeur (CPV) ont été effectués sur un appareil Intersmatt IGC 120 FL avec détection par ionisation de flamme et programmation de température (colonne SE 30, 10% sur Chromosorb WAW 80/100 1,90 m de longueur et de 1/8 de pouce de diamètre).

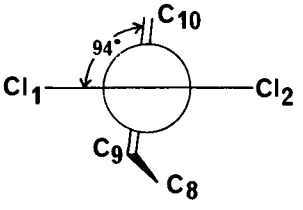


Fig. 3. Projection de Newman des ligands du platine dans le complexe **2** (3,3p) suivant l'axe Pt–M (M milieu de la double liaison).

Préparation des ligands Lm et L'ni

Elle a été précédemment décrite pour m = 2, 4, 6, 8, n = 1, 2 et i = p, s, t.[5] L'acide hexène-5 oïque, précurseur du ligand L3, a été préparé par carbonatation du magnésien du bromo-1 pentène-4 commercial (Fluka) (Rdt. = 80%)–(Eb_{12} = 99–100°) ou obtenu par bromation du pentène-4-ol-1 par PBr_3 (Rdt. = 65%). Le pentène-4-ol-1 a été préparé selon M. P. Dreyfuss[14] avec un rendement de 72%.

Les anhydrides mixtes énoïques-acétiques ont été préparés par action d'un excès de cétène sur les acides correspondants en solution dans le benzène.[8] Ils sont obtenus purs par distillation sous pression réduite (Rdt ≃ 75% après distillation) L3: $Eb_{0.02}$ = 66°, L4: $Eb_{0.02}$ = 76–78°. Les caractéristiques spectroscopiques de ces anhydrides mixtes ont été décrites précédemment.[5]

En liquide pur, ces anhydrides se dismutent rapidement même à 0°. La réaction de dismutation est équilibrée. La position de cet équilibre est identique pour tous les termes de la série ($2 \leq m \leq 8$) et a été déterminée par RMN ^{1}H à 90 MHz dans le benzène. A l'équilibre, dans ce solvant et à 34°, on dose 50% d'anhydride mixte et 25% d'anhydride

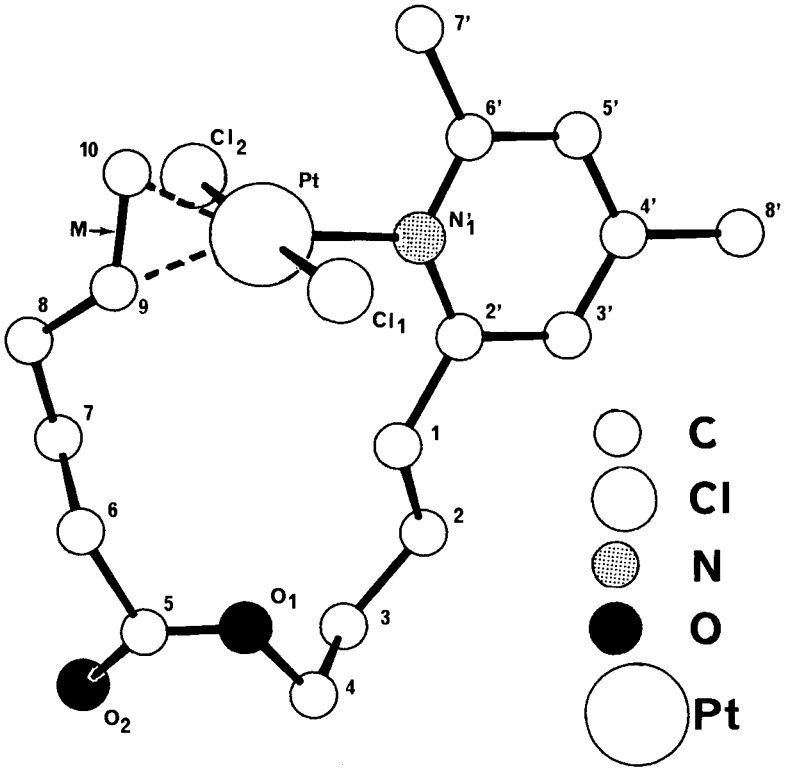


Fig. 2. Vue perspective du complexe **2** (3, 3p).

Tableau 3. Distances interatomiques et angles des liaisons des complexes **2** (3,3p) et trans-{$PtCl_2(C_2H_4)$(diméthyl-2,6-pyridine)}.

	2 (3,3p)[a]	trans-[$PtCl_2(C_2H_4)$(diméthyl-2,6-pyridine)][13]
Pt-Cl	2,299(3) A	2,291(3) A
Pt-N_1'	2,15	2,084(11)
Pt-C_9	2,12	
Pt-C_{10}	2,20	
Pt-M[b]	2,06	2,05
N1'-Pt-Cl_1	88°	89,3°(1)
N1'-Pt-C_9	162	
N1-Pt-C_{10}	158	
Cl_1-Pt-M	100	
Pt-M-C_{10}	95	

a) l'écart type n'est pas précisé pour les atomes légers à cause du mode d'affinement utilisé (cf. partie expérimentale).

b) M est le milieu de la liaison C_9-C_{10}.

acétique. Le signal (singulet) du groupe acétyle de l'anhydride mixte apparait à 4,5 Hz vers les champs faibles par rapport au signal (singulet) du groupe acétyle de l'anhydride acétique. Le même échantillon ne présente pas de variation notable de l'intensité relative des deux signaux observés à 70° après 30 mn à cette température. En solution environ 10^{-3} M dans le tétrachlorure de carbone, les anhydrides mixtes sont stables pendant des mois à 0–5° et sont dismutés à moins de 5% après 48 h de chauffage à 70(±1)°.

Les (diméthyl-2,4 pyridyl-6)-4 butanol-1 (L'3p) et (diméthyl-2,4 pyridyl-6)-5 pentanol-2 (L'3s) ont éte préparés avec des rendements de l'ordre de 65–75% à partir du (diméthyl-2,4 pyridyl-6)-méthyllithium et des oxétanes adéquats.[15]

$$L'3p{:}Eb_{0,2} = 135\text{–}136°$$

$$F = 33\text{–}34° \text{ (éther)}$$

$$L'3s{:}Eb_{0,05} = 117\text{–}118°$$

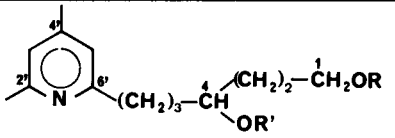
Le (diméthyl-2,4 pyridyl-6)-8 hydroxy-5 octanol-1 (**3**) a été préparé en deux étapes. La première étape (Rdt. = 53%) est la réaction du magnésien de l'éther pyrannylé du chloro-4 butanol-1 sur le (diméthyl-2,4-pyridyl-6)-4 butanal lui-même obtenu par désacétalisation dans l'acide formique à 98%[16] de l'acétal diméthylique correspondant préparé selon W. A. Ayer *et al.*[17] La deuxième étape est le chauffage de l'éther pyrannylé en liquide pur à 200° pendant 30 min. en présence d'un cristal de H_3PO_4. Le produit est distillé sous pression réduite. On obtient ainsi le diol **3**, avec un rendement de 100%. $Eb_{0,05}$ = 168–171° F = 77–78° (acétone- éther, feuillets blancs). RMN ^{1}H ($CDCl_3$–TMS δ, ppm, (J), Hz) 1,5–2,05 (m), 10 H; 2,24 (s), 3 H; 2,45 (s), 3 H; 2.75 (t) (6 Hz), 2 H; 3,63 (t) + (m) (6 Hz), 3 H; 6,78 (s), 2H. RMN ^{13}C-tableau 4. IR (KBr) νOH=3340 cm^1 (F)–νCC, νCN=1605 cm^{-1} (tF) et 1563 m^{-1}(m). SM (m^+/e) 233 (M^+ − 18). 148, 134, 121 (pic de base).

(Diméthyl-2,4-pyridyl-6)-8 (hexène-5 carboxyl)-5 octanol-1 (**4**) (ester authentique correspondant à l'acylation 1 de l'hydroxyle secondaire du diol par l'anhydride mixte L3). Il a été préparé selon W. Steglich *et al.*[18] à partir du diol 1,5 pyrannylé en position 1.

L'alcool primaire est libéré par désacétalisation en milieu biphasique éther/H_2SO_4 0,5 N. La réaction est complète en deux jours. A côté du produit attendu se forme un peu de diol résultant de l'hydrolyse de l'ester. Le produit **4** est obtenu pur (CCM) par chromatographie sur colonne de silice (éluant $CHCl_3$) Rdt. = 55%, huile incolore. RMN ^{1}H ($CDCl_3$–TMS)–δ, ppm–(J), Hz) 1,5–2,5 (m) 16 H; 2,23 (s), 3 H; 2,47 (s), 3 H; 2,68 (m), 2 H; 3,60 (t) (5,5) 2 H; 4,8–5,2 (m), 3 H; 5,6–6,0 (m), 1 H; 6,8 (s), 2 H. RMN ^{13}C, voir Tableau 4.

Acétate de (diméthyl-2,4 pyridyl-6)-8 hydroxy-5 octanol-1 (**5**). Il a été préparé par réaction équimoléculaire du diol 1-5 avec le *N*-acétylimidazole dans CH_2Cl_2 en présence d'une quantité catalytique d'acide acétique. La réaction est complète après 4 jours à température ambiante. A côté de l'acétate **5** (95%) se forment environ 5% de produits acétylés en position 5. L'acétate **5** est une huile incolore. RMN ^{1}H ($CDCl_3$–TMS, δ, ppm–(J), Hz). 1,5–2,0 (m), 10H; 2,05, (s), 3 H; 2,24 (s), 3 H; 2,47 (s), 3 H; 3,65 (m), 1 H; 4,05 (t) (6), 2 H; 6,80 (s), 2H. RMN ^{13}C. Tableau 4.

Tableau 4. Caractéristiques RMN ^{13}C du (diméthyl-2,4 pyridyl-6)-8 hydroxy-5 octanol-1, **3**, et de ses dérivés **4** et **5**.[a]



3	C_1	61,91	C_6	36,93	C_2'	156,74					
	C_2	32,59	C_7	26,18	C_3'	120,56					
	C_3	22,04	C_8	37,44	C_4'	147,49					
	C_4	36,93	CH_3 2'	24,05	C_5'	121,33					
	C_5	70,46	CH_3 4'	20,94	C_6'	160,82					
4	C_1	61,72	C_6	33,69	C_2'	156,74	C_1''(CO)	172,73	C_6''	114,86	
	C_2	32,40	C_7	25,73	C_3'	120,17	C_2''	32,91			
	C_3	21,52	C_8	37,70	C_4'	147,10	C_3''	24,05			
	C_4	33,69	CH_3 2'	24,05	C_5'	121,21	C_4''	33,69			
	C_5	73,50	CH_3 4'	20,74	C_6'	160,24	C_5''	137,13			
5	C_1	64,11	C_6	36,60	C_2'	156,35	C_1''(CO)	170,21			
	C_2	28,45	C_7	25,73	C_3'	120,10	C_2''	21,91			
	C_3	21,46	C_8	37,19	C_4'	146,97					
	C_4	36,60	CH_3 2'	23,72	C_5'	120,88					
	C_5	69,94	CH_3 4'	20,55	C_6'	160,43					

a) Bruker WH 90, 90MHz-$CDCl_3$, TMS, δ en ppm.

Mode opératoire des réactions d'acylation compétitives entre les complexes **1** *(m,ni) et le décanol*-1. Il a été décrit précédemment.[5] Pour minimiser les réactions de dismutation de l'anhydride mixte, la préparation des complexes **1** (m, ni) est réalisée en concentration inférieure à 10^{-1} M dans le benzène, solvant dans lequel la réaction de dismutation est facilement contrôlable (vide supra). A ces concentrations, pour tous les anhydrides mixtes, excepté L2, le taux de dismutation est inférieur à 5% (30% pour L2) au terme ($\simeq$1 h à température ambiante) de la réaction d'échange d'oléfines. Le solvant utilisé pour les réactions compétitives est le tétrachlorure de carbone sauf dans le cas de l'acylation du diol **3** par l'anhydride mixte L3 au sein du complexe **1** correspondant qui pour des raisons de solubilité nécessite l'emploi du dichloro-1,2 éthane (conservé sur alumine). Dans tous les cas, le temps de réaction est fixé à 45 h et la température à 70 ($\pm$1)°. Les réactions de référence citées dans le texte ont toutes été conduites dans les mêmes conditions que les réactions de proximité.

Analyse quantitative des produits des réactions de proximité. Elle a été réalisée par CPV et a déjà été décrite.[5] Dans le cas de l'acylation intracomplexe du diol 1,5, **3**, par l'anhydride mixte L3 le mélange brut des produits de réaction, après décoordination des ligands par la triphénylphosphine, est analysé par RMN ^{13}C en présence d'acétylacétonate de Cr(III). Le bilan de la réaction est effectué par mesure de l'intensité relative des signaux des carbones portant les substituants acyloxy et hydroxy primaires et secondaires, identifiés d'après les spectres RMN ^{13}C des produits authentiques **4** et **5**, (Tableau 4).

Les caractéristiques analytiques des complexes **2** (m, ni) sont présentées dans les Tableaux 5 et 6.

Molarité effective de l'alcool L'3s au sein du complexe **1** (3, 3*s*). Elle a été calculée à partir des constantes de vitesse de la réaction intramoléculaire **1** (3, 3s) → **2** (3, 3s) (réaction 1, Fig. 1) et de la réaction intermoléculaire de référence entre l'anhydride mixte L3 et le phényl-4 butanol-2. La réaction d'acylation intracomplexe de l'alcool L'3s a été conduite avec 0,5 mmole de complexe **1** (3,3s) (dont la pureté a été établie par RMN ^1H dans C_6D_6-vide supra) dissous dans 143 ml de tétrachlorure de carbone (c = 3,5 × 10^{-3} M) et portés à 70 ($\pm$1)°. A chaque prélèvement (10 ml) sont ajoutées les quantités calculées de n.heptadécane (étalon interne) et de triphenylphosphine (2 équivalents). Après évaporation du solvant au rotavapor, les ligands sont repris dans l'éther et injectés en CPV. La stabilité du mélange réactionnel dans les conditions d'analyse a été établie. Le Tableau 7 présente les rendements en ester d'acylation 1 (Fig. 1) calculés d'après une courbe d'étalonnage établie avec l'ester authentique.

La réaction d'acylation intermoléculaire du phényl-4 butanol-2 par l'anhydride mixte L3 a été conduite avec 0,5 mmole de chaque réactif dissous dans 14 ml de tétrachlorure de carbone et de la quantité calculée de n.heptadécane (3,5 × 10^{-2} M). Les prélèvements sont analysés directement par CPV. Le Tableau 8 présente les rendements en hexène-5-oate de phényl-4 butanol-2 calculés d'après une courbe d'étalonnage établie avec l'ester authentique. Le traitement mathématique de ces données (Hewlett-Packard HP 67 programmé pour "ajustement de courbes") donne par régression linéaire les résultats suivants (r^2 = coefficient de corrélation):

$$k_{intra} = (2{,}05 \pm 0{,}1) \times 10^{-3}\ mn^{-1} \qquad r^2 = 0{,}990$$

$$k_{inter} = (4{,}75 \pm 0{,}5) \times 10^{-3}\ M^{-1}\ mn^{-1} \qquad r^2 = 0{,}977$$

la molarité effective est donnée par le rapport k_{intra}/k_{inter}

$$ME = \frac{k\ intra}{k\ inter} = 0{,}43 \pm 0.06\ M$$

Structure cristalline du complexe **2** (3, 3*p*)

Les cristaux du composé **2** (3, 3p) sont des plaquettes jaunes très fragiles. Le cristal utilisé pour la détermination de la structure était un fragment de forme irrégulière d'environ 0,50 × 0,2 × 0,03 mm^3. Les dimensions de la maille cristalline orthorhombique ont été mesurées au diffractomètre (λMoKα = 0,7107 Å a = 19,558(5), b = 11,944(4) et c = 8,404(4) Å. La densité mesurée par flottation dans une solution aqueuse d'iodure de potassium et de bromure de zinc, est de 1,87. La densité calculée est de 1,83 pour quatre molécules dans la maille élémentaire. Les extinctions systématiques (0kl, k + 1 = 2n et h0l, h = 2n) correspondent aux groupes spatiaux Pnam (Z = 8) et $Pna2_1$ (Z = 4). Ce dernier groupe spatial a donc été adopté.

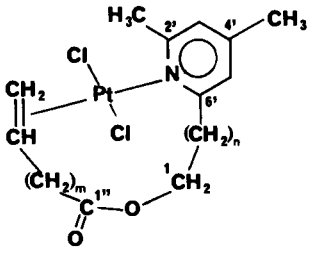
Tableau 5. Caractéristiques analytiques des complexes **2** (m, ni).

2 (m,ni)	**2**(3 2p)	**2**(3,2s)	**2**(3,3p)	**2**(3,3s)	**2**(4,2p)	**2**(4,2s)
Rdt. (%) en complexe isolé [a]	60	52	63	65	60	55
F(°C)[b]	170-172	pâteux	155-160	pâteux	185-187	176-178
SM m^+/e [c]	526 M-35, M-70 355,341,327 260,164,148,121*	540 M-35, M-70 355,327 178,162,134,121*	540 M-35, M-70 355,341 275,178,164,148,121*	554 M-35, M-70 368,341* 290,192,176,148,121	540 M-35, M-70 341,327 275,164,148,121*	554 M-35, M-70 355,327 178,162,134,121*
IR (cm^{1})						
νPt-Cl	375(ep.)355(m)	372(ep.)357(m)	373(m),362(ep.)350(m)	360(m)	372(m)355(F)	370(F)348(m)
νCO	1722(tF)	1725(tF)	1730(tF)	1725(tF)	1727(tF)	1720(tF)
νCC,νCN	1625(F),1573(m)	1625(F),1565(m)	1625(F),1563(m)	1625(F),1563(m)	1625(F),1570(m)	1625(F),1565(m)
νC=C	1520(tf)	1512(tf)	1512(tf)	1512(tf)	1515(tf)	1515(tf)
RMN ^1H						
H3' et 5'	7,10(s) et 7,07(s)	7,04(s)	7,07(s)	7,07(s) et 7,03(s)	7,11(s) et 7,08(s)	7,06(s)
$CH_{3\ 2'}$,[d]	3,17(12)	3,17(11,8)et3,14(12)	3,20(12,8)	3,23(12)et3,21(12)	3,26(12,5)	3,23(12,5)
$CH_{3\ 4'}$	2,36(s)	2,33(s)	2,37(s)	2,38(s)	2,38(s)	2,38(s)
CH_2=CH-	5,85-3,75(m)	5,9-4,07(m)	5,85-4,43(m)	5,9-4,23(m)	6,0-3,45(m)	5,9-4,17(m)
(CH)CH_2-O			4,33(m)			
CH_3-CH=O		1,32(6,3)		1,29(6,5)et 1,27(6,6)		1,35(6,3)et 1,33(6,0)
Analyse tr (calc.)						
C	37,01(36,43)		37,67(37,70)		37,47(37,70)	
H	4,65(4,36)	e	4,62(4,62)	e	4,59(4,62)	e
Cl	14,39(13,47)		13,73(13,12)		13,13(13,12)	
N	2,76(2,65)		2,29(2,58)		2,45(2,58)	

a) après chromatographie sur colonne de Florisil (60-100 Mesh)-éluant :$CHCl_3$.
b) fusion avec décomposition.
c) l'ion moléculaire correspond à l'isotope ^{35}Cl. pic de base (*).

d) (J $^{195}Pt-^{1}H$) en Hz pour $CH_{3\ 2'}$.
e) analyse élémentaire imparfaite ; ces complexes sont isolés huileux (mélange de diastéréoisomères).

Tableau 6. Caractéristiques RMN ^{13}C des métallamacrolactones **2** (m, np).[a,b]



2(m,np)

	C_1	63,21		C_2'	157,78		CH_3 2'	25,60	(23,44)	C_4''	32,46	(26,37)
	C_2	29,48		C_3'	124,64	(26,36)	CH_3 4'	20,81		C_5''	100,10	(161,13)
2 (3,2p)	C_3	36,67	(16,11)	C_4'	151,11		C_1''(CO)	172,34		C_6''	71,43	(158,20)
				C_5'	125,54	(26,36)	C_2''	33,56				
				C_6'	160,82		C_3''	23,66	(18,58)			
	C_1	64,63		C_2'	157,78		CH_3 2'	25,73	(23,43)	C_4''	32,72	(24,43)
	C_2	27,15		C_3'	123,28	(27,83)	CH_3 4'	20,81		C_5''	98,16	(162,59)
2 (3,3p)	C_3	28,58		C_4'	150,85		C_1''(CO)	172,73		C_6''	72,01	(159,66)
	C_4	38,54	(20,5)	C_5'	125,22	(26,36)	C_2''	33,56				
				C_6'	161,53		C_3''	24,63	(26,36)			
	C_1	63,66		C_2'	157,58		CH_3 2'	25,40	(24,90)	C_4''	24,17	
	C_2	28,58		C_3'	123,73	(26,36)	CH_3 4'	20,81		C_5''	32,91	(21,97)
2 (4,2p)	C_3	36,86	(19,04)	C_4'	150,98		C_1''(CO)	172,60		C_6''	98,74	(161,31)
				C_5'	125,61	(26,36)	C_2''	34,98		C_7''	72,01	(164,06)
				C_6'	161,01		C_3''	27,48	(21,97)			

a) Bruker WH 90 MHz. $CDCl_3$, TMS, δ en ppm. ($J^{195}Pt-^{13}C$), Hz.
b) Nomenclature adoptée pour désigner les carbones du ligand bidenté :
Les carbones du reste L m sont notés $\underset{1''}{CO}-\underset{2''}{CH_2}-,\ldots C_{(m+3)''}$

Les carbones du reste L'n sont notés $-O-\underset{1}{CH_2}-,\ldots,-C_{(n+1)}$

Les carbones du noyau pyridyl sont notés $C_{2'},\ldots C_{6'}$.

Les données ont été enregistrées avec un diffractomètre automatique PW 1100, en utilisant la radiation Kα du molybdène isolée par un monochromateur au graphite. Trois réflexions de référence ont été mesurées toutes les deux heures sans qu'une décomposition soit observée. Parmi 6333 réflexions mesurées, seulement 1152 avaient une intensité significativement supérieure au bruit de fond ($I \geq 2\sigma(I)$). Les corrections de Lorentz et de polarisation ont été appliquées aux données, mais aucune correction n'a été introduite pour l'extinction secondaire ou l'absorption, bien que cette dernière soit importante ($\mu = 78\,cm^{-1}$).

Les positions des atomes de platine et de chlore ont été déduites de l'examen de la fonction de Patterson. Un affinement préliminaire des paramètres correspondant à ces atomes (coordonnées, anisotropie d'agitation thermique, diffusion anormale du platine[19] a conduit à un facteur

Tableau 7. Détermination de la constante de vitesse k_{intra} de la réaction de proximite **1** (3,3s) → **2** (3,3s) en solution $3,5 \times 10^{-3}$ M dans CCl_4 à 70(±1)°C.

t(mn)	rendement (%) en ester [a]	x X 10^{-4} [b]	Log (a_o/a_o-x)[b].
30	4,6	1,6	0,0470
45	8,7	3,0	0,0910
60	10,6	3,7	0,1120
75	13,4	4,7	0,1438
105	18,0	6,3	0,1984
120	22,2	7,8	0,2510
150	27,7	9,7	0,3243
180	29,4	10,3	0,3482

a - L'erreur relative sur les rendements est estimée à ±10%.

b - a_o = concentration initiale du complexe **1**(3,3s).
x = concentration du complexe **2**(3,3s) au temps t.

Tableau 8. Détermination de la constante de vitesse k_{inter} de la réaction de référence (L_3 + phényl-4 butanol-2) en solution $3,5 \times 10^{-2}$ M dans CCl_4 à 70(±1)°C.

t(mn)	rendement (%) en ester [a]	x X10^4 [b]	$1/a_0-x$
45	2,5	8,8	29,30
75	2,9	10,2	29,44
105	3,6	12,6	29,65
135	4,0	14,0	29,76
165	5,1	17,9	30,11
240	5,5	19,3	30,24
300	6,4	22,4	30,52
360	7,3	25,6	30,83

a- L'erreur relative sur les rendements est estimée à ±10%
b- a_o = concentration initiale de chaque réactif.
x^o = concentration en hexène-5 oate de phényl-4 butanol-2 au temps t.

d'accord $R = \Sigma||F_0| - |F_c||/\Sigma|F_0|$ de 0,082. Une série de Fourier-différence a donné les positions des autres atomes à l'exception des atomes d'hydrogène.

Un nouvel affinement par les moindres carrés a été alors effectué, en considérant l'agitation thermique des atomes légers comme isotrope. Cet affinement n'ayant pas sensiblement amélioré le facteur d'accord (R = 0,077), une nouvelle série-différence a été calculée. Des résidus de densité électronique symétriques des atomes légers par rapport au plan perpendiculaire à c passant par le platine ont été observés. Nous avons alors admis l'existence d'un désordre statistique par rapport à ce plan, ce qui conduisait à adopter le groupe spatial Pnam. On peut considérer que le groupe spatial est $Pna2_1$ au niveau de la maille élémentaire, mais que la moitié des mailles possède l'axe z orienté dans un sens, la moitié dans l'autre sens. Le groupe spatial au niveau du cristal devient Pnam, avec l'atome de platine dans un plan miroir, un atome de chlore hors de ce plan, et la partie organique du complexe étant affectée de coefficients d'occupation moitié. Les distances en général faibles de ces derniers atomes au plan miroir nous ont conduits à adopter un procédé d'affinement un peu particulier: la diméthyl-2,4 pyridine a été considérée comme un seul bloc rigide, et la chaîne organique a été affinée en utilisant un programme écrit par C. Riche[20] d'après Waser,[21] introduisant des contraintes pondérées sur les distances et angles de liaison.

Le facteur d'accord final est également de 0,077. La précision sur les positions atomiques de la partie organique est difficile à évaluer en raison du procédé d'affinement utilisé. Elle est faible (de l'ordre de 0,1 Å et 5°), mais cependant suffisante pour confirmer la structure du complexe dont une vue en perspective est donnée Figure 2. Les valeurs finales des distances et angles intermoléculaires figurent dans le Tableau 3.

Remerciements—Nous remercions vivement Melle Derouet pour l'enregistrement des spectres de ^{13}C et la Délégation Générale à la Recherche Scientifique et Technique pour l'aide financière accordée au titre du contrat 75–7–0086 A.S.C.O. et la Société Engelhard Industries (France) pour un don de sel de platine.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 41 to 53, 1981
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0040-4020/81/Suppl. 1-0041-13 $02.00/0
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PROPRIETES CHIMIQUES DES α-HYDROXYNITRONES CYCLIQUES: ACTION DU BOROHYDRURE DE SODIUM, DU CHLORURE DE BENZOYLE ET DE *p*-TOLUENE SULFONYLE. SYNTHESE PARTIELLE DE DERIVES DU PREGNANE FONCTIONNALISES SUR LE CARBONE-18

J. P. ALAZARD, H. DADOUN et X. LUSINCHI*

Institut de Chimie des Substances Naturelles du CNRS, 91190 Gif-sur-Yvette, France

(*Received in France* 18 *March* 1980)

Abstract—Pregnane derivatives with different functions on C-18 and C-20 are obtained from the pyrrolinic isomeric steroïdal hydroxynitrones **2** and **3** by reaction with sodium borohydride and with acid chlorides. In particular, the benzoylation of hydroxynitrone **3** leads to pregnane-18-al-20-one with the carbonyl group at C-20, protected as its oxime ester. This enables selective oxydation and reduction of the free aldehyde at C-18.

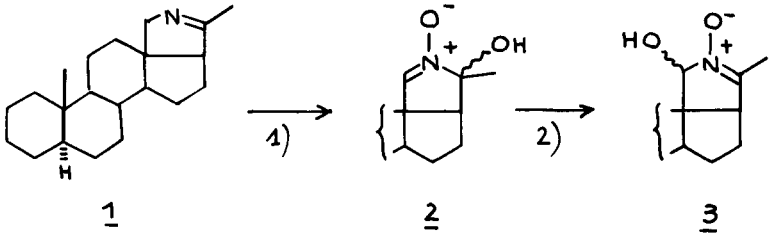
Résumé—L'action du borohydrure de sodium et des chlorures d'acide sur les hydroxynitrones pyrroliniques stéroïdiques isomères **2** et **3**, permet d'accéder à des dérivés du pregnane diversement fonctionnalisés sur C-18 et C-20. En particulier, la benzoylation de l'hydroxynitrone 3, conduit à la pregnanal-18 one-20 avec le carbonyle en C-20, protégé sour forme d'ester d'oxime **20**, ce qui permet une oxydation et une réduction sélective de la fonction aldehyde libre en C-18.

L'oxydation par un peracide de l'imine pyrrolinique stéroïdique **1**[a] conduit à l'hydroxynitrone **2** puis à l'hydroxy nitrone **3** par isomérisation en milieu acide (Schéma 1).[1,2]

Ces hydroxy-nitrones qui correspondent à des dérivés de la (5α)-prégnanal-18 one-20 peuvent être envisagées comme intermédiares pour la préparation de dérivés de la prégnanone-20 diversement fonctionnalisés sur C-18.

L'étude des propriétés chimiques de ces hydroxynitrones dont le comportement en milieu acide et alcalin a été précédemment décrit a été poursuivie par l'étude de leur réduction par le borohydrure de sodium et de leur réaction en présence d'un chlorure d'acide.

L'obtention, en particulier, dans de bonnes conditions, à partir de l'hydroxynitrone **3** de l'ester d'oxime-aldéhyde **20** (Schéma 9) permet d'accéder facilement au prégnane substitué en 18 par une



1) acide para-nitroperbenzoïque (2 equivalents)
2) acide p. toluene-sulfonique hydraté, benzène

Schéma 1.

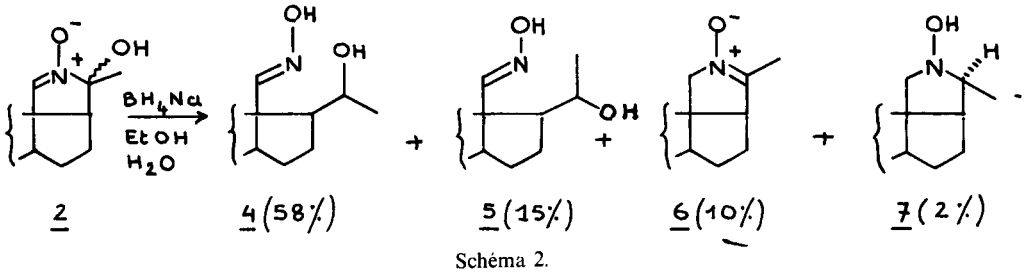


Schéma 2.

[a] Obtenue à partir de la conessine **16**.[3]

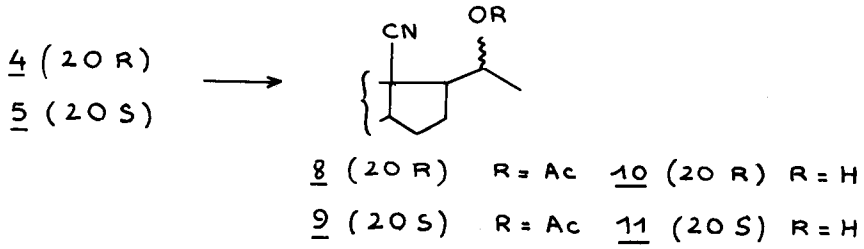
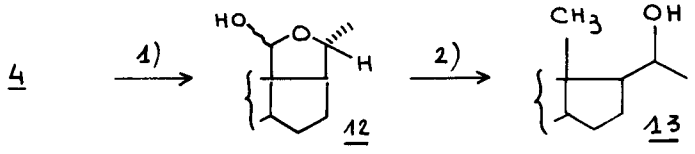


Schéma 3.



1) NO_2Na; AcOH; H_2O; temp. amb., 10 mn
2) N_2H_4, H_2O; glycolate de sodium

Schéma 4.

fonction alcool ou une fonction acide. Cette voie offre une alternative à celle qui utilise un intermédiaire nitrile-18 prégnanone-20 antérieurement suivie pour une hémisynthèse à partir de la conessine **16** de l'hydroxy-18 progesterone.[4]

Action du borohydrure de sodium sur les hydroxynitrones 2 *et* 3

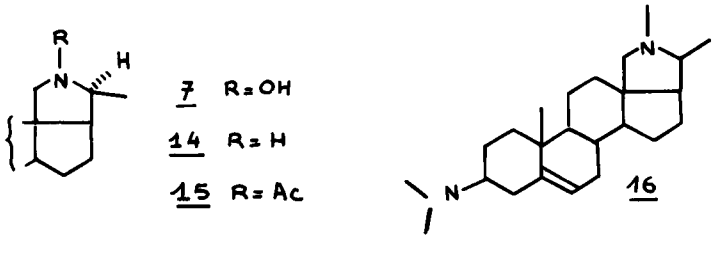
Traitée par un excès de borohydrure de sodium dans l'éthanol à 95°, l'hydroxynitrone **2** conduit à un mélange dont ont été isolés l'oxime-alcool (20R) **4** (58 %), l'oxime-alcool (20S) **5** (15 %), la nitrone **6** (10 %) et l'hydroxylamine **7** (2 %)

Les structures proposées, en accord avec les données analytiques et spectrales sont confirmées par les propriétés chimiques suivantes. L'action de l'anhydride acétique, à reflux, sur les oxime-alcools **4** et **5**, suivie d'hydrolyse alcaline, conduit au nitrile-esters et aux nitrile-alcools **8**, **9**, **10**, **11**, dont le dernier, seul connu, présente des caractéristiques analytiques et spectrales voisines de celles du produit décrit[5] (Schéma 3). Par action du nitrite de sodium en milieu acide,[6] suivie d'une réduction selon Wolff-Kishner, l'oxime-alcool **4** conduit successivement à l'hémiacétal **12** puis au prégnanol (20R) **13** (Schéma 4). Ce dernier, connu,[5] a été identifié à un échantillon de référence préparé, par réduction, selon Wolff–Kishner de la (5α) prégnanol-20β one-3,[7] ce qui confirme la configuration en 20 des alcools et des esters obtenus.

La nitrone **6**, réduite par le borohydrure de sodium, conduit à l'hydroxylamine **7** et cette dernière, oxydée à l'air en présence d'un sel cuivrique[8] redonne la nitrone **6** accompagnée du'un faible pourcentage de la nitrone **17** qui sera décrite plus loin (Schéma 6). Ces propriétés, jointes aux caractéristiques analytiques et spectrales de ces composés établissent sans ambiguité leur structure.

La réduction de la nitrone **6** est stéréospecifique et conduit à une seule hydroxylamine ayant la configuration H20α (20S). Celle-ci a été établie par action du zinc en présence d'acide chlorhydrique sur l'hydroxylamine **7**, qui conduit à l'amine secondaire **14**, qui, après acétylation de l'azote, a été identifiée avec un échantillon de réference préparé à partir de la conessine **16** selon Cerny et Sorm.[3]

L'hydroxynitrone **3** réduite dans les mêmes conditions que l'hydroxynitrone **2** conduit à un mélange de la nitrone **17** et de l'hydroxylamine **7** (Schéma 6).



7 → **14** Zn, AcOH, EtOH; **14** → **15** Ac_2O, MeOH;
16 → **15** suite de réactions selon la référence (3)

Schéma 5.

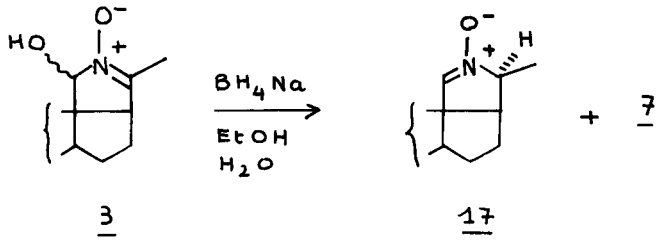


Schéma 6.

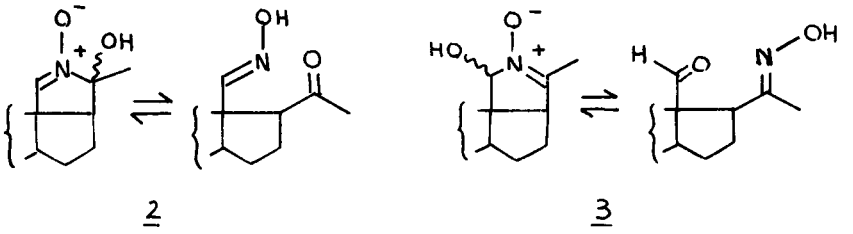


Schéma 7.

Une prolongation du temps de réduction permet d'obtenir la seule hydroxylamine **7** avec un rendement pratiquement quantitatif. En abaissant la température de la réaction à 2°C, il est possible de diminuer de façon significative la vitesse de réduction de la nitrone **17** par rapport à celle de l'hydroxy-nitrone **3** et d'élever de cette façon le rendement en nitrone **17** (90%).

La différence de réactivité observée entre les hydroxy nitrones **2** et **3** peut s'interpréter à partir d'équilibres entre structure cyclisée et structure ouverte (Schéma 7).

Une étude précédente a montré que ces deux dérivés se présentent toujours sous une forme cyclique, en présence d'une base comme d'un acide. Cependant l'existence, en équilibre, d'une structure ouverte en faible concentration peut être raisonnablement envisagée et a pu être expérimentalement établie pour l'hydroxynitrone **2**.[2]

Le schéma 7 fait ressortir la présence de fonctions nitrones et carbonyles, réductibles par le borohydrure de sodium et de fonctions oximes non réductibles. Le carbone 18 d'un dérivé du prégnane étant plus encombré que le carbone 20[b] les fonctions réductibles les plus accessibles sont pour l'hydroxynitrone **2** le carbonyle en 20 de la forme ouverte et pour l'hydroxynitrone **3** la nitrone en 20 de la forme cyclisée. D'autre part la vitesse d'une réaction dépendant de la concentration des réactifs, ce facteur est en faveur d'une réaction plus rapide des formes cyclisées, seules observables.

Pour l'hydroxy-nitrone **3** ces deux facteurs stérique et de concentration convergent pour favoriser la réduction de la forme cyclisée. Ils divergent pour l'hydroxynitrone **2** qui réagit préférentiellement sous la forme ouverte, la moins encombrée, mais aussi pour une part sous la forme cyclisée, la plus concentrée.

Action du chlorure de benzoyle et du chlorure de toluène-p-sulfonyle sur les hydroxy-nitrones **2** *et* **3**

Une étude préliminaire avait montré que l'action de l'oxychlorure de phosphore dans la pyridine sur l'hydroxy-nitrone **2** conduisait quantitativement au céto-nitrile **19**.[1]

Dans les mêmes conditions, l'hydroxynitrone **3** conduit à un mélange de produits qui n'ont pu être définis. Les études parues depuis concernant l'action des chlorures d'acide sur les nitrones[9] incitaient à réexaminer l'action de ces réactifs sur les hydroxynitrones **2** et **3**. Le chlorure de benzyole et le chlorure de toluène-p-sulfonyle ont été choisis en raison de leur différence de réactivité avec la fonction nitrone, en relation avec la nature différente des groupes partants benzoyloxy ou toluene-p-sulfonyloxy.[9c]

Avec le chlorure de benzoyle en milieu alcalin hétérogène (agitation d'une solution benzénique du substrat au contact d'une solution aqueuse de soude) l'hydroxy-nitrone **2** conduit à l'ester d'oxime **18** (Schéma 8). Ce dérivé est stable dans le milieu réactionnel, mais conduit partiellement au céto-nitrile **19** au cours de l'isolement. Il peut cependant être obtenu suffisamment pur pour que son spectre de masse et de RMN puisse être décrit. Chauffé dans le benzène il conduit quantitativement au céto-nitrile **19**.

Un résultat analogue est obtenu si la benzoylation est effectuée dans un milieu hétérogène acide (agitation d'une solution benzénique au contact d'une solution aqueuse d'acide sulfurique) ainsi que dans le benzène seul. L'examen par RMN de la solution organique avant isolement, montre que, dans ces conditions, les seuls signaux observables correspondent à la structure ouverte **18**.

Dans un milieu alcalin homogène (méthanol-potasse) à la température ambiante le dérivé **18** revient au produit de départ **2**. La benzoylation en milieu

[b] La réduction s'effectuant perpendiculairement à la double liaison réduite, l'examen d'un modèle moléculaire fait ressortir pour une structure cyclique, un moindre encombrement de la face α par rapport à la face β et pour l'attaque par la face α une gène stérique en 18 introduite par le carbone en 12. Dans la structure ouverte la conformation stable d'une aldoxime peut être considéré comme voisine de la structure cyclique.

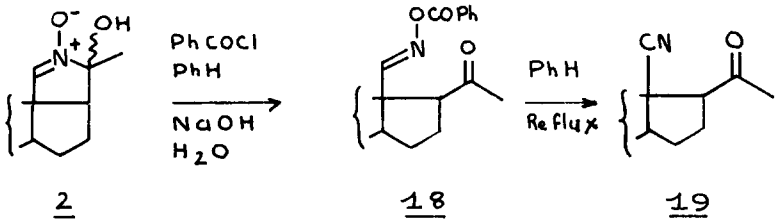


Schéma 8.

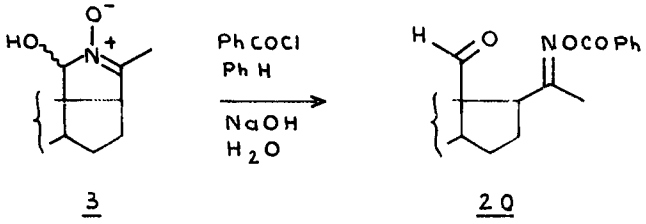


Schéma 9.

alcalin hétérogène de l'hydroxynitrone isomère **3**, conduit à l'ester d'oxime-aldéhyde **20** (Schéma 9). La réaction est quantitative et le dérivé **20** est stable. En milieu alcalin homogène il retourne quantitativement au produit de départ, mais n'évolue pas après plusieurs jours de maintien dans les conditions de son obtention.

Si la benzoylation est effectuée au contact d'une solution aqueuse acide la formation d'un mélange des esters d'oxime **18** et **20** est observée, qui, si la réaction est prolongée, conduit finalement au seul dérivé **18**. La réaction peut être suivie par RMN le milieu ne contenant que les structures ouvertes **18** et **20** qui peuvent être facilement distinguées. Une réaction analogue est observée dans le benzène seul avec formation après 48 heures d'un mélange dont le constituant principal est le dérivé **18**, accompagné du dérivé **20** et du céto-nitrile **19** en faibles quantités.

Avec le chlorure du p-toluène sulfonyle en milieu alcalin hétérogène l'hydroxy-nitrone **2** conduit au céto nitrile **19**. La réaction est lente et nécessite un excès de chlorure d'acide (2,2 équivalents). Dans les mêmes conditions et toujours avec un excès de réactif, l'hydroxy-nitrone **3** conduit à un dérivé aldéhydique ouvert analogue au dérivé **20** avec un groupement toluène-p-sulfonyle au lieu du groupement benzoyle. Ce produit est accompagné de nombreux produits secondaires à l'état de traces et n'a pu être purifié. Une chromatographie sur couche épaisse de silice conduit au céto-nitrile **19** (70 %).

Après 20 h dans le benzène, en présence de 1,1 équivalents de chlorure de toluène-p-sulfonyle, suivi d'agitation avec une solution aqueuse alcaline les deux hydroxynitrones **2** et **3** conduisent quantitativement au céto-nitrile **19**. Ce dernier n'est que partiellement formé avant l'alcalinisation, le milieu contenant une structure toluène-p-sulfonée décelable par RMN.

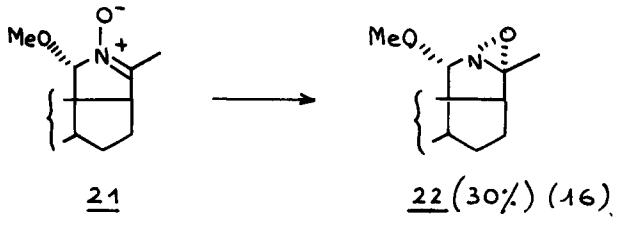


Schéma 10.

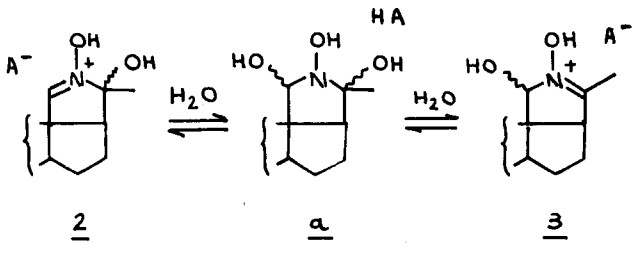


Schéma 11.

Action du chlorure de benzoyle et du chlorure toluène-p-sulfonyle sur la nitrone méthoxylée **21**

La méthoxy-nitrone **21** connue,[2] réagit avec le chlorure de benzoyle, en milieu alcalin hétérogène pour conduire au céto-ester d'oxime **18**.

Avec le chlorure de p-toluène sulfonyle un mélange de produits est obtenu dont a été isolé l'oxaziranne α méthoxylé **22** (30%) (Schéma 10). Cette réaction a été précédemment décrite,[2] l'oxaziranne instable est obtenu avec un mauvais rendement. Il a été vérifié d'autre part par analyse sur couche mince que le mélange de produits obtenu ne contient pas le céto-nitrile **19**.

En milieu homogène ($CHCl_3$) le dérivé **21** réagit avec le chlorure de p-toluène sulfonyle pour conduire à un mélange dont aucun produit défini n'a pu être isolé. Le spectre de RMN du produit brut ne contient pas de signal pouvant être attribué à la présence d'un méthyle-**21**. Il est donc probable que cette position a été fonctionnalisée.

Commentaires sur l'action des chlorures d'acide

Une étude précédente[2] a permis d'établir qu'en milieu neutre ou alcalin à la température ambiante les hydroxynitrones **2** et **3** n'additionnent pas des nucléophiles tels que l'eau ou le méthanol. L'addition est par contre possible en présence d'un acide qui active la nitrone par protonation. Cette réaction est concrétisée par l'isomérisation en présence d'eau et d'un acide, de l'hydroxynitrone **2** pour conduire à l'hydroxynitrone **3**, plus stable, selon le Schéma 11. Ces structures sont, par ailleurs, en équilibre avec les formes ouvertes oxime-carbonyle, mais seules les structures cyclisées sont observables par RMN.

L'activation par protonation permet l'addition d'un nucléophile faible, tel que l'anion $CF_3CO_2^-$. Cette particularité permet d'observer l'isomérisation **2** ⇌ **3**, en l'absence d'eau ajoutée, une molécule d'eau pouvant être libérée selon le Schéma 12.

L'acylation de la fonction nitrone se traduit par la formation de structures ouvertes ester d'oxime-carbonyle (**18** et **20**; Schéma 13).

En présence d'un acide, l'observation de l'isomérisation **20** → **18**, permet de conclure à la présence de formes cyclisées en équilibre (Schéma 13). La présence du seul dérivé **18**, après equilibration établit qu'il est plus stable que son isomère **20**. Le fait que ce dernier soit observé en début de réaction montre, par ailleurs, que l'ouverture de cycle est plus rapide que l'addition d'eau.

En présence d'une base alcaline, le fait que chaque hydroxynitrone conduise au dérivé ouvert correspondant, stable dans le milieu réactionnel, s'interprète par une ouverture de cycle plus rapide que l'addition d'eau, cette ouverture étant irréversible dans les limites de temps étudiées (plusieurs jours).

Une hypothèse selon laquelle, comme pour les hydroxynitrones, l'eau ne s'additionnerait pas sur les

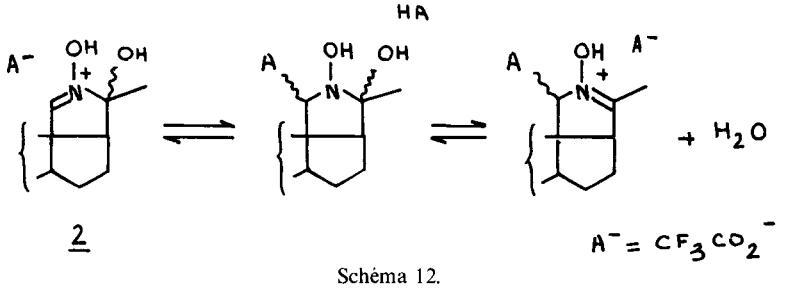


Schéma 12.

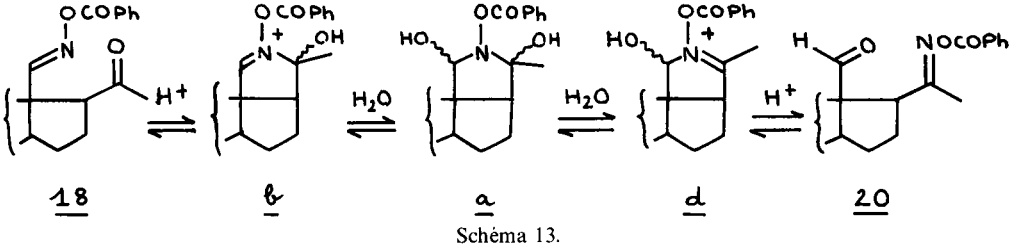


Schéma 13.

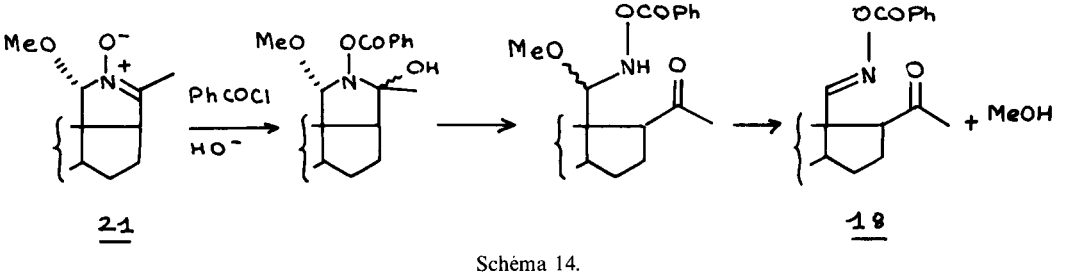


Schéma 14.

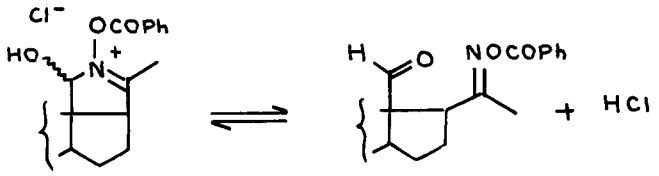


Schéma 15.

structures immoniums en milieu alcalin ne peut être retenue. L'acylation doit raisonnablement se traduire par une activation analogue à celle obtenue par protonation. Cette activation est expérimentalement constatée avec la méthoxy-nitrone **21** qui conduit à la benzoyloxime **18** en milieu alcalin (Schéma 14).

Il est à remarquer que l'isomérisation **20** → **18** (Schéma 13) est encore observée en l'absence d'acide et d'eau ajoutés au milieu. Cette particularité est due au fait que l'acylation rend disponible une molécule d'acide selon le Schéma 15, et que cette dernière peut intervenir dans une réaction analogue à celle décrite dans le Schéma 12 ce qui rend disponible une molécule d'eau. Les conditions permettant aux équilibres du Schéma 13 de s'établir sont donc réunies.

L'action du chlorure de toluène-p-sulfonyle est comparable à celle du chlorure de benzoyle. En milieu alcalin chaque hydroxynitrone conduit à la structure ouverte O-sulfonée correspondante, avec, pour l'ester d'oxime en 18, une élimination rapide d'acide p-toluène sulfonique avec formation du céto-nitrile **19**. Ce nitrile est également obtenu à partir de l'hydroxy nitrone **3** après une action suffisamment prolongée du chlorure d'acide en milieu neutre suivie de passage en milieu alcalin. Une isomérisation analogue à l'isomérisation **20** → **18** (Schéma 13) a donc également lieu avec le chlorure de toluène-p-sulfonyle en l'absence d'eau et d'acide ajoutés.

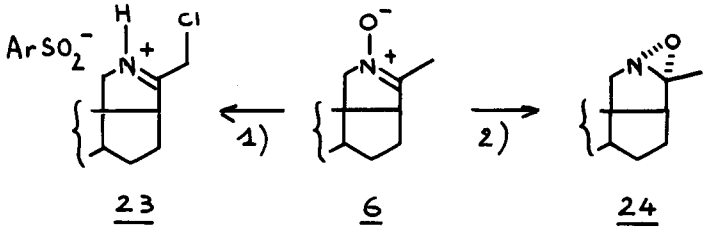
La comparaison des hydroxy-nitrones **2** et **3** et de leur dérivés O-estérifiés permet de conclure: les hydroxy nitrones sont stables sous leur forme cyclisée, elles sont en équilibre avec les formes ouvertes en milieu acide comme en milieu alcalin, elles n'additionnent l'eau à la température ambiante qu'en présence d'un acide. Les structures N,O-estérifiées correspondantes sont ouvertes en milieu acide comme en milieu alcalin, elles ne sont en équilibre avec les structures cycliques qu'en présence d'un acide et elles additionnent l'eau en milieu acide comme en milieu alcalin.

Il est à remarquer que la formation d'un oxaziranne ou d'une imine fonctionnalisée en α, obtenue par action du chlorure de p-toluène sulfonyle sur la nitrone **6** non hydroxylée en 18 (Schéma 16)[9c] n'est pas observée avec l'hydroxynitrone **3**

La non formation de l'oxaziranne en milieu alcalin est en accord avec l'hypothèse faite précédemment, d'une ouverture de cycle plus rapide que l'addition d'eau et non réversible. Dans le cas contraire la formation de la structure pseudobasique correspondante se traduirait par la formation d'un oxaziranne, ce qui n'est pas observé (Schéma 17).

L'oxaziranne est effectivement obtenu si l'hydroxyle en 18 est remplacé par un méthoxyle (Schéma 10).

En présence d'un acide, les structures cycliques étant en équilibre avec les formes ouvertes, les raisons d'une non fonctionnalisation en 21 selon le schéma 16 paraissent plus difficiles à définir. Il ne semble pas que l'explication soit donnée par une évolution irréversible vers le céto-nitrile **19**, car cette évolution est moins rapide, plusieurs heures, que la fonctionnalisation en 21 de la nitrone **6**, quelques minutes.[9c] Il semble que la fonctionnalisation soit elle-même inhibée par la présence de l'hydroxyle en 18. Le remplacement de



1) $ArSO_2Cl$, PhH 2) $ArSO_2Cl$, CH_2Cl_2, NaCH, H_2O

Ar = p.tolyl

Schéma 16.

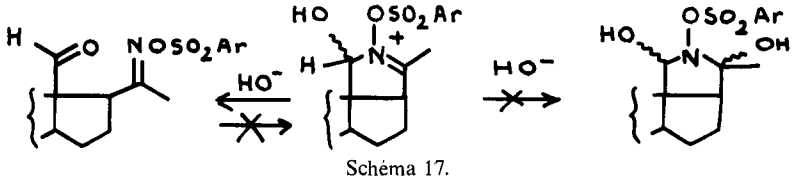
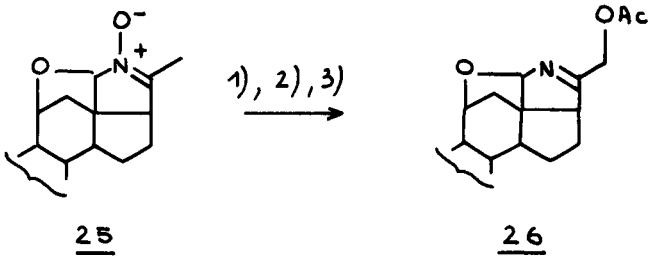


Schéma 17.



1) Ac_2O 2) H_2O 3) chauffage (10)

Schéma 18.

l'hydroxyle par un méthoxyle modifie effectivement le cours de la réaction, mais celle-ci n'a pas conduit à l'isolement d'un produit défini. Cependant il est à noter que Barton *et al.*[10] ont pu réaliser une telle fonctionnalisation avec la nitrone stéroïdique **25** dont la fonction éther est intégrée dans un cycle (Schéma 18).

Propriétés de l'ester d'oxime aldehyde **20**

Le Schéma 19 résume quelques réactions qui ont été effectuées à partir de ce dérivé.

L'oxydation de l'aldéhyde en 18 par une solution de permanganate de potassium dans un mélange d'acétone et d'eau conduit à l'ester d'oxime-acide **27** (89%) dont la fonction ester est hydrolysée par la potasse dans le méthanol.

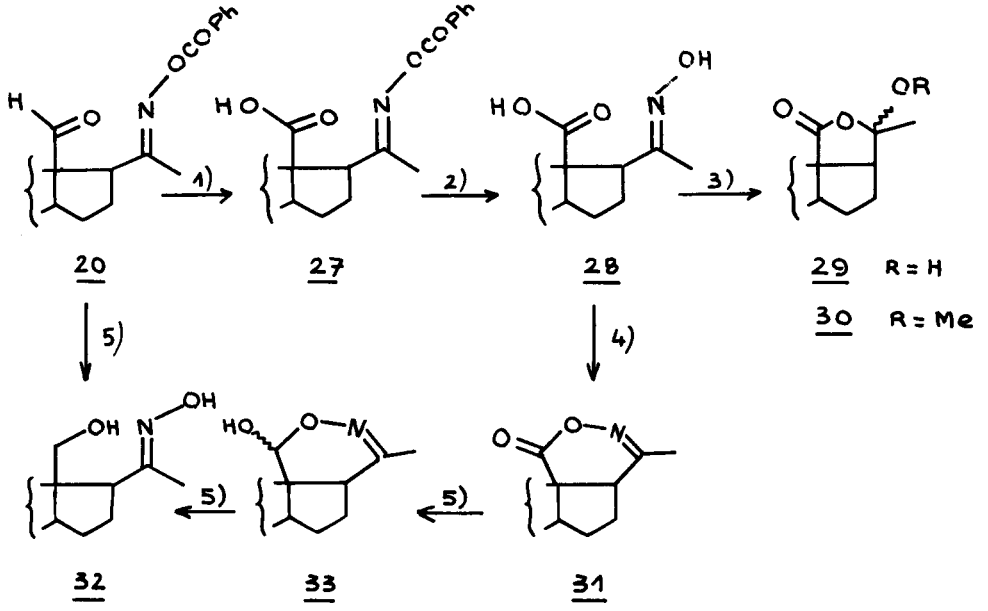
Chauffé à reflux dans une solution aqueuse-méthanolique d'H_2SO_4 le dérivé **28** conduit à un mélange de l'hydroxy-lactone **29** et du dérivé O-méthylé correspondant **30**. La même réaction est observée, mais beaucoup plus lente à la température ambiante. L'utilisation d'un mélange de tetrahydrofuranne et d'eau acide permet d'éviter la formation du dérivé méthoxylé, l'hydroxy-lactone **29** étant obtenue quantitativement.

L'hydroxy-lactone **29** a été préparée parallèlement à partir du cétonitrile **19** selon le Schéma 20. L'identité des produits obtenus confirme les structures proposées.

Dissous, à la température de 0°, dans l'acide sulfurique concentré, l'acide oxime **28** conduit à l'ester d'oxime cyclique **31** (73%).

Au contraire du dérivé **28** le dérivé **31** n'est pas hydrolysé en solution hydrométhanolique acide et reste pratiquement inchangé après 31 h de reflux dans ces conditions.

Le dérivé **31** réduit par le borohydrure de sodium conduit au dérivé hémiacétalique **33**, réduit à son tour par le même réactif mais beaucoup plus lentement avec formation de l'oxime alcool **32**. Ce même dérivé **32** a été obtenu par réduction de l'adéhyde ester d'oxime **20**, la réduction s'accompagnant d'une hydrolyse de la fonction ester.



1) MnO_4K, acétone, eau, reflux 2) MeOH, KOH puis H_2SO_4
H_2O 3) MeOH, H_2O, H_2SO_4 4) H_2SO_4 conc. 5) BH_4Na

Schéma 19.

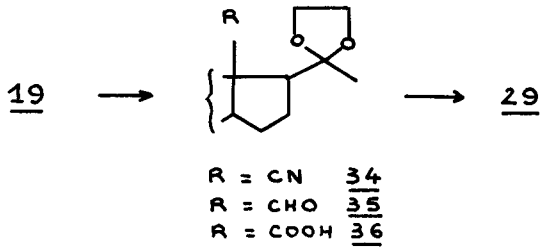


Schéma 20.

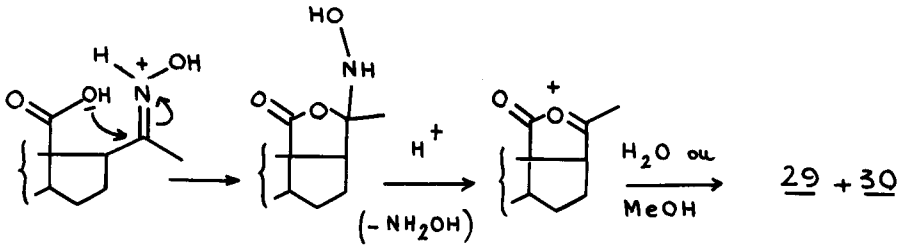


Schéma 21.

La résistance à l'hydrolyse de l'ester d'oxime cyclique **31** est remarquable et signifie que dans les conditions acides utilisées aucune addition d'eau ne s'est faite ni en 18 ni en 20. Il est donc vraisemblable que l'hydrolyse de la fonction oxime en 20 du dérivé **28** est assistée par la fonction acide en 18 (Schéma 21).

Il est à noter qu'en milieu acide aucune réaction de proximité entre la fonction oxime et la fonction acide n'est observée qui aurait pu conduire à une cétonitrone cyclique. La formation d'une telle nitrone a été invoquée pour interpréter l'obtention d'un acide hydroxamique par action du borohydrure de lithium dans le tetrahydrofuranne à reflux sur l'ester oxime **37**[11] (Schéma 22).

Une cyclisation est cependant observée dans l'acide sulfurique concentré qui conduit à un ester cyclique d'oxime **31**. Il s'agit vraisemblablement dans ce cas de la réaction intramoléculaire d'une structure doublement protonée sur le carbonyle et sur l'azote avec isomérisation de la fonction oxime (Schéma 23).

Une autre interprétation faisant intervenir une déviation de la transposition de Beckmann ne paraît pas devoir être retenue (Schéma 24). Le mécanisme de cette transposition est en effet concerté et les intermédiaires décelables correspondent à des produits transposés (nitrilium) ou fragmentés (carbocation).[12]

Si une cyclisation faisant intervenir l'azote de l'oxime n'est pas observée en milieu acide, le Schéma 22 montre qu'elle peut avoir lieu dans d'autres conditions. En fait en présence de cyclohexylcarbodiimide dans le dioxanne[13] l'oxime-acide **28** réagit, dès la température

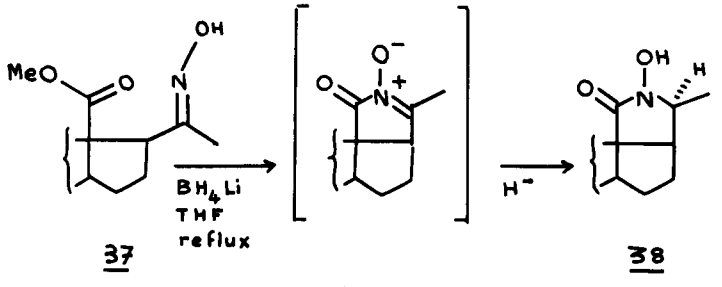


Schéma 22.

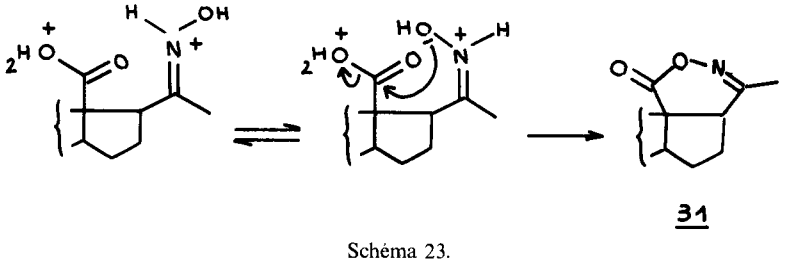
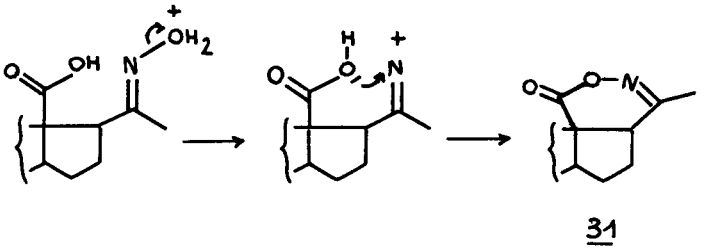


Schéma 23.



31

Schéma 24.

ambiante, mais il se forme un mélange de nombreux produits qui n'ont pu être identifiés. Un résultat analogue est obtenu dans un mélange de dioxanne et d'eau. Il est vraisemblable qu'une céto-nitrone est obtenue dans un premier temps qui évolue ensuite de façon complexe.[14] Une même interprétation permet de rendre compte de l'action de la potasse en milieu hydrométhanolique sur l'ester méthylique obtenu par action du diazométhane sur l'acide **27**. Il se forme également un mélange de produits qui peuvent être attribués à l'évolution complexe d'une céto- nitrone intermédiairement formée, mais qui peut être piégée in situ par réduction selon le Schéma 22.

La réduction de l'ester d'oxime cyclique **31** par le borohydrure de sodium est en rapport avec les données récentes publiées par Ganem[15] sur la réduction de cette fonction qui réagit de façon générale avec les réducteurs nucléophiles par la fonction ester. La réduction très lente de l'hémiacétal formé **33** est vraisemblablement en rapport avec une faible concentration de la structure ouverte en équilibre, seule réductible.

La réduction de l'hémiacétal **33** et de l'aldéhyde **20** conduisent au même alcool-oxime **32** ayant l'hydroxyle de l'oxime en position trans par rapport au squelette stéroïde. Une isomérisation de l'oxime dans ce sens a pu être mise en évidence en laissant l'hémiacétal **33** dans les conditions alcalines de la réduction mais sans le réducteur. Une isomérisation très lente est observée qui conduit après 4 jours principalement à l'hydroxynitrone **3** (59%) accompagné de l'hydroxynitrone **2** (19%) et du produit de départ (17%).

La configuration de l'oxime en **20** s'est donc lentement isomérsée en milieu alcalin (Schéma 25).

En presence de borohydrure cette isomérisation est plus lente que la réduction du carbonyle en 20, la formation de produits résultant de la réduction de l'hydroxynitrone **3** (Schéma 6) n'étant pas observée.

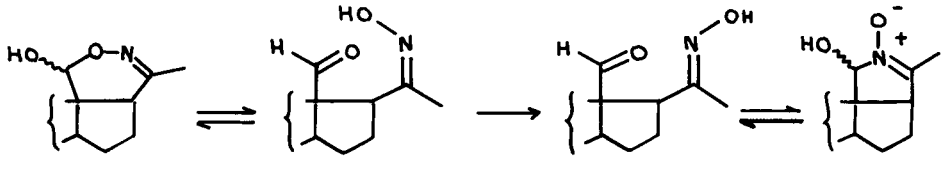
En conclusion les hydroxynitrones stéroïdiques **2** et **3** facilement accessibles à partir de la pyroline **1**, permettent d'accéder á des dérivés du prégnane substitués sur le carbone 18 par une fonction alcool, aldéhyde, acide ou nitrile tout en conservant une fonction carbonyle en 20. Par ailleurs l'hydroxynitrone **3** conduit par réduction à l'hydroxylamine cyclique **7** ou à la nitrone **17** (Schéma 6). La nitrone **6** obtenue avec un faible rendement à partir de l'hydroxynitrone **2** a pu être obtenue, par ailleurs, dans de bonnes conditions par isomérisation de l'oxaziranne **24** obtenu par oxydation de la pyroline **1**.[16]

PARTIE EXPERIMENTALE

Les points de fusion sont pris en tube capillaire et corrigés. Les spectres de masse (SM) sont exprimés en *m/e*. Les spectres IR effectués dans le Nujol, sont exprimés en nombre d'ondes (cm^{-1}). Les pouvoirs rotatoires sont mesurés dans le chloroforme. Les spectres de RMN ^1H sont effectués dans le $CDCl_3$ avec le TMS comme référence interne, les déplacements chimiques étant exprimés en δ et les constantes de couplage en Hertz; les hydrogènes mobiles sont déterminés par deutériation. Les analyses élémentaires ont été déterminées dans le laboratoire de microanalyse du C.N.R.S. Les chromatographies sur couche mince (CCM) sont effectuées sur plaque de gel de silice neutre et révélées par pulvérisation de réactif de Draggendorf puis d'acide sulfurique à 60% suivie de calcination. Les chromatographies sur couche épaisse (CCE) sont effectuées sur plaque de silice (Kieselgel G) en couche d'épaisseur moyenne de 1,5 mm et extraites par un mélange chlorure de méthylène/méthanol 9/1.

Réduction de l'hydroxynitrone **2**: *hydroxyimino*-18 (5α) *pregnanol*-(20*R*) **4**. *Hydroxyimino*-18(5α) *pregnanol*-20(*S*) **5**. *N-Oxy N-demethyl*(5α) *conénine*-20(*N*)**6**. *N-Hydroxy-N-demèthyl* (5α)-*conanine* **7**.

Une solution de 2,994 g (9 mmole) d'hydroxy-nitrone **2** dans 1 l, d'éthanol à 95° est additionnée de 3 g (79 mmole) de borohydrure de sodium. Après 5 h 30 min d'agitation à la température ambiante, l'éthanol est évaporé en partie (300 ml



33 3

Schéma 25.

de volume résiduel). Le milieu dilué à l'eau extrait par un mélange d'éther et de chlorure de méthylène (9/1). Le résidu (3,16 g) est chromatographié sur une colonne de silice. Elution: benzène–ether (98/2) 0.075 g mélange; 0,116 g mélange, la cristallisation dans le méthanol fournit 0,054 g (2%) de **7**; 0,206 g mélange; 1,74 g, **4** (58%); 0,103 mélange; benzène–éther (1/1): 0,468 g, **5**, (15%); chlorure de méthylène-méthanol (98/2), **6** (10%). **7**: F 182–189° (méthanol) fusion sur plusieurs degrés due à une oxydation par l'air de l'hydroxylamine en nitrone au voisinage du point de fusion, $[\alpha]_D^{20}$ + 49° (c = 1,8). Analyse: $C_{21}H_{35}NO$ = 317,50. tr. %. (Calc. %): C, 79,61 (79,44) H, 11,13 (11,11); N, 4,56 (4.41); O, 5,36 (5,04); SM 317 ($M^{+\cdot}$)–IR: 3,200–3,100 (OH); 1,240, 1200, 1050, 920, 800 (forte); RMN: 0,74 s (Me 19); 1,16 d, J = 6 (Me 21 et H-20); 2,46 et 3,21 2*d* = 10 (système AX, $\Delta\delta$ = 0,75, CH_2 18); 6,80 m (OH). **4**: F 167° (acétone/hexane); $[\alpha]_D^{20}$ + 34° (c=0,9). Analyse: $C_{21}H_{35}NO_2$ = 333,50; tr % (Calc.%) C, 75,43 (75,63); H, 10,33 (10,58) N, 4,16 (4,20); O, 9,59 (9,60). SM 333 ($M^{+\cdot}$). IR: 3,300 à 3,100 (OH), 1650 (C=N, faible), 1150, 1110, 1090, 950, 920. RMN: 0,73 *s* (Me 19); 1,11 *d* J = 6 (Me 21); 3,53 *m* (H 20); 7,35 *s* (H 18); 8,9 m (OH). **5**: F 197–198° (acétone-hexane), $[\alpha]_D^{20}$ + 25,2° (c = 1,6). Analyse: $C_{21}H_{35}NO_2$ = 333,50, tr. % (calc. %): C, 75,41 (75,63); H, 10,75 (10,58); N, 4,27 (4,20); O, 9,86 (9,60). SM: 333 (M+·). IR: 3200 et 3100 (OH), 1650 (C=N, faible), 1,200, 1100, 920, 800. RMN: 0,75 *s* (Me 19): 1,16 *d* J = 6 (Me 21); 3,93 *m* (H 20); 7,41 *s* (H 18). **6**: F 197–198° (acétone), $[\alpha]_D^{20}$ + 118,1° 1 (c=1). Analyse: $C_{21}H_{33}NO$ = 315,48 tr. % (Calc. %): C, 79,96 (79,94); H, 10,50 (10,54); N 4,46 (4,44). SM 315 ($M^{+\cdot}$), 299 (M-16), 298 (M-17). 271. UV: λ_{max} 232 nm (ε 9,100). IR: 1640 (nitrone), 1200. RMN: 0.76 *s* (Me 19); 2,01 *s* élargi (Me 21); 3,8 *m* à allure de singulet ($CH_2$18); 2,81 *m* (H 17) (l'allure des signaux correspondant au méthyle 21 et au méthylène 18 est due à des couplages homoallyliques qui ont été mis en évidence avec des dérivés de structure analogue.[17]

Nitrilo 18, *acetoxy*-20 (R) (5α) *prégnane* **8**

Une suspension de 0,200 g d'oxime-alcool **4** dans 3 ml d'anhydride acétique est chauffée à 130° pendant 1 h 30 min. La solution obtenue est évaporée sous vide. Le résidu cristallin, trituré dans l'eau, essoré, lavé, séché sous vide et sur anhydride phosphorique fournit 0,203 g (94% de dérivé **8**. F 169–170° (méthanol), $[\alpha]_D^{20}$ + 11° (c = 2,4). Analyse: $C_{23}H_{35}NO_2$: 357,52 tr. % (calc. %) C, 77,21 (77,26); H 9,48 (9,87); N 3,67 (3,92); O 9,21 (8,95). SM: 357 ($M^{+\cdot}$) 297 (M-60). IR: 2,200 (C≡N), 1720 (CH_3-CO), 1240, 1100, 1080, 1050, 1030, 950, 900, 850.

Nitrile 18, (5α) *pregnanol*-20 (R) **10**

Une solution de 0,350 g de **8** dans 5 ml de méthanol et 2 ml de potasse aqueuse 5N est portée à reflux pendant 2 h. Le milieu, dilué avec de l'eau, fournit 0,300 g (97%) de **10**, cristallisé, qui est isolé par essorage. F 160–161° (acétone–hexane), $[\alpha]_D^{20}$ + 2,1° (c = 1,9). Analyse: $C_{21}H_{33}NO$ = 315,48, tr. % (calc. %): C 79,85 (79,94); H 10,47 (10,54); N 4,47 (4,44). SM = 315° ($M^{+\cdot}$). IR: 3500 à 3300 (large, OH), 2,210 (C≡N), 1300, 1100, 1090, 1050, 940, 860. RMN: 0,80 *s* (Me 19); 1,18 *d* J = 6 (Me 21); 1,7 *s* (OH 20); 4,0 *m* (H 20).

Nitrile-18 *acetoxy*-20 (S) (5α) *prégnane* **9**

Le mode opératoire décrit pour le dérivé **8** (0.200 g de **4**, 3 ml d'anhydride acétique) fournit 0,200 g (94%) de **9**. F 103° (méthanol), $[\alpha]_D^{20}$ + 15° (c = 1,03). Analyse: $C_{23}H_{35}NO_2$ = 357,52 tr. % (calc. %): C 77,42 (77,26); H 9,60 (9,87); N 3,92 (3,92); O 8,96 (8,95). SM: 357 ($M^{+\cdot}$), 297 (M-60). IR: 2,200 (C≡N), 1730 (CH_3-CO), 1230, 1090, 1050 et 1030, 960, 880.

Nitrile-18 (5α) *prégnanol*-20 (S) **11**

Le mode opératoire décrit pour le dérivé **10** (0,350 g de **8**) fournit 0,297 g (97%) de **11**. F 130–132° (acétone–hexane), $[\alpha]_D^{20}$ + 25° (c = 1,1). Analyse: $C_{21}H_{33}NO$ = 315,48 tr. % (calc. %): C 79,87 (79,94); H 10,68 (10,54); N 4,20 (4,44); O 5,49 (5,07). SM: 315 ($M^{+\cdot}$). IR: 3450 à 3300 (large, OH), 2200 (C≡N), 1280, 1190, 1080, 1070, 1050, 940, 860. RMN: 0,80 *s* (Me 19); 1,28 *d*, J = 6 (Me 21); 4,0 *m* (H 20).

Hydroxy-18 (R + S), *oxido*-20 (R), 18 (R + S) (5α) *prégnane* **12**, *hémiacetal du* (5α) *prégnanol*-18 *ol*-20 (R)

Une solution de 0,300 g de **4** dans 20 ml d'acide acétique est additionnée goutte à goutte de 10 ml d'une solution de nitrite de sodium dans l'eau (5%). Après 10 mn d'agitation à la température ambiante le milieu dilué à l'eau fournit 0,283 g (98%) de **12** cristallisé, qui est isolé par essorage. Le produit n'est pas homogène à la CCM (2 taches de R_f voisins). F 155–159°, $[\alpha]_D^{20}$ 30–31° après stabilisation. (C = 1,9 et 2,8). Le pouvoir rotatoire d'une solution, mesuré immédiatement est plus élevé (40–45°) et évolue pendant environ 1 h 30 pour se stabiliser (mutarotation). Analyse: $C_{21}H_{34}O_2$: 318,48 tr. % (calc. %) C 79,03 (79,19); H 10,67 (10,76); O 10,38 (10,05). SM: 318 ($M^{+\cdot}$), 300 (M-18), 272, 257, 243. IR: 3,330 (forte, OH), 1290, 1140, 1160, 1100, 1000, 950, 910, 870. RMN: 0,72 *s* (faible), 0,79 *s* (forte) (2CH_3 à C-19); 1,25 *d* J = 6.5 (fort) 1,29 *d* J = 6.5 faible (2 Me 21); 2,04 signal (OH); 4 *m* (H 20); 5,2 *m* (H-18). Tous les signaux s'affinent après deutériation, le signal à 2,04 disparaissant, le multiplet à 5,2 reste cependant complexe. Le point de fusion est peu net et le pouvoir rotatoire variable au cours du temps sont significatifs de deux structures épimères en équilibre. L'IR ne présente pas de bande carbonyle.

(5α)-*Prégnanol*-20 (R) **13**

Une solution de 0,200 g de **12** dans 2 ml d'éthanol absolu est additionné de 1 ml d'hydrate d'hydrazine, puis portée à reflux pendant 1.5 h. L'éthanol est évaporé sous vide et le résidu est additionné d'une solution de glycolate de sodium (0,4 g de sodium dans 7 ml de glycol), de 1 ml d'hydrate d'hydrazine. Après 20 min à reflux le milieu refroidi et extrait à l'éther fournit 0,192 g de dérivé **13**. F 142–143° (acétone), $[\alpha]_D^{20}$ + 5° (c = 2,6) Litt[5] F 142–143° $[\alpha]_D^{20}$ + 5°.

Les spectres IR du dérivé **13** et d'un échantillon de référence **7** sont identiques.

Réduction par le zinc de la N-hydroxy N-démethyl (5α) *conanine* **7** *N-acétyl-N desméthyl* (5α) *conanine* **15**

Une solution de 0,150 g de **7** (0,47 mmole) dans 5 ml d'éthanol est additionnée de 10 ml d'acide acétique, puis de 2 g de farine de zinc. Le mélange est porté à reflux durant 18 h. Après filtration et lavage du zinc par une solution aqueuse d'acide acétique, le filtrat alcalinisé par l'ammoniaque et extrait à l'éther fournit 0,137 g d'une laque incolore. Celle-ci est dissoute dans 0,5 ml de méthanol additionné de 0,2 ml d'anhydride acétique. Après 18 h à la température ambiante le milieu, dilué à l'eau est extrait à l'éther. Après lavage avec une solution aqueuse d'acide chlorhydrique, puis de carbonate de sodium, puis à l'eau, sont obtenus 0,148 g de dérivé **15**. F 121° (acétone), $[\alpha]_D^{20}$= +56° (c = 1,4). Analyse: $C_{23}H_{37}NO_2$ = 359.59, tr. % (calc. %): C 76,64 (76,83); H 10,59 (10,37); N 3,97 (3,90); O 8,80 (8,90). IR: 1695 (CO–CH_3), 1220, 1100, 950, 920, 850. Le dérivé **15** a été identifié (PF, PF mélangé, $[\alpha]_D$, IR) à un échantillon obtenu par acétylation de la N-desméthylconanine préparée selon Cerny et Sorm à partir de la conessine.[3]

Réduction de l'hydroxynitrone **3**. *N-oxy N-déméthyl* (5α) *conénine* 18 (N) **17**

Une solution de 0,782 g (2,35 mmole) d'hydroxynitrone **3** dans 100 ml d'éthanol à 95° est additionnée de 0,8 g de borohydrure de sodium (~35 éq) et agitée pendant 1.25 h à la température ambiante. Le milieu est dilué à l'eau puis extrait à l'éther. Après traitement on recueille 0,770 g de produit brut qui est chromatographié sur silice. Elution: benzène, 0,201 g, **7** (26%); benzène–chlorure de méthylène (9/1), 0,031 g mélange; chlorure de méthylène, 0,377 g, **17**, (51%). F 182–183°, $[\alpha]_D^{20}$ = −9°84 (c = 2). Analyse: $C_{21}H_{33}NO$ = 315,48 tr. % (calc. %): C 79,83 (79,94) H 10,67 (10,54); N 4,28 (4,44); O 4,95 (5,07). SM 315 ($M^{+\cdot}$) 300 (M-15), 298 (M-17), 270,242. UV (EtOH): λ_{max} 239 nm, ε 10,700. IR 1,580

(forte, nitrone), 1300, 1200, 1080, 950, 800. (dans CCl_4): 1 590, 1450 (nitrone), 1300, 1100, 1050, 930. RMN: 0,77 *s* (Me 19); 1,38 *d* J = 7 ($CH_3$21); 4,4 *m* signal à allure de quintuplet (H 17 couplé au méthyle 21 et à l'H 18); 6,80 *d*, J = 2,5 (H 18).

Si le temps de réaction est prolongé la réduction en hydroxylamine **7** est totale (analyse par CCM). A partir de 3 g d'hydroxy nitrone **3** sont obtenus après cristallisation dans le méthanol, 2,65 g d'hydroxylamine pure (93,6 %). Les eaux mères évaporées à sec (0,160 g) contiennent les nitrones **6** et **17** provenant d'une autoxydation de l'hydroxylamine **7**. Si la réduction est effectuée à la température du bain de glace pendant 5 h, le produit brut obtenu correspond principalement à la nitrone **17**. Une chromatographie sur colonne sèche de silice fournit par élution au benzène: 5 % d'hydroxylamine **7**, 89,5 % de nitrone **17**, 4 % d'hydroxynitrone **3**.

Action du chlorure de benzoyle sur l'hydroxy-nitrone **2** *O-benzoyloximino*-18 (5α) *pregnanone*-20, **18**. -*Nitrile* 18 *pregnanone*-20, **19**

Dans le benzène en présence d'une solution aqueuse acide. Une solution de 0,150 g (0,45 mmole) de **2** dans 7,5 ml de benzène deutérié est agitée au contact de 7,5 ml d'une solution aqueuse d'acide sulfurique 2N et additionnée de 0,06 ml de chlorure de benzoyle (0,5 mmole; 1·1 éq). Le spectre de RMN de la solution benzénique effectué après 30 mn correspond à l'ester d'oxime carbonyle **18** (0,78 *s* Me 19; 1,97 *s* Me **21**; 7,77 *s* H 18; protons aromatiques de 6,93–7,2 et 7,83–8.1. Le spectre de RMN ne contient pas de signaux correspondant au cetonitrile **19** dont l'absence est verifiée par CCM). Aucun changement du spectre de RMN n'est décelé après 20 h. La solution benzénique est décantée et agitée pendant 2.25 h au contact de 10 ml d'une solution aqueuse de soude (5 g/100 ml). La spectre de RMN établit qu'aucune modification n'est intervenue. La solution, lavée et séchée, est évaporée à sec. Le résidu, 0,18 g, correspond au dérivé **18** (91 %), contenant des traces de nitrile **19** (*s* à 1,80 Me 21). Pour $C_{28}H_{37}NO_3$ = 435,58. SM: 435 ($M^{+\cdot}$ faible), 313 (M-122, perte de C_6H_5 COOH). RMN ($CDCl_3$): 0,78 *s* (Me 19); 2.28 *s* (Me 21); 7,96 *s* (H 18); de 7,4 à 7,9 et de 8,2 à 8,5 massif (H aromatiques). RMN (C_6D_6): 0,78 *s* (Me 19); 1,96 *s* (Me 21); 7,76 *s* (H 18).

Une solution benzénique du dérivé **18** brut est chauffée à reflux pendant 5 h. Le résidu après évaporation du benzène (0,187 g) est chromatographié sur couche épaisse de silice neutre (élimination de l'acide benzoïque). L'élution (hexane–ether 1/1) et l'extraction (CH_2Cl_2–MeOH, 98/2) fournissent 0,138 g (97 %) de cétonitrile, **19**. F 142°, $[\alpha]_D^{20}$ + 20° (c = 1,7). Analyse: $C_{21}H_{31}NO$ = 317,47 tr. % (calc. %) C 80,61 (80,45); H 10,02 (9,96); N 4,39 (4,46); O 5,25 (5,10). SM 313 ($M^{+\cdot}$). IR: 2,212 (C≡N), 1706 (C = O). RMN: 0,81 *s* (Me 19); 2,16 *s* (Me 21); dans C_6D_6: 0,75 *s* (Me 19); 1,78 *s* (Me 21).

Ces résultats établissent la présence de la seule forme ouverte **18** en présence d'un acide et la stabilité de cette structure dans un milieu hétérogène acide ou alcalin. Le produit brut contenant des traces de nitrile traité à la température ambiante pendant 1 h par une solution de potasse dans le méthanol (8 g/100 ml) conduit à l'hydroxy-nitrone **2** contenant des traces de nitrile **19**.

Dans le benzène seul et en présence d'une solution aqueuse alcaline. Le produit brut obtenu par action de 1,1 éq. de chlorure de benzoyle est identique à celui obtenu en présence d'une solution aqueuse acide et correspond au dérivé **18** contenant une petite quantité du céto-nitrile **19**. Avant isolement le spectre de RMN du milieu (C_6D_6) montre la présence du seul dérivé ouvert **18** et l'absence du ceto-nitrile **19**.

Action du chlorure de p-toluene sulfonyle sur l'hydroxynitrone **2**

Dans le chloroforme en présence d'une solution aqueuse alcaline. Une solution de 0,112 g (0,34 mmole) de **2** dans 20 ml de chloroforme est additionnée de 0,071 g de chlorure de p-toluène-sulfonyle (0,37 mmole, 1,1 éq) est agitée au contact d'une solution aqueuse de soude (5 g/100 ml). La réaction est suivie par CCM qui ne révèle que la présence de deux dérivés, le produit de départ et le céto-nitrile **19**. Le milieu qui n'évolue plus après 17 h contient toujours les deux produits. Du chlorure de p-toluène sulfonyle est ajouté (1,1 éq). Après 73 h la CCM ne révèle plus qu'une trace du produit de départ. Le produit brut isolé correspond au ceto-nitrile **19** (94 %) contenant une trace d'hydroxy-nitrone **2** (RMN et CCM).

Dans le benzène seul, avec 1,1 éq. de chlorure de p-toluène sulfonyle après 23 h, la RMN du produit brut correspond à un mélange qui contient le ceto-nitrile **19** (0,75 *s* Me 19; 1,78 *s* Me 21), et une structure p-toluène sulfonée. La réaction est poursuivie 47 h sans variation significative du spectre de RMN. Le milieu agité pendant 24 h au contact d'une solution aqueuse de soude (5 g/100 ml) conduit au céto-nitrile **19** (rendement quantitatif).

Action du chlorure de benzoyle sur l'hydroxy-nitrone **3**. *O-benzoyl-oximino*-20 (5α) *prégnanal*-18, **20**

Dans le benzène en présence d'une solution aqueuse alcaline. Une solution de 0,550 g (1,66 mmole) de **3** dans 100 ml de benzène est agitée au contact de 100 ml d'une solution aqueuse de soude (5 g/100 ml) et additionnée de 0,46 ml de chlorure de benzoyle (0,556 g, 3,95 mmole, 2,37 eq). Après 18 h le milieu dilué par un mélange éther–chlorure de méthylène (9/1), lavé, séché et évaporé à sec fournit 0,737 g (quantitatif) de **20**. F 156° (acétone) $[\alpha]_D^{20}$ + 46° (c = 1,08). Analyse: $C_{28}H_{37}NO_3$ = 435,58 tr. % (calc. %): C 77,05 (77,20); H 8,51 (8,56); N 3,47 (3,22); O 10,95 (11,02). SM: 435 ($M^{+\cdot}$), 420 (M-15), 314, 296, 285 (M-150), 270, 244, 229, 105 (pic de base). IR: 1730 (benzoyle), 1700 (H-C=O), 1625 (C=N) 1,265, 1080, 1065, 1020, 905, 705. RMN ($CDCl_3$): 0,71 *s* (Me 19); 2,03 *s* (Me 21); de 2,5 à 2,9 massif (H 17 et 12); de 7,4 à 7,7 *m* (3H aromatiques); de 8 à 8,3 *m* (2H aromatiques); 9,96 *s* (H-C=O). RMN (C_6D_6): 0,60 *s* (Me 19); 1,57 *s* (Me 21); 10,0 *s* (H-C=O). La réaction effectuée en présence d'un excès de chlorure d'acide conduit à un excellent rendement. Un contrôle par CCM montre qu'après 5 min de réaction le produit de départ a pratiquement entièrement réagi. Il est cependant nécessaire de prolonger le temps de réaction jusqu'à destruction du chlorure de benzoyle. Le procédé qui consiste à éliminer le chlorure de benzoyle en excès par complexation avec la pyridine et lavage à l'eau n'est pas applicable dans ce cas. Si la pyridine est ajoutée au milieu en présence de chlorure de benzoyle le produit isolé est l'oxime benzoylée en 18, **18**, bien que le produit effectivement présent avant l'addition de la pyridine soit l'oxime benzoylée en 20, **20**, (contrôle par RMN). Le dérivé **20** est stable en milieu hétérogène alcalin (benzène, H_2O NaOH) pendant plusieurs jours.[6] En milieu alcalin homogène (**20**: 0,104 g, solution de potasse dans le méthanol 8 g/100 ml, 1 h à la température ambiante) il conduit quantitativement à l'hydroxy-nitrone **3**.

Dans le benzène en présence d'une solution aqueuse acide. Une solution de 0,150 g d'hydroxy-nitrone **3** dans 7 ml de C_6D_6 est additionnée de 0,070 g (1,1 éq) de chlorure de benzoyle et agitée au contact d'une solution aqueuse d'acide sulfurique 1 N). Le spectre de RMN de la phase organique établit la présence des deux esters d'oxime **20** (0,60 *s* Me 19; 1,57 *s* Me 21; 10,0 *s* H-C=O) et **18** (0,78 *s* Me 19; 1,96 *s* Me 21; 7,76 *s* H 18) le premier disparaissant progressivement au dépend du second. Après 7 jours le milieu ne contient pratiquement que l'ester d'oxime **18** et le ceto-nitrile **19** est absent. Après dilution à l'éther, lavage avec une solution alcaline, séchage et évaporation le produit brut correspond au dérivé **18** accompagné d'une petite quantité du céto-nitrile **19** et conduit quantitativement à ce dernier par chauffage dans le benzène. Un comportement analogue est observé dans le benzène seul. Après 48 h de réaction en présence de 1,1 éq de chlorure de benzoyle le produit brut isolé contient comme produit principal l'ester d'oxime **18** accompagné de petites quantité de l'ester d'oxime **20** et du céto-nitrile **19**.

Action du chlorure de p-toluène sulfonyle sur l'hydroxy-nitrone **3**

Dans le benzène en présence d'une solution aqueuse alcaline. Une solution de 0,165 g de **3** (0,5 mmole) dans 30 ml

de benzène est agitée au contact d'une solution aqueuse de soude (5 g/100 ml) et additionnée de 0,286 g de chlorure de p-toluène sulfonyle (1,5 mmole, 3 éq). Après 42 h à la température ambiante le milieu, dilué à l'éther, lavé, séché et évaporé conduit à un produit brut (0,256 g) constitué d'un produit principal accompagné de nombreux produits secondaires à l'état de traces (analyse par CCM). Le spectre de RMN du produit brut correspond à celui du produit principal, dérivé de même structure que l'ester d'oxime **20** un groupement p-toluène sulfonyle remplaçant le groupement benzoyle: 0,70 *s* (Me 19); 1,88 *s* (Me 21); 2,42 *s* (Me du groupement p-toluène sulfonyle); 9,50 *s* (H-C=O). Un essai de purification du produit brut par cce (elution CH_2Cl_2–MeOH, 95/5) a conduit à l'isolement de 0,106 g (70 %) de ceto-nitrile **19**.

Dans le benzène seul. L'action de 1,1 eq de chlorure de p-toluène sulfonyle conduit à un mélange dont le spectre de RMN évolue dans le temps pour se stabiliser après 17 h. Le spectre contient alors les signaux caractéristiques du ceto-nitrile **19** (dans C_6D_6: 0,75 *s* Me 19; 1,75 *s* Me 21) et des signaux attribuables à une structure O-toluène sulfonée et à de l'acide p-toluène sulfonique. Agité au contact d'une solution aqueuse de soude (5 g/100 ml) pendant 24 h ce mélange conduit quantitativement au céto-nitrile **19**.

Action du chlorure de benzoyle sur la methoxy-nitrone **21**

Une solution de 0,227 g (0,65 mmol) de **21** dans 10 ml de benzène est additionnée de 0,01 g de chlorure de benzoyle (0,71 mmole, 1,1 éq). Après 4 h d'agitation le produit brut récupéré correspond à l'ester d'oxime **18** (RMN). Chauffé à reflux pendant 2 h 30 dans 20 ml de benzène ce produit conduit à 0,197 g (97 %) de céto-nitrile **19**. Dans le benzène en présence de 1,1 eq de chlorure de benzoyle et de triethylamine la méthoxy-nitrone **21** réagit pour conduire à un mélange complexe dont aucun composé défini n'a pu être isolé.

Action du chlorure de p-toluène sulfonyle sur la méthoxy-nitrone **21**

Dans le chlorure de méthylène en présence d'une solution aqueuse alcaline. Cette réaction précédemment décrite,[2] conduit à un mélange dont est isolé par cce l'oxaziranne **22** (30 %). L'absence du céto-nitrile **19** est constatée.

Dans le chlorure de méthylène seul. L'action de 1,1 eq de chlorure de p-toluène sulfonyle pendant 3 h conduit à un mélange de huit produits (analyse par CCM) qui n'ont pu être séparés. Le spectre de RMN du produit brut après lavage alcalin ne contient pas de signaux pouvant être attribués à un méthyle 21 ou à un groupement OMe.

Benzoyloximino-20 (5α) pregnanoïque 18, **27**

Une solution de 0,664 g de benzoyloxime-aldehyde **20** (1,53 mmole) dans 100 ml d'acétone est portée à reflux et additionnée en deux fois d'une solution aqueuse de MnO_4K (5,2 g/l), 50 ml puis 100 ml après 1 h. Le reflux est arrêté après 2 h et la solution laissée à la température ambiante pendant 16 h. Le précipité d'oxyde de manganèse est essoré et lavé avec de l'acétone à chaud. Le filtrate évaporé à sec laisse un résidu qui est agité en présence d'un mélange éther-chlorure de méthylène (95/5) et d'une solution aqueuse d'acide sulfurique (15 %). La phase organique, après traitement, laisse 0,612 g (89 %) de dérivé **27**. F 235–237 dec, $[\alpha]_D^{20}$+ 4° (c = 0,22). Analyse: $C_{28}H_{37}NO_4$ = 451,58; tr. % (calc. %): C 74,16 (74,47); H 8,26 (8,40); N 2,86 (3,10). IR: 3,180 (large, OH), 1,745 et 1,715 (carbonyles), 1625, 1605, 1590 (bandes faibles-oxime aromatique), 1255, 1245 (forte, ester), 1085, 1070, 1030, 705. RMN: 0,66 *s* (Me 19); 2,0 *s* (Me 21); 8,66 massif (H acide); 7,2 à 7,6 *m*, 7,8 à 8,1 m (H aromatiques).

Le spectre de masse a été effectué sur l'ester méthylique obtenu par action du diazométhane: pour $C_{29}H_{39}O_4N$ = 465,61; SM 465 ($M^{+\cdot}$) (faible), 434 ($M-CH_3O$), 343 (M-PhCOOH).

Oximino-20 (5α) prégnanoïque 18, **28**

Une solution de 0,204 g (0,45 mmole) du benzoyloxime acide **27** dans 20 ml de méthanol est additionnée de 10 ml d'une solution de potasse dans le méthanol (8 g/100 ml). Après 2 h 30 min d'agitation à la température ambiante le milieu, refroidi à 0°, est additionné d'une solution aqueuse d'acide sulfurique à 10 % jusqu'à pH acide. Après élimination du méthanol sous vide, une extraction au chlorure de méthylène fournit 0,193 g (92 %) de dérivé **28**. F: 210–230 dec $[\alpha]_D^{20}$+ 96° (c = 0,37). Analyse: $C_{21}H_{33}NO_3$ = 347,48 tr. % (calc. %) 72,51 (72,58), H 9,42 (9,57), N 3,75 (4,03); O 13,52 (13,81). SM = 347 ($M^{+\cdot}$) 330 (M-OH), 329 ($M-H_2O$). UV (EtOH, 95 %) λ_{max} 255 nm (ε 256). IR ($CHCl_3$): 3,260 (OH), 1690 (-COOH), 1655 (C=N). RMN ^1H: 0,68 *s* (Me 19); 1,98 (Me 21); 11,0 (OH). RMN ^{13}C: 158,0 (C_{20}); 178,9 (C_{18}).

Hydrolyse acide de l'oximino-20 (5α) pregnanoïque 18, **28**

Une suspension de 0,140 g de **28** dans 80 ml de méthanol, additionnée de 40 ml d'une solution aqueuse d'acide sulfurique (2N) est chauffée à reflux pendant 3 h. Le milieu analysé par CCM et RMN contient uniquement l'hydroxylactone **29** et le dérivé méthoxylé **30** décrits ci-après. Après 67 h dans un mélange tetrahydrofuranne eau-acide sulfurique (15/9, 0,75 N) l'hydroxylactone **29** est obtenue quantitativement.

Ethylene dioxy-20, 20 nitrile-18 (5α) pregnane **34**

Une solution de 1,86 g (5,95 mmole) de ceto-nitrile **19** dans 5 ml de glycol est additionnée de 125 ml de benzène anhydre et de 0,250 g de monohydrate de l'acide p-toluènesulfonique Après 4 h distillation du benzène, dont le volume initial est maintenu par addition de benzène anhydre, le milieu est concentré puis agité en présence d'éther et d'une solution aqueuse de carbonate de sodium (10 g/100 ml). La phase éthérée fournit 2,05 g (97 %) de dérivé **34**. F 121–122° (Ethanol aqueux), $[\alpha]_D^{20}$ + 23° (c = 1,6). Analyse: $C_{23}H_{35}NO_2$: 357,52, tr. % (calc. %): C 77,56 (77,26); H 9,81 (9,87); N 3,74 (3,92); O 8,89 (8,95). IR: 2,200 (nitrile), 1250, 1150, 1100, 990, 880.

Ethylenedioxy-20, 20 (5α) pregnanal-18 **35**

Une solution de 2,2 g (57 mmole) d'aluminohydrure de lithium dans 150 ml d'éther anhydre est versée dans une solution de 2,05 g (5,7 mmole) de nitrile-dioxolanne **34** dans 150 ml d'éther anhydre. Après 4 h à la température ambiante sous azote sec le milieu, traité par 300 ml de potasse aqueuse 1 N et extrait à l'éther, fournit 2,011 g de produit brut. Une chromatographie sur alumine hydratée à 6 % fournit 1,581 g (élution à l'hexane-benzène, 1/1) de dérivé **35** (76 %). F 162° (Méthanol), $[\alpha]_D^{20}$ + 51° (c = 1,03). Analyse. $C_{23}H_{36}O_3$ = 360,52, tr. % (calc. %) C 76,88 (76,62); H 10,13 (10,07); O 13,23 (13,31). SM: 360 ($M^{+\cdot}$). IR 1710 (C=O), 1250, 1150, 1050, 960, 880.

Ethylènedioxy-20. 20 (5α) pregnanoïque -18, **36**

Une solution de 0,300 g d'aldehyde dioxolanne **35** dans 30 ml de benzène anhydre, est agitée énergiquement en présence de 2 g d'oxyde d'argent, à la température ambiante, pendant 90 h. Le mélange est filtré sur célite et le filtrat dilué à l'éther (200 ml) lavé plusieurs fois avec une solution aqueuse de cyanure de sodium, puis à l'eau. La phase éthérée fournit 0,237 g (70 %) de dérivé **36**. F 194° (méthanol), $[\alpha]_D^{20}$ + 62° (c = 1,4). Analyse. $C_{21}H_{32}O_3$ = 332,47, tr. % (calc. %): C 75,79 (75,86) H 9,72 (9,70); O 14,49 (14,44). SM: $M^{+\cdot}$ = 332. IR: 3590–3570 (OH), 1680 (C=O), 1380, 1370, 1290, 1260, 1130, 950.

Oxydo-18, 20ξ, prégnanone-18, ol-20ξ, **29**

Une solution de 0,054 g de l'acide-dioxolanne **36** dans 5 ml d'acide acétique et 5 ml d'eau est portée à reflux. Après 1 h 15 min, le milieu refroidi et extrait avec un mélange ether chlorure de méthylène (9/1) fournit 0,038 g (73 %)

d'hydroxylactone **29**. F 193° (benzène), $[\alpha]_D^{20}$ + 20° (c = 1,1). Analyse. $C_{21}H_{32}O_3$ = 332,47; tr.% (calc. %): C 76,01 (75,86); H 9,66 (9,70); O 14,33 (14,44). SM: 332 ($M^{+\cdot}$), 314 (M-18), 298, 243, 67, 55. IR: 3350 (OH), 1750 (lactone), 1200 900, 700. RMN: 0,85 *s* (Me 19); 1,60 *s* (Me 21); 4,6 *m* (OH).

Oxydo-18,20 *méthoxy*-20 (R + S) (5α) *pregnanone*-18 **30**

Une solution de 0,050 g (0,15 mmole) d'hydroxylactone **29**, dans 5 ml de méthanol, refroidie à 0° additionnée de 0,05 ml d'acide sulfurique concentré est agitée à la température ambiante Après 12 h le milieu dilué à l'eau, alcalinisé avec de la soude à 5% et extrait avec un mélange éther/chlorure de méthylène (9/1) fournit 0,043 g (88%) du mélange des deux épimères 20-méthoxylés **30** dont l'un est très largemenent majoritaire. F 137–138° (acétone). $[\alpha]_D^{20}$+ 31,5°. Analyse: $C_{22}H_{34}O_3$ = 346,49 tr.% (calc. %) C 75,97 (76,26); H 10,03 (9,89); O 13,69 (13,85). SM: 346 ($M^{+\cdot}$). IR: 1770 (C=O), 1280, 1200, 1110 (bandes C-O), 880, 740. RMN: 0,93 *s* (Me 19); 1,50 *s* (Me 21); 3,30 *s* (OMe), 3,43 *s* (faible, OMe d'un épimère en 20).

Nor-18 (5α) *androstano* [17,13-d] *méthyl*-3' *dihydro*-4',5' *oxo*-6 [1,2] *oxazine* **31**

L'oxime-acide **28** est dissous dans de l'acide sulfurique concentré (10 ml) refroidi à 0°. Après 20 min le milieu versé sur de la glace, alcalinisé avec une solution de soude à 5% et extrait au chlorure de méthylène fournit 0,107 g (73%) de dérivé **31**. F 214° (acétone), $[\alpha]_D^{20}$ = 12° (c = 0,12). Analyse: $C_{21}H_{31}NO_2$ = 329,46 tr.% (calc. %): C 76,24 (76,55); H 9,31 (9,48); N 4,49 (4,25), O 9,56 (9,71). SM 329 ($M^{+\cdot}$), 314, 301 (M-CO), 284 (pic de base, M-CO-OH). IR: 1750 (C=O), 1625 (C=N). RMN ^{1}H: 0,83 *s* (Me 19); 2,07 (Me 21). RMN ^{13}C 163,9 (C_{20}) 171,9 (C_{18}).

Nor-18 (5α) *androstano* [17,13-d] *méthyl*-3' *dihydro*-4',5' *hydroxy* 6'ξ [1,2) *oxazine*, **33**

Une solution de 0,318 g (0,96 mmole) d'ester d'oxime cyclique **31** dans 150 ml d'éthanol à 95° est additionnée de 0,318 g (8,4 mmole) de borohydrure de sodium. Après 6 h d'agitation, le milieu dilué à l'eau et extrait à l'éther fournit 0,320 g d'un mélange qui séparé par cce (élution, chlorure de methylène) fournit 0,197 g (59,5%) de dérivé **33** et 0,048 g de produit de départ **31**. **33**: F 208–210° (acétone), $[\alpha]_D^{20}$ + 60° (c = 0,18). Analyse: $C_{21}H_{33}NO_2$ = 331,47 tr.% (calc. %): C 75,94 (76,09); H 9,87 (10,03); N 4,37 (4,23); O 9,87 (9,65). SM: 331 ($M^{+\cdot}$) IR: 3,400 (OH) 1622 (C=N). RMN: 0,80 *s* (Me 19); 2,0 *s* (Me 21) 4,3 signal (OH); 5,42 *s* (s'affine après deutériation (H-18)).

Hydroxy-18 *oximino*-20 (5α) *prégnane* **32**

A partir de l'aldéhyde-ester d'oxime **20**. Une solution de 0,091 g de **20** dans 200 ml d'éthanol à 95° est additionnée de 0,096 g de borohydrure de sodium. Après 3 h d'agitation à la température ambiante, le milieu, après évaporation de l'éthanol sous vide est additionné d'eau. Une extraction au chlorure de méthylène fournit 0,070 g (100%) d'oxime-alcool **32**. F 229–231° (acétone), $[\alpha]_D^{20}$ + 44° (c = 0,05). Analyse. $C_{21}H_{35}NO_2$ = 333,50 tr.% (calc. %) C 75,50 (75,63); H 10,27 (10,58), N 4,22 (4,20); O 9,66 (9,60). SM: 334 ($M^{+\cdot}$), 316 (M-18), 301 (M-33). IR: 3125 (OH), 1652 (faible, oxime), 1247, 1219, 1053, 1042, 1031, 985 (N-O). RMN: 0,78 *s* (Me 19); 1,88 *s* (Me 21); 3,53 *s* élargi (CH_2 18).

A partir du dérivé hémiacétalique **33**. Une solution de 0,100 g de dérivé **33** dans 50 ml d'éthanol à 95° est additionnée de 0,100 g de borohydrure de sodium. Après 72 h d'agitation à la température ambiante, l'éthanol est évaporé sous vide et le milieu est additionné d'eau. L'extraction au chlorure de méthylène fournit 0,113 g d'un mélange de l'oxime-alcool **32** et de produit de départ **33** (environ à parties égales par examen de spectre de RMN). Une cristallisation dans l'acétone fournit 0,041 g d'oxime-alcool **32**. F 226–228°, $[\alpha]_D^{20}$ + 42° (c = 0,13). F mélangée avec le dérivé précédent F 228–230°.

Isomérisation en milieu alcalin de l'hémiacetal **33**

Une solution de 0,095 g de dérivé **33** dans 35 ml de méthanol est additionnée de 15 ml d'une solution aqueuse de soude 3,3N. Après 106 h le méthanol est éliminé sous vide. Le milieu, dilué à l'eau est extrait au chlorure de méthylène. Le produit brut 0,095 g fournit par cce (elution par un mélange méthanol/chlorure de méthylène 5/95) 0,056 g (59%) d'hydroxynitrone **3**, 0,019 g (20%) d'hydroxynitrone **2** et 0,016 g (17%) de produit de départ.

Remerciements—Nous remercions le Prof. D. H. R. Barton pour une lecture critique du manuscrit, ainsi que le Prof. A. Cave qui nous a aimablement confié un échantillon de (5α) prégnanol-20 (R).

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Tetrahedron, Vol. 37. Supplement No. 1, pp. 55 to 59
Printed in Great Britain.

0040-4020/81/Suppl. 1—0055-05 $02.00/0
Pergamon Press Ltd.

THERMAL REARRANGEMENTS OF TRICYCLO[4.2.2.0^{2,5}]DECATRIENE DERIVATIVES

I. G. DINULESCU, E. G. GEORGESCU, LYGIA STĂNESCU and MARGARET AVRAM*
Center of Organic Chemistry, Spl. Independenţei 202 B, 78100 Bucharest 12, Romania

(*Received in UK* 20 *June* 1980)

Abstract—The behaviour of tricyclodecatriene derivatives **1** and **8** in short-time and/or static thermolysis was investigated. The intermediate **8** in the transformation of **1** in naphthalene derivatives and the reversible rearrangement **1** ⇄ **8** were evidenced. Some mechanistic aspects of **1** or **8** rearrangement into naphthalene derivatives are discussed.

The application of the concept of orbital symmetry to the interpretation of the concerted reactions—a fundamental contribution to chemical theory due to Woodward and Hoffmann[1]—has stimulated the investigation of the thermal and photochemical interconversions of the $(CH)_n$ hydrocarbons. Among $(CH)_n$ hydrocarbons, the $(CH)_{10}$ valence isomer with tricyclo[4.2.2.0^{2,5}]deca-3,7,9-triene skeleton, namely Nenitzescu's hydrocarbon,[2] as well as its benzo and dibenzo derivatives, have received considerable attention.[3]

There are, however, few data concerning the mechanism of the rearrangement of 7,8-dicarbomethoxy-tricyclo [4.2.2.02.5]deca-3,7,9-triene (**1**),[4] the first compound of the series to have been converted into naphthalene derivatives.[2b,5]

The mechanism by which **1** rearranges to naphthalene derivatives **2**–**4**, proposed by C. D. Nenitzescu,[2b,5] involves the following key steps: (a) *anti* → *syn* rearrangement of cyclobutene ring and formation of tricyclo[4.4.0.0^{2,5}]decatriene **5**; (b) rearrangement of **5** to a [10]annulene **6**: (c) rearrangement of [10]annulene **6** to 9,10-dihydronaphthalene **7**; (d) transformation of **7** in the naphthalene **4** and dihydroderivatives, for which the structures **2** and **3** were established.[6]

The mechanistic hypothesis accounted for the unexpected rearrangement during which the two COOR groups change from vicinal positions in the starting compound (**1**) to the distant positions in the final products (**2**–**4**).

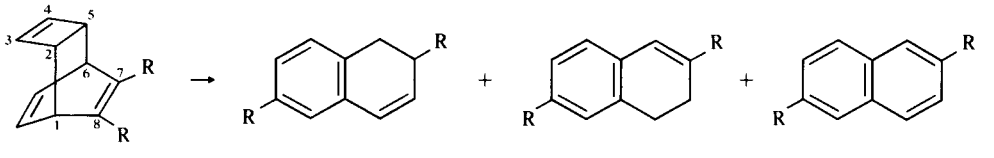
Although the key steps of the process were correctly formulated, the proposed configurations as well as the mechanistic details are somewhat different from those expected on the basis of modern chemical concepts.[1]

In order to gain some insight into the mechanism, we tried to detect unstable intermediates and to establish whether the compounds previously isolated (in the thermolysis of **1** in static system) are primary products or are formed in subsequent reactions. The thermolysis of **1** was therefore reinvestigated. Two experimental techniques were adopted: the short-time thermolysis and the thermolysis in a static system.

The preliminary thermolysis of **1** using both techniques revealed a new reactive intermediate **8**, together with the earlier described[5,6] ones, **2**, **3** and **4**, as well as two new products, **9** and **10**.

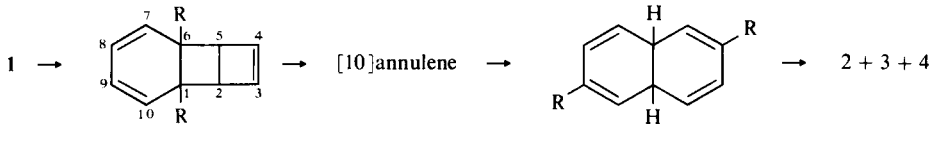
The intermediate **8** was isolated in a pure state by preparative glc; the starting material was a mixture (**1** 70% and **8** 30%) resulting from distillation of crude **1** on a very efficient column. Large amounts of **8** were prepared by treating the mixture of **1** and **8** with bis-benzonitrile · $PdCl_2$ (BNP) and removing the instantly formed **1** · $PdCl_2$ complex.[7]

The structure and configuration of **8** were based on spectral data and chemical behaviour.



1 **2** **3** **4**

R = $COOCH_3$



5 **6** **7**

The spectral data (Table 1) correspond to a structure involving five olefinic protons (but two of them are non-equivalent cyclobutenic protons), three saturated protons and two different carbomethoxy groups (one of them included in a α,β-unsaturated system).

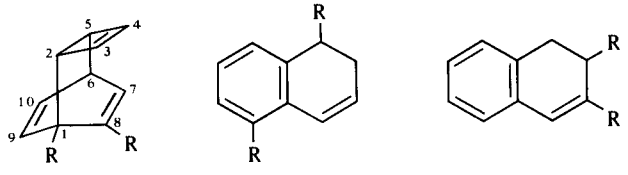
Among the 12 valence isomers which could be formed by Cope rearrangements of **1**, only 1,8-dicarbomethoxy-*syn*-tricyclo[4.2.2.0^{2,5}]deca-3,7,9-triene is acceptable as **8** and supported by its chemical behaviour which is characteristic of tricyclo[4.2.2.0^{2,5}] decadiene and triene derivatives. The treatment of **8** with BNP affords the complex **8**·$PdCl_2$ (**11**). **8** was regenerated from **11** by stirring with 20% aqueous NaCN.

Alternatively, by reducing the carbomethoxy groups with $LiAlD_4$ and acetylating the diol formed (**12**) with $(CD_3CO)_2O$, the bis-deuterioacetyl derivative **13** was prepared. The spectral parameters of **12** and **13**, shown in Table 2, confirm the proposed structure of **8**.

One should note the *exo–cis* addition of deuterium to the 7,8 double bond, which is reflected in the *endo* configuration of H-7 (unshielded by the neighbouring cyclobutene double bond) and of the 8-acetoxymethyl-d_5 group (H-3 and H-4 are magnetically equivalent).

In order to obtain more information on the conversion of **1** to **8** and to elucidate the role of **8** in the thermal transformation of **1** to naphthalene derivatives, the thermal behaviour of **1** and **8** over a broad range of temperature and thermolysis time was investigated.

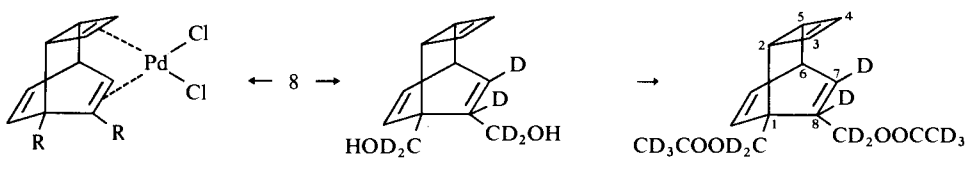
The short-time thermolysis was carried out between 200° and 400°; below 200° there is no significant transformation. The results of the short-time thermolysis of **1** and **8** show that the thermolysis of **1** leads to significant amounts of **8**, while **8** undergoes isomerization to **1**. The maximum amount of isomerization (nearly 25%) is reached at 350°. Above this temperature, **1** and **8** rapidly decay to naphthalene derivatives. The observed reversible isomerization



8 **9** **10**

Table 1. Spectral parameters of **8**

IR (CCl_4) cm^{-1}	1723 (α,β-unsaturated ester), 1740 (saturated ester) 1590, 1612 (C=C)			
NMR (C_6D_6, δ, ppm)	olefinic H		saturated H	$COOCH_3$
	5.87, 6.37 system AB (H-3, H-4)	6.14 (t, H-10) 6.70 (d, H-9) 6.98 (d, H-7)	2.44 (t, H-5) 2.88 (d, H-2) 3.20-3.70 m (H-6 covered)	3.88 s 3.70 s
	coupling (J, Hz): $J_{9.10}$=7.0; $J_{6.10}$=$J_{6.7}$=6.5; $J_{2.5}$=$J_{5.6}$=4.0			
UV (EtOH)	λ_{max} 223.4 nm (ε=3366) (α,β-unsaturated carbonyl)			



11 **12** **13**

Table 2. Spectral parameters of products obtained by reduction of **8**

	H-3 H-4	H-9	H-10	H-2	H-5	H-6	H-7	IR
12	6.03 s	5.80 - 6.50 m		2.20 d	2.53 t	3.20 m	1.95 d	3575 (OH) 3620
13	6.13 s	6.20 dd	6.50 dd	2.40 d	2.60 t	3.33 m	2.00 d	1718 (CO)
	$J_{6.7}$=$J_{2.5}$=4.0, $J_{5.6}$=3.5, $J_{9.10}$=6.0, $J_{6.9}$=1.5, $J_{6.10}$=7.5							

Table 3. The thermolysis of esters **1** and **8**

	Products (% moles)							
	phthalic ester	esters		naphthalene derivatives				
		8	**1**	**10**	**9**	**2**	**3**	**4**
	The short-time thermolysis of ester **1**							
200°	0.6	4.3	90.9					
250	0.7	5.0	90.0					
300	0.8	10.3	85.0		0.6	0.1		0.1
350	1.0	26.5	55.8	0.1	1.8	4.9	2.9	1.0
400	1.8	8.6	12.0	0.7	7.4	28.4	17.4	2.0
	The short-time thermolysis of ester **8**							
200°	0.4	92.6	2.0					
250	1.3	92.4	1.7			0.1		0.1
300	1.4	79.7	7.5	1.3	1.3	2.3	1.3	0.9
350	1.6	29.4	27.3	2.5	1.8	16.4	9.9	3.7
400	2.2	4.5	9.0	2.8	6.2	34.2	21.8	3.8
	The static thermolysis of ester **1** at 250°							
0 min		3.9	96.1					
2.5	4.3	28.0	52.0	1.0	1.2	6.4	4.0	3.1
5	9.7	23.9	38.2	1.3	1.4	6.9	7.9	7.7
10	15.7	11.0	15.0	2.3	2.6	16.4	16.9	17.6
20	23.7	4.9	6.7	2.5	2.3	14.8	19.7	25.5
30	26.1	2.3	2.9	3.0	1.7	9.9	17.4	34.6
60	29.7	0.4	1.1	3.1	1.1	3.4	15.2	42.8
120	29.7			3.2	0.8	0.1	8.8	55.0
	The static thermolysis of ester **8** at 250°							
0 min		99.0	1.0					
3	11.5	21.8	24.1	1.0	1.9	18.9	14.4	6.4
5	15.4	11.5	13.5	1.1	2.9	25.1	20.2	9.5
10	16.3	5.9	7.8	1.9	3.0	28.6	23.6	11.8
20	19.2	0.6	2.1	3.9	3.2	27.7	25.7	16.9
25	20.0		1.0	4.0	3.2	25.1	25.9	19.6

1 ⇄ **8** was proved by separation of both components.

Other important observations are the formation of naphthalene compounds above 300° and the fact that the major components are the dihydro derivatives **2** and **3**.

The thermolysis of **1** and **8** was carried out in a static system at 150°, 200° and 250°. The results obtained at 250° (where the reaction is more significant) indicate that the maximum of interconversion **1** ⇄ **8** is reached after 2.5–3 min of heating.

Concerning the distribution of naphthalene derivatives, the results clearly indicate that the primary products are the dihydro derivatives **2** and **3**; a subsequent step (experimentally proved) involves the dehydrogenation of **2** and **3** (easier for the former compound), leading to the stable derivative **4**.

DISCUSSION

The conversion of **1** to naphthalene compounds is a multistep process. Experimental results show that the isomerization of **1** and **8** take place in two ranges of temperature. The formation of isomeric esters **8** and **1**, respectively, predominate and that of naphthalene compounds is not significant at lower temperatures. The latter derivatives become the main products over a critical range of temperature (300–350°). For this reason, two series of reactions can be considered.

(a) The interconversion of **1** and **8** involves the reversible change of the *anti* cyclobutene ring orientation in **1** to *syn* in **8**.

Since the interconversion **1** ⇄ **8** occurs at relatively low temperature, and no other major products could be found, we assume that a concerted reaction takes place, involving [3.3]sigmatropic (Cope) rearrangement,[1,8–10] governed by the conservation of orbital symmetry rules. The demonstration of the reversible isomerization **1** ⇄ **8**, for the first time proved in the $(CH)_{10}$ series by direct isolation of the isomers, is a decisive argument in favour of this reaction route.

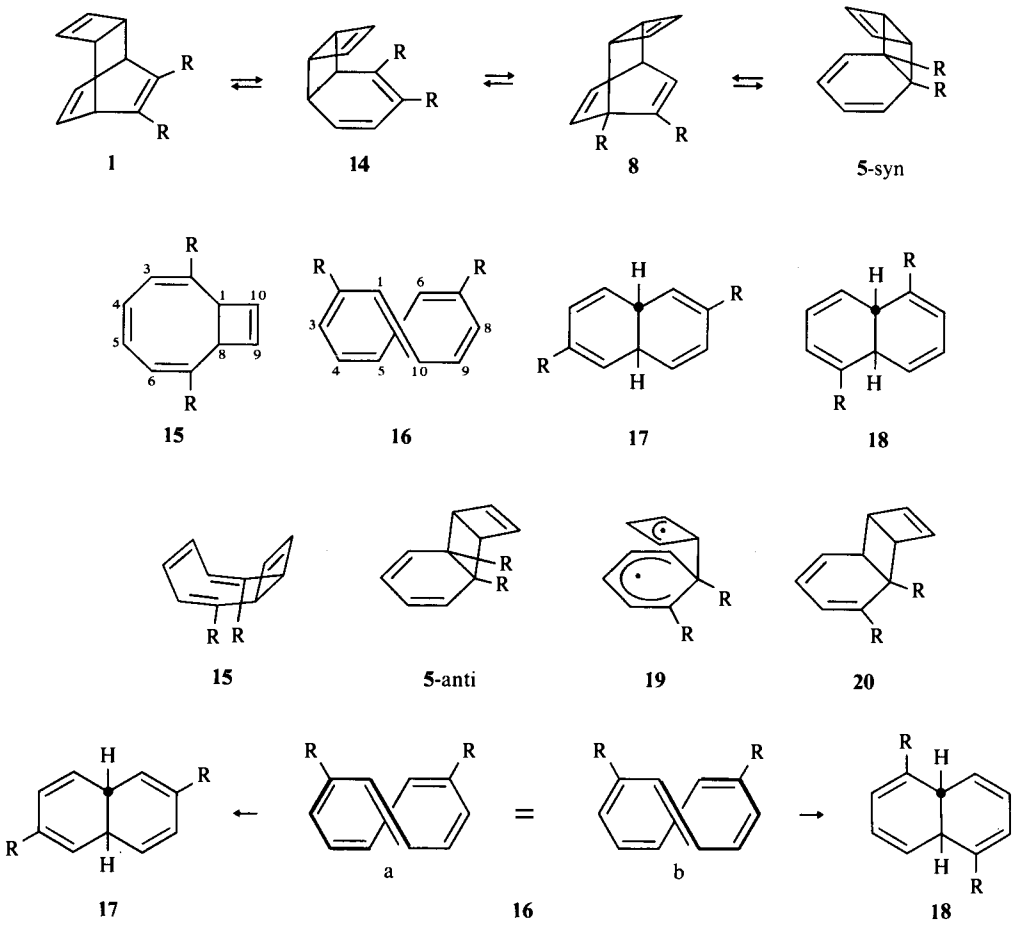
In this interpretation, the esters **1** and **8** are thermally equilibrated with tricyclo[4.4.0.0^{2,5}]decatriene valence isomers **14** and **5**-*syn*, the latter[2b,5] having been earlier proposed as key intermediate in the conversion of **1** to naphthalene derivatives.

The failure to detect the intermediates **14** and **5**-*syn* is undoubtedly due to the greater thermal stability of [4.2.2.0^{2,5}] systems as compared to [4.4.0.0^{2,5}] systems.[9,10]

(b) For the further isomerization of **5**-*syn* into naphthalene compounds, only hypothetical mechanistic aspects can be taken into account.

A disrotatory, thermally forbidden, cyclobutene ring opening of **5**-*syn* to 9,10-dicarbomethoxy-*cis*-9,10-dihydronaphthalene can be *a priori* excluded on theoretical as well as experimental grounds; studies concerning the thermal behaviour of the latter compound[11] show a different distribution of naphthalene derivatives from that observed in the thermolysis of **1** and **8**.

The formation of dihydronaphthalenes **2**, **3** and **9** as final products supports the formation of *trans*-9,10-dihydronaphthalene derivatives as intermediates. For this reason, the following intermediates were considered to be involved: **15**, **16**, **17** and **18**.

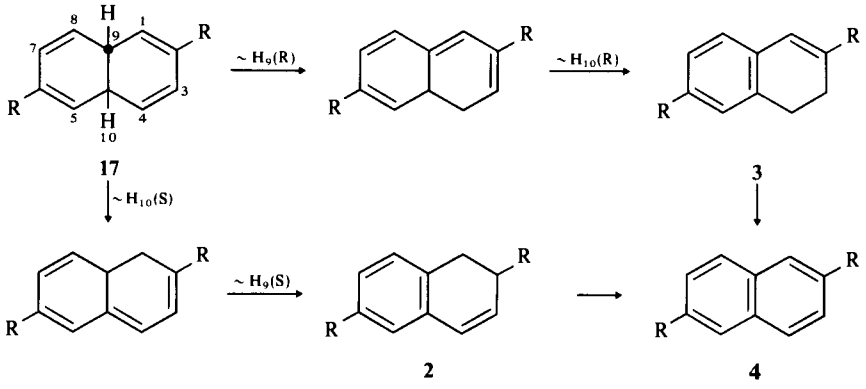


Electrocyclic or homolytic ring opening of **5**-*syn* involving the bond between the two carbomethoxy groups,[12] leading to **15**, may be favoured by the presence and vicinal position of these groups.

The 1,2 bond cleavage leading to the free rotating diradical **19**, although less favoured, could take place in minor amounts. Reclosure of **19** to **5**-*anti* seems to be sterically hindered by the vecinity of carbomethoxy groups; reclosure to **20** could explain the small quantities (less than 5 %) of **10** observed, but **10** could be formed also from **14**.

Furthermore, **15** undergoes a thermally allowed electrocyclic conrotatory opening process to *trans–cis*[4]-cyclodecapentaene (**16**). In the latter, there are two possibilities of transannular ring closure in a disrotatory process. Both involve hexatriene systems having in common the *trans*-1,10 double bond. The experimental evidence that the closure of the hexatriene system unsubstituted at the terminal double bond (**16a**), namely that leading to 2,6-disubstituted *trans*-9,10-dihydronaphthalene **17**, is prefered.

A consecutive [1.5]sigmatropic suprafacial hydrogen migration[13] in **17** and **18** explains the formation of dihydro derivatives **2**, **3** and **9**, respectively, as primary products of thermolysis. These compounds undergo further aromatization only at higher temperature or after prolonged heating.



EXPERIMENTAL

All m.ps and b.ps are uncorrected. IR spectra were obtained with a Jena UR 20 spectrometer. UV spectra were taken with a Jena Specord spectrophotometer. ^{1}H NMR spectra were measured with a Varian A-60A instrument, with signals reported to internal TMS, δ 0.00 ppm; coupling constants given in Hz. Glc analysis were carried out on a Carlo Erba 2450 chromatograph, equipped with a flame ionization detector, using a 2 m × 3 mm of 10% QFl on Gas Chrom Q glass column; carrier gas: nitrogen, 30 ml/min. Preparative glc were carried out on a Carlo Erba GV chromatograph, equipped with catharometer, using a 2 m × 10 mm of 20% QFl on Chromosorb W column; detector temp 200°; carrier gas: hydrogen, 300 ml/min.

Starting material. Compound **1** was prepared from cyclooctatetraene and dimethyl acetylenedicarboxylate, using a procedure similar to that developed by Reppe.[4] NMR (C_6D_6): 2.61 (bs, H-1, H-6), 3.55–3.90 (bs, H-2, H-5), 3.51 (s, two carbomethoxy groups), 5.84 (s, H-3, H-4), 5.95 (m, H-9, H-10).

Static thermolysis of **1**. The ester **1** was heated at 330° for 5 min; from the product (composition: **1** 0.5–1.5%, **8** 0.4–0.5%, **10** 2.4–3.7%, **9** 1.8–2.4%, **2** 9.0–12.0%, **3** 18.7–23.7%, **4** 30.0–39.5%) the naphthalene derivatives **2**, **3**, **4**, **9** and **10** were obtained by preparative glc.

2,3-*Dicarbomethoxy*-1,2-*dihydronaphthalene* (**10**). NMR ($CDCl_3$): 3.30 (m, H-1), 3.50–4.00 (m, H-1, H-2 and two groups $COOCH_3$ which appear as singlets at 3.60 and 3.83), 7.21 (s, 4 aromatic H), 7.64 (s, H-4).

1,5-*Dicarbomethoxy*-1,2-*dihydronaphthalene* (**9**). NMR ($CDCl_3$): 3.20–3.80 (m, H-1, 2H-2), 3.73 and 3.91 (s, two $COOCH_3$ groups), 6.11 and 6.55 (2bd, H-3, H-4, $J_{3,4}$ = 10.0), 7.25–8.15 (m, 3 aromatic H).

2,6-*Dicarbomethoxy*-1,2-*dihydronaphthalene* (**2**). M.p. 75°; NMR (CCl_4): 2.90–3.55 (m, 2H-1, H-2), 3.70 and 3.85 (s, two $COOCH_3$ groups), 6.08 (dd, H-3, $J_{2,3}$ = 2.5, $J_{3,4}$ = 10.0), 6.56 (dd, H-4, $J_{2,4}$ = 1.5, $J_{3,4}$ = 10.0), 7.15 (d, H-8, $J_{7,8}$ = 7.0), 7.60–7.90 (m, H-5, H-7).

2,6-*Dicarbomethoxy*-3,4-*dihydronaphthalene* (**3**). M.p. 126°; NMR (CCl_4): 2.40–3.20 (m, 2H-3, 2H-4), 3.81 and 3.90 (s, two $COOCH_3$ groups), 7.21 (d, H-8, $J_{7,8}$ = 8.0), 7.48 (s, H-1), 7.75–8.00 (m, H-5, H-7).

2,6-*Dicarbomethoxy-naphthalene* (**4**). M.p. 188°; NMR ($CDCl_3$): 4.03 (s, two $COOCH_3$ groups), 8.11 (s, H-3, H-4, H-7, H-8), 8.65 (s, H-1, H-5).

Thermolysis experiments. The static thermolysis technique consisted of heating the compound to the desired temperature for a definite time. The short-time thermolysis technique used a modified vaporizer of a Carlo Erba 5460 gas chromatograph, heated at the desired temp. Time of pyrolysis was about 0.75 sec. The method allows direct analysis of the products (carrier gas: argon; the above described column was heated at 180°). The products formed in both types of thermolysis of **1** and **8** are presented in Table 3.

1,8-*Dicarbomethoxy*-syn-*tricyclo* [4.2.2.0^{2,5}]-*deca*-3,7,9-*triene* (**8**). Distillation *in vacuo* of the crude starting material on a spinning band column Normag–Wingler–Fritz, afforded a fraction with b.p. 153–158°/4 mm, containing (glc) 70% **1** and 30% **8**. Pure **8** was isolated by preparative glc. IR, NMR and UV data are shown in Table 1.

A preparative route to **8**. Bis-benzonitrile · $PdCl_2$ (6.0 g, 15.6 mmoles) was dissolved in 250 ml benzene and 5.0 g of the above fraction (containing 3.5 g, 14.2 mmoles, **1** and 1.5 g, 6.1 mmoles, **8**) were added. The mixture was allowed to stand at room temp for 24 hr, and the yellow crystalline ppt of **1** · $PdCl_2$ was filtered off and washed with benzene. The solvent was removed *in vacuo* and the oily residue was dissolved in petroleum ether–ether (3:1) and chromatographed on alumina Grade II. The colourless soln was evaporated and the residue heated at 70°/1 mm until all benzonitrile was removed; 1.1–1.2 g (73–80%) **8** were obtained.

The complex of **8** *with* $PdCl_2$ (**11**). A soln of 0.50 g (2 mmoles) **8** in 2 ml benzene was treated with a soln of 0.85 g (2.2 mmoles) BNP in 40 ml benzene, and the mixture allowed to stand for 48 hr at room temp. The yellow–orange crystals were filtered off and washed with 3 ml benzene, yielding 0.35 g (41%) complex **11**, m.p. 205° (dec); IR (KBr): 1630, 1410, 1486 (complexed C=C), 1728, 1740 (C=O) cm^{-1}. (Found: C, 40.31; H, 3.43; Cl, 15.14; Pd, 25.24. Calc. for $C_{14}H_{12}Cl_2O_4Pd$: C, 39.89; H, 2.87; Cl, 16.82; Pd, 25.24%.)

The complex **11** treated with an aqueous soln of KCN yielded **8** in a 80% yield.

1,endo-8-*Di*-(*acetoxymethyl*-d_5)-exo-cis-7,8-*dideuterio-tricyclo*[4.2.2.0^{2,5}]*deca*-3,9-*diene* (**13**). The reduction of **8** with $LiAlD_4$ afforded the dihydroxy-derivative **12** in a 80% yield. Crude **12** treated with perdeuterioacetanhydride, in presence of catalytic amounts of pyridine, afforded **13** in a 80% yield. Spectral properties are shown in Table 2.

Acknowledgement—We are indebted to Dr. Ing. M. Elian for helpful discussions.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 61 to 71, 1981
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0040-4020/81/Suppl. 1-0061-11 $02.00/0
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SYNTHESE TOTALE DES C-NOR D-HOMOSTEROIDES†—III‡

ERIC BROWN* et MICHEL RAGAULT

Laboratoire de Synthèse Organique, E.R.A. n° 07.0394, Faculté des Sciences, Route de Laval, B.P. 535, 72017 Le Mans, France

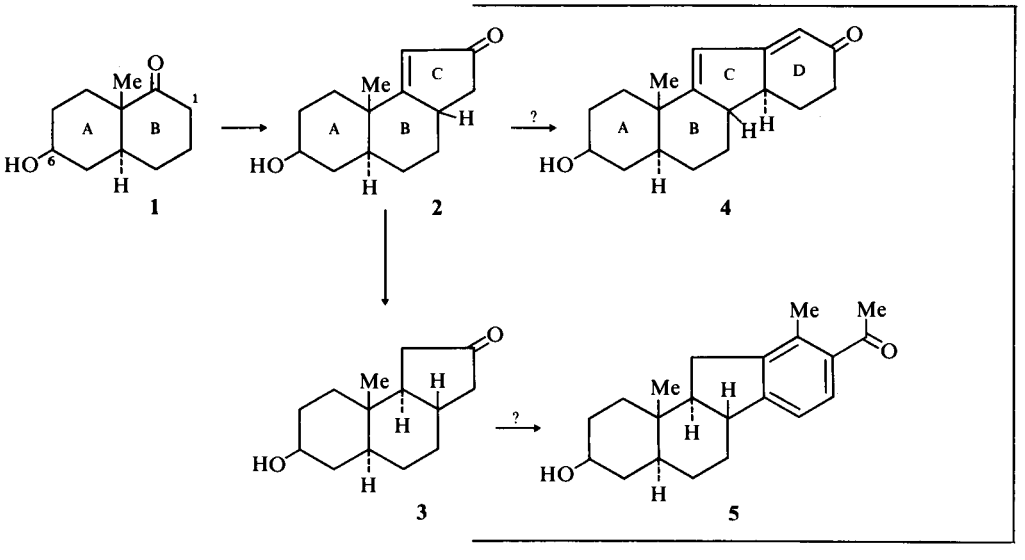
(*Received in France* 23 *June* 1980)

Résumé—Nous décrivons la synthèse totale du C-nor D-homostéroïde connu **4** (qui présente la configuration naturelle), en onze étapes à partir de la cétone de Wieland et Miescher **6**, et selon un schéma original du type A → B → C → D. Le composé **4** est un intermédiaire dans la synthèse totale de la vérarine par Kutney.

Abstract—We describe the total synthesis of the known C-nor D-homosteroid compound **4** (of natural configuration), in eleven steps from the Wieland–Miescher ketone **6**, and following an original scheme of the A → B → C → D type. Compound **4** was an intermediate in Kutney's total synthesis of verarine.

Nous nous sommes proposé d'étudier une nouvelle voie d'accès aux C-nor D-homostéroïdes, selon un schéma de synthèse linéaire du type A → B → C → D, et dont les intermédiaires principaux sont représentés ci-aprés. L'intérêt de cette séquence réside dans le fait que les composés tétracycliques **4** et **5** ont été utilisés comme relais, respectivement par Kutney[1] et Johnson,[2] dans leurs synthèses totales de la vérarine, de la vératramine et des composés apparentés.

laborieuse. En ce qui nous concerne, nous avons réalisé l'acétalisation du carbonyle en 1 de la cétone de Wieland et Miescher **6**,[4] en contrôlant soigneusement la quantité d'eau produite, ce qui a fourni uniquement le monocétal **7**.[5,6] La réduction de Birch, effectuée sur le monocétal **7**,[7,8] conduit au composé de réduction **8** qui est trans et que nous avons obtenu à l'état cristallisé (F = 34,5–37°), bien qu'il ait été décrit comme un liquide par Prelog.[3]



Construction du système tricyclique ABC: synthèses des hydrobenz(e)indénones-2 **2** *et* **33–36**

Par réduction microbiologique de la (±) *trans* décalinedione-1,6 **9**, Prelog et Zach[3] ont obtenu l'énantiomère (6S, 8aS) du cétol *trans* **1** en très faibles quantités, mélangé avec d'autres produits de réduction et n'ont pu l'isoler qu'après une séparation longue et

Pour nous assurer de la stéréochimie au niveau de la jonction des cycles, nous avons préparé l'isomère *cis* **10** du composé **8**, par hydrogénation catalytique du monocétal **7**. Après recristallisation, le monocétal décrit **10** ainsi obtenu fond à 51–52,5°, alors que la littérature[6] indique un F = 54–54,5°. Les points de fusion nettement distincts des isomères **8** et **10**, et le fait que leur mélange soit *liquide* à température ambiante, montrent qu'il s'agit bien de deux composés différents.

Par action d'un excès de borohydrure de sodium sur la cétone *trans* **8** (cristallisée), en solution dans l'éthanol,[8] nous avons isolé le cétol protégé **11** avec un

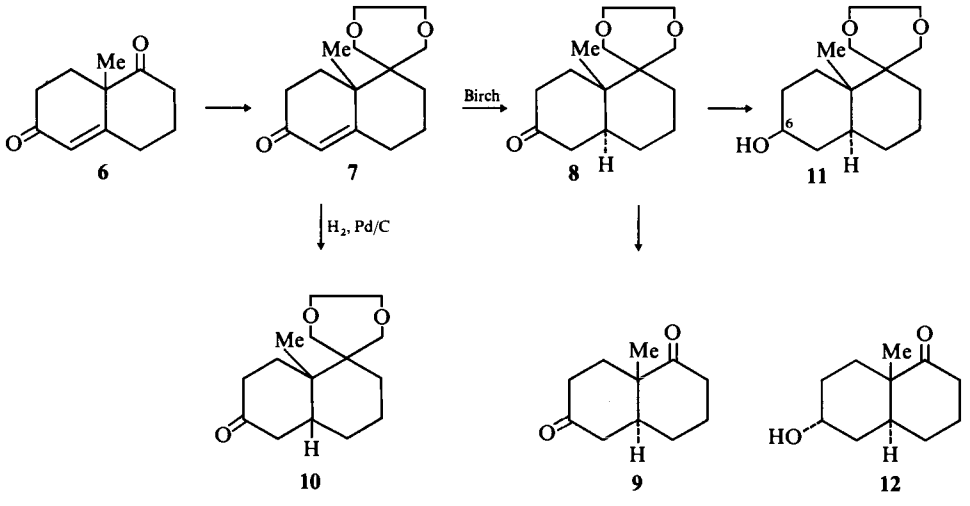
†Note préliminaire: E. Brown et M. Ragault, *Tetrahedron Letters* 393 (1978).

‡Mémoire précédent: E. Brown, M. Ragault et J. Touet, *Bull. Soc. Chim. Fr.* 212 (1972).

rendement quantitatif. Postérieurement à ce travail, d'autres auteurs[9] ont effectué la synthèse de **11** par réduction de **7** au moyen d'un grand excès de sodium dans l'ammoniac liquide.

A l'époque de ces travaux, d'autres auteurs[10] ont mis en évidence la formation de produits inattendus (tels que des cyclopropanes) lors de la réduction de Birch de la cétone de Wieland et Miescher **6** ou d'un de ses homologues.

Par contre, l'alcoylation de la cétone **19** par le chlorure de méthallyle en présence de *t*-butylate de potassium a conduit avec un rendement quantitatif à la méthallylcétone **22**. L'ozonolyse dans le méthanol de la méthallylcétone **22** brute, suivie de l'élimination du groupement protecteur, a fourni l'acétonyl-2 hydroxy-6β méthyl-8a *trans* décalone-1 **13** sous la forme d'un liquide visqueux, lequel, après chromatographie sur alumine, a donné une analyse élémentaire

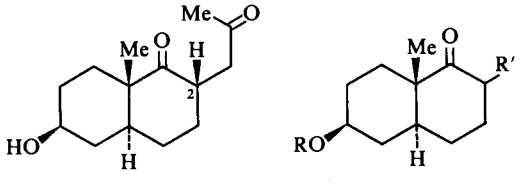


L'hydrolyse du dioxolanne **11** a fourni le cétol **1** attendu avec un bon rendement. La stéréochimie 6β de l'hydroxyle de **1** est confirmée par le fait que l'isomère 6α **12** a été décrit par Ireland,[11] et fond à 112–114°.

Il était logique de penser que la cétone tricyclique **2** pourrait dériver de la décalone **1** par l'intermédiaire de la γ-dicétone **13**. Nous nous sommes donc efforcés d'alcoyler le cétol **1** en position 2 à l'aide de réactifs convenables susceptibles d'être transformés en groupements acétonyles par la suite. A notre connaissance, la seule étude parue dans la littérature concernant l'alcoylation des méthyl-8a décalones-1 est due à House[12] et traite uniquement de la méthylation.

et des spectres IR et de RMN corrects. Par la suite, cependant, nous avons invariablement échoué dans toutes nos tentatives de crotoniser la γ-dicétone **13** en vue d'obtenir la benz(e)indénone-2 **2**.

L'alcoylation de **23** par le chlorure de méthallyle, en présence de *t*-butylate de potassium fournit, d'après la chromatographie sur couche mince, un mélange de trois produits, le plus polaire étant le composé de départ **23**. Ce mélange a pu être séparé par cristallisation fractionnée et chromatographie sur colonne, et nous avons isolé la méthallylcétone **26**, F = 141–142°, ainsi que la *bis*-méthallylcétone **27**, F = 108–110°. On atteint un rendement de 40% en



13

THP = tétrahydropyrranyl; Tr = trityl

14, R = H, R' = $COCO_2Me$
15, R = H, R' = CHO (énol)
16, R = H, R' = $CH_2C{\equiv}CH$
17, R = Me_3Si, R' = H
18, R = Me_3Si, R' = $COCO_2Me$
19, R = THP, R' = H
20, R = THP, R' = CHO (énol)
21, R = THP, R' = CH_2 $C{\equiv}CH$
23, R = Tr, R' = H
24, R = Tr, R' = $COCO_2Me$
25, R = Tr, R' = CHO (énol)

Nous avons invariablement échoué dans nos différentes tentatives de préparer, selon des méthodes classiques,[13–19] une γ-dicétone du type **13** après activation préalable de la position en α du carbonyle de la décalone de départ. Notamment, parmi les différents composés **14–21** et **23–25** dont nous avons tenté la synthèse, seuls les composés **19**, **20**, **23** et **25** ont pu être obtenus et caractérisés.

méthallylcétone **26** purifiée en tenant compte du produit de départ **23** récupéré inchangé.

L'ozonolyse de la méthallylcétone **26** en présence de pyridine,[20] conduit à un mélange de deux produits principaux qui ont été séparés par chromatographie sur colonne. Le plus polaire s'est avéré être l'acétonyldécalone **28** cherchée, l'autre étant le composé **29**, pour lequel l'analyse élémentaire et la

spectrométrie de masse conduisent à la formule brute $C_{33}H_{36}O_4$, soit un gain de deux oxygènes et la perte d'un groupement méthylène par rapport à **26**. La structure d'ozonide interne avancée pour **29** est en accord avec les résultats connus concernant les mécanismes de formation et de transposition des ozonides.[21,22] Ceci étant, il semblait possible de passer de l'ozonide **29** à la γ-dicétone **28** cherchée, en utilisant un réducteur plus énergique que la pyridine utilisée pour l'ozonolyse de la méthallylcétone **26**. Et, en effet, nous avons constaté que lorsque le produit brut d'ozonolyse de **26** dans le mélange pyridine/chlorure de méthylène était traité par le zinc dans l'acide acétique,[23] on isolait la γ-dicétone **28** avec un rendement de 63% après purification par chromatographie sur colonne. Par la suite, nous avons introduit une simplification notable dans la synthèse de la γ-dicétone **28**. Cette simplification consiste à ozoner directement le mélange de monométhallylcétone **26** et de *bis*-méthallylcétone **27** issu de la chromatographie. En effet, la séparation de **26** et **27** est délicate et se fait avec de mauvais rendements. Tandis que nous avons constaté que leurs produits d'ozonolyse respectifs, à savoir l'acétonyl décalone **28** et la diacétonyl décalone **30**, sont aisément séparés par chromatographie et cristallisation.

La crotonisation intramoléculaire de la dicétone **28** par le-*t*-butylate de potassium dans le *t*-butanol, conduit à un mélange de deux benz(e)indénones isomères **31**, F = 209–212°, et **32**, F = 208–210°, difficilement séparables par cristallisation fractionnée et inséparables par chromatographie. Par contre, si l'on opère la crotonisation de **28** dans le milieu *aprotique* *t*-butylate de sodium/benzène, la seule cétone obtenue est la cétone conjuguée "normale" **31**.

Il semble donc que le milieu alcalin et protique *t*-BuOK/*t*-BuOH utilisé au cours des premiers essais favorise une isomérisation de la cétone **31** en **32**, selon un mécanisme passant par l'intermédiaire de la cétone déconjuguée correspondante. Ainsi, nous avons vérifié qu'en traitant la cétone conjugée "normale" **31** par le *t*-butylate de potassium dans le *t*-butanol, nous obtenions bien le mélange de **31** et **32**.

Par action de l'acide bromhydrique sec dans l'acide acétique,[17] les cétones **31** et **32** sont détritylées et conduisent aux hydroxy benz(e)indénones **2** et **33** correspondantes, sans qu'on observe de migration de double liaison. Le composé **2** est un liquide que nous ne sommes pas parvenus à faire cristalliser, alors que son isomère **33** est un solide fondant à 138–141°. Pas plus que leurs dérivés tritylés **31** et **32**, nous ne sommes parvenus à séparer par chromatographie le mélange des cétones **2** et **33** (qui ont été obtenues à partir des dérivés tritylés correspondants et préalablement purifiés).

Par réduction de Birch dans des conditions soigneusement contrôlées (tout particulièrement en ce qui concerne la quantité de lithium), suivie de retritylation de l'hydroxyle, les deux cétones isomères **31** et **32** *conduisent au même composé, lequel ne peut être que la cétone trans-anti-trans* **34**. Le composé **34** a été caractérisé dans les deux cas par la RMN, l'IR et le point de fusion (F = 176–183° et F = 181–187°).

Par hydrogénation catalytique (Pd/C) de la cétone **31**, nous avons obtenu un composé unique, différent de l'isomère **34**, et qui est donc nécessairement la cétone *trans-syn-cis* **35** (F = 164–168°). Ce résultat paraît contredire la règle de l'encombrement catalytique d'Auwers–Skita qui laisse prévoir que **34** doit être aussi le produit d'hydrogénation catalytique de **31**. Pour expliquer les exceptions à la règle d'Auwers–Skita, dont l'hydrogénation de **31** constitue un exemple, nous avions proposé il y a quelques années *la règle de la compacité maximum.*[24] Cette règle postule que lors d'une hydrogénation catalytique, l'étape de *désorption* de la molécule réduite est d'autant plus rapide que cette molécule est plus compacte, et par conséquent, moins apte à s'associer avec le catalyseur et avec les autres molécules adsorbées à proximité.

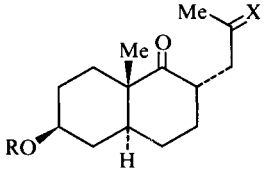
La réduction catalytique de la cétone **32** conduit quant à elle à un troisième composé qui est *nécessairement* la cétone *trans-anti-cis* **36** (F = 236–237°). Par ailleurs, on observe sur les spectres de RMN des cétones saturées **34**, **35** et **36** un effet de blindage de la cyclopentanone sur le méthyle angulaire, de même que pour les cétones éthyléniques **31** et **32**, cet effet étant d'autant plus marqué que le plan du cycle fait un angle *plus faible* avec l'axe de la liaison C 9a–CH_3.[24]

La quatrième cétone saturée possible qui est le composé **37**, possède des hydrogènes 3aα et 9bβ et ne devrait donc pas se former à partir de l'une ou l'autre des deux cétones éthyléniques **31** et **32**.

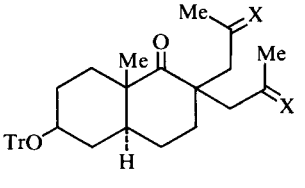
La cétone **34**, qui possède la stéréochimie *trans-anti-trans* des cycles A, B et C des C-nor D-homostéroïdes naturels, n'a jamais pu être obtenue avec des rendements supérieurs à 15–20%, ce qui exclut son utilisation comme intermédiaire dans la suite de la synthèse totale des C-nor D-homostéroïdes. Pour cette raison, nous avons décidé de poursuivre notre synthèse en cherchant à construire un cycle D sur la benz(e)indénone-2 éthylénique **31** qui peut être disponible en quantités importantes.

Construction du cycle D: nouvelle synthèse totale d'un C-nor D-homo stéroïde décrit (composé **4***)*

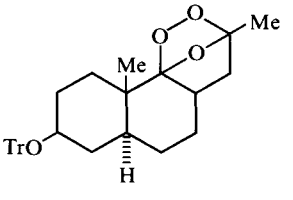
La préparation du composé tétracyclique **4**[1] à partir de la benz(e) indénone **31** nécessite l'alcoylation de



22, R = THP, X = CH_2
26, R = Tr, X = CH_2
28, R = Tr, X = O



27, X = CH_2
30, X = O



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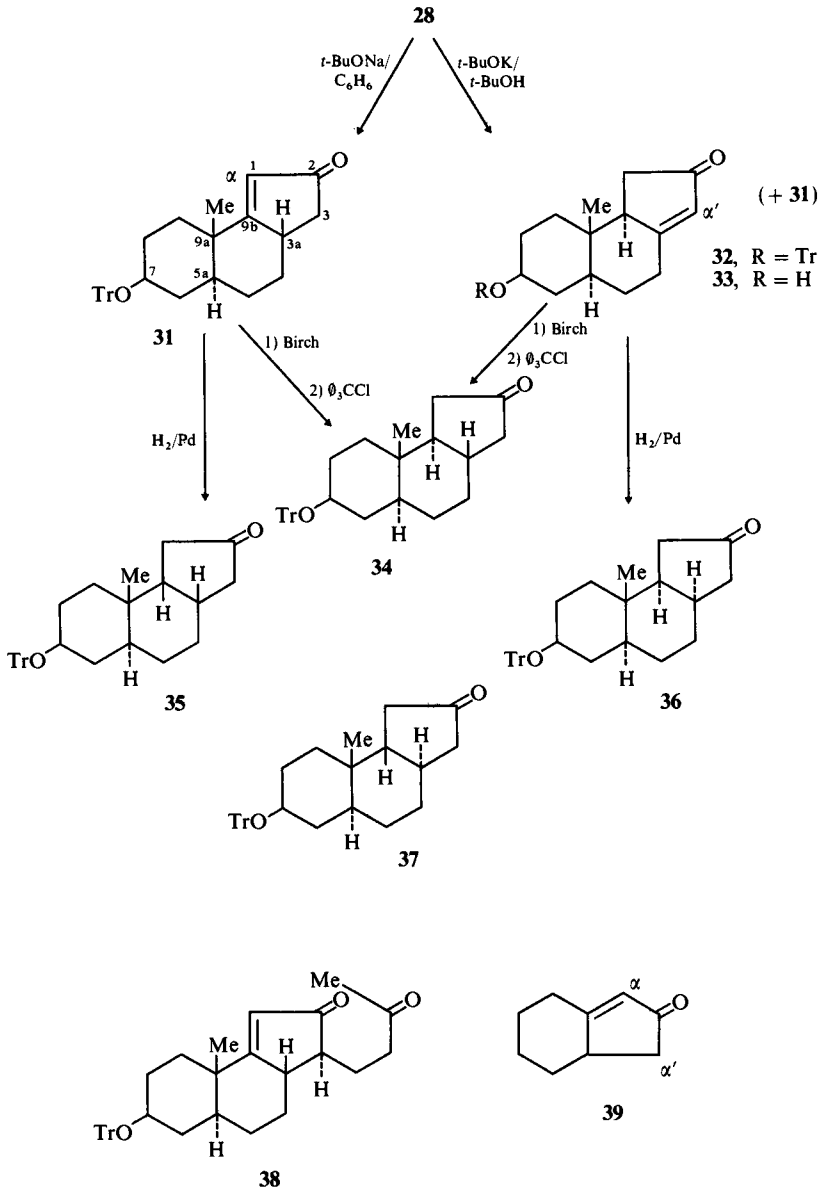


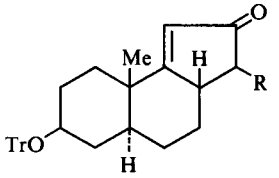
cette cétone en position 3, en vue d'obtenir la δ-dicétone **38** intermédiaire, qui sera ultérieurement cyclocrotonisée.

La synthèse de la δ-dicétone **38** pose des problèmes intéressants, surtout si l'on considère qu'elle se ramène à l'alcoylation en position α' d'une α-cyclopenténone. En effet, bien que les cyclopenténones soient en elles-mêmes bien connues, rares sont les auteurs qui ont étudié l'alcoylation de ces composés,[25,26] en raison sans doute de leur instabilité en milieu alcalin. Les résultats les plus encourageants semblent avoir été décrits par Smith et coll.,[26] qui ont réussi à méthyler l'hydrindénone **39** en α' du carbonyle, en s'inspirant de travaux connus concernant l'alcoylation cinétique ou thermodynamique des α-cyclohexénones.[27-30]

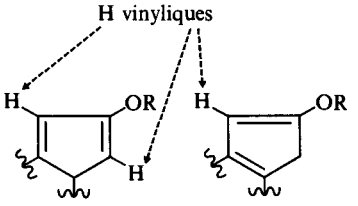
Diverses tentatives pour *activer* la position 3 de **31**, avec soit l'oxalate de méthyle pour obtenir l'α-méthoxalyl cétone **40**, soit le carbonate de méthyle pour obtenir le β-céto ester **41**, se sont avérées infructueuses.

Par contre, la condensation, selon la méthode classique, du formiate d'éthyle sur la cétone **31** nous a fourni l'α-hydroxyméthylène cétone **42** attendue, mais de façon peu reproductible et avec des rendements très variables. Les spectres IR et de RMN du composé **42**, F = 100–120°, étant en accord avec la structure avancée, nous avons tenté une réaction de Michael entre la MVC et l'anion de l'énol **42**. Après chromatographie, nous avons obtenu une faible quantité d'un composé liquide dont les spectres IR et de RMN étaient identiques aux spectres correspondants d'un échantillon authentique de δ-dicétone **38** préparée selon une autre méthode (voir ci-après). Toutefois, cette séquence a dû être abandonnée, compte tenu des mauvais rendements obtenus.

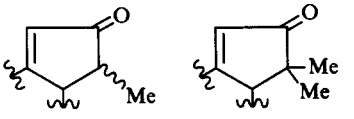
Nous avons alors envisagé d'alcoyler la cétone **31** en position 3, dans des conditions cinétiques soigneusement contrôlées. La cétone **31** est susceptible de donner naissance à deux énolates **43** et **44**, le premier étant très probablement l'énolate cinétique.[31] Afin de



40, R = $COCO_2Me$
41, R = CO_2Me
42, R = CHO (forme énolique)



43 **44**



45 **46**

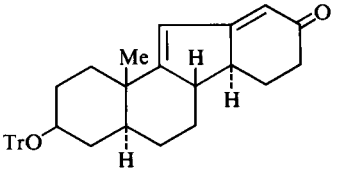
vérifier cette hypothèse, nous avons tenté la préparation de l'énolate de **31** à basse température, en utilisant un solvant aprotique et une base forte et encombrée, le diisopropylamidure de lithium, en vue de piéger ensuite cet énolate sous forme d'éther de triméthylsilyle.[32,33] L'éther d'énol ainsi obtenu est liquide. Son spectre de RMN indique la présence d'un méthyle angulaire à δ 1,05 ppm et de *deux* protons vinyliques centrés sur δ 5,5 ppm et δ 5,05 ppm (le proton vinylique de **31** résonne à δ 5,63 ppm). L'éther d'énol cinétique de **31** a donc la structure **43** (R = $-SiMe_3$), la structure **44** pouvant être écartée d'emblée, puisqu'elle ne comporte qu'*un seul* proton vinylique en position/1. L'iodure de méthyle en excès réagit presque instantanément à 0° sur l'énolate **43** (R = Li) préparé *in situ*, pour conduire à un mélange de deux produits séparables par chromatographie sur couche mince, le dérivé monométhylé **45** et le dérivé diméthylé **46**, lesquels ont été caractérisés par leurs spectres de masse, de RMN et IR. Le spectre IR de **45** et **46** laisse apparaître un carbonyle de cyclopenténone conjugée à 1705 cm^{-1}, de même que pour **31**, par conséquent. En RMN, le méthyle angulaire de **45** résonne à δ 1,05 ppm, ce qui est comparable à la valeur δ 1,08 ppm observée pour le signal du méthyle de **31**. De même, le proton vinylique de **45** résonne à δ 5,62 ppm, valeur voisine de celle observée pour le proton vinylique de **31**. Disons enfin que les spectres de RMN des deux cétones méthylées **45** et **46** indiquent l'absence de méthyle sur double liaison et que, d'autre part, le signal du méthyle en 3 de **45** sort sous forme d'un doublet. Les résultats précédents sont très importants, parce qu'ils montrent que l'alcoylation régiosélective de **31** est possible dans le sens souhaité, c'est-à-dire en position 3, sous réserve d'utiliser un agent alcoylant suffisamment réactif pour piéger l'énolate cinétique **43** (R = Li), avant l'équilibration ou la décomposition de ce dernier.

Différents essais d'alcoylation de l'énolate cinétique **43** (R=Li) par la MVC, la chloro-4 butanone-2, l'éthylènedioxy-2,2 iodo-4 butane et le dichloro-1,3 butène-2 s'étant soldés par des échecs, nous avons alors envisagé l'emploi de la méthyl (α-triméthylsilyl)-vinylcétone **47**, qui a été préconisée par Stork,[34,35] afin d'éviter les problèmes posés par la MVC lors des réactions de Michael, effectuées dans des conditions cinétiques.

$CH_2{=}C(SiMe_3){-}COMe$ **47**

Nous avons constaté que la réaction de Michael entre l'énolate **43** (R=Li) et la vinylcétone **47** est totale et instantanée à $-78°$, d'après la chromatographie sur couche mince. Le spectre de RMN du produit brut formé comporte vers δ 0 ppm le massif caractéristique du groupement triméthylsilyle, et vers δ 2 ppm trois grands singulets de méthyl cétone.

Nous avons eu la satisfaction de constater que, par simple chromatographie sur colonne de l'adduit précédent, celui-ci perdait son groupement triméthylsilyle pour conduire à la δ-dicétone **38** attendue, F = 119–125°. La δ-dicétone **38** a été caractérisée par son spectre de masse, son spectre IR et son spectre de RMN, sur lequel on note entre autres un proton vinylique à δ 5,6 ppm, le méthyle d'acétyle à δ 2,09 ppm et le méthyle angulaire à δ 1,03 ppm, ce qui tend à indiquer qu'il n'y a pas eu de migration de double liaison. Les spectres IR et de RMN du composé **38** ainsi obtenus sont identiques à ceux du produit de réaction de la MVC sur l'α-hydroxyméthylène cétone **42**, et dont nous avons déjà fait état précédemment.



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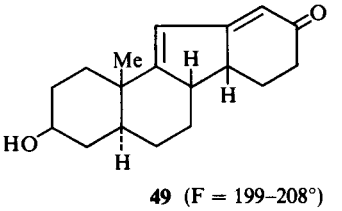

49 (F = 199–208°)

Par crotonisation intramoléculaire en présence de *t*-butylate de potassium, la δ-dicétone **38** fournit le composé tétracyclique tritylé **48**, F = 196–206°. Après détritylation du produit *brut* de crotonisation de **38** à l'aide de HBr/AcOH, suivie de chromatographie, nous avons obtenu un mélange cristallisé de deux C-n or D-homostéroïdes isomères (dont l'un est très largement majoritaire), qui sont séparables par cristallisation fractionnée, mais qui n'ont pu être séparés par chromatographie sur couche mince. Les constantes spectrales (IR, UV et RMN) de l'isomère le plus abondant, F = 155–158°, sont, à très peu de chose près, identiques à celles indiquées par Kutney[1] pour le composé **4** qu'il décrit par ailleurs comme fondant à 199–203°. Notre composé minoritaire, quant à lui, n'a pu être obtenu à l'état pur: même après plusieurs recristallisations, ce dernier fond à 199–208°, valeur très voisine par conséquent de la valeur annoncée par Kutney[1] pour le C-nor D-homostéroïde **4**. Toutefois, le spectre de RMN de notre isomère minoritaire, F = 199–208°, présente des différences sensibles avec le spectre de **4** décrit par Kutney, notamment en ce qui concerne les déplacements chimiques du méthyle angulaire et des deux protons vinyliques. Les principales constantes spectrales de **4** et des deux isomères que nous avons obtenus sont rassemblées dans le Tableau 1.

Il résulte de ce qui précède que nous sommes en droit d'affirmer que notre isomère majoritaire, F = 155–158°, est bien le C-nor D-homostéroïde **4** obtenu par Kutney, le point de fusion F = 199–203°, indiqué par cet auteur étant en réalité celui de l'isomère **49**. Cette erreur de Kutney serait probablement due au fait qu'en recristallisant son mélange de composés **4** et **49**, il a en réalité purifié l'isomère **49** à haut point de fusion, l'isomère **4** restant dans les eaux-mères.[36]

CONCLUSION

Nous avons réalisé une synthèse totale stéréospecifique et rapide des C-nor D-homostéroïdes, selon un schéma original du type A → B → C → D.

La voie adoptée, qui prévoit une tritylation précoce, a permis d'obtenir à chaque étape des produits cristallisés dont la structure a pu être identifiée sans ambiguïté.

Enfin, notre schéma réactionnel devrait pouvoir être utilisé sans difficultés pour préparer des C-nor D-homostéroïdes optiquement actifs, puisque notre produit de départ, la cétone de Wieland et Miescher, est elle-même disponible sous forme optiquement active.

PARTIE EXPERIMENTALE

Les spectres infra-rouges ont été enregistrés avec un spectrophotomètre Perkin–Elmer, modèle 257. Les spectres de résonance magnétique nucléaire du proton ont été enregistrés soit sur un spectromètre Varian A 60, soit sur un Jeol MH 100, soit sur un Hitachi Perkin–Elmer R 24. La référence interne utilisée est le tétraméthylsilane (TMS). Les spectres de RMN du ^{13}C ont été pris avec un spectromètre Varian XL 100, au Centre de Spectrométrie de l'Université de Paris VI. Les spectres dans l'ultra-violet ont été enregistrés en solution dans l'éthanol, soit sur un spectromètre Beckmann Acta III, soit sur un Beckmann DK II A. Les spectres de masse ont été pris avec un spectromètre Varian MAT 311 (service de spectroscopie de masse de l'Université de Rennes).

Les abréviations suivantes sont utilisées: TA, température ambiante; DM, distillation moléculaire; CCM, chromatographie sur couche mince; THF, tétrahydrofuranne; MVC, méthyl vinyl cétone.

trans-*Ethylènedioxy*-1,1 *méthyl*-8*a* *décahydro*-1,2,3,4,4*a*,-5,6,7,8,8*a* *naphtalénone*-6 (**8**)

Le mode opératoire s'inspire de la littérature.[3,7,8] Dans un réacteur de 6 l muni d'une agitation mécanique, d'une ampoule à addition et de 2 entrées de gaz, on place 6 g (0,86 mol) de lithium coupé en morceaux, on agite, puis à l'aide d'une bouteille d'ammoniac et d'un bain d'acétone-carboglace, on piège 4 l d'ammoniac liquide dans le réacteur. Après avoir laissé le mélange revenir à la température d'ébullition de l'ammoniac, on ajoute en 1 h et en agitant vigoureusement 40 g (0,18 mol) du monocétal **7** en solution dans 400 cm^3 d'éther anhydre. La coloration bleue est alors détruite au bout de 30 mn par addition d'une solution aqueuse saturée de NH_4Cl. Après évaporation de l'ammoniac (1 nuit), le résidu solide est repris par l'eau et l'éther.

Après lavage des phases éthérées jusqu'à pH neutre, séchage (Na_2SO_4) et évaporation, on recueille 38,6 g (96%) d'une huile jaune épaisse qui est chromatographiée sur 250 g d'alumine Merck (Activité III, éluant éther de pétrole/benzène 2/1). Le premier litre d'éluat fournit par évaporation 29,5 g de produit dont 20 g (50%) d'acétal **8** cristallisé, F = 34,5–37° (éther isopropylique). Le deuxième litre fournit 0,61 g de produit incristallisable. IR (Nujol): ν = 1715 cm^{-1}; RMN (A 60) (CCl_4) (ppm): δ 1,15 (s) (3 H) (Me–8a); δ 1,2 à 2,4 (13 H) (–CH_2–); δ 3,9 (s) (4 H) (dioxolanne).

cis-*Ethylènedioxy*-1,1 *méthyl*-8*a* *décahydro*-1,2,3,4,4*a*,-5,6,7,8,8*a* *naphtalénone*-6 (**10**)

Nous avons utilisé le mode opératoire de McMurry.[6] L'hydrogénation catalytique de 5 g de cétone éthylénique **7** dans 100 cm^3 d'éthanol en présence de 1 g de Pd/C (à 10% de Pd), à pression atmosphérique, est terminée en 2 h environ, le volume d'hydrogène absorbé étant de 550 cm^3. On recueille une huile incolore cristallisable (4 g, 80%). Par recristallisation dans l'éther isopropylique, on obtient un échantillon, F = 51–52,5° (Litt.[6], F = 54–54,5°). IR (Nujol): ν = 1715 cm^{-1}; RMN (A 60) (CCl_4) (ppm): δ 1,18 (s) (3 H)

Tableau 1. Principales constantes spectrales (RMN, IR et UV) des composés C-nor D-homostéroïdes

Composé	F (°C)	δ Me_{11b} (ppm)	δ H_{10} et δ H_{11} (ppm)	ν CO (cm^{-1})	λ max (nm)	ε
4 de Kutney[1]	199-203°	1,03	5,75 et 5,95	1635	295	23990
isomère majoritaire	155-158°	1,04	5,76 et 5,98	1630	295	23760
isomère minoritaire	199-208°	1,16	5,88 et 6	1630	295	22460

(Me en 8a); δ 1,3 à 2,5 (13 H) ($-CH_2-$); δ 3,9 (s) (4 H) (dioxolanne).

trans-*Ethylènedioxy*-1,1 *hydroxy*-6β *méthyl*-8aβ *décahydro*-1,2,3,4,4*a*,5,6,7,8,8*a* *naphtalène* (**11**)

A une solution agitée de 23,7 g (0,106 mol) de cétone *trans* **8** cristallisée dans 1 l d'éthanol absolu, en ajoute on 15 min 3,6 g (0,095 mol) de $NaBH_4$ finement broyé (la température du mélange s'élève de 18–25°). Après 30 min, l'excès de borohydrure est détruit par quelques gouttes d'acide acétique concentré. Lorsque le dégagement gazeux a cessé, on ajoute $NaHCO_3$ solide, un peu d'eau et on évapore l'éthanol à TA sous vide. Après extraction du résidu à l'éther, lavages des phases éthérées à l'eau, séchage (Na_2SO_4) puis évaporation du solvant, on isole 25 g (100 %) d'une huile épaisse incolore, qui cristallise entièrement, F = 60–75°, et que l'on purifie par DM en vue de l'analyse F = 86–88° (éther/éther de pétrole) (Litt.[9]: F = 90–92°). Calc. ($C_{13}H_{22}O_3$): C, 69,05; H, 9,74; Tr.: C, 68,62; H, 9,85 %; IR (film): ν = 3400 cm^{-1}; RMN (A 60) (CCl_4) (ppm): δ 0,92 (s) (3 H) (Me en 8a); δ 1 à 1,9 (13 H) (CH_2); δ 3,2 à 3,5 (1 H) (H tertiaire en 6); δ 2,95 (s) (1 H) (H d'hydroxyle); δ 3,25 (s) (4 H) (dioxolanne).

trans-*Hydroxy*-6β *méthyl*-8aβ *décahydro*-1,2,3,4,4*a*,5,6,7,8,8*a* *naphtalénone*-1 (**1**)

On chauffe pendant 15 min au bain-marie un mélange de 25 g (0,106 mol) du dioxolanne **11** précédent, 250 cm^3 d'acétone et 120 cm^3 de HCl 3N. Après refroidissement, neutralisation par $NaHCO_3$ solide, évaporation sous vide à TA et extraction à l'éther, on obtient 16,2 g (81 %) d'une huile jaune très pâle qui cristallise entièrement au dessiccateur, F = 36–38° (éther de pétrole) (cristaux blancs huileux). IR (Nujol): ν = 3300, 1705 cm^{-1}; RMN (A 60) (CCl_4) (ppm): δ 1,1 (s) (3 H) (Me en 8a); δ 1,2 à 2,3 (13 H) (CH_2); δ 2,95 (s) (1 H) (proton d'hydroxyle); δ 3,2 à 3,6 (1 H) (proton/tertiaire en 6).

Para-*nitrobenzoate du cétol* **1**

On chauffe 0,3 g du cétol **1** précédent et 0,5 g de chlorure de *para*-nitrobenzoyle pendant 15 min au bain-marie, puis on traite le mélange par une solution saturée de $NaHCO_3$ pendant 1 nuit à TA, et enfin on filtre le précipité. Le *para*-nitrobenzoate brut est recristallisé dans l'éthanol, F = 117–119°. Calc. ($C_{18}H_{21}NO_5$): C, 65,25; H, 6,35; Tr: C, 65,09; H, 6,75 %.

trans-*Méthyl*-8aβ (*tétrahydro pyrranyl*-2) *oxy*-6β *décahydro*-1,2,3,4,4*a*,5,6,7,8,8*a* *naphtalénone*-1 (**19**)

On utilise une méthode inspirée de Dauben et Bradlow.[16] Dans un ballon de 50 cm^3 avec entrée d'azote, garde à $CaCl_2$ et agitation magnétique, on mélange 2 g (11 m.mol) de cétol **1** dissous dans quelques cm^3 de benzène sec, 2 cm^3 de dihydropyranne et 1 goutte de HCl concentré. On laisse une nuit à TA en agitant sous azote. Le mélange est neutralisé par $NaHCO_3$, évaporé à sec sous vide, puis repris à l'éther et lavé avec un peu d'eau. Après séchage (Na_2SO_4) des phases organiques et évaporation de l'éther, on recueille 2,72 g (93 %) d'une huile incolore. IR (film): ν = 1710 cm^{-1}.

trans-*Hydroxyméthylène*-2 *méthyl*-8aβ (*tétrahydropyrranyl*-2) *oxy*-6β *décahydro*-1,2,3,4,4*a*,5,6,7,8,8*a* *naphtalénone*-1 (**20**)

Dans un tricol de 100 cm^3 muni d'une entrée d'azote, d'un réfrigérant avec garde à $CaCl_2$ et d'une ampoule à addition, on place 0,8 g de HNa à 50 % dans l'huile (lavé 2 fois avec du benzène sec), on le recouvre de benzène sec et on refroidit le mélange dans la glace en agitant. On ajoute alors lentement 2,72 g (10,2 m.mol) de l'acétal **19** en solution dans quelques cm^3 de benzène sec et on laisse le mélange 2 jours à TA. On reprend alors par de l'eau froide et on lave les phases benzéniques à la potasse à 2 %. Les phases aqueuses sont réunies, lavées avec un peu d'éther, acidifiées avec précaution par HCl concentré jusqu'à pH 4, puis extraites avec de l'éther. Les phases éthérées sont réunies et lavées à l'eau jusqu'à neutralité, puis séchées (Na_2SO_4) et évaporées sous vide. On recueille 2,72 g (91 %) d'une huile jaune. Par trituration dans le méthanol, on obtient des cristaux blancs pâteux, F = 76–84°. Par recristallisation dans le méthanol, F = 88–92°, avec ramollissement vers 70°. Calc. ($C_{17}H_{26}O_4$): C, 69,40; H, 8,85; Tr.: C, 69,63; H, 8,87 %.

trans-*Méthallyl*-2 *méthyl*-8aβ (*tétrahydropyrannyl*-2) *oxy*-6β *décahydro*-1,2,3,4,4*a*,5,6,7,8,8*a* *naphtalénone*-1 (**22**)

Dans un ballon de 500 cm^3 équipé d'une agitation magnétique, d'une entrée d'azote et d'un réfrigérant surmonté d'une gardè à $CaCl_2$, on place 9,3 g (1,5 éq.) de *tertio*-butylate de potassium sec que l'on recouvre de 100 cm^3 de benzène sec. On ajoute alors 13,6 g (55 m.mol) d'acétal **19** en solution dans 50 cm^3 de benzène sec, puis 12 cm^3 (2 éq.) de chlorure de méthallyle distillé, dilué par 50 cm^3 de benzène sec. Le mélange est laissé 24 h à TA, puis porté à reflux pendant 24 h. On refroidit la solution jaune, la lave 2 fois par 50 cm^3 d'eau et les phases aqueuses sont extraites à l'éther. Après séchage (Na_2SO_4) et évaporation des solvants, on recueille 17,5 g (100 %) d'une huile jaune pâle épaisse. Malgré plusieurs essais de DM, nous n'avons pas pu obtenir de bonne analyse pour ce composé **22**. IR (film): ν = 3080, 1710, 1650 cm^{-1}; RMN (A 60) (CCl_4) (ppm): δ 1,1 (3 H) (Me en 8a); δ 1,3 à 2 (23 H) ($-CH_2-$); δ 3,25–4 (3 H) (H tertiaire en position 6 et $-CH_2-$ en α de l'oxygène du pyranne); δ 4,45–5 (3 H) (méthylène *exo* et hydrogène tertiaire en α des deux oxygènes).

trans-*Acétonyl*-2 *hydroxy*-6β *méthyl*-8aβ *décahydro*-1,2,3,4,4*a*,5,6,7,8,8*a* *naphtalénone*-1 (**13**)

On effectue l'ozonolyse de la méthallylcétone **22** (2 g) en solution dans le méthanol, refroidie par un bain d'acétone–carboglace. On laisse barboter l'ozone 45 min et on détruit l'ozonide en 2 h par un mélange de 20 g d'iodure de potassium et de 20 cm^3 d'acide acétique. La solution est décolorée par du bisulfite de soude, diluée avec un peu d'eau, traitée par $NaHCO_3$ jusqu'à neutralité, et concentrée sous vide à TA. Par extraction à l'éther, séchage (Na_2SO_4) des phases organiques et évaporation, on recueille 1,57 g d'une huile pratiquement incolore.

On porte à reflux 2 h sous azote, une solution du produit précédent (1,57 g), 100 mg d'acide *para*-toluène sulfonique et 50 cm^3 d'éthanol. Après refroidissement et addition de 100 mg de $NaHCO_3$, on évapore l'éthanol à TA sous vide et on extrait à l'éther. Après séchage (Na_2SO_4) et évaporation de l'éther, on recueille 1 g (67 %) d'une huile jaune, qui est purifiée par chromatographie sur 30 g d'alumine. On recueille ainsi 730 mg d'une huile jaune pâle homogène en CCM analytique. Calc. ($C_{14}H_{22}O_3$): C, 70,60; H, 9,24; Tr.: C, 70,47; H, 9.34 %; IR (film): ν = 1710, 3400 cm^{-1}; RMN (A 60) (CCl_4) (ppm): δ 1,1 (s avec épaulement) (3 H) (Me en 8a); δ 1,2 à 2,7 (massif contenant l'acétyle à δ 2,2 et l'OH à δ 2,5 pour un total de 19 H); δ 3,3 à 3,7 (1 H) (hydrogène tertiaire en 6).

trans-*Méthyl*-8aβ *trityloxy*-6β *décahydro*-1,2,3,4,4*a*,5,6,7,8,8*a* *naphtalénone*-1 (**23**)

Le mode opératoire s'inspire de la littérature.[17] On porte à 110–120° sous azote pendant 4 h 30 min une solution de 37,3 g (0,205 mol) du cétol **1** et de 57,5 g (0,205 mol) de chlorure de trityle dans 140 cm^3 de pyridine anhydre.

Après refroidissement, la solution est diluée par 300 cm^3 d'eau et extraite au chlorure de méthylène, les phases organiques sont lavées par HCl 3N, puis à l'eau, séchées ($MgSO_4$) et évaporées. On obtient 76,3 g de produit brut qui, par recristallisation dans le benzène, fournit 50 g (58 %) d'un solide blanc, F = 175–180°. Pour analyse, recristallisation dans le benzène, F = 180–181°. Calc. ($C_{30}H_{32}O_2$): C, 84,87; H, 7,60; Tr.: C, 84,83; H, 7,68 %; IR (Nujol): ν = 1705, 1600 cm^{-1}; RMN (A 60) (CCl_4) (ppm): δ 1,03 (s) (3 H) (Me angulaire); δ 0,95–3,5 (14 H) ($-CH_2-$ et H tertiaire 6α); δ 7–7,6 (15 H) (protons aromatiques).

trans-*Hydroxyméthyléne*-2 *méthyl*-8aβ *trityloxy*-6β *décahydro*-1,2,3,4,4*a*,5,6,7,8,8*a* *naphtalénone*-1 (**25**)

Le mode opératoire utilisé s'inspire de Corey.[18] A une suspension de 0,76 g (16 m.mol) d'hydrure de sodium dans

25 cm³ de glyme, sous azote et agitation magnétique, on ajoute 12 cm³ de formiate d'éthyle, puis 1,696 g (4 m.mol) de cétone **23** en solution dans 25 cm³ de glyme. On laisse 3 h à 30°, puis on hydrolyse à pH 6 par NH_4Cl et HCl, extrait au chloroforme, lave, sèche ($MgSO_4$) et évapore la phase organique. Par cristallisation du résidu (1,7 g, 94 %) dans l'acétone, on isole 0,9 g (50 %) de cristaux, F = 154–157°. Calc. ($C_{31}H_{32}O_3$): C, 82,06; H, 7,13; Tr.: C, 82,13; H, 7,21 %; IR (Nujol): ν = 1580, 1630 cm⁻¹.

trans-*Méthallyl*-2 *méthyl*-8*aβ trityloxy*-6*β décahydro*-1,2,3,4,4*a*,5,6,7,8,8*a naphtalénone*-1 (**26**) *et* trans-bis-*méthallyl*-2,2 *méthyl*-8*aβ trityloxy*-6*β décahydro*-1,2,3,4,4*a*,5,6,7,8,8*a naphtalénone*-1 (**27**)

On porte à reflux 20 h sous azote un mélange de 55,5 g (131 millimol) de cétone **23**, 14,7 g (1 éq.) de *tertio*-butylate de potassium, 350 cm³ de benzène sec et 39 cm³ (393 m.mol) de chlorure de méthallyle. Après hydrolyse du mélange réactionnel, lavage, séchage ($MgSO_4$) et évaporation de la phase organique, on recueille 60,5 g de produit brut. Par trituration dans 500 cm³ d'éther de pétrole, on obtient 28,4 g de produit solide constitué essentiellement du composé de départ **23** et d'un peu de monométhallyl cétone **26**. Le résidu (32,4 g) laisse déposer une fraction de 5,8 g de mono méthallyl cétone **26** cristallisée et une chromatographie du deuxième résidu fournit un autre lot de 10,85 g de mono méthallylcétone **26**.

Soit un total de 16,6 g (Rdt = 26,8 % par rapport à la cétone **23** mise en oeuvre et Rdt = 40 % compte tenu de la cétone **23** récupérée inchangée). Recristallisé pour l'analyse, F = 141–142° (éther). Calc. ($C_{34}H_{38}O_2$): C, 85,31; H, 8,00; Tr.: C, 85,60; H, 8,09 %; IR (Nujol): ν = 3070, 1715, 1650, 1600 cm⁻¹; RMN (A 60) (CCl_4) (ppm); δ 1,05 (s) (3 H) (Me angulaire); δ 1,6 (s) (3 H) (Me sur double liaison); δ 0,9 à 3,65 (15 H) (–CH_2– et proton 6α); δ 4,45 à 4,75 (2 H) (protons vinyliques); δ 7 à 7,65 (15 H) (protons aromatiques).

La bis-*méthallyl cétone* **27**, F = 108–110° (pentane), est isolée dans les premières fractions de la chromatographie. IR (film): ν = 1700, 1645, 1600 cm⁻¹. RMN (A 60) (CCl_4) (ppm); δ 0,98 (s) (3 H) (Me angulaire); δ 1,5 et 1,65 (s) (6 H) (Me sur double liaison); δ 0,9 à 3,65 (16 H) (–CH_2– et H 6α); δ 4,45 à 4,9 (4 H) (H vinyliques); δ 7 à 7,65 (15 H) (H aromatiques).

trans-*Acétonyl*-2 *méthyl*-8*aβ trityloxy*-6*β décahydro*-1,2,3,4,4*a*,5,6,7,8,8*a naphtalénone*-1 (**28**)

L'ozonolyse de **26** est effectuée selon la littérature.[20] On fait barboter pendant 90 min un courant d'oxygène ozoné dans une solution de 12,7 g (26,6 m.mol) de méthallylcétone **26** dans 300 cm³ de chlorure de méthylène et 12 cm³ de pyridine à −78°, puis on verse cette solution sur une suspension refroidie de 25 g de poudre de zinc dans, 50 cm³ d'acide acétique. On laisse agiter pendant 90 min, puis on lave à l'eau, sèche ($MgSO_4$) et évapore la phase organique. Le produit brut (12 g, 95 %) est dissous dans l'éther, filtré et concentré à 30 cm³, ce qui fournit 6 g de γ-dicétone **28** (cristallisée). Par chromatographie du résidu, on obtient encore 2,5 g de γ-dicétone **28**. Total: 8,5 g (63 %), F = 152–154° (éther). Recristallisé pour l'analyse, F = 158–159° (éther/CH_2Cl_2). Calc. ($C_{33}H_{36}O_3$): C, 82,46; H, 7,55; Tr.: C, 82,47; H, 7,58 %; IR (Nujol): ν = 1715, 1705, 1600 cm⁻¹; RMN (A 60) ($CDCl_3$) (ppm): δ 1,12 (s) (3 H) (Me angulaire); δ 2,15 (s) (3 H) (CH_3–CO–); δ 1 à 3,6 (15 H) (–CH_2– et H 6α); δ 7,15 à 7,7 (15 H) (H aromatiques).

Ozonide **29**

On fait barboter pendant 25 min un courant d'oxygène ozoné dans une solution refroidie à −78° de 4 g (8,37 m.mol) de méthallyl cétone **26** dans 100 cm³ de chlorure de méthylène et 4 cm³ de pyridine, puis on laisse revenir à TA. La solution est alors lavée avec HCl à 2 %, séchée et évaporée. Après chromatographie du produit brut (4,4 g), on isole 1,3 g (33 %) de γ-dicétone **28**, F = 154–155°, et 1 g (24 %) d'ozonide **29**, F = 133–140°. Echantillon de pureté analytique: F = 132–138° (éther). Calc. ($C_{33}H_{36}O_4$): C, 79,80; H, 7,30; Tr.: C, 80,33; H, 7,40 %; SM. Calc.: 496,261344; Tr.: 496,2617; IR (Nujol): ν = 1600 cm⁻¹; RMN (R 24) ($CDCl_3$) (ppm): δ 0,9 et 1,5 (Me sur trioxacyclopentane, 2 isomères); δ 1,5 (s) (3 H) (Me); δ 0,9 à 3,6 (15 H); δ 7,15 à 7,7 (15 H).

trans-bis-*Acétonyl*-2,2 *méthyl*-8*aβ trityloxy*-6*β décahydro*-1,2,3,4,4*a*,5,6,7,8,8*a naphtalénone*-1 (**30**)

Par ozonolyse de 14,3 g de mélange chromatographié de méthallyl cétone **26** et de *bis*-méthallyl cétone **27** dans 200 cm³ de chlorure de méthylène et 10 cm³ de pyridine, suivie d'un traitement par 10 g de zinc dans 30 cm³ d'acide acétique, on obtient un produit qui, après filtration sur silice fournit 12,7 g d'un mélange de γ-dicétone **28** et de tricétone **30**. Par chromatographie de ce mélange, on isole 4,5 g de γ-dicétone **28** et 5,6 g de tricétone **30**. La tricétone **30** brute est cristallisée dans un mélange éther de pétrole/acétate d'éthyle: 2,1 g, F = 176–179°. Calc. ($C_{36}H_{40}O_4$): C, 80,56; H, 7,51; Tr.: C, 80,08; H, 7,64 %; IR (Nujol): ν = 1690–1720 (bande large), 1600 cm⁻¹; RMN (A 60) ($CDCl_3$) (ppm): δ 1,03 (s) (3 H) (Me angulaire); δ 1,95 et 2,02 (2 s) (3 H chacun) (CH_3CO): δ 7,1 à 7,7 (15 H) (H aromatiques).

2H-*Décahydro*-3,3*a*,4,5,5*a*,6,7,8,9,9*a méthyl*-9*aβ trityloxy*-7*β AB* trans *benz(e)indénone*-2 (**31**)

A une suspension de 1,2 g (12,5 m.mol) de *tertio*-butylate de sodium dans 50 cm³ de benzène sec, on ajoute à TA sous azote une solution de 2 g (4,16 m.mol) de γ-dicétone **28** dans 20 cm³ de benzène. On laisse 3 h à TA, puis on hydrolyse, lave, sèche ($MgSO_4$) et évapore la phase organique. Le résidu obtenu (1,89 g, 98 %) est cristallisé dans l'éther (1 g, 52 %), F = 160–207°. Recristallisé pour l'analyse dans l'acétate d'éthyle ou l'éthanol, F = 209–212°. Calc. ($C_{33}H_{34}O_2$): C, 85,67; H, 7,41; Tr.: C, 85,72; H, 7,42 %; IR (Nujol): ν = 1705, 1615 cm⁻¹; RMN (A 60) ($CDCl_3$) (ppm): δ 1,08 (s) (3 H) (Me angulaire); δ 0,9 à 3,6 (15 H) (–CH_2– et proton 7α); δ 5,63 (1 H) (H vinylique en 1); δ 7,1 à 7,7 (15 H) (H aromatiques).

2H-*Décahydro*-1,4,5,5*a*,6,7,8,9,9*a*,9*b méthyl*-9*aβ trityloxy*-7*β A-B* trans *benz(e)indénone*-2 (**32**)

A une solution de 3,26 g (29 m.mol) de *tertio*-butylate de potassium dans 26 cm³ de *tertio*-butanol sec, on ajoute à TA 4,65 g (9,65 m.mol) de γ-dicétone **28** en solution dans 55 cm³ de benzène sec. On laisse 22 h à TA, puis on hydrolyse par 34 cm³ de HCl 3N, lave la phase organique à l'eau, sèche ($MgSO_4$) et évapore. Par cristallisation dans l'éther du résidu (4,23 g, 95 %) on obtient 1,78 g (40 %) de cétone **32**, F = 189–204°. Le filtrat abandonne 0,5 g (11 %) de la cétone **31** isomère contaminée par un peu de cétone **32**. La cétone **32** est purifiée en vue de l'analyse, F = 208–210° (éther/CH_2Cl_2). Calc. ($C_{33}H_{34}O_2$): C, 85,67; H, 7,41; Tr.: C, 85,28; H, 7,41 %; IR (Nujol): ν = 1705, 1630 cm⁻¹; RMN (A 60) ($CDCl_3$) (ppm): δ 0,58 (s) (3 H) (Me angulaire); δ 0,9 à 3,7 (15 H) (CH_2 et H 7α); 5,8 (1 H) (H vinylique en 3); δ 7,1 à 7,7 massif (15 H) (H aromatiques).

Isomérisation de la cétone **31** *en cétone* **32**

On agite sous azote à TA pendant 24 h un mélange de 2 g (4,35 m.mol) de cétone **31**, 2 g de *tertio*-butylate de potassium, 20 cm³ de *tertio*-butanol et 20 cm³ de toluène. Après hydrolyse par HCl 3N, extraction, lavage, séchage ($MgSO_4$) et évaporation des solvants, on obtient 2 g (100 %) du mélange brut de **31** et **32**. Par cristallisation dans l'éther, on isole 0,78 g (39 %) de l'isomère **32**, F = 189–204°.

3*aH*-*Décahydro*-2,3,4,5,5*a*,6,7,8,9,9*a hydroxy*-7*β méthyl*-9*aβ A-B* trans *benz(e) indénone*-2 (**2**)

La détritylation de **31** est effectuée d'après la littérature.[17] On traite une solution de 2 g (4,34 m.mol) de l'éther trityle **31** dans 10 cm³ d'acide acétique, par 2 cm³ d'une solution saturée d'acide bromhydrique sec dans l'acide acétique. Au bout de 45 secondes à TA, on filtre le précipité obtenu et on verse le filtrat dans 200 cm³ d'eau. On extrait au chloroforme,

lave les phases organiques, sèche ($MgSO_4$) et évapore le solvant. On obtient 2,1 g (~100%) de produit brut dont la chromatographie fournit 0,68 g (72%) de l'hydroxy cétone **2** qui est incristallisable, quoique homogène en CCM. IR (film): ν = 3400, 1705, 1615 cm^{-1}; RMN (A 60) ($CDCl_3$) (ppm): δ 1,13 (s) (3 H) (Me angulaire); δ 1,2 à 3,8 (16 H) (CH_2, H 7α et H de l'hydroxyle); δ 5,80 (1 H) (H vinylique en 1).

2H-Décahydro-1,4,5,5a,6,7,8,9,9a,9b hydroxy-7β méthyl-9aβ A-B trans *benz(e)indénone-2* (**33**)

On traite une solution de 1 g (2,16 m.mol) de l'éther tritylé **32** dans 5 cm^3 d'acide acétique, par 0,5 cm^3 d'une solution saturée d'acide bromhydrique dans l'acide acétique.[17] Au bout de 45 secondes à TA, on filtre et verse le filtrat dans 200 cm^3 d'eau. On extrait au chloroforme, lave, sèche ($MgSO_4$) et évapore le solvant. Par recristallisation dans l'acétate d'éthyle du résidu (0,576 g, ~100%), on obtient 67 mg (14%) de *cétol* **33**, pur, F = 138–141°. Calc. ($C_{14}H_{20}O_2$): C, 76,3; H, 9,15; Tr.: 76,26; H, 9,08%; IR (Nujol): ν = 3400, 1700, 1630 cm^{-1}; RMN (A 60) ($CDCl_3$) (ppm): δ 0,60 (s) (3 H) (Me angulaire); δ 1 à 3,9 (16 H) (CH_2, H 7α et H de l'hydroxyle); δ 5,90 (1 H) (H vinylique en 3).

1H-Dodécahydro-2,3,3a,4,5,5a,6,7,8,9,9a,9b méthyl-gaβ trityloxy-7β trans-anti-trans *benz(e) indénone-2* (**34**)

(a) *Préparation à partir du composé* **31**. On ajoute en 15 min une solution de 0,862 g (1,87 m.mol) de cétone éthylénique **31** dans 50 cm^3 de THF anhydre, à une solution de 90 mg (12,9 m.mol) de lithium dans 300 cm^3 d'ammoniac liquide. Au bout de 30 min, on ajoute NH_4Cl solide, évapore l'ammoniac, hydrolyse et extrait au chloroforme. Après lavage, séchage ($MgSO_4$) et évaporation du solvant, on recueille 0,593 g de produit brut que l'on dissout dans 2 cm^3 de pyridine. On ajoute 388 mg (1,385 m.mol) de chlorure de trityle et on chauffe sous azote 3 h à 110–120°. Après refroidissement, on reprend par de l'eau, extrait au chloroforme, lave, sèche ($MgSO_4$) et évapore le solvant. Repris par du benzène, le produit brut (0,855 g) laisse déposer 238 mg de triphénylméthane. Après évaporation de la liqueur mère et chromatographie du résidu, on obtient 183 mg (21%) de cétone réduite **34**, F = 178–186° (éthanol). Calc. ($C_{33}H_{36}O_2$): C, 85,30; H, 7,81; Tr.: C, 85,15; H, 7,66%; IR (Nujol): ν = 1740; RMN (MH 100) ($CDCl_3$) (ppm): δ 0,76 (s) (3 H) (Me angulaire); δ 0,8–3,5 (18 H) (CH_2 et H 7α); δ 7–7,7 (15 H) (H aromatiques).

(b) *Préparation à partir du composé* **32**. On ajoute en 25 min une solution de 0,565 g (1,22 m.mol) de cétone éthylénique **32** dans 35 cm^3 de THF anhydre à une solution de 59 mg (8,4 m.mol) de lithium dans 200 cm^3 d'ammoniac liquide. Après 20 min, on détruit l'excès de réactif par NH_4Cl solide, évapore l'ammoniac à TA, reprend par l'eau et extrait au chloroforme. Les phases organiques sont lavées à l'eau jusqu'à neutralité, séchées et évaporées. On obtient 0,533 g de produit que l'on met en solution dans 2 cm^3 de pyridine et que l'on traite par 338 mg (1,21 m.mol) de chlorure de trityle. Le mélange est chauffé 3 h à 100–110° sous azote. Après refroidissement, on reprend par l'eau et extrait au chloroforme; les phases organiques sont lavées à l'eau jusqu'à neutralité, séchées ($MgSO_4$) et évaporées. Repris par le benzène, le produit brut (0,728 g) laisse déposer 151 mg de triphénylméthane. Le résidu de cristallisation est chromatographié, ce qui fournit 85 mg (15%) de cétone hydrogénée **34**, F = 181–187° (éthanol). Point de fusion de mélange avec le composé préparé au §(a) ci-dessus: F = 173–178°. Spectres IR et de RMN identiques à ceux du composé préparé au § (a) ci-dessus.

1H-Dodécahydro-2,3,3a,4,5,5a,6,7,8,9,9a,9b méthyl-9aβ trityloxy-7β trans-syn-cis *benz(e)indénone-2* (**35**)

On hydrogène sous 3 atm 0,203 g (0,44 m.mol) de cétone éthylénique **31** en présence de Pd/C à 10% dans 50 cm^3 d'acétate d'éthyle, pendant 45 h à TA. Par chromatographie du produit de réaction (0,316 g, ~100%), on obtient 0,116 g (57%) de cétone hydrogénée **35**, F = 152–159 , (éther). Recristallisée dans l'éthanol, F = 164–168°. Calc. ($C_{33}H_{36}O_2$): C, 85,30; H, 7,81; Tr.: C, 85,06; H, 7,58%; IR (Nujol): ν = 1730 cm^{-1}; RMN (MH 100) ($CDCl_3$) (ppm): δ 0,96 (s) (3 H) (Me angulaire); δ 0,8–2,6 (17 H) (CH_2); δ 3,2–3,5 (1 H) (H en 7α); δ 7–7,6 (15 H) (H aromatiques).

1H-Dodécahydro-2,3,3a,4,5,5a,6,7,8,9,9a,9b méthyl-9aβ trityloxy-7β trans-anti-cis *benz(e)indénone-2* (**36**)

On hydrogène sous 1,3 atm 0,462 g (1 m.mol) de cétone éthylénique **32** en présence de Pd/C à 10% dans 50 cm^3 d'acétate d'éthyle pendant 4 h à TA. Par chromatographie sur silice du produit de réaction (0,44 g, 95%), on obtient 55 mg (12%) de cétone hydrogénée **36**, F = 236–237° (acétate d'éthyle). Calc. ($C_{33}H_{36}O_2$): C, 85,30; H, 7,81; Tr.: C, 85,40; H, 7,63%; IR (Nujol): ν = 1740 cm^{-1}; RMN (MH 100) ($CDCl_3$) (ppm): δ 0,7 (s) (3 H) (Me angulaire); δ 0,8–3,8 (18 H) (CH_2 et H en 7α); δ 7,2–7,7 (15 H) (H aromatiques).

*3aH-Décahydro-2,3,4,5,5a,6,7,8,9,9a hydroxyméthylène-3 méthyl-9aβ trityloxy-7β A,B-*trans *benz(e)indénone-2* (**42**)

On mélange sous azote une solution de 3,5 g (7,6 m.mol) de cétone **31** dans 10 cm^3 de benzène sec, avec une suspension de 2,26 g (20 m.mol) de *tertio*-butylate de potassium, dans le même solvant, puis on ajoute 40,5 cm^3 de formiate d'éthyle distillé, et on chauffe à 50–60° pendant 6 h. On reprend par de l'acide étendu, on lave et sèche ($MgSO_4$) les phases organiques. Par évaporation du solvant, on recueille 4 g (~100%) de produit résineux qui, après filtration sur silice, fournit 3,2 g (86%) d'hydroxy méthylène cétone **42** brute. Par recristallisation dans l'éther, on obtient 2,3 g (62%) d'hydroxyméthylène cétone **42**, F = 100–123°. IR (Nujol): ν = 3600–2500 (énol), 1670, 1600 cm^{-1}; RMN (MH 100) ($CDCl_3$) (ppm): δ 1,07 (s) (3 H) (Me angulaire); δ 0,7 à 2,3 (15 H); δ 3–3,7 (2 H); δ 5,65 et 5,83; δ 7,1; δ 7,2–7,7 (15 H) (H aromatiques); δ 7,8–8,3 (1 H).

*Obtention de la 3aH-décahydro-2,3,4,5,5a,6,7,8,9,9a méthyl-9aβ (oxo-3 butyl)-3 trityloxy-7β A,B-*trans *benz(e)indénone-2* (**38**) *à partir de l'α-hydroxyméthylène cétone* **42**

A une suspension de 220 mg (2 m.mol) de *tertio*-butylate de potassium dans 5 cm^3 de benzène sec sous azote à TA, on ajoute une solution de 1 g (2 m.mol) de l'α-hydroxyméthylène cétone **42**, puis 320 μl (2 éq.) de MVC fraîchement distillée. On laisse 2 h à TA, puis reprend par l'eau, neutralise la solution et extrait au benzène. Après séchage ($MgSO_4$) des phases organiques et évaporation, on obtient 990 mg (91%) de produit brut, dont la chromatographie fournit 269 mg (25%) de δ-dicétone **38** que nous ne sommes pas parvenus à faire cristalliser. IR (film) ($CDCl_3$): ν = 1710, 1690, 1615 cm^{-1}; RMN (A 60) ($CDCl_3$) (ppm): δ 1,05 (s) (3 H) (Me angulaire); δ 2,09 (s) (3 H) (CH_3CO); δ 0,8 à 3,6 (24 H); δ 5,57 (1 H) (H vinylique); δ 7,1 à 7,7 (15 H) (H aromatiques).

*3aH-Octahydro-4,5,5a,6,7,8,9,9a méthyl-9aβ triméthylsiloxy-2 trityloxy-7β A,B-*trans *benz(e)indène* (**43**, R = $SiMe_3$)

Le mode opératoire s'inspire de la littérature.[32,33] A 0 , sous azote, on prépare une solution de diisopropylamidure de lithium, à partir de *n*-BuLi 1,75 M (0,3 cm^3, 0,53 m.mol) dans le THF (2 cm^3) et de diisopropylamine distillée (60 μl), puis on ajoute une solution de cétone **31** (92 mg, 0,2 m.mol) en solution dans 2 cm^3 de THF. Au bout de quelques instants, on ajoute 0,3 cm^3 d'une solution constituée d'un mélange centrifugé de 2 cm^3 de chlorure de triméthyl silyle et de 0,5 cm^3 de triéthylamine. On laisse à 0 quelques minutes, et on isole le produit de réaction de la façon habituelle, après hydrolyse, extraction et lavage des phases organiques, séchage ($MgSO_4$) et évaporation du solvant. On obtient ainsi 74 mg (17%) d'éther d'énol silylé **43** (R = $-SiMe_3$) brut. Les spectres suivants ont été pris avec le produit brut. IR (film): ν = 1625 cm^{-1} (pas de carbonyle ni d'hydroxyle); RMN (A 60) ($CDCl_3$ sans TMS) (ppm): δ 0,1 à 0,3 (~9 H) (Me_3Si); δ 1,08 (s) (3 H) (Me angulaire); δ 0,8–1,7 (15 H); δ 5,05 et 5,55 (2 H) (H vinyliques); δ 7,15–7,7 (H aromatiques).

*3aH-Décahydro-2,3,4,5,5a,6,7,8,9,9a diméthyl-3,9aβ trityloxy-7β A,B-*trans *benz(e)indénone-2* (**45**) et *3aH-décahydro-2,3,4,5,5a,6,7,8,9,9a triméthyl-3,3,9aβ trityloxy-7β A,B-*trans *benz(e)indénone-2* (**46**)

A 0°, sous azote, on prépare une solution de diisopropylamidure de lithium à partir de BuLi 1,75 M (0,5 cm^3, 0,88 m.mol) dans 2 cm^3 de THF, et de 100 μl de diisopropylamine distillée, puis on ajoute une solution de cétone **31** (184 mg, 0,4 m.mol) dans 2 cm^3 de THF. Au bout de quelques minutes, on ajoute 60 μl d'iodure de méthyle, on laisse à TA pendant 20 min, puis on hydrolyse et extrait au chloroforme. Les phases organiques sont lavées, séchées ($MgSO_4$) et évaporées, abandonnant 147 mg du mélange brut de **45** + **46**. Par chromatographie du produit brut sur plaques "préparatives", on obtient ainsi 36 mg (18%) d'α-diméthylcétone **46** qui ne cristallise pas, et 28 mg (15%) d'α-méthylcétone **45** qui cristallise dans l'éther, F = 185–189°. **45** et **46** ont des R_f nettement différents du R_f de **31**.

α-Méthylcétone **45**

SM. Calc.: 476,271516; Tr.: 476,2712 pour la formule brute $C_{34}H_{36}O_2$; IR (Nujol): ν = 1705, 1615 cm^{-1}; RMN (A 60) ($CDCl_3$) (ppm): δ 1,05 (s) (3 H) (Me angulaire); δ 1,18 et 1,05 (d) (3 H) (Me en 3); δ 0,9–3,8 (20 H dont 6 pour les 2 Me); δ 5,62 (1 *H*) (H vinylique en 1); δ 7,15–7,7 (15 H) (H aromatiques).

α-Diméthylcétone **46**

Sm. Calc.: 490,287165; Tr.: 490,2868 pour la formule brute $C_{35}H_{38}O_2$; IR (CCl_4): ν = 1705,1615 cm^{-1}; RMN (A 60) ($CDCl_3$) (ppm): δ 0,9, 1,05 et 1,08 (s) (3 × 3 H) (Me angulaire et Me en 3); δ 0,9–3,7 (22 H dont 9 H dans 3 Me); δ 5,6 (1 H) (H vinylique en 1); δ 7,15–7,7 (15 H) (H aromatiques).

*3aH-Décahydro-2,3,4,5,5a,6,7,8,9,9a méthyl-9aβ (oxo-3 butyl)-3 trityloxy-7β A,B-*trans *benz(e) indénone-2* (**38**)

On prépare à −78° sous azote une solution de diisopropylamidure de lithium, à partir de BuLi 1,9 M (4,74 cm^3, 9 m.mol) et de diisopropylamine (1,26 cm^3, 9 m.mol) dans 5 cm^3 de THF. Puis on ajoute une solution de 2,76 g (6 m.mol) de cétone **31** dans 30 cm^3 de THF. On attend 15 min, puis on introduit 1,482 cm^3 (9 m.mol) de la vinylcétone silylée **47**.[34,35] On laisse revenir à TA, puis on hydrolyse à l'eau acidulée. On extrait le mélange au chlorure de méthylene, lave les phases organiques à l'eau, sèche et évapore le solvant. Le produit brut obtenu (3,7 g) est chromatographie, ce qui fournit 2,4 g (75%) de δ-dicétone **38**, F = 119–125°. SM. Calc.: 532,297728; Tr.: 532,2970 pour la formule brute $C_{37}H_{40}O_3$; IR (film) ($CDCl_3$): ν = 1700 (large), 1615 cm^{-1}; RMN (A 60) ($CDCl_3$) (ppm): δ 1,03 (s) (3 H) (Me angulaire); δ 2,09 (s) (3 H) (CH_3CO); δ 0,9 à 3,8 (24 H, y compris les 2 Me); δ 5,6 (1 H) (H vinylique); δ 7,1 à 7,7 (15 H) (H aromatiques).

6aH-Dodécahydro-1,2,3,4,4a,6,6b,7,8,9,11b méthyl-11bβ trityloxy-3β chrysofluorénone-9 (**48**)

On agite sous azote à TA un mélange de *tertio*-butylate de potassium (1,5 g, 13 m.mol), d'alcool *tertio*-butylique (9 cm^3), de toluène (9 cm^3), et d'une solution de δ-dicétone **38** cristallisée (1,8 g, 3,38 m.mol) dans 15 cm^3 de toluène, pendant 4 h. On refroidit le mélange réactionnel dans la glace, hydrolyse à l'eau acidulée, extrait au toluène, lave, sèche et évapore la phase organique, ce qui fournit ainsi 1,46 g (84%) de composé **48** brut, cristallisable dans l'éther, F = 196–206°. La RMN du produit brut montre que la δ-dicétone **38** a été entièrement crotonisée. SM. Calc.: 514,287166; Tr.: 514,2863 pour la formule brute $C_{37}H_{38}O_2$; IR (Nujol): ν = 1650, 1615, 1595 cm^{-1}; RMN (A 60) ($CDCl_3$) (ppm): δ 0,97 (s) (3 H) (Me angulaire); δ 0,9 à 3,8 (21 H, dont le Me angulaire et H 3α); δ 5,7 et 5,8 (2 H) (H vinyliques); δ 6,9 à 7,7 (15 H) (H aromatiques).

6aH-Dodécahydro-1,2,3,4,4a,5,6,6b,7,8,9,11b hydroxy-3β méthyl-11bβ chrysofluorénone-9: C-nor D-homostéroide **4** *et épimère H-6bβ* **49**

Le produit brut (1,46 g, 2,8 m.mol) de crotonisation de la δ-dicétone **38** chromatographiée, mis en solution dans l'acide acétique (10 cm^3), est traité par 1,5 cm^3 d'une solution saturée de HBr dans l'acide acétique. On laisse reposer 1 min, puis on vers dans de l'eau froide, et extrait avec CH_2Cl_2. Après lavage (H_2O), séchage et évaporation des extraits organiques, il reste 1,418 g d'un mélange de triphényl méthanol et de composés **4** et **49**, que l'on dissout dans l'acétate d'éthyle, ce qui fournit 188 mg de cristaux, F = 170–187° (mélange environ 50:50 de **4** et **49**). Par recristallisations successives de ce solide, on obtient 10 mg de l'épimère **49** purifié, F = 199–208° (AcOEt). Le résidu de la première cristallisation est chromatographié, ce qui donne 236 mg (31%) de C-nor D-homostéroïde **4** purifié, F = 153–158°.

Composé **4**:

Calc. ($C_{18}H_{24}O_2$): C, 79,37; H, 8,88; O, 11,74; Tr.: C, 79,37; H, 8,93; O, 11,94%; SM. Calc.: 272,177620; Tr.: 272,1774 pour la formule brute $C_{18}H_{24}O_2$; IR (Nujol): ν = 1630, 1605, 1575 cm^{-1}; UV (éthanol) (Acta III); λ_{max} = 295, nm, ε = 23760; RMN (MH 100) ($CDCl_3$) (ppm): δ 1,04 (s) (3 H) (Me angulaire); δ 0,9–3,9 (22 H, dont le Me angulaire, H 3α et H hydroxylique); δ 5,76 et 5,98 (2 × 1 H) (H vinyliques).

Composé **49**:

IR (Nujol): ν = 1630, 1610, 1580 cm^{-1}; UV (éthanol) (DK IIA): λ_{max}: 295 nm, ε = 22460; RMN (MH 100) ($CDCl_3$) (ppm): δ 1,16 (s) (3 H) (Me angulaire; contaminé par un peu de **4**, Me angulaire à 1,04); δ 0,9 à 3,9 (22 H); δ 5,88 et 6 (2 × 1 H) (H vinyliques).

Remerciements—Nous tenons à remercier le Professeur J. P. Kutney pour les spectres et l'échantillon de produit qu'il nous a aimablement fait parvenir.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 73 to 79, 1981
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0040-4020/81/Suppl. 1-0073-07 $02.00/0
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FUNCTIONAL GROUP OXIDATION BY PENTAVALENT ORGANOBISMUTH REAGENTS†

DEREK H. R. BARTON, JONATHAN P. KITCHIN, DAVID J. LESTER, WILLIAM B. MOTHERWELL* and M. TERESA BARROS PAPOULA

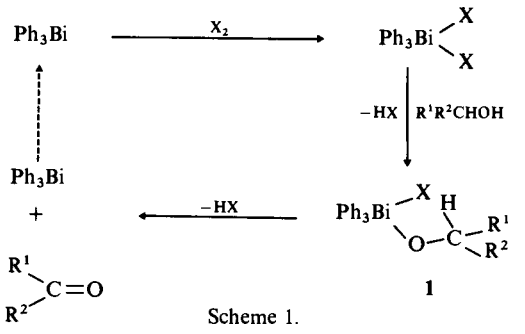
Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France

(*Received in U.K.* 18 *June* 1980)

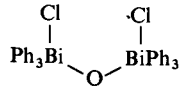
Abstract—Full experimental details are given for the oxidation of organic substrates by a variety of pentavalent organobismuth reagents. The remarkable selectivity of these reagents, particularly for oxidation of the allylic OH group under mild conditions, is exemplified. The mechanisms of alcohol oxidation and glycol cleavage are discussed.

The development of new methods for the selective oxidation of the OH group under neutral conditions continues to be a fundamental objective of modern organic synthesis. A major disadvantage of the numerous chromium based reagents lies in problems associated with their electrophilic nature and with the generation of intermediates formed by transfer of a single electron.[1] We conceived[2] that the inherent capability of the two electron bismuth (V)–bismuth (III) change should provide a convenient source of oxidising power (see (1)) and also afford the potential opportunity of developing a catalytic cycle based on trivalent bismuth (Scheme 1). Furthermore, we were attracted by the wide variety of crystalline pentavalent triaryl bismuth derivatives available.[3] Many of these substances are readily prepared, indefinitely stable, and reasonably soluble in organic solvents.

Examination of the literature revealed that very limited use had been made of bismuth (V) organic derivatives. Inorganic reagents, such as sodium bismuthate,[4] and bismuth trioxide[5] have been employed, normally under acidic conditions, to effect glycol cleavage and specific oxidation of acyloins to α-diketones. We were particularly encouraged by an isolated observation of Challenger and Richards[6] that oxidation of ethyl n- and iso-propyl alcohols with the unstable reagent, triphenylbismuth dihydroxide, led to the formation of the corresponding carbonyl compounds. These were isolated as their 2,4-dinitrophenyl-hydrazone derivatives in unspecified yield.



Scheme 1.



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Initially, we chose to investigate the properties of μ-oxobis (chlorotriphenylbismuth) (**2**), which is readily prepared by the action of alkali on triphenylbismuth dichloride.[7] The results obtained (Table 1) indicate that excellent yields of aldehydes and ketones can be obtained from a variety of hydroxy containing compounds under very mild conditions. We wish to emphasize that the oxidation of allylic alcohols by this method is a particularly facile process and that cleavage of 1,2-glycols also proceeds smoothly and in high yield. The selective oxidation of methyl hederagenin (**7**) to the ketone **8** without concomitant retroaldol reaction represents an improvement over the published method.[8]

We subsequently undertook a more detailed investigation of the reagent (**2**) and of its pentavalent congeners Ar_3BiX_2. As expected, introduction of electron withdrawing substituents on the aromatic ring led to an enhanced rate of reaction (*p*-tolyl : phenyl : *p*-chlorophenyl : *m*-nitrophenyl = 1 : 1.5 : 6 : > 10). However, under the standard conditions which we had developed for the reagent **2** using carbonate or bicarbonate anion as the "base", it was initially surprising to observe that the rate of the reaction was unaltered by the nature of the leaving group in the series X = Cl, Br, ONO_2. In addition, replacement of carbonate or bicarbonate by pyridine or collidine led to sluggish reactions and substantial loss of oxidizing power. It was therefore reasonable to conclude that the active oxidant produced in all of these reactions involved the formation of a pentavalent triarylbismuth intermediate possessing a carbonate ligand.

Triphenylbismuth carbonate itself was simply prepared by reaction of triphenylbismuth dichloride with potassium carbonate in aqueous acetone.[9] In contrast to the previously described reagents this amorphous substance appears to have a limited

†Dedicated with respect to the memory of Robert Burns Woodward.

Table 1. Oxidation of the hydroxyl group, by μ-oxo-bis-(chlorotriphenylbismuth)

ALCOHOL	TIME (H)	TEMP. °C	BASE	PRODUCT	YIELD %
PRIMARY					
1-PENTANOL	6	60	A	PENTANAL [a]	79
SECONDARY					
CHOLESTANOL	30	21	B	CHOLESTANONE	75
TIGOGENIN (3)	4	60	A	TIGOGENONE	80
α-AMYRIN (4)	15	21	B	α-AMYRONE	86
TESTOSTERONE (5)	4	60	A	ANDROST-4-ENE-3,17-DIONE	88
CHOLESTAN-3β,6β-DIOL (6)	15	21	B	CHOLESTAN-3β-OL-6-ONE	50
				CHOLESTAN-3,6-DIONE	25
PRIMARY v. SECONDARY					
METHYLHEDERAGENIN (7)	24	21	B	METHYLHEDERAGONATE (8)	36
BENZYLIC					
BENZYL ALCOHOL	15	21	B	BENZALDEHYDE [a]	82
P-NITROBENZYL ALCOHOL	1	60	A	P-NITROBENZALDEHYDE [a]	87
ANISYL ALCOHOL	1	60	A	ANISALDEHYDE [a]	75
ALLYLIC					
CHOLEST-1-EN-3β-OL (9)	6	21	B	CHOLEST-1-EN-3-ONE	85
CHOLEST-4-EN-3β-OL	6	21	B	CHOLEST-4-EN-3-ONE	89
(-)-CARVEOL	6	21	B	CARVONE [a]	84
CROTYL ALCOHOL	5	60	A	CROTONALDEHYDE [a]	76
CINNAMYL ALCOHOL	15	21	B	CINNAMALDEHYDE [a]	83
GERANIOL	15	21	B	GERANIAL [a]	95
3-METHYL-BUT-2-EN-1-OL	2	60	A	3-METHYL-BUT-2-EN-AL [a]	90
VITAMIN A ALCOHOL	15	21	A	VITAMIN A ALDEHYDE [a]	68
α-GLYCOL CLEAVAGE					
MESO-HYDROBENZOIN	3	21	B	BENZALDEHYDE [a]	80
1,2,5,6-DI-O-ISOPROPYLIDENE-D-MANNITOL	0.25	60	A	2,3-ISOPROPYLIDENE-D-GLYCERALDEHYDE	76

(a) isolated as the 2,4-dinitrophenylhydrazone derivative.
A Sodium Bicarbonate
B Potassium Carbonate

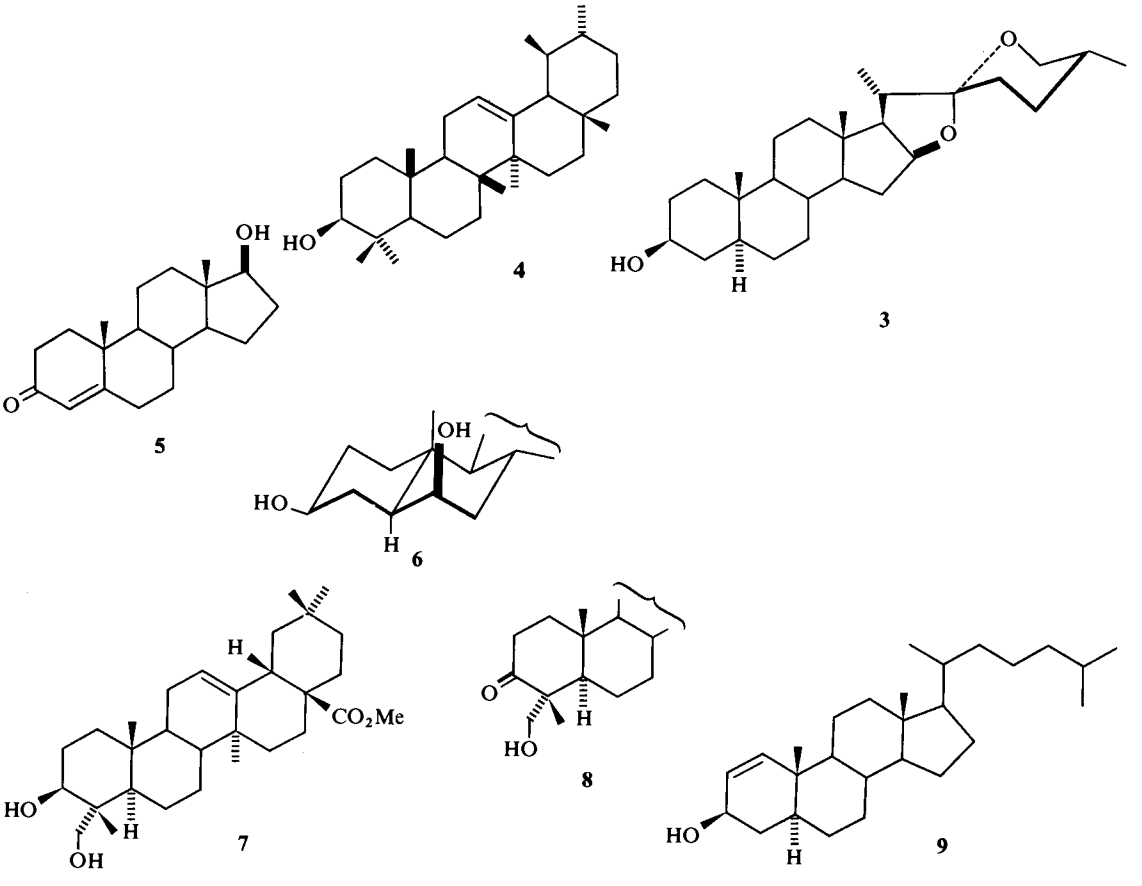


Table 2. Functional group selectivity in oxidation with triphenylbismuth carbonate.

SUBSTRATE	TIME (H)	TEMP. °C	PRODUCT	YIELD %
SECONDARY ALCOHOL				
t-BUTYLPHENYLMETHANOL ≠	18	40	t-BUTYLPHENYL KETONE	90
ALLYLIC ALCOHOL				
(-)-CARVEOL	1.5	40	(-)-CARVONE	84
CHOLEST-4-EN-3 -OL	18	20	CHOLEST-4-EN-3-ONE	97
GERANIOL	2.5	40	GERANIAL[a]	95
SELECTIVITY				
ANDROST-4-EN-3β,17β-DIOL	43	20	TESTOSTERONE[b]	51
			ANDROST-4-EN-3,17 DIONE	15
			ANDROST-4-EN-3β,17β-DIOL	22
CHOLESTAN-3β-OL (1 EQUIV.) + CHOLEST-4-EN-3 -OL (1 EQUIV.)	5.5	40	CHOLESTAN-3β-OL	80
			CHOLEST-4-EN-3-ONE	89
THIOPHENOL (1 EQUIV.) + CHOLEST-4-EN-3β-OL (1 EQ.)	24	20	CHOLEST-4-EN-3-ONE	76
ISO-BUTYLTHIOL (1 EQUIV.) + CHOLEST-4-EN-3β-OL (1 EQUIV.)	23	40	CHOLEST-4-EN-3-ONE	95
PYROLLIDINE (1 EQUIV.) + (-)-CARVEOL (1 EQUIV.)	18	20	(-)-CARVONE	87
INDOLE (1 EQUIV.) + (-)-CARVEOL (1 EQUIV.)	24	24	(-)-CARVONE	80
β-METHYLSELENOTETRADECAN-7-OL (10)	48	40	β-METHYLSELENOTETRADECAN-7-ONE	86
N-ACETYLEPHEDRINE	18	40	N-ACETYL-α-METHLAMINO-PROPIOPHENONE	75
EPHEDRINE (11)	1.5	40	BENZALDEHYDE[a]	100
THIOLS				
THIOPHENOL	18	20	DIPHENYLDISULPHIDE	70
ORTHO-THIOCRESOL	3	20	DI-ORTHO-TOLYLDISULPHIDE	90
PARA-THIOCRESOL	3	20	DI-PARA-TOLYLDISULPHIDE	89
MISCELLANEOUS				
5-α-CHOLESTAN-3-ONE OXIME	15	20	5-α-CHOLESTAN-3-ONE	90
BENZOPHENONE HYDRAZONE	5	20	DIPHENYLDIAZOMETHANE	97
HYDRAZOBENZENE	1.5	20	AZOBENZENE	90
PHENYLHYDRAZOTRIPHENYL-METHANE	4	20	PHENYLAZOTRIPHENYLMETHANE	89
1,2,5,6-DI-O-ISOPROPYLIDENE-3(N-4-NITROPHENYLTHIONO-CARBAMATO)-α-D-GLUCOFURA-NOSE (12)	17	40	DISULPHIDE (13)	91
2,3,4,6-TETRA-O-BENZYL-α-D-GLUCOPYRANOSE (14) ≠	4	40	2,3,4,6-TETRA-O-BENZYL-GLUCONIC ACID δ LACTONE	89
GLYCOL CLEAVAGE				
CIS-CYCLOHEXANE 1,2 DIOL	2	40	1,6-HEXANEDIAL	100
MESO-HYDROBENZOIN	1.5	40	BENZALDEHYDE	97
1,2,5,6-DI-O-ISOPROPYLI-DENE D-MANNITOL	2	40	2,3-O-ISOPROPYLIDENE-D-GLYCERALDEHYDE	89

The following compounds were not oxidised by the reagent, (compound, temp., time). Benzophenone phenylhydrazone, 40, 24 ; Benzophenone 2,4 dinitrophenylhydrazone, 40, 24 ; Benzophenone semicarbazone, 20, 72 ; 5α-cholestan-3-one tosylhydrazone, 20, 24 ; Tri-O-acetyl glucal, 20 , 24 ; Aniline, 20, 18 ; N,N-dimethylaniline, 20 , 24 ; 3-pyrollidino-cholesta-3,5 diene, 20, 24 ; Di-t-butyl thionoketone. 40, 16 ; 3β-cholestanyl-S-methyl xanthate, 40, 24 ; 3β-cholestanyl-N,N diethyl thionocarbamate 40, 24,

(a) Isolated as the 2,4 dinitrophenylhydrazone derivative.
(b) The reagent was prepared in situ by reaction of Ph_3BiCl_2 and K_2CO_3.
≠ Experiment performed by Mlle. B. Charpiot.

solubility in common organic solvents. Nevertheless, it is a highly selective non-electrophilic oxidant for a variety of functional groups (Table 2). Once again, allylic oxidation and glycol cleavage occur rapidly and in high yield. The selective oxidation of an allylic alcohol in the presence of a secondary alcohol is noteworthy, as is the oxidation of the hydroxy selenide (**10**). The thiocarbonyl group in xanthates, dialkylaminothionocarbamates, or in di-t-butyl thionoketone is unaffected, but oxidation of the mono-arylthionocarbamate (**12**) gave the disulphide (**13**). Although C–C bond cleavage with formation of benzaldehyde was observed on attempted oxidation of ephedrine (**11**), oxidation of the derived acetamide gave the corresponding ketone. Treatment of the carbohydrate hemiacetal (**14**) gave the known lactone which was further characterised by formation of a crystalline hydroxy amide.[10] The competitive oxidation of an allylic alcohol in the presence of a thiol is without precedent. Since aniline, dimethylaniline, pyrollidine, indole and 3-pyrollidino-cholesta 3,5-diene are inert under standard conditions the reagent should find application in complex natural product synthesis.

We have also discovered that homogeneous oxidation of allylic alcohols can be accomplished by employing triphenylbismuth diesters (X = acetate, benzoate and trifluoroacetate) in the presence of

strong bases such as tetramethyl-guanidine (TMG) and 1,5 diazabicyclo |5,4,0| undec-5-ene (DBU).

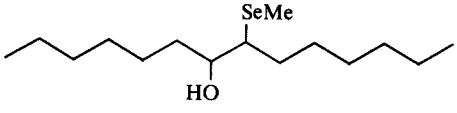
Several features of mechanistic interest deserve some comment. The selective oxidation of the more hindered 6β-OH group in cholestan-3β,6β-diol (**6**) would suggest that the normal rate determining step involves breakdown of an intermediate of type **1**. However, there was no observable difference in rate between the oxidation of benzyl alcohol and *p*-nitrobenzyl alcohol nor between benzyl alcohol and anisyl alcohol when a mixture of the two alcohols was allowed to compete for a deficiency of oxidant. In the oxidation of t-butylphenylmethanol by chromium trioxide the intermediate chromate (IV) ester is known to undergo electron transfer with elimination of the t-Bu radical and formation of benzaldehyde.[11] However, oxidation with triphenylbismuth carbonate proceeds cleanly to give the corresponding ketone.

We have consistently monitored the yield of recovered triarylbismuth after oxidation with the objective of developing a catalytic cycle based on bismuth (III). This yield should, if the above mechanism is operative, be comparable with the yield of the oxidised organic substrate, since we have shown that triphenylbismuth itself is stable under the conditions of the reaction. In the event, however, significant variation has been observed according to the nature of the leaving group X. Thus, in the oxidation of (−)-carveol by triphenylbismuth diacetate, ditrifluoroacetate and carbonate the recovered yields of triphenylbismuth are 32%, 0% and 50% respectively. Accordingly, it was of interest to examine the reaction mixture directly by NMR spectroscopy. Oxidation of (−)-carveol with triphenylbismuth dibenzoate in deuterochloroform containing tetramethylguanidine resulted in the growth of an aromatic singlet (δ 7.24) whose chemical shift was identical with benzene. Moreover, it was possible to isolate toluene by repetition of the experiment using tri-*p*-tolyl-bismuth dibenzoate in tetralin as solvent. Finally, oxidation of deuteriocarveol (**5**) with tri-*p*-methoxyphenyl bismuth carbonate furnished exclusively *p*-deuterioanisole as established by 400 MHz NMR spectra. It is thus apparent that the facile cleavage of the bismuth-aryl bond results in two competitive pathways for the breakdown of the organobismuth ester intermediate **1** (Scheme 2).

The addition of nitrosomesitylene or nitrosobenzene does not alter the course of a typical oxidation reaction and we do not consider that free radicals are involved in normal Bi(V) reactions.

The mechanism of glycol cleavage is entirely different. The cleavage of *cis*-1,2-cyclohexanediol is considerably faster than that of the *trans*-isomer and yields of recovered triphenylbismuth are essentially quantitative in all cases so far studied. These results provide strong presumptive evidence for the preferential formation of a cyclic organobismuth intermediate (**17**) which breaks down with exclusive formation of triphenylbismuth. A catalytic cycle for glycol cleavage is therefore a practical possibility. Preliminary studies (Table 3) indicate that cleavage of hydrobenzoin by hydrogen peroxide in the presence of sodium bicarbonate, or by tertiary butyl hydroperoxide can be catalysed by triphenylbismuth. Attempts to extend this reaction to other glycols have so far been unsuccessful.

In summary, pentavalent organobismuth reagents are mild, nonelectrophilic and highly selective



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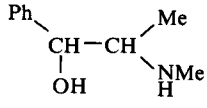

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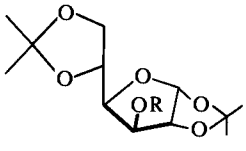

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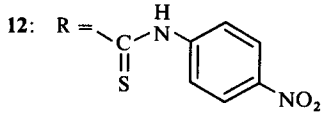

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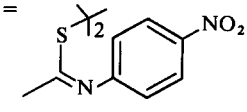

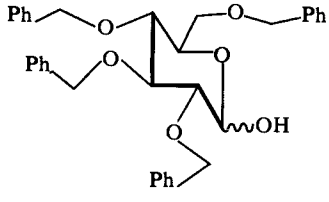

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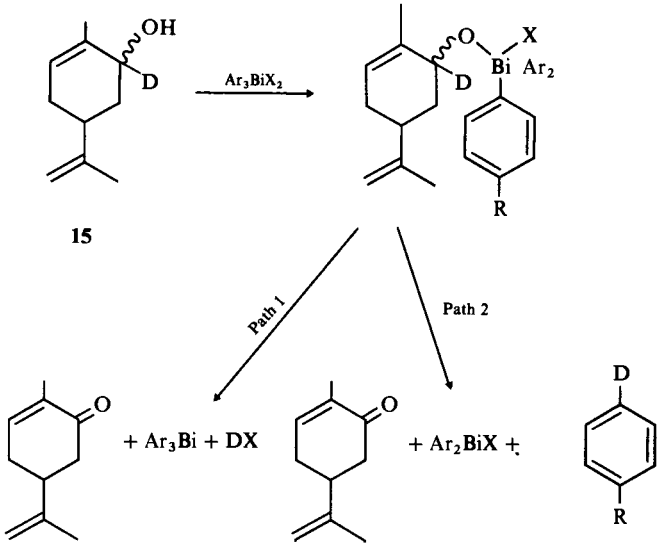

Scheme 2.

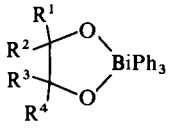

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Table 3. Cleavage of *meso*-hydrobenzoin catalysed by triphenylbismuth

TRIPHENYLBISMUTH N° OF EQUIV.	BENZALDEHYDE YIELD %			
	HYDROGEN PEROXIDE (3 EQ.) + $NaHCO_3$ (9 EQ.)	TIME H.	T-BUTYL HYDROPEROXIDE (3 EQ.)	TIME H.
1.0	98	1	93	2.5
0.5	-	-	93	2.5
0.25	94	1	90	16
0.1	73	2	84	16
0.05	70	16	-	

oxidants. From the practical standpoint, anhydrous conditions are not necessary, and unlike manganese dioxide,[12] chromium trioxide-pyridine[13] and silver carbonate on celite,[14] a large excess of reagent is not required.

EXPERIMENTAL

M.ps were determined with a Kofler hot stage apparatus and are uncorrected. NMR spectra were determined for solns in (^{2}H) chloroform with TMS as internal standard on Varian T-60 and Varian E.M. 360 instruments. IR spectra were recorded on a Perkin Elmer 257 instrument. Optical rotations were measured on a Perkin Elmer 141 polarimeter and mass spectra were recorded with an AEI M.S 9 instrument. Organic extracts were dried over Na_2SO_4 and evaporated at reduced pressure. All solvents and reagents were purified and dried by standard techniques.

Preparation of organobismuth reagents

Triphenylbismuth was prepared by reaction of bismuth trichloride with phenylmagnesium bromide.[15] Tri(*p*-tolyl)bismuth, [16]tri(*p*-methoxyphenyl) bismuth[17] and tri(*p*-chlorophenyl) bismuth[18] were prepared in an analogous manner. Triphenylbismuth dibromide,[19] triphenylbismuth dichloride,[20] tri(*p*-tolyl)bismuth dichloride,[21] tri(*p*-methoxyphenyl)bismuth dibromide[22] and tri(*p*-chlorophenyl)bismuth dichloride[23] were prepared by the action of the halogen with the triarylbismuth. Triphenylbismuth diacetate[24] and triphenylbismuth di(trifluoroacetate)[25] were prepared by the reaction of triphenylbismuth carbonate[9] with the acid. Triphenylbismuth dibenzoate[26] was prepared by reaction of triphenylbismuth with dibenzoyl peroxide. Trephenylbismuth dinitrate[27] and tri(*p*-tolylbismuth) dinitrate[28] were prepared from the corresponding dichlorides by reaction with silver nitrate. Nitration of triphenylbismuth dinitrate with fuming nitric acid gave tri (*m*-nitrophenyl) bismuth

dinitrate.[29] μ-oxo-bis(chlorotriphenylbismuth) was prepared by reaction of the dichloride with alkali.[7]

Improved preparation of triphenylbismuth carbonate[9]

To a well stirred soln of triphenylbismuth dichloride (13 g) in acetone (100 ml) was added a soln of K_2CO_3 (3.6 g) in water (20 ml). After 5 min, the precipitated triphenylbismuth carbonate was filtered off, washed with acetone, and dried, yield 12.7 g (100%) m.p. 155° (dec), lit.[9] 164°. (Found: C, 45.31; H, 3.17. Calc. for $C_{19}H_{15}BiO_3$: C, 45.61; H, 2.94%).

General procedure for oxidation with μ-oxobis(chlorotriphenylbismuth) (**2**) (Table 1).

μ-oxobis(chlorotriphenylbismuth) is soluble in dichloromethane, chloroform, tetrahydrofuran and hot benzene. In a typical oxidation procedure, the alcohol (0.25 mmole) and the reagent **2** (0.20 mmole) in dichloromethane or chloroform (2 ml) are stirred with an excess of K_2CO_3 or $NaHCO_3$ (200 mg) until reaction is complete by aliquot monitoring. The mixture is filtered and the solvent evaporated. Chromatography on silica gel separates the product from non-polar triphenylbismuth. Alternatively, acid stable oxidation products may be isolated by heating the entire mixture on a steam bath for 30 min with glacial AcOH to destroy triphenylbismuth. The resulting soln is then poured into water and thoroughly extracted with ether. The combined ethereal extracts are washed successively with $NaHCO_3$ aq and then brine, dried, and the crude product purified by crystallisation. Reaction conditions and yields for a variety of alcohols are given in Table 1.

General procedure for oxidation by triphenylbismuth carbonate (Table 2)

Triphenylbismuth carbonate (1·1–2 equiv.) is added all in one portion to a well stirred soln of the substrate (1 equiv) in dichloromethane as solvent. As reaction proceeds the soln becomes homogeneous. When all starting material has been consumed, the mixture is filtered, the solvent removed and the product purified by chromatography (or as described above). Reaction conditions and yields for a variety of functional groups are tabulated (Table 2).

Oxidation of 1,2,5,6,Di-O-isopropylidene-3-(N-4′-nitrophenylthionocarbamato)-α-D-glucofuranose (**12**) *with triphenylbismuth carbonate*

Oxidation of **13**[30] as described above led to the isolation of the disulphide **14**) 81%. Recrystallisation from hexane gave a white solid, m.p. 83–85° $|\alpha|_D^{20}$ − 87.7 (*c* 0.22, $CHCl_3$); ν_{max} ($CHCl_3$) 1640, 1590, 1340 cm^{-1}; *m/e* (chemical ionisation, isobutane) 863 ($M^+ - CH_3$); (Found: C, 52.24; H, 5.19; N, 6.14; S, 7.05. Calc. for $C_{38}H_{46}O_{16}N_4S_2$: C, 51.95; H, 5.28; N, 6.38; S, 7.30%).

Homogeneous oxidation of (−)-carveol by triphenylbismuth diesters in the presence of base

To a soln of (−)-carveol (31.2 mg, 0.2 mmol) in chloroform (2 ml) was added the base (0.5 mmole) and the triphenylbismuth diester (0.2 mmole). The mixture was stirred at room temp until reaction was complete. Purification of (−)-carvone was achieved by preparative thick layer chromatography. The following results were obtained (ester, base, time h., (−)-carvone %). Diacetate, TMG 18, 87; diacetate, DBU 4, 89; dibenzoate, TMG 18, 81; ditrifluoroacetate, TMG, 1.5, 64.

Competition experiments for the oxidation of allylic alcohols by triphenylbismuth dihalides

A 1:1 mixture of two triarylbismuth dichlorides $Ar^1_3BiCl_2$ and $Ar^2_3BiCl_2$ was allowed to compete for a deficiency of an allylic alcohol (typically cholest-1-en-3-ol or cholest-4-en-3-ol) in dichloromethane soln with K_2CO_3 as base. The mixture of triarylbismuths Ar^1_3Bi and Ar^2_3Bi formed in the reaction was isolated by preparative tlc and the resultant ratio of the two compounds was determined by NMR'. In this way it was possible to construct a series of relative rate values which showed *p*-tolyl: phenyl: *p*-chlorophenyl: *m*-nitrophenyl = 1:1.5:6:>10.

Repetition of the above experiments with $Ar^1_3BiX_2$ and $Ar^2_3BiY_2$ and subsequently with $Ar^1_3BiY_2$ and $Ar^2_3BiX_2$ showed that, after correction for the effect of the aryl group, the ratio of triarylbismuths Ar^1_3Bi and Ar^2_3Bi was unaffected by the nature of X and Y. (X, Y = Cl, Br, ONO_2).

Competition experiments for oxidation of benzylic alcohols

To a mixture of benzyl alcohol (0.2 mmole) and *p*-nitrobenzyl alcohol (0.2 mmole) in chloroform (4 ml) containing μ-oxobis(chlorotriphenylbismuth) (0.1 mmole) was added K_2CO_3 (200 mg), and the mixture was stirred and heated at 60° for 1 hr. The cooled mixture was filtered and the solvent evaporated. After purification by plc the ratio of the two resultant aldehydes was determined by NMR. No preferential oxidation was observed. The above experiment was repeated with *p*-anisyl alcohol and benzyl alcohol and the same result was obtained. By using deuterochloroform as solvent, it was possible to determine the ratio of the two aldehydes directly in the crude reaction mixture by NMR.

Oxidation of (−)-carveol with tri-p-tolylbismuth dibenzoate

Isolation of toluene. Tri-*p*-tolylbismuth dibenzoate (2.76 g) was added all in one portion to a stirred soln of (−)-carveol (0.35 g) and DBU (0.4 g) in tetralin (10 ml) as solvent. After 20 hr at room temp, the volatile portion of the reaction was isolated by high vacuum trap to trap distillation at room temp and shown by NMR to contain toluene. Addition of further toluene to the NMR sample led only to signal enhancement. Repetition of the experiment using (−)-α-deuteriocarveol (**16**), prepared by lithium aluminum deuteride reduction of (−)-carvone, led to the isolation of a mono-deuterio-toluene. τ 2.6 (4 H, unresolved multiplet), 7.5 (3 H, s) *m/e* 93 (M^+ for C_7H_7D).

Oxidation of (−)-α-deuteriocarveol (**15**) *with tri-p-methoxyphenylbismuth carbonate*

Isolation of p-*deuteroanisole.* To a soln of (−)-carveol (30.2 mg, 0.2 mmole) in dichloromethane (2 ml) was added tri-*p*-methoxyphenylbismuth carbonate (118 mg, 0.2 mmole) and the stirred suspension was heated to reflux. Aliquot monitoring by tlc indicated that reaction was complete after 2 days. Purification by preparative tlc afforded anisole (19,7 mg), (−)-carvone (27.0 mg, 89%) and tri-*p*-methoxyphenyl bismuth (21.3 mg), all products being identical with authentic samples. Repetition of the experiment using (−)-α-deuteriocarveol (**16**) led to the isolation of *para*-deuterioanisole. *m/e* 109. (M^+), 79, 66 (of anisole M^+ 108, 78, 65), τ (400 MHz) 2.82 and 3.21 (4 H, ABq, J = 8 Hz), 6.24 (3 H, s, OMe).

Oxidation of (−)-Carveol by triphenylbismuth dibenzoate in the presence of nitrosomesitylene and nitrosobenzene

To a soln of (−)-carveol (31.2 mg, 0.2 mmole) in dichloromethane (1 ml) was added nitrosomesitylene (30 mg, 0.2 mmole), triphenylbismuth dibenzoate (160 mg, 0.2 mmole) and DBU (30 mg). The mixture was stirred at room temp for 30 min. Purification by preparative tlc afforded nitrosomesitylene (21.9 mg, 73%), (−)-carvone (20.0 mg, 64%) and triphenylbismuth (17.2 mg, 20%). Repetition of the experiment in the presence of a two molar excess of nitrosobenzene led to the same result. Diphenylnitroxide was not detected in the reaction mixture by tlc comparison with an authentic sample.

Glycol cleavage catalysed by triphenylbismuth. Typical experimental procedure

(a) *With Hydrogen peroxide and sodium bicarbonate.* To a stirred soln of hydrobenzoin (107 mg, 0.5 mmol) and triphenylbismuth (220 mg, 0.5 mmol) in acetone (2 ml) containing $NaHCO_3$ (378 mg) was added dropwise at room temp a soln of H_2O_2 (1.5 mmol) in aqueous acetone (0.9 ml).

The mixture was heated at 40° until reaction was complete (tlc; 1 hr), filtered, and solvent removed *in vacuo*. Benzaldehyde was isolated in the form of its 2,4-dinitrophenylhydrazone dirivative (98%) m.p. 238°.

(b) *With t-butyl hydroperoxide.* To a stirred soln of hydrobenzoin (107 mg, 0.5 mmol) and triphenylbismuth (220 mg, 0.5 mmol) in acetone (3 ml) was added dropwise at room temp t-butylhydroperoxide (1.5 mmole, 0.15 ml) in acetone (0.5 ml) and the mixture was then heated at 40° until reaction was complete. Removal of solvent followed by treatment with 2,4-dinitrophenylhydrazine in the usual manner led to benzaldehyde 2,4-dinitrophenylhydrazone (93%), m.p' 238°.

Acknowledgements—One of us (MTBP) thanks the Instituto Nacional Investigacaçao Cientifica and the Instituto Universitario Evora, Portugal for sabbatical leave. We are also grateful to Mr. S. K. Kan for 400 MHz NMR facilities and to Mr. M. Thomas for skilful technical assistance. We thank Professor A. Krief (Namur)[31] for compound (11), Dr. M. Barbier for a generous gift of geraniol and Miss B. Charpiot for the two experiments indicated.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 81 to 90, 1981
Printed in Great Britain.

0040-4020/81/Suppl. 1 0081-10/$02.00/0
Pergamon Press Ltd.

THE STRUCTURE OF FACTOR III

A TRIMETHYL ISOBACTERIOCHLORIN INTERMEDIATE IN THE BIOSYNTHESIS OF VITAMIN B_{12}†

GERHARD MÜLLER* and K. D. GNEUSS

Institut für Organische Chemie Biochemie und Isotopenforschung, Universität Stuttgart, Azenbergstrasse 18, D-7000 Stuttgart 1, West Germany

H.-P. KRIEMLER

Z-F.F., Ciba-Geigy AG, CH-40002, Basel, Switzerland

and

ANTHONY J. IRWIN and A. I. SCOTT*

Department of Chemistry, Texas A & M University, College Station, TX 77843, U.S.A.

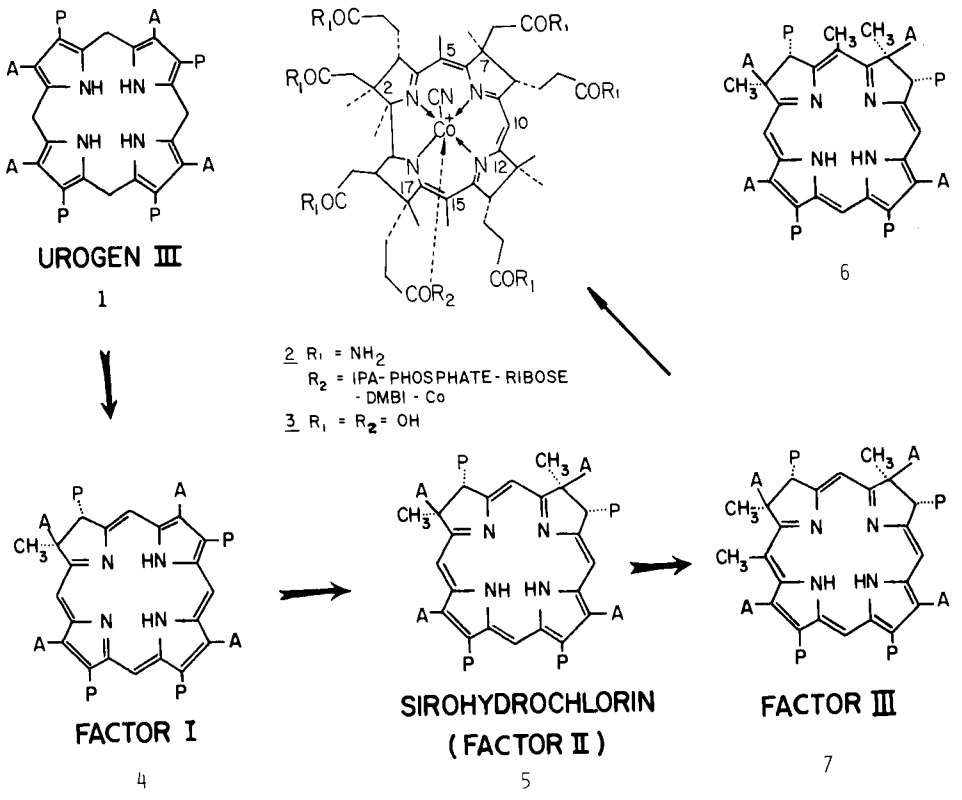
(*Received in U.S.A.* 27 *May* 1980)

Abstract—Factor III, an intermediate in corrin biosynthesis isolated from *Propionibacterium shermanii*, is shown to be a 3,7,20-trimethylisobacteriochlorin (20-methylsirohydrochlorin) by examination of the CMR spectrum of a biosynthetically enriched specimen derived from [5-^{13}C]-δ-aminolevulinic acid and [$^{13}CH_3$]-L-methionine. In cell-free extracts of *Clostridium tetanomorphum* the conversion of Factor III to cobyrinic acid involves loss of C-20 together with the methionine-derived methyl group attached to this position. The implications of these observations, which cast a new light on the uro'gen-corrin connection, are discussed.

The discovery of a series of methylated isobacteriochlorins from preparations of *P. shermanii* and *C. tetanomorphum* has already led to a deeper understanding of the biochemical processes which connect uro'gen III[1,2] (**1**) with vitamin B_{12} *in vivo* and with cobyrinic acid (**3**) *in vitro*. On the basis of mass and UV-visible spectral analysis and of biochemical evidence, Factors I,[3] II[3,4] and III[4] were assigned the constitutions **4**, **5** and **6**, respectively, i.e. a mono-, di- and tri-methylated isobacteriochlorin, although at the time the full structural and stereochemical details could not be determined. Subsequently, Factor II and sirohydrochlorin, the metal-free prosthetic group of nitrite-sulfite reducing enzyme, siroheme,[5] were shown to be identical and to have the absolute stereochemistry (**5**).[6–9] By analogy and on the basis of the PMR data for the lactonic form of Factor III (= corriphyrin **3**), the 5-methylated isomer (**6**) was preferred[8,10] for the structure of Factor III, especially since a methyl group is present in the 5-position of the natural corrins. Factor I, from the outset presumed to be the ring-A mono-methylated dihydroporphyrin, has recently been assigned[11] this structure and the stereochemistry shown in **4**. The proven biochemical relationships within this series is shown in Scheme 1 where the experimental observation of incorporation of Factors II and III, but only the *reduced* forms of Factor I and of uro'gen III suggest that an oxido-reductase system is present in cell-free extracts which, although incapable of reducing either uro'III to uro'gen-III or Factor I to the tetrahydro level, can effect such reduction on administered samples of Factors II and III. The alternative explanation is that the isobacteriochlorins II and III in fact represent the physiological oxidation level of the incorporated substrates, i.e. the biochemical transformations Factor II → Factor III → corrin take place at the fully oxidised state which corresponds to the structure of these factors as isolated from the bacterial preparations. At present this point remains unresolved but obviously must be settled in order to rationalise the mechanism of the isobacteriochlorin → corrin transformation.

We next describe the evidence for structure **7** for Factor III, which leads to a revision of the earlier postulate.[8,10] Factor III was isolated from δ-aminolevulinic acid (ALA)-supplemented cobalt-free incubations of *P. shermanii* (ATCC 9614) and from a B_{12}-deficient mutant of this organism.[12] High resolution FD mass spectrometry of the octamethyl ester established the formula $C_{51}H_{64}N_4O_{16}$ (988.4281) while the mass spectrum of the octa-ester isolated from incubation with [methyl-$^2H_3$]-L-methionine exhibited peaks at *m/e* 997, 994, 991 and 988 corresponding to enrichment with a maximum of three (M + 9) CD_3 groups. The presence of three such methyl groups was also confirmed by analysis of the ^{1}H NMR spectrum recorded on a sample of Factor III methyl ester (400 μg) prepared from a suspended cell incubation of *P. shermanii* containing [$^{13}CH_3$]-methionine and [5-^{13}C]-ALA followed by esterification of the metabolite and purification by HPLC. The

†Dedicated to the memory of Prof. R. B. Woodward.



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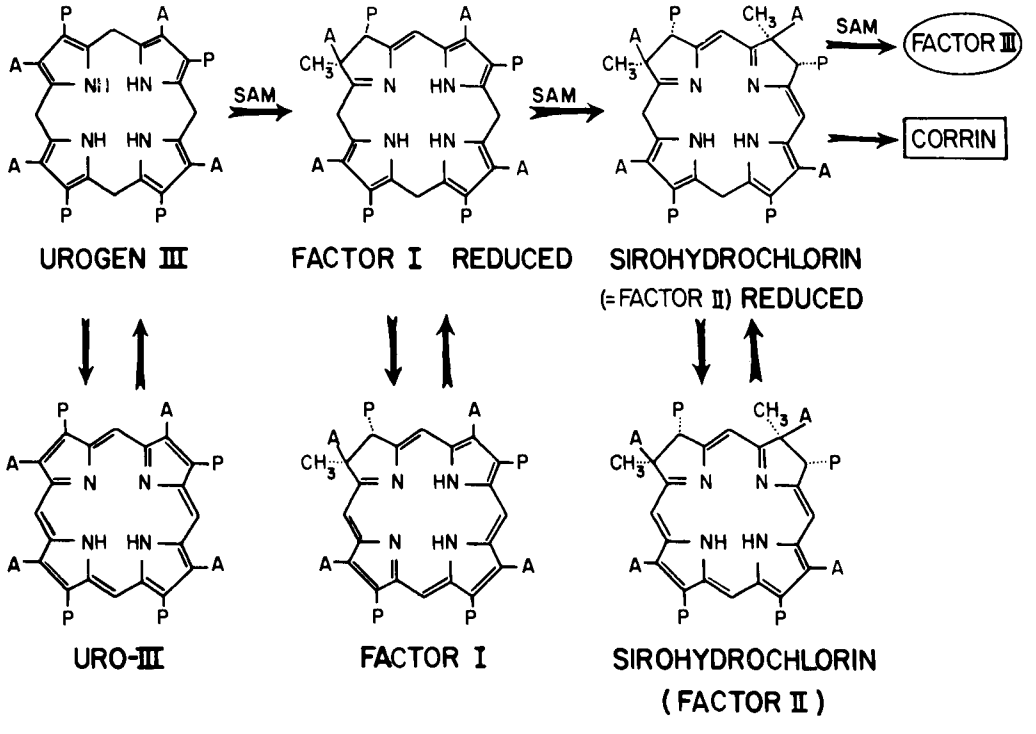


Scheme 1.

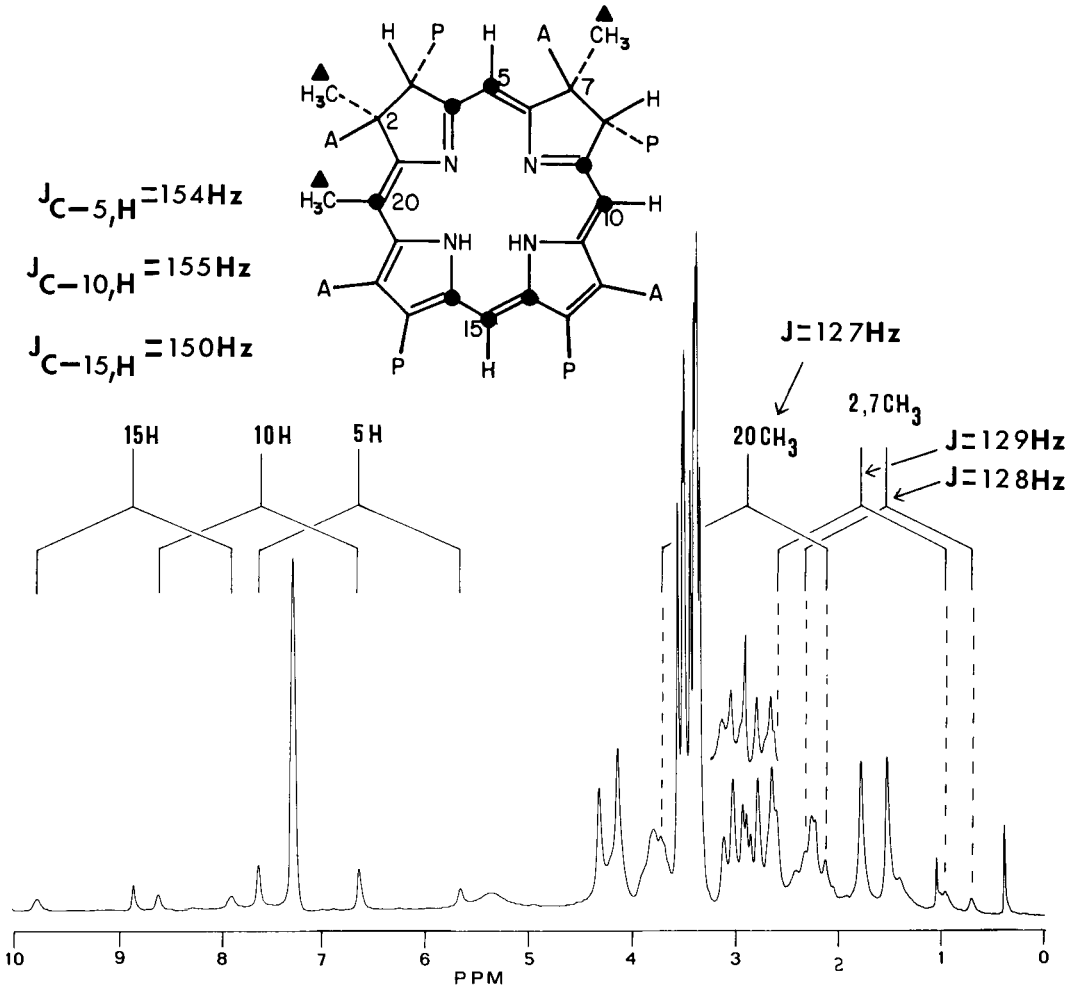


Fig. 1. The 300 MHz ^{1}H NMR spectrum (C_6D_6) of [5-^{13}C]-ALA- and $^{13}CH_3$]-methionine enriched 20-methylsiro-hydrochlorin octamethyl ester. Inset: The 20-methyl proton resonance (δ 2.98 ppm) of 20-methylsirohydrochlorin at natural abundance.

proton spectrum (300 MHz) of this ^{13}C-enriched sample is shown in Fig. 1 where the methyl resonances at 1.5 and 1.8 ppm (CH_3's on sp^3 carbon) are assigned provisionally to the 2 and 7 positions (J_{H-C} = 128 and 129 Hz) whilst a resonance at δ 2.98 (J = 127 Hz), although almost obscured in the ^{13}C-enriched spectrum, is clearly discerned in the natural abundance spectrum (see inset in Fig. 1) and can be assigned to CH_3 attached to a sp^2 center. Aside from clean resolution of the eight methoxy resonances of the octa-ester (δ 3.2–3.6) the most important features of this proton spectrum are signals at δ 6.43, 7.21 and 8.33 ppm, corresponding to only *three* of the *meso*-proton resonances of an isobacteriochlorin. In contrast, Factor II (**5**) exhibits *four* well-defined signals in this region which have been assigned to the four *meso*-protons at C-5, C-10/C-20, and C-15 (δ 6.78, 7.36/7.46 and 8.54, respectively). Factor III must therefore be methylated at C-10 or C-20.

When this ^{13}C-enriched species (as the octamethyl ester) was examined by ^{13}C NMR spectroscopy (Fig. 2), it became possible to deduce the complete structure (**8**). First, the *downfield* position of the C-15 meso-carbon triplet at δ 108.98 (J = 72 Hz) confirms that rings A and B are methylated,[6] and since the *meso*-carbon signals at δ 89.5 and 95.4 each shown ^{13}C-^{13}C coupling to an enriched sp^2 neighbor (J $\approx$ 70 Hz), these are assigned to C-5 and C-10, respectively, by analogy with the corresponding resonances in sirohydrochlorin derived by biochemical enrichment with [5-^{13}C]-ALA.[6] Thus, the remaining *meso*-carbon resonance at δ 104.8 consists of a doublet (J = 44.2 Hz) and must correspond to C-20, with additional fine structure due to long-range coupling with C-4 and C-16. That the ^{13}C–^{13}C coupling constant of 44.2 Hz for C-20 is due to substitution by a methionine-derived methyl group is confirmed by inspection of the *methyl* region of the ^{13}C NMR spectrum which displays three enriched species consisting of singlets at δ 20.17 and 19.62 and a doublet at δ 18.79 (J = 44.2 Hz). It can be seen that, owing to different efficiences of incorporation of [^{13}C]-methionine and of [5-^{13}C]-ALA, the enrichments in the methyl groups and in the ALA-derived sp^2 carbons are not identical, the satellite intensities reflecting a greater enrichment in C-20 than in its pendant Me group.

The other sp^2 carbon resonances (Fig. 3) were assigned as follows on the basis of the reciprocity of the

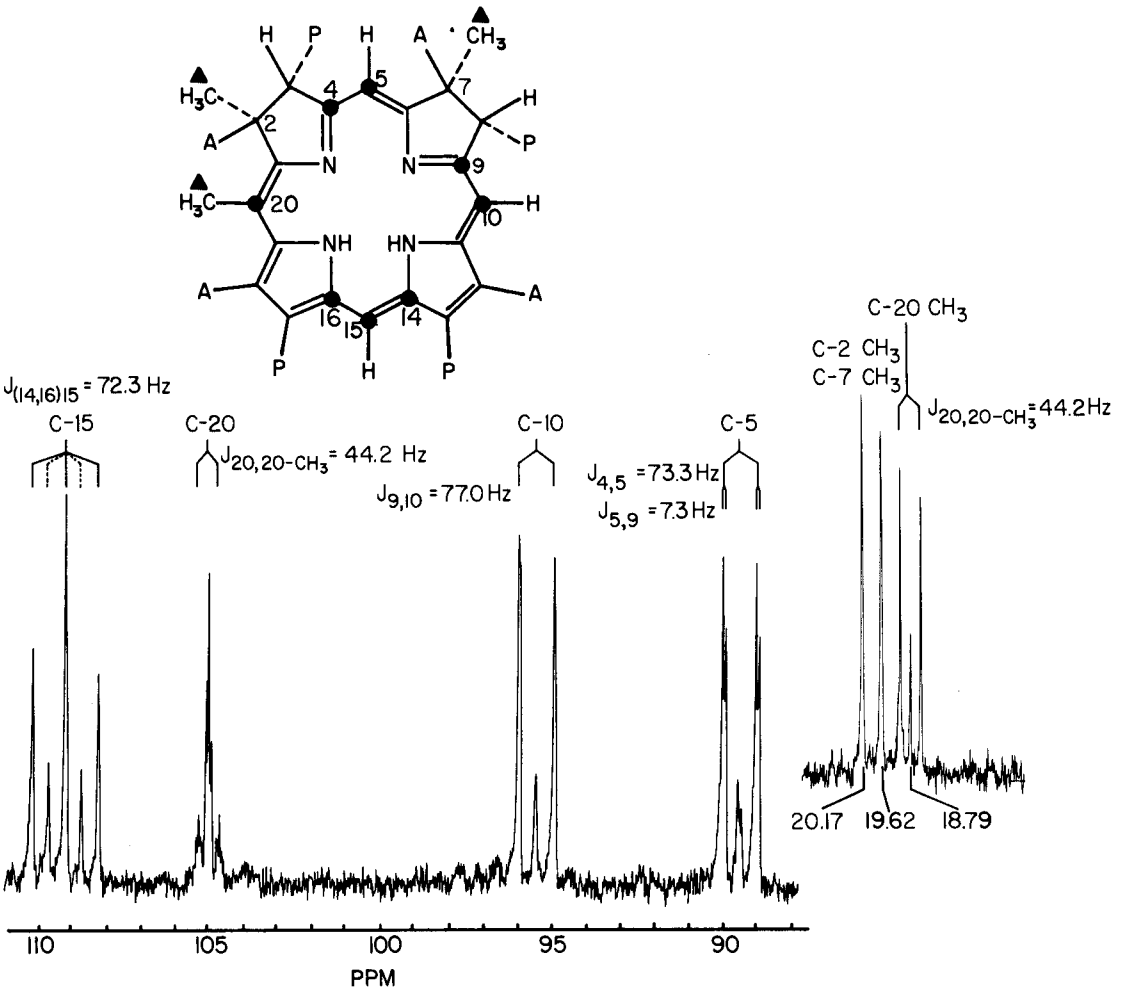


Fig. 2. The *meso*-carbon resonances of the proton noise decoupled ^{13}C-FT spectrum of [5-^{13}C]-ALA- and [$^{13}CH_3$]-methionine labelled 20-methylsirohydrochlorin octamethyl ester. Inset: The methyl carbon resonances of the same sample. The spectrum was obtained in C_6D_6 at 75 MHz.

coupling constants with C-5, 10, 15 and 20 and by analogy with the chemical shift data for sirohydrochlorin, similarly enriched with ^{13}C. Thus C-4 and C-9 resonate at 159.6 and 158.3 ppm, respectively, ($J_{4,5}$ = 73 Hz; $J_{9,10}$ = 77 Hz) with additional long-range coupling to C-20 and C-5 observed ($J_{4,20}$ = 5 Hz; $J_{5,9}$ = 7.3 Hz). A distinction can be made between the (usually) ambiguous assignment of C-14 and C-16 in this spectrum on the basis of the observed long-range coupling between C-16 and C-20 (J = 2.8 Hz) observed for both enriched centers. The long-range coupling between C-10 and C-14 is not resolved. Although C-14 and C-16 have almost identical one-bond coupling constants ($J_{15,16}$ = 73 Hz; $J_{14,15}$ = 72 Hz), they can be assigned to the signals at 136.5 and 132.3 ppm, respectively.

Hence Factor III is **7**, i.e. 20-methylsirohydrochlorin rather than the C-5 methylated isobacteriochlorin (**6**), contrary to what had previously been thought.[8,10] The absolute stereochemistry of Factor III and its relationship to cobyrinic acid was obtained by the following experiments.

Incorporation into cobyrinic acid of Factor III labelled from [4-^{14}C]-ALA was demonstrated in earlier experiments using cell-free extracts of *C. tetanomorphum*,[3,4] but at that time the structural assignment (now shown to be **7**) had not been made. In order to trace the fate of the methyl groups during the conversion of Factor III (**7**) to cobyrinic acid (**3**), specimens of Factor II (**5**) and Factor III (**7**) were prepared from whole-cell incubations of *P. shermanii* using [*methyl*-^{14}C]-L-methionine and [2,3-$^3H_4$]-ALA. By this strategem, **7** is labelled as shown in Scheme 1 (● = ^{3}H; ▲ = ^{14}C]. Taking the value of 2.00 for the methyl group number in Factor II (Experiments A: 1a, 2a, 3a, 4a, Table 1), the ^{14}C/^{3}H ratios in Factors III and IIIa are in good accord with the presence of three methyl groups in both of these isobacteriochlorins (Experiments A: 1b, 1c, 2b, 3b, 4c, Table 1), while Factor IIa is seen to contain two such methionine-derived methyl groups (Experiment A: 4b, Table 1). The structures of Factors IIa and IIIa, isomeric with Factors II and III, respectively, are under investigation (s Experimental) but their lack of incorporation into cobyrinic acid (Table 1) removes them as serious contenders for intermediacy in the corrin pathway. In this connection, an isomer of Factor II (3-epi-sirohydrochlorin) has recently been

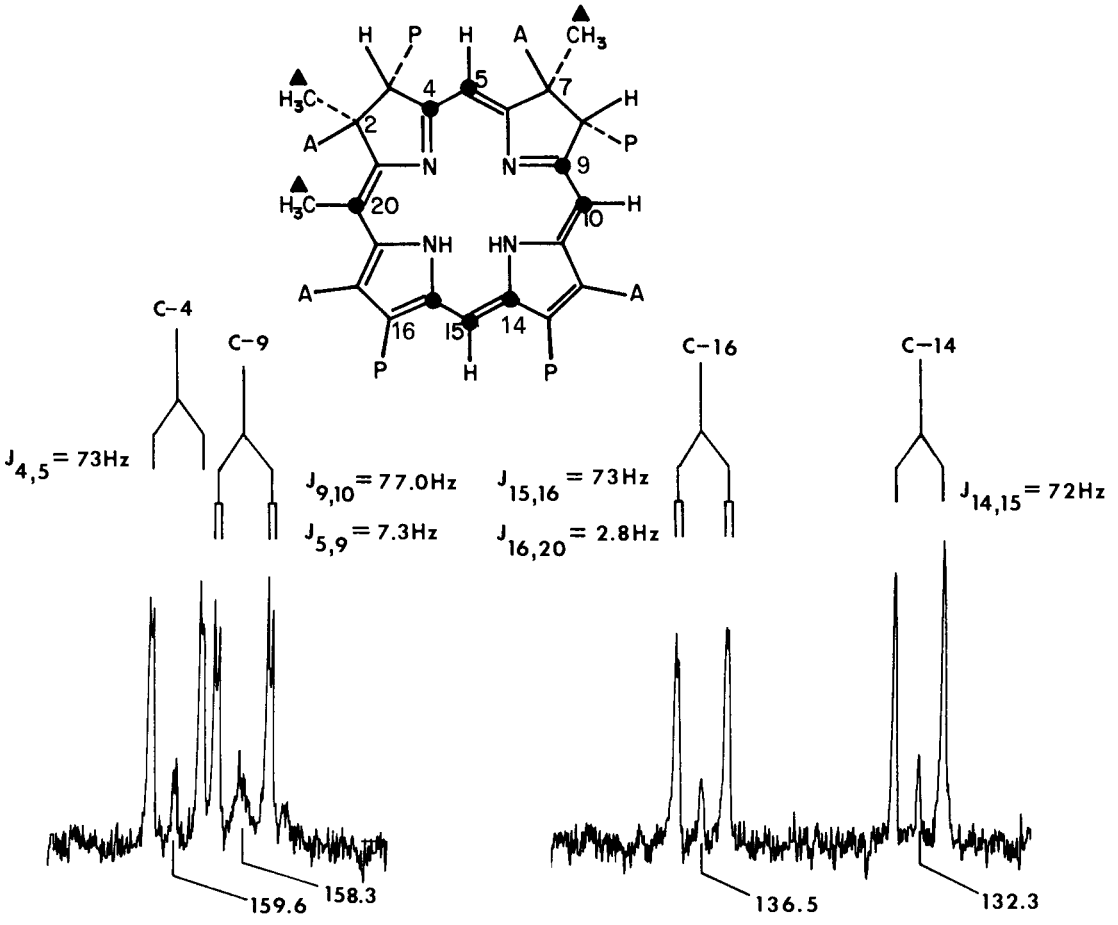


Fig. 3. The proton decoupled downfield portion of the 75 MHz ^{13}C-FT spectrum of 20-methylsirohydrochlorin (C_6D_6) showing the sp^2 resonances associated with C-4, C-9, C-14 and C-16 enriched from [5-^{13}C]-ALA.

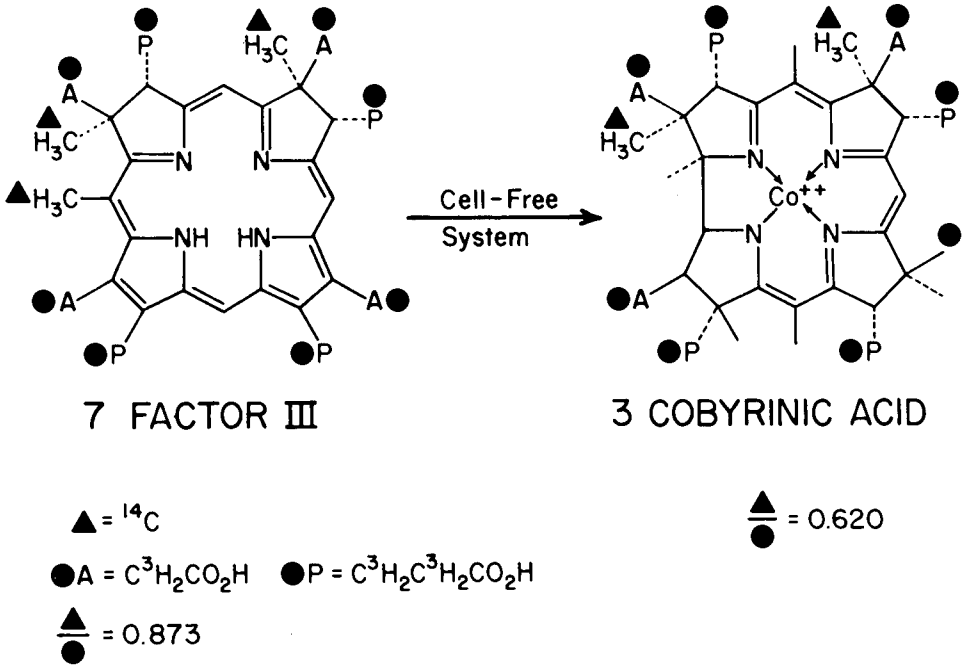
Table 1. Comparative studies on the incorporation of di- and trimethylisobacteriochlorins from *P. shermanii* into cobyrinic acid

	A. Double labeling of cobyrinic acid intermediates					B. Incorporation of intermediates into cobyrinic acid(3)			
				radioactivity ratio of intermediate		added ^{3}H-radio-activities of		radioactivity ratio of cobyrinic acid	
expt	inter-mediate	added substrate	μCi	^{14}C/^{3}H	with ref to methyl groups	isobacterio-chlorins, dpm	incorpn, %*	^{14}C/^{3}H	with ref to methyl groups
1a	5	[methyl-^{14}C]Met	350	0.600	2.00	1.84 X 10^6	15.3	0.620	2.00
		[2,3-^{3}H]ALA	500						
b	7			0.873	2.91	1.57 X 10^6	16.1	0.620	2.00
c	7			0.873	2.91	1.65 X 10^6	14.3	0.660	2.13
2a	5	dto	250	0.092	2.00	1.63 X 10^6	4.0	0.109	2.00
b	7		1200	0.141	3.06	1.62 X 10^6	9.9	0.102	1.87
3a	5	dto	250	0.376	2.00	1.27 X 10^6	4.9	0.400	2.00
b	7		300	0.537	2.86	1.20 X 10^6	11.5	0.405	2.03
4a	5	dto	250	0.376	2.00	1.59 X 10^5	9.6		
b	FIIa		300	0.391	2.08	0.95 X 10^5	0.8		
c	FIIIa			0.543	2.89	1.59 X 10^5	0.9		

A: Series of incubations with cell suspensions of P. shermanii (1-4) for the preparation of [^{14}C/^{3}H]-doubly labelled isobacteriochlorins from [methyl-^{14}C] Met and [2,3-^{3}H] ALA; isolated isobacteriochlorins were methyl esters.

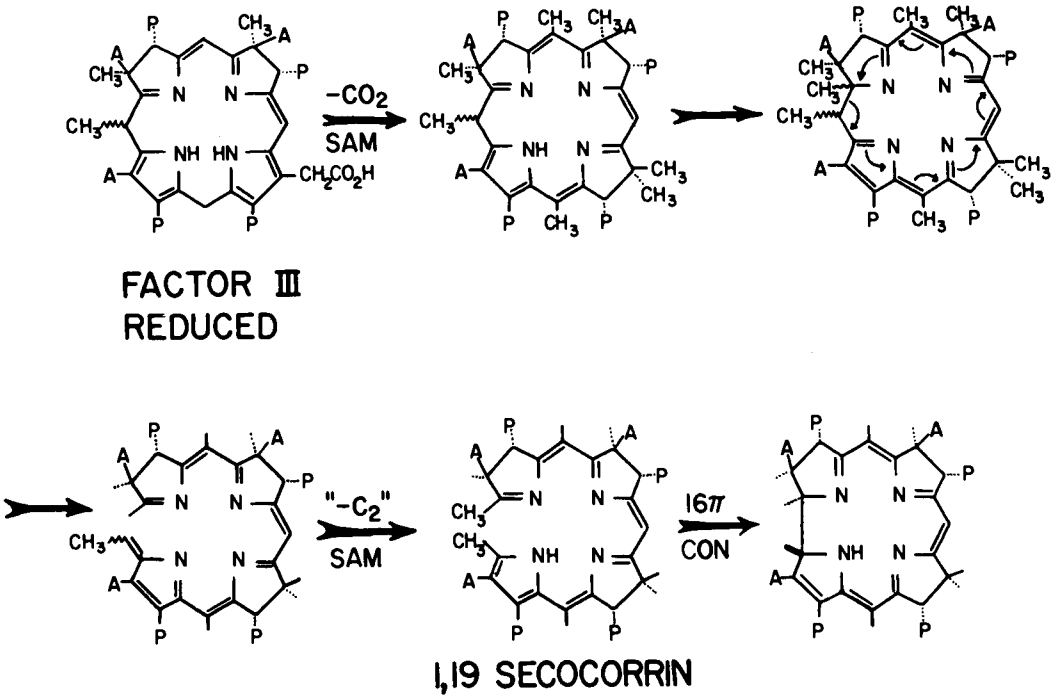
B: Experiments for incorporation of the [^{14}C/^{3}H]-labelled isobacteriochlorins (obtained from methyl esters by 2 M piperidine hydrolysis) into cobyrinic acid by tetrapyrrole-free cell extracts from C. tetanomorphum.

* % incorporation: ^{3}H-radioactivity of formed cobyrinic acid/added ^{3}H-radioactivity of substrate x 100.

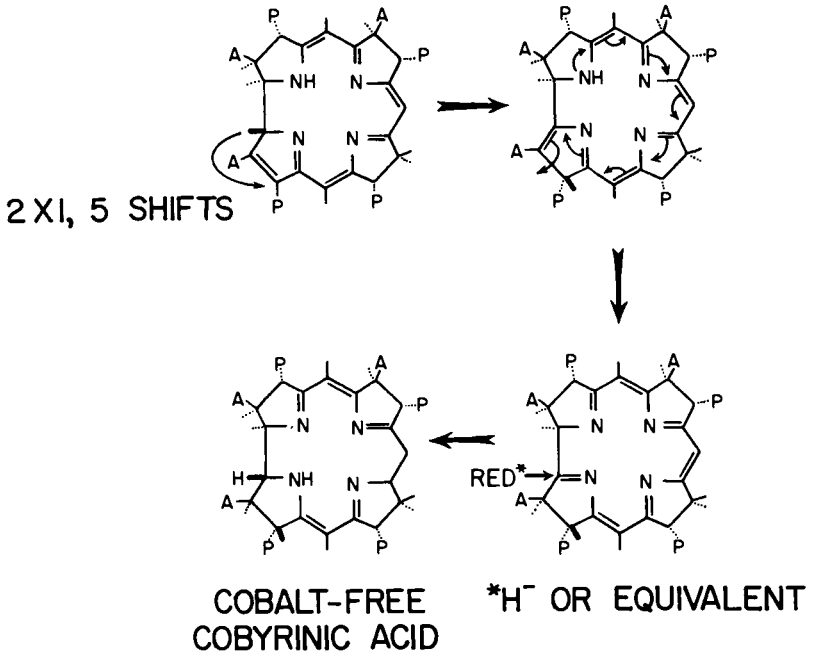


Scheme 2.

characterized by Battersby *et al.*[13] and may indeed correspond to Factor IIa, since it is not a precursor of cobyrinic acid. When Factors II and III doubly labelled in this way (see Table 1) were re-incubated with the *C. tetanomorphum* cell-free system, the derived cobyrinic acid, obtained with excellent overall incorporation (5–16%), contains only *two* methionine-derived methyl groups in each case (Experiments B: 1a–c, Table 1). In order to remove any possibility of cross contamination, separate samples of doubly labelled **5** and **7** were again chromatographed to constant, but *different* radioactivity ratios (Experiments A: 2a, 2b and 3a, 3b, Table 1). Pure Factor III of Experiment 2 was mixed with



Scheme 3.



Scheme 4.

sirohydrochlorin (Factor II) from Experiment 3 (and *vice versa*) and the methyl esters were separated, purified and again administered (after hydrolysis) to the cobyrinic acid synthesizing system (Experiments B: 2a, 2b and 3a, 3b, Table 1). In each experiment the isolated cobyrinic acid contains a $^{14}C/^{3}H$ ratio compatible with only *two* ^{14}C Me groups. These experiments show that (a) there is no possibility of cross-contamination of Factors II and III during isolation, (b) Factor III is converted to cobryinic acid in good radiochemical yield (10–15%) with the loss of C-20 and its attached methyl group (the nature of the "C_2" fragment remains to be determined[14]), and (c) the absolute stereochemistry of Factor III (as 7) follows from its relationship to cobyrinic acid. These conclusions summarized in Scheme 2 have been independently confirmed by the work of the Cambridge group.[17]

It thus appears that, in order to achieve the intercorrin A → D ring junction, the biosynthetic route requires not only the specific formation and subsequent disruption of the type III uro'gen macrocycle but the sacrifice of at least one methionine-derived methyl group and the carbon to which it is attached (C-20), since *both* of these must be excised from the species undergoing (or having undergone) secocorrin → corrin[2] closure. This apparently prodigal series of events can be accommodated within several hypotheses consonant with published data. On the assumption that the incorporation of Factor III occurs at the *dihydro*-level *in vivo* and *in vitro*, i.e. a reductase system is present in the cell-free extracts, one such hypothetical scheme is shown in Scheme 3 where the oxidation level of both the ejected "C_2" unit and the substrate for this cleavage reaction are still unknown. The net result of the 1,19 secocorrin closure is to furnish a 1,19-dimethyl dehydrocorrin by an allowed 16π conrotatory electrocyclic ring closure, thus setting the C-1 and C-19 methyl groups in the correct absolute stereochemistry for eventual 1,5 shifts of C-19 methyl to C-17 as proposed earlier (see Scheme 4). These and related ideas are now under experimental scrutiny.[18]

EXPERIMENTAL

Determination of radioactivity. Water soluble radioactive samples (e.g. cobyrinic acid) were measured with modified Bray's dioxan scintillator (PPO, 5 g; POPOP, 0.1 g; naphthalene, 180 g in dioxan, 1 l) using a Beckman LS250 counter; for all other samples a toluene scintillator was used (PPO, 5 g; POPOP, 0.5 g in toluene, 1 l). For doubly labelled (^{3}H; ^{14}C) samples the screening method of Tykva[19] was employed.

Spectral measurements. UV-visible spectra were recorded with a Beckman ACTA MVI spectrophotometer, photometric determinations of sample concentrations with a Carl Zeiss PMQII instrument and FD mass spectra as described previously.[3,20] PMR spectra and CMR spectra with Varian FT-80 and SC-300 instruments in "100%" C_6D_6 (Merck) distilled from calcium hydride.

Chromatography. HPLC was performed with a Waters Associates ALC/GPC 204 instrument using C-18 μ-Bondapak columns in 80% $MeOH/H_2O$.

Tlc for purifications and separations of Factors II, IIa and III, IIIa methyl esters were carried out on Merck Silica gel (tlc aluminum sheets, 20 × 20 cm, 0.2 mm thickness) and on precoated cellulose plates (20 × 20 cm, 0.5 mm thickness: Schleicher and Schüll G 1805; 0.1 mm thickness: tlc aluminum sheets, Merck). Heptamethyl cobyrinate was purified using KCN saturated solvents throughout. Column chromatographic (C.C.) purifications were performed on Merck silica gel 60 for column chromatography, 230–400 mesh (usual size: 5 cm × 1.5 cm). The following solvent systems were used as indicated below.

System I	Benzene/Ethyl Acetate/Methanol (60:38.5:1.5; v/v/v)
System II	Hexane/2-Propanol/Methanol (5:2:1; v/v/v)
System III	Hexane/Chloroform/1-Propanol/2-Propanol (94:4:2:0.5; v/v/v/v)
System IV	CH_2Cl_2/Chloroform (2:1; v/v)
System V	Chloroform/Methanol (95:5; v/v)
System VI	Chloroform/Methanol (99:1; v/v)

Paper electrophoresis. Cobyrinic acid was purified on Schleicher and Schüll paper Nos. 2043 and 2045 using the following KCN saturated buffers:

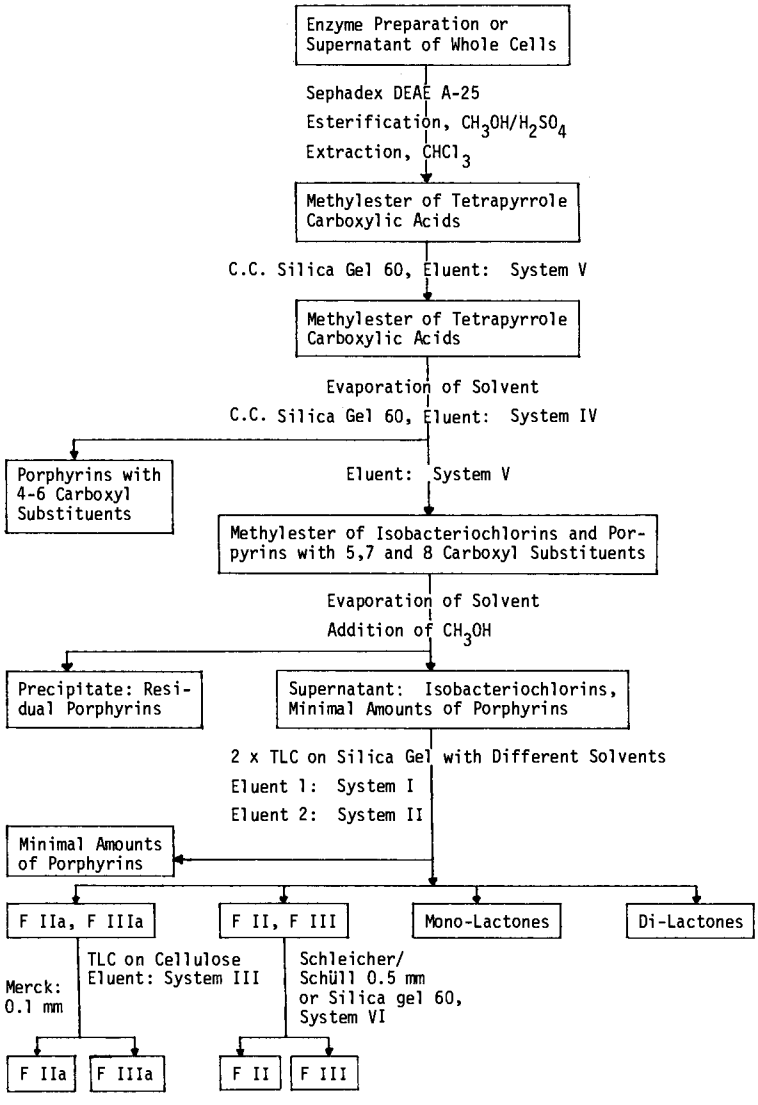
(a) Buffer pH 2.7, 0.5 M acetic acid,

(b) Buffer pH 8.6, 0.01 M veronal

Reagents. Adenosine-5′-triphosphate cryst. di-sodium salt $\times 3H_2O$ (Boehringer, Mannheim); S-Adenosyl-L-methionine $\cdot HSO_4$ (Boehringer, Mannheim); 5-Aminolevulinic acid $\cdot$ HCl (prepared by a method of Zav'yalov *et al.*[21]); [2,3-^{3}H]-5-Aminolevulinic acid (specific activity 28 mCi/μmol) (Isotopendienst West, Frankfurt); [4-^{14}C]-5-Aminolevulinic acid (specific activity 59 μCi/μmol (Isotopendienst West, Frankfurt); L-Cysteine $\cdot$ HCl (Serva Feinbiochemica, Heidelberg); Cobyrinic acid (prepared from acid methanolysis of vitamin B_{12} followed by hydrolysis); L-Glutathione (red) (Serva Feinbiochemica, Heidelberg); L-Methionine (Merck, Darmstadt); [Me-^{14}C]-L-methionine (specific activity 56 μCi/μmol) (Amersham; Buchler, Braunschweig); [Me-$^2H_3$]-D,L-methionine (prepared as described in l.c.[22]); β-nicotinamide-adenine-dinucleotide, reduced form, di-sodium salt (Boehringer, Mannheim); β-nicotinamide-adenine-dinucleotide, oxidized form, free acid (Boehringer, Mannheim); Vitamin B_{12} (Merck, Darmstadt).

Incubations with cell suspensions of P. shermanii. Freshly harvested wet cells (90 g) of *P. shermanii*[3,4,20] were suspended in degassed, nitrogen saturated 52 mM phosphate buffer, pH 7.7 (300 ml). 5-Aminolevulinic acid hydrochloride (20 mg; 0.12 mmole) and L-methionine (4 mg; 27 μmole) were added before and after 20 hr of incubation which was continued for a further 20 hr, with regular pH adjustment (to 7.7).

Isolation of the tetrapyrrolic methyl esters. The pH of the above cell suspension was adjusted to 7–8 to avoid formation of the lactones of Factors II and III and after



Isolation and Purification of Methylated Isobacteriochlorins from P. shermanii or C. tetanomorphum.

Scheme 5.

centrifugation Sephadex DEAE A-25 (previously washed with degassed phosphate buffer pH 7.7 (52 mM) was added to the supernatant. After 2–3 hr the Sephadex was filtered, washed with degassed distilled water and dried with MeOH (200 ml). The residue was freeze-dried and suspended in $MeOH/H_2SO_4$ (95:5; v/v; 100 ml) and allowed to stand (in the dark) at room temp for 24 hr. Addition of $CHCl_3$ (20 ml) and aqueous $NaHCO_3$, followed by extraction of the aqueous layer with $CHCl_3$ (3 × 20 ml), drying (Na_2SO_4) and evaporation of solvent afforded a mixture of tetrapyrrole methyl esters which were purified and separated on small silica gel 60 columns (5 cm × 1.5 cm) and by tlc using solvent systems as shown above. The structures of factors IIa and IIIa are under further investigation.

Isolation and purification of the isobacteriochlorin methyl esters. The procedure is described in Scheme 5 where F II, III, etc. refer to methyl esters of Factors II, III, etc.

Chromatographic separation of the methyl esters of factors II, IIa, III *and* IIIa *and their γ-mono- and di-lactones on silica gel.* The chromatographic steps as well as the R_f values of the single compounds are summarized in Table 2. The methyl esters of the isobacteriochlorins were first separated on precoated silica gel plates using solvent system I and then rechromatographed several times. The bands containing the methyl esters of Factors IIa and IIIa and II and III as well as their γ-mono- and di-lactones were scraped carefully and eluted with chloroform/methanol (99:1; v/v). It is necessary to chromatograph the isobacteriochlorin bands on silica gel using solvent system II in order to separate them from the traces of porphyrin esters. All the above chromatographic steps were carried out in subdued light. The isolated isobacteriochlorin methyl esters are blue-violet in soln and show strong orange fluorescent under long-wave UV light (366 nm).

Separation of factor II *and* III *methyl esters.* Traces of silica gel were separated by solution in CH_2Cl_2 and filtration. The ester mixture was then chromatographed on precoated cellulose plates (Schleicher and Schüll, 0.5 mm) using solvent system III and/or on precoated silica gel 60 aluminum sheets (Merck, 0.2 mm) using solvent system VI. In both cases Factor II methyl ester (orange fluorescence) runs just ahead of Factor III methyl ester (red fluorescence).

The pigments were purified by rechromatography on silica gel plates using solvent systems I or II.

Preparation of [^{3}H,^{14}C]*-labelled isobacteriochlorins.* The freshly harvested wet cells (90 g) were suspended in nitrogen phosphate buffer (52 mM) at pH 7.7. 5-Aminolevulinic acid (40 mg; 0.24 mmol) and L-methionine (8 mg; 54 μmol) plus [2,3-^{3}H]-5-aminolevulinic acid and [Me-^{14}C]-L-methionine were added to the suspension (Table 1). The added radioactivities of the labelled substrates are summarized in Table 1; the specific radioactivities are summarized under reagents. The radioactive labelled pigments were purified to constant specific activities using the tlc systems described above.

Incorporation experiments to form cobyrinic acid with porphyrinogen-free cell extracts of C. tetanomorphum. Porphyrinogen-free cell extracts of *C. tetanomorphum*[3,4] (40 ml) were used for each experiment (Table 1). S-adenosyl-L-methionine (5 mg; 10 μmol), glutathione (reduced; 4 mg; 13 μmol), ATP (7 mg; 13.8 μmol), NAD (3 mg; 4.5 μmol), NADH (6 mg; 8.5 μmol) and 1-cysteine (1 mg; 5.7 μmol) were dissolved in buffer and added to the soln together with aqueous $Co(NO_3)_2$ soln (0.5 ml; 39 mM). After the addition of the radioactive labelled substrates, obtained from their methyl esters by hydrolysis in 2 ml degassed 2 M piperidine soln (8 hr, 4°), evaporation of the piperidine–water mixture *in vacuo* and dissolution of residue in a few ml distilled and degassed water, the suspension was incubated in the dark at 37°, for 20 hr under N_2.

Isolation and purification of cobyrinic acid. Unlabelled cobyrinic acid (957 μg; 0.92 μmol), KCN soln (1 ml; 1 M; pH 7.8) and glacial AcOH were added to the suspension after incubation. The suspension was allowed to stand for 15 min at 4°. The cobyrinic acid was isolated from the incubation media by DEAE-fixation[4] and esterified with 50 ml $MeOH/HSO_4$ (95:5; v/v). The cobester was extracted with chloroform and purified by the following procedure.

Table 2. Estimated R_f values in solvent systems used for the separation of the methylesters from porphyrins and isobacteriochlorins isolated from incubations with cell suspensions of *P. shermanii*

Methylesters of	TLC on silica gel 60 system I	TLC on silica gel 60 system II	TLC on cellulose system III	TLC on silica gel 60 system VI
Coproporphyrin	0.59	0.75	0.80	0.55
Pentacarboxyporphyrin	0.49	0.61		0.49
Hexacarboxyporphyrin	0.39	0.50		0.44
Heptacarboxyporphyrin	0.30	0.38	0.21	0.39
Uroporphyrin	0.19	0	0	0.34
Factor IIa	0.30	0.48	0.54*	0.31
Factor IIIa	0.30	0.48	0.60*	0.31
Factor II	0.29	0.46	0.40**	0.31
Factor III	0.29	0.46	0.20**	0.25
Factor-II-γ-monolacton	0.25	0.39		0.30
Factor-III-γ-monolacton	0.20	0.31		0.31
Factor-II-γ-monolacton	0.18	0.29	broad badly separated bands from 0.1 to 0.2	0.29
Factor-II-γ-dilacton	0.15	0.24		0.28
Factor-III-γ-dilacton	0.14	0.24		0.25

*Merck, aluminum sheets, 0.1 mm

**Schleicher and Schüll, G 1805, 0.5 mm

(1) Chrom AR sheet 1000 (Malinckrodt), solvent system I. Porphyrin methyl esters and starting substrates were separated from cobester which remained at the origin.

(2) Silica gel tlc plates, solvent system II (saturated with KCN). The R_f value of cobester is 0.4. The cobester band was scraped off, eluted with $CHCl_3$/MeOH (99:1; v/v) and evaporated *in vacuo*. To separate traces of silica gel the cobester was dissolved in CH_2Cl_2 and filtered through a cotton plug. The cobester was then hydrolysed with 2 ml degassed 2 M piperidine soln for 24 hr at 4°. The piperidine–water mixture was evaporated under vacuum and cobyrinic acid dissolved in a small amount of distilled water, containing 5% HCN, and electrophoresis of the cobyrinic acid was carried out at pH 8.6. Thereafter the cobyrinic acid band was eluted with HCN-containing distilled water, and after evaporation of water an electrophoresis at pH 2.7 was carried out.

In order to control the radiochemical purity of the isolated cobyrinic acid, the radioactive distribution was measured along the electropherogram and the specific radioactivity of cobyrinic acid determined after each electrophoresis.[20]

The results of the incorporation data are given in Table 1.

Preparation of ^{13}C-*labelled* 20-*methylsirohydrochlorin*. δ-[5-^{13}C]-aminolevulinic acid (90 atom %, 100 mg) and $^{13}CH_3$-L-methionine (Merck, 90 atom %, 100 mg) were incubated for 50 hr with *P. shermanii* (ATCC 9614). The mixture was then centrifuged (20,000 g, 20 min) and the supernatant was filtered through DEAE cellulose (Whatman DE-23, 10 gm) which had been previously equilibrated with 0.02 M potassium phosphate buffer pH 7.6. The cellulose was freeze-dried and then stirred for 18 hr in the dark under argon with MeOH (250 ml) containing 5% HSO_4. The solution was poured into $CHCl_3$ (250 ml and neutralized with sat $NaHCO_3$ aq. The aqueous phase was extracted several times with $CHCl_3$ and the combined organic layers were dried ($NaSO_4$) and evaporated. The residue was chromatographed (TLC) using benzene-EtOH-MeOH (80:16:4). The fluorescent orange band at R_f 0.6 was eluted (10% MeOH in benzene) and subjected to hplc purification using a Waters C-18 μ-Bondapak column in 80% MeOH/water. The two main fractions consisting of sirohydrochlorin and 20-methylsirohydrochlorin octamethyl esters were collected. The latter was rechromatographed on the same column in 70% acetonitrile/H_2O to remove a trace impurity not resolved in the MeOH/water system. Collected fractions were evaporated in the dark at <50° and used directly for the NMR experiments.

Acknowledgments—We thank the National Institutes of Health (Grant AM 20528), the Robert A. Welch Foundation and Deutsche Forschungsgemeinschaft for generous support of this work and Prof. K. L. Rinehart, Jr. and Mr. J. Carter Cook, Jr. (Illinois) for high resolution FD mass spectra. High-field NMR spectra were recorded at the University of Utah through the courtesy of Prof. D. Grant (N.I.H. Grant RR00575-07).

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[14]In earlier experiments it was clearly shown[1a,15] that, under carefully controlled conditions, [^{14}C]-formaldehyde could be trapped from the C-20 position of uro'gen III. The data can be interpreted in several ways: (a) methylation at C-20 is followed by loss of a "C_2" unit which is further cleaved to "C_1" units, one of which is trapped as formaldehyde; (b) the formaldehyde is released (under enzymic control[16]) *only* from the uro'gen III molecule and *not* from Factor III; (c) more than one pathway exists for the biotransformation of uro'gen III to cobyrinic acid.

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Note added in press. 'The "missing" C-2 fragment has been identified as acetic acid by independent work in our laboratory (with A. J. Irwin and I. Ichinose) and in Cambridge, Zürich, and Stuttgart. We thank Professors A. R. Battersby, D. Arigoni and G. Müller for informing us of their work, and Professor A. Eschenmoser for communicating his results on a model system which generates corrins from isobacteriochlorin via "Acetate extrusion."'

Tetrahedron, Vol. 37, Supplement No. 1, pp. 91 to 97, 1981
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0040-4020/81/Suppl. 1-0091-07 $02.00/0
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THE STRUCTURE OF ACUMYCIN

A 16-MEMBERED RING MACROLIDE ANTIBIOTIC

JON CLARDY and JANET FINER-MOORE

Department of Chemistry, Cornell University, Ithaca, NY 14853, U.S.A.

LARRY WEILER*

Department of Chemistry, University of British Columbia, Vancouver, British Columbia, Canada V6T 1Y6

and

DON C. WILEY

Department of Biochemistry and Molecular Biology, Harvard University, Cambridge, MA 02138, U.S.A.

(*Received in U.S.A.* 3 *April* 1980)

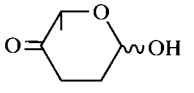
Abstract—The structure of acumycin, an antibiotic isolated from *Streptomyces griseoflavus*, was determined from spectroscopic and X-ray studies. Acumycin was found to be a 16-member ring macrolide with two sugars attached. One of the sugars had earlier been shown to be D-mycaminose. From the known absolute configuration of D-mycaminose we have been able to determine the absolute stereochemistry of acumycin. The stereochemistry in acumycin is compared with the predictions based on a biogenetic model proposed by Celmer. Acumycin because of its large number of chiral centers provided the most demanding test of the model to date and the model was found to be consistent with the experimental results from acumycin in every detail but one. These results suggest a refinement of Celmer's model for 16-member ring macrolides.

The macrolide antibiotics[1] have played a central role in the chemistry of natural products over the past three decades. Several members of this family are the most complex natural products whose structures have been elucidated by spectroscopic and chemical methods. More recently X-ray crystallography and solution NMR have been utilized to determine the stereochemistry and conformations of these highly substituted, large ring systems. The biogenesis of the macrolides was the subject of many hypotheses which have subsequently been tested in numerous biosynthetic studies. Recently the macrolide antibiotics have been the goal of several elegant synthetic studies. Many of these areas of macrolide chemistry have been reviewed.[2–7]

In 1962, Bickel *et al.* isolated an antibiotic from *Streptomyces griseoflavus* which they called acumycin.[8] From the results of combustion and functional group analyses, spectroscopic studies and some preliminary chemical reactions it appeared that acumycin was another member of the macrolide family of antibiotics and that it might be related to magnamycin (also called carbomycin).[1,9] Acumycin may be crystallized from ethyl acetate to yield prismatic crystals, m.p. 230–233°. Results from elemental analysis suggested that acumycin had the molecular formula $C_{38}H_{61}NO_{12}$ (MW 723).[8] However, the mass spectrum of acumycin did not show any peak at *m/e* 723, but it did show a significant peak at *m/e* 709. The mass spectral results along with the analytical data lead to the molecular formula $C_{37}H_{59}NO_{12}$ for acumycin. This formula was verified by a high resolution mass measurement of the peak at *m/e* 709. A preliminary X-ray crystallographic study of acumycin had also led to a molecular weight of 708 ± 2 for acumycin. All of this evidence was consistent with the molecular formula of $C_{37}H_{59}NO_{12}$ for acumycin.

The IR spectrum of acumycin has a weak band at 2725 cm^{-1} which is indicative of an aldehyde group in the molecule. A one-proton singlet at δ 9.72 in the ^{1}H NMR spectrum (Fig. 1) verifies the presence of an aldehyde. The IR spectrum of acumycin has bands at 1685 and 1615 cm^{-1} which may be attributed to an α,β-unsaturated ketone moiety. A strong absorption in the UV spectrum at 241 nm (ε 15,500) corroborates the presence of a conjugated enone. The ^{1}H NMR spectrum of acumycin has an AB quartet (J = 16 Hz) at δ 6.49 which suggests that the double band of the enone is trans disubstituted.

Mild acid hydrolysis of acumycin yielded a hexose[8] which was subsequently shown to be 2,3,6-trideoxyhexopyranos-4-ulose (**1**). This sugar derivative has also been isolated from the antibiotics



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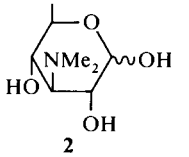

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cenerubin A[10] and B-58941,[11] and it has been synthesized.[12] Vigorous acid hydrolysis of acumycin yielded D-mycaminose (**2**).[8] The structure, including absolute stereochemistry, of D-mycaminose has been

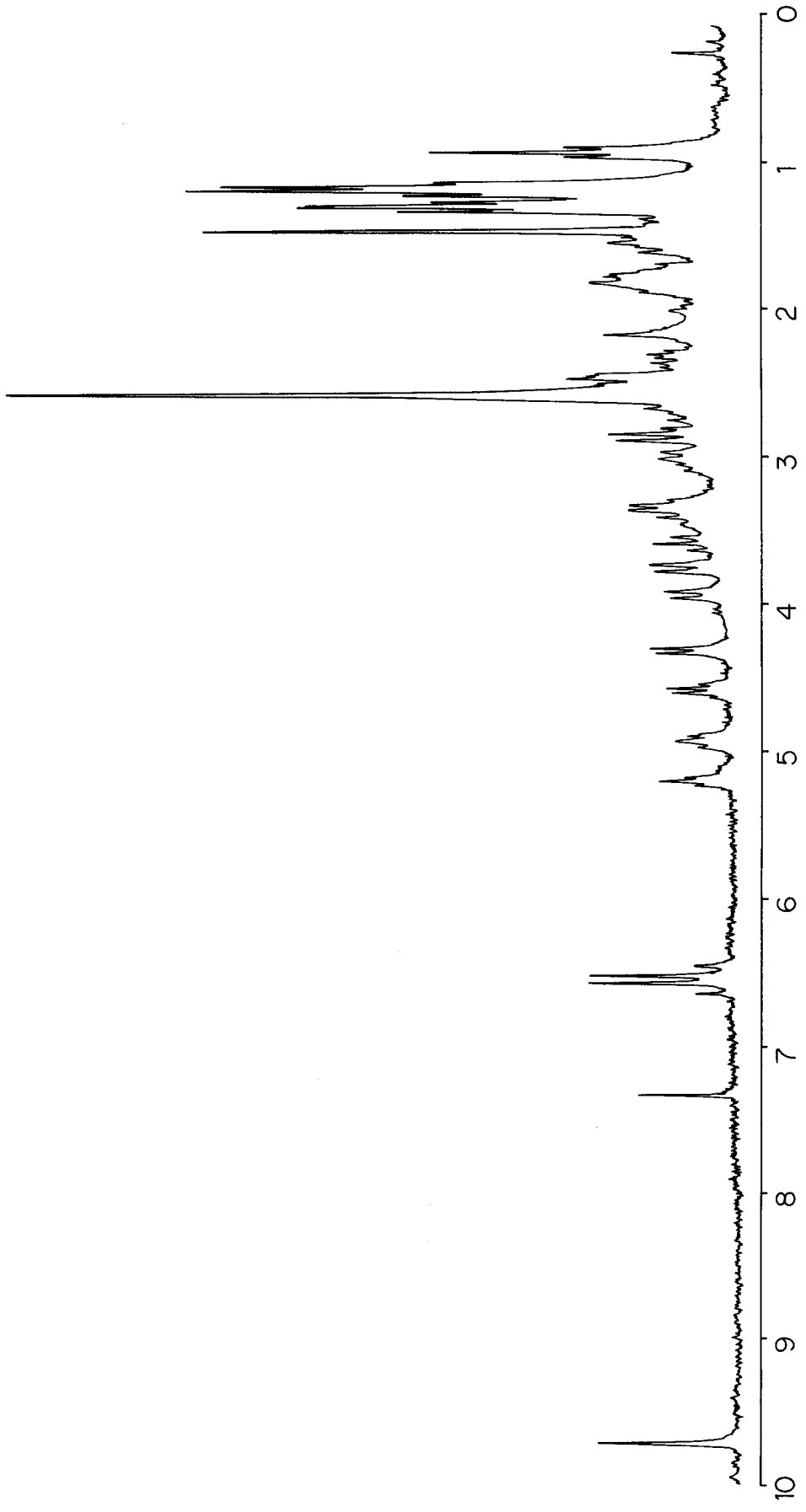
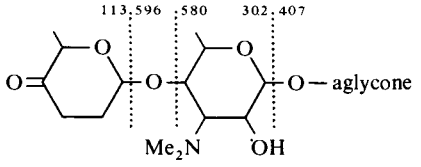


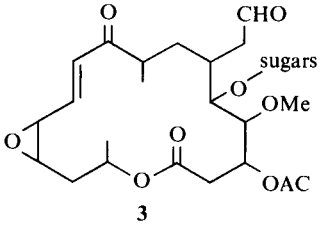
Fig. 1. 220 MHz ^{1}H NMR spectrum of acumycin in $CDCl_3$.

determined by chemical degradation,[13] ^{1}H NMR spectroscopy,[14] and synthesis.[15] The six-proton singlet at δ 2.56 in the ^{1}H NMR spectrum was assigned to the dimethylamino group in acumycin.[8] The results of pK_a measurements of acumycin and its hydrolysis products led to the suggestion that the two sugar moieties were linked together in acumycin.[8] The mass spectrum of acumycin supports this finding. Significant peaks occur at *m/e* 596, 580, 407, 302 and 113. The following fragmentation scheme can accommodate formation of these ions, and their composition was confirmed by high resolution mass measurements.



Kuhn-Roth oxidation indicated that acumycin possesses *seven* C-Me groups.[8] The ^{1}H NMR spectrum of acumycin also suggested that there are a large number of C-Me groups in the molecule. A three-proton triplet (J = 7 Hz) at δ 0.87 could be assigned to the Me of an Et side chain. In addition the ^{1}H NMR spectrum has a three-proton singlet at δ 1.41 and a series of signals between δ 1.0 and 1.4 attributed to five additional Me groups.

Originally, Woodward suggested that the macrolide antibiotics were synthesized in nature by the condensation of acetate and propionate units.[1] This hypothesis has been confirmed for a number of macrolides.[3,6,7] If we assume that acumycin has the same basic carbon framework as magnamycin A (**3**)



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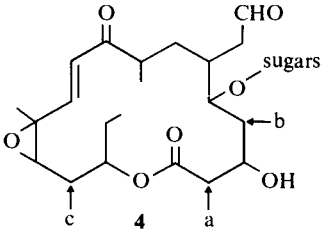
and the additional Me groups in acumycin are incorporated as propionate units in place of acetate units, we arrive at the following possible structures (**4**) for acumycin. There are three possibilities which could not be distinguished from the available data. In addition we have no experimental evidence for any of



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(Me groups at two of a, b, or c sites)

the relative stereochemical arrangements around the aglycone ring, except for the trans geometry of the double band. At this stage we turned to X-ray crystallography to provide insight about the structure of acumycin and to obtain some information about the stereochemistry of the substituents on the aglycone.

The X-ray structure was determined from orthorhombic crystals and the results are given in Fig. 2. Table 1 contains the fractional coordinates and errors for acumycin. Since the absolute stereochemistry of D-mycaminose is known,[16] the absolute stereochemistry of each asymmetric center in acumycin was established. First we note that the terminal hexose is (5*S*)-2,3,6-trideoxyhexopyranos-4-ulose and the sugar is linked via an α-glycosidic linkage to C-4 of D-mycaminose. The mycaminose in turn is linked to the aglycone via a β-glycosidic bond. The stereochemistry of the macrolide ring can be specified as 3*R*, 4*S*, 5*S*, 6*R*, 8*R*, 12*S*, 13*S*, 14*S*, 15*R*. The X-ray structure of acumycin contains all of the structural features anticipated from the spectral data and the two additional methyl groups are located at sites b and c in 4.

Acumycin is another member of the 16-member ring macrolides and it has the same gross structure as the aglycones in antibiotic B-58941,[11] cirramycin A,[17] and rosamicin.[18] In fact acumycin has the same structure,

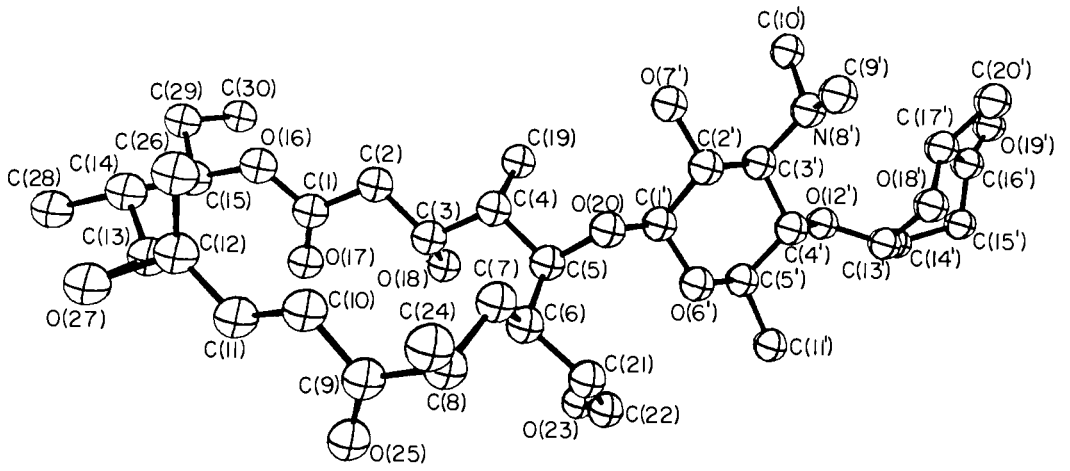


Fig. 2. X-ray structure of acumycin.

Table 1. Final fractional coordinates for acumycin. The primed numbers designate sugar atoms. The hydrogens are given the same numbers as the atoms to which they are bonded. In parentheses following each coordinate is the estimated standard deviation of its least significant figure

C(1)	.0854(3)	.4071(3)	-.77309(7)
C(2)	.1359(3)	.3239(3)	-.74349(7)
C(3)	.1907(3)	.3919(3)	-.71022(7)
C(4)	.2513(3)	.3037(3)	-.68225(7)
C(5)	.3254(3)	.3691(2)	-.65113(6)
C(6)	.4308(3)	.4635(2)	-.66395(6)
C(7)	.5348(3)	.4073(3)	-.69004(7)
C(8)	.6182(3)	.4998(3)	-.71196(7)
C(9)	.5387(3)	.5621(3)	-.74198(7)
C(10)	.4853(3)	.4855(3)	-.77246(7)
C(11)	.4168(3)	.5342(3)	-.80016(7)
C(12)	.3579(3)	.4655(3)	-.83121(7)
C(13)	.2278(3)	.5115(3)	-.84553(7)
C(14)	.1245(3)	.4315(3)	-.86437(7)
C(15)	.0126(3)	.4040(3)	-.83664(7)
O(16)	.0758(2)	.3457(2)	-.80472(4)
O(17)	.0563(2)	.5124(2)	-.76925(5)
O(18)	.0863(3)	.4609(2)	-.69193(6)
C(19)	.1439(4)	.2177(3)	-.66712(9)
O(20)	.3956(2)	.2763(1)	-.63004(4)
C(21)	.5017(3)	.5209(3)	-.63081(7)
C(22)	.4231(5)	.5975(3)	-.60591(9)
O(23)	.3133(4)	.6284(3)	-.60984(9
C(24)	.7402(4)	.4349(4)	-.72835(9)
O(25)	.5179(3)	.6717(2)	-.74125(6)
C(26)	.3991(4)	.3357(3)	-.83732(9)
O(27)	.3477(2)	.5398(2)	-.86509(5)
C(28)	.0689(4)	.4984(4)	-.89826(8)
C(29)	-.0933(4)	.3164(3)	-.84958(8)
C(30)	-.2019(4)	.2940(5)	-.82118(10)
C(1')	.3465(3)	.2507(3)	-.59514(7)
C(2')	.3962(3)	.1257(3)	-.58415(7)
C(3')	.3491(3)	.0924(3)	-.54537(7)
C(4')	.3869(3)	.1961(3)	-.51905(7)
C(5')	.3458(4)	.3221(3)	-.53365(7)
O(6')	.4004(2)	.3383(2)	-.57015(4)
O(7')	.3460(3)	.0343(2)	-.60877(5)
N(8')	.3931(3)	-.0258(3)	-.53180(7)
C(9')	.2992(8)	-.1256(4)	-.53951(12)
C(10')	.5302(6)	-.0572(5)	-.54070(11)
C(11')	.3992(6)	.4283(3)	-.51138(8)
O(12')	.3149(2)	.1775(2)	-.48519(5)
C(13')	.3897(4)	.1814(4)	-.45264(8)
C(14')	.2883(5)	.1811(4)	-.42114(8)
C(15')	.3426(5)	.1031(6)	-.38935(9)
C(16')	.3591(5)	-.0233(5)	-.40329(13)
C(17')	.4217(5)	-.0323(5)	-.44058(11)
O(18')	.4807(3)	.0820(3)	-.44983(6)
O(19')	.3225(4)	-.1121(5)	-.38633(15)
C(20')	.5267(9)	-.1329(9)	-.44203(16)
H(2A)	.206(5)	.267(4)	-.755(1)
H(2B)	.064(4)	.278(4)	-.736(1)
H(3)	.112(4)	.446(4)	-.698(1)
H(4)	.318(3)	.255(3)	-.695(1)
H(5)	.258(3)	.411(3)	-.635(1)
H(6)	.378(3)	.534(3)	-.677(1)
H(7A)	.486(3)	.352(3)	-.709(1)
H(7B)	.597(3)	.348(2)	-.676(1)
H(8)	.647(4)	.567(3)	-.695(1)
H(10)	.499(2)	.395(2)	-.771(1)
H(11)	.404(3)	.626(3)	-.799(1)
H(13)	.188(3)	.587(3)	-.832(1)
H(14)	.169(3)	.351(3)	-.871(1)
H(15)	-.023(3)	.487(3)	-.828(1)
H(19A)	.081(5)	.251(4)	-.652(1)
H(19B)	.102(4)	.162(4)	-.688(1)
H(19C)	.185(4)	.155(4)	-.651(1)
H(21A)	.546(4)	.449(3)	-.616(1)
H(21B)	.589(4)	.569(3)	-.637(1)
H(22)	.469(3)	.634(3)	-.579(1)
H(24A)	.787(6)	.493(5)	-.744(1)
H(24B)	.798(5)	.405(5)	-.709(1)
H(24C)	.705(4)	.348(3)	-.743(1)
H(26A)	.366(4)	.289(4)	-.816(1)
H(26B)	.359(4)	.292(4)	-.857(1)
H(26C)	.492(4)	.337(4)	-.837(1)
H(28A)	.030(4)	.582(4)	-.891(1)
H(28B)	.149(4)	.517(4)	-.913(1)
H(28C)	-.010(5)	.451(4)	-.909(1)
H(29A)	-.133(4)	.341(4)	-.871(1)
H(29B)	-.057(4)	.236(4)	-.856(1)
H(30A)	-.241(5)	.376(4)	-.817(1)
H(30B)	-.267(5)	.230(4)	-.831(1)
H(30C)	-.161(5)	.260(4)	-.797(1)
H(1')	.246(3)	.253(3)	-.594(1)
H(2')	.498(3)	.124(3)	-.584(1)
H(3')	.243(3)	.092(3)	-.543(1)
H(4')	.482(3)	.197(2)	-.515(1)
H(5')	.243(4)	.318(4)	-.535(1)
H(9'A)	.293(5)	-.147(5)	-.565(1)
H(9'B)	.322(5)	-.198(4)	-.528(1)
H(9'C)	.213(5)	-.091(5)	-.531(1)
H(10'A)	.583(4)	.010(4)	-.529(1)
H(10'B)	.546(5)	-.143(5)	-.531(1)
H(10'C)	.545(5)	-.071(4)	-.570(1)
H(11'A)	.390(4)	.497(4)	-.522(1)
H(11'B)	.349(5)	.424(4)	-.487(1)
H(11'C)	.510(5)	.416(4)	-.512(1)
H(13')	.449(4)	.260(3)	-.452(1)
H(14'A)	.263(4)	.278(4)	-.415(1)
H(14'B)	.202(4)	.143(3)	-.431(1)
H(15'A)	.416(5)	.146(5)	-.382(1)
H(15'B)	.279(5)	.106(5)	-.370(1)
H(17')	.352(4)	-.044(4)	-.458(1)
H(20'A)	.490(6)	-.194(5)	-.430(1)
H(20'B)	.575(5)	-.134(5)	-.464(1)
H(20'C)	.597(6)	-.107(5)	-.423(1)

devoid of stereochemical detail, as antibiotic B-58941. A comparison of the published physical and spectroscopic properties indicates that these two antibiotics are identical.

Stereochemistry. Celmer has proposed a stereochemical model for the macrolide antibiotics based on biogenetic considerations.[7] This model predicts the *absolute* configuration of the macrolide sugars, including glycosidic linkages, and the absolute configuration of every chiral center on the aglycone. The Celmer model has been remarkably successful. The model is consistent with the stereochemistry of every single chiral center in the 12- and 14-member ring macrolides.[7] In fact, it has been so successful that every "exception" to the model was subsequently reinvestigated and the original stereochemical assignment was found to be in error.

The X-ray structure reported here is the first X-ray structure of 16-member ring macrolide with the sugars attached and thus allows us to test all aspects of the Celmer stereochemical model as it applies to the 16-lactones. First, Celmer suggests that if a macrolide has a sugar at C-5 of the aglycone, the sugar should be of the D-series. Acumycin has D-mycaminose linked to C-5 of the macrolide ring. In addition, the model predicts that this sugar should form a β-glycosidic link to the lactone ring. The above X-ray results confirm this prediction for D-mycaminose. The model goes on to predict that there are two possible sites for attachment of an L-sugar, should the antibiotic contain one. These sites are (i) β to the site of attachment of the D-sugar to the lactone ring, or (ii) on C-4 of D-mycaminose. Furthermore, the model predicts that this L-sugar should be joined to the site (i) or (ii) via an α-glycosidic bond. The X-ray results show that the configuration and location of the 2,3,6-trideoxyhexopyranos-4-ulose is in full accord with these predictions. In summary, the Celmer model for the location, configuration and

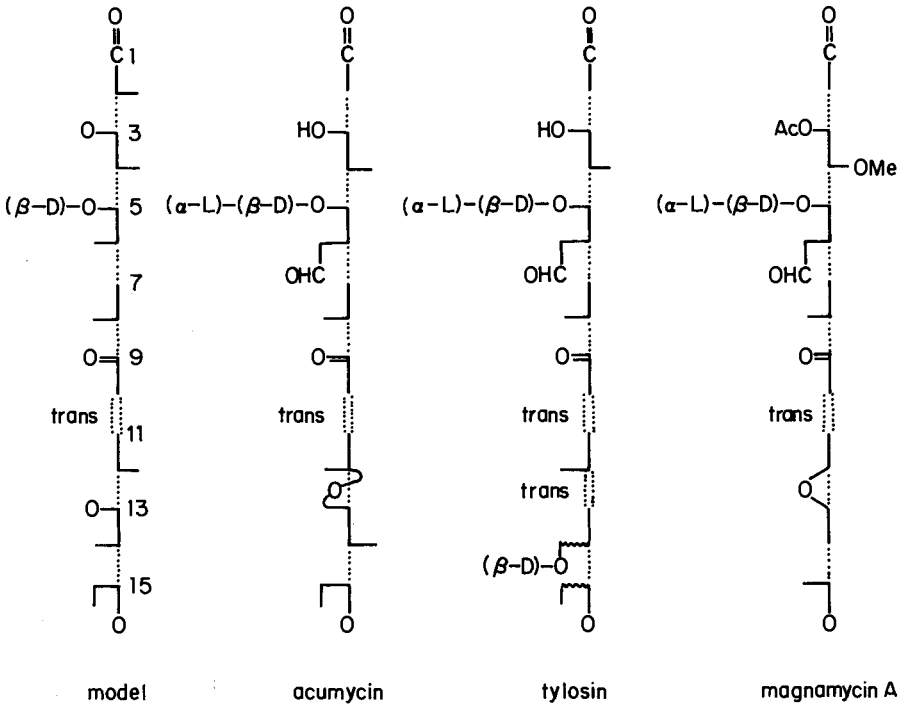


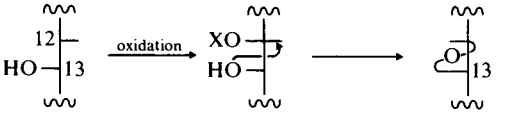
Fig. 3. Celmer's stereochemical model for 16-member macrolides and the absolute stereochemistry of acumycin, tylosin and magnamycin A (Fisher projection), all shown in Fisher projection.

geometry of the glycosidic linkages for the carbohydrate moieties in the macrolides is totally consonant with the X-ray structural results for acumycin.

The Celmer model also predicts the chirality at the asymmetric centers in the macrolide ring.[7] This model is based on a biogenetic proposal for the stereospecific addition of acetate or propionate units in the biosynthesis of the macrolide ring. The model for the 16-member ring lactones is shown above (Fig. 3). In this model the aglycone is considered to be formed from seven "propionate" units and one "acetate" unit. It was recognized that some of the propionate units might be replaced by acetate units which would remove a chiral center for each replacement. Also, Celmer noted that extra oxygens were occasionally found attached to the even-numbered carbons (model in Fig. 3). It was reasoned that these oxygens were introduced late in the biosynthetic pathway. Since most oxygenases involve retention of configuration,[19] it was a straightforward matter to incorporate these extra oxygens at any of the methyl substituted carbons in the lactone ring.

Figure 3 shows the absolute stereochemistry of the aglycone of acumycin (drawn in a Fisher projection) and compares this structure with the Celmer model for the 16-member lactones. Carbon atoms 3 and 4 are the first asymmetric centers in the lactone ring of acumycin and their absolute configuration is in accord with the model. The next four-carbon unit in acumycin, C-5 and C-6 and the side-chain aldehyde, is a feature which is unique to the 16-member macrolides. The biosynthetic origin of this fragment appears to involve incorporation of a butyrate unit[20] rather than a propionate unit. Nevertheless, the configuration at C-5 and C-6 of acumycin agrees with the model. The stereochemistry of the methyl at C-8 is also in agreement with the model. Celmer suggests that the olefinic bonds in the aglycone should be trans and the C-10,11 double bond of acumycin is. Thus, the six asymmetric centers and the geometry of the double band from C-1 to C-11 of acumycin are in full agreement with the predictions based on the Celmer model.

Carbon-12 is a special case with the branching methyl and an "extra" oxygen. As pointed out above, in the model these "extra" oxygens are introduced with retention of configuration. In this case, it would appear that the stereochemistry at C-12 is a violation of the model. However, this oxygen is unique in that it forms an epoxide bridge to C-13 and the configuration at C-13 agrees with the model. The epoxide formation might involve an inversion of configuration at C-12 as shown schematically in **5**.



5

The configuration at C-14 is *S* and this is a clear violation of the predictions based on the model! There appears to be no apparent resolution of this problem within the framework of the current model. The configuration of this center (where it is substituted) is not known for any of the other 16-member ring macrolides (vide infra). Finally the configuration of C-15 in acumycin agrees with Celmer's model.

To date there are only two substitution patterns found for the 16-member ring lactones in the macrolide antibiotics. The two basic structures differ only in the number of acetate versus propionate units in the lactone skeleton. Acumycin is a member of the group which contain five propionate units, two acetate units, and a butyrate unit in the aglycone. Magnamycin A (**3**)[1,9,21] is an example of the second family which contain only one propionate unit, six acetate units, and one butyrate unit in the aglycone.

As we see in Fig. 3, the stereochemistry of C-14 in acumycin conflicts with the predictions of Celmer's model. Unfortunately the stereochemistry of this center is not known for any of the antibiotics directly related to acumycin, namely, antibiotic B-5894,[11] cirramycin A_1,[17] rosamicin,[18] and antibiotic M-4365 A_2.[22] There are other 16-member ring macrolides related to acumycin, in that the aglycone of these antibiotics can be considered to consist of five propionate units, one acetate, and one butyrate. The most extensively studied member of this group is tylosin[23] and the stereochemistry of carbons 1–13 have been proposed.[23c] These results based on chemical degradation and spectroscopic studies are in agreement with the Celmer model (Fig. 3). Unfortunately there is no data available on the absolute stereochemistry at C-14 and C-15 in tylosin or in any of its related antibiotics. Hence, we are unable at this time to define the scope of the exception to Celmer's model found at C-14 in acumycin.

The second family of 16-member macrolides represented by magnamycin[1,9,21] includes leucomycin A_3,[24] niddamycin[25] and spiramycin III.[26] The absolute stereochemistry in this family is known from chemical studies in the case of magnamycin[1,21] and from X-ray studies in the case of leucomycin A_3.[24] Again we see complete agreement between the observed configuration and the predictions of Celmer's model for all of the asymmetric centers. Note that C-14 is unsubstituted in this family.

In summary the X-ray structural data for acumycin have allowed the most extensive evaluation of Celmer's stereochemical model[7] to date. The model and experimental results were consistent in all aspects but one. The significance of this single known exception to Celmer's model must await further structural studies on related macrolides. But these results suggest that the Celmer model may have to be refined in extending the model to C-14 in the 16-membered ring macrolides.

EXPERIMENTAL

A 100-mg sample of crude acumycin (m.p. 215–219°, dec) was chromatographed on 50 g of silica gel and the product was eluted with EtOAc. The fractions with high concentrations of acumycin were combined. The solvent was removed under reduced pressure and the resulting colourless oil was immediately dissolved in a minimum volume of hot EtOAc. When the solution cooled 30 mg of pure acumycin crystallized, m.p. 230–233°, dec (lit. m.p. 233–237°, dec[11]). These crystals were of sufficiently high quality to be used directly in the X-ray study.

The mass spectrum (AEI MS-9 mass spectrometer operating at 70 eV) had the following peaks *m/e* 709 (10), 693 (1), 691 (1), 596 (0.5), 580 (0.5), 407 (1), 302 (4), 286 (16), 174 (11), 173 (14), 122 (12), 115 (20), 114 (21), 113 (23), 109 (20), 98 (14) and 87 (100). High resolution mass measurement gave 709.4031, calc. for $C_{37}H_{59}NO_{12}$: 709.4037. (Found: C, 62.64; H, 8.31; N, 1.90). Calc. for $C_{37}H_{59}NO_{12}$: C, 62.60; H, 8.37; N, 1.9.

X-ray structure determination. Preliminary X-ray photographs showed orthorhombic symmetry for acumycin crystals. Accurate unit cell constants, determined from a least-squares fit of fifteen diffractometer measured 2θ-values, were $\mathbf{a} = 9.996\,(2)$, $\mathbf{b} = 10.892\,(2)$ and $\mathbf{c} = 36.315\,(6)$ Å. Systematic extinctions, chirality and an observed density of 1.19 g/cm^3 were uniquely accommodated by space group $P2_12_12_1$ with one molecule of $C_{37}H_{59}NO_{12}$ per asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were recorded by an automated four-circle diffractometer using an ω-scan technique and graphite monochromated CuKα (1.54178 Å) radiation. Of the 3064 reflections surveyed, 2581 (84%) were judged observed after correction for Lorentz, polarization and background effects ($|F_0| \geq 3\sigma(F_0)$).

The angular dependence of the scattering was removed as the data were converted to normalized structure factors and the 350 largest of these were assigned phases using a multisolution weighted tangent formula approach.[27] An E-synthesis computed from the best solution showed a plausible 24 atom fragment. This fragment was used in a tangent formula recycling procedure and the improved phases yielded a synthesis from which 40 of the atoms could be identified.[28] These atomic coordinates were refined by a least-squares procedure and a subsequent electron density synthesis revealed all 50 non-hydrogen atoms.[29] H atoms were located in a difference synthesis and full-matrix least-squares refinements converged to a final crystallographic discrepancy index of 0.041 for the observed reflections.[30]

Acknowledgement—This paper is dedicated to the memory of R. B. Woodward who initiated the study with careful supervision and sustained it with his enthusiasm.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 99 to 109, 1981
Printed in Great Britain

0040-4020/81/Suppl. 1-0099-11 $02.00/0
Pergamon Press Ltd.

SYNTHESIS AND REACTIONS OF 5,6,11,12-TETRADEHYDRODIBENZO[*a,e*]CYCLOOCTENE AND 5,6-DIDEHYDRODIBENZO[*a,e*]CYCLOOCTENE†[1,2]

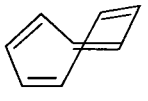
HENRY N. C. WONG[3] and FRANZ SONDHEIMER*

Chemistry Department, University College London, 20 Gordon Street, London WC1H 0AJ, England

(*Received in U.K.* 17 *July* 1980)

Abstract—Syntheses of 5,6,11,12-tetradehydrodibenzo[*a,e*]-cyclooctene (**5**) and 5,6-didehydrodibenzo[*a,e*]cyclooctene (**6**) by dehydrobromination with potassum *t*-butoxide of 5,6,11,12-tetrabromo-5,6,11,12-tetrahydrodibenzo[*a,e*]cyclooctene (**9**) and 5,6-dibromo-5,6-dihydrodibenzo[*a,e*]cyclooctene (**8**), respectively, are described. Compounds **5** and **6** are unusual, essentially planar, conjugated anti-aromatic 8-membered ring systems, the reactions of which have been studied. The diacetylene **5** readily underwent Diels–Alder reaction with 1,3-diphenylisobenzofuran and furan to give the bis-adducts **13** and **14**, respectively. [2+2]Cycloaddition between **5** and dichloroketene and subsequent hydrolysis of the gem-dichloride yielded 2,3,6,7-dibenzobicyclo[6.2.0]deca-2,6,8-trien-4-yne-9,10-dione (**21**). The monoacetylene **6** readily underwent Diels–Alder reaction with 1,3-diphenylisobenzofuran and furan to give the mono-adducts **24** (*endo* and *exo* isomers) and **25**, respectively. 1,3-Dipolar cycloaddition of phenylazide to **6** led to the 1-phenyl-1H-triazole derivative **27**, whereas [2+2]cycloaddition between **6** and dichloroketene and hydrolysis yielded 2,3,6,7-dibenzobicyclo[6.2.0]deca-2,4,6,8-tetraene-9,10-dione (**30**). Spectral, as well as chemical and electrochemical reductions, of **5** and **6** have been studied. For instance, treatment of the monoacetylene **6** with a potassium mirror gave the aromatic 10π-electron dianion **34**.

The work described in this paper arose from our interest in the synthesis and study of planar conjugated 8-membered ring compounds, which were expected to be anti-aromatic 4*n* π-electron systems. Unfortunately, cycloocta-1,3,5,7-tetraene (**1**), itself exists in the strainless nonplanar D_{2d} "tub" conformation **1**, due to the strain inherent in a planar structure.[4]



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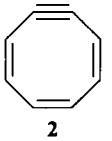

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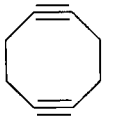
A possible way to modify cyclooctatetraene so as to make it planar is to replace one or more of the double bonds by an acetylene,[5] and Krebs and Byrd[6] have attempted to prepare such a molecule, cycloocta-1,3,5-trien-7-yne (**2**), by dehydrobromination of 1-bromocycloocta-1,3,5,7-tetraene with potassium t-butoxide. However, it was not possible to isolate **2** due to its reactivity, and its existence as a transient intermediate could only be inferred from its transformation products.[6]

Shortly before we started our work in this field, the rather surprising finding was announced by Kloster–Jensen and Wirz[7] that cycloocta-1,5-diyne (**3**), containing two highly strained acetylenic bonds, could be isolated as a relatively stable crystalline compound.



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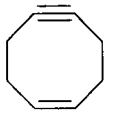

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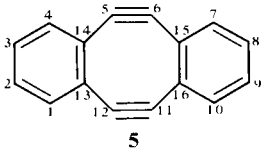
Subsequently, Leupin and Wirz[8] succeeded in isolating the less stable cyclooct-1-en-5-yne (**4**). In view of the isolation of **3**, we considered that it might be possible to prepare the related 5,6,11,12-tetradehydrodibenzo[*a,e*]cyclooctene (**5**), a conjugated cycloocta-1,5-diyne containing two annelated benzene rings. We also decided to investigate the synthesis of 5,6-didehydrodibenzo[*a,e*]cyclooctene (**6**), a conjugated dibenzanneleted cyclooct-1-en-5-yne derivative, formally related to **4**. We chose first to work in the



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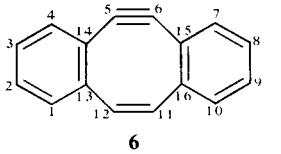

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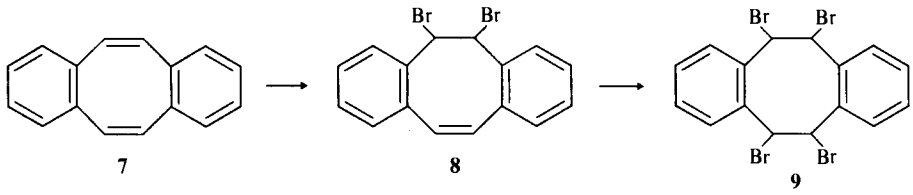
dibenz[*a,e*]cyclooctene series, since the presence of the fused benzene rings was expected to stabilize the molecules, and to prevent the formation of cumulene linkages by base treatment of suitable precursors. We now report the synthesis and study of compounds **5** and **6**, which could be isolated as crystalline compounds.[9,10,11]

SYNTHESIS AND REACTIONS OF 5,6,11,12-TETRADEHYDRODIBENZO[*a,e*]CYCLOOCTENE (5)

The starting material for the synthesis of 5,6,11,12-tetradehydrodibenzo [*a,e*]cyclooctene (**5**) was 5,6,

†This paper is dedicated to the memory of the late Prof. R. B. Woodward.



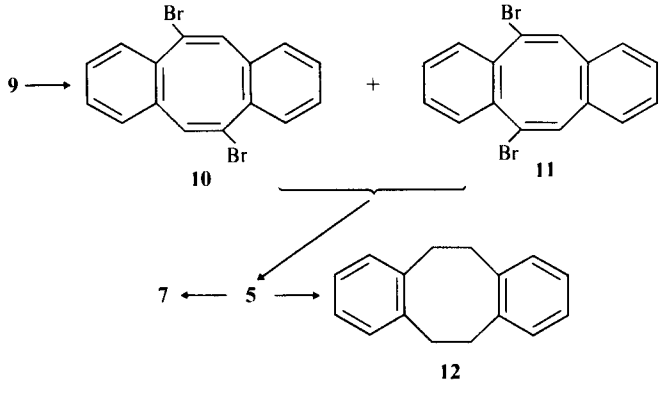
11,12-tetrabromo-5,6,11,12-tetrahydrodibenzo-[*a,e*]cyclooctene (**9**), which had been prepared a number of years ago by the addition of bromine[12] to dibenzo[*a,e*]cyclooctene (**7**).[13,14] It is of interest that the conversion of **7** to the dibromide **8** proceeds readily in dichloromethane or chloroform at 0–5°,[12] whereas addition of the second molecule of bromine is a much less facile process (requiring irradiation of a carbon tetrachloride solution with an ultraviolet lamp at 60° or higher[12]) presumably for steric reasons. Only one stereoisomer of the tetrabromide **9** (m.p. 191–193°) appears to be formed, but its stereochemistry has not been determined.

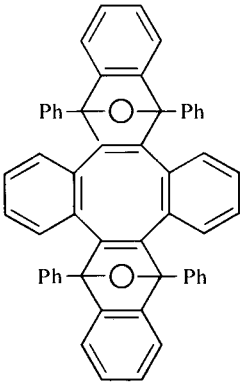
Dehydrobromination of the tetrabromide **9** with an excess of 1,5-diazabicyclo[4.3.0]non-5-ene in boiling benzene resulted in the loss of only one molecule of hydrogen bromide from each of the two 1,2-dibromo groupings, and led to 81% of a mixture of the divinyl dibromides **10** and **11** as an apparently homogeneous crystalline product, m.p. 137–138°. The gross structure of the mixture of **10** and **11** was established by the elemental analysis, the mass spectrum, and by hydrogenation in ethanol over a Pd–C catalyst to give 5,6,11,12-tetrahydrodibenzo[*a,e*]cyclooctene (**12**),[15] identical to a sample obtained by similar hydrogenation of dibenzo[*a,e*]cyclooctene (**7**). That the dibromides, which could not be separated, were a mixture of **10** and **11** was shown by the presence of two singlets at δ 7.34 and 7.30 in the 220 MHz ^{1}H NMR spectrum.

Dehydrobromination of the tetrabromide **9** with a stronger base (potassium t-butoxide) in tetrahydrofuran at room temperature resulted in the loss of four molecules of hydrogen bromide, and gave the diacetylene **5** as pale yellow crystals in 70% yield, which could also be obtained (in 28% yield) under similar conditions from the divinyldibromides **10** and **11**. The structure of the diacetylene **5** was confirmed by the IR spectrum (C≡C stretching band at 2180 cm^{-1}), the mass spectrum (M^+ at *m/e* 200), and by hydrogenation experiments. Dibenzo[*a,e*]cyclooctene (**7**) was obtained in 31% yield when a solution of **5** in ethyl acetate in the presence of a Pt catalyst was allowed to absorb *ca* 2 molar equivalents of hydrogen, whereas 5,6,11,12-tetrahydrodibenzo[*a,e*]cyclooctene (**12**)[15] was formed when the hydrogenation of **5** under these conditions was allowed to proceed to completion. Rather surprisingly, the diacetylene **5** proved to be a comparatively stable compound, although some decomposition was observed after several days when the solid was allowed to stand at room temperature without protection from light or air.

The acetylenic bonds in the diacetylene **5** are considerably strained, and this is shown by their enhanced reactivity. Thus, compound **5** (formed *in situ* from **10**, **11**, and potassium t-butoxide) underwent ready Diels–Alder reaction with 1,3-diphenylisobenzofuran at room temperature. The bis-adduct **13**, isolated in 57% yield, formed pale pink crystals, m.p. 274–275°. It appeared to be a mixture of the *endo* and *exo* isomers, but separation could not be achieved. Similarly, Diels–Alder reaction of **5** with furan at room temperature afforded the bis-adduct **14**. This substance was not isolated, but was converted by catalytic hydrogenation in ethyl acetate over Pt to the corresponding tetrahydro-compound, which was then dehydrated to tetraphenylene (**15**)[17] (16% yield based on **5**) by means of phosphorus pentoxide in orthophosphoric acid.[16] 5,6,11,12-Tetrahydrodibenzo[*a,e*]cyclooctene (**12**), derived from unchanged **5**, was also isolated in 9% yield.

The strain of the acetylenes in **5** was also indicated by the [2+2]cycloaddition between **5** and dichloroketene[18,19] (generated *in situ* from dichloroacetyl chloride and triethylamine),[20] which led to 28% (42% based on converted **5**) of the red mono-adduct **16**, m.p.





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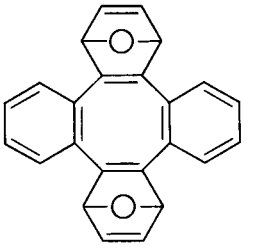

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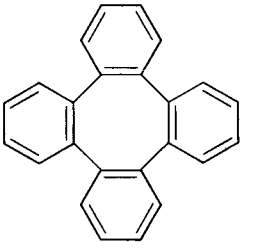

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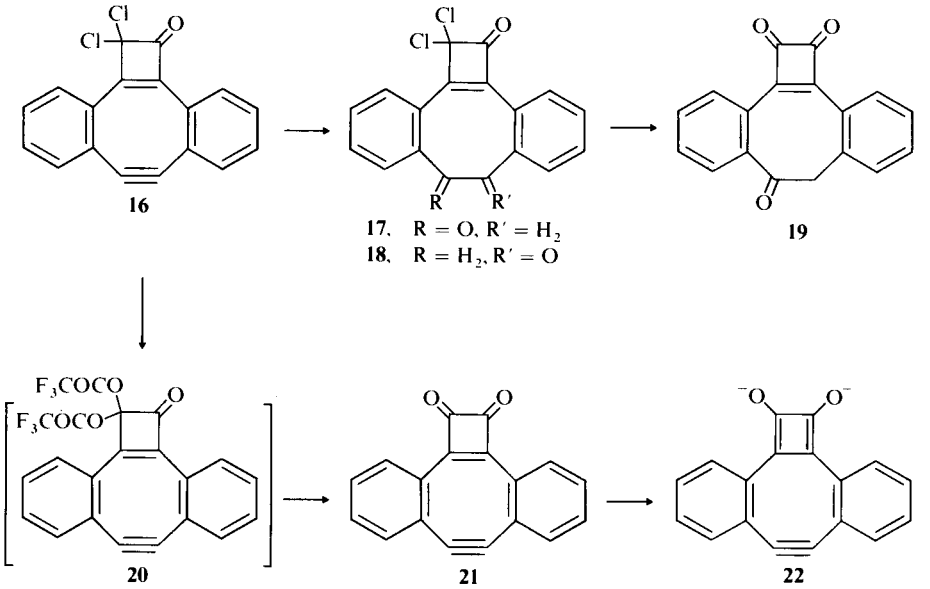
144–145° dec.[21,22] It was of interest to convert the dichloroketone **16** to the annelated cyclobutene-1,2-dione **21**. In practice, attempted hydrolysis of **16** to **21** with concentrated sulphuric acid[23] at 65° for 2 hours resulted also in hydration of the acetylene, and gave the yellow trione **19**, m.p. 173–174°, in 70% yield. Unfortunately, hydration of the strained acetylenic bond in **16** appears to take place prior to hydrolysis of the gem-dichloride, since treatment of **16** with concentrated sulphuric acid under milder conditions (20° for 10 seconds) led to a mixture of the hydrated products **17** and **18**, m.p. 123–125°.

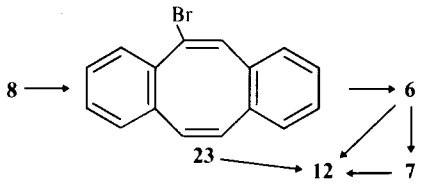
After some experimentation, it was found that the desired diketone **21** could be obtained conveniently by treatment of the dichloroketone **16** with silver trifluoroacetate[24] in boiling benzene, followed by hydrolysis of the presumed intermediate gem-bis-(trifluoroacetate) **20** with water.[21] The diketone **21**, an interesting compound consisting of a cyclobutene-1,2-dione ("cyclobutadienequinone") annelated to a presumably planar conjugated 8-membered ring (see below), was obtained as an unstable red crystalline solid. Although the yield was good, the exact yield could not be determined due to the instability of the substance.

The electrochemical reduction of the quinone **21** to the radical anion, and then to the dianion **22**, has been studied (for details, see Ref. 21). The interesting observation was made that the reduction of **21** is relatively facile, suggesting that the fusion of two planar anti-aromatic $4n$ π-electron rings in **22**, the core of which is a $(4n + 2)$ π-electron cyclobutadieno-cyclooctatetraene system, has resulted in aromatic stabilization.

SYNTHESIS AND REACTIONS OF 5,6-DIDEHYDRODIBENZO[*a,e*]CYCLOOCTENE (6)

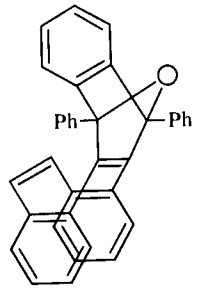
The starting material for the synthesis of 5,6-didehydrodibenzo[*a,e*]cyclooctene (**6**) was the previously mentioned 5,6-dibromo-5,6-dihydrodibenzo[*a,e*]cyclooctene (**8**), readily obtained in 85% yield by bromination[12] of dibenzo[*a,e*]cyclooctene (**7**). Dehydrobromination of **8** with 1,5-diazabicyclo-[4.3.0]non-5-ene in boiling benzene gave 80% of the



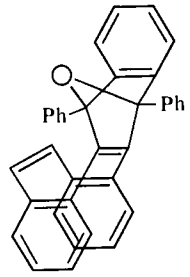


vinyl bromide **23**, m.p. 76–78°. Dehydrobromination of either the dibromide **8** or the monobromide **23** with potassium t-butoxide in tetrahydrofuran at room temperature for 1–2 min led to the monoacetylene **6** (34% yield from **8**, 24% yield from **23**) as golden yellow crystals, which proved to be very unstable. Thus, it decomposed after being allowed to stand for a few min at room temperature without protection from light or air, and was generally prepared immediately before it was required for the various measurements and reactions described subsequently.[25] It was found important that the dehydrobromination of **8** or **23** with potassium t-butoxide was allowed to proceed for only a short time, since longer reaction times resulted in drastic reductions in the yield of **6**. Catalytic hydrogenation of **6** in ethyl acetate over a Pt catalyst yielded dibenzo[*a,e*]cyclooctene (**7**) in 14% yield when *ca* 1 molar equivalent of hydrogen was allowed to be absorbed, whereas 5,6,11,12-tetrahydrodibenzo-[*a,e*]cyclooctene (**12**) was obtained when the hydrogenation of **6** under these conditions was allowed to proceed to completion. Compound **12** was also obtained by catalytic hydrogenation of the vinyl bromide **23** in ethanol over a Pd–C catalyst.

As in the diacetylene **5**, the acetylenic bond in the monoacetylene **6** is strained, and this is shown by its enhanced reactivity. For instance, Diels–Alder reaction of **6** (formed *in situ* from **8** and potassium *tert*-butoxide) with 1,3-diphenylisobenzofuran at room temperature led to 25% of the *endo* adduct **24a**, m.p. 282–285°, and 4.5% of the *exo* adduct **24b** m.p. 268–270°. Unlike in the case of the *endo* and *exo* adducts **13**, separation between **24a** and **24b** could be achieved simply by preparative layer chromatography. The stereochemical assignments are based on ^{1}H NMR spectrometry. The olefinic protons in the isomer m.p. 282–285° resonate at considerably higher



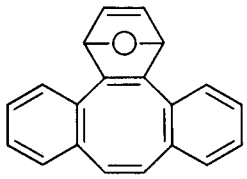
24a



24b

field (δ 6.14) than in the isomer m.p. 268–270° (δ 6.70 or at lower field). Since the olefinic protons are expected to be shielded by the dihydroisobenzofuran ring in the *endo* adduct **24a**, but not in the *exo* adduct **24b**, the higher melting isomer is assigned the *endo* structure **24a**, and the lower melting isomer the *exo* structure **24b**.

Similarly, Diels–Alder reaction of **6** with furan at room temperature gave 51% of the adduct **25**, m.p. 182–183°, which on catalytic hydrogenation in ethyl acetate over Pd–C and subsequent dehydration of the resulting dihydro-compound with phosphorus pentoxide in orthophosphoric acid[16] led to 13,14-dihydrotribenzo[*a,c,e*]cyclooctene (**26**)[26] in 27% yield.



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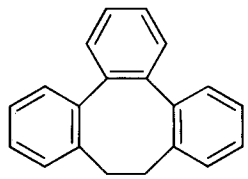

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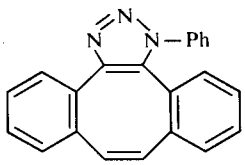
An example of a 1,3-dipolar cycloaddition to the acetylene in **6** was provided by the reaction with phenylazide[27] in ether at room temperature, whereby the annelated 1-phenyl-1H-triazole derivative **27**, m.p. 223–224°, was obtained in 66% yield. In the same way as the diacetylene **5**, the monoacetylene **6** underwent smooth [2+2]cycloaddition with dichloroketene



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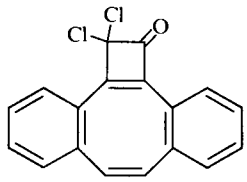

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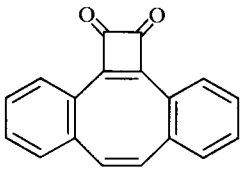

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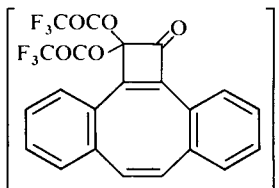

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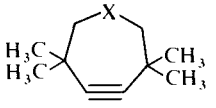
(generated *in situ* from dichloroacetyl chloride and triethylamine),[20] whereby the yellow dichloroketone **28** m.p. 158–160°, was obtained in 17% yield.[21] Treatment of **28** with silver trifluoroacetate in boiling benzene, followed by hydrolysis of the resulting gem-bis(trifluoroacetate) **29** with water, then led in low yield to the relatively stable compound **30**, consisting of a cyclobutene-1,2-dione ("cyclobutadienequinone") annelated to cyclooctatetraene, as pale yellow crystals, m.p. 198–199°.[21]

SPECTRAL AND OTHER PROPERTIES OF 5,6,11,12-TETRADEHYDRODIBENZO[*a,e*]CYCLOOCTENE (5) and 5,6-DIDEHYDRODIBENZO[*a,e*]CYCLOOCTENE (6)

A number of spectral and other properties of **5** and **6**, not previously mentioned in this paper, have been investigated. Much of this work has already been published elsewhere, and this and the next section will therefore be confined mainly to a description of previously unpublished material, as well as drawing attention to the published work.

X-Ray crystallographic analyses of the diacetylene **5**[28] and the monoacetylene **6**[29] have been carried out. As expected, the eight-membered ring in **5** was found to be essentially coplanar, and the acetylenic bonds are highly strained (average angular deformation. 24.2°).[28] The monoacetylene **6** crystallized as two different molecules (molecules A and B).[29] The 8-membered ring in molecule A is also essentially coplanar, but a significant deviation from coplanarity was observed in molecule B.[29] The average deviation of the acetylenic bond from the normal value in compound **6**, molecule A, was 24.5°, and in **6**, molecule B, it was 27.5°.[29] There is only one report of a more highly strained cyclic acetylene, namely 3,3,6,6-tetramethyl-1-thiacycloheptyne (**31**), in which the deformation of the acetylene was found to be 34.2° by an electron diffraction study of the molecule in the gas phase.[30]



31. X = S
32. X = CH_2

The strain of the acetylenes in the cyclic acetylenes **5** and **6** was also demonstrated by the ^{13}C NMR spectra (Table 1). Compared with an unstrained acetylene, such as 2,2,5,5-tetramethylhex-3-yne, the ^{13}C resonances have shifted to much lower field, the value being similar to that of the highly strained cycloheptyne derivatives **31**[31] and **32**.[32]

Since compounds **5** and **6** contain essentially coplanar conjugated 8-membered rings, their ^1H NMR spectra were expected to show them to be paratropic ("antiaromatic"). Preliminary ^1H NMR spectral results, reported in 1974,[9] confirmed this expectation. More recently, a complete analysis of the ^1H NMR spectrum of the diacetylene **5** has been carried out by Günther *et al.*[33] This gave definite support for the antiaromaticity of the 8-membered ring of **5**, a fact demonstrated most convincingly by the Q-value method.[33]

A well-resolved ^1H NMR spectrum of the monoacetylene **6** has recently been carried out by Günther *et al.* at 400 MHz.[34] This spectrum (in acetone-d_6) appears as a 4 H multiplet at δ 6.86 (H(2), H(3), H(8), H(9)), a 2 H doublet at δ 6.67 (H(4), H(7) or H(1), H(10)), a 2 H doublet at δ 6.51 (H(1), H(10) or H(4), H(7)), and a 2 H singlet at δ 5.45 (H(11), H(12)). By comparison, in the ^1H NMR spectrum of dibenzo[*a,e*]cyclooctene (**7**)[35] containing an atropic nonplanar 8-membered ring,[35] the benzenoid protons (in $CDCl_3$) resonate at δ 7.11 (H(2), H(3), H(8), H(9)) and 7.02 (H(1), H(4), H(7), H(10)), and the olefinic protons at δ 6.71. The relatively high-field resonance of the benzenoid protons of **6**, and especially the high-field resonance of the 8-membered ring olefinic protons as compared with those of **7**, clearly indicates the existence of a paramagnetic ring current in the 8-membered ring of **6**.

The electronic spectra of 5,6,11,12-tetradehydrodibenzo[*a,e*]cyclooctene (**5**) and 5,6-didehydrodibenzo-[*a,e*]cyclooctene (**6**), which proved to be quite complex, are given in Figs. 1 and 2, respectively, as well as in Table 2. The main maxima are at 271 and 275 nm, respectively, with high molecular extinction coefficients (179,800 and 119,400,[36] respectively). These characteristics, the complexity of the spectra, as well as the fine structure in the *ca* 315–460 nm region (Figs. 1 and 2), must be due to the essentially planar conjugated 8-membered rings in **5** and **6**. By

Table 1. ^{13}C NMR spectral resonances of cyclic acetylenes (in ppm downfield from internal tetramethylsilane)

Compound	Solvent	δ
2,2,5,5-Tetramethylhex-3-yne [a]	CCl_4	87.0
3,3,8,8-Tetramethylcyclo-1-octyne [a]	CCl_4	97.6
3,3,6,6-Tetramethyl-1-thiacyclohept-4-yne (31) [a]	CCl_4	108.5
5,6,11,12-Tetradehydrodibenzo[a,e]cyclooctene (5) [b]	CCl_4	109.3
5,6-Didehydrodibenzo[a,e]cyclooctene (6) [b]	CCl_4	108.5
3,3,7,7-Tetramethylcyclohept-1-yne (32) [c]	$CDCl_3$	109.8

[a] Reference 31; [b] H. Günther, private communication; [c] reference 32.

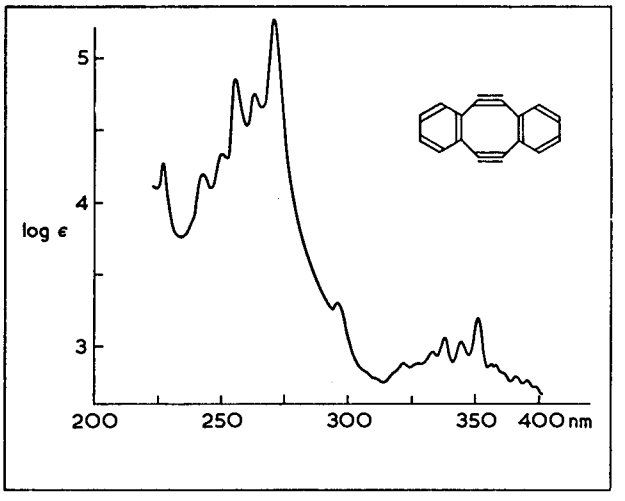
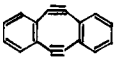
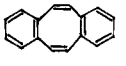
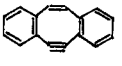
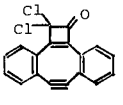
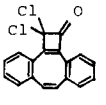
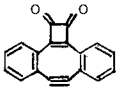
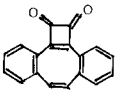


Fig. 1. Electronic absorption spectrum of 5,6,11,12-tetradehydrodibenzo[*a*,*e*,]cyclooctene (**5**), in hexane.

Table 2. Main electronic absorption maxima of compounds **5**, **6**, **7**, **16**, **21**, **28**, and **30** (ε values and solvents in parentheses)

Essentially planar 8-ring		Nonplanar 8-ring	
 **5**	271 nm (179,800, hexane)		
		 **7**	242 nm (25,200, hexane)
 **6**	275 nm (119,400,[a] hexane)		
 **16**	283 nm (97,300, cyclohexane)	 **28**	259 nm (33,900, cyclohexane)
 **21**	282 nm (31,700,[a] ethanol)	 **30**	265 nm (13,700, ethanol)

[a]The ε value is a minimum one, due to the instability of the compound.

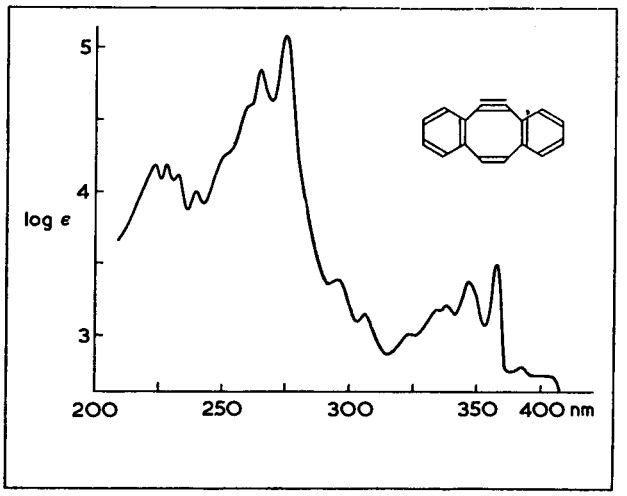


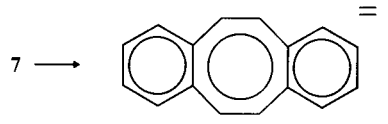
Fig. 2. Electronic absorption spectrum of 5,6-didehydrodibenzo[*a,e*]cyclooctene (**6**), in hexane.

comparison, the electronic spectrum of the nonplanar dibenzo[*a,e*]cyclooctene (**7**) shows a single maximum at 242 nm (ε 25,200), without fine structure. The considerable bathochromic shift and increase in the ε value in **5** and **6** as compared to **7** is also apparent in the presumably planar 5,6-didehydrodibenzo[*a,e*]-cyclooctene-derivatives **16** and **21**, as compared with the corresponding nonplanar dibenzo[*a,e*]cyclo-octene-derivatives **28** and **30** (see Table 2).

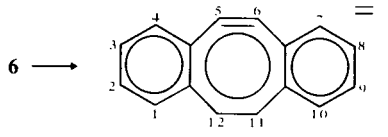
CHEMICAL AND ELECTROCHEMICAL REDUCTIONS OF 5,6,11,12-TETRADEHYDRODIBENZO[*a,e*]CYCLOOCTENE (5) AND 5,6-DIDEHYDRODIBENZO[*a,e*]CYCLOOCTENE (6)

It has been shown that treatment of dibenzo[*a,e*]-cyclooctene (**7**), containing a nonplanar atropic 8-membered ring, with an alkali metal, leads to the dianion **33** in which the 8-membered ring is now a planar 10π-electron system.[37] It was to be expected that the dehydro derivatives **5** and **6** of **7**, containing essentially planar paratropic 8-membered rings, could also be converted to 10π-dianions corresponding to **33** by treatment with an alkali metal.[38]

In practice treatment of the diacetylene **5** in tetrahydrofuran-d_8 with a potassium mirror at −20° resulted in polymerization, perhaps because the presence of two acetylenes promotes anion polymerization.[39] On the other hand, similar treatment of the monoacetylene **6** with a potassium mirror led to a deep green solution of the di-potassium salt of the dianion 34.[9,40] Comparison of the ^{1}H NMR spectrum of the dianion **34** (100 MHz, −40°) with that of the precursor **6** shows that the H(2), H(3), H(8), and H(9) benzenoid proton resonances have shifted upfield from δ 6.86 to 6.2, the H(1), H(4), H(7), and H(10) benzenoid proton resonances have shifted downfield from δ 6.51 and 6.67 to 7.75, and the olefinic proton resonances have shifted downfield from δ 5.45 to 6.67. The observed downfield shift by *ca* 1.2 ppm of the olefinic 8-membered ring proton resonances, as well as those of the benzenoid protons adjacent to the 8-membered ring (despite the introduction of two negative charges), is fully in accord with the conversion of a paratropic to a diatropic system, by formation of the dianion.



33



34

The conversion of dibenzo[*a,e*]cyclooctene (**7**) to the corresponding radical anion, and the study of its structure by ESR spectrometry, have been described.[37,41,42] The preparation and the study of the structures of the radical anions of **5** and **6** by ESR spectrometry have been reported subsequently.[42] In connection with this work, the catalytic deuteration of 5,6,11,12-tetradehydrodibenzo[*a,e*]cyclooctene (**5**) to 5,6,11,12-tetradeuteriodibenzo[*a,e*]cyclooctene (**7**-d_4) was carried out, followed by bromination to the corresponding 5,6-dibromide (**8**-d_4), and dehydrobromination to 5,6-didehydro-11,12-dideuteriodibenzo[*a,e*]cyclooctene (**6**-d_2).[42]

The electrochemical reduction of the three dibenzo[*a,e*]cycloctene derivatives **5**–**7** has been studied, and the results have been published.[43]

EXPERIMENTAL

Microanalyses were carried out by the microanalytical section of the Chemistry Department, University College London. M.ps were determined on a Kofler hot-stage microscope apparatus, and are uncorrected. B.ps are also uncorrected. The electronic spectra were determined on a Unican SP 800 recording spectrophotometer. IR spectra were recorded on a Unican SP 200 spectrophotometer. ^{1}H NMR spectra were determined on a Varian HA-100 or T-60 spectrometer in $CDCl_3$, unless stated otherwise, and the

chemical shifts are reported as δ values in ppm downfield from $SiMe_4$ as internal standard. High resolution mass spectra were recorded on an AE1 MS9 mass spectrometer at 70 eV. Tlc plates were prepared with Merck Kieselgel HF_{254}, or were obtained commercially (pre-coated Merck Kieselgel 60 F_{254} plates, layer thickness, 0.25 mm). Al_2O_3 for column chromatography was Woelm neutral grade III. KO^{t}Bu was obtained from Fluka Chemicals Ltd., and was used without purification unless stated otherwise. Solvents were purified and dried by standard methods. All solvents were removed under reduced pressure.

Dibenzo[a,e]cyclooctene (7). Dibenzobicyclo-[2.2.2]octatriene was prepared by addition of an excess of *cis*-1,2-dichloroethylene to anthracene in a sealed tube at 250° for 24 hr to give 70% of *cis*-2,3-dichlorodibenzobicyclo-[2.2.2]octatriene,[44] from which the chloro groups were reduced in 90% yield by reduction with sodium in boiling n-amyl alcohol.[44,45] A soln of dibenzobicyclo[2.2.2]octatriene (1 g) in dry THF (250 ml) was irradiated[14] with a medium pressure UV lamp (Hanovia, 125 W) for 24 hr under N_2. The solvent was evaporated, the residue was extracted with petroleum ether (b.p. 40–60°), and decanted from insoluble material. Evaporation and crystallization from EtOH gave **7** (0.75 g, 75%), colourless crystals, m.p. 105–106° (lit[46] m.p. 106.2–106.9°); ^{1}H NMR δ 7.09 (m, AA',BB', 8 H), 6.75 (s, 4 H); UV λ_{max} (hexane) 242 nm (ε 25,200).

5,6,11,12-*Tetrabromo*-5,6,11,12-*tetrahydrodibenzo*[a,e]-*cyclooctene* (**9**).[12] A soln of Br_2 (0.78 g, 4.88 mmol) in CCl_4 (5 ml) was added dropwise to a soln of **7** (0.5 g, 2.45 mmol) in CCl_4 (5 ml). The soln was heated to 75° and irradiated with a medium pressure UV lamp (Hanovia, 125 W) until the soln became light yellow. Evaporation of solvent and crystallization from cyclohexane gave **9** (0.80 g, 62%), colourless crystals, m.p. 191–193° (lit[12] m.p. 195–197°, 202°); ^{1}H NMR δ 7.80–6.62 (m, 8 H), 5.28, 6.29 (ABq, 4 H, J = 10 Hz).

5,11-*Dibromodibenzo*[a,e]*cyclooctene* (**10**) *and* 5,12-*dibromodibenzo*[a,e]*cyclooctene* (**11**). A soln of **9** (500 mg, 0.95 mmol) and 1,5-diazabicyclo[4.3.0]non-5-ene (1.3 g, 10.5 mmol) in benzene (4 ml) was boiled under reflux under N_2 for 2 hr. The soln was cooled and then washed with 2N H_2SO_4aq and H_2O. The benzene layer was dried ($MgSO_4$) and evaporated. Crystallization from EtOH gave **10** and **11** (280 mg, 81%), which could not be separated by column chromatography on Al_2O_3 or SiO_2, colourless crystals, m.p. 137–138°; ^{1}H NMR δ (220 MH) 7.42–6.98 (m, 10 H), including singlets at δ 7.34, 7.30 (total 2 H); MS measured M^+ 359.9156. Calc. for $C_{16}H_{10}{}^{79}Br_2$: 359.9150 (Found: C, 52.86; H, 2.67; Br, 44.34. $C_{16}H_{10}Br_2$ requires: C, 53.04; H, 2.77; Br, 44.19%).

5,6,11,12-*Tetradehydrodibenzo*[a,e]*cyclooctene* (**5**)

(a) *By dehydrobromination of* **9** *with* KO^{t}Bu. A soln of **9** (206 mg, 0.39 mmol) in dry THF (3 ml) was added dropwise during 1 min to a stirred soln of KO^{t}Bu (400 mg, 3.57 mmol; purified by sublimation) in dry THF (20 ml) at room temp under N_2, and the soln was then stirred for 10 min. 2N HCl aq was added, followed by extraction with ether. The organic layer was washed with H_2O, and dried ($MgSO_4$). Evaporation, chromatography on Al_2O_3, and elution with pentane, gave **5** (55 mg, 70%), pale yellow plates which decomposed at *ca* 110° on attempted m.p. determination; δ ^{1}H NMR δ 7.24–6.36 (AA'BB') (for complete analysis see ref. 33); ^{13}C NMR (CCl_4, see Table 1 and Ref. 34a) δ 133.2 (C(13), C(14), C(15), C(16)), 128.3, 126.3 (C(1), C(2), C(3), C(4), C(7), C(8), C(9), C(10)), 109.3 (C(5), C(6), C(11), C(12)); UV (hexane) (see Fig. 1, Table 2) λ_{max} 227 nm (ε 18,000), 243 (15,700), 249 (21,300), 256 (69,700), 263 (56,200), 271 (179,800), 296 (1900), with a weak broad band between *ca* 315 and 430 nm showing considerable fine structure (maximum ε 1570 at 352 nm); IR (KBr) ν_{max} 2180 cm^{-1} (w); measured M^+ 200.0632, Calc. for $C_{16}H_8$: 200.0626. (Found: C, 95.91; H, 4.02. $C_{16}H_8$ requires: C, 95.97; H, 4.03%).

(b) *By dehydrobromination of* **10** *and* **11** *with* KO^{t}Bu *in THF*. A mixture of **10** and **11** (200 mg, 0.55 mmol) in dry THF (2.5 ml) was added dropwise during 3 min to a stirred soln of KO^{t}Bu (365 mg, 3.26 mmol) in dry THF (200 ml) at room temp. under N_2, and the soln was then stirred for 30 min. 2N HCl aq was added, followed by extraction with ether. The organic layer was washed with H_2O and dried ($MgSO_4$). Evaporation, chromatography on Al_2O_3, and elution with pentane, gave **5** (30.5 mg, 28%), identical in all respects with the material obtained by method (a). The yield of **5** from **10** and **11** was 24% when the dehydrobromination was carried out with KO^{t}Bu in benzene at 65°.

Dibenzo[a,e]cyclooctene (7) *from* **5**. A soln of **5** (42 mg, 0.21 mmol) in EtOAc (5 ml) was added to pre-hydrogenated $PtO_2.H_2O$ (5 mg) in EtOAc (10 ml), and the mixture was stirred vigorously in H_2 at room temp and atmospheric pressure until 10.2 ml of H_2 had been absorbed (theoretical uptake, 9.5 ml, 0.42 mmol). Removal of the catalyst, evaporation of the solvent, PLC on Merck Kieselgel 60 PF_{254} (pentane-ether, 10:1), and crystallization from EtOH, yielded **7** (13.2 mg, 31%), colourless crystals, m.p. 102–104°, identical with an authentic sample.

5,6,11,12-*Tetrahydrodibenzo*[a,e]*cyclooctene* (**12**).

(a) *By hydrogenation of* **7**. A soln **7** (20 mg, 0.098 mmol) in EtOH (2 ml) was shaken in H_2 over a 10% Pd–C catalyst (10 mg) at room temp and atmospheric pressure for *ca* 90 min. The catalyst was removed, the solvent was evaporated, and the residue was extracted with CCl_4. Evaporation of the solvent and crystallization from MeOH gave **12** as colourless crystals, m.p. 109–110° (lit[15] m.p. 109.4–109.9°); ^{1}H NMR δ 6.99 (s, 8 H), 3.10 (s, 8 H).

(b) *By hydrogenation of* **10** *and* **11**. A soln of **10** and **11** (103 mg, 0.28 mmol) in 95% EtOH (4 ml) was stirred in H_2 over a 10% Pd–C catalyst (14 mg) at room temp and atmospheric pressure for *ca* 5 hr. The catalyst was removed, the solvent was evaporated, and the residue was extracted with CCl_4. Evaporation of the solvent and crystallization from EtOH gave **12** as colourless crystals, m.p. 109–110°, undepressed on admixture with a sample prepared by method (a).

(c) *By hydrogenation of* **5**. A soln of **5** (11 mg, 0.055 mmol) in EtOAc (4 ml), added to pre-hydrogenated $PtO_2.H_2O$ (4 mg) in EtOAc (10 ml), and the mixture was stirred vigorously in H_2 at room temp and atmospheric pressure until no further absorption occurred (uptake of H_2, 5.0 ml, *ca* 0.23 mmol). Removal of the catalyst, evaporation of the solvent, and crystallization from MeOH yielded **12** as colourless crystals, m.p. 108–109°, identical with that prepared by methods (a) and (b).

Bis-adduct **13**. A mixture of **10** and **11** (362 mg, 1 mmol), KO^{t}Bu (682 mg, 6.1 mmol), and 1,3-diphenylisobenzofuran (542 mg, 2 mmol) in ether (25 ml) was stirred at room temp for 80 hr. H_2O was added, the mixture was filtered, and the solid was combined with the residue obtained by evaporation of the dried ($MgSO_4$) filtrate. Repeated crystallization of the combined solids from CCl_4–EtOH yielded **13** (422 mg, 57%), presumably a mixture of *endo* and *exo* isomers, as pale pink crystals, m.p. 274–275°; ^{1}H NMR δ 7.90–7.10 (m, 26 H), 7.10–6.50 (m, 8 H), 6.50–6.15 (m, 2 H); MS measured M^+ 740.2648, Calc. for $C_{56}H_{36}O_2$: 740.2715. (Found: C, 90.46; H, 4.89. $C_{56}H_{36}O_2$ requires: C, 90.81; H, 4.86%).

Tetraphenylene (**15**). A soln of **5** (90 mg, 0.45 mmol) in furan (10 ml) was stirred for *ca* 100 hr. The excess furan was evaporated from the resulting **14**, the residue was dissolved in EtOAc (9 ml), added to pre-hydrogenated $PtO_2.H_2O$ (15 mg) in EtOAc (10 ml) and shaken in H_2 at room temp and atmospheric pressure. The uptake of H_2 was 22 ml (*ca* 0.98 mmol). The catalyst was removed, the solvent was evaporated, and P_2O_5 (7 g) and orthophosphoric acid (8 ml) were added to the mixture. The mixture was heated at 140° for 2 hr,[16] cooled, and poured into ice–water (50 ml). Ether was added, the organic extract was washed with H_2O, dried (Na_2SO_4), and evaporated. Plc of the residue on Merck

Kieselgel 60 PF_{254} (pentane–ether, 10:1) yielded two products. The less polar compound was **12** (8.2 mg, 9%), identified with an authentic sample. The more polar compound on crystallization from EtOH proved to be **15** (21.7 mg, 16%), colourless crystals, m.p. 239–240° (lit[17] m.p. 233°); ^{1}H NMR δ 7.26 (br s); MS measured M^+ 304.1271, calc. for $C_{24}H_{16}$: 304.1252.

9,9-*Dichloro*-2,3,6,7-*dibenzobicyclo*[6.2.0]*deca*-2,6,8-*trien*-4-*yn*-10-*one* (**16**). A soln of dichloroacetyl chloride (60 mg, 0.41 mmol) in pentane (10 ml) was added dropwise during 1 hr to a stirred soln of **5** (35 mg, 0.18 mmol) and NEt_3 (60 mg, 0.59 mmol) in pentane (10 ml) at room temp, and the mixture was stirred for *ca* 12 hr. The mixture was washed with 10% $NaHCO_3$ aq and then with H_2O. The organic layer was dried (Na_2SO_4) and evaporated. Plc of the residue on Merck Kieselgel 60 PF_{254} (pentane–ether, 10:1) yielded two products. The less polar compound (12 mg, 34%) proved to be unchanged **5**. The more polar compound on crystallization from EtOH proved to be **16** (15 mg, 28%, 42% based on converted **5**), red crystals m.p. 144–145° dec.; ^{1}H NMR δ 8.16–7.80 (m, 2 H) 7.26–6.88 (m, 4 H), 6.80–6.60 (m, 2 H); UV (cyclohexane) (see Table 2) λ_{max} 250 nm (ε 32,500), 275 (80,000), 283 (97,300), 310 (2740), 326 (2200), 362 (6970), 382 (7800); IR (KBr) ν_{max} 1760 cm^{-1} (s); MS measured M^+ 309.9953, Calc. for $C_{18}H_8{}^{35}Cl_2O$: 309.9935. (Found: C, 69.51; H, 2.73; Cl, 23.15. $C_{18}H_8Cl_2O$ requires: C, 69.45; H, 2.57; Cl, 22.83%).

9,9-*Dichloro*-2,3,6,7-*dibenzobicyclo*[6.2.0]*deca*-2,6,8-*triene*-4,10-*dione* (**17**) *and* 9,9-*dichloro*-2,3,6,7-*dibenzobicyclo*-[6.2.0]*deca*-2,6,8-*triene*-5,10-*dione* (**18**). Compound **16** (4.5 mg, 0.015 mmol) was stirred in conc H_2SO_4 (1 ml) until all the red crystals had disappeared (*ca* 10 sec). The soln was immediately poured into ice, and ether was added. The ether extract was washed with 10% $NaHCO_3$ aq and H_2O, and was then dried (Na_2SO_4) and evaporated. Plc on Merck Kieselgel 60 PF_{254} (pentane-ether, 10:1) yielded unchanged **16** and then a mixture of **17** and **18**, pale yellow crystals, m.p. 124°, from ether–pentane. Analytical tlc showed two proximate spots, indicating the presence of both possible isomers; MS measured M^+ 328.0032, Calc. for $C_{18}H_{10}{}^{35}Cl_2O_2$: 328.0058.

2,3,6,7-*Dibenzobicyclo*[6.2.0]*deca*-2,6,8-*triene*-4,9,10-*trione* (**19**). Compound **16** (30 mg, 0.1 mmol) and conc H_2SO_4 (7 ml) were heated at 65° for 2 hr. The soln was cooled, poured into ice, and ether was added. The ether extract was washed with 10% $NaHCO_3$ aq and H_2O, and was then dried (Na_2SO_4) and evaporated. Crystallization from EtOH gave **19** (18.5 mg, 70%) as pale yellow crystals, m.p. 173–174°; ^{1}H NMR δ 9.16–9.00 (m, 1 H), 8.30–8.04 (m, 2 H), 7.96–7.42 (m, 5 H), 3.95 (s, 2 H); IR (KBr) ν_{max} 1760 (s), 1690 cm^{-1} (m); MS measured M^+ 274.0641, Calc. for $C_{18}H_{10}O_3$: 274.0631. (Found: C, 78.14; H, 3.67. $C_{18}H_{10}O_3$ requires: C, 78.82; H, 3.68).

2,3,6,7-*Dibenzobicyclo*[6.2.0]*deca*-2,6,8-*trien*-4-*yne*-9,10-*dione* (**21**). Silver trifluoroacetate (25.8 mg, 0.12 mmol) in benzene (2 ml) was added to **16** (6.2 mg, 0.02 mmol) in benzene (2 ml), and the soln was boiled under reflux for 1 hr under N_2. The precipitated AgCl was removed by filtration, washed with benzene, and the resulting soln of **20** was hydrolyzed by being shaken vigorously several times with 250 ml portions of H_2O. The organic extract was dried (Na_2SO_4) and evaporated. The resulting **21** was separated from insoluble polymeric material by extraction with an appropriate solvent (EtOH, $CHCl_3$, ether, etc.), depending on which solution was required for further study. If necessary, the solvent was evaporated as quickly as possible; the resulting **21** formed orange-red crystals, which decomposed rapidly in the neat state; ^{1}H NMR δ 8.55–6.55 (complex m); UV (EtOH) (see Table 2)[36] λ_{max} 272 nm (ε 23,800), 282 (31,700), 363 (2700), 382 (2700); IR (KBr) ν_{max} 1770 (s), 1750 cm^{-1} (s); MS measured M^+ 256.0537, Calc. for $C_{18}H_8O_2$: 256.0524.

5,6-*Dibromo*-5,6-*dihydrodibenzo*[*a,e*]*cyclooctene* **8**. A soln of Br_2 (2 g, 12.5 mmol) in CH_2Cl_2 (1 ml) was added dropwise during 5 min to a soln of **7** (2 g, 9.8 ml) at 0°, and the soln was then stirred at 0° for 20 min. Evaporation of solvent and crystallization from cyclohexane–CCl_4 yielded **8** (3.03 g, 85%), colourless crystals, m.p. 157–159° (lit[12] m.p. 157°, 162–163°); ^{1}H NMR δ 7.70–6.90 (m, 10 H), 5.83 (s, 2 H).

5-*Bromodibenzo*[a,e]*cyclooctene* (**23**). A soln of **8** (100 mg, 0.275 mmol) and 1,5-diazabicyclo[4.3.0]non-5-ene (0.35 g, 0.28 mmol) in benzene (2 ml) was boiled under reflux under N_2 for 2 hr. The soln was cooled and then washed with 2N H_2SO_4 aq and H_2O. The benzene layer was dried ($MgSO_4$) and evaporated. Slow crystallization from EtOH gave **23** (62.5 mg, 80%), colourless crystals, m.p. 76–78°; ^{1}H NMR δ 7.50–7.10 (m, 9 H), including 7.33 (d, J = 4 Hz) and 7.17 (br s), 6.80 (s, 2 H); measured M^+ 282.0034, Calc. for $C_{16}H_{11}{}^{79}Br$: 282.0044. (Found: C, 67.66; H, 3.78; Br, 28.33. $C_{16}H_{11}Br$ requires: C, 67.84; H, 3.89; Br. 28.27%).

5,6-*Didehydrodibenzo*[a,e]*cyclooctene* (**6**)

(a) *By dehydrobromination of* **8** *with* KO^{t}Bu. A soln of **8** (204 mg, 0.56 mmol) in dry THF (2.5 ml) was added dropwise during 1 min to a stirred soln of KO^{t}Bu (200 mg, 1.78 mmol; purified by sublimation) in dry THF (20 ml) at room temp under N_2, and the soln was then stirred for 1 min. 2N HCl aq was added, followed by extraction with ether. The ether extract was washed with H_2O, dried ($MgSO_4$), and evaporated. Chromatography of the residue on Al_2O_3 and elution with pentane yielded **6** (38.5 mg, 34%) as unstable golden yellow crystals, which decomposed at *ca* 85° on attempted m.p. determination (rapid heating); ^{1}H NMR δ 7.0–6.5 (m, 8 H), 5.50 (s, 2 H), and Discussion Section (Ref. 34) ^{13}C NMR (CCl_4, see Table 1 and ref. 34a) δ 134.9, 132.0, 129.5, 129.0, 125.8 (C(1), C(2), C(3), C(4), C(11)), 146.7, 123.0 (C(13), C(14)), 108.5 (C(5), C(6)); UV (hexane) (see Fig. 2, Table 2)[36] λ_{max} 224 nm (ε 15,100), 228 (15,500), 233 sh (13,100), 240 (10,000), 252sh (18,000), 260 (39,500), 265 (68,200), 275 (119,400), 296 (2500), 306 (1400), with a weak broad band between *ca* 315 and 460 nm showing considerable fine structure (maximum ε 3100 at 365 nm); MS measured M^+ 202.0796, Calc. for $C_{16}H_{10}$: 202.0783. (Found: C, 94.67; H, 4.84. $C_{16}H_{10}$ requires: C, 95.02; H, 4.98%).

(b) *By dehydrobromination of* **23** *with* KO^{t}Bu *in THF*. A soln of **23** (203 mg, 0.72 mmol) in dry THF (2 ml) was added dropwise during 2 min to a stirred solution of KO^{t}Bu (244 mg, 218 mmol) in dry THF (20 ml) at room temp under N_2, and the soln was then stirred for 5 min. 2N HCl aq was added, followed by extraction with ether. The organic layer was washed with H_2O and dried ($MgSO_4$). Evaporation, chromatography on alumina, and elution with pentane, yielded **6** (35 mg, 24%), identical in all respects with the material obtained by method (a). The yield of **6** from **23** was 29% when the dehydrobromination was carried out with KO^{t}Bu in benzene at 65°.

Dibenzo[a,e]*cyclooctene* (**7**) *from* **6**. A soln of **6** (30 mg, 0.15 mmol) in EtOAc (10 ml) was added to pre-hydrogenated $PtO_2 \cdot H_2O$ (7 mg) in EtOAc (10 ml), and the mixture was stirred vigorously in H_2 at room temp and atmospheric pressure until 3 ml (0.14 mmol) of H_2 had been absorbed. Removal of the catalyst, evaporation of the solvent, and crystallization from EtOH yielded **7** (4.3 mg, 14%), m.p. 103–106°, identical with an authentic sample.

5,6,11,12-*Tetrahydrodibenzo*[a,e]*cyclooctene* (**12**)

(a) *By hydrogenation of* **6**. A soln of **6** (10 mg, 0.05 mmol) in EtOAc (5 ml) was added to pre-hydrogenated $PtO_2 \cdot H_2O$ (15 mg) in EtOAc (5 ml), and the mixture was stirred in H_2 at room temp and atmospheric pressure for 2 hr. Removal of the catalyst, evaporation of the solvent, and crystallization from EtOH gave **12**, m.p. 108–109°, identical with an authentic sample.

(b) *By hydrogenation of* **23**. A soln of **23** (21 mg, 0.07 mmol) in 95% EtOH (2 ml) was stirred in H_2 over a 10% Pd–C catalyst (3.5 mg) at room temp. and atmospheric pressure for *ca* 3 hr. Removal of the catalyst, evaporation of the solvent, and crystallization from MeOH gave **12**, m.p. 107–109°, identical with an authentic sample.

Adducts **24a**, **24b** (endo *and* exo *isomers*). A mixture of **8** (364 mg, 1 mmol) KO^{t}Bu (910 mg, 8.12 mmol) and 1,3-diphenylisobenzofuran (270 mg, 1 mmol) in ether (25 ml) was stirred at room temp for 100 h. H_2O was added, the mixture was filtered, and the solid was combined with the residue obtained by evaporation of the dried (Na_2SO_4) filtrate. Plc of the combined solids on Merck Kieselgel 60 $PF_{254+366}$ ($CHCl_3$–CCl_4, 1:4) gave two isomers of **24**. The more polar compound (118 mg, 25%) is the *endo* isomer **24a**, colourless crystals, m.p. 282–285°, from $CHCl_3$–EtOH; ^{1}H NMR δ 7.41 (s, 8 H), 7.29–6.79 (m, 12 H), 6.45–6.29 m (2 H), 6.14 (s, 2 H); MS measured M^+ 472.1842, Calc. for $C_{36}H_{24}O$: 472.1828. The less polar compound (21.7 mg, 4.6%) was the *exo* isomer **24b**, colourless crystals, m.p. 268–270°, from $CHCl_3$–EtOH; ^{1}H NMR δ 7.76–6.70 (m); MS measured M^+ 472.1848; Calc. for $C_{36}H_{24}O$: 472.1828. [Found (mixture of isomers): C, 91.08; H, 5.15. $C_{36}H_{24}O$ requires: C, 91.50; H, 5.12%].

5,8-*Dihydro*-5,8-*epoxytribenzo*[a,c,e]*cyclooctene* (**25**). A soln of **8** (1 g, 2.75 mmol) in THF (10 ml) was added dropwise during 10 min to a stirred soln of KO^{t}Bu (1.91 g, 17 mmol) in furan (30 ml) and THF (30 ml) at room temp under N_2. The mixture was stirred for 48 hr, and H_2O and ether were then added. The organic extract was washed with H_2O, and dried ($MgSO_4$). Evaporation and crystallization from cyclohexane yielded crude **25** (380 mg, 51%); repeated crystallization gave colourless crystals, m.p. 182–183°; ^{1}H NMR δ 7.41 (d, J = 1 Hz, 2 H), 7.23–7.07 (m, 6 H), 6.77–6.68 (m, 2 H), 6.65 (s, 2 H), 5.45 (d, J = 1 Hz, 2 H); MS measured M^+ 270.1042, calc. for $C_{20}H_{14}O$: 270.1044. (Found: C, 88.73; H, 5.36. $C_{20}H_{14}O$ requires: C, 88.86; H, 5.22%).

13,14-*Dihydrotribenzo*[a,c,e]*cyclooctene* (**26**). A soln of crude **25** (335 mg, 1.24 mmol) in EtOAc (10 ml) was shaken in H_2 with a 10% Pd–C catalyst (25 mg) at room temp and atmospheric pressure.[16] The uptake of H_2 was 48.7 ml (*ca.* 2.17 mmol). The catalyst was removed, the solvent was evaporated, and P_2O_5 (5 g) and orthophosphoric acid (7 ml) were added to the residue. The mixture was heated at 150° for 2 hr,[16] cooled, and poured into ice–water (20 ml). Ether was added, the organic extract was washed with H_2O, dried ($MgSO_4$), and evaporated. Plc of the residue on Merck Kieselgel 60 $PF_{254+366}$ (pentane–ether, 10:1) and crystallization from EtOH gave **26** (85 mg, 27%) as colourless crystals, m.p. 110–112° (lit.[26] m.p. 111–113°); ^{1}H NMR δ 7.46–6.86 (m, 12 H), 3.06–2.86 (AA′BB′, 4 H); MS measured M^+ 256.1255, Calc. for $C_{20}H_{16}$: 256.1252.

4,5,8,9-*Dibenzo*-1-*phenyl*-1 H-*cyclooctatriazole* (**27**). A mixture of **8** (364 mg, 1 mmol) phenylazide (124 mg, 1.04 mmol)[27] and KO^{t}Bu (686 mg, 6.13 mmol) in ether (25 ml) were stirred at room temp for 100 hr. H_2O was added, the precipitate was collected by filtration, and added to the residue obtained by evaporation of the dried ($MgSO_4$) ethereal layer. Crystallization of the combined solids from cyclohexane–CCl_4 gave **27** (213 mg, 66%) as colourless crystals, m.p. 223–224°; ^{1}H NMR δ 7.72–6.90 (m, 13 H, with a sharp s at 7.38), 6.82 (s, 1 H), 6.72–6.64 (m, 1 H); MS measured M^+ 321.1273, Calc. for $C_{22}H_{15}N_3$: 321.1266. (Found: C, 82.24; H, 4.77; N, 12.99. $C_{22}H_{15}N_3$ requires: C, 82.22; H, 4.71; N, 13.08%).

9,9-*Dichloro*-2,3,6,7-*dibenzobicyclo*[6.2.0]*deca*-2,4,6,8-*tetraene*-10-*one* (**28**). Compound **6** was prepared from the dibromide **8** (200 mg, 0.55 mmol) and KO^{t}Bu as described previously. The pentane eluent from the column chromatography was concentrated to *ca* 15 ml and added to NEt_3 (210 mg, 2.08 mmol) in pentane (5 ml). Dichloroacetyl chloride (210 mg, 1.43 mmol) in pentane (10 ml) was then added dropwise over 1 hr with stirring overnight. The resulting mixture was filtered, the filtrate was washed with satd Na_2CO_3 aq, water, and dried (Na_2SO_4). Evaporation of the pentane, followed by plc of the residue on Merck Kieselgel 60 PF_{254} (pentane–ether, 8:1), and crystallization from ether–EtOH yielded **28** (30 mg, 17%) as yellow crystals, m.p. 158–160°; ^{1}H NMR δ 8.08–7.94 (m, 1 H), 7.51–7.04 (m, 7 H), 6.55 (s, 2 H); IR (KBr) ν_{max} 1780 cm^{-1} (s). (Found: C, 68.95; H, 3.24. $C_{18}H_{10}Cl_2O$ requires: C, 69.03; H, 3.20%).

2,3,6,7-*Dibenzobicyclo*[6.2.0]*deca*-2,4,6,8-*tetraene*-9,10-*dione* (**30**). Silver trifluoroacetate (19.9 mg, 0.09 mmol) in benzene (2 ml) was added to a stirred soln of **28** (5.8 mg, 0.02 mmol) in benzene (2 ml), and the soln was boiled under reflux for 5 hr. The precipitated AgCl was removed by filtration, washed with benzene, and the resulting soln of **19** was hydrolyzed by being shaken several times vigorously with 250 ml portions of H_2O. The organic extract was dried (Na_2SO_4) and evaporated. Plc of the residue on Merck Kieselgel 60 PF_{254} (pentane–ether, 7:1) and crystallization from ether–pentane gave **30** (1.1 mg, 6.7%) as pale yellow crystals, m.p. 198–199°; ^{1}H NMR δ 7.60–7.14 (m, 8 H, incorporating a sharp s at 7.24), 6.47 (s, 2 H); UV (EtOH) (Table 2) λ_{max} 265 nm (ε 13,600), 315sh (2700); IR (KBr) 1780s, 1765sh cm^{-1} (s); MS measured M^+ 258.0683, calcd. for $C_{18}H_{10}O_2$: 258.0681.

Di-potassium salt of the dianion **34** *of* 5,6-*didehydrodibenzo*[a,e]*cyclooctene* (**6**). (Experiment carried out with Dr. P. J. Garratt). A sealed NMR tube containing a soln of **6** in THF-d_8 (dried over K on a vacuum line) and a K mirror was prepared as described by Okamura and Katz[47] and Garratt *et al.*[38] When the tube was shaken at −20°, the soln turned red and the ^{1}H NMR spectrum of **6** disappeared, presumably due to the formation of the radical anion.[42] Further shaking at −20° gave a deep green solution of the di-K salt of the dianion **34**; for the ^{1}H NMR spectrum, see Discussion.

Acknowledgements—We thank Dr. P. J. Garratt for carrying out the conversion of **6** to the dianion **34**, as well as Prof. H. Günther (Gesamthochschule Siegen) and Prof. A. Krebs (University of Hamburg) for providing unpublished spectral data. H.N.C.W. acknowledges with thanks the award of a Shell Postgraduate Scholarship, administered by the Chinese University of Hong Kong.

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Tetrahedron, Vol. 37, Supplment No. 1, pp. 111 to 115, 1981
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0040-4020/81/Suppl. 1-0111-05 $02.00/0
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CAPTO-DATIVE SUBSTITUENT EFFECTS—VIII[1]

BRIDGED DEHYDRODIMERISATION AS A GENERAL METHOD OF SYNTHESIS: C_4-BRIDGING WITH α-TERT-BUTYLMERCAPTOACRYLONITRILE

S. MIGNANI, M. BEAUJEAN, Z. JANOUSEK, R. MERENYI and H. G. VIEHE*

University of Louvain, Laboratory of Organic Chemistry, Place L. Pasteur, 1, B-1348 Louvain-la-Neuve, Belgium

(*Received in U.K.* 11 *July* 1980)

Abstract—Dehydrodimerization is suppressed completely in the presence of radicophiles such as cd-substituted olefins. Particularly α-t-butylmercaptoacrylonitrile (TBMA) has been examined as a trapping agent for carbon centered radicals. The adducts dimerize thus building C_4-bridges between the original radicals. This general principle is synthetically useful as demonstrated by C_4-bridging of alkanes, ethers, amines, amides, aldehydes and ketones.

Apart from concerted reactions C–C bond formation is most frequently achieved through the interaction of electron deficient (electrophilic) centers with electron-rich (nucleophilic) ones, i.e. by polar reaction pathways. Radical reactions represent the alternative fundamental approach to achieve this goal. Radical additions to olefins followed by polymerization or hydrogen abstraction as well as dehydrodimerisation[1] are well-established applications.[2,3,4]

Recently we introduced the term of radicophilicity to describe the propensity of olefins bearing simultaneously electron-withdrawing and donating groups to undergo *twofold* carbon radical addition leading to diadducts **2** or adduct-dimers **1**.[3,6] Following this principle many new examples of C–C bond formation become possible. Whereas generally C–H oxidations in the pure phase lead to dehydrodimerization, in the presence of radicophiles C_4-bridged dehydrodimerization becomes the exclusive reaction path.

From the many radicophilic olefins available, TBMA has proven to be a powerful radical scavenger in a wide temperature range[7] and it represents a valuable complement to the known reagents. Besides giving easily detectable radical adducts,[7] TBMA adds preparatively both electrophilic and nucleophilic radicals leading in the majority of cases to high yields of C_4-bridged dehydrodimers **4** as a mixture of *d*, *l* and *meso* forms.

Upon heating, **4** dissociate reversibly back to **3** as shown by ESR measurements and interconversion of pure isomers to give the equilibrium mixture.[7,8]

From the point of view of synthesis both the thioether and cyano groups are useful functions which can be modified selectively and **4** are moreover masked α-diketones.[9]

In all reactions t-butyloxy radicals served as the oxidizing agent, and mostly di-t-butylperoxide (DTBP) at 130° was used as their precursor but di-t-butylperoxalate can be used at 60° if milder conditions are required. The initially formed electrophilic t-BuO radicals may further decompose to acetone and nucleophilic Me radicals. The latter can abstract H atoms from electron-poor substrates (e.g. nitriles, ketones and esters) whereas t-BuO radicals fail. Thus a great number of C–H bonds can be oxidized to radicals which are then "C_4-bridged" via addition to TMBA followed by dimerisation. The addition of methyl radicals to TBMA however, leading to **4a**, may become a competitive reaction in the case of acceptor substituted substrates. Table 1 summarises the Bridged Dehydrodimerisation of alkanes, ethers, amines, amides and ketones. Analogous reactions with cd-substituted dienes and styrenes are being investigated.

EXPERIMENTAL

1 H NMR: Measured in $CDCl_3$ soln at 60 or 200 MHz on Varian EM-360 and XL-200 spectrometers. 13C NMR: measured at 20 MHz on Varian CFT-20 spectrometer (Multiplicity due to one-bond couplings: S = singlet, D = doublet, T = triplet, Q = quadruplet, M = multiplet; multiplicity due to long range coupling: s. d, t, q, ... sept. and m) IR: Perkin–Elmer 297 infrared spectrometer, measured in $CHCl_3$. Mass: Varian MAT-44S spectrometer.

General procedure using di-t-butylperoxalate[10]: 0.01 M (1.41 g) TBMA,[11] 0.005 M (1.17 g) peroxalate and 0.1 M of the substrate R–H are placed in an ampoule which is then degassed in three freeze-thaw cycles and sealed. After heating for 6 hr to 60°, the ampoule is cooled in liquid N_2 and opened. The excess of substrate is recovered by distillation and the residue is crystallised or chromatographed. The procedure with DTBP is the same except that the ampoule is heated for 12 hr to 130°. Caution: the reactions are done behind safety shields and all organic peroxides must be handled with due care.

The adduct dimers **4** are obtained as a mixture of 2, or 6 stereomers depending on the number of chiral sites, e.g. 2 or 4. The total yield on isolated product is indicated in Table 1. Full product analysis including separation of the stereomers and their characterisation shall be published independently. Here only the crystallised fractions are described.

Compound **4b**, recrystallisation from ether/hexane gives the *meso* stereomer,[12] m.p.: 162–163°. 1 H NMR: $\delta = 1.58$ (s, 9 H), 1.3–2.5 (m, 9 H), 1.96 (dd, 1 H, $J_{gem} = 13.5$ Hz, $J_{vic} = 2.8$ Hz) 2.60 (dd, 1 H, $J_{gem} = 13.5$ H, $J_{vic} = 8.5$ Hz).

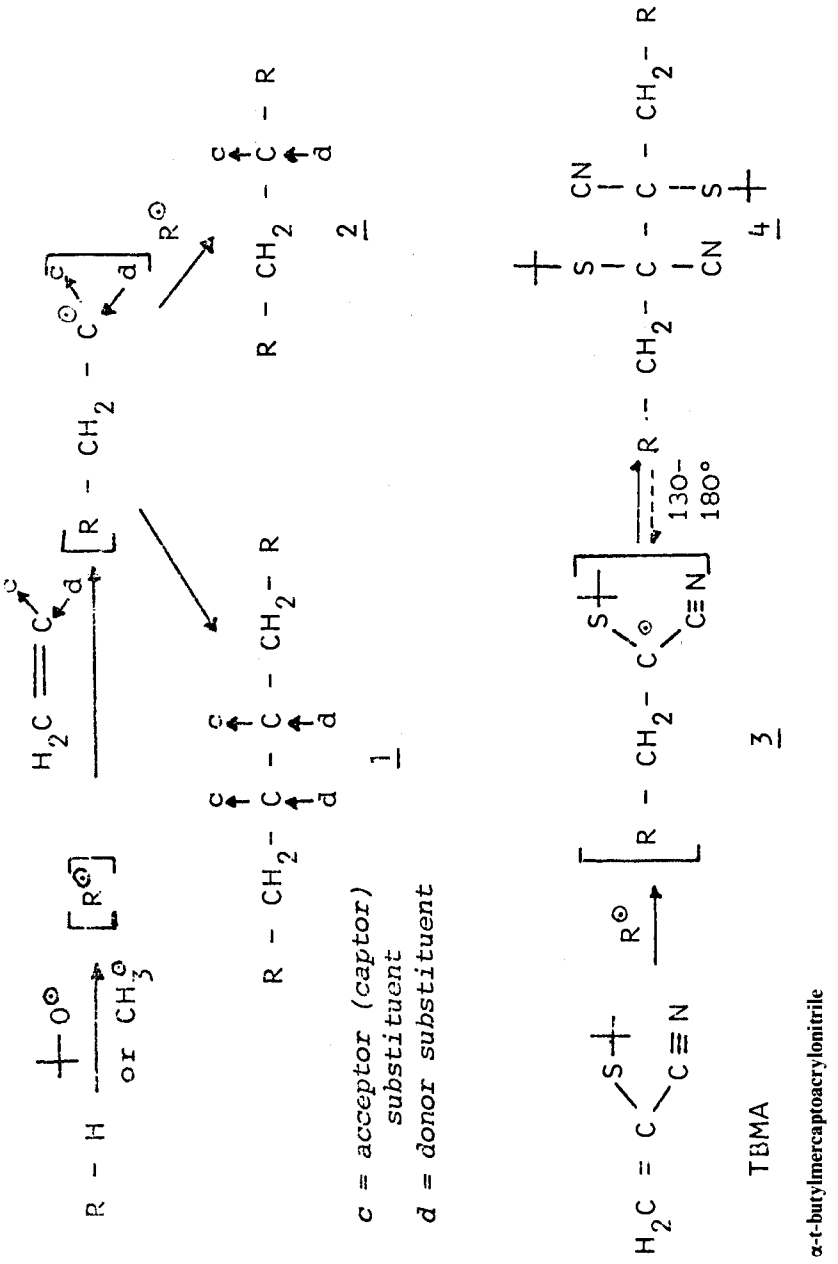
R - H
or $CH_3^{\odot}$
$R^{\odot}$
$H_2C = C$
R - CH_2 - C
R - CH_2 - C - C - R
R - CH_2 - C - C - R
1
2
c = acceptor (captor) substituent
d = donor substituent
$H_2C = C$
R - CH_2 - C
R - CH_2 - C - C - CH_2 - R
130-180°
3
4
TBMA
α-t-butylmercaptoacrylonitrile

Table 1. Adduct dimers *4* from TBMA and various radicals

	RH	$R^{\odot}$	*Yield of 4 (%)* DTBP	Di-tert-butyl-peroxalate
a		$CH_3^{\odot}$	32[6]	48
b				77
c			52	79
d				68
e				66
f	CH_3	$\overset{\odot}{C}H_2$		51
g	CH_3-O-CH_3	$CH_3-O-\overset{\odot}{C}H_2$	51	
h			52	72
i	$CH_3-CH_2-O-CH_2-CH_3$	$CH_3-CH_2-O-\overset{\odot}{C}H-CH_3$	55	61
j			59	63
k			41	58
l				54
m	$CH_3-\underset{\underset{O}{\|}}{C}-H$	$CH_3-\underset{\underset{O}{\|}}{C}^{\odot}$		67
n	$CH_3-(CH_2)_4-\underset{\underset{O}{\|}}{C}-H$	$CH_3-(CH_2)_4-\underset{\underset{O}{\|}}{C}^{\odot}$		68
o	CH_3 $\underset{\underset{O}{\|}}{C}$ - H	CH_3 $\underset{\underset{O}{\|}}{C}^{\odot}$		70
p	$\underset{\underset{O}{\|}}{C}$ - H	$\underset{\underset{O}{\|}}{C}^{\odot}$		63
q	H	$\underset{\underset{O}{\|}}{}^{\odot}$		54
r	$CH_3 - \underset{\underset{O}{\|}}{C} - N(CH_3)_2$	$CH_3 - \underset{\underset{O}{\|}}{C} - N(\overset{\odot}{C}H_2)(CH_3)$		74
s	$CH_3 - \underset{\underset{O}{\|}}{C} - CH_3$	$CH_3 - \underset{\underset{O}{\|}}{C} - \overset{\odot}{C}H_2$		38
t				46
u				47
v	$N(CH_3)_2$	$N(CH_3)(\overset{\odot}{C}H_2)$	50	
w	N - CH_3	N - $\overset{\odot}{C}H_2$	70	

13C NMR: δ = 24.7, 25.6, 35.2 and 36.7 (T, m) 4 ring CH_2; 32.7 (D.m) ring CH; 31.8 (Q.sept) and 50.2 (S, m) t-butyl; 45.0 (T, m) and 55.9 (S, m) CH_2–C–; 117.8 (S.d; ^3J = 10.3 Hz) C≡N. IR: 2240 cm^{-1} (ν C≡N, w); MS: M^+ 420; 275, 243, 211, 155, 41. (Found: C, 68.48; H, 9.59; N, 6.38; S, 14.88. $C_{24}H_{40}N_2S_2$ requires: C, 68.52; H, 9.58; N, 6.65; S, 15.24%.)

Compound **4c**, recrystallisation from ether/hexane gives the *meso* stereomer. M.p. 143–144°. 1 H NMR: δ = 1.58 (s, 9 H), 1.1–1.9 (m, 12 H), 2.45 (dd, 1 H, J_{gem} = 14 Hz, J_{vic} = 6 Hz). IR = 2230 cm^{-1} (ν C≡N, w). MS = M^+ 448, 225, 169. (Found: C, 69.59; H, 9.96; N, 6.14; S, 14.16. $C_{26}H_{44}N_2S_2$ requires: C, 69.58; H, 9.88; N, 6.24; S, 14.28%).

Compound **4d**, purified by column-chrom. on silicagel (CH_2Cl_2), recrystallisation from ether/hexane, gives the *meso* stereomer. M.p. 142–143°, 1 H NMR: δ = 1.58 (s, 9 H), 1.5–2.1 (m, 14 H), 2.54 (dd, 1 H, J_{gem} = 13.6, J_{vic} = 6.4 Hz. IR: 2240 cm^{-1} (ν C≡N, w). M^+: 476, 239; 183, 138, 41. (Found: C, 70.55; H, 10.13; N, 5.92; S, 13.40. $C_{28}H_{48}N_2S_2$ requires: C, 70.53; H, 10.15; N, 5.87; S, 13.45%.)

Compound **4e**, purified by column chrom. on silicagel (CH_2Cl_2), recrystallisation from ether gives the meso isomer. M.p.: 155–156°. 1 H NMR: δ = 1.59 (s, 9 H), 1.4–1.8 (m, 14 H), 2.0–2.1 (m, 2 H), 2.54 (dd, 1 H, J_{gem} = 14 Hz, J_{vic} = 7 Hz); 13C NMR: δ = 24.6, 25.9, 26.3, 26.8, 27.4, 34.4 and 35.9 (T.m) 7 ring CH_2; 32.3 (D.m) ring CH: 32.0 (Q.sept) and 50.4 (S.m) t-butyl; 46.5 (T.m) and 56.2 (S.m) CH_2–C– 117.4 (S.dd), ^3J = 10.5 and 1.5 Hz) C≡N. IR: 2230 cm^{-1} (ν C≡N, w). M^+: 504, 253, 195, 138. (Found: C, 71.46; H, 10.41; N, 5.59; S, 12.60. $C_{30}H_{52}N_2S_2$ requires: C, 71.37; H, 10.38; N, 5.55; S, 12.70%.)

Compound **4f**, purified by chromatography on silicagel (CH_2Cl_2), recryst. from benzene. Mixture of stereomers M.p.: 164–166° 1 H NMR: δ = 1.60 (s, 9 H) 2.1–3.3 (m, 4 H) 7.0–7.6 (m, 5 H). IR: 2240 cm^{-1} (ν C≡N, w). MS: M^+: 465; 290, 234, 207, 176, 57, 43. (Found: C, 71.61; H, 7.71; N, 6.11; S, 13.49. $C_{28}H_{36}N_2S_2$ requires: C, 72.36; H, 7.81; N, 6.03; S, 13.80%.)

Compound **4g**, recrystallisation from hexane gives the *meso* isomer, m.p.: 150–151° 1 H NMR: δ = 1.59 (s, 9 H), 2.13 (d.t, 1 H, J_{gem} = 13.6, J_{vic} = 6.5 Hz), 3.02 (d.t, 1 H, J_{gem} = 13.6, J_{vic} = 7.6 Hz), 3.40 (s, 3 H), 3.87 (d.d, 2 H). 13 C NMR: δ = 31.6 (Q) and 50.7 (S) t-butyl; 37.8 (T) and 52.9 (S) CH_2–C–; 58.7 (Q) and 69.4 (T) H_3C–O–CH_2–) IR: 2230 cm^{-1} (ν C≡N, w). MS: M^+ = 372; 315, 243, 227, 186, 163. (Found: C, 58.30; H, 8.56; N, 7.51; O, 8.79; S, 17.19. $C_{18}H_{32}N_2O_2S_2$ requires: C, 58.03; H, 8.66; N, 7.52; O, 8.59; S, 17.21%.)

Compound **4h** *with DTBP*. Chromatography on silicagel ($CHCl_3$), recryst. from ether/hexane. M.p.: 151–153°; with Ditert-butylperoxalate: recryst. from ether/hexane: mixture of the stereomers. M.p.: 151–153; 1 H NMR: δ = 1.61 (s, 9 H), 1.75–3.0 (m, 2 H), 3.4–5.25 (m, 7 H). IR: 220 cm^{-1} (ν C≡N, w), 1100 cm^{-1} (ν C–O, s). MS: DCI NH_3, (M + NH_4): 474; 296, 247, 52. (Found: C, 57.60; H, 7.98; N, 5.83; O, 13.6; S, 13.90. $C_{22}H_{36}O_4S_2N_2$ requires: C, 57.86; H, 7.94; N, 6.13; O, 14.013; S, 14.042%).

Compound **4i** *with DTBP*. Chromatography on silicagel ($CHCl_3$). With ditert-butylperoxalate: recryst. from hexane. M.p.: 136–138° 1 H NMR: δ = 1.2–1.4 (m, 6 H), 1.56 (s, 9 H), 2.3–3.0 (m, 2 H), 3.2–4.2 (m, 3 H). IR: 2240 cm^{-1} (ν C≡N, w), 1090 cm^{-1} (ν C–O, s). MS: DCI CH_4(M + H)$^+$: 429, 271, 216, 57. (Found: C, 61.73; H, 9.25; O, 7.57; N, 6.21; S, 14.81; $C_{22}H_{40}N_2O_2S_2$ requires: C, 61.63; H, 9.40; O, 7.46; N, 6.534; S, 14.95%.)

Compound **4j**, chromatography on silicagel (ethylacetate/-CH_2Cl_2, 4/3) and crystallisation in hexane gives a mixture of the 3 stereomers having the meso configuration on the central carbon. M.p.: 170–171°. ^{1}H NMR: δ = 1.57, 1.58 and 1.59 (s, 9 H) 1.5–2.3 (m, 5 H), 2.60, 2.75 and 2.98 (dd, 1 H, $J_{gem} \approx$ 14 Hz, $J_{vic} \approx$ 7.5 Hz), 3.71 (m, 1 H), 3.8–4.0 (m, 1 H), 4.35–4.5 (m, 1 H). IR: 2250 cm^{-1} (ν C≡N, w). MS: M^+ 424; 247, 213, 157, 123, 71, 68, 57, 43. (Found: C, 61.92; 4, 8.42: S, 15.18. $C_{22}H_{36}N_2O_2S_2$ requires: C, 62.22; H, 8.54; S, 15.10%.)

Compound **4k** *with DTBP*. Chromatography on silicagel (ethyl acetate CH_2Cl_2, 4/3) recryst. from hexane, M.p.: 143–145°. 1 H NMR: δ = 1.56 (s, 9 H), 2.2–3.3 (m, 8 H), 3.4–4.3 (m, 3 H). IR: 2240 cm^{-1} (ν C≡N, w). MS: M^+ 452, 275, 227, 171, 138, 85. (Found: C, 63.40; H, 9.16; S, 14.71, $C_{24}H_{40}N_2O_2S_2$ requires: C, 63.67; H, 8.90; S, 14.16%.)

Compound **4l** *with DTBP*, purified by chromatography on silicagel (CH_2Cl_2) recryst. from pet. ether 40–60°. Ditert-butylperoxalate: recryst. from hexane. M.p.: 135–136°, mixture of isomers. 1 H NMR: δ = 1.56 (s, 9 H), 1.6–3.0 (m, 10 H), 3.4–4.3 (m, 3 H). IR: 2230 cm^{-1} (ν C≡N, w). MS: M^+: 481, 425, 298, 242, 184, 99, 57. (Found: C, 65.01; H, 9.20; N, 5.81; O, 6.64; S, 13.32. $C_{26}H_{44}O_2N_2S_2$ requires: C, 64.95; H, 9.23; N, 5.83; O, 6.66; S, 13.34%.)

Compound **4m**, chromatography on silicagel ($CHCl_3$), recrystallisation from $CHCl_3$–ether gives one of the isomers m.p.: 210–211°. 1 H NMR: δ = 1.57 (s, 9 H); 2.30 (s, 3 H); 3.31 (d, 1 H); 3.79 (d, 1 H), J_{gem} = 15.7 Hz. IR: KBr, 2220 cm^{-1} (ν C≡N, w), 1700 (ν CO, s). MS: M^+ 368; 127, 56, 43. (Found: C, 58.41; H, 7.61; N, 7.35; O, 8.28; S, 16.53. $C_{18}H_{28}N_2O_2S_2$ requires: C, 58.66; H, 7.65; S, 17.39; O, 8.68%.)

Compound **4n**, recrystallisation from ether; one of the stereomers is isolated. M.p.: 161°. 1 H NMR: δ = 1.53 (s, 9 H), 0.92 (m, 9 H), 1.20–1.60 (m, 6 H), 3.21 (d, 1 H) 3.70 (d, 1 H) J_{gem} = 16.0 Hz. 13 C NMR: δ = 14.2 (Q.m), 22.7, 31.5, 23.3 and 45.2 (T.m) CH_3–CH_2–CH_2–CH_2–CH_2–, 31.5 (Q, sept) and 52.1 (S.m) t-butyl; 48.9 (DD.s, ^1J = 127.5 and 132.8) and 51.0 (S.m) CH_2–C–; 116.0 (S.dd, ^3J = 9.7 and 2.4 Hz)–C≡N; 201.7 (S.m) C=O. IR: 2250 cm^{-1} (ν C≡N, w), 1710 (ν CO, s); MS: DCI (CH_4), (M + H)$^+$: 481, 296, 240. (Found: C, 64.93; H, 9.21; N, 5.81; O, 6.69; S, 13.39. $C_{26}H_{44}N_2O_2S_2$ requires: C, 64.95; H, 9.23; N, 5.83; O, 6.66; S, 13.34%.)

Compound **4o**, recrystallisation from benzene: mixture of stereomers. M.p.: 194–195°. **Meso**: 1 H NMR: = 1.63 (s, 9 H), 2.44 (s, 3 H), 3.86 (d, 1 H), 4.35 (d, 1 H) J_{gem} = 15.6 Hz, 7.4 (m, 2 H), 7.8 (m, 2 H) **d, l**: 1 H NMR: = 1.60 (s, 9 H), 2.44 (s, 3 H), 4.15 (d, 1 H), 4.28 (d, 1 H), J_{gem} = 15.8 Hz, 7.4 (m, 2 H), 7.8 (m, 2 H). IR: 2230 cm^{-1} (ν C≡N, w), 1690 (ν CO, s). MS: M^+ –$(CH_3)_3CSH$: 430, 259, 190, 119, 91, 57. (Found: C, 69.16; H. 6.85; N, 5.11; O, 6.46; S, 12.25. $C_{30}H_{36}N_2O_2S_2$ requires: C, 69.19; H, 6.97; N, 5.38; O, 6.14; S, 12.31%.)

Compound **4p**, recrystallisation from benzene, m.p.: 196–197° 1 H NMR: = 1.56 (s, 9 H), 3.60 (d, 1 H), 4.16 (d, 1 H) J_{gem} = 15.9 Hz; 6.56 (q, 1 H), 7.25 (d, 1 H), 7.60 (s, 1 H). IR: 2240 cm^{-1} (ν C≡N, w); MS: M^+ 472, 295, 181, 95, 41: (Found: C, 68.21; H, 6.62; N, 5.66; O, 6.31; S, 13.25. $C_{28}H_{32}N_2O_2S_2$, requires: C, 68.25; H, 6.60; N, 5.68; O, 6.49; S, 13.01%.)

Compound **4q**, recrystallisation from benzene, m.p.: 183°. 1 H NMR: δ = 1.59 (s, 9 H), 3.90 (d, 1 H), 4.39 (d, 1 H) J_{gem}: 15.7 Hz; 6.55 (dd, 1 H), 7.25 (dd, 1 H), 7.60 (dd, 1 H); IR: 2230 cm^{-1} (ν C≡N, w); MS: M^+ 368; 185, 127, 112, 56, 43. (Found: C, 60.99; H, 5.95; N, 5.90; O, 13.39; S, 13.22. $C_{24}H_{28}N_2O_4S_2$ requires: C, 60.99; H, 6.00; N, 5.93; O, 13.54; S, 13.57%.)

Compound **4r** recrystallised from $CHCl_3$–ether, m.p.: 160–163°, mixture of stereomers. 1 H NMR: δ = 1.59, 1.60 and 1.68 (s, 9 H); 2.10, 2.12, 2.19 and 2.21 (s, 3 H); 2.0–2.4 (m, 2 H); 2.98, 3.00, 3.07 and 3.09 (s, 3 H), 3.3–4.0 (m, 2 H); IR: 2240 cm^{-1} (ν C≡N, w), 1610 cm^{-1} (ν CO, s). MS: M^+ 455; 277, 229, 171, 128, 83, 28. (Found: C, 57.72; H, 8.26; N, 12.09; O, 6.65; S, 13.97; $C_{22}H_{38}N_4O_2S_2$ requires: C, 58.12; H, 8.42; N, 12.32; O, 7.03; S, 14.10%.)

Compound **4s**, chromatography on silicagel ($CHCl_3$), recryst. from $CHCl_3$–ether: mixture of the stereomers. M.p.: 154–155° 1 H NMR: δ = 1.59 (s, 9 H), 2.26 (s, 3 H), 1.8–3.1 (m, 4 H). IR: 2230 cm^{-1} (ν C≡N, w), 1705 (ν CO, s). MS: DCI NH_3 (M + NH_4)$^+$: 414; 372, 236, 194, 136, 74, 52. (Found: N, 6.74; O, 8.08; S, 15.97, $C_{20}H_{32}N_2O_2$ requires: N, 7.09; O, 8.07; S, 16.16%.)

Compound **4t**, chromatography on silicagel ($CHCl_3$), recryst. from $CHCl_3$-ether, m.p. 218–219°, mixture of

stereomers. 1 H NMR: $\delta = 1.56$ (s, 9 H), 1.2–2.8 (m, 9 H). IR: 2240 cm^{-1} (ν C≡N, w), 1740 (ν CO, s). MS: DCI NH_3, $(M + NH_4)^+$: 466; 257, 134, 74, 52.

Compound **4u**, chromatography on silicagel (CH_2Cl_2-ether; 4/1), recryst. from $CHCl_3$–ether, m.p.: 225°, mixture of stereomers. 1 H NMR: $\delta = 1.56$ (s, 9 H), 1.2–2.8 (m, 11 H); IR: 2240 cm^{-1} (ν C≡N, w); 1730 (ν CO, s). MS: DCI NH_3, $(M + NH_4)^+$ 494; 238, 128, 74, 52. (Found: H, 8,21; N, 5.81; O, 6.68; S, 13.77. $C_{26}H_{40}N_2O_2S_2$ requires: H, 8.45; N, 5.87; O, 6.71; S, 13.45%.)

Compound **4v**, chromatography on silicagel (benzene), recryst. from $CHCl_3$–ether: one of the stereomers, m.p. 162° 1 H NMR: $\delta = 1.57$ (s, 9 H), 2.05 (m, 1 H), 2.79 (m, 1 H), 2.93 (s, 3 H), 3.81 (m, 2 H), 6.65–6.76 (m, 3 H), 7.21 (m, 2 H). IR: 2230 cm^{-1} (ν C≡N, w); MS: M^+–$(CH_3)_3CSH$: 433, M^+–HCN = 406, significant fragments: 344, 300, 262, 121. (Found: C, 68.69; H, 8.03; N, 10.51; S, 12.54. $C_{30}H_{42}N_4S_2$ requires: C, 68.66; H, 8.45; N, 10.68; S, 12.22%.)

Compound **4w** chromatography on silicagel (benzene), recryst. from $CHCl_3$–ether: one of stereomers m.p.: 204° 1 H NMR: $\delta = 1.59$ (s, 9 H), 2.3 (m, 1 H), 2.95 (m, 1 H) 4.28 (m, 1 H), 4.58 (m, 1 H), 6.20 (m, 2 H), 6.73 (m, 2 H). IR: 2240 cm^{-1} (νC≡N, w). MS: M^+: 442; 264, 221, 200, 165, 138, 131, 105.

Acknowledgements—One of us (S.M.) is greatly indebted to the Rhône-Poulenc Industries for a grant. Further, we gratefully acknowledge generous support from the Ministère de la Politique Scientifique.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 117 to 123, 1981
Printed in Great Britain.

0040-4020/81/Suppl. 1-0117-07 $02.00/0
Pergamon Press Ltd.

APPROACHES TO THE SYNTHESIS OF TRITERPENOIDS—VII[a-c]

THE SYNTHESIS OF SOME REDUCED CHRYSENE DERIVATIVES AS SUITABLE INTERMEDIATES FOR PENTACYCLIC TRITERPENES. SYNTHESIS VIA BCDE RING CONSTRUCTION

JOHN W. APSIMON*, AUSTIN M. GREAVES and NGUYEN-DINH THO[d]
Department of Chemistry, Carleton University, Ottawa, Ontario, Canada K1S 5B6

and

CAROL P. HUBER
Division of Biological Sciences, National Research Council of Canada, Ottawa, Ontario, Canada K1A 0R6

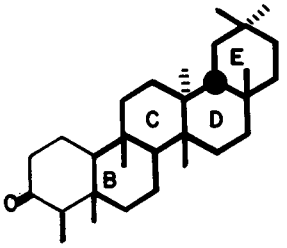
(*Received in U.S.A.* 22 *August* 1980)

Abstract—The synthesis and X-ray crystal structure determination of 8-methoxy-3,3,10bα, 12aβ-tetramethyl-1,2,5,6,10b,11,12,12a-octahydro-4(3H)-chrysenone is described. This and related compounds represent useful intermediates for pentacyclic triterpene synthesis.

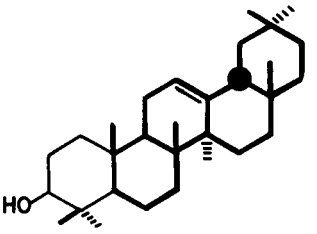
As part of our continuing studies in the area of pentacyclic triterpene synthesis[1-3] we have examined a pathway based on construction of the BCDE rings of target molecules such as friedelin **1** and β amyrin **2** as illustrated by the thickened bonds in the structures. Our synthetic subgoals were reduced chrysenes such as **3** and **4**, and although our studies towards this end have not been completely successful, our observations are now presented.

The basic strategy of this work parallelled our recently reported route to the pentacyclic compound **5** using an intramolecular aldol condensation as shown.[3] Thus, we reasoned that a precursor such as **6** might exhibit preferential cyclisation of one of its constituent racemates,[e] a tactic that had previously been used to advantage by us.[3].

Alkylation of the methoxy tetralone **7**[4] with the tosylate **8**[3] yielded the mixture of diastereomers **6a** and **6b** after deketalization of the reaction products. Reaction of this mixture in dimethoxyethane with a tetrahydrofuran solution of t-butylmagnesium chloride[3,5] led to the formation of three compounds, **9**



1



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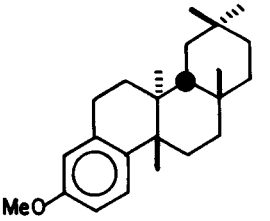

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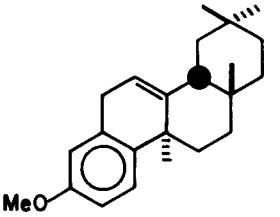


4

* To whom inquiries should be addressed.

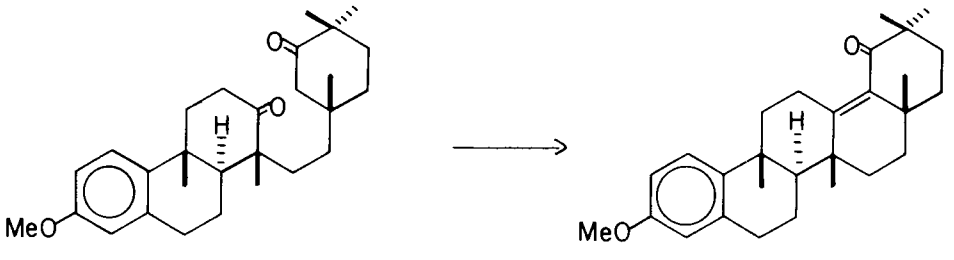
[a] Dedicated to the memory of R. B. Woodward.

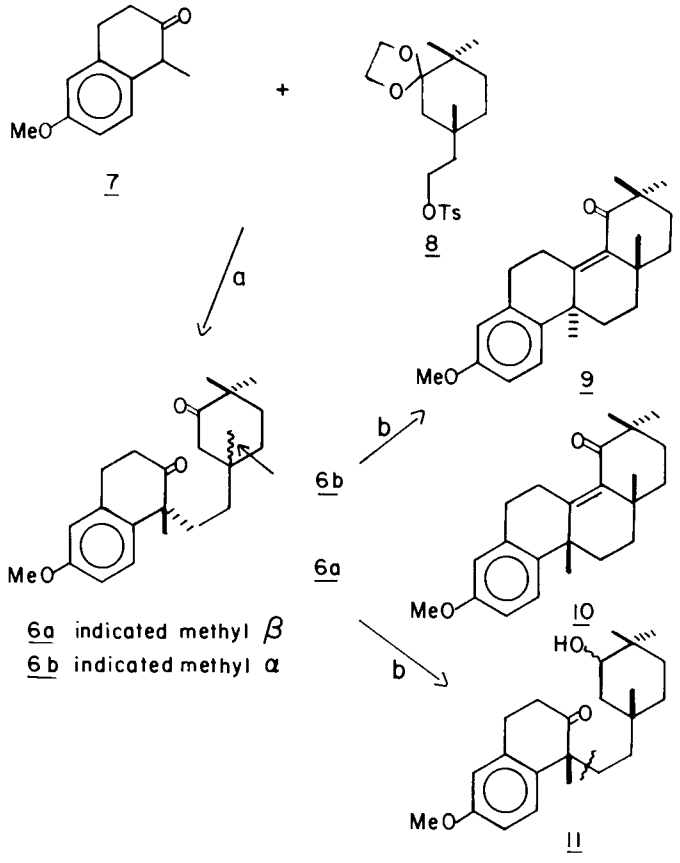
[b] For part VI see J. W. ApSimon and K. Yamasaki, *Can. J. Chem.* In press.

[c] NRCC No. 18726.

[d] Portions of this work are described in the Ph.D. thesis of AMG (Carleton University 1980) and the M.Sc. thesis of N.D.T. (1978).

[e] With the exception of structures **1** and **2**, which represent natural products, all structures used in this paper represent racemates. Only that enantiomer bearing a direct relationship to the natural series is shown for convenience. It is to be noted that condensation of **7** and **8** (Scheme 1) leads to a mixture of diastereoisomers represented as **6a** and **6b**.





Reagents: a. i KOtAm / benzene, i aq oxalic acid ; b- t-BuMgCl .

Scheme 1.

(45%), **10** (<3%) and **11** (30%) separated by column chromatography.[f] The major cyclised product, **9** was subjected to a single crystal X-ray structure determination and a stereoscopic view of the molecule produced by ORTEP II[12] is provided in Fig. 1. The final atomic parameters are listed with their e.s.d.'s in Table 1.

[f]For brevity we choose to describe unexceptional spectroscopic properties in the experimental section only. All data is in accord with structures depicted herein.

The anisotropic thermal parameters were analysed for rigid-body motion using the MGTLS program of Schomaker and Trueblood[6]. The rigid-body approximation was found not to apply to the molecule as a whole, but is appropriate for two portions, one consisting of atoms C(1), C(2)...C(10) and the other comprising C(8), C(9), C(11)...C(18). The r.m.s. differences between the observed and calculated U_{ij}'s are 0.0021 and 0.0029 Å^2 for the first and second groups respectively. Rotational oscillation (libration) for the first group is very anisotropic, with principal

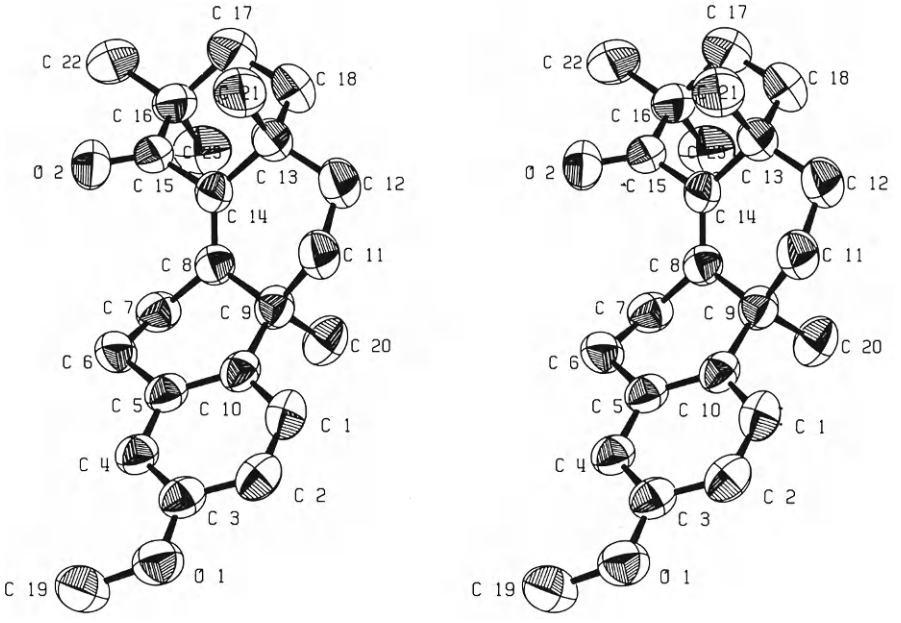


Fig. 1. A stereoscopic view of the molecule showing the numbering scheme used in the analysis. The thermal ellipsoids enclose 50% probability.

axis values corresponding to 6.1, 2.3 and 1.4°. The largest libration is about an axis nearly parallel to the C(3)...C(8) direction. For the second group the principal libration axes correspond to 4.9, 3.5 and 2.4°. Translational vibration for both groups is more nearly isotropic, with r.m.s. displacements varying between 0.20 and 0.29 Å. The bond length corrections calculated from the two libration tensors vary from 0.002 to 0.008 Å (up to twice the corresponding e.s.d.'s) and are included in the bond lengths presented in Fig. 2 except for C(19)–O(1), O(1)–C(3), O(2)–C(15), C(20)–C(9), C(21)–C(13), C(22)–C(16) and C(23)–C(16), which include "riding-motion" corrections[7] instead.

The bond lengths in this structure are very similar to those observed in the related pentacyclic compound **5**[3] and require no special comments. C-H bond lengths in the present compound vary from 0.91 to 1.08 Å, with mean 1.00 Å.

Conformation. The aromatic ring (A) is planar within experimental error ($x^2 = 2.28$), and the OMe group is approximately coplanar with it. The C(19)–O(1)–C(3)–C(4) torsional angle is 4.4°. (E.s.d.'s of the torsional angles are about 0.3°.) Both rings B

Table 1(a). Fractional coordinates, vibration tensor components (Å^2) for the expression $T = \exp[-2\pi^2(U_{11}\, a^{*2}h^2 + \ldots\ldots + 2U_{23}\, b^*c^*Kl + \ldots\ldots)]$, and their e.s.d.'s for the carbon and oxygen atoms. All quantities $\times 10^4$

	X	Y	Z	U_{11}	U_{22}	U_{33}	$2U_{23}$	$2U_{13}$	$2U_{12}$
O(1)	8198(1)	-5061(3)	3890(1)	821(13)	777(13)	703(12)	241(21)	311(20)	-108(21)
O(2)	8999(1)	2669(3)	930(1)	650(12)	998(16)	966(15)	331(26)	528(22)	319(23)
C(1)	6593(2)	-1906(4)	2909(2)	570(16)	740(19)	769(18)	-116(31)	413(28)	-117(28)
C(2)	6934(2)	-3330(4)	3311(2)	702(17)	697(19)	705(18)	- 33(31)	495(29)	-259(30)
C(3)	7913(2)	-3620(4)	3479(1)	715(17)	691(18)	487(15)	-118(27)	272(25)	-134(30)
C(4)	8540(2)	-2455(4)	3241(1)	602(16)	719(18)	490(15)	- 51(27)	199(24)	-150(28)
C(5)	8188(2)	-1010(4)	2832(1)	622(16)	703(18)	450(13)	- 76(26)	227(24)	-185(28)
C(6)	8907(2)	225(4)	2597(2)	539(15)	818(21)	671(16)	263(31)	52(25)	-157(29)
C(7)	8479(2)	1991(4)	2433(1)	689(17)	746(20)	557(15)	- 38(29)	146(27)	-273(30)
C(8)	7549(2)	1839(3)	1903(1)	585(15)	589(16)	539(15)	-129(26)	202(24)	30(26)
C(9)	6770(2)	878(4)	2220(1)	583(16)	675(18)	610(16)	-127(28)	282(25)	16(28)
C(10)	7204(2)	- 700(4)	2654(1)	576(15)	666(17)	498(15)	-178(26)	291(23)	- 95(27)
C(11)	5968(2)	318(4)	1586(2)	550(16)	905(22)	776(20)	- 52(35)	152(28)	- 25(31)
C(12)	5662(2)	1782(5)	1044(2)	571(17)	1048(25)	819(20)	- 66(38)	58(29)	85(34)
C(13)	6480(2)	2394(4)	662(2)	617(16)	860(21)	588(16)	- 74(31)	113(27)	267(31)
C(14)	7416(2)	2457(4)	1210(1)	558(15)	641(17)	585(15)	- 90(27)	262(24)	206(27)
C(15)	8223(2)	3359(4)	913(1)	635(16)	753(19)	498(15)	9(28)	237(24)	200(30)
C(16)	8016(2)	5133(4)	587(2)	835(19)	805(21)	615(16)	241(31)	367(29)	236(33)
C(17)	7063(3)	5070(5)	36(2)	965(23)	985(25)	845(23)	424(40)	253(38)	372(42)
C(18)	6254(2)	4219(5)	345(2)	699(19)	1100(28)	879(23)	256(42)	4(33)	460(39)
C(19)	9188(2)	-5324(4)	4128(2)	841(20)	863(23)	766(20)	259(36)	- 10(33)	-124(36)
C(20)	6344(2)	2072(4)	2761(2)	849(20)	797(22)	840(21)	-186(36)	687(34)	104(34)
C(21)	6610(2)	1156(5)	27(2)	923(22)	1195(29)	657(20)	-407(41)	82(34)	133(44)
C(22)	8820(3)	5746(6)	195(2)	1100(27)	1337(34)	924(25)	885(50)	642(43)	- 5(51)
C(23)	7946(3)	6331(4)	1244(2)	1439(32)	704(23)	919(25)	26(40)	434(46)	289(45)

Table 1(b). Fractional coordinates ($\times 10^3$), isotropic temperature factors ($Å^2$) for the expression $T = \exp(-B \sin^2\theta/\lambda^2)$, and their e.s.d.'s for the hydrogen atoms

	X	Y	Z	B
H(11)	590(2)	-180(3)	280(1)	5.0(0.6)
H(21)	651(2)	-415(4)	348(1)	5.7(0.6)
H(41)	925(1)	-255(3)	338(1)	3.9(0.5)
H(61)	915(2)	- 23(4)	213(2)	8.0(0.8)
H(62)	948(2)	27(3)	295(1)	5.2(0.6)
H(71)	896(2)	282(3)	227(1)	4.5(0.5)
H(72)	836(2)	247(3)	286(1)	4.1(0.5)
H(111)	541(2)	- 13(3)	175(1)	5.5(0.6)
H(112)	623(2)	- 74(4)	133(2)	7.0(0.7)
H(121)	542(2)	278(4)	130(2)	6.4(0.7)
H(122)	510(2)	136(4)	71(2)	6.7(0.7)
H(171)	721(2)	425(4)	- 41(2)	9.4(0.9)
H(172)	693(3)	641(5)	- 9(2)	10.5(1.1)
H(181)	567(2)	407(4)	0(2)	7.6(0.8)
H(182)	608(2)	491(4)	77(2)	8.2(0.8)
H(191)	928(2)	-642(5)	444(2)	10.2(1.0)
H(192)	953(2)	-440(4)	440(2)	7.8(0.8)
H(193)	954(2)	-549(4)	371(2)	8.2(0.8)
H(201)	606(2)	316(4)	252(2)	7.7(0.8)
H(202)	690(2)	245(4)	318(2)	6.9(0.7)
H(203)	578(2)	142(4)	292(2)	7.3(0.8)
H(211)	665(2)	- 7(4)	22(2)	8.3(0.8)
H(212)	603(2)	132(4)	- 39(2)	7.9(0.8)
H(213)	718(2)	143(4)	- 21(2)	8.8(0.9)
H(221)	864(3)	699(6)	- 1(2)	12.4(1.3)
H(222)	941(2)	573(4)	55(2)	8.8(0.9)
H(223)	888(3)	503(5)	- 25(2)	11.7(1.2)
H(231)	778(2)	745(5)	106(2)	9.9(1.0)
H(232)	734(3)	598(6)	151(2)	12.3(1.2)
H(233)	859(2)	629(5)	164(2)	9.3(0.9)

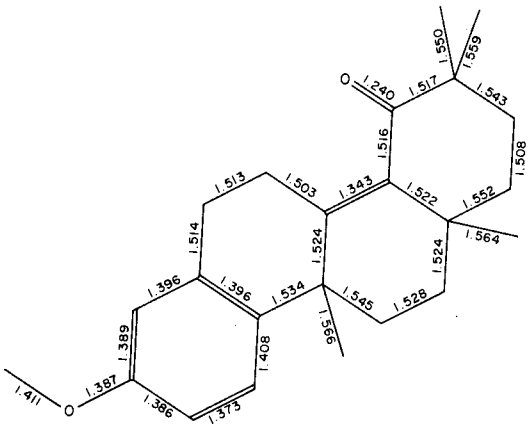


Fig. 2. Final bond lengths. The bonds comprising the ring skeleton have been corrected for rigid-body motion, while bonds involving substituents have been corrected for "riding" motion.

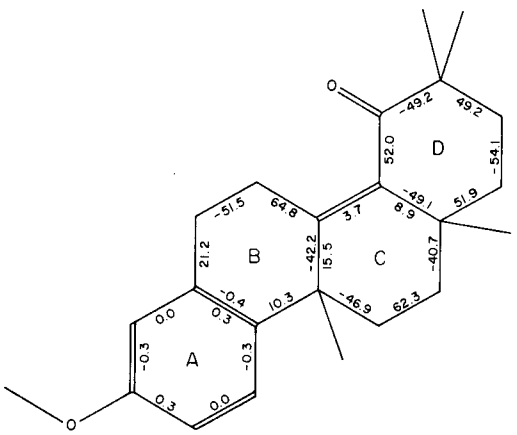


Fig. 3. Endocyclic torsional angles.

and C have slightly distorted half-chair forms, the distortion in ring C being mainly a flattening of the ring at C(13). Ring D has the chair form, somewhat flattened at C(16) because of the two Me groups, and also at the quaternary C(13). Endocyclic torsional angles are shown in Fig. 3. Me groups C(20) and C(21) are *trans* across the ring skeleton.

As in the related pentacyclic compound **5**[3], there appears to be no conjugation between the C(8)–C(14) double bond and the C(15)–0(2) CO group. The C(8)–C(14)–C(15)–0(2) torsional angle is 54.3° and the C(14)–C(15) bond length, 1.516 Å, is about 0.08 longer than expected in a conjugated system. The twist of C(15)–0(2) out of the C(7)–C(8)–C(14) plane is necessary to avoid very short H(71)...0(2) and C(7)...0(2) non-bonded contact distances. In the crystal structure these are 2.45 and 3.00 Å respectively. The C(7)...O(2) and H(71)...O(2) non-bonded repulsion is probably also responsible for the extra puckering of ring B at C(7); the displacements of C(7) and C(8) from the mean plane through C(6), C(5), C(10), C(9) are −0.50 and 0.25 Å respectively, whereas in an ideal half-chair, the displacements would be equal in magnitude.

There are no intermolecular contacts shorter than the corresponding van der Waals distances.

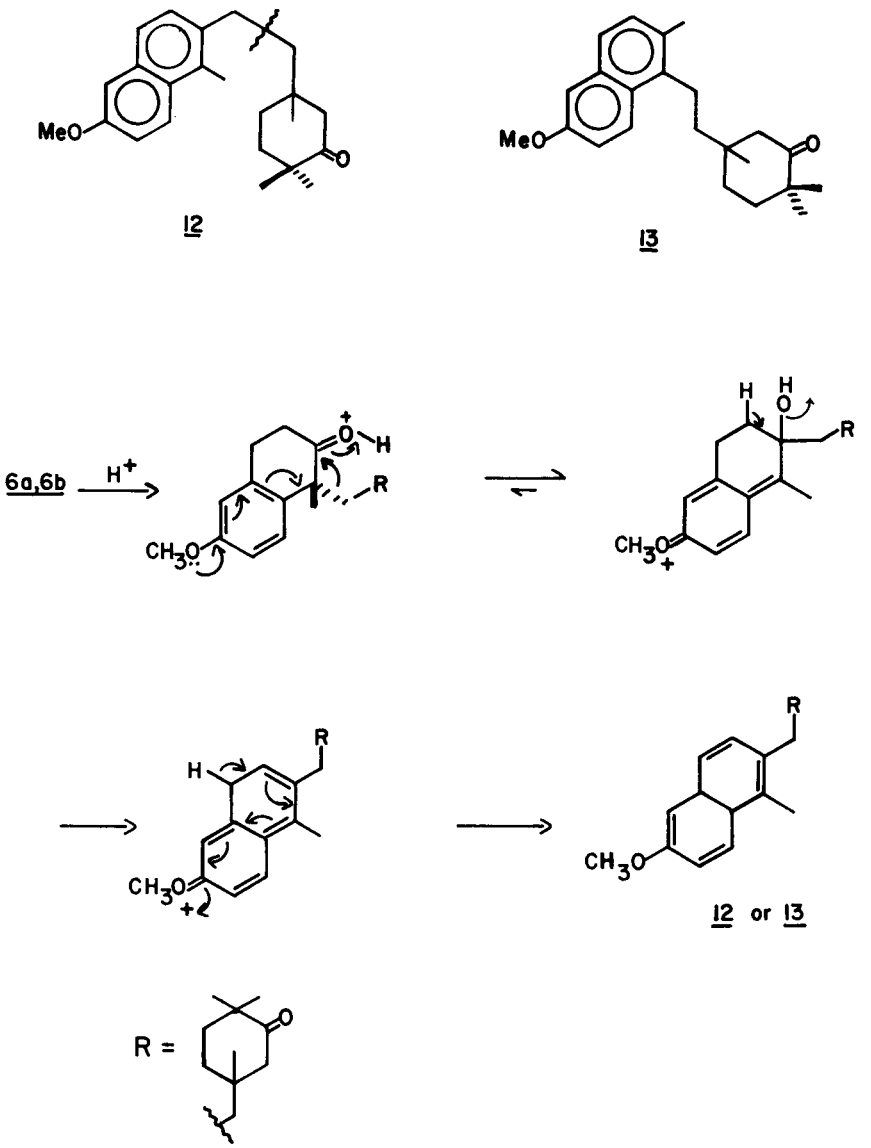
With structure **9** secure it is a simple matter to assign structure **10**. Compound **11** exhibited, besides the expected spectroscopic properties, a peak at *m/e* 189 in its mass spectrum indicative of cleavage as indicated in structure **11** and confirming the site of the OH group in this compound.

These observations provide direct evidence that our original surmise concerning the different reactivities of **6a** and **6b** towards cyclisation was correct. Thus, **9** arises from **6b** while **10** and **11** are derived from **6a**. The stereoelectronic requirements of the aldol process presumably dictate this selectivity. Apparently, the

cyclisation of **6b** is very efficient (45% of **9** is equivalent to 90% cyclisation of one component of the mixture) whilst **6a** is relatively unreactive to cyclisation, preferring a hydride transfer route in the reaction with Grignard reagent.[3,8] Confirmation of these cyclisation routes was obtained by separation of **6a** and **6b** initially by column chromatography and later by high performance liquid chromatography (hplc) and exposure of both compounds to the cyclisation conditions. Further, compound **11** could be converted to **6a** on mild oxidation.

Whilst it is gratifying that the conceptual basis of the selective cyclisation approach has been demonstrated, it was disappointing to us that **6b** rather than **6a** underwent this cyclisation especially as we had predicted the reverse selectivity from an inspection of molecular models! Nevertheless, compound **9** is now available to us in gram amounts and although of no use in a friedelin (**1**) synthesis it is a promising precursor for approaches to the β-amyrin (**2**) nucleus. We hope to be able to report on our work to this end in subsequent papers in this series.

While one synthetic subgoal is complete, the obtention of larger amounts of **10** would be of particular interest for our other goals. In a large series of base-catalysed reactions both in the presence and absence of bivalent metal ions we have been unable to detect any enhanced yield of this material. Bearing in mind our previous success[3] with acid catalysis in the aldol process we therefore examined the reaction of **6a** and **6b**, either as a mixture or separately with *p*-toluenesulfonic acid in *p*-xylene. Whilst both materials underwent cyclisation to **10** and **9** respectively, the yields were low (~20%). In both cases we isolated



Scheme 2.

another transformation product in 30–40% yield. The same material was isolated from both **6a** and **6b** and has been assigned structure **12** or **13** based on spectroscopic data and our previous experience.[9] In particular the mass spectrum of this material indicated at intense fragment at *m/e* 185, resulting from benzylic cleavage as indicated in **12**. The origin of this species can best be accounted for by the route outlined in Scheme 2, although doubt still exists as to which group has migrated. For convenience we have depicted only side chain migration in Scheme 2. Thus, acid-catalysed cyclisation has proved to be of no utility for triterpene synthesis.

Our continuing studies are presently directed towards other modes of cyclisation of species such as **6**.

EXPERIMENTAL

General. All mps were determined on a Fisher–Johns apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer Model 237B IR spectrometer, UV spectra on a Perkin–Elmer 202 UV-Visible Spectrophotometer. Mass spectra were obtained on an AEI MS12 Instrument at Trent University. NMR spectra were measured on a Varian T-60 (^{1}H) or Varian HA-100 (^{1}H and ^{13}C), using TMS as an internal standard. Chemical shifts are expressed in the δ scale with the following designations; s, singlet; d, doublet; t, triplet; m, multiplet. Combustion analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Michigan, and Guelph Chemical Labs. Ltd. Guelph, Ontario.

All reactions and chromatograms were routinely monitored by analytical tlc (Merck 60 PF-254 plates, 0.25 mm). Spots were developed by exposing to I_2 vapour, or by spraying with ceric sulfate and heating. Preparative tlc was carried out on Merck 60 F-254 precoated silica gel plates of 2.0 mm thickness. Bands were visualized by viewing under an UV source or by staining one edge with ceric sulfate/heating. Silica gel (Davison Chemical Co., grade 923 (100–200 mesh) was used for column chromatography. Flash chromatography refers to elution of material on a silica gel pad (silica gel 60H-E.M. Reagents, sintered glass funnel) using water aspirator suction, with collection and analysis of 50–150 ml fractions. HPLC was performed using a Waters Prep 500 High Performance Liquid Chromatograph.

The term "dry benzene" and "dry toluene" refer to benzene or toluene which was distilled and stored over Na. Dry THF and dry dimethoxyethane were obtained by distillation from LAH. "Anhydrous ether" was available from Mallinckrodt Canada Ltd. Petroleum ether refers to the fraction boiling at 30–60°.

1-Methyl-1[2-(3-keto-1,4,4-trimethylcyclohexyl)ethyl]-6-methoxy-3,4-dihydro-2(1H)-naphthalenones **6a** and **6b**

K metal (1.5 g, 38 mmol) t-amyl alcohol (6 g, 68 mmol) and dry benzene (200 mL) were refluxed for 2 hr, (until all K dissolved), the soln was cooled to room temp, then **7**[4] (6.3 g; 33.5 mmol) in benzene (25 ml) was added dropwise. Benzene/t-amyl alcohol were then removed by azeotroping whilst the solvent level was kept constant by addition of fresh benzene over a 1–2.5 hr period. The mixture was then recooled to room temp and **8**[3] (12 g, 31.4 mmol) in benzene (30 ml) was added slowly, and the reaction stirred overnight at room temp and then refluxed for 25 hr. The cooled mixture was poured into ice/water and extracted with ether (×2). The cold yellow aqueous layer was then acidified carefully with a few drops of conc H_2SO_4 and immediately extracted with ether (×3). The combined organic layers were washed with satd. $NaHCO_3$ aq; satd. NaCl aq and dried ($MgSO_4$). Concentration yielded 17.5 g of an oil which was dissolved in EtOH (250 ml). Satd aqueous oxalic acid (250 ml) was added and the mixture refluxed for 1.5 hr. Water and EtOH were removed under reduced pressure and ether and water were added. The layers were separated and the aqueous layer was extracted with ether (×3). The combined organic layers were washed with satd. $NaHCO_3$ aq; water and satd. NaCl aq, then dried ($MgSO_4$). In earlier experiments column chromatography of this mixture (silica gel/petroleum ether–ether) afforded unreacted starting materials plus **6a** and **6b** (54%) as a colorless oil. In this case, repetitive HPLC of the concentrated material gave (a) 2.6 g of **7** (b) 1.8 g of **6b** (c) 3.2 g of a mixture of **6a** and **6b** (d) 1.4 g of **6a** contaminated with a trace of **6b**. The yield of **6a** and **6b** was 59%. Analytical data of the mixture: IR (neat) ν_{max} 1700, 1705 cm^{-1} (2 C = 0). NMR ($CDCl_3$) δ ppm: 1.0 (2s. 6H gem di-C$\underline{H}_3$) 1.4 (s. 3H. C-1′CH_3) 1.5 (s. 3H C-1 CH_3) 2.0 (s. 2H. CH_2CO) 4.0 (s. 3H OCH_3) 6.6–7.2 (m. 3H. ArH). Mass Spec. *m/e* (r.i.) 356 (M^+, 15) 203 (100), 175 (33). (Found: C: 77.25, H: 9.11. Calc: for $C_{23}H_{32}O_3$: C: 77.52; H: 8.98.

Spectral data for **6a** and **6b** were indistinguishable except for the relative chemical shifts of the Me and OMe group protons in the presence of Euroshift reagent which was used to monitor the isomeric purity of **6a** and **6b**.

Reaction of diastereoisomeric **6a** *and* **6b** *with t-butylmagnesium chloride:*

Synthesis of 8-methoxy-3,3,10bα,12aβ-tetramethyl-1,2,5,6,10b,11,12,12a-octahydro-4(3H)-chrysenone **9**. A mixture of Mg metal (36 g dried in an oven at 160°) freshly distilled THF (30 mL), dried over Na metal and a few crystals of I_2 was refluxed for 15 min. To initiate the reaction, 40 drops of freshly distilled t-BuCl were added. The soln was refluxed for 30 min at which time the I_2 colour had disappeared. A soln of t-BuCl (7.5 g) in THF (40 ml) was added dropwise and the mixture was refluxed for another 30 min. The soln was cooled to room temp and a titration showed the molarity to be 1 M.

The diastereoisomeric mixture **6a** and **6b** (1.50 g, 4.35×10^{-3} moles) dissolved in dimethoxyethane (150 mL) (DME) at −78° under N_2. After 10 min, t-BuMgCl (1.74×10^{-2} moles) was added and a pale yellow ppt appeared after 3 min. The mixture was kept stirring for 30 min longer then refluxed for 24 hr. After cooling, ether (100 ml) was added and the mixture was poured into a mixture of ice and ammonium chloride. Work-up in the usual manner afforded 1.50 g crude product. Column chromatography (silica gel–petroleum-ether afforded 0.70 g pure **9** that was recrystallized from pet. ether to give colorless blocks m.p.: 87–88°; IR (CH_2Cl_2); ν_{max} 1660 (α,β-unsaturated C = 0), 1635 cm^{-1} (C = C); NMR ($CDCl_3$): δ 0.89 (s, 3, CH_3 at C_{12}), 1.12 (s, 3, $-OCH_3$): mass spectrum: *m/e* (relative intensity): 338 (36) (M^+), 324 (23); 323 (100). UV (CH_3OH): λ_{max}: 285 (ε = 2460), 250 (ε = 5450). (Found: C: 81.71; H: 9.07. Calc. for $C_{23}H_{30}O_2$: C: 81.67; H: 8.87).

Later fractions from this column provided trace amounts (15 mg) of **10** as colorless needles, m.p.: 125–126°; IR (CH_2Cl_2): 1665 (α,β-unsaturated C = O); 1635 cm^{-1} (C = C). NMR ($CDCl_3$): δ 1.00 (s, 3, CH_3 at C_{12}); 1.06 and 1.12 (s, 6, *gem*-dimethyl); 1.43 (s, 3, CH_3 at C_{10b}); 3.73 (s, 3-0-CH_3). Mass spectrum: *m/e* (relative intensity): 338 (35) (M^+) 324 (23), 320 (100). UV (CH_3OH): λ_{max}: 2870 (ε = 2470); 250 (ε = 5470). (Found: C: 81.61; H: 9.05. Calc. for $C_{23}H_{30}O_2$: C: 81.67; H: 8.87).

Finally **11** (0.45 g, 30%) was obtained, IR (neat). 3450 (OH); 1710 cm^{-1} (C = 0). NMR ($CDCl_3$): δ 0.73 and 0.8 (s, 6, gem-dimethyl); 0.96 (s, 3, CH_3 at C_1); 1.30 (s, 3, CH_3 at C_1); 3.76 (s, 3, O-CH_3). Mass spectrum: *m/e* (relative intensity): 356 (11) (M^+); 189 (100). (Found: C: 76.92; H: 9.52. Calc. for $C_{23}H_{32}O_3$: C: 77.48; H: 9.05.)

1-[2-(3-Keto-]-1,4,4-trimethylcyclohexyl)ethyl]-2-methyl-6-methoxynaphthalene **12**

A mixture of **6a** and **6b** (3.9 g, 11 mmol) *p*-toluenesulfonic acid (14 g) in *p*-xylene (300 m) were refluxed for 6 hr. Water (100 ml) was added to the cooled soln. The aqueous layer was extracted with ether (×2) and the combined organic extracts

washed with satd. $NaHCO_3$ aq, water and satd NaCl aq; then dried ($MgSO_4$). Concentration and chromatography (silica gel) gave 260 mg of **9** (spectral data identical to authentic sample), and 1.56 g (42%) of **12** m.p. 109–110° IR (KBr) ν_{max} 1710 (C = 0) 1610, 1625 cm^{-1} (C = C) UV λ_{max} 273, 285 ($\varepsilon = 8.1 \times 10^3$), 290. NMR ($CDCl_3$) δ: 1.03 (S. CH_3), 1.10 (s, 6, 2 × CH_3), 2.6 (s, 3, Aromatic CH_3), 3.9 (s, 3, OCH_3); 7.2–8.0 (1 m, 5, naphthalenic H's). Mass spec: *m/e* (r.i.) 338 (M^+ 100) 185 (98) 199 (12) 139 (28). (Found: C: 81.38; H: 9.17. Calc. for: $C_{23}H_{30}O_2$: C: 81.67, H: 8.87).

A soln of 230 mg (6.4 × 10^{-4} mole) of **6a**, 836 mg (4.4 × 10^{-3} mole) *p*-toluenesulfonic acid in 25 ml of *p*-xylene under an N_2 was refluxed for 6 hr. Water was added and the xylene layer separated. The aqueous layer was extracted (× 3) with ether. The combined extracts were washed with a 5% $NaHCO_3$ aq, water and sat brine soln and dried over Na_2SO_4. Evaporation of the solvent gave an oil (230 mg) which was chromatographed on silica gel using a mixture of petroleum-ether and ether as eluent to afford 42 mg of **10** and 80 mg of **12**. Total yield: 56%.

A soln of 430 mg of **6b**, 1.60 g *p*-toluenesulfonic acid in 50 mL *p*-xylene under N_2 was refluxed for 6 hr. Work-up in the usual manner afforded 425 mg crude product (oil) which was chromatographed on silica gel when a mixture of petroleum ether and ether as eluent afforded 143 mg of **9** and 197 mg of **12**, total yield: 83%.

X-ray data collection.[g] Compound **9** crystallized from petroleum ether containing a few drops of ether as large colourless blocks elongated along c*. Preliminary photography showed monoclinic symmetry and systematic extinctions OkO with k odd and h0l with l odd. For data collection a specimen was cut to approximate dimensions 0.20 × 0.30 × 0.35 mm and was mounted with b as rotation axis. Crystal data are as follows: $C_{23}H_{30}O_2$, Mol. wt. = 338.5. Monoclinic, **a** = 14.066 (2), **b** = 7.781 (3), **c** = 18.271(3) Å, β = 99.65(5)° (based on λ (CuKα_1) = 1.54051 and λ (CuKα_2) = 1.54433 Å), V = 1971.4 $Å^3$, z = 4, d_x = 1.14 g cm^{-3}. Space group: $P2_1/c$. μ (CuKα) = 5.56 cm^{-1}. Cell dimensions and relative intensities were measured at room temp with Ni-filtered Cu radiation on a Picker diffractometer equipped with a scintillation counter and pulse-height analyser. The $\theta/2\theta$ scan mode was used, with scan ranges from 2.0 to 4.0° and a 2θ scan speed of 2°/min. A 10 sec, background count was taken at the end of each scan. Two octants (hkl and hk$\bar{l}$) were surveyed to a $\sin\theta/\lambda$ limit of 0.575 $Å^{-1}$. The intensities of two standard reflections were measured at intervals of approximately 30 reflections throughout the data collection, and were used to scale all the data. Fluctuations in the standard counts appeared to be random. Of the 3134 independent reflections measured, 961 were classified as 'unobserved', having net counts less than 10 decacounts or less than 10% of the total background count. These were assigned zero weight in subsequent least-squares calculations. No absorption corrections were applied.

The structure was solved by the symbolic addition procedure and refined by block-diagonal least-squares, minimizing $\Sigma\,\omega(|F_0| - |F_c|)$.[2] All H atoms were located on a different map and were refined isotropically while the C and O atoms were refined anisotropically. Scattering factors for C and O were those of Hanson, Herman, Lea and Skillmann[10] and bonded H scattering values were taken from Stewart, Davidson and Simpson.[11] The weighting scheme used for the later cycles of refinement was

$$\omega = 1/[1.0 + \{(|F_o| - 6.0)/10.0\}^2]: 1.6 < F_o < 106.4$$

and

$$\omega = \omega \times (0.45/\sin^2\theta) \text{ if } \sin^2\theta > 0.45.$$

This reduced the dependence of $\langle\omega\Delta^2\rangle$ on $|F_o|$ and on $\sin^2\theta$. It was noted that some of the strongest reflections appeared to be unaffected by secondary extinction. The ten reflections with highest net counts were therefore excluded from the final least-squares cycles, as was one other reflection (1 0 0) which showed poor agreement. In the final least-squares cycle the average (shift/e.s.d.) was 0.08 and the largest (Δ/σ) was 0.43. For all (2173) observed reflections the final conventional R value ($= \Sigma||F_o| - |F_c||/\Sigma|F_o|$) is 0.062. A difference map computed from the final structure factors* showed no density outside the range −0.16 to +0.15 e $Å^{-3}$.

Acknowledgements—We thank the National Research Council of Canada and the Natural Sciences and Engineering Research Council of Canada for generous financial assistance of our research as well as the Hoffman La Roche Institute Foundation which supported the earlier portions of this work.

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[g] Copies of tables of observed and calculated structure factors and of uncorrected bond lengths and angles are available, at a nominal charge, from the Depository of Unpublished Data, CISTI, National Research Council of Canada, Ottawa, Canada K1A 0S2.

Tetrahedron, Vol. 37, Supplement No. 1, pp. 125 to 141, 1981
Printed in Great Britain

0040-4020/81/Suppl. 1-0125-17 $02.00/0
Pergamon Press Ltd.

DI-π-METHANE HYPERSURFACES AND REACTIVITY; MULTIPLICITY AND REGIOSELECTIVITY; RELATIONSHIP BETWEEN THE DI-π-METHANE AND BICYCLE REARRANGEMENTS

MECHANISTIC AND EXPLORATORY ORGANIC PHOTOCHEMISTRY[1,2]†

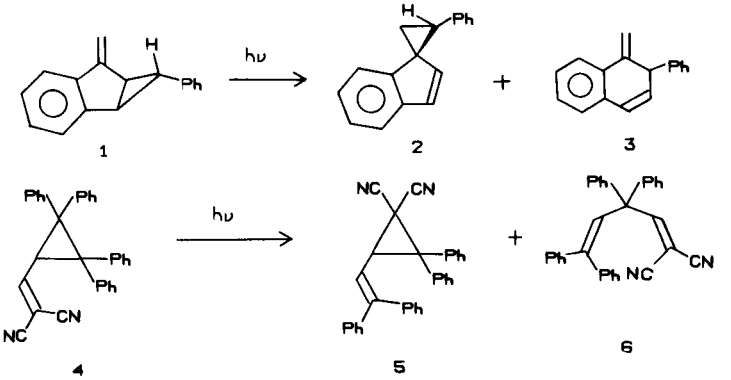
HOWARD E. ZIMMERMAN and RONDA E. FACTOR

McElvain Laboratories of the Chemistry Department of the University of Wisconsin, Madison, WI 53706, U.S.A.

(*Received in U.S.A.* 6 *March* 1980)

Abstract—The photochemistry of 1,1-dicarbomethoxy-3,3,5,5-tetraphenyl-1,4-pentadiene and 3,3-dicarbomethoxy-1,1,5,5-tetraphenyl-1,4-pentadiene was investigated. Both direct and sensitized photolyses of the 3,3-diester afforded 1,1-dicarbomethoxy-2,2-diphenyl-3-(2′,2′-diphenylvinyl)cyclopropane with quantum yields of 0.42 and 0.32, respectively. Direct irradiation of the 1,1-dicarbomethoxy-pentadiene gave this same diphenylvinyl-cyclopropane product (Ø = 0.39), while acetophenone sensitization of the 1,1-dicarbomethoxy-pentadiene led to the regioisomeric 1,1,2,2-tetraphenyl-3-(2′,2′-dicarbomethoxyvinyl) cyclopropane (Ø = 0.92). Thus the unsymmetrically substituted cyclopropyldicarbinyl diradical opened one or the other of two three-ring bonds depending on multiplicity. Direct irradiation of the dicarbomethoxyvinylcyclopropane resulted in a bicycle rearrangement affording the diphenylvinyl-cyclopropane (Ø = 0.10); additionally, the 1,1-dicarbomethoxy-pentadiene was formed (Ø = 0.069) in this photolysis. The second product can be viewed as arising from a reverse di-π-methane rearrangement or, alternatively, as deriving from partial bicycling of the diphenylcarbon moiety. To confirm that the bicycling process was intramolecular rather then by disengagement of a diphenylcarbene followed by readdition, a crossover experiment was run using 1,1-dicarbomethoxy-4,4-di-*p*-tolylbutadiene. However, no diphenylcarbene transfer was seen. Single photon counting was employed to obtain unimolecular rate constants for the S_1 excited states undergoing the di-π-methane rearrangements. A plot of the log of the S_1 rates for centrally disubstituted 1,1,5,5-tetraphenyl-1,4-pentadienes—having central carbomethoxy, cyano or methyl groups—vs Hammett ground state sigma constants proved linear with a rho value of −2.53. The various excited states, intermediate species and the related hypersurfaces were subjected to SCF and SCF-CI calculations. The delta-P treatment showed that excitation is concentrated in the cyclopropyldicarbinyl diradical moiety as the di-π-methane rearrangement proceeds. The calculations also suggest that for a successful bicycle rearrangement excitation energy needs to be distributed into the three-ring bond not conjugated with the vinyl group. Triptych correlation diagrams were constructed using SCF and SCF-CI energies and are used to interpret the photochemistry. The differing singlet versus triplet regiochemistry was found to follow the "small K vs large K" generalization used previously.

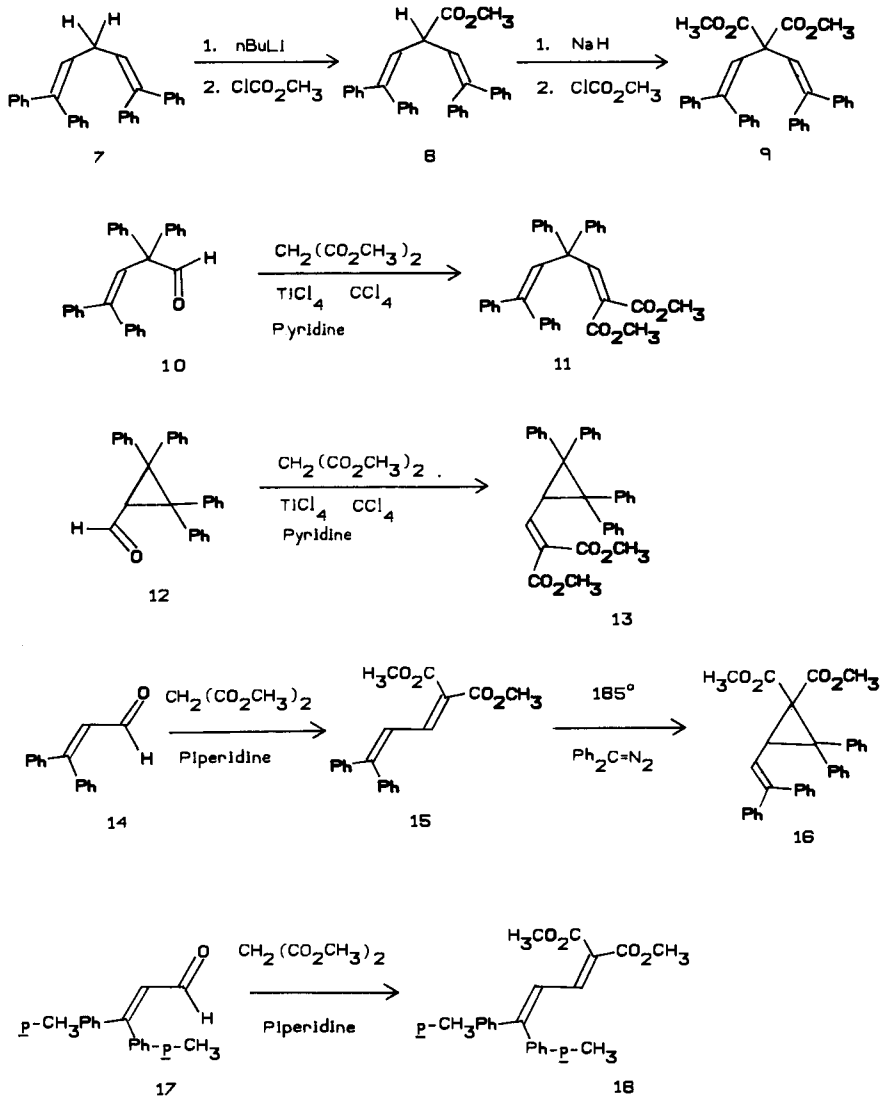
One of the basic aims of organic photochemistry is to uncover new and general reactions as well as to study their mechanisms. The photochemical bicycle rearrangement is an intriguing reaction whose generality we have been investigating. Two illustrative examples are depicted in eqns (1) and (2). The reaction in eqn(1)[3] is more typical. Here a divalent carbon moves along the surface of a benzofulvene system with stereospecificity. Several similar examples have been studied in our previous investigations.[4,5]



(1)

(2)

†This paper pays tribute to Robert B. Woodward and his chemistry.



Scheme 1. Synthesis of photochemical reactants and photoproducts.

The reaction in eqn (2)[2] provides the first example of an acyclic bicycle rearrangement wherein the bicycling C atom, here diphenylmethylene, moves along the surface of an acyclic system.

The present investigation had the goal of broadening the scope of the acyclic bicycle rearrangement as well as studying related di-π-methane rearrangement photochemistry. The compounds of interest for photochemical study were parallel to those in eqn (2) with carbomethoxy substitution rather than cyano. Additionally, it was of interest to investigate a di-π-methane system having both diphenylvinyl and dicarbomethoxyvinyl moieties as well as central phenyl substitution.

Synthesis of compounds of photochemical interest

Results. These syntheses are depicted in Scheme 1 and detailed in the Experimental. The synthesis of 3,3-dicarbomethoxy-diene **9** was one developed earlier in our laboratories.[6] The philosophy paralleled that of the synthesis of the corresponding dicyano-diene of our earlier study.[2b] The regioselective central carbethoxylation and cyanation of the 1,1,5,5-tetraphenylpentadienyl carbanion derives from the central carbon (i.e. C-3) having the highest electron density, a situation characteristic of such conjugated anions.[7]

Exploratory photochemistry of the dienes

Results. The photochemistry of the 3,3-dicarbomethoxy diene **9** was investigated first. A remarkably facile rearrangement was observed. The product proved to be the diphenylvinyl cyclopropane **16** synthesized earlier (note above). This photoproduct (i.e. **16**) is that expected from a typical di-π-methane rearrangement.[8] Surprisingly however, the rearrangement proceeded not only on direct irradiation, as is characteristic of acyclic diene photoreactivity in the di-π-methane rearrangement but also afforded the same product, with comparable facility on sensitization with acetophenone. These reactions are summarized in Scheme 2 eqn (3). Commonly, the di-π-methane rearrangement proceeds only inefficiently when sensitized in examples which are structurally very

similar, for example where carbomethoxyl groups **9** are replaced by methyls.[8b,9,10]

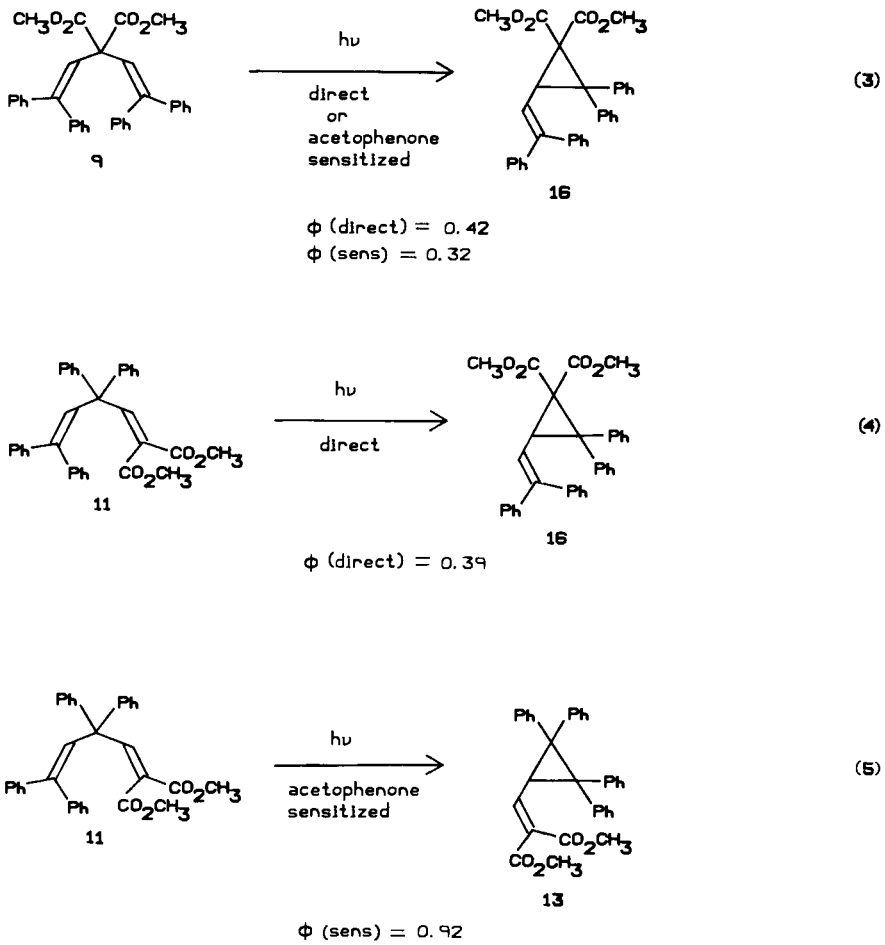
Attention was next turned to the photochemistry of the 1,1-dicarbomethoxy diene **11**. Direct irradiation afforded the same photoproduct, **16**, as encountered in the photochemistry of the 3,3-dicarbomethoxy isomer (*cf* eqn (4), Scheme 2). Formation of this product was not surprising, since it was one of two mechanistically possible regioisomeric di-π-methane photoproducts deriving from the 1,1-dicarbomethoxydiene **11**. Strikingly, however, acetophenone sensitized irradiation of **11** afforded the other possible regioisomer, **13**, from di-π-methane rearrangement of diene **11** (*cf* eqn (5), Scheme 2). The structure of this product, (i.e. **13**) was established by its identity with the previously synthesized material (note above in the synthetic section).

Thus, in the photochemistry of 1,1-dicarbomethoxy diene **11** one regioisomeric product (i.e. **16**) is formed on direct irradiation and the other regioisomeric product (i.e. **13**) results from the sensitized photolysis.

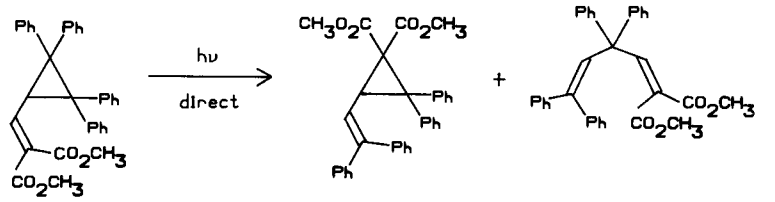
In the case of the 1,1-dicarbomethoxy diene photochemistry, two questions arise in each of the types of irradiation, direct and sensitized. One question is whether the regioisomer not observed was merely destroyed under reaction conditions. The second question is whether the regioisomer not encountered was an unobserved reaction intermediate.

In the direct irradiation, the first question was answered by a control run in which 0.2 percent of dicarbomethoxyvinyl cyclopropane **13** was added to the diene **11** being photolyzed. After 12 % conversion it was found that 76 % of the added cyclopropane **13** was still present and thus would have been observed in ordinary runs if it had been formed. This also answers the second question, for had cyclopropane **13** been an intermediate in the photochemistry it would have survived and been observed.

In the case of the sensitized irradiation of **11** a control was run. This revealed that the sensitized irradiation of diphenylvinyl cyclopropane **16** did not lead to formation of the sensitized di-π-methane product deriving from the 1,1-dicarbomethoxy diene **11**. Therefore isomer **16** could not be an intermediate in the rearrangement. Further evidence derived from the very high, nearly unity quantum yield for the di-π-methane rearrangement (note below). With such a high quantum yield, a two-step, two-photon mechanism is precluded. Similarly, the other possibility accounting for high observed regioselectivity,[11] namely destruction of the non-observed diphenylvinylcyclopropane **16**, is also precluded by the high quantum efficiency which permits no appreciable



Scheme 2. Photochemical transformations of dienes.



$\phi = 0.10$ $\phi = 0.069$ (6)

side reactions. Finally, the 95–96 % mass balances add weight to the reality of the observed regioselectivity.

Hence, the striking conclusion is that the singlet of diene **11** affords the diphenylvinyl regioisomer (i.e. **16**) while the triplet of **11** leads to the dicarbomethoxyvinyl counterpart (i.e. **13**).

Observation of a bicycle rearrangement and reverse di-π-methane rearrangement by one of the vinylcyclopropanes

Results. For a thorough understanding of the diene photochemistry, it was necessary to investigate the behavior of their photoproducts. Of the two vinylcyclopropanes, **13** was unreactive under sensitized conditions and **16** was only very slightly reactive (note Experimental).

In contrast, direct irradiation of the dicarbomethoxyvinyl cyclopropane **13** led to a modestly facile rearrangement. The two products observed were the diphenylvinyl cyclopropane **16** and the 1,1-dicarbomethoxy diene **11** in a 1.5:1 ratio. Note eqn (6). The formation of diphenylvinyl cyclopropane **16** from its regioisomer **13** provides still another example of the bicycle rearrangement.[2b,3–5] Interestingly, the bicycling was unidirectional and not reversible, since irradiation of the diphenylvinyl photoproduct **16** gave no reaction. Finally, it is seen that the formation of the 1,1-dicarbomethoxyvinyl diene **11** from vinylcyclopropane **13** represents a "reverse di-π-methane rearrangement".

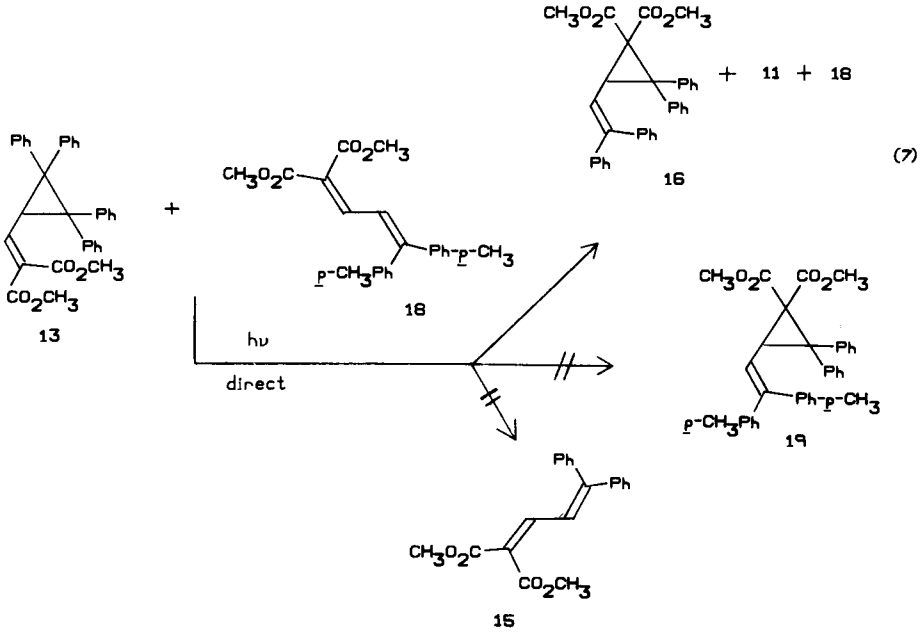
One mechanism for formation of the photoproducts **11** and **16** (note eqn 6) involves the disengagement of diphenylmethylene leaving 1,1-dicarbomethoxy-4,4-diphenylbutadiene and then readdition of the carbene to the diene, however at different sites to lead to **11** and **16**. Thus a crossover experiment was designed in which the photolysis of dicarbomethoxyvinyl cyclopropane **13** was run in a three-fold excess of 1,1-dicarbomethoxy-4,4-di-p-tolylbutadiene. At 47 percent conversion a 99 % mass balance was observed and only the normal photochemical products were isolated in addition to essentially quantitative recovery (99 %) of the di-*p*-tolyl diene. No crossover photoproducts were detectable.

This result is shown in eqn (7):

Quantum yield and excited singlet rate determinations

Results. For quantum yield determinations both the Black Box apparatus[12] and the semimicro optical bench[12] previously described were used. Additionally, the electronic actinometer[13] used in our photochemistry generally was calibrated with ferrioxalate[14] for each run; but for each wavelength the calibration was essentially invariant with time. The quantum yield results are given in Scheme 2 and also eqn (6). Details are given in the Experimental.

Since reactivity is better correlated to excited state rate constants than to quantum efficiencies as we have noted earlier[15,16] we turned to the method of single photon counting used in our earlier studies[2b,3,15,17–19]



(7)

Table 1. Summary of singlet rates and lifetimes[a,b,c]

Compound	Temp, K	M[d]	τ, ps	$^1k_{d(tot)}, s^{-1}$	k_r, s^{-1}
3,3-Dicarbomethoxy-diene, 9	293	21	39.4	2.63×10^{10}	1.10×10^{10}
	77		827.	1.25×10^{9}	----------
1,1-Dicarbomethoxy-diene, 11	293	197	1.66	6.01×10^{11}	2.34×10^{11}
	77		330.	3.05×10^{9}	----------

[a]See Experimental Section for full details. [b]All runs were made in methylcyclohexane-isopentane (4:1). [c]Estimated probable error limits ± 10%. [d]Average value of several runs.

to determine the rates of S_1 decay and rearrangement. The modification originally described in 1974 uses an on-line minicomputer to serve as a multichannel analyzer and to perform an iterative simulated deconvolution. The method assumes a decay function which is the sum of negative exponentials with variable pre-exponential constants and variable rate constants as the exponentials. With the profile of the lamp flash collected and an initially assumed sum of exponentials as the decay function, the minicomputer calculates the predicted profile of the fluorescence emission. The deviation of the prediction from the observed sample emission profile is used by an efficient algorithm[15] to determine the optimum choice of exponentials for the next iteration. The process is repeated until the experimental curve is reproduced. Our most recent results were obtained on a PDP-11/55 and with improved programming[20] so that printout of the rate constants is complete within two minutes of completion of the experiment, thus making single photon counting a routine tool.

The results of single photon counting measurements are given in Table 1. As in our past studies where exceptionally rapid rates of decay are involved, we made use of the inhibition of decay and reaction rates by temperature lowering. With the 77K decay rates available, the multiplier M converting these to room temperature rates is defined as $Ø_f^{77}/Ø_f^{RT} = M$.[15] These values are also included in Table 1.

Due to very weak emission single photon counting studies were not carried out on the dicarbomethoxy-vinyl cyclopropane **13**.

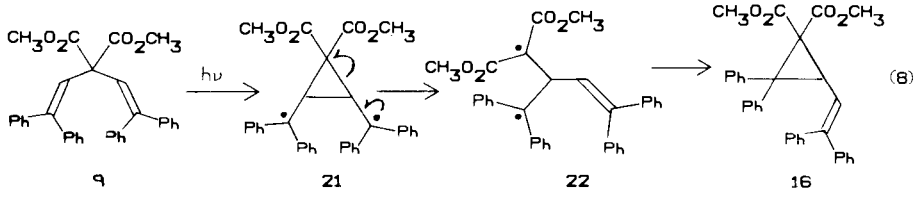
The overall reaction mechanism of the di-π-methane rearrangement of the 3,3-*dicarbomethoxy diene* **9**

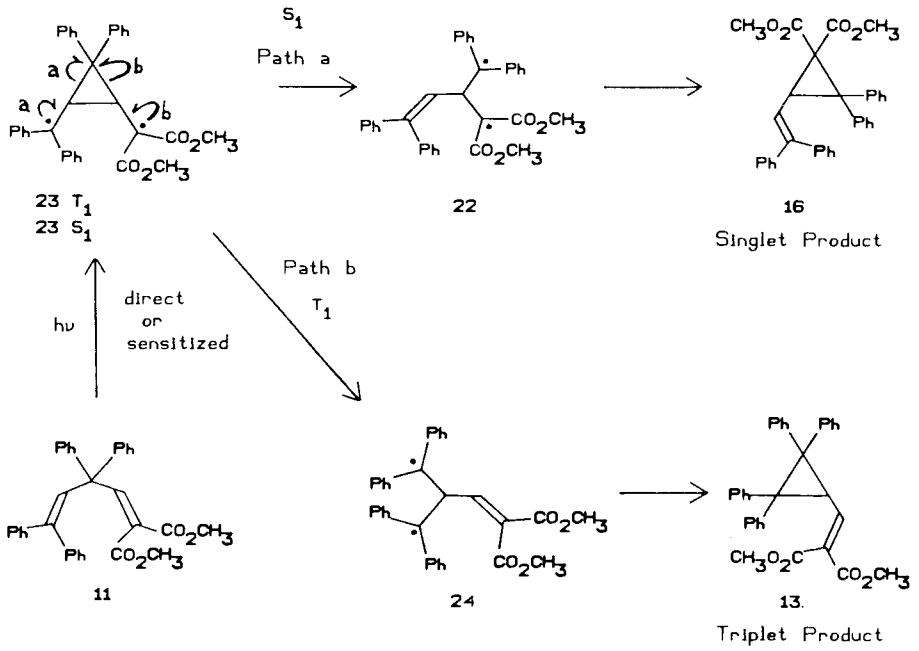
Interpretative discussion. The rearrangement of the 3,3-dicarbomethoxy diene **9** follows a typical di-π-methane mechanism as depicted in eqn (8). A number of aspects involving the reaction efficiency and the excited state rates are of special interest, but discussion is deferred for consideration of the quantitative aspects of the photochemistry of all the systems under study. For the moment it is sufficient to note that in contrast to most examples of the di-π-methane rearrangement not only the singlet but also the triplet reacts with facility. In the closely related example of 1,1,5,5-tetraphenyl-3,3-dimethyl-1,4-pentadiene (**20**)[8b] the triplet was found to rearrange only with extreme reluctance.[8b]

Inspection of the mechanism in eqn (8) reveals that ring opening of the cyclopropyldicarbinyl diradical **21*** leads to an especially stabilized triplet 1,3-diradical **22**. The success of the di-π-methane rearrangement of the triplet presently discussed may derive from the ring opening process competing more successfully with intersystem crossing to ground state cyclopropyldicarbinyl diradical **21**. It has been our general observation[5,15,22,23] that ground state cyclopropyldicarbinyl diradicals tend to undergo 1,4-diradical-2,3-fragmentation. Hence, intersystem crossing to ground state leads back to di-π-methane reactant, and the more rapid three-ring opening thus prevents reversion to reactant. Interestingly, central cyano substitution[2b] and also central phenyl substitution[2b,24] afforded di-π-methane systems with reactive triplets. Hence the evidence is accumulating that it is the increased rate of three-ring opening resulting from stabilization of the triplet 1,3-diradicals which is the common feature in all of these cases.

Consideration of the reaction pathways of the 1,1-*dicarbomethoxy diene* **11**

Interpretative discussion. The most striking observation in the photochemistry of the 1,1-dicarbomethoxy diene **11** is the different regiochemistry observed in the direct and the sensitized runs, this reflecting the different reactivity of the singlet and the triplet excited states of the diene (i.e. **11**). The overall mechanisms involved are outlined in Scheme 3. It is again seen that the triplet is reactive, here as a result of the central phenyl substitution. This has precedent.[22] In Scheme 3 the partition between the singlet and triplet pathways begins with three-ring opening of the cyclopropyldicarbinyl diradical species.





Scheme 3. Overall reaction mechanisms of the 1,1-dicarbomethoxy diene **11**

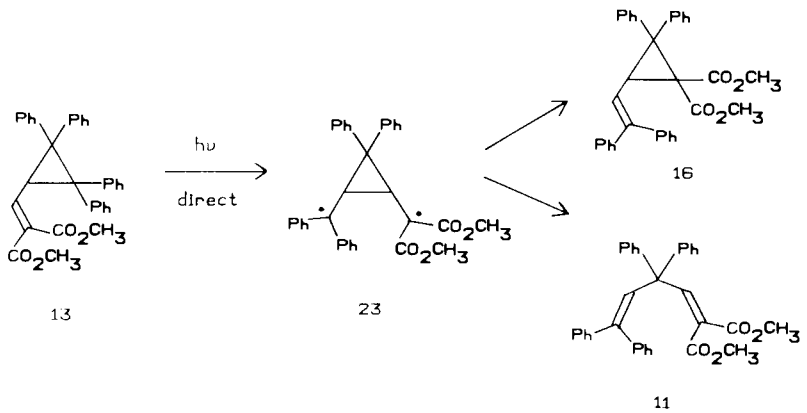
This multiplicity dependence on the regioselectivity[11] of the di-π-methane rearrangement also has precedent. To begin with, the reaction of the excited singlets of dienes bearing electron withdrawing moieties at one end of the di-π-methane system tends to prefer formation of that regioisomer having the electron withdrawing group on the product cyclopropyl ring rather than on the double bond.[16b,17,18,25] Conversely, electron donors tend to appear on the product vinyl group.[17,18,26] This generalization has been noted by us previously.[17,27]

Furthermore, in two instances the triplet excited states of di-π-methane type dienes bearing cyano[2b] or carbomethoxy[28] terminal substituents have been observed to give regioselectivity which is unusual in that the electron withdrawing moiety is found on the product double bond rather than the three-ring. Additionally, in both the cyano and carbomethoxy examples[2b,28] direct irradiation was observed to give partially reversed regioselectivity in which the product with the electron withdrawing cyano or carbomethoxy group on the three ring constituted approximately half of the di-π-methane product. That the above generalization regarding the regioselectivity of singlets does not apply exactly to the direct irradiations may derive[2b] from intersystem crossing in part in these cases.

It is seen that the presently investigated example of 1,1-dicarbomethoxy diene **11** exhibits a very pretty and unambiguous dependence of its regioselectivity on the reaction multiplicity. The source of this phenomenon has been considered in our earlier studies[2b] and is analyzed in detail below in the theoretical section.

General mechanisms in the photochemistry of dicarbomethoxyvinyl cyclopropane **13**

Interpretative discussion. The intriguing bicycling rearrangement and reverse di-π-methane reaction observed for the singlet of the 1,1-dicarbomethoxyvinyl cyclopropane **13** are qualitatively understood in terms of the mechanisms outlined in Scheme 4. The two processes can be seen to be related



Scheme 4. Overall mechanism of the photochemistry of dicarbomethoxy cyclopropane **13**.

Table 2.

Compd	Central Substitution	σ	Φ	k_r^{RT}, s^{-1}	k_r^{RT}/k_o [a]	$\log k_r^{RT}/k_o$
26	CN	0.66	0.11	0.92×10^9	8.42×10^{-2}	-1.08
9	CO_2CH_3	0.39	0.42	1.1×10^{10}	1.00	0.00
20	CH_3	-0.17	0.080	1.4×10^{11}	12.7	1.10

[a] $k_0 = k_r^{RT}$ for cmpd 9.

Table 3. Rates and efficiencies for terminally substituted dienes

Compd	Temp, K	M	$^1k_{d(tot)}, s^{-1}$	Φ	k_r, s^{-1}	k_d, s^{-1} [c]
1,1-Dimethyl-diene 25[a]	293 77	216	1.13×10^{11} 5.3×10^8	0.076	8.5×10^9	1.05×10^{11} (ref 24)
1,1-Dicyano-diene 6[b]	293 77	247	1.11×10^{12} 4.49×10^9	0.044	4.93×10^{10}	1.06×10^{12} (ref 2b)
1,1-Dicarbo-methoxy diene 11	293 77	197	6.01×10^{11} 3.05×10^9	0.39	2.34×10^{11}	3.67×10^{11} (this study)

[a] Data from ref 24. [b] Data from ref 2b. [c] $k_d = k_{d(tot)} - k_r - k_f$.

with the first bicycling step leading to the common cyclopropyldicarbinyl diradical structure **23**. The diphenylvinyl cyclopropane product **16** arises from a second bicycling step while the 1,1-dicarbomethoxy diene **11** derives from a 1,4-diradical-2,3-fragmentation.[29] One aspect worthy of comment is that species **23** is a general one which, in principle, might represent any of several electronic states of this cyclopropyldicarbinyl diradical—S_0, S_1 or T_1. As noted before S_0 is the configuration which most commonly undergoes the 1,4-diradical-2,3-fragmentation while the continued bicycling of **23** is more characteristic of S_1.[5,15,22,23]

Excited state rates of reaction and quantum efficiencies

Interpretative Discussion. One of the most interesting features of the rate data derives from comparison of the rates at which the singlets of 3,3-disubstituted-1,1,5,5-tetraphenyl dienes rearrange as a function of central substitution. Referring to Table 2 we note that the fastest rearranging system has central methyl substitution (i.e. diene **20**[8b,15]). The centrally cyano-substituted diene has a slower reacting singlet.[2b] The presently investigated 3,3-dicarbomethoxy diene **9** is intermediate in reactivity. An interesting correlation between the log of these unimolecular rate constants and the Hammett sigma values[31] was found and is illustrated in Fig. 1.

We note with interest that this linear relationship is between ground state (i.e. Hammett) constants and excited state rates.

This suggests that the portion of the molecule bearing the cyano, carbomethoxy or methyl group must be unexcited both in the vertical excited state reactant (i.e. reactant S_1) and also at the rate limiting stage along the excited state hypersurface. This point is

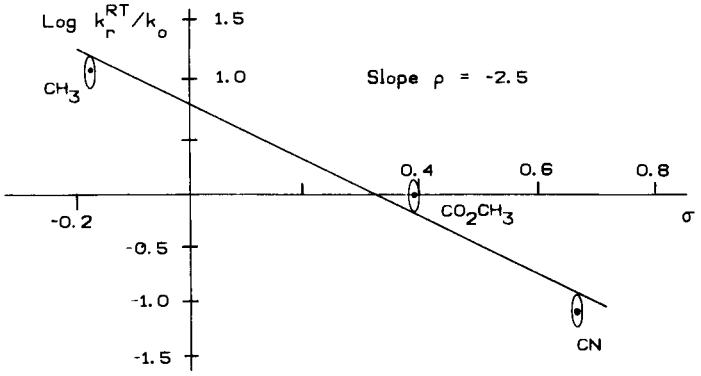


Fig. 1. Plot of $\log(k_r/k_o)$ versus the Hammett sigma constants. Here k_o is the rate for carbomethoxy substitution. Correlation coefficient, 0.98.

considered below in connection with our delta-P partition of excited state energies.

It is interesting to compare the S_1 rate for the 1,1-dicarbomethoxy diene **11** with that for the corresponding analog **25**[15,24] in which the carbomethoxy groups are replaced by methyls. The rate for the dicarbomethoxy diene **11** is 2.3×10^{11} while that for the dimethyl analog **25** is $8.5 \times 10^{9}\,\text{sec}^{-1}$. The dicyano diene **6** also has a high S_1 rate but smaller than that of the presently studied dicarbomethoxy diene (i.e. **11**). These comparisons are seen by reference to Table III.

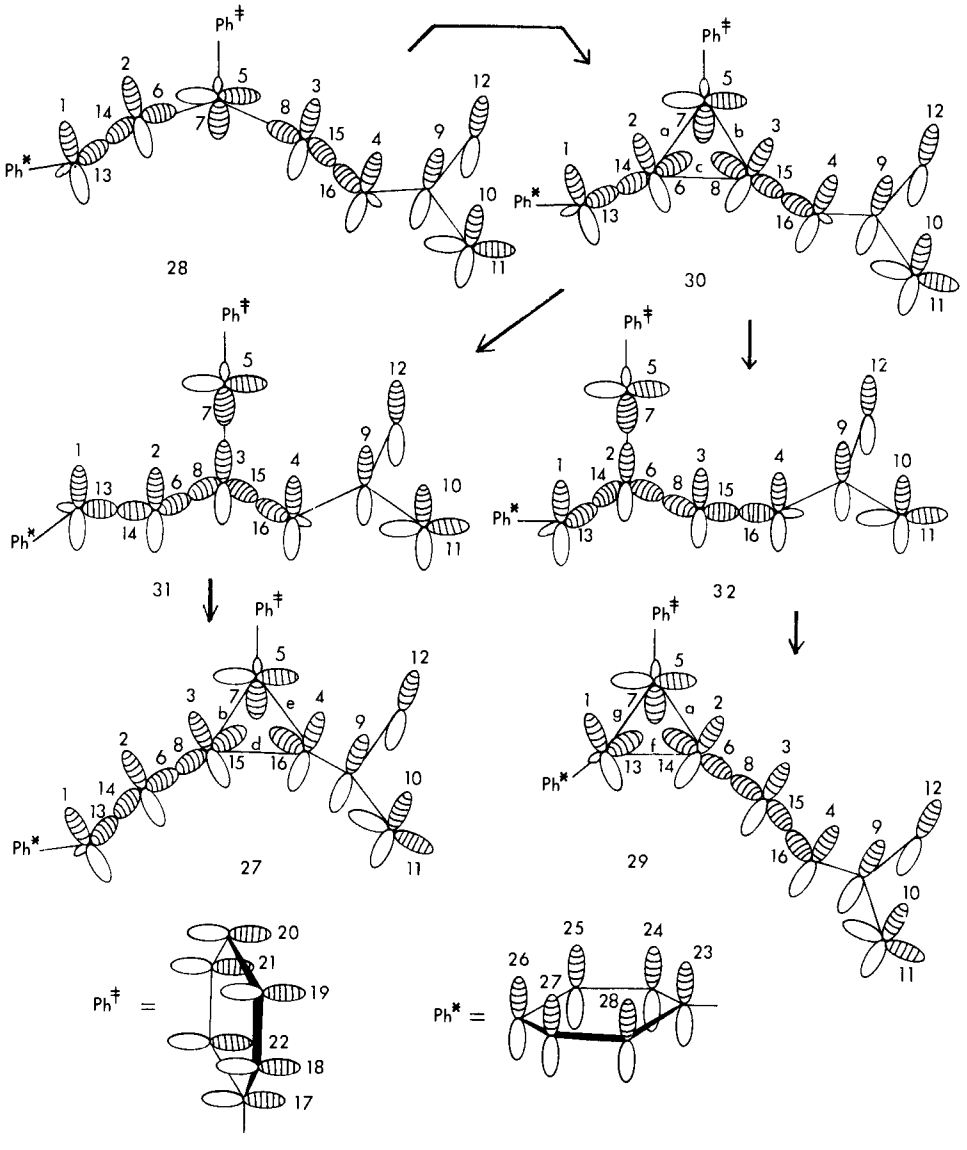
A summary of the situation is that the dicarbomethoxy diene has both a faster k_r and k_d, but the enhancement in k_r is greater than that in k_d with the result of a very high quantum efficiency for the dicarbomethoxy diene **11**.

Theoretical considerations

Calculations. SCF and SCF-CI calculations were carried out on a truncated set of basis orbitals. The orbitals selected were those involved in electronic excitation as chromophores and also those orbitals involved in bonding changes along the reaction coordinate for the di-π-methane and bicycle processes. Where carbomethoxy substituents were present, one of these was introduced rather than two. Phenyl substitution was similarly provided by one phenyl group at each site bearing two. For interest's sake, the calculations were also carried out without phenyl substitution. The reactions of interest, with basis orbitals defined, are outlined in Scheme 5. Details are given in the Section on calculations.

Correlation diagrams and hypersurfaces

Interpretative discussion. SCF calculations were used to construct MO correlation diagrams for the di-π-methane and bicycle rearrangements. Inspection of Schemes 3 and 4 reveals that the 1,1-dicarbomethoxy diene **11**, the diphenylvinyl cyclopropane **16**, and the dicarbomethoxyvinyl cyclopropane **13** are interconverted via the common structure, the



Scheme 5. Reactions with basis orbitals defined

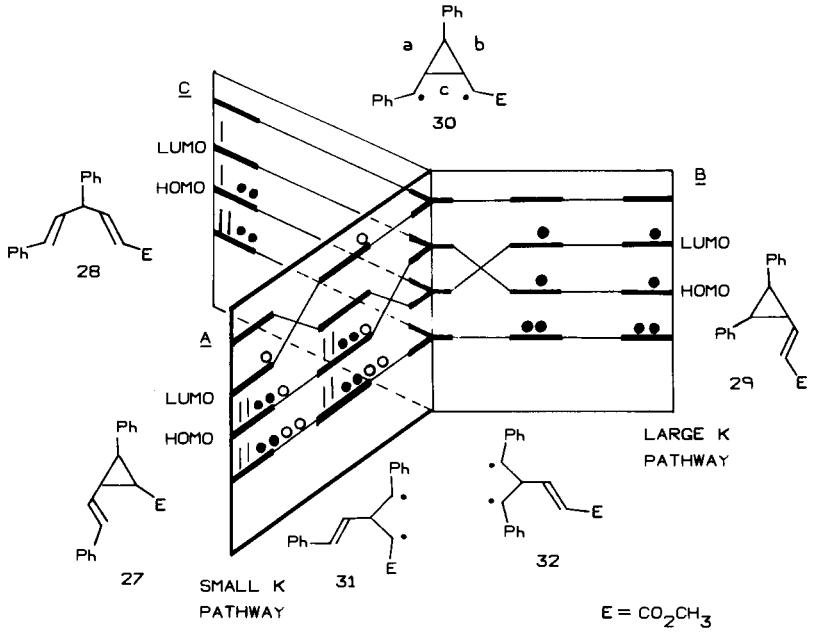


Fig. 2(a). SCF Correlation diagram for di-π-methane rearrangement of the 1-carbomethoxy diene and for bicycling (phenyl groups included). ○ Electron configuration in reactions from bridge A, ● from bridge B, from bridge C.

cyclopropyldicarbinyl diradical **23**, although different electronic configurations of **23** seem involved in the different reactions. With three compounds and one interposed structure, we turned to the triptych representation for the correlation diagrams as used in our earlier study on the cyano substituted systems.[2b] This is shown in Figs. 2(a) and 2(b).

The two correlation diagrams are similar in many respects but do differ as a result of phenyl substitution (in the case of Fig. 2a) being introduced. Thus, the HOMO-LUMO crossings in bridges *A* and *B* are found for both phenylated and non-phenyl substituted systems. Additionally, there is a LUMO-LUMO + 1 crossing in bridge *A* of both triptych's. However, phenyl substitution removes the LUMO-LUMO + 1 crossing in bridge *B*.

We now need to refer individually to the three excited states, each one corresponding to one excited reactant of interest. If we focus attention on the excited state in bridge *A* it is seen that this quickly leads to an upper, and very high energy, configuration. This corresponds to a bicycle process which does not occur.

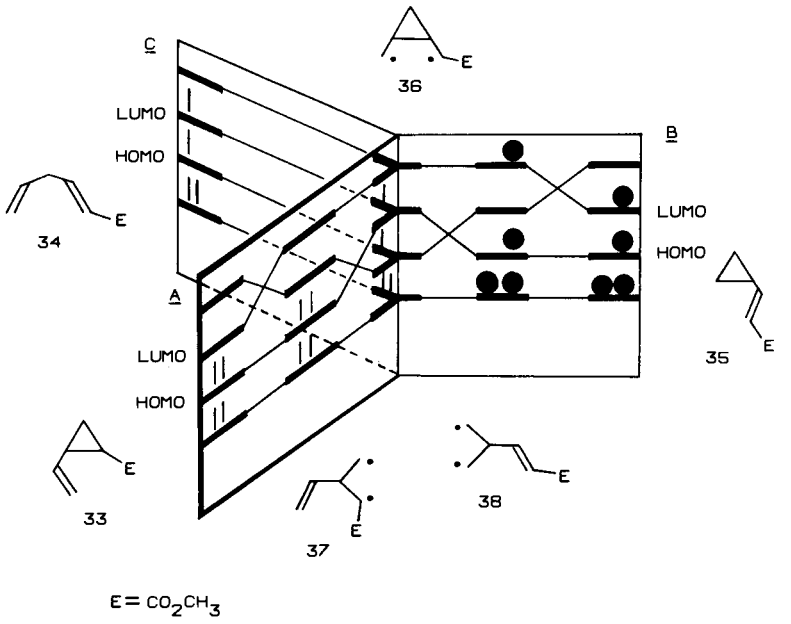


Fig. 2(b). SCF correlation diagram without phenyl groups.

Turning now to the di-π-methane reactant **28** in bridge *C*, we find that the cyclopropyldicarbinyl diradical **30** is formed in its excited state (note the triptych central axis approached from *C*) and that crossing points,[32] or bifunnels,[5,33] affording a possible leakage to ground state products are found in each of bridges *A* and *B*. Indeed, both vinylcyclopropanes **27** and **29** are found experimentally as products, one (i.e. **27**) from the singlet and the other (i.e. **29**) from the triplet.

Lastly in connection with the correlation diagrams, we consider the carbomethoxyvinyl cyclopropane reactant in bridge *B*. Here, Figure 2a reveals the excited state configuration shown arrives at the central triptych axis after passing a HOMO-LUMO crossing point (i.e. a bifunnel) and thus the cyclopropyldicarbinyl diradical is likely to be partitioned between ground and excited state configurations. The excited state configuration of diradical **30** is forced, by the usual disinclination for formation of upper configurations, to proceed into bridge *A*. The ground state configuration of the diradical is forced to proceed into bridge *C*. Experimentally, starting with the carbomethoxyvinyl cyclopropane both bicycling and reverse di-π-methane rearrangements are observed (*vide supra*).

Interestingly, without phenyl substitution, the LUMO-LUMO + 1 crossing in bridge *B* would be expected to inhibit both bicycling and reverse di-π-methane rearrangements. This, too, accords with fact, since with diminished phenyl substitution (i.e. no benzylic-benzylic bond remote from the vinyl group), di-π-methane products do not exhibit a reverse reaction.[9,8b,18] All the examples which do show this reactivity have PhC-CPh substitution on the three ring remote from the vinyl group.

SCF-CI calculations were also carried out. While the advantage of the SCF one-electron calculations is that these show MO correlations and thus intended state crossings, the CI allows us to determine where crossings are avoided. These SCF-CI calculations are depicted in a triptych representation in Fig. 3. The reaction coordinates are the same as for the SCF diagrams in Figs. 2(a) and 2(b).

One important result is that at each HOMO-LUMO crossing point of the SCF treatment (note Fig. 2a) there is a corresponding approach of S_0 and S_1, that is, a bifunnel.[5,32,33]

Furthermore, perusal of the CI-triptych in Fig. 3 provides an interesting understanding of the experimentally observed photochemistry. Thus, starting with the di-π-methane reactant (note bridge *C* of the triptych) and the S_1 vertical excited state of **28** we find a hypersurface leading to the cyclopropylidicarbinyl diradical **30**, at the central triptych axis, in its S_1 (i.e. singly excited) state. This species can be seen to select bridge *A* over bridge *B* since the bridge *A* S_1 hypersurface leads downward in energy to a bifunnel whereas the bridge *B* surface has a maximum interposed between the central axis and a less efficient (more widely spaced S_0–S_1 gap) bifunnel. The bifunnel in bridge *A* leads to the observed singlet di-π-methane product, the regioisomer bearing a carbomethoxy group on the three-ring (note **27** in bridge *A*).

The reactivity of the carbomethoxyvinyl cyclopropane **29**, represented in bridge *B*, can be accounted for in either of two ways; and both may be operative. A bifunnel is encountered in bridge *B* before reaching the central axis and the cyclopropyldicarbinyl diradical. Either total or partial funneling to ground state occurs here. If total conversion to S_0 occurs here, then the ground state diradical just partitions itself between the reverse di-π-methane process leading to bridge *C* and the bicycling process requiring surmounting a small (<0.4 eV) S_0 barrier leading to bridge *A*.

Alternatively, if internal conversion in the bridge *B*

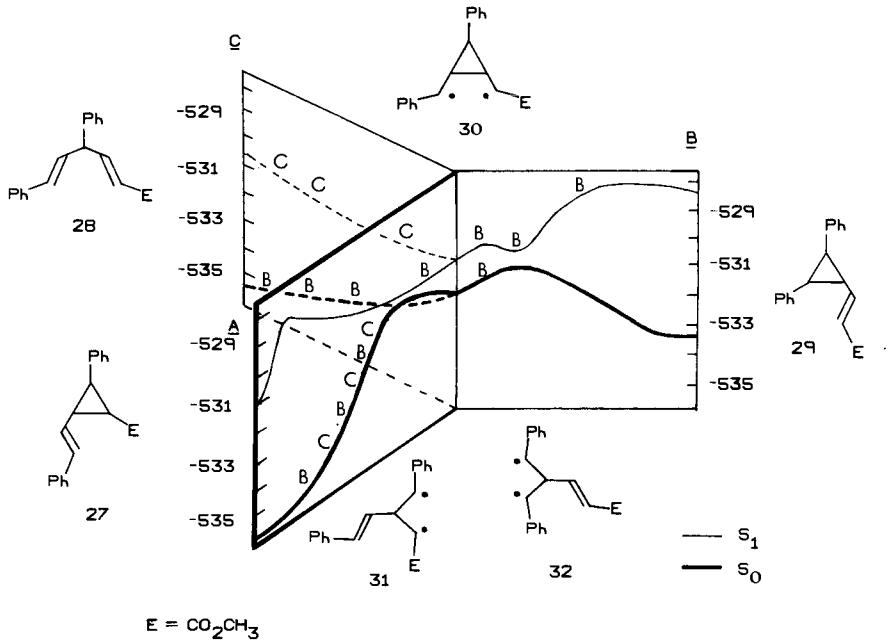


Fig. 3. SCF-CI reaction hypersurfaces.

bifunnel is not totally efficient, then the cyclopropyl-dicarbinyl diradical at the central axis is formed in two states, S_1 and S_0. S_0 can proceed into bridge *C* without encountering a barrier and this affords reverse di-π-methane product **28**. S_1 diradical, following the downward curvature of the excited surface, arrives at the efficient bifunnel in bridge *A* and internal coversion to S_0 leads to phenylvinyl cyclopropane **27** in an overall bicycling process.

Lastly, reaction of the phenylvinyl cyclopropane involves formation of an S_1 state (note bridge *A*) confronted with a large energy barrier. No reaction is encountered experimentally.

The nature of bifunnels

Interpretative discussion. The role of HOMO-LUMO crossings in enhancing conversion of excited state reactant to ground state product was suggested in 1966.[8a,32a,34] Since that time the point has received considerable attention.[2b,5,33,35,36] One interesting point has been made by Oosterhoff[35] who pointed out that the S_0–S_2 approach (a bifunnel) is perhaps adventitiously intersected by S_1 which is the surface actually involved in the photochemistry. Thus the application of the Woodward–Hoffmann[37] and the Zimmerman Möbius–Hückel[32,34] concepts to photochemistry seems to derive from this apparently accidental crossing of S_1 and S_2. Similar findings derive from the work by Devaquet.[36]

However, the purity of S_0 and S_2, relative to S_1 weighting, derives from S_1 having different symmetry in the model systems (e.g. cyclobutene–butadiene) studied.[38] Inspection of the CI wavefunctions throughout the regions of the two bifunnels in the present study (of Fig. 3) reveals that the lower state in each bifunnel, having an energy maximum is weighted most heavily in S_0 but contains contributions from both S_1 and S_2 configurations. The first excited state (i.e. the bifunnel upper surface) is weighted most heavily in the S_1 (i.e. HUMO-LUMO) configuration and also quite heavily in S_0 and S_2 configurations. The weighting of S_2 and S_0 in the first excited state diminishes as one proceeds away from the bifunnel.

The very heavy inclusion of S_1 in the upper portion of a bifunnel thus comes from its ability to admix with S_2 which, in turn, admixes with S_0. The absence of S_1 in completely symmetrical cases is artificial since it is not likely that a symmetrical geometry will correspond to the optimum energy pathway.

Interestingly, the admixture of these configurations can be understood as analogous to the admixture of three contiguous atomic orbitals of unequal energy in an "allyl-like" array except that here the matrix elements are positive MO repulsion integrals and nodal characteristics should approximate an "energetically inverted allyl" species. To the extent that upper configurations are included and important, the pattern expected for the inverted allyl-like species will be affected. For a pure "inverted allyl" species $\mathbf{S_0}$ would be weighted as $S_0 - S_2 + S_1$. Here the italicized symbols are configurations prior to configuration interaction and the boldfaced symbols are final state functions resulting from CI. The $\mathbf{S_1}$ state should contain $S_0 + S_2 - S_1$. Also the ground state should have S_0 and S_2 weighted with opposite signs while $\mathbf{S_1}$ and $\mathbf{S_2}$ should have S_0 and S_2 weighted with the same sign. This last expectation is found throughout while the "allyl-like" pattern is found to be approximated in the actual calculations and of help in understanding the CI wavefunctions; deviations from the pattern seem to come from admixture of higher energy configurations.

While upper configurations are found to be admixed to some extent, the preceding analysis focuses attention on just three configurations of particular interest and most involved.

The important conclusion, however is that the first excited singlet does lead directly to the upper surface of the photochemical bifunnel.

Exchange integral control of regioselectivity and reactivity

Interpretative discussion. Previously[2b] we have noted that where there is a marked difference in singlet–triplet splitting for the surfaces corresponding to two reaction pathways available to an excited state, the reaction pathway with the smaller singlet–triplet splitting will be preferred by the singlet while the pathway with the larger singlet–triplet splitting will be preferred by the triplet. This assumes that there are not extraneous factors (e.g. steric, energy dissipation mechanisms) to favor one reaction pathway or inhibit another. Note Fig. 4.

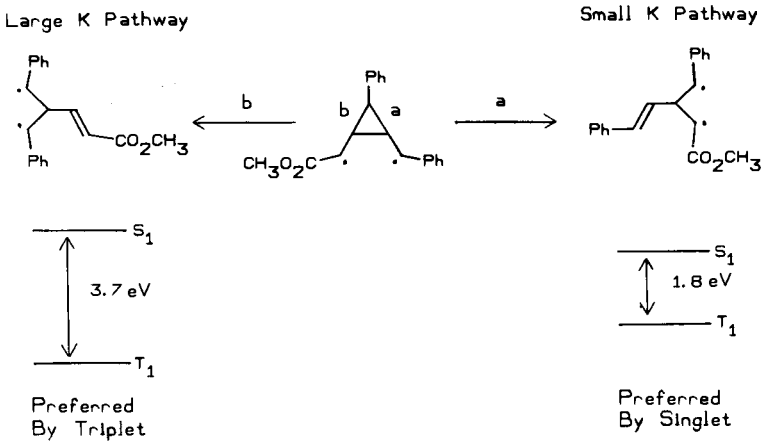


Fig. 4. Exchange integral control of regioselectivity.

For a single (singly excited) configuration the singlet–triplet splitting is given by 2K (e.g. with K being the exchange integral between HOMO and LUMO). Where an electronegative group, or other group polarizing the system, is placed on one of two diradicaloid centers, one can expect a small exchange integral. This results since the atomic orbitals weighted heavily in HOMO are not in LUMO and vice versa. More details have been discussed earlier.[2b] Thus, having carbomethoxy groups on a diradical center of the 1,3-diradical, resulting from di-π-methane three-ring opening, lowers the value of the exchange integral K and leads to a preference for pathway by the singlet. Without carbomethoxy substitution on a diradicaloid center, a larger K results and this pathway is the one preferred by the triplet. This is schematically shown in Fig. 4 using CI energies as an approximation.

Thus, had complete surfaces been determined for the triplet species in analogy to the triptych representation for the singlets, one would expect a lower barrier in bridge *B* compared with bridge *A* in contrast to the singlet situation.

Delta-P determination of excitation energy distribution

Interpretative discussion. A useful technique in considering photochemical reactivity is determination of delta-P and delta-E matrices.[3,5,17,18,27,39] The delta-P matrix has at its elements the difference in corresponding bond orders and electron densities in proceeding from the ground to the excited state of interest. In those portions of the molecule, where the differences are near zero, there is no appreciable electronic excitation. In other portions where there is a large difference, the molecule has been excited. A negative change means that the given site has become more antibonding while a positive change corresponds to increased bonding. This provides a simple way of comparing ground and excited state wavefunctions. The delta-E matrix is the counterpart in which local bond orders have been converted to local energy contributions. This has an advantage where hybrid orbitals are included since changes in overlap populations between s-weighted orbitals have a larger energetic effect than changes involving just p-orbitals.

Table 4 lists some delta-P and delta-E values of particular interest for the vertical excited state, for the cyclopropyldicarbinyl diradical, and for the two vinylcyclopropane products.

As expected, the excitation energy of the di-π-methane reactant is seen to be localized very heavily in the styryl moiety and much less so in the carbomethoxyvinyl group. The C-3 phenyl group is seen to be devoid of excitation. These conclusions are apparent in both the delta-P and the delta-E versions.

In looking at the cyclopropyldicarbinyl diradical species we find that the large delta-P and delta-E

Table 4. Use of delta-P and delta-E to identify sites of electronic excitation

Orbitals	1,4-Diradical 30		Orbitals	Vinylcyclopropane 27		Orbitals	Vinylcyclopropane 29	
r,t	ΔP_{rt}	ΔE_{rt},ev	r,t	ΔP_{rt}	ΔE_{rt},ev	r,t	ΔP_{rt}	ΔE_{rt},ev
2,5	-0.0779	0.4659	4,5	-0.0512	0.3583	1,5	-0.0814	0.5766
6,7	-0.0102	0.1944	4,7	-0.0054	0.0308	1,7	-0.0070	0.0396
5,6	-0.0769	0.3636	5,16	-0.0133	0.0759	5,13	-0.0081	0.0459
2,7	0.0206	-0.0860	7,16	0.0053	-0.1009	7,13	0.0016	-0.0305
Bond a		0.9379	Bond e		0.3641	Bond g		0.6316
3,5	-0.0119	0.0731	3,4	-0.0806	0.5685	1,2	-0.0612	0.4315
7,8	-0.0014	0.0271	3,16	-0.0087	0.0494	1,14	-0.0157	0.0892
5,8	-0.0499	0.2318	15,16	0.0008	0.0152	2,13	-0.0181	0.1026
3,7	0.0238	-0.0994	4,15	-0.0043	0.0243	13,14	0.0039	-0.0742
Bond b		0.2326	Bond d		0.6574	Bond f		0.5491
2,3	0.0732	-0.4333	3,5	-0.0832	0.5925	2,5	-0.0584	0.4110
3,6	-0.0413	0.1934	7,15	-0.0019	0.0362	2,7	-0.0191	0.1084
6,8	0.0189	-0.3605	3,7	-0.0096	0.0542	5,14	-0.0180	0.1024
2,8	-0.0147	0.0555	5,15	-0.0050	0.0782	7,14	0.0036	-0.0685
Bond c		-0.5449	Bond b		0.7611	Bond a		0.5533
1,2	-0.1868	1.345						
1,23	0.0588	-0.3759						
23,24	-0.0295	0.2219						
24,25	-0.0047	0.0371						
25,26	-0.0020	0.0154						
Carbinyl Phenyl		0.1729						
3,4	-0.1457	1.0199						
5,17	0.0569	-0.3366						
17,18	-0.0283	0.2175						
18,19	0.0112	-0.0875						
19,20	-0.0163	0.1269						
Cyclopropyl Phenyl		0.1772						

[a]All phenyl bonds are included in the total ΔE.

Orbitals	Di-π-methane Diene 28	
r,t	ΔP_{rt}	ΔE_{rt},ev
1,2	-0.1999	1.833
1,23	0.1017	-0.06053
23,24	-0.0398	0.3025
24,25	0.0031	-0.0244
25,26	-0.1356	1.0348
Styryl[a]		2.5406
3,4	0.0003	-0.6053
4,9	0.0020	-0.0116
9,10	-0.0012	0.0109
9,12	-0.0011	0.0105
Carbomethoxy Vinyl		0.0070
5,17	0.0000	0.0000
17,18	0.0000	0.0000
18,19	0.0000	0.0000
19,20	0.0000	0.0000
Central Phenyl[a]		0.0000

values are largely in the cyclopropyldicarbinyl moiety itself with comparable values only in the C-1 and ortho locations of the phenyl substituent on the carbinyl carbon. This migration of energy of excitation from the vertically excited chromophore into the cyclopropyldicarbinyl diradical moiety has been noted before[23,39] and seems to be general in the di-π-methane rearrangement.

The same treatment applied to the bicycle rearrangement requires the delta-P and delta-E values for the vinylcyclopropanes (note Table 4 again). The reactive vinylcyclopropane (i.e. the carbomethoxyvinylcyclopropane **29**) is the one having a benzylic–benzylic three-ring bond g. This isomer has its excitation energy heavily weighted in this three-ring sigma bond remote from the vinyl group, and it is this remote sigma bond which opens in the bicycling process. In contrast for the unreactive vinylcyclopropane **27** the bond e which needs to break is considerably less energy rich than the other two bonds b and d. Reversible opening at these bonds affords a mechanism for energy dissipation and does not lead to bicycling (note Scheme 5 for labeling).

Finally, the delta-P treatment leads to an understanding of why ground state sigma constants correlate well with the log of the S_1 rates for centrally substituted di-π-methane systems. We note that a central phenyl group (Table 4) has much lower delta-E values than found in the three ring (here delta-P's are less helpful). This is true both for the vertical excited state and for the cyclopropyl–dicarbinyl diradical whose formation is thought to be rate limiting. To the extent that this is general for the groups presently under discussion—CN, Me, COOMe—one is indeed dealing with ground state moieties and ground state sigma constants are applicable.

Conclusion

The bicycle rearrangement is seen to be a reaction of ever increasing generality and intimately tied to the di-π-methane rearrangement in mechanism. Regioselectivity dependence on multiplicity is a phenomenon which also requires more attention in the future.

EXPERIMENTAL[40]

3-Carbomethoxy-1,1,5,5-tetraphenyl-1,4-pentadiene. A soln of 5.04 g (13.6 mmol) of 1,1,5,5-tetraphenyl-1,4-pentadiene[41] in 100 ml anhyd THF was cooled to 0° and 9.03 mL (13.6 mmol 1.5 M hexane soln) of n-BuLi was added dropwise. The soln was stirred 25 min and transferred under N_2 via canula to a stirred soln of 3.12 mL (40.3 mmol) methyl chloroformate in 100 mL THF. After the addition, the mixture was stirred for 30 min, poured into 500 mL sat NH_4Cl aq and ether extracted. The extracts were washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo* to give 4.79 g (82.9%) of 3-carbomethoxy-1,1,5,5-tetraphenyl-1,4-pentadiene, m.p. 163–165°. Recrystallization from CH_2Cl_2 and hexane yielded 4.57 g (79%) of the 3-carbomethoxy diene, m.p. 164–165°.

The spectral data were: NMR ($CDCl_3$) δ 7.4–6.8 (m, 20 H, arom), 6.16 (d, 2 H, J = 10 Hz, vinyl), 4.21 (t, 1 H, J = 10 Hz, methine), 3.68 (s, 3 H, $CO_2\underline{CH_3}$); IR (KBr) 3086, 3058, 3021, 2959, 1733, (s, C = 0) cm^{-1}; MS *m/e* 430.19329 (Calc. for $C_{31}H_{26}O_2$, *m/e* 430.19199). (Found: C, 86.44; H, 6.26 Calc. for $C_{31}H_{26}O_2$: C, 86.48; H, 6.09%).

3,3-Dicarbomethoxy-1,1,5,5-tetraphenyl-1,4-pentadiene. Sodium hydride (0.576 g, 0.012 mmol, 50% in mineral oil) was washed free of mineral oil with hexane. A soln of 4.30 g (0.010 mmol) of 3-carbomethoxy-1,1,5,5-tetraphenyl-1,4-pentadiene in 60 mL anhyd THF was added to the sodium hydride under N_2 and the mixture was refluxed for 12 hr. The mixture was allowed to cool to room temp and 1.55 mL (0.020 mmol) methyl chloroformate was added. The mixture was refluxed for 25 min, cooled, poured into sat NH_4Cl aq and extracted with CH_2Cl_2. The organic extracts were washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The yellow solid obtained was recrystallized from CH_2Cl_2 and hexane to yield 2.98 g (61.1%) of 3,3-dicarbomethoxy-1,1,5,5-tetraphenyl-1,4-pentadiene, m.p. 139–140°.

The spectral data were: NMR ($CDCl_3$) δ 7.4–6.96 (m, 20 H, arom), 6.63 (s, 2 H, vinyl), 3.39 (s, 6 H, CO_2CH_3); IR (KBr) 3086, 3058, 3030, 2994, 2950, 2841, 1736 (s, C=O); UV (Et_2O) λ_{max} 257.5 nm (ε 24.300), 295 (ε 3310): MS *m/e* 488.19949 (Calc. for $C_{33}H_{28}O_4$, *m/e* 488.19876). (Found: C, 81.31; H, 5.61. Calc. for $C_{33}H_{28}O_4$: C, 81.13; H, 5.78%).

1,1-Dicarbomethoxy-3,3,5,5-tetraphenyl-1,4-pentadiene. The titanium tetrachloride method described by Lehnert[42] was applied. To a soln of 100 mL dry THF at 0° under N_2 was added 5.70 mL (51.9 mmol) titanium tetrachloride in 13 mL CCl_4. To this mixture was added 1.50 mL (13.1 mmol) dimethyl malonate and 5.02 g (13.4 mmol) 2,2,4,4-tetraphenyl-3-butenal.[24] The mixture was allowed to stir at 0° for 20 min followed by addition of 8.30 ml (103 mmol) dry pyridine in 17.0 mL THF. The soln was allowed to warm to room temp and stirred under N_2 an additional 24 hr, diluted with 30 mL water and poured into 100 mL ether. The aqueous layer was ether extracted and the combined extracts washed with water, $NaHCO_3$, brine, dried and concentrated *in vacuo* leaving 6.27 g of a yellow oil. Chromatography on a 2.5 × 95 cm silica gel column slurry packed in 2% ether in hexane with elution in 250 mL fractions gave: fractions 1–5, 2% ether in hexane, nil; 6–7, 4% ether in hexane, 696 mg dimethyl malonate; 8, a mixture of 131 mg of dimethyl malonate and 326 mg (4.98%) 1,1-dicarbomethoxy-3,3,5,5-tetraphenyl-1,4-pentadiene, 9–10, 3.15 g (49.1%) 1,1-dicarbomethoxy-3,3,5,5-tetraphenyl-1,4-pentadiene, m.p. 122–124°. Recrystallization from EtOH gave 2.87 g (43.8%) colorless crystals, m.p. 123–125°.

The spectral data were: NMR ($CDCl_3$) δ 7.62 (s, 1 H, $-C\underline{H}=C(COOCH_3)_2$, 7.40–6.80 (m, 21 H, arom and $Ph_2C=C\underline{H}-$) 3.67 (s, 3 H, $-CO_2\underline{CH_3}$), 3.16 (s, 3 H, $-CO_2\underline{CH_3}$); IR ($CHCl_3$) 3060, 3020, 2955, 1725 (s, C=O), 1630, 1598, 1492, 1445, 1438, 1372, 1252, 1215, 1070, 1030, 1025, 1002, 985, 700 cm^{-1}; UV (EtOH) λ_{max} 250 nm (ε 19,866); MS *m/e* 488.1986 (Calc. for $C_{33}H_{28}O_4$, *m/e* 488.1988. (Found: C, 81.29; H, 5.90. Calc. for $C_{33}H_{28}O_4$: C, 81.13; H, 5.78%).

1,1,2,2-Tetraphenyl-3-(2,2-dicarbomethoxyvinyl) cyclopropane. Using the titanium tetrachloride procedure described above,[42] a mixture of 10 mL THF, 0.570 mL (5.19 mmol) titanium tetrachloride in 1.30 mL CCl_4, 0.150 mL (1.31 mmol) dimethyl malonate, 500 mg (1.34 mmol) 2,2,3,3-tetraphenylcyclopropane-1-carboxaldehyde[2b] and 0.830 mL (10.3 mmol) pyridine in 1.70 ml THF was reacted for 24 hr to yield 636 mg yellow oil. Chromatography on a 2.5 × 30 cm silica gel column slurry packed in 2% ether in hexane with elution in 100 mL fractions gave: fractions 1–5, 2% ether in hexane, nil; 6–8, 3% ether in hexane, 45.0 mg dimethyl malonate; 9, nil; 10–11, 0.431 g (65.9%) 1,1,2,2-tetraphenyl-3-(2,2-dicarbomethoxyvinyl) cyclopropane, m.p. 216–218°. Recrystallization from EtOH gave 409 mg (62.5%) of colorless crystals, m.p. 217–218°.

The spectral data were: NMR ($CDCl_3$) δ 7.60–6.84 (m, 21 H, arom and vinyl), 4.01 (s, 3 H, $-CO_2\underline{CH_3}$), 3.95 (d, 1 H, J = 6 Hz, cyclopropyl), 3.71 (s, 3 H, $-CO_2\underline{CH_3}$); IR ($CHCl_3$) 3055, 3020, 2950, 1720 (s, C=O), 1622, 1595, 1490, 1442, 1435, 1350, 1258, 1230, 1152, 1100, 1065, 1030, 985, 700 cm^{-1}; UV (EtOH) λ_{max} 223 nm (ε 20,333), 250 (ε 10,167); MS *m/e* 488.1963 (Calc. for $C_{33}H_{28}O_4$, *m/e* 488.1988). (Found: C, 81.29; H, 5.90). Calc. for $C_{33}H_{28}O_4$: C, 81.13; H, 5.78%).

1,1-Dicarbomethoxy-4,4-diphenyl-1,3-butadiene. To a soln of 1.49 g (7.16 mmol) 3,3-diphenylacrolein[43] in 15 mL dioxane was added 1.08 mL (9.45 mmol) dimethyl malonate

and 0.85 mL (8.59 mmol) piperidine. The mixture was stirred under N_2 for 24 hr, poured into 100 mL water and ether extracted. The extract was washed with 10% HCl, $NaHCO_3$, brine, dried and concentrated *in vacuo*. The solid residue obtained (2.21 g) was recrystallized from 95% EtOH, yielding 1.20 g (52.0%) 1,1-dicarbomethoxy-4,4-diphenyl-1,3-butadiene, m.p. 85–85.5°.

The spectral data were: NMR ($CDCl_3$) δ 7.57–7.03 (m, 12 h, arom and vinyls), 3.82 (s, 3 H, $-CO_2\underline{CH_3}$), 3.69 (s, 3 H, $-CO_2\underline{CH_3}$); IR ($CHCl_3$) 3010, 2945, 1715, 1605, 1590, 1445, 1435, 1375, 1345, 1270, 1250, 1190, 1175, 1145, 1070, 700 cm^{-1}; MS *m/e* 322.1210 (Calc. for $C_{20}H_{18}O_4$, *m/e* 322.1205). (Found: C, 80.91; H, 5.79. Calc. for $C_{33}H_{28}O_4$: C, 81.13; H, 5.78%).

1,1-*Dicarbomethoxy*-4,4-*di*-p-*tolyl*-2,3-*butadiene*. To a soln of 2.20 g (9.32 mmol) 3,3-di-*p*-tolylacrolein[2b] in 11.4 mL dioxane was added 1.41 mL (12.3 mmol) dimethyl malonate and 1.10 mL (11.1 mmol) piperidine. The mixture was stirred under N_2 for 15 hr, poured into water, ether extracted, the ether extract was washed with 10% HCl, $NaHCO_3$, brine, dried and concentrated *in vacuo*. The solid residue obtained (3.55 g) was recrystallized from 95% EtOH, yielding 2.33 g (71.4%) 1,1-dicarbomethoxy-4,4-di-*p*-tolyl-1,3-butadiene, m.p. 120–121°.

The spectral data were: NMR ($CDCl_3$) δ 7.48–6.82 (m, 10 H, arom and vinyl), 3.80 (s, 3 H, $-CO_2\underline{CH_3}$), 3.66 (s, 3 H, $-CO_2\underline{CH_3}$), 2.36 (s, 3 H, p-$\underline{CH_3}$Ph), 2.30 (s, 3 H, p-$\underline{CH_3}$Ph); IR ($CHCl_3$), 3010, 2950, 1718 (s, C=O), 1592, 1435, 1375, 1270, 1250, 1225, 1190, 1175, 1140, 1070, 825; UV (EtOH) λ_{max} 236 nm (ε 15,641), 255 (ε 13,235); MS *m/e* 350.1523 (Calc. for $C_{22}H_{22}O_4$, *m/e* 350.1518. (Found: C, 75.60; H, 6.34. Calc. for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33%).

General procedure for exploratory photolyses. All direct and sensitized exploratory irradiations used a 450-W medium pressure mercury lamp immersion apparatus or the Black Box apparatus[12] as specified for each run. For Black Box photolyses the band-pass was controlled by filter solutions in a three compartment quartz faced cell.[12] The solns employed were: Filter A–Cell 1, 2.0 M nickel sulfate in 10% H_2SO_4, Cell 2, 0.8 M cobalt sulfate in 10% H_2SO_4, Cell 3, 2.46 × 10^{-4} M bismuth trichloride in 40% HCl. The transmission was 0% below 254 nm, 26% at 285 nm and 0% above 307 nm.

All quantum yield photolyses were purged with purified N_2 for 1 hr before and during each run.

Exploratory direct photolysis of 3,3-*dicarbomethoxy*-1,1,5,5-*tetraphenyl*-1,4-*pentadiene*.[6] A soln of 500 mg (1.02 mmol) 3,3-dicarbomethoxy-1,1,5,5-tetraphenyl-1,4-pentadiene in 480 mL t-BuOH was irradiated for 1.5 hr with the 450-W lamp through a Corex filter and then concentrated *in vacuo*. The crude photolysate was chromatographed on a 3 × 57 cm silica gel column with elution in 40 mL fractions using 2% CH_2Cl_2 in hexane: 196–256, 220 mg (44.2%) of starting diene; 257–340, 274 mg (55%) of 1,1-dicarbomethoxy-2,2-diphenyl-3-(2,2-diphenylvinyl)cyclopropane as colorless crystals, m.p. 135–136°. The spectral data were identical to independently synthesized material.

Exploratory senitized photolysis of 3,3-*dicarbomethoxy*-1,1,5,5-*tetraphenyl*-1,4-*pentadiene*. A soln of 101 mg (0.207 mmol) 3,3-dicarbomethoxy-1,1,5,5-tetraphenyl-1,4-pentadiene and 4.60 g (38.3 mmol) acetophenone in 101 mL benzene was irradiated for 0.31 hr through filter A using the Black Box apparatus. The light absorbed was 0.183 mEinsteins. Concentration *in vacuo* left 4.78 g of a yellow oil. Bulb to bulb distillation (0.015 Torr, 30°) removed the acetophenone leaving 100 mg solid residue. The NMR showed this to be a 3:1 mxture of 3,3-dicarbomethoxy-1,1,5,5-tetraphenyl-1,4-pentadiene and 1,1-dicarbomethoxy-2,2-diphenyl-3-(2,2-diphenylvinyl)-cyclopropane.

The crude photolysate was chromatographed on a 1.5 × 90 cm silica gel column slurry packed in 3% ether in hexane with elution in 150 mL fractions: 16, 71.8 mg (71.1%) 3,3-dicarbomethoxy diene; 17, 23.8 mg (23.6%) diphenylvinyl cyclopropane. The overall mass balance was 94.7%.

Exploratory direct photolysis of 1,1-*dicarbomethoxy*-3,3,5,5-*tetraphenyl*-1,4-*pentadiene*. A soln of 121 mg (0.248 mmol) 1,1-dicarbomethoxy-3,3,5,5-tetraphenyl-1,4-pentadiene in 120 mL *t*-BuOH was irradiated 2 hr through Pyrex using the 450 watt immersion apparatus and then concentrated *in vacuo* leaving 124 mg solid. The NMR spectrum showed total conversion to 1,1-dicarbomethoxy-2,2-diphenyl-3-(2,2-diphenylvinyl) cyclopropane. Recrystallization from 95% EtOH gave 78.3 mg colorless crystals, m.p. 136–137°. Concentration of the mother liquors and chromatography on a 1.5 × 60 cm silica gel column slurry packed in 5% ether in hexane in 250 ml fractions gave in 13 and 14 an additional 36.2 mg diphenylvinyl cyclopropane, m.p. 135–137° (total 114.5 mg, 94.6%). The spectral data were identical to that of independently synthesized material.

Exploratory sensitized photolysis of 1,1-*dicarbomethoxy*-3,3,5,5-*tetraphenyl*-1,4-*pentadiene*. A soln of 200 mg (0.410 mmol) 1,1-dicarbomethoxy-3,3,5,5-tetraphenyl-1,4-pentadiene and 8.03 g (66.9 mmol) acetophenone in 200 ml benzene was irradiated for 30 min through a Pyrex filter and then concentrated *in vacuo* leaving a yellow oil. Subsequent bulb to bulb distillation (0.015 Torr, 30°) was used to remove the acetophenone leaving 202 mg white crystals. The NMR showed total conversion to 1,1,2,2-tetraphenyl-3-(2,2-dicarbomethoxyvinyl) cyclopropane. Recrystallization from ether/hexane gave 161 mg of colorless crystals, m.p. 216–217°. Concentration of the mother liquor and chromatography of the residue on a 1.5 × 60 cm silica gel column slurry packed in 5% ether in hexane with elution in 250 mL fractions gave in 17 and 18 an additional 30.2 mg tetraphenyl cyclopropane, m.p. 217–218°, (total 191.2 mg, 95.6%). The spectral data were identical to that of independently synthesized material. The same results were obtained when the photolysis was performed in *t*-BuOH.

Exploratory direct photolysis of 1,1,2,2-*tetraphenyl*-3-(2,2-*dicarbomethoxyvinyl*)*cyclopropane*. A soln of 205 mg (0.420 mmol) 1,1,2,2-tetraphenyl-2-(2,2,-dicarbomethoxyvinyl) cyclopropane in 200 mL-*t*-BuOH was irradiated 30 min through Pyrex and concentrated *in vacuo* leaving 210 mg solid residue. Analysis by 270 MHz NMR showed a mixture of starting material, 1,1-dicarbomethoxy-3,3,5,5-tetraphenyl-1,4-pentadiene and 1,1-dicarbomethoxy-2,2-diphenylvinyl-cyclopropane in a ratio of *ca* 4.2:1:1.5.

The crude photolysate was chromatographed on a 1.5 × 90 cm silica gel column slurry packed in 3% ether in hexane with elution in 150 mL fractions gave: fractions 17, 18, 43.6 mg (21.3%) diphenylvinyl cyclopropane; 19–20, 29.3 mg (14.7%) 1,1-dicarbomethoxy diene; 21, 128 mg (62.4%) dicarbomethoxyvinyl cyclopropane. The overall mass balance was 98%.

Prolonged irradiation (10 hr) for a 102 mg soln of dicarbomethoxyvinyl cyclopropane in 102 mL of t-BuOH under the same conditions yielded 91 mg (89.2%) diphenylvinyl cyclopropane as the only photoproduct.

Control experiment

Direct photolysis of 1,1-*dicarbomethoxy*-2,2-*diphenyl*-3-(2,2-*diphenylvinyl*) *cyclopropane*. A soln of 98 mg (0.201 mmol) 1,1-dicarbomethoxy-2,2-diphenyl-3-(2,2-diphenylvinyl)-cyclopropane in 100 mL t-BuOH was irradiated 2 hr through Pyrex and concentrated *in vacuo* leaving 95.6 mg (97.5%) white crystals, m.p. 135–136°, identical with starting material.

Control experiment

Sensitized photolysis of 1,1,2,2-*tetraphenyl*-3-(2,2-*dicarbomethoxyvinyl*)*cyclopropane*. A soln of 101 mg (0.207 mmol) 1,1,2,2-tetraphenyl-3-(2,2-dicarbomethoxyvinyl)cyclopropane and 3.94 g (32.8 mmol) acetophenone in 100 mL benzene was irradiated 45 min through Pyrex and concentrated *in vacuo* leaving a yellow oil. Bulb to bulb distillation (0.010 Torr, 30°) removed acetophenone leaving 99.0 mg (98.0%) white crystals, m.p. 216–217°, identical with starting material.

Control experiment

Direct photolysis of 1,1-*dicarbomethoxy*-3,3,5,5-*tetraphenyl*-1,4-*pentadiene and* 1,1,2,2-*tetraphenyl*-3-(2,2-*dicarbo*-

methoxyvinyl) cyclopropane. A soln of 502 mg (1.03 mmol) 1,1-dicarbomethoxy-3,3,5,5-tetraphenyl-1,4-pentadiene and 1.03 mg (2.11×10^{-3} mmol) 1,1,2,2-tetraphenyl-3-(2,2-dicarbomethoxyvinyl)-cyclopropane in 750 mL t-BuOH was irradiated 4.26 hr through filter A on the Black Box apparatus using 2.66 mEinsteins. Analysis, under identical conditions to quantum yield determinations described above, detected 86% of starting 1,1-2,2-tetraphenyl-3-(2,2-dicarbomethoxyvinyl)cyclopropane. Therefore conversion to the tetraphenyl cyclopropane was $\Phi < 7.93 \times 10^{-4}$.

Control experiment

Direct photolysis of a mixture of 1,1,2,2-tetraphenyl-3-(2,2-dicarbomethoxyvinyl)cyclopropane and 1,1-dicarbomethoxy-4,4-p-tolyl-1,3-butadiene. A soln of 75 mg (0.154 mmol) 1,1,2,2,-tetraphenyl-3-(2,2-dicarbomethoxyvinyl)cyclopropane- and 168 (0.0480 mmol) 1,1-dicarbomethoxy-4,4-*p*-tolyl-1,3-butadiene in 250 mL t-BuOH was irradiated 45 min through Pyrex and concentrated *in vacuo* leaving 248 mg yellow oil. Chromatography on a 1.5 × 90 cm silica gel column slurry packed in 2% ether in hexane with elution in 150 mL fractions gave: fractions 14–15, 166 mg (98.8%) dicarbomethoxy-di-*p*-tolyl-butadiene; 18–19, 3% ether in hexane, 21.2 mg (28.3%) diphenylvinyl cyclopropane; 20–21, 13.9 mg (18.5%) 1,1-dicarbomethoxy diene; 22, 38.4 mg (51.2%) dicarbomethoxyvinyl cyclopropane. The overall mass balance was 98.6%.

Control experiment

Sensitized photolysis of 1,1-dicarbomethoxy-2,2-diphenyl-3-(2,2-diphenylvinyl)cyclopropane. A soln of 250 mg (0.512 mmol) 1,1-dicarbomethoxy-2,2-diphenyl-3-(2,2-diphenylvinyl)-cyclopropane and 9.1 g (75.8 mmol) acetophenone in 250 mL benzene was irradiated 2.31 hr through filter A on the Black Box apparatus with 1.44 m Einsteins. Bulb to bulb distillation (0.010 Torr, 30°) removed acetophenone and analysis under identical conditions to quantum yield determinations described was performed. No dicarbomethoxyvinyl cyclopropane was detected. A control mixture containing 0.654% dicarbomethoxyvinyl cyclopropane was examined under identical conditions and this conversion would have been measurable. Therefore conversion was <0.654%, $\Phi < 1.42 \times 10^{-3}$.

Photolysis apparatus for quantum yield determinations. All quantum yield determinations were run on either the Black Box apparatus[12] or semimicroptical bench.[12] Light output was measured using a digital actinometer[13] calibrated by ferrioxalate actinometry.[14] Microoptical bench photolyses employed an Osram HBO 200-W high-pressure mercury lamp and Bausch and Lomb Model 33-86-79 monochromator with a 5.4-mm entrance slit and 3.0-mm exit slit giving a band-pass of 22 nm a half-peak height. For Black Box photolyses the band pass was controlled by the filter solutions described above.

Summary of quantum yield results. All runs were analyzed by high-pressure liquid chromatography using a 4.0 × 270 mm column packed with 5-10 μ silica beads[44] eluted with 15% anhyd ether in anhyd hexane. The internal standard used was *p*-cyanoanisole. The data are reported in Tables 5–9.

Emission studies magic multipliers.[15] The fluorescence spectrum of each compound was measured in a 4:1 methylcyclohexane–isopentane soln at 77°K and 295°K using an Aminco-Keirs spectrofluorometer equipped with a Hanovia 901C-1 150-W Xenon arc lamp. Concentrations of solns were adjusted to give optical densities of 0.8–0.9. All solns were thoroughly degassed immediately before the spectra were obtained. Emission wavelength maxima were found to be independent of excitation wavelength over a 50 nm range. Magic Multiplers were calculated by dividing the integrated intensity of fluorescence at 77°K by the integrated intensity of fluorescence at 295°K. The average value obtained for each compound was: 3,3-dicarbomethoxy-1,1,5,5-tetraphenyl-1,4-pentadiene, M = 21.0 (3 runs); 1,1-dicarbo-methoxy-3,3,5,5-tetraphenyl-1,4-pentadiene, M = 197 (3 runs).

Single photon counting. The apparatus and procedure have been described previously.[15,20] Individual samples were prepared in 4:1 methylcyclohexane-isopentane to give an optical density in the range of 0.8–0.9, thoroughly degassed immediately before counting, and counted at 77°K. Data was collected at less than 5% lamp flash frequency to insure exclusion of double photon counting. Excitation wavelength was varied over the range 275 and 310 nm and emission was monitored over the range 305 to 360 nm with an RCA 8850 photomultiplier. The decay range was found to be independent of excitation wavelength, emission wavelength and optical density to within 5% using the "A" value[15] as a measure of the fit of calculated to experimentally observed decay rate. The data are reported as follows: compound, average lifetime, average decay rate, number of runs, A-value.

(1) 3,3-Dicarbomethoxy-1,1,5,5-tetraphenyl-1,4-pentadiene, 0.827 ns, $1.25 \times 10^{9}\,s^{-1}$, 7, 0.037.

Table 5. Photolysis of 3,3-dicarbomethoxy-1,1,5,5-tetraphenyl-1,4-pentadiene to afford 1,1-dicarbomethoxy-2,2-diphenyl-3-(2,2-diphenylvinyl) cyclopropane

Run	Reactant, mmol	light absorbed mEinstein	% convn	photoproduct mmol	Φ
1[a]	1.11×10^{-1}	2.40×10^{-1}	7.20	8.00×10^{-3}	0.34
2[a]	1.04×10^{-1}	4.40×10^{-1}	15.4	1.60×10^{-2}	0.23
3[a]	1.04×10^{-1}	1.70×10^{-1}	23.7	2.50×10^{-2}	0.14

[a]Black Box, 80 mL of cyclohexane, filter A.

Table 6. Sensitized photolysis of 3,3-dicarbomethoxy-1,1,5,5-tetraphenyl-1,4-pentadiene to afford 1,1,2,2-tetraphenyl-3-(2,2-dicarbomethoxyvinyl) cyclopropane

Run	Reactant, mmol	added sens, mmol	light absorbed, mEinstein	% convn	photoproduct mmol	Φ
1[a]	7.05×10^{-2}	29.2	2.14×10^{-3}	0.912	6.43×10^{-4}	0.30
2[a]	6.39×10^{-2}	26.7	4.26×10^{-3}	1.93	1.23×10^{-3}	0.29
3[a]	6.52 x 10-2	26.7	6.66×10^{-3}	2.79	1.82×10^{-3}	0.27

[a]microoptical bench, 40 mL of benzene, 340 nm.

Table 7. Photolysis of 1,1-dicarbomethoxy-3,3,5,5-tetraphenyl-1,4-pentadiene to afford 1,1-dicarbomethoxy-2, 2-diphenyl-3-(2,2-diphenylvinyl) cyclopropane

Run	Reactant, mmol	light absorbed mEinstein	% convn	photoproduct mmol	Φ
1[a]	5.97×10^{-1}	1.50×10^{-2}	0.985	5.38×10^{-3}	0.39
2[a]	1.83×10^{-1}	2.12×10^{-2}	4.11	7.52×10^{-3}	0.36
3[a]	2.30×10^{-1}	7.32×10^{-2}	11.2	2.57×10^{-2}	0.35
4[a]	3.85×10^{-1}	1.26×10^{-1}	17.4	6.68×10^{-2}	0.30

[a]Black Box, 250 mL of tert-butyl alcohol, filter A.

Table 8. Sensitized photolysis of 1,1-dicarbomethoxy-3,3,5,5-tetraphenyl-1,4-pentadiene to afford 1,1,2,2-tetraphenyl-3-(2,2-dicarbomethoxyvinyl) cyclopropane

Run	Reactant, mmol	added sens, mmol	light absorbed mEinstein	% convn	photoproduct mmol	Φ
1[a]	6.91×10^{-2}	28.3	1.45×10^{-3}	1.91	1.32×10^{-3}	0.91
2[a]	7.66×10^{-2}	30.0	6.88×10^{-3}	7.86	6.02×10^{-3}	0.88
3[a]	6.45×10^{-2}	25.7	1.01×10^{-2}	13.1	8.46×10^{-3}	0.84

[a]microoptical bench, 40 mL of benzene, 340 nm.

Table 9. Photolysis of 1,1,2,2-tetraphenyl-3-(2,2-dicarbomethoxyvinyl) cyclopropane to afford 1,1-dicarbomethoxy-2,2-diphenyl-3-(2,2-diphenylvinyl) cyclopropane and 1,1-dicarbomethoxy-3,3,5,5-tetraphenyl-1,4-pentadiene

Run	Reactant, mmol	light absorbed mEinstein	% convn	photoproduct mmol	Φ
1[a]	7.76×10^{-2}	9.52×10^{-3}	2.00	9.24×10^{-4}[b] 6.29×10^{-4}[c]	9.7×10^{-2} 6.6×10^{-2}
2[a]	4.00×10^{-2}	1.18×10^{-2}	4.50	1.06×10^{-3}[b] 7.33×10^{-4}[c]	9.0×10^{-2} 6.2×10^{-2}
3[a]	6.66×10^{-2}	3.36×10^{-2}	6.87	2.75×10^{-3}[b] 1.84×10^{-3}[c]	8.2×10^{-2} 5.5×10^{-2}

[a]microoptical bench, 40 mL of tert-butyl alcohol, 285 nm. [b]1,1-Dicarbomethoxy-2,2-diphenyl-3-(2,2-diphenylvinyl)-cyclopropane. [c]1,1-Dicarbomethoxy-3,3,5,5-tetraphenyl-1,4-pentadiene.

(2) 1,1-Dicarbomethoxy-3,3,5,5-tetraphenyl-1,4-pentadiene, 0.330 ns, $3.05 \times 10^9\ s^{-1}$, 6, 0.031.

Calculations. The method employed was described previously.[3,5,17,19] Standard geometries for styryl vinyl methanes, vinyl cyclopropanes and 1,3-biradicals were established using a geometry program[45] with standard[46] bond lengths and angles. Geometries for 1,4-biradical species were taken from a reported INDO calculation with geometry optimization for the ground state 2-vinylcyclopropylcarbinyl radical.[47]

Calculations were performed with Fortran IV programs[48] on a PDP-11/T55 computer having 32 K words of memory. Direct access to and from two disks of 1.2×10^6 words per disk allowed storage and use of the large matrices encountered in configuration interaction calculations.

Acknowledgement—Support of this research by the National Science Foundation, by NIH Grant GM07487 and by the U.S. Army Research Office is gratefully acknowledged. Also thanks are due to Dr. Thomas P. Gannett for exploratory studies in the photochemistry of the 3,3-dicarbomethoxy diene.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 143 to 147, 1981
Printed in Great Britain

0040-4020/81/Suppl. 1-0143-05 $02.00/0
Pergamon Press Ltd.

THE STEREOCHEMISTRY OF 2-t-BUTYL-2-CYANO-3-PHENYLCYCLOBUTANONE BY COMPLETE ANALYSIS OF ITS ^{1}H NMR SPECTRUM

ADDITIONAL EVIDENCE FOR A $_2\pi_s + {}_2\pi_a$ CYCLOADDITION OF t-BUTYLCYANOKETENE TO STYRENE[1]

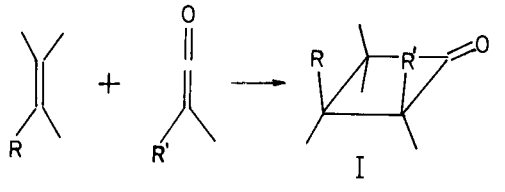
MIRCEA D. GHEORGHIU,* LUMINITA PÂRVULESCU, CONSTANTIN DRÂGHICI and MIHAI ELIAN

Laboratory of Organic Chemistry, Faculty of Chemical Technology, Polytechnic Institute-TCH, Spl. Independenței 313, 77206-Bucharest-16, Romania

(*Received in U.K.* 21 *July* 1980)

Abstract—The unique ^{1}H NMR spectral parameters obtained by computer simulation of the experimental spectrum of the three protons belonging to the 4-membered ring of the title cyclobutanone, can be rationalized if is accepted that the phenyl and t-Bu groups are *vicinal* and *cis*. The spectra parameters have been retained as results of the analysis of the six real solutions for the experimental ^{1}H NMR spectrum of the title cyclobutanone in chloroform-d. ^{1}H NMR spectra of deuterium labelled cyclobutanones obtained from mono- and dideuteriated styrenes and t-butylcyanoketene support the preferred theoretical solution. The conservation of the configuration of monodeuteriated styrenes in the cycloaddition reaction with t-butylcyanoketene strengthens our proposal that in this reaction the Woodward–Hoffmann $_2\pi_s + {}_2\pi_a$ reaction mode is operating.

The formation of the most crowded isomer I in the cycloadditions of a ketene to a nonpolar alkenes, was interpreted as an evidence for a $_2\pi_s + {}_2\pi_a$ reaction mode,[2] being evidenced convincingly on numerous alkenes.[3–25]



The discovery in 1970 by Moore[25a] of t-butylcyanoketene (TBCK), a very reactive ketene, provided the possibility for enlarging the area of examples of cycloadditions occurring via a $_2\pi_s + {}_2\pi_a$ reaction mode.[15,19–25] Indeed, TBCK adds according to these rules to *cis* and *trans*-cyclooctene,[15,25a] styrene, indene and acenaphthalene,[19] bicyclo-(2.2.1)heptene derivatives[21–23] and 3,3-dimethylcyclopentene.[24]

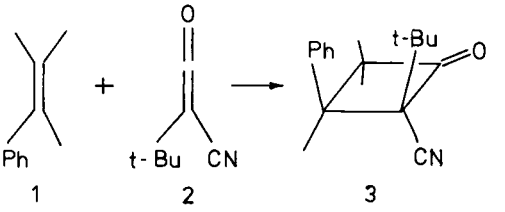
In a previous communication[19] one of us (MDG) based on the chemical shifts of the protons of the t-Bu group of the title cyclobutanone, relative to suitable models represented by 2-t-butyl-2-cyanocyclobutanones reported in the literature or synthesized in this laboratory, concluded that the stereochemistry of the title cyclobutanone has the phenyl and the t-Bu groups *vicinal* and *vis*. In other words the cycloadduct has the stereochemistry that one would expect if the styrene reacts with TBCK via a $_2\pi_s + {}_2\pi_a$ reaction mode.

Here, we would like to present new arguments, which independently support the same stereochemistry for the 2-t-butyl-2-cyano-3-phenylcyclobutanone as proposed previously.[19] Our conclusions resulted from the exact analysis[26,27] of all theoretical NMR spectral frequencies of the experimental ^{1}H NMR spectrum of the three protons belonging to the 4-membered ring. Only one set of the spectral parameters gave theoretical intensities which fitted with the experimental spectrum. The accepted spectral parameters are easily rationalized if one accepts as structural model a cyclobutanone having the t-Bu and phenyl groups both *vicinal* and *cis*. The chemical shifts and the coupling constants generally in accordance with other NMR studies on cyclobutanones,[28–33] obtained from the exact analysis of the experimental spectrum, are nicely supported by deuterium labelled cyclobutanones prepared from α, *cis*-, *trans*-, or β,β'-di-deuteriated styrene and TBCK. It also remarkable to note that the relative configuration of deuteriated styrenes are preserved during the cycloaddition to TBCK, suggesting a concerted mode for these reactions.

DISCUSSION OF THE RESULTS

The phenyl and t-butyl groups are vicinal *and* cis

The experimental ^{1}H NMR spectrum of the cyclobutanone **3** in $CDCl_3$ is best simulated with the following parameters $\delta_{H^1} = 4.41$ ppm, $\delta_{H^2} = 3.85$ ppm, $\delta_{H^2} = 3.44$ ppm, $J^{gem} = -18.24$ Hz, $J^{cis} = 11.14$ Hz and $J^{trans} = 10.07$ Hz. We consider that the chemical shifts obtained are best rationalized as follows.



The proton appearing at $\delta = 4.41$ ppm could be assigned as the benzylic proton H^1. Let us examine the chemical shift of such a proton in some 3-phenylcyclobutanones. Thus in 3-phenylcyclobutanone (**4**)[34] the chemical shift of the benzylic proton is at $\delta = 3.45$–3.78 ppm, in 2,2-dimethyl-3-phenylcyclobutanone (**5**)[35] the benzylic proton signal has the chemical shift at $\delta = 3.25$ ppm, while on replacement of the dimethyl groups with diphenyl groups as in cyclobutanone **6**, the benzylic proton is shifted downfield to 4.32 ppm[36] (or 4.48 ppm[37]). We conclude that, indeed, the H^1 proton in the cyclobutanone **3** has a deshielded shift. The acceptance of this deshielded position for the benzylic proton in the cyclobutanone **3** is crucial for the configurational assignment. The *cis* proximity of the cyano group is responsible for the position of the downfield shift of the benzylic proton in the cyclobutanone **3**. Furthermore the above quoted value for the chemical shift of the benzylic proton from the cyclobutanone **3** was confirmed by the exact analysis of its proton spectrum in various solvents and with shift reagents.[38] Then, we have obtained from β,β'-dideuteriated styrene and TBCK, the cyclobutanone **8** in which the benzylic proton appears at $\delta = 4.37$ ppm.

The chemical shift of the remaining protons, H^2 and H^3 fit well with structure **3**.

The chemical shift occurring at $\delta = 3.85$ ppm, we assign to proton H^2, which is *cis* to the phenyl group

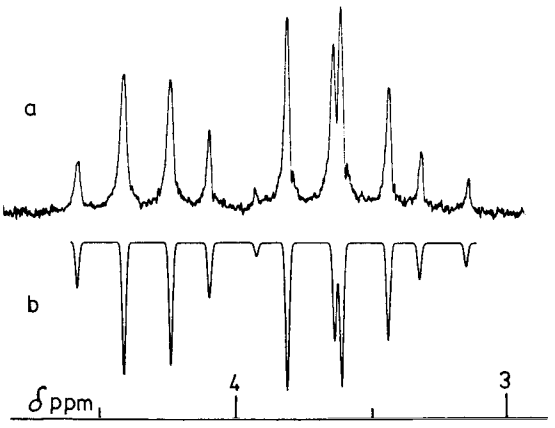
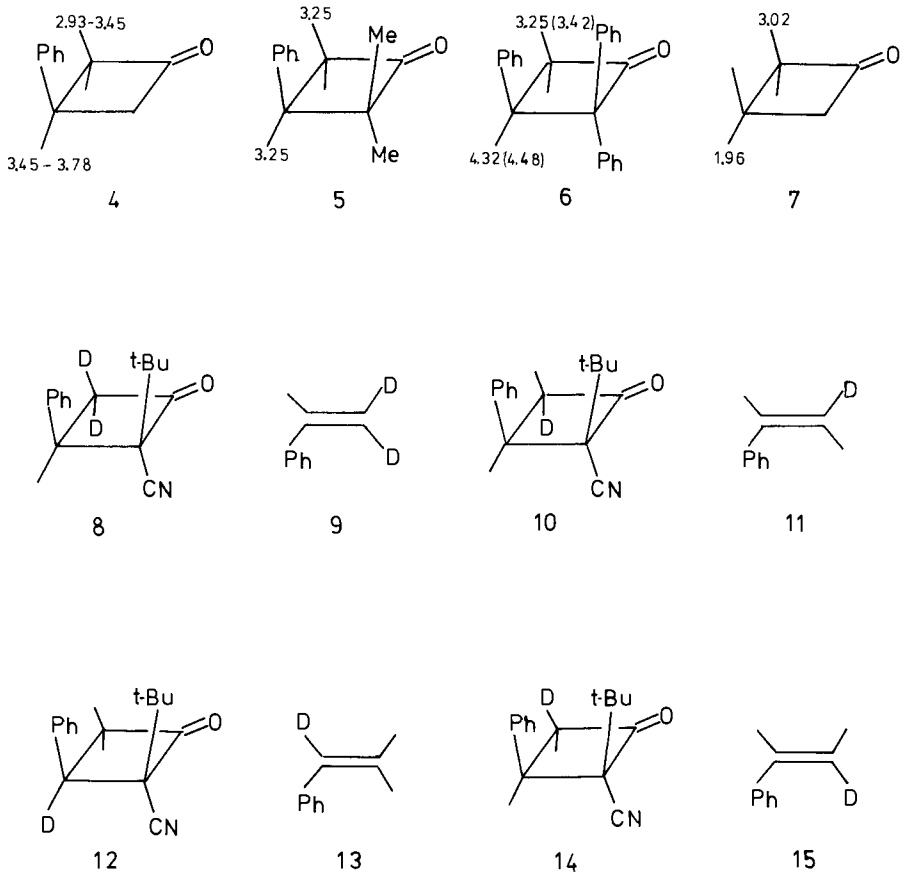


Fig. 1. (a) Experimental spectrum of cyclobutanone **3**. (b) The simulated spectrum.

(Fig. 2). Its position is shifted with *ca* 0.8 ppm toward lower fields than the same proton in the parent cyclobutanone **7**[28–32] and with *ca* 0.5 ppm with respect to the position found in the 3-phenylcyclobutanones **4**, **5** and **6**. We consider this relative deshielding of H^2 in the cyclobutanone **3**, as a result of its position near or in the plane of the phenyl ring, as a consequence of the locking or only slightly oscilating Ph group by the neighboring t-Bu group (Fig. 2). If the phenyl group in the cyclobutanone rotated freely, as in the case of the



cyclobutanones **4**, **5** and **6**, its average magnetic effect upon H^2 would have conferred a higher-field chemical shift. Again, the theoretical chemical shift for H^2 from cyclobutanone **3**, is supported by experimental value obtained from the ^1H NMR spectra of the deuteriated cyclobutanones **10** and **12**, obtained from *trans*- and α-deuteriated styrenes with TBCK (Table 1).

The theoretical chemical shift for H^3 as proposed above is supported by value obtained from the ^1H NMR spectra of deuteriated cyclobutanones **12** and **14** obtained from α-deuteriated styrene (**13**) and *cis*-deuteriated styrene (**15**) with TBCK.

At this point we would like to comment the magnitude and the signs of the coupling constants, belonging to the accepted solution chosen from the six real ones for the experimental spectrum in $CDCl_3$.

The calculated geminal coupling constant of −18.24 Hz is only slightly different in magnitude from that obtained in the case of the parent cyclobutanone.[28–32] The absolute value of the geminal coupling constant has also resulted from the AB ^1H NMR spectrum of the monodeuteriated cyclobutanone 12.

The *cis* coupling constant, 10.07 Hz, is also fairly close to the magnitude of the same coupling constant found in the case of the parent cyclobutanone **7**.

The *trans* coupling constant, 11.14 Hz, is however higher than the calculated value, 6 Hz, in the case of the parent cyclobutanone. We believe that this discrepancy results from the distorsions between the t-butyl group and the phenyl group. It is, however, less obvious why only *trans* coupling constant is affected by these conformational changes while the *cis* coupling constant is virtually unaffected.

The cycloaddition of TBCK to styrene derivatives is a concerted reaction

The concertedness of the cycloaddition of ketenes to nonpolar alkeneis is receiving an increasing attention, not only on a particular substrate as it was for many years the case of cyclopentadiene,[2b] but also with an increasing number of other substrates belonging, in general, to nonpolar alkenes. Evidence for such a reaction course is based predominantly on the stereochemistry of the only cyclobutanone derivative resulted in the cycloaddition, which according to the Woodward–Hoffmann mechanism, if the reaction is concerted, should give the most sterically crowded isomer.[2] Along with these steric arguments, the concertedness of a few cycloadditions of ketene to alkenes was also supported by kinetic results and isotopic effects.[37,40]

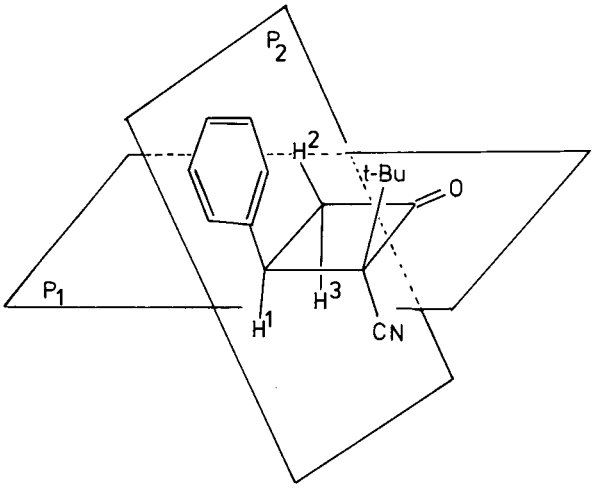
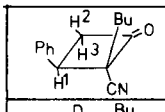
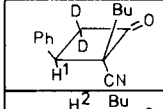
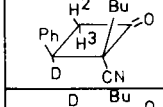
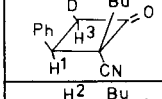
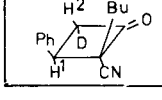


Fig. 2. Structure and protons assignment for cyclobutanone **3**

As in our previous paper,[19] we would like to conclude again that the reaction of styrene with TBCK is concerted. This conclusion is based on the fact that in the reaction of TBCK with deuteriated styrenes, *the original configuration of alkenes is preserved in the resulting cyclobutanones.* In the previous contributions regarding the cycloaddition of diphenylketene to deuteriated styrenes such observation were not commented.[37,40] In our case, *cis*- and *trans*-

Table 1. Calculated (first entry) and experimental chemical shifts (δ, ppm) and coupling constants (in Hz) for the parent and deuteriated cyclobutanones

	H^1	H^2	H^3	$J_{H^2H^3}$	$J_{H^1H^2}$	$J_{H^1H^3}$
	4.41	3.85	3.44	-18.24	11.14	10.07
	4.37	—	—	—	—	—
	—	3.81	3.42	18.0	—	—
	4.37	—	3.41	—	—	10.0
	4.39	3.80	—	—	11.0	—

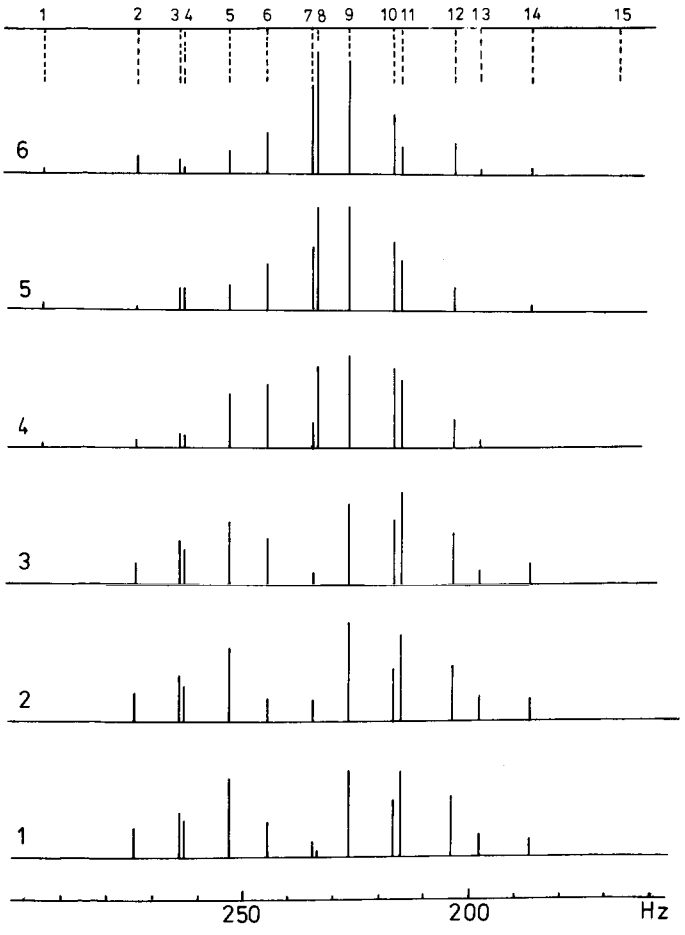


Fig. 3. Theoretical frequencies solutions obtained from the experimental spectrum of cyclobutanone **3** (in $CDCl_3$). The true spectral parameters are generating solution 1. The pairs of conjugated solutions are 1 with 6, 2 with 4 and 3 with 5.

deuteriated styrenes gave with TBCK cyclobutanones **10** and **14**, respectively. Styrenes substituted at the alkenic double bond with methyl or phenyl groups, as markers for the study of the stereochemistry of the reaction course, have so far failed to react with TBCK in our hands. Therefore, we evaluate our results regarding the cycloaddition of TBCK to deuteriated styrenes, as being among the few examples of concerted cycloaddition of a ketene to a cyclic and/or nonrigid alkene.[26,41]

EXPERIMENTAL

Compound **9**, was obtained from 1-phenyl-ethanol-2-d_3 and 30% phosphoric acid. The 1-phenylethanol-2-d_3 was obtained from acetophenone-d_3[42] by reduction with LAH.

The monodeuteriated styrenes were obtained from the corresponding bromostyrene by conversion into Grignard derivatives and then quenching with D_2O. The α-bromo, *trans*-bromo, and *cis*-bromostyrenes were treated with Mg turnings in absolute ether or THF using an excess of EtMgBr to ensure the retention of the original configuration of the bromostyrene in the Grignard derivative.[43] α-Bromostyrene was obtained from styrene dibromide and NaOH aq (1:1 molar ratio dibromo derivative: NaOH).[44]

cis-Bromostyrene was obtained from *trans*-cinamic acid dibromide and sodium carbonate in dry acetone.

trans-Bromostyrene (80% purity) was obtained from the same dibromide as above but with an aqueous solution of sodium hydroxide.[45,46]

The content of deuteriated styrenes, estimated from ^{1}H NMR spectra were for *cis*-deuteriostyrene 90%, *trans*-deuteriostyrene 93%, α-deuteriostyrene 90%, β,β'-dideuteriostyrene 100%.

All the cycloaddition were carried out in anhyd benzene under argon. TBCK was obtained as soln in benzene, by thermolysis of 2,5-diazido-3,6-di-t-butylbenzoquinone, using for synthesis of the latter compound a modified version[47,48] of Moore's procedure.[25b]

The exact analysis of the experimental ^{1}H NMR spectrum of **3** was carried out using programmes written in BASIC for a Hewlett Packard 9830A calculator. The calculations were run in two distinctive steps. In the first step we calculated the real solns of the experimental spectrum of the cyclobutanone **3**, using the procedure devised by Castellano and Waugh[26] and Cavanaugh.[27] The resulting spectral parameters were fed into a second program designed to calculate the corresponding theoretical spectrum and to plot the spectrum (considering the signals as gaussian curves) with a Hewlett Packard 9862A Calculator Plotter.

Acknowledgements—We are grateful to Prof. E. Ciorănescu-Nenitzescu Director of the Center of Organic Chemistry (Bucharest) for much understanding and support which made possible this project to be carried out. We are also

grateful to Prof. Lawrence T. Scott (University of Nevada, Reno, Nevada) for providing a copy of the NMR spectrum of 3-phenylcyclobutanone.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 149 to 156, 1981
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0040-4020/81/Suppl. 1-0149-08 $02.00/0
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SYNTHESIS OF THE O-ANTIGENIC POLYSACCHARIDE OF *SALMONELLA NEWINGTON* AND OF ITS ANALOGUE DIFFERING IN CONFIGURATION AT THE ONLY GLYCOSIDIC CENTRE

N. K. KOCHETKOV,* V. I. BETANELI, M. V. OVCHINNIKOV and L. V. BACKINOWSKY

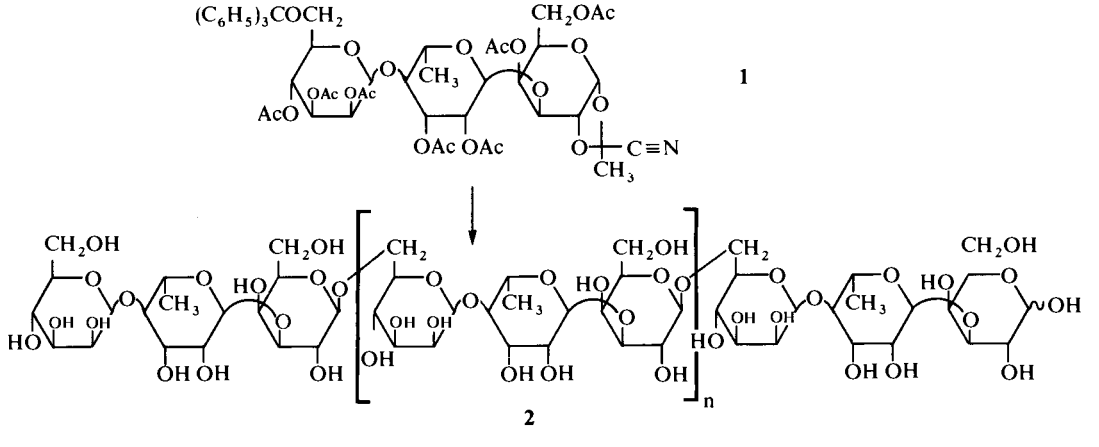
N. D. Zelinsky Institute of Organic Chemistry, Academy of Sciences of the U.S.S.R., Moscow, U.S.S.R.

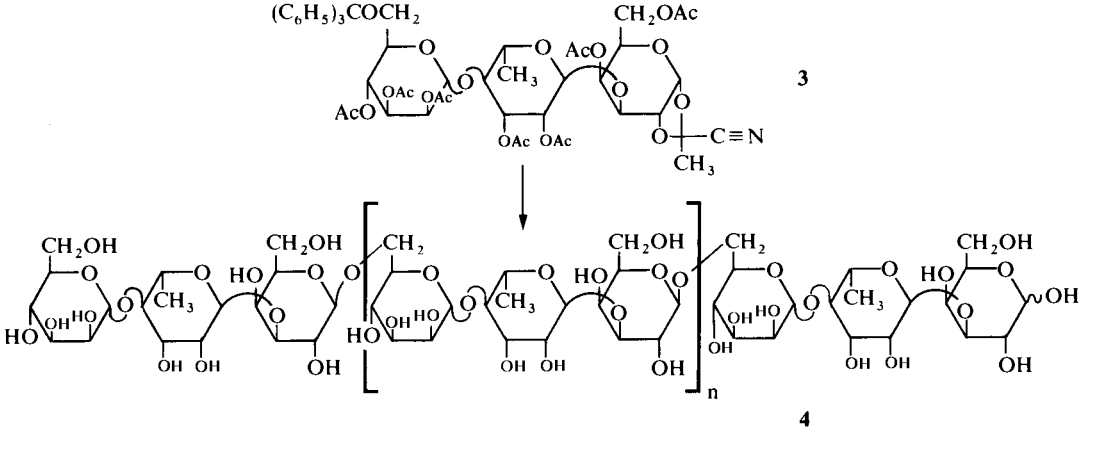
(*Received in U.K.* 22 *April* 1980)

Abstract—Stereospecific polycondensation of trityl ethers of trisaccharide 1,2-O-cyanoethylidene derivatives (**1** and **3**) followed by deprotection afforded regular heteropolysaccharides (**2** and **4**) built up of repeating trisaccharide units,*viz* (→6)-β-D-Man*p*-(1→4)-α-L-Rha*p*-(1→3)-β-D-Gal*p*-(1→ and →6)-α-D-Man*p*-(1 → 4)-α-L-Rha*p*-(1 → 3)-β-D-Gal*p*-(1 →, respectively. The synthetic polysaccharide **2** exhibited the high biological specificity of the natural one, whilst its analogue **4** was found to be practically inactive. The necessary monomers for polycondensation, **1** and **3**, were obtained from the respective trisaccharide α-decaacetates (**5** and **7**) by successively converting them into glycosyl bromides and 1,2-O-cyanoethylidene derivatives which, in turn, were subjected to deacylation followed by tritylation.

Chemical synthesis of complex heteropolysaccharides is a difficult problem due to the necessity to ensure strict regio- and, especially, stereospecificity of all the intermonomeric glycosidic linkages in the polysaccharide to be synthesized. Such a synthesis has not been accomplished yet despite numerous polysaccharides (e.g. microbial capsular and outer-membrane polysaccharides, connective tissue polysaccharides, carbohydrate chains of different glycoproteins, etc.) belong to this important class of biopolymers.

Here we describe the first synthesis of a biologically specific heteropolysaccharide **2** (preliminary communication see Ref. 1) and of its analogue **4**, which



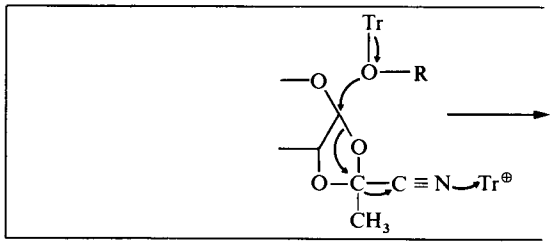


is based on (a) the use of tritylated 1,2-O-cyanoethylidene sugar derivatives for the synthesis of regular polysaccharides[2,3] and (b) general method of synthesis of sugar 1,2-O-cyanoethylidene derivatives.[4]

Immunological specificity of bacterial O-antigens is well known[5] to be determined by definite chemical structure of polysaccharide chains of respective lipopolysaccharides attached to the outer cell membrane. According to the literature data[5,6] O-specific chains of the lipopolysaccharide of gram-negative bacterium *Salmonella newington* are the linear heteropolysaccharides represented by formula **2**, containing from 2 to 29 repeating trisaccharide units[7] (n = 0–27). The chemical synthesis of this polysaccharide and its analogue containing α-mannopyranosyl residues is the subject of this communication.

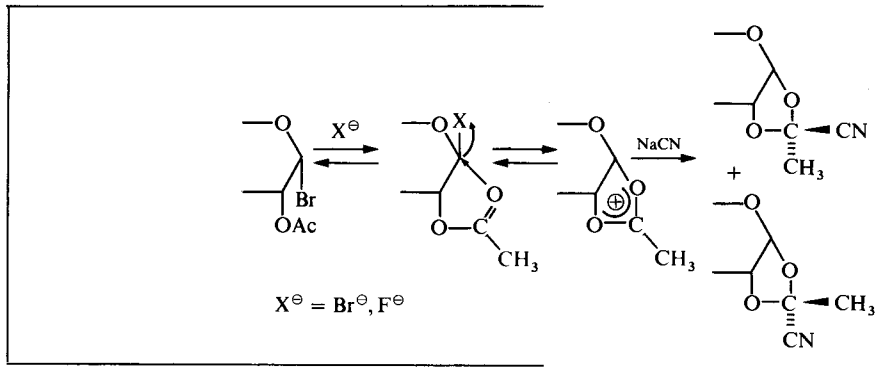
RESULTS AND DISCUSSION

The chemical synthesis of polysaccharides **2** and **4** has been accomplished by polycondensation of respective bifunctional monomers **1** and **3** according to the following scheme. Peracetylated trisaccharides were converted into glycosyl bromides which were treated with sodium cyanide to yield 1,2-O-cyanoethylidene derivatives. The latter were deacetylated, tritylated and acetylated to afford the necessary monomers—peractylated trityl ethers of the trisaccharide 1,2-O-cyanoethylidene derivatives.

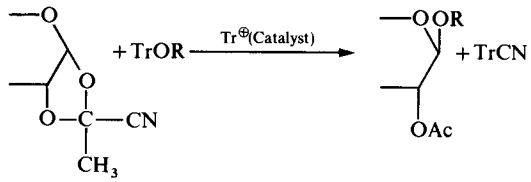


Polycondensation of these monomers in dichloromethane in the presence of catalytic amount of triphenylmethylium perchlorate gives rise to free polysaccharides following deprotection.

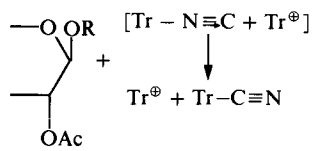
Treatment of the trisaccharide α-decaacetates **5**, **7** and **9**, whose practical synthesis has been reported recently,[8] with hydrogen bromide in glacial acetic acid gave the chromatographically homogeneous acetylglycosyl bromides quantitatively; they exhibited higher mobilities in tlc than the starting decaacetates. These glycosyl bromides without additional purification were treated with sodium cyanide in acetonitrile in the presence of tetra-n-butylammonium iodide at room temperature, as described earlier for the synthesis of 1,2-O-cyanoethylidene derivatives of neutral mono- and disaccharides with gluco-, galacto- and manno-configurations.[4] This reaction afford 1,2-O-cyanoethylidene derivatives as the mixtures of diastereomeric pairs differing in configuration at C-2 of the dioxolane ring (CN-*exo*-and CN-*endo*-isomers). Their formation was rationalized[4] as follows:



It is noteworthy that both individual CN-*exo*- and -*endo*-isomers and their mixtures which are formed under the above conditions proved to be highly effective and stereospecific glycosylating agents.[9] When reacted with trityl ethers in the presence of triphenylmethylium perchlorate as a catalyst they afford stereospecifically 1,2-*trans*-glycosides according to the following overall scheme:



Extremely high stereospecificity of this glycosylation reaction may be accounted for by the following tentative push-pull process of substitution at C-1:



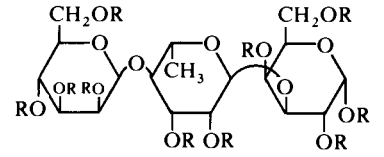
Octaacetates of 1,2-O-cyanoethylidene derivatives of trisaccharides, **10**, **12** and **14**, obtained under the aforementioned conditions, were isolated as chromatographically homogeneous mixtures of CN-*exo*- and -*endo*-isomers. Data on their PMR and Raman spectra are listed in Table 1 [those of 1,2-O-(1-cyanoethylidene)-3,4,6-tri-O-acetyl-α-D-galactopyranose[4] are given for comparison].

The presence of 1,2-dioxolane ring at galactopyranose residues was evident from characteristic singlet signals of C–CH_3 groups (δ 1.76–1.87 ppm) and

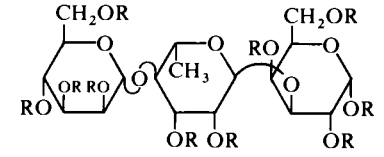
doublets of H-1 (δ 5.68–5.86 ppm), and that of CN-group—from Raman spectra, the latter method proved to be a reliable one for identification of the cyano-group in compounds of this type.[4] Data presented in Table 1 together with analytical ones prove the structures of compounds **10**, **12** and **14**. Thus the previously proposed method[4] is really a general synthetic route to 1,2-O-cyanoethylidene derivatives of mono- and oligosaccharides.

These trisaccharide 1,2-O-cyanoethylidene derivatives had to be deacetylated. It has been shown earlier[10] that treatment of 1,2-O-[1-(*exo*-cyano)-ethylidene]-3,4,6-tri-O-acetyl-α-D-glucopyranose with excess of 0.1M sodium methoxide in abs. methanol for 16 hr at 6° afforded an imino-ester derivative, whose formation can be formally regarded as a result of addition of methanol to the nitrile group of the cyanoethylidene derivative. We succeeded in avoiding this undesirable side reaction by performing the deacetylation with 0.01M sodium methoxide (0.02 equivalents) in abs. methanol containing *ca* 10% of abs. chloroform; complete deacetylation proceeded within 30 min at room temperature.

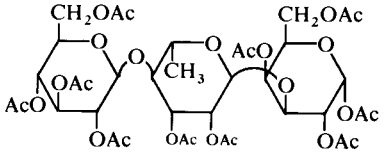
Free 1,2-O-cyanoethylidene derivatives obtained after deacetylation of **10** and **12** were subjected to alkylation with triphenylchloromethane in abs. pyridine. The reaction mixtures revealed in tlc (following peracetylation) a zone of highest mobility,



5 R = Ac
6 R = H



7 R = Ac
8 R = H



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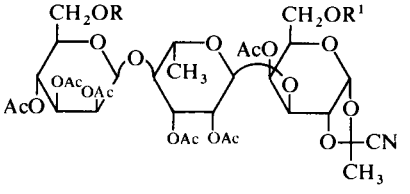
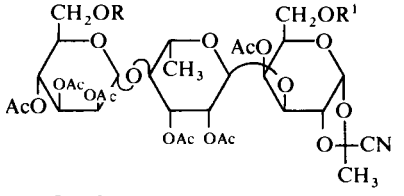
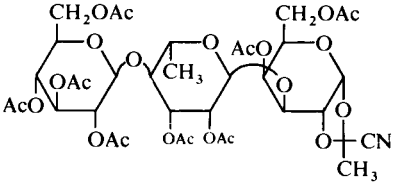


10 R = R′ = Ac
1 R = Tr; R′ = Ac
11 R = R′ = Tr



12 R = R′ = Ac
3 R = Tr, R′ = Ac
13 R = R′ = Tr



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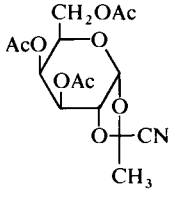


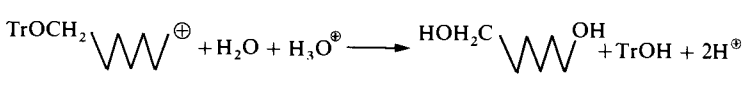
15

containing di-O-trityl derivatives, a less mobile broad zone of mono-O-trityl derivatives, and a zone corresponding to the starting octaacetates **10** and **12**. The use of 1.0 equivalent of triphenylchloromethane resulted in insufficiently effective tritylation and recovery of considerable amount of the starting products. Alkylation with 2–3 equivalents gives rise to di-O-trityl ethers **11** and **13** as the main products. The best results were obtained when the reaction was performed with 1.2–1.5 equivalents of triphenylchloromethane at room temperature for 48–72 hr followed by acetylation.

The necessary monomers **1** and **3** were isolated by column chromatography in 15 and 27% yields, respectively. Their structures followed from the 2:1 ratio of integral intensities of signals of all the Me-groups (including those of rhamnose moiety, cyanoethylidene and acetyl groups) to those of aromatic protons in their PMR spectra, as well as from data on methylation analysis.[11] Mono-O-trityl derivatives **1** and **3** afforded acetates of 2,3-di-O-methyl-rhamnitol, 2,3,4-tri-O-methyl-mannitol and 4,6-di-O-methyl-galactitol in the ratio of 1:1:1 identified by glc-MS. In the case of **3** these main components were accompanied by no more than 5% of 1,5-di-O-acetyl-2,3,4,6-tetra-O-methylmannitol and 1,2,3,5,6-penta-O-acetyl-4-O-methyl-galactitol due to possible admixture of the mono-tritylated at the galactose moiety product. The structures of di-O-trityl derivatives **11** and **13** was elucidated analogously. Thus the PMR spectra allowed to estimate the amount of trityl residues in the molecules whereas methylation analysis—to localize them. The persistence of the nitrile group in the product obtained evidenced from the presence of a band at 2240 cm^{-1} in the Raman spectrum of **13** (*cf* Table 1).

The polycondensation of monomers **1** and **3** was performed in dichloromethane in the presence of 0.1 equivalent of triphenylmethylium perchlorate at room temperature for 65 hr using vacuum technique. The reaction mixtures obtained did not contain even traces of the starting monomers (tlc). All the carbohydrate products remained at the application point (development in 1:1 benzene—ethyl acetate) and contained triphenylmethyl group (spraying with sulphuric acid produced bright-yellow colouration darkening upon heating); development in 3:7 acetone–chloroform solvent system revealed a mixture of products with R_f from 0 to 0.5 with the same colouration pattern, the main portion remaining at the application point.

The yellow reaction mixtures were treated with excess of 90% aqueous trifluoroacetic acid to neutralize cations present at the reducing termini of the growing chains and to detritylate the nonreducing termini:



Thereafter tlc revealed a mixture of products (R_f from 0 to 0.4 in 1:1 acetone–chloroform), darkening upon spraying with sulphuric acid followed by heating, the main portion remaining at the application point.

The yellow-greenish reaction mixtures were neutralized by addition of excess of pyridine, which was accompanied by decolouration, deacetylated with sodium methoxide, and gave after neutralisation the polysaccharides **2** and **4**. In the PMR spectra (14% solution in D_2O) were absent signals of the cyanoethylidene and acetyl groups at δ 1.5–2.5 ppm (an intensive doublet of the CH_3 group of rhamnose moiety was present at δ 1.2 ppm, J = 6 Hz), as well as those of trityl group (δ 6–8 ppm). According to analytical gel-chromatography data these polysaccharides were eluted as broad zones, whose beginning coincided with the void volume for Bio-Gel P-4 and retarded from that for Bio-Gel P-6. This indicates to the polymeric nature of **2** and **4**, whose maximum molecular mass lies in the range of 4,000–6,000.

Polysaccharides **2** and **4** were subjected to fractionation on Bio-Gel P-4 into three fractions **2a**, **2b**, **2c** and **4a**, **4b** and **4c** (Table 2).

The products of fractions **2c** and **4c** were eluted earlier than trisaccharides **6** and **8** upon gel-chromatography on Sephadex G-15 as well and thus they are at least hexasaccharides ($n \geq 0$, cf. formulae **2** and **4**).

Total acid hydrolysis of all the fractions afforded only rhamnose, mannose and galactose in the ratio of 1:1:1, thus proving their monosaccharide composition.

Methylation analysis of fractions **2a** and **2b** gave only acetates of 2,3-di-O-methyl-rhamnitol, 2,3,4,6-tetra-O-methyl-mannitol, 2,3,4-tri-O-methyl-mannitol and 2,4,6-tri-O-methyl-galactitol, thus indicating the regiospecificity of linkages in the polysaccharide **2**, whose structure corresponds to that of the natural polysaccharide from *Salmonella newington*. In the case of the polysaccharide **4** the aforementioned methylated sugar derivatives were accompanied by small amount of 1,3,5,6-tetra-O-acetyl-2,4-di-O-methyl-galactitol, originating probably due to the admixture present in the starting monomer.

The most critical point of the synthesis—the stereospecificity of the galactosyl-mannose linkages formed—was established from the Smith degradation (i.e. periodate oxidation, borohydride reduction and mild acid hydrolysis) of fractions **2c** and **4c**. Glc-analysis of the product obtained following acetylation revealed the presence of but 1-O-β-D-galactopyranosyl-glycerol, the amount of α-anomer found to be less than 1% (authentic 1-O-β- and -α-D-galactopyranosyl-glycerols, obtained as described in,[12] served as reference compounds). It thus follows that the anomeric purity of the β-(1–6)-galactopyranosyl-mannose linkages between the trisaccharide repeating units in **2** and **4** is better than 99%, and the polycondensation process can be considered as a reaction with practically absolute stereospecificity.

The molecular mass of the polysaccharides **2** and **4**

was additionally established by two more methods. Borohydride reduction of fractions **2a**, **2b** and **4a** under mild conditions excluding β-elimination from the 3-O-substituted reducing galactopyranose terminus[13] afforded the reduced polysaccharides bearing galactitol at the reducing extremity. Glc-analysis of the products obtained upon methanolysis and acetylation (with authentic samples as reference compounds) allowed to evaluate the molecular mass from the ratio of the peak area of methyl rhamnosides to that of galactitol.

Secondly, the reducing power of the fractions **2a**, **2b**, **4a** and **4b** was measured (with trisaccharide **8** as a reference compound) according to the Park–Johnson method.[14] The data obtained by both methods were very close to each other (Table 2). The structure of the synthetic polysaccharide **2** was confirmed by high-resolution ^{13}C NMR spectroscopy. Spectra of **2** prior to fractionation and of fractions **2a** and **2b** were qualitatively very similar. The spectrum of **2a** exhibited three signals of approximately equal intensities in the region of anomeric carbons resonance at δ 104.3, 103.4 and 101.8 ppm, which correspond to C-1 of β-D-galactopyranose, α-L-rhamnopyranose and β-D-mannopyranose, respectively.[15–17] The comparable intensities of these signals and the absence of signals due to reducing galactose moiety serve as an additional proof of the polymeric nature of **2a**. The presence of signals of C-6 of D-galactopyranose (δ 62.1 ppm) and of L-rhamnopyranose (δ 18.5 ppm) of equal intensities evidenced to the regularity of the polysaccharide obtained. The positions of substitution of the monosaccharide residues followed unequivocally from the down-field chemical shifts of C-3 of D-galactopyranose (δ 81.8 ppm), of C-4 of L-rhamnopyranose (δ 80.8 ppm) and of C-6 of D-mannopyranose (δ 70.25 ppm). Analysis of the interpreted spectrum justifies the high regio- and stereospecificity of the synthetic polysacchride **2a** and is in full agreement with the expected structure.

These arguments hold true for polysacchride **2b** as well, though this fraction possessed lesser molecular mass, and, consequently, signals were present at δ 97.5 and 93.5 ppm, which correspond to C–1 of the reducing galactose moiety. Complete interpretation of spectra of fractions **2a** and **2b** (Table 3) has been performed by comparison with the spectra of model compounds discussed earlier.[16,17]

Preliminary serological assays of the products obtained were carried out as described recently.[18] Polysaccharide **2a** possessed high inhibitory properties in the passive haemagglutination reaction in the *Salmonella* O-factor 3–anti-3 system, it was 8-fold as active as the β-mannose trisaccharide **6**. This is thus indicative of the high biological activity of the synthetic natural polysaccharide **2**. As to trisaccharide **8** and polysaccharide **4a**, both containing α-D-mannopyranose residues, they appeared to be practically inactive in the system mentioned (their activities were by 2 orders less). It demonstrates high biological specificity of the synthesized natural polysaccharide **2**. The detailed data of these serological data will be published elsewhere.

Table 1. Data of PMR ($CDCl_3$) and Raman spectra

Compound	Yield, % [a]	exo-CN to endo-CN ratio [b]	Chemical shifts, δ, ppm (J, Hz): CH_3- of Rha	$>C<$ CN / CH_3	CH_3CO	H-1 of Gal	ν_{CN}, cm^{-1} Raman spectrum
10	63	3.5:1	1.36 (6)	1.85 endo 1.78 exo	1.98; 2.02x2; 2.08x2; 2.14; 2.18x2	5.85(5) exo-CN 5.68(5) endo-CN	2240
12	62	3.7:1	1.39 (6)	1.87 endo 1.76 exo	1.96; 1.98; 2.00; 2.06x2; 2.10; 2.14x2	5.86(5) exo-CN 5.72(5) endo-CN	2240
14	43	3.2:1	1.30 (6)	1.82 endo 1.76 exo	1.96x2; 1.98; 2.06x3; 2.12x2	5.82(5) exo-CN 5.70(5) endo-CN	2240
15 [c]	95	2.8:1	-	1.85 endo	2.06x2; 2.11 exo-CN	5.88(5) exo-CN	2235
			-	1.76 exo	2.06x2; 2.09 endo-CN	5.72(5) endo-CN	2238

[a] After column chromatography on silica gel

[b] Determined from the ratio of integral intensities of signals of CH_3-groups of the dioxolane ring

[c] Data from Ref. 4

Table 2. Products of fractionation of the polysaccharides **2** and **4** on Bio-Gel P-4

Product	Elution time, min [a]	Yield, mg (%)	$[\alpha]_D^{20}$ (H_2O, equil.)	Molecular mass (n) determined from	
				Glc analysis	Reducing power
2a	42	40(34)	-23.9°	5.2×10^3(9)	5.8×10^3(10)
2b	75	30(25.5)	-21.8°	2.4×10^3(3)	2.4×10^3(3)
2c	93	40(34)	+1.5°	-	-
4a	42	30(33)	+27.8°	5.6×10^3(10)	6.3×10^3(11)
4b	70	20(22)	+50.3°	-	3.4×10^3(5)
4c	95	30(33)	+29.2°	-	-

[a] Upon analytical gel-chromatography on a Bio-Gel P-4 column, elution times of dextrane T-40, trisaccharide **8** and D-mannose were 42, 103 and 115 min, respectively

Table 3. Data of ^{13}C NMR spectra of the polysaccharides **2a** and **2b** (δ, ppm)

	2a			**2b**		
	Man [a]	Rha	Gal	Man [a]	Rha	Gal
C-1	101.8	103.4	104.3	101.8	103.45	104.3
C-2	71.6	71.4	71.4	71.6	71.4	71.4
C-3	74.3	71.6	81.8	74.2	71.8	81.7
C-4	68.0	80.8	69.7	68.0	80.8	69.6
C-5	76.25	69.1	76.45	76.25	69.1	76.6
C-6	70.25	18.5	62.1	70.3	18.25	62.1

[a] C-5 and C-6 of the terminal mannopyranose residue resonate at 77.5 and 62.25 ppm, respectively

CONCLUSION

As has been already mentioned, the synthesis of the O-antigenic polysaccharide of *Salmonella newington* presented here, is the first synthesis of a biologically active and highly specific polysaccharide. It demonstrates the possibilities of the method of synthesis of polysaccharides developed in our laboratory for solution of complex problems in this field.

EXPERIMENTAL

Optical rotations were determined with a Perkin–Elmer 141 polarimeter at 20°, m.ps—with a Kofler apparatus. PMR spectra were recorded with a Tesla BS-497 spectrometer (100 MHz, CSSR) with Me_4Si as the internal standard. ^{13}C-NMR spectra were obtained with a Bruker HX-90E-WH-360 spectrometer (90.5 MHz) having a 16/8 K memory. The number of transients was *ca* 30,000, the pulse width 17 μsec and the aquisition time 0.7 sec. Spectra were recorded at 20° for 13% solns of free polysaccharides in D_2O with MeOH as an internal standard (δ 50.15 ppm relative to Me_4Si). All chemical shifts are expressed in δ. Glc-MS was carried out on a Varian MAT-111 (GNOM) instrument on a steel 1 m-long column packed with 5% of SE-30 on Chromaton N-AW-DMCS (A) using helium as a carrier gas. The same packing in a glass 1m-long column fitted in Pye Series 105 Chromatograph and 6% of NPGS + 4% of Apiezon L on Chromaton N-AW (B) in a steel 2m-long column fitted in LChM-8MD instrument with nitrogen as a carrier gas were used for glc. Raman spectra were recorded on a "Spex Ramalog-6" spectrometer, excitation wavelength being 514.5 nm, excitation power—100–200 mW. Column chromatography was performed on silica gel L 100/250 μ (Chemapol) (50 g per 1 g of a mixture) with gradient elution from benzene to EtOAc; tlc—on silica gel LS 5/40 μ (Chemapol) with detection by spraying with 25% HSO_4 aq followed by heating at *ca* 150°. PC was carried out by descending method on Filtrak FN-11 paper, visualization of spots by KIO_4–$AgNO_3$–KOH reagent.[19] The following solvent systems were used for chromatography: benzene–ethyl acetate 1:1 (C), toluene–EtOAc 1:1 (D), BuOH–pyridine–H_2O 6:4:3 (E). Ion-exchange chromatography of neutral sugars was carried out with the Technicon SC-II system on a column (25 × 0.6 cm) packed with anion-exchange resin DA × 4 (Durrum, U.S.A.) in 0.5 M sodium borate buffer (pH 9.0) at 55°. The elution rate was 1 ml/min. Analytical gel chromatography was performed on columns with Bio-Gel P-6, 200-400 mesh (40 × 1.5 cm) and Bio-Gel P-4, 100–200 mesh (57 × 1.0 cm). The orcinol–sulphuric acid reagent was used to monitor separations. Solutions were concetrated *in vacuo* at 40°.

Acetonitrile was dried with $CaCl_2$ and distilled from $CaCl_2$ and then from CaH_2. Nitromethane was distilled over urea at 100 mm Hg and then from CaH_2. CH_2Cl_2 and $CHCl_3$ were washed with conc. H_2SO_4 and water, dried with $CaCl_2$ and distilled from CaH_2. Pyridine was distilled from KOH and then from metallic Na. Acetic anhydride was distilled from P_2O_5.

Triphenylchloromethane was recrystallised twice from a toluene–heptane mixture containing *ca* 5% of acetyl chloride, the crystals were separated by decantation and dried *in vacuo* at room temp.

Triphenylmethylium perchlorate was obtained as described in[20] and purified by reprecipitation before use as follows: 1.2 g of the product were dissolved in nitromethane (10 ml) at room temp and precipitated by addition of abs. ether (50 ml). The soln was removed by decantation and the bright-yellow crystals (0.7 g) were dried *in vacuo*.

4,6-*Di*-O-*acetyl*-3-O-[2,3-*di*-O-*acetyl*-4-O-(2,3,4,6-*tetra*-O-*acetyl*-*β*-D-*mannopyranosyl*)-α-L-*rhamnopyranosyl*]-1,2-O-(1-*cyanoethylidene*)-α-D-*galactopyranose* **10**. Decaacetate **5** (3.3 g, 3.6 mmol) was treated with a soln of HBr (40% w/w) and Ac_2O (1% w/w) in glacial AcOH as described earlier.[8] The chromatographically homogeneous glycosyl bromide obtained (its mobility in tlc relative to **5** in solvent system C is equal to 1.13) was treated with NaCN (890 mg, 18.2 mmol) and tetra-n-butylammonium iodide (1.3 g, 3.5 mmol) in acetonitrile (10 ml) at room temp for 15 hr with stirring. The mixture was worked-up as described earlier[4] for synthesis of **15** to give after chromatography **10** (2.0 g, 63%) as a white solid, mobility in tlc relative to **5** is equal to 1.21 (C), $[\alpha]_D$ − 8.5° (*c* 2.30, $CHCl_3$). (Found: C, 50.52; H, 5.77; N, 1.62%. Calc. for $C_{37}H_{49}O_{23}N$: C, 50.74; H, 5.64; N, 1.60%.) Data of PMR and Raman spectra are given in Table 1.

4,6-*Di*-O-*acetyl*-3-O-[2,3-*di*-O-*acetyl*-4-O-(2,3,4,6-*tetra*-O-*acetyl*-α-D-*mannopyranosyl*)-α-L-*rhamnopyranosyl*]-1,2-O-(1-*cyanoethylidene*)-α-D-*galactopyranose* **12**. This compound was obtained analogously, starting from **7** (6.5 g, 7.15 mmol), in a yield of 3.88 g (62%), white solid, mobility in tlc relative to **7** is equal to 1.35 (C), $[\alpha]_D$ + 26.9° (*c* 2.65, $CHCl_3$). (Found: C, 50.79; H, 6.12; N, 1.57%). Calc. for $C_{37}H_{49}O_{23}N$: C, 50.74; H, 5.64; N, 1.60%). Data of PMR and Raman spectra see Table 1. Crystallisation from abs. MeOH at −5° afforded crystalline sample of **12**, m.p. 180–182°, $[\alpha]_D$ + 26.2° (*c* 1.45; $CHCl_3$), whose PMR spectrum was superimposable with that of an amorphous sample.

4,6-*Di*-O-*acetyl*-3-O-[2,3-*di*-O-*acetyl*-4-O-(2,3,4,6-*tetra*-O-*acetyl*-*β*-D-*glucopyranosyl*)-α-L-*rhamnopyranosyl*]-1,2-O-(1-*cyanoethylidene*)-α-D-*galactopyranose* **14**. Decaacetate **9** (2.9 g, 3.2 mmol) was converted into glycosyl bromide as described above and then treated with NaCN (780 mg, 15.9 mmol) and tetra-n-butyl-ammonium iodide (1.2 g, 2.7 mmol) in acetonitrile (20 ml) to yield **14** (1.2 g, 43%) as a white solid, mobility in tlc relative to **9** is equal to 1.28 (C), $[\alpha]_D$ − 6.2° (*c* 3.36, $CHCl_3$). (Found: C, 50.67; H, 5.83; N, 1.83. Calc. for $C_{37}H_{49}O_{23}N$: C, 50.74; H, 5.64; N, 1.60%). Data of PMR and Raman spectra see Table 1.

4,6-*Di*-O-*acetyl*-3-O-[2,3-*di*-O-*acetyl*-4-O-(2,3,4-*tri*-O-*acetyl*-6-O-*triphenylmethyl*-*β*-D-*mannopyransyl*)-α-L-*rhamnopyranosyl*]-1,2-O-(1-*cyanoethylidene*)-α-D-*galactopyranose* **1**. To a soln of **10** (1.64 g, 1.8 mmol) in $CHCl_3$ (2 ml) were added abs. MeOH (10 ml) and 0.1 M methanolic NaOMe (2 ml) and the soln was kept for 30 min at ambient temp. The mixture was neutralized with 0.1 M methanolic AcOH (0.22 ml) and concentrated to a thick syrup. The residue was coevaporated with pyridine (2 × 5 ml), dissolved in pyridine (9 ml) and triphenylchloromethane (775 mg, 2.7 mmol) was added. After 48 hr at room temp the mixture was chilled to 0°, Ac_2O (4 ml) was added and the mixture was left at room temp for 15 hr. To the chilled (0°) soln MeOH (3 ml) was added and the mixture was left at room temp. After 1 hr the mixture was diluted with 1:2 $CHCl_3$–hexane (150 ml) and washed with water (4 × 100 ml). The upper, organic layer was separated, concentrated and coevaporated with heptane to dryness. The residue was dried *in vacuo* and applied onto a column with silica gel (silica gel slurry for the column packing was made in benzene containing 1% of pyridine). Chromatography gave the starting **10** (270 mg, 17%), a mixture of mono-O-trityl derivatives (590 mg) and **11** (530 mg, 23%), white solid, mobility in tlc relative to **10** is equal to 1.78 (D), $[\alpha]_D$ −13.5° (*c* 0.74, $CHCl_3$). PMR data (CCl_4): 1.4–2.2 (24 H, CH_3 of rhamnopyranose, cyanoethylidene and acetyl groups), 7.0–7.4 (30 H, aromatic). Methylation analysis revealed the presence of acetates of 2,3-di-O-methyl–rhamnitol, 2,3,4-tri-O-methyl–mannitol and 4-O–methyl–galactitol 1:1:1 (glc–MS).

The repeated column chromatography of a mixture of monotrityl ethers gave **1** (290 mg, 15%), white solid, mobility in tlc relative to **10** is equal to 1.59 (D), $[\alpha]_D$ −9.8° (*c* 2.60; $CHCl_3$). PMR data (CCl_4): 1.4–2.2 (27 H, CH_3 of rhamnopyranose, cyanoethylidene and acetyl groups), 7.0–7.4 (15 H, aromatic). Methylation analysis revealed the presence only of acetates of 2,3-di-O-methyl–rhamnitol, 2,3,4-tri-O-methyl–mannitol and 4,6-di-O-methyl–galactitol in the ratio 1:1:1 (glc–MS).

4,6-*Di*-O-*acetyl*-3-O-[2,3-*di*-O-*acetyl*-4-O-(2,3,4-*tri*-O-*acetyl*-6-O-*triphenylmethyl*-α-D-*mannopyranosyl*)-α-L-*rhamnopyranosyl*]-1,2-O-(1-*cyanoethylidene*)-α-D-*galactopyranose* **3**. The amorphous **12** (880 mg, 1 mmole) was deacetylated as described above, the product treated with triphenylchloromethane (330 mg, 1.2 mmol) in pyridine (5 ml) for 72 hr at room temp and the mixture was worked-up as above. Column chromatography afforded **12** (220 mg, 25%), a mixture of mono-trityl ethers (300 mg) and **13** (100 mg, 8%), white solid, mobility in tlc relative to **12** is equal to 1.88 (D), $[\alpha]_D$ + 22.6° (*c* 2.00, $CHCl_3$), PMR data (CCl_4): 1.4–2.2 (24 H, CH_3 of rhamnopyranose, cyanoethylidene and acetyl groups), 7.0–7.4 (30 H, aromatic), a band at 2240 cm^{-1} was present in the Raman spectrum. Methylation analysis gave acetates of 2,3-di-O-methyl–rhamnitol, 2,3,4-tril-O-methylmannitol and 4-O–methyl–galactitol 1:1:1 (glc–MS).

The repeated chromatography of a mixture of mono-trityl ethers gave **3** (290 mg, 27%), white solid, mobility in tlc relative to **12** is equal to 1.57 (D), $[\alpha]_D$ +33.1° (*c* 1.19, $CHCl_3$), PMR data (CCl_4): 1.4–2.2 (27 H, CH_3 of rhamnopyranose, cyanoethylidene and acetyl groups), 7.0–7.4 (15 H, aromatic). Methylation analysis revealed the presence of acetates of 2,3-di-O-methyl-rhamnitol, 2,3,4-tri-O-methyl-mannitol and 4,6-di-O-methyl-galactitol (1:1:1) and, besides, no more than 5% of 1,5-di-O-acetyl-2,3,4,6-tetra-O-methyl–mannitol and 1,2,3,5,6-penta-O-acetyl–4-O–methyl–galactitol (glc–MS).

Polycondensation. In one limb of a tuning fork-shaped tube fitted with a ground joint, which enables its connection to a vacuum system, was placed a soln of monomer **1** (260 mg, 0.24 mmol) in abs. benzene (1.5 ml), and in the other −0.1 M soln of triphenylmethylium perchlorate in nitromethane (0.24 ml) and the solns were freeze-dried (10^{-3} mm Hg). Nitromethane (twice distilled from CaH_2 at 10^{-3} mm Hg) (1.0 ml) was distilled into the first limb, and lyophilisation was repeated followed by drying of the residues for several hr. CH_2Cl_2 (twice distilled from CaH_2 at 10^{-3} mm Hg) (2.0 ml) was distilled into the tube, and the solns of monomer and catalyst were mixed and a yellow transparent soln left at room temp for 65 hr in the darkness. The reaction vessel was connected with atmosphere and the yellow mixture was treated with 90% aqueous trifluoroacetic acid (1.0 ml) for 30 min at room temp. Pyridine (1.0 ml) was then added, the discoloured soln was diluted with $CHCl_3$ (50 ml) and washed with water (3 × 50 ml). The organic layer was separated, taken to dryness and dried *in vacuo*. The residue (250 mg) was dissolved in $CHCl_3$ (6 ml), abs. MeOH (20 ml) and M methanolic NaOMe (2.0 ml) were added. A white floccular ppt appeared in *ca* 20 min and the mixture was stirred at room temp overnight. It was diluted with water (40 ml), whereupon complete dissolution occurs, and neutralized with a cation-exchange resin KU-2 (H^+). The resin was filtered off, washed with water (3 × 10 ml) and the combined aqueous soln was washed with $CHCl_3$ (3 × 50 ml). The aqueous layer was

separated, clarified by centrifugation and evaporated. The residue was dried *in vacuo* to yield the polysaccharide **2** (127 mg), $[\alpha]_D$ −15.2° (*c* 1.27, H_2O, equilibrium).

Analogously, starting from the monomer **3** (200 mg, 0.19 mmol), the polysaccharide **4** (84 mg) was obtained, $[\alpha]_D$ +32.5° (*c* 0.84, H_2O, equilibrium).

Fractionation of polysaccharides. The polysaccharides obtained were fractionated on a Bio-Gel P-4 column (100–200 mesh, 58 × 1.8 cm, V_0 43 ml, elution with 0.1 M AcOH, elution rate 0.8 ml/min; dextrane T-40 and mannose were eluted from this column at 43-rd and 150-th minutes, respectively) and three fractions were collected: (a) 28–63 ml; (b) 64–95 ml, and (c) 96–120 ml. The pooled fractions were concentrated and freeze-dried to yield products **2a**, **2b**, **2c**, **4a**, **4b** and **4c**, whose yields and properties are listed in Table 2.

The material of each fraction (*ca* 0.5 mg) was heated in 0.3 M HCl (2 ml) at 100° for 20 hr, the solns were coevaporated with water (3 × 5 ml) and the hydrolysates were analysed by anion-exchange chromatography. In all cases only rhamnose, mannose and galactose were detected in the ratio of 1:1:1, equimolar mixture of the above authentic monosaccharides serving as a reference.

Determination of configuration of galactosyl-mannose linkages. Polysaccharide **2c** (40 mg) was dissolved in 0.1 M sodium periodate (5 ml) and the soln was left at room temp for 65 hr in the darkness. $NaBH_4$ (30–40 mg) was added and the soln was left at room temp for 15 hr. The soln was acidified with AcOH and desalted by passing through a column of Sephadex G-15. The eluate was taken to dryness and the residue was treated with 0.5 M HCl (2 ml) at room temp for 48 hr. The hydrolysate was coevaporated with water, dried *in vacuo* and acetylated with 1:1 Ac_2O–pyridine (2 ml) at room temp for 15 hr. To the mixture EtOH (2 ml) was added, the soln left at room temp for 1 hr, diluted with $CHCl_3$ (20 ml) and washed with water (3 × 20 ml). The $CHCl_3$ layer was separated and taken to dryness. According to tlc examination, a product with R_f 0.5–0.6 (D), which coincided with authentic samples of anomeric 1-O-D-galactopyranosyl-glycerols acetates,[12] constituted no less than 80%. It was isolated by column chromatography and subjected to glc (250°, column A). In comparison with authentic samples 1-O-β-D-galactopyranosyl-glycerol acetate was identified as the only product (retention time 18.0 min); the corresponding α-anomer has a retention time of 13.2 min. Analogous results were obtained upon Smith degradation of the polysaccharide **4c**.

Determination of degree of polymerization of polysaccharides. According to PC (E), the polysaccharides **2a** and **4a** remain at the application point after 7 days. The bulk of polysaccharides **2b** and **4b** behave similarly and faint zones were also detected with mobilities of 0.1–0.2 relative to trisaccharide **6**, which, in turn, had a migration of 36 cm.

Polysaccharides **2a**, **2b** and **4a** (trisaccharide **8** was studied simultaneously) (ca 2–3 mg) were dissolved in 1% aqueous boric acid (2 ml) and portions of $NaBH_4$ (3 × 5 mg) were added within 5 hr. The mixture was left at +5° for 15 hr, deionized with a cation-exchange resin KU-2 (H^+), the latter was filtered off and washed with water (2 × 3 ml). The combined aqueous solns were taken to dryness and coevaporated with MeOH (3 × 5 ml). The residue was dissolved in M methanolic HCl (1 ml) and heated in a sealed tube at 100° for 20 hr. The methanolysate was taken to dryness and then acetylated and worked-up as above. The $CHCl_3$ layer was investigated by glc (column B, 175°, 3°/min). In comparison with authentic samples were found acetates of methyl rhamnosides (retention time 4.8 min), methyl galacto- and mannosides (retention time 11.0 min) (rhamnitol acetate emerges at 9.2 min under the above conditions) and two products with retention times of 10.0 and 15.5 min. The latter coincided with authentic galactitol acetate, while the former is apparently an acetate of anhydrogalactitol(s) (it was found in a control experiment) formed upon methanolysis and acetylation. The degree of polymerization was calculated from the ratio of the peak area of methyl rhamnosides to the sum of peak areas of galactitol and its anhydroderivative(s).

Acknowledgements—The authors express their gratitude to Dr. A. S. Shashkov for recording and aid in interpretation of the ^{13}C NMR spectra, to Dr. Yu. Ya. Tendetnick for serological assays and to Dr. V. V. Berdjugin for recording of the Raman spectra.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 157 to 164, 1981
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0040-4020/81/Suppl. 1-0157-08 $02.00/0
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A NEW SYNTHETIC ROUTE TO (±) LYSERGIC ACID[1]

R. RAMAGE†*, V. W. ARMSTRONG and S. COULTON
The Robert Robinson Laboratories, University of Liverpool, Liverpool L69 3BX, England

(*Received in UK* 24 *July* 1980)

Abstract—A route to the synthesis of lysergic acid, **1** is described based on a mechanism proposed for the racemisation of lysergic acid and related compounds. The strategy involves cyclisation of the aminodienoic esters **19** and **22** to produce tetrahydropyridine systems. A modified Curtius degradation sequence is described.

Ergot is the product of the filamentous fungus *Claviceps purpurea* (Fries) Tulasne which grows parasitically on the rye plant and as early as the seventeenth century it was established[2–4] that ergot was responsible for epidemics known as St. Anthony's Fire. From historical survey it became clear that outbreaks of such epidemics followed wet and barren seasons when the flour of rye, infested by ergot, was used for bread manufacture. Of the two forms of the disease convulsive ergotism caused twitching and convulsions whilst gangrenous ergotism was characterised by violent burning pains in the limb which often resulted in amputation. Although the adverse results of the pharmacological activity of ergot alkaloids have long been known, as well as the more recent recognition of the hallucinatory properties of lysergic acid diethylamide,[5] it is important to remember that ergot alkaloids exhibit a broad and useful spectrum of pharmacological properties. The positive pharmacological importance of ergot alkaloids was first recognised during the Middle Ages and led to introduction of crude preparations of ergot into medical practice for induction of uterine contractions.

During the twentieth century isolation and structural elucidation of the components of ergot have led to the identification of two main classes of ergot alkaloids,[6,7] one of which is based on the structure of lysergic acid **1**[8–10] and is constituted of amides having the following representative structures: ergine **2**, ergonovine **3**, and a series of peptide alkaloids having the general formula **5**. The naturally occurring alkaloids are known in isomeric pairs which differ only in the stereochemistry at C–8. This epimerisation may be accomplished by either acid or alkali and it is of significance that the constituents of fresh ergot are optically active and belong to the pharmacologically active 8β-series. The acidity of the C–H bond at C–8 also plays an important role in the chemistry and stability of lysergic acid and its derivatives. Careful stereochemical arguments based on hydrogenation studies,[11–12] as well as the transformation of both lysergic and isolysergic acids by hot acetic anhydride into the same lactam **10**,[9] showed that isolysergic acid **6** is epimeric at C–8 but retains the same configuration at C–5 as in lysergic acid **1**. The absolute configurations of the two acids were elucidated by both optical rotary dispersion[13] and degradative methods.[14] In 1974 the conjugated acid, **8**, was isolated[15] from saprophytic cultures of a strain of *Claviceps paspali* (Stevens and Hall) whereupon it was established[16] that this isomer could be transformed easily by alkaline treatment into lysergic acid **1** in which the olefinic bond is preferentially conjugated with the indole system rather than the carbonyl function. From a biosynthetic standpoint[17] it is interesting to note that free lysergic acid **1** is never found in large quantities whereas paspalic acid **8** occurs abundantly in certain *Claviceps* strains.

The retrosynthetic planning which controlled our approach to the synthesis of *racemic* lysergic acid **1** was founded upon the observation[18] that both (+)-lysergic acid **1** and (+)-isolysergic acid **6** could be converted into *racemic* lysergic acid **1** by barium hydroxide in aqueous solution at high temperatures. Further evidence of the stereochemical lability of the lysergic system is to be found in the formation of the *racemic* hydrazide **7** by hydrazine treatment of the natural alkaloids having the general structure **5**.[19] These two observations involve loss of stereochemical integrity at both the C-5 and C-8 positions which is at first sight surprising since only the carboxyl function at C-8 would be expected to undergo the epimerisation which relates **1** and **6**. In order to rationalise the epimerisation at the apparently unactivated C-5 position Woodward proposed[20] that the racemisation process proceeded through the achiral tricyclic intermediate **9** which could be formed by retro-Michael fragmentation of **1**, **6** or **8**. Since the postulated intermediate **9** is achiral, any subsequent cyclisation of the amino function by Michael addition to the dienoic acid system to form ring D must produce racemic products which would be epimeric at C-8. It has to be assumed that the isolation of (±)-lysergic acid **1** and the (±)-hydrazide **7** is due to the equilibria in these reactions being displaced by the greater insolubility of the β- and α- epimers of these compounds respectively under the reaction conditions employed. The failure to isolate (±)-paspalic acid **8** from the cyclisation of intermediate **9** can be explained by the aforementioned facile equilibration of **8** to lysergic acid **1** as a consequence of their relative thermodynamic stabilities. A major consideration in favour of the intermediacy of **9** is that such a structure

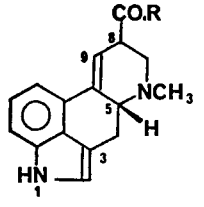
†Dedicated to the late Prof. R. B. Woodward with whom it was both a privilege and a pleasure to be associated in research.

*Present address: Department of Chemistry, UMIST, Manchester M60 1QD

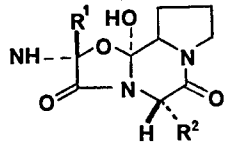
would be chemically stable towards hydrolytic cleavage under the alkaline reaction conditions. Alternative mechanisms involving imonium intermediates would be expected to yield hydrolysis products during the prolonged alkaline treatment leading to racemisation. It is significant to note, in the context of the racemisation mechanism proposed by Woodward, that the alternative mode of cleavage of ring D in lysergic acid **1** is responsible for the formation of the chiral methylene lactam **10** from **1** and **6** on treatment[9] with acetic anhydride by a path which probably proceeds *via* the chiral intermediate **11**.

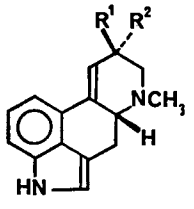
Thus if the elegant explanation put forward by Woodward for the facile racemisation of lysergic acid **1** is correct then it follows that synthesis of the intermediate **9** would, in fact, produce (±)-lysergic acid **1** by spontaneous cyclisation. In order to circumvent the anticipated problems associated with indole-naphthalene tautomerism in **9** it was decided to aim for the modified target **19** which has the masked indolic system employed in the two preceding synthesis[21,22] of (±)-lysergic acid **1** in which the final stage involves oxidation of the indoline system of **30**. The first[21] total synthesis of this important substance was achieved in 1955 by a collaboration of Woodward and the Eli Lilly group. In the course of this classical work a route to the aldehyde **12** was developed, which we have optimised to allow satisfactory production of this key intermediate for the synthesis of **19**. After abortive attempts to synthesise a phosphorane capable of reacting with **12** to give **19** directly it was decided to utilise the readily accessible reagent **13**[22] and introduce the amino function later by selective degradation of a carboxylic acid group using the Curtius degradative procedure.

The stereochemistry of the olefinic double bond formed in the Wittig reaction involving the phosphorane **13** should lead to the *E*-configuration required for the projected synthesis by analogy with the work of House[24] who showed that Wittig reactions involving resonance stabilised ylides afford the predominant stereoisomer having the carbonyl function *trans* to the larger group at the β-position. Reaction of **13** with benzaldehyde afforded **34** as the sole isolated product, the NMR spectrum of which exhibited a 1 H resonance at 7.38 δ consistant with that expected[25] for the β-proton deshielded by the adjacent *cis* ester function. Furthermore reaction of **12** with carbomethoxymethylenetriphenylphosphorane gave the dienoic ester **35** in which the acyclic proton β- to the ester function was found in the NMR spectrum to be deshielded into the aromatic region in accordance with the *E*- configuration shown. The complementary part of the AB system (J = 16 Hz) due to the acyclic

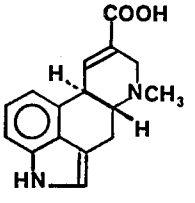


1, R=OH
2, R=NH_2
3, R=NH.CH(Me).CH_2OH
4, R=NH.CH(Et).CH_2OH

5,R= 



1; R^1=COOH, R^2=H
6; R^1=H, R^2=COOH
7; R^1=H, R^2=CO.$NHNH_2$



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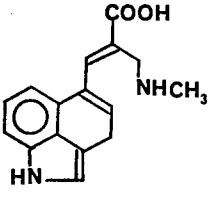

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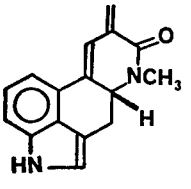

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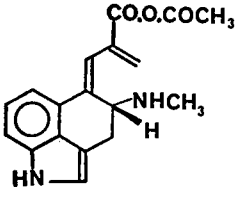

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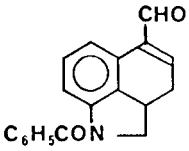

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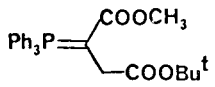

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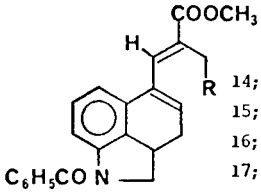
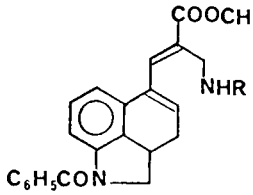
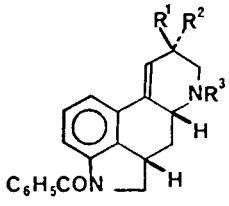


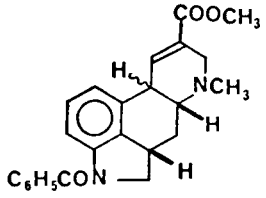
14; R=COOBu^t
15; R=COOH
16; R=CON$_3$
17; R=NCO



18; R=H
19; R=Me
20; R=COCF$_3$
21; R=COOMe
22; R=CHO



23; R'=COOMe, R^2=H, R^3=Me
24; R'=H, R^2=COOMe, R^3=Me
25; R'=COOMe, R^2=R^3 =H
26; R'=R^3=H, R^2=COOMe
27; R'=COOMe, R^3=CHO R^2=H
28; R'=H, R^2=COOMe, R^3=CHO



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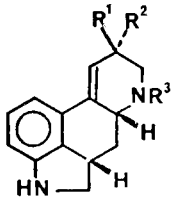


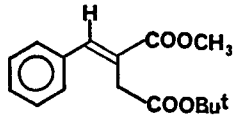
30; R'=COOMe, R^2=H, R^3=Me
31; R'=H, R^2=COOMe, R^3=Me
32; R'=COOMe, R^2=R^3=H
33; R'=R^3=H, R^2=COOMe

proton α to the ester group can be observed approximately 1.2 ppm upfield at 6.35 δ together with the olefinic proton of the tricyclic system. As expected for such a diene, **35** reacted smoothly with 4-phenyl-1,2,4-triazoline-3, 5-dione to give a Diels Alder adduct in almost quantitative yield. Two isomers were formed in the ratio of 9:1 and these were easily separated due to the insolubility of the minor isomer. Consideration of molecular models and the Woodward Hoffmann[26] selection rules strongly indicate that the major isomer has the relative stereochemistry represented in **36** arising from attack of the azo-dienophile from the α-face of the diene system. This allows ring D of the pentacyclic structure to adopt a boat conformation enabling maximum overlap of the π-orbitals in the styrene system which is a consequence of the C–H bonds at C-3 and C-5 being *cis* and quasi axial. The same argument has been invoked by the Sandoz researchers[27] in the course of structural assignment of 2,3-dihydrolysergic acid (+)-butanolamide, which is produced by Zn/HCl reduction of the indole ring in the corresponding lysergic acid derivative **4**. As a result of these considerations we would assign the structure **37** to the minor Diels Alder product. It can readily be seen that this synthetic approach could lead to the interesting 7-aza-lysergic system with judicious choice of the azo-dienophile component for reaction with **35**.

The reaction between **12** and **13** was found to be slow but could be induced to give the required diester **14** in 79% yield using benzene/t-butanol (1:1) as solvent at reflux for 4 days. Only one isomer, as indicated by NMR, hplc and tlc analysis was isolated in which the acyclic olefinic double bond may be assigned the *E*-configuration, since the acyclic olefinic proton resonance was observed together with the aromatic protons in the region 6.7–7.8 δ in accord with the chemical shifts quoted for the reference compounds **34** and **35**. With the diester **14** in hand the next task was to effect the transformation to the intermediate **19** required for the crucial cyclisation to the tetracyclic products **23**, **24** and **29**. After acidolytic cleavage of the t-butyl ester function produced the corresponding acid **15**, the introduction of the amino function was accomplished by the Curtius degradation procedure in overall yield of 80%. This optimisation was the result of many preliminary experiments in which the acid azide formation was investigated using carboxyl activation as the acid chloride or carbonic mixed anhydride with either sodium azide or tetramethylguanidinium azide,[28] or directly using diphenylphosphonic azide,[29] The sele ted conditions employed tetramethylguanidinium azide and the diphenylphosphinic mixed anhydride[30] in CH_2Cl_2. Thermal rearrangement of the acid azide **16** to the isocyanate **17**

proceeded smoothly in refluxing benzene, however it was anticipated that hydration of the isocyanate and decarboxylation of the resulting carbamic acid under the usual aqueous acid conditions would cause untoward hydrolytic side reactions. In order to avoid this occurring, it was decided to effect the acid catalysted hydration using *p*- toluenesulphonic acid monohydrate in anhydrous medium on the premise that the reatent contains sufficient water for hydration and that the subsequent decarboxylation step would be driven by formation of the amine salt. This result was realised by performing the reaction in benzene/ether as solvent, whereupon the *p*-toluenesulphonate of **18** crystallised from the reaction mixture.

The free amine **18** was found to be exceedingly reluctant to cyclise to the tetracyclic compounds, however this result did not cause undue anxiety that the corresponding secondary amine **19** might also be recalcitrant when called upon to cyclise since the work of Harley–Mason[31] on the oxidative cyclisation of a series of substituted dopamines **38** to the bicyclic quinones **39** showed the secondary amines to be vastly superior in this respect. Indeed it was possible to prepare derivatives of the amine **18** such as the trifluoroacetamide **20** and the urethane **21** which were also found to exist as the tricyclic structures in which the N–H IR absorption was particularly diagnostic. If the Woodward hypothesis is a correct representation of the mechanism of lysergic acid racemisation then it follows that any methylation method which produces the secondary amine **19**, however transiently, should afford the 2,3-dihydrolysergic system as a result of spontaneous cyclisation. The method selected for the purpose was the Eschweiler–Clarke reaction using HCOOH/HCHO involving hydride reduction of the intermediate imonium species. Although this would normally be expected to give the dimethylated amine it was found that the intermediate secondary amine preferred to cyclise rather than undergo the second methylation step. This reaction gave 62% yield of three tetracyclic isomers in the ratio 9:3:2 which were assigned the structures **23**, **24** and **29** respectively. Hydrogenation of these compounds in methanol using 10% Pd/C indicated that only one olefinic double bond was present and, therefore, that the products were tetracyclic. A combination of crystallisation and chromatography allowed a separation of the components of the mixture, although the minor isomer **29** could not be isolated in pure form due to contamination with **24** as a result of rearrangement induced by silica chromatography. The major products **23** and **24** exhibited IR CO absorption bands corresponding to saturated ester functions and the UV spectra were in agreement with that expected for the 2,3-dihydrolysergic system.[27] Although both major isomers clearly incorporated an olefinic proton, as indicated by the NMR spectra, it was noteworthy that the signals in **23** (6.52 δ) and **24** (6.19 δ) were consistent with known lysergic and isolysergic analogues. The relative stereochemical assignments at C-8 were clarified by equilibration studies using conditions which are known to favour methyl lysergate over methyl isolysergate.[16] It was found that **24** could be epimerised to **23** in refluxing MeOH whereas, under the same conditions, **23** was unchanged. The relative configuration at C-3 and C-5 are determined during the cyclisation of **13**, and, under thermodynamic control, it is to be expected that the developing π-overlap between the 9, 10 double bond and the



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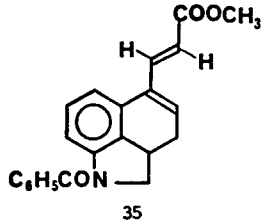

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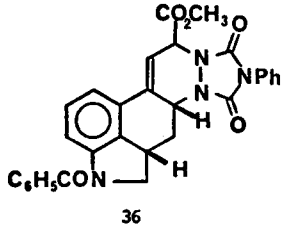

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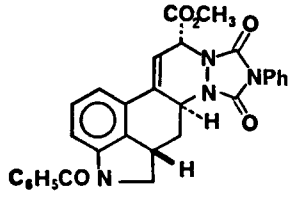

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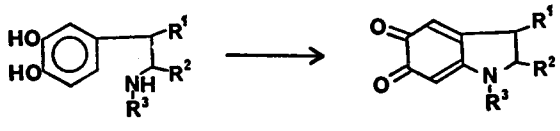

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aromatic ring should be the dominant factor in product development. This would result in the C-3 and C-5 C–H bonds being *cis* as represented in **23** and **24**. Stadler *et al.*[27] have used the same argument for the relative stereochemistry at C-3 and C-5 in the 2,3-dihydrolysergic system; in their case the C-3 sp^3 stereochemistry was introduced relative to C-5.

The minor product **29** arising from the cyclisation of **19** exhibited the expected IR absorption at 1708 cm^{-1} attributed to the conjugated ester function compared with **23** (1728 cm^{-1}) and methyl lysergate (1728 cm^{-1}). The assignment of the $\Delta^{8,9}$ double bond was also supported by comparison of the UV spectra, the NMR signal due to the 9-H deshielded by the COOMe group to 7.37 δ, and the finding that **29** underwent facile rearrangement to the $\Delta^{9,10}$ isomer **24**. This latter observation is consistent with the known propensity[16] of paspalic acid **8** to rearrange to lysergic acid **1**. The relative stereochemistry at C-3 and C-5 in **29** is the same as in **23** and **24**, however, the assignment at C-10 is not certain.

The mixture of **23** and **24** was treated with HCl in MeOH to afford a mixture of methyl 2,3-dihydrolysergate **30** and the 8α-epimer, **31** in the ratio 5:2. Methanolysis of the N-benzoyl group of **23** or **24** separately gave the same mixture of **30** and **31** which was found to be identical in all respects with material used in the first synthesis of lysergic acid **1**.[21] Although this had been thought to be solely the 8β-epimer **30**, the mixture of epimers could be detected only by NMR, and hplc; two techniques not available to the researchers in 1955. Accurate mass fragmentation data on **23** and **30/31** exhibited an important ion corresponding to P-C_2H_5N which would result from retro-Diels Alder fragmentation of ring D. Since the intermediate methyl 2,3-dihydrolysergate **30** together with the 8α-epimer **31** have previously been transformed into lysergic acid **1** by Kornfeld *et al.*[21] the route described above not only constitutes a synthesis of lysergic acid but also lends support to Woodward's proposal about the racemisation mechanism and, additionally, helps to rationalise the greater thermal and photochemical stability of the 9,10-dihydro series of lysergic acid derivatives.

In order to extend this synthetic route based on cyclisation of **19** other derivatives of the parent amine **18** were prepared. As stated previously the trifluoroacetamide **20** and the urethane **21** did not cyclise to tetracyclic structures analoguous to **23**, however formylation of the primary amine **18** using formic–acetic mixed anhydride gave the mixture of isomers **27** and **28** which could be separated by fractional crystallisation. The tetracyclic nature of the products was substantiated by hydrogenation with 10% Pd/C to afford dihydro compounds which could be compared readily with the product derived by hydrogenation and formylation of **18**. Support for the structures **27** and **28** was afforded by the IR data which lacked the NH absorption expected for **22**, which would be a tricyclic product of similar type to **20** and **21**, but did exhibit an absorption at 1725 cm^{-1} due to the saturated ester functions of cyclised products. The NMR spectrum of the epimeric mixture of **27** and **28** displayed singlets due to the formyl protons at 8.16 and 8.21 δ in addition to the important olefinic resonances at 6.28 and 6.50 δ due to the vinyl proton at C-9 in the two epimers. The absence of signals due to the N–H proton and the associated characteristic 2 H doublet at 4.2 δ of the methylene protons adjacent to the non-indoline nitrogen in tricyclic structures such as **20** and **21** further supports the tetracyclic structure as opposed to **22**. Further evidence for the structures **27** and **28** was given by the UV maxima at 251 and 304 nm which are consistant with that expected for the 2,3-dihydrolysergic system.[16] Having obtained the tetracyclic N-formyl derivatives it was hoped to methanolyse selectively the formamide function to give both epimeric secondary amines **25/26** which would then allow structural modification specifically at N–6.[32] Unfortunately this could only be accomplished in low yield; the major product being the *bis*-secondary amine as a mixture of 8α and 8β epimers **32** and **33** which were isolated as the mixture of bis-hydrochlorides. This route to the lysergic system through N-formylation and cyclisation of intermediates derived from **18** has great potential for producing a range of N-alkylated derivatives of lysergic acid which would be of considerable pharmacological interest.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were determined using a Unicam SP200 and UV spectra obtained using a Unicam SP800 spectrometer. Mass spectra were obtained from AEI MS12 and MS902 instruments (the latter with an on-line computer). NMR spectra were measured using Varian HA100, XL100 spectrometers. Hplc was carried out using a Waters ALC204 machine with a Model 440 UV detector and M660 solvent gradient system.

1-*Benzoyl*-5-*formyl*-1,2,2*a*,3-*tetrahydrobenz*[cd]*indole*[21], **12**. To MeCN (320 ml) at 58° were added the Na salt of 1-benzoyl-5-carboxymethyl-α, 5-epoxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole[21] (16.0 g, 44.8 mmole) and pyridinium hydrobromide perbromide (14.4 g, 45 mmole). The stirred mixture was illuminated for 15 min with a 750 watt lamp, and then cooled to 40° without illumination. A soln of semicarbazide HCl (14.98 g, 134.3 mmole) and NaOAc.3H_2O (7.39 g, 54.33 mmole) in H_2O (30 ml) was added then the mixture stirred at 40° for 3 hr. The solvent was removed *in vacuo* followed by addition of H_2O (350 ml) and filtration. The crude solid product was washed with H_2O then digested with hot MeOH, Et_2O and dried to give the semicarbazone of **12** (12.2 g, 79%), m.p. 227–9° (lit.[21] m.p. 231–2°).

The semicarbazone of **12** (26.5 g, 76.6 mmole) was suspended in $CHCl_3$ (332 ml) and on addition of freshly distilled MeCO.COOH (102.5 g, 1.16 mmole) and *p*-toluenesulphonic acid H_2O (0.265 g, 1.39 mmole) soln was attained. After addition of H_2O (26.5 ml) the soln was stirred at 25° for 18 hr. The precipitated solid was filtered and washed with $CHCl_3$, then the $CHCl_3$ filtrate was washed with H_2O (3x), sat. $NaHCO_3$ and dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded the crude aldehyde **12** which was digested with hot MeOH, filtered then washed with MeOH, Et_2O and dried to give **12** (20.7 g, 94%) m.p. 177–179° (lit.[21], 179.5–180.5°) which was identical with authentic material.

t-Butyl-3-*methoxycarbonyl*-4-*phenyl*-3-*propenate*, **34**. Distilled PhCHO (0.41 g, 3.87 mmole) was added to **13**[23] (2.0 g, 4.46 mmole) in dry t.BuOH under N_2 atmosphere. After 48 h reflux the solvent was removed *in vacuo* leaving crude product which was chromatographed on grade III alumina (60 g). Elution with benzene—40/60 petroleum ether (4:1) gave the diester which crystallised from hexane (0.97 g, 87%) m.p. 55–6°; ν_{max}($CHCl_3$) 1700, 1720, 1640 cm^{-1}; λ_{max}(EtOH) 267 nm (ε 15,800); ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9 H) 3.47 (s, 2 H), 3.79 (s, 3 H), 7.32 (s, 5 H), 7.83 (s, 1 H) (Found: C, 69.77; H, 7.54. $C_{16}H_{20}O_4$ Requires: C, 69.54; H, 7.33%).

1-*Benzoyl*-1,2,2*a*,3-*tetrahydro*-5-(2′-*methoxycarbonylethylene*)*benz*[*cd*]*indole*, **35**. A soln of **12** (15.0 g, 52 mmole) and methoxycarbonylmethylenetriphenylphosphorane (17.37 g, 52 mmole) in dry benzene (1.3 l) was refluxed under N_2 for 18 hr. The soln was concentrated to 30 ml *in vacuo* then chromatographed on grade III alumina (1 kg). Elution with benzene gave the product **35** which was crystallised from EtOAc–60/80 petroleum ether (7.50 g, 42%); m.p. 131–3°; ν_{max} ($CHCl_3$) 1705, 1635, 1615 cm^{-1}; λ_{max}(EtOH) 250 nm (ε 29,000); ^1H NMR ($CDCl_3$) δ 7.0–7.8 (9 H, m), 6.2–6.5 (2 H, m), 4.41 (1 H, m), 3.75 (3 Hs), 3.3–3.9 (2 H, m) 2.0–2.9 (2 H, m); *m/e* 345.1362–$C_{22}H_{19}NO_3$ (−1 ppm), 286.1208–$C_{20}H_{16}NO$ (−8 ppm), 240.1017–$C_{15}H_{14}NO_2$ (−3 ppm) (Found: C, 76.49; H, 5.47; N, 4.18. $C_{22}H_{19}NO_3$ Requires: C, 76.50; H, 5.55; N, 4.06%).

4-*Phenyl*-1,2,4-*triazoline*-3,5-*dione adducts*, **36/37**. The ester **35** (6.0 g, 17.4 mmole) and 4-phenyl-1, 2,4-triazoline-3,5-dione (3.05 g, 17.4 mmole) were dissolved in dry acetone (11) and the soln refluxed under N_2 for 2 hr. During this time the deep red soln became colourless and the solvent was removed *in vacuo* to give a white solid which was digested in EtOAc and filtered to afford two isomeric adducts (8.28 g, 92%) in the ratio 9:1. Crystallisation from EtOAc effected separation of the soluble isomer **36**, m.p. 263–6°, ν_{max}($CHCl_3$) 1775, 1750, 1720, 1640, 1610, 1595 cm^{-1}; λ_{max}(EtOH) 228 (ε 24550), 245 (ε 23, 443), 305 (ε 4898) nm; ^1H NMR ($CDCl_3$) δ 7.0–7.8 (13 H, m), 6.35 (1 H, dd, J = 5), 5.26 (1 H, dd, J = 5), 4.45 (2 H, m), 3.77 (3 H, s), 1.2–3.9 (4 H, m). (Found: C, 68.89; H, 4.52; N, 10.46. $C_{30}H_{24}N_4O_5$ Requires: C, 69.22; H, 4.65; N, 10.76%). The least soluble isomer was extremely insoluble hence a comparable spectral analysis could not be obtained for **37**, m.p. 295°; ν_{max}(Nujol) 1762, 1735, 1700, 1642, 1590 cm^{-1}; *m/e* 520 –$C_{30}H_{24}N_4O_5$.

1-*Benzoyl*-1,2,2*a*,3-*tetrahydro*-5-(2′-*methoxycarbonyl*-2′-*t*-*butyloxycarbonylmethylethylene*)*benz*[*cd*]-*indole*, **14**. A soln of **13** (56.0 g, 12.5 mmole) in dry benzene/t-BuOH (1:1; 480 ml) was added to a suspension of **12** (24.2 g, 8.35 mmole) in dry benzene/t-BuOH (1:1; 300 ml) and the mixture refluxed under N_2 for 4 days. After removal of the solvent *in vacuo* the residue was dissolved in benzene and washed with 2 N HCl, H_2O, sat. $NaHCO_3$ then dried ($MgSO_4$). Concentration of the solution *in vacuo* followed by chromatography on silica (2 kg). Elution with benzene/EtOAc (9:1) gave an oil which crystallised from EtOAc–60/80 petroleum ether to afford **14** (26.11 g, 79%) m.p. 162–4°; ν_{max} ($CHCl_3$) 1710, 1640, 1620, 1600 cm^{-1}; λ_{max}(EtOH) 235 (ε 26, 303), 254 (ε 26, 915) nm; ^1H NMR ($CDCl_3$) δ 6.7–7.7 (9 H, m), 6.05 (1 H, br. d), 4.4 (1 H, m), 3.4–3.9 (2 H, m), 3.80 (3 H, s), 3.34 (2 H, s), 2.0–2.9 (2 H, m), 1.44 (9 H, s); *m/e* 459.2067—$C_{28}H_{29}NO_5$ (+5 ppm), 403.1433—$C_{24}H_{21}NO_5$ (+3 ppm), 105.0342—C_7H_5O (+2 ppm) (Found: C, 73.00, H, 6.28; N, 3.08. $C_{28}H_{29}NO_5$ Requires: C, 73.18; H, 6.36; N, 3.05%).

1-*Benzoyl*-1,2,2*a*,3-*tetrahydro*-5-(2′-*methoxycarbonyl*-2′-*carboxymethylethylene*)*benz*[*cd*]*indole*, **15**. The diester **14** (10.0 g, 24.8 mmole) in 90% TFA (100 ml) was allowed to stand for 2 hr at 25° then diluted with benzene (100 ml). After removal of the solvent *in vacuo* the crude product was azeotroped with benzene (3x) then dissolved in benzene and extracted with sat.$NaHCO_3$ (2x). The aqueous extracts were combined, washed with benzene and acidified with 2 N HCl. After extraction of the product with $CHCl_3$ (2x), the organic solution was dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product which on crystallisation from MeOAc/Et_2O (1:1) afforded **15** (7.73 g, 88%) m.p. 175–7°; ν_{max}($CHCl_3$) 2500–3500, 1710, 1610, 1590 cm^{-1}; λ_{max} (EtOH) 254 (ε 26, 915) nm; ^1H NMR ($CDCl_3$) δ 9.80 (1 H, br.s), 6.7–7.7 (9 Hm), 6.04 (1 H, br. d), 4.40 (1 H, br. m), 3.5–3.9 (2 H, m), 3.74 (3 H, s), 3.45 (2 H, s), 2.0–2.8 (2 H, m); ^{13}C NMR δ 28.4 (t), 33.8, 33.9 (t), 52.2 (q), 58.7 (t), 118.1 (d), 127.2, 127.4, 128.5, 129.5, 130.5, 130.8, 131.3, 132.7 (s). 138.9 (d), 140.7 (s), 167.2 (s), 168.9 (s), 175.0 (s); *m/e* 403.1438—$C_{24}H_{21}NO_5$ (+4 ppm), 385.1298—$C_{24}H_{19}NO_4$ (−4 ppm), 372.1259—$C_{23}H_{18}NO_4$ (+6 ppm), 358.1472—$C_{23}H_{20}NO_3$ (+8 ppm), 344.1254—$C_{22}H_{18}NO_3$ (−10 ppm) (Found; C, 71.57; H, 5.40, N, 3.53. $C_{24}H_{21}NO_5$ Requires: C, 71.45; H, 5.25; N, 3.47%).

p-*Toluenesulphonate salt of* 1-*benzoyl*-1,2,2*a*,3-*tetrahydro*-5-(2-*methoxycarbonyl*-2′-*aminomethylethylene*)*benz*[*cd*]*indole* **18**. The acid **15** (4.0 g, 9.94 mmol) was dissolved in CH_2Cl_2 (250 ml) and cooled to −20°. N-methylmorpholine (1.02 g, 9.94 mmole) and diphenylphosphinyl chloride (2.56 g, 10.82 mmole) were added to the mixture which was then stirred at −20° for 30 min. Tetramethylguanidinium azide (1.86 g, 11.76 mmole) in dry CH_3CN (20 ml) was added to the mixture which was then stirred at 0° for 90 min. The mixture was then poured on to ice-water and the organic layer separated and dried ($MgSO_4$). Removal of the solvent *in vacuo* at 25° gave **16** as a yellow oil, ν_{max} (film) 2150, 1710, 1640 cm^{-1}.

The acid azide was dissolved in dry benzene (50 ml) and refluxed under N_2 for 1 hr. Removal of the solvent *in vacuo* afforded **17** as a yellow oil, ν_{max} (film) 2250, 1705, 1640 cm^{-1}.

The isocyanate was then dissolved in dry benzene (200 ml) and stirred at 25° for 16 hr with a soln of *p*-toluenesulphonic acid. H_2O (1.90 g, 10 mmole) in a minimum volume of dry Et_2O. During this time the product crystallised from the soln to give the *p*-toluenesulphonate of **18** (4.30 g, 80%), m.p. 166–170 ν_{max} (KBr) 2700–3300, 1730, 1640, 1620, 1600 cm^{-1}; λ_{max} (EtOH) 234 (ε 16, 982), 255 (ε 18, 621) nm; ^1H NMR (TFA) δ 6.9–8.2 (15 H, m), 6.26 (1 H, br. s), 6.05 (1 H, br. d), 4.03 (3 H, s), 3.6–4.5 (5 H, m), 2.42 (3 H, s), 2.6–3.2 (2 H, m) (Found: C, 65.54; H, 5.64, N, 4.96. $C_{30}H_{30}N_2O_6S$ Requires: C, 65.92; H, 5.53, N, 5.12%).

1-*Benzoyl*-1,2,2*a*,3-*tetrahydro*-5-(2′-*methoxycarbonyl*-2′-*trifluoroacetamidomethylethylene*)*benz*[*cd*]*indole*, **20**. The *p*-toluenesulphonate of **18** (275 mg, 0.50 mmole) was dissolved in pyridine/benzene (1:1, 20 ml) and stirred at 25° for 3 days with trifluoroacetic anhydride (1.49 mg, 0.71 mmole). After removal of the solvent *in vacuo* the residual oil was dissolved in CH_2Cl_2 and washed with 2N.HCl, H_2O then dried ($MgSO_4$). Removal of the solvent *in vacuo*, followed by crystallisation of the residue from EtOAc, gave **20** (127 mg, 54%), m.p. 200–3°; ν_{max} ($CHCl_3$) 3450, 1720, 1640, 1602, 1540. 1500 cm^{-1}; λ_{max} (EtOH) 253 (ε 21, 380) nm; ^1H NMR ($CDCl_3$) δ 6.8–7.8 (8 H, m), 6.73 (1 H, d, J = 8), 6.12 (1 H, br. d, J = 6), 5.03 (1 H, m), 4.32 (2 H, d, J = 6), 4.1–4.6 (1 H, m), 3.84 (3 H, s), 3.3–4.0 (2 H, m), 2.0–3.0 (2 H, m); *m/e* 470.1447—$C_{25}H_{21}N_2O_4F_3$ (−1 ppm), 105.0299—C_7H_5O (−39 ppm), HPLC (Corsasil II-500 p.s.i., 2 ml/min^{-1}, 100% $CHCl_3$) Rt = 18.4 min. (Found: C, 63.35; H, 4.25; N, 6.04, $C_{25}H_{21}N_2O_4F_3$ Requires: C, 63.83; H, 4.50, N, 5.95%).

1-*Benzoyl*-1,2,2*a*,3-*tetrahydro*-5-(2′-*methoxycarbonyl*-N-*methoxycarbonyl*-2′-*aminomethylethylene*)*benz*[*cd*]-*indole*, **21**. The isocyanate **17**, prepared from **15** (1.00 g, 2.49 mmole) as previously described, in dry benzene (125 ml) was treated with *p*-toluenesulphonic acid H_2O (475 mg, 2.5 mmole) in MeOH (10 ml). After 16 hr at 25° the solvent was removed *in vacuo* and the residue chromatographed on silica (30 g). Elution with benzene/EtOAc (4:1) yielded **21** (561 mg, 52%) m.p. 139–140° (crystallised from EtOAc/hexane); ν_{max} ($CHCl_3$) 3440, 1715, 1630, 1600, 1570 cm^{-1}; λ_{max} (EtOH) 255 (ε 29, 512) nm; ^1H NMR ($CDCl_3$) δ 6.9–7.7 (8 H, m), 6.74 (1 H, d, J = 7), 6.18 (1 H, br. s), 5.30 (1 H, br. s), 4.10 (2 H, d, J = 6) 3.78 (3 H, s), 3.56 (3 H, s) 3.3–4.6 (3 H, m) 2.0–3.0 (2 H, m); *m/e* 432.1698—$C_{25}H_{24}N_2O_5$ (+3 ppm), 358.1445—$C_{23}H_{20}NO_3$ (+1 ppm); HPLC (Microporasil 2000 p.s.i., 2.5 ml. min^{-1}, 10% Me CN in CH_2Cl_2) R = 1.9 min. (Found: C, 69.61; H, 5.55; N, 6.70. $C_{25}H_{24}N_2O_5$ Requires: C, 69.43; H, 5.59; N, 6.48%).

Methyl-1-*benzoyl*-2,3-*dihydrolysergate* **23**, *methyl*-1-*benzoyl*-2,3-*dihydroisolysergate* **25** *and* 1-*benzoyl*-2,3-*dihydro*-6-*methyl*-8-*carbomethoxy*-$\Delta^{8,9}$-*ergoline*, **29**. The *p*-toluenesulphonate salt of **18** (4.0 g, 7.31 mmole) was dissolved in CH_2Cl_2 (250 ml) and stirred with K_2CO_3 soln. The CH_2Cl_2 layer was separated, washed with H_2O and dried ($MgSO_4$) followed by removal of the solvent *in vacuo* to give **18** as an oil, which was dissolved in H.COOH (98%, 200 ml) and H.CHO soln (40%, 40 ml) and heated for 3 hr. After cooling, the

solvent was removed *in vacuo* and the residue partitioned between CH_2Cl_2 and 4 N NaOH. The CH_2Cl_2 layer was washed with H_2O then dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded an oil which was chromatographed over grade III alumina (80 g). Elution with benzene–EtOAc (4:1) gave an oil which was crystallised from EtOAc–hexane to give a mixture (1.76 g, 62%) of **23**, **24** and **29** (9:3:2). Slow crystallisation of this mixture from EtOAc gave **24**, m.p. 149–153°; ν_{max} ($CHCl_3$) 1733, 1633, 1610, 1580 cm^{-1}; λ_{max} 242 (ε 19,953), 305 (ε 4,766) nm; ^1H NMR ($CDCl_3$) δ 6.9–7.6 (8 H, m), 6.19 (1 H, br. s $W_{\frac{1}{2}}$ 6 Hz), 4.2–4.6 (2 H, m), 3.73 (3 H, s), 3.0–3.7 (5 H, m), 2.38 (3 H, s), 1.8–2.9 (2 H, m); *m/e* 388; hplc (Corasil II, 1000 p.s.i., 1.0 m. min^{-1}, 10% i-PrOH in CH_2Cl_2) Rt = 10.5 min. A soln of **24** in MeOH was refluxed under N_2 for 2 hr. HPLC and NMR indicated quantitative epimerisation to **23**.

The total mixture of **23** and **29** (1.5 g) was separated by preparative TLC (7% MeOH in $CHCl_3$; silica) to give **23**, m.p. 165–168 (crystallised from EtOAc); ν_{max} ($CHCl_3$) 1728, 1632, 1604, 1590, 1578 cm^{-1}; λ_{max} (EtOH) 253 (ε 38, 900), 307 (ε 7, 762) nm; ^1H NMR ($CDCl_3$) δ 6.8–7.7 (8 H, m), 6.52 (1 H, br. s. $W_{\frac{1}{2}}$ 6 Hz), 4.1–4.5 (1 H, br. m), 3.73 (3 H, s), 2.4–3.7 (7 H, m), 2.48 (3 H, s), 1.2–1.6 (1 H, q, J = 9 Hz), *m/e* 388.1756—$C_{24}H_{24}N_2O_3$ (−8 ppm), 345.1375—$C_{22}H_{19}NO_3$ (+3 ppm), 329.1620—$C_{22}H_{21}N_2O$ (+10 ppm), 105.0363—C_7H_5O (+22 ppm); HPLC (Corasil II, 1000 p.s.i., 1.0 ml min^{-1}, 10% i-PrOH in CH_2Cl_2) Rt = 10.5 min. (Found: C, 74.09; H, 6.11; N, 7.20. $C_{24}H_{24}N_2O_3$ Requires: C, 74.21; H, 6.23; N, 7.21%).

The $\Delta^{8,9}$-ergoline isomer **29**, which was isolated by preparative tlc, could not be obtained completely pure due to transformation on silica to **24**, exhibited the following characteristics m.p. 152–7° (crystallised EtOAc-hexane); ν_{max} ($CHCl_3$) 1708, 1635, 1607, 1598, 1576 cm^{-1}; λ_{max} (EtOH) 220, 292 nm; ^1H NMR ($CDCl_3$) δ 6.9–7.7 (8 H, m), 7.37 (1 H, d), 3.73 (3 H, s), 2.44 (3 H, s), 1.50 (1 H, t, J = 8 Hz); *m/e* 388.1791—$C_{24}H_{24}N_2O_3$ (+1 ppm), 373.1536—$C_{23}H_{21}N_2O_3$ (−4 ppm), 345.1366—$C_{22}H_{19}NO_3$ (0 ppm), 329.1644—$C_{22}H_{21}N_2O$ (−3 ppm); HPLC (Corasil II, 1000 p.s.i., 1.0 ml min^{-1}, 10% i-PrOH in CH_2Cl_2) Rt = 6.0 min.

Hydrogenation of the mixture of isomers **23**, **24**, and **29** (100 mg) in MeOH (50 ml) using 10% Pd/C (50 mg) gave a dihydro- product (100 mg), *m/e* 390.1917—$C_{24}H_{26}N_2O_3$ (−7 ppm).

Methyl 2,3-dihydrolysergate, **30** *and methyl 2,3-dihydroisolysergate*, **31**. The epimeric mixture of **23** and **24** (500 mg, 1.29 mmole) was dissolved in dry MeOH (55 ml) containing conc.HCl (5 ml) and the soln refluxed under N_2 for 6 hr followed by removal of the solvent *in vacuo*. The residue was dried *in vacuo* over P_2O_5 for 16 hr. then dissolved in dry MeOH (20 ml) and a 2 M soln of HCl/MeOH (3.0 ml, 6 mmole). After 24 hr stirring under N_2 the solvent was removed *in vacuo* and the residue partitioned between CH_2Cl_2 and the minimum volume of sat. K_2CO_3 soln required for neutralisation whilst maintaining the soln at 0°. The CH_2Cl_2 layer was washed with H_2O and dried ($MgSO_4$) followed by evaporation *in vacuo* to give the crude product which crystallised from Et_2O to give a mixture of **30**, **31** in the ratio 5:2 (203 mg, 55%) m.p. 157–161°; ν_{max} ($CHCl_3$) 3500, 1730, 1615, 1600 cm^{-1}; λ_{max} 243 (ε 25, 704), 318 (ε 2, 291) nm; ^1H NMR ($CDCl_3$) δ 7.01 (2 H, m), 6.49 (2 H, m), singlets (3 H) at 3.74 (β-COOMe) and 3.71 (α-COOMe), 2.5–3.7 (9 H, m), singlets (3 H) at 2.53 and 2.50, 1.1–1.6 (1 H, m); *m/e* 284.1554—$C_{17}H_{20}N_2O_2$ (+10 ppm), 241.1098—$C_{15}H_{15}NO_2$ (−2 ppm), 225.1378—$C_{15}H_{17}N_2$ (−6 ppm), 182.0964—$C_{13}H_{12}N$ (−3 ppm); HPLC (Microporasil, 2000 p.s.i. 2.5 ml $min.^{-1}$, 15% MeCN in CH_2Cl_2) Rt = 7.6 min. (minor isomer) and R = 9.0 min. (major isomer).

This product was identical in every respect with an authentic sample kindly supplied by Dr. E. C. Kornfeld and prepared by the first route[21] to lysergic acid.

Epimeric mixture of 1-benzoyl-2,3-dihydro-6-formyl-8-methoxycarbonyl-$\Delta^{9,10}$-ergolines, **27** *and* **28**. The free amine **18**, derived from the *p*-toluenesulphonate (1.2 g, 2.20 mmole), was treated with a soln of H.COOH (60 ml) and Ac_2O (21 ml) which had been precooled to 0°. After 1 hr at 0° followed by 16 hr at 25° the reaction was quenched by the addition of iced water (120 ml) and concentrated *in vacuo* to yield an oil. Crystallisation from EtOAc–hexane gave the pure mixture (1:1) of **27** and **28** (768 mg, 87%), m.p. 236–239°; ν_{max}($CHCl_3$) 1725, 1670, 1655, 1610, 1595 cm^{-1}; λ_{max} (EtOH) 251 (ε 22, 909), 304 (ε 5, 129) nm; ^1H NMR ($CDCl_3$) δ singlets at 8.16 and 8.21 (1 H), 6.9–7.7 (8 H, m) doublets at 6.50 and 6.28 (1 H, J = 6), 4.54–5.00 (1 H, m), singlets at 3.72 and 3.74 (3 H), 3.1–4.5 (6 H, m), 1.6–2.6 (2 H, m); *m/e* 402.1558—$C_{24}H_{22}N_2O_4$ (+5 ppm), 105.0345 — C_7H_5O (+5 ppm); HPLC (Corasil II, 1000 p.s.i., 1.5 ml min^{-1}, 3% i-PrOH in CH_2Cl_2) Rt = 5.1 min. (Found: C, 71.46; H, 5.46; N, 6.94. $C_{24}H_{22}N_2O_4$ Requires: C, 71.62; H, 5.51; N, 6.9%). The two epimers could be separated by fractional crystallisation from CH_2Cl_2/EtOAc. The most soluble epimer exhibited m.p. 208–233°; ^1H NMR ($CDCl_3$) δ 8.16 (1 H, s), 6.9–7.7 (8 H, m), 6.28 (1 H, d, J = 6 Hz), 4.71 (1 H, t, J = 10 Hz); 4.07–4.57 (1 H, m), 3.96 (1 H, d, J = 15 Hz), 3.74 (3 H, s), 3.23–3.85 (4 H, m), 1.7–2.5 (2 H, m).

The epimeric mixture **27**/**28** (500 mg, 1.24 mmole) in dry DMF (125 ml) was hydrogenated using 10% Pd–C (135 mg). After filtration and evaporation of the solvent *in vacuo* the residue was chromatographed over grade III alumina. Elution with CH_2Cl_2 gave a colourless oil which crystallised from EtOAc to give a mixture (3:3:1) of 3 isomers of 1-benzoyl-2,3-dihydro-6-formyl-8-methoxycarbonylergoline (352 mg, 70%) m.p. 214–6°; ν_{max} ($CHCl_3$) 1735, 1655, 1610, 1595 cm^{-1}; λ_{max} (EtOH) 261 (ε 13, 490), 290 (ε 8, 709) nm; ^1H NMR ($CDCl_3$) δ singlets at 8.45, 8.25 (minor) and 8.13 (1 H); *m/e* 404.1762 — $C_{24}H_{24}N_2O_4$ (+6 ppm), 260.1069 — $C_{18}H_{14}NO$ (−2 ppm), 149.0240 — $C_8H_5O_3$ (1 ppm) (Found: C, 71.26; H, 6.13; N, 6.84. $C_{24}H_{24}N_2O_4$ Requires: C, 71.27; H, 5.98, N, 6.93%).

Bishydrochloride salt of 2,3-dihydro-8-methoxycarbonyl-$\Delta^{9,10}$-ergoline, **32**/**33**. The epimeric mixture of **27** and **28** (800 mg, 2.0 mmole) was dissolved in dry MeOH (88 ml) and conc. HCl (8 ml) and the soln refluxed under N_2 for 2 hr. The solvent was then removed *in vacuo* and the residue crystallised from MeOH–Et_2O to give the di-HCl salt of **32**/**33** (400 mg). A further quantity of product was obtained by esterification (MeOH–HCl) of the mother liquors to give a total yield of 560 mg (82%) m.p. > 205°; ν_{max} (KBr) 2300–3000, 1730, 1595, 1580 cm^{-1}; λ_{max} (EtOH) 253 (ε 10,000), 322 (ε 1, 778) nm; ^1H NMR (TFA) δ 9.25 (2 H, br.) 7.56 (3 H, m), singlets at 6.86 and 6.52 (1 H), 3.93 (3 H, s), 3.5–4.8 (7 H, m), 1.9–3.1 (2 H, m); *m/e* (of free diamine) 270.1358–$C_{16}H_{18}N_2O_2$ (−4 ppm), 241.1104 — $C_{15}H_{15}NO_2$ (Oppm), 211.1246 — $C_{14}H_{15}N_2$ (+5 ppm) (Found: C, 54.78; H, 6.08; N, 8.19; Cl, 20.17. $C_{16}H_{20}N_2O_2Cl_2.0.5H_2O$ Requires: C, 54.55; H, 6.01; N, 7.95; Cl, 20.13%).

Acknowledgements—We thank SRC for a postgraduate award for S.C. and SRC/Eli Lilly for a CASE award V.W.A. It is a pleasure to thank Dr. E. C. Kornfeld (Eli Lilly) for donation of starting materials and comparative samples.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 165 to 173, 1981
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0040-4020/81/Suppl. 1-0165-09 $02.00/0
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STEREOCHEMISTRY OF MACROLIDES—IV[1]

CONFORMATIONAL STUDIES ON 14-MEMBERED MACROLIDE—"DIAMOND LATTICE" CONFORMATION MODELS

HARUO OGURA* and KIMIO FURUHATA
School of Pharmaceutical Sciences, Kitasato University, Minato-ku, Tokyo 108, Japan

HARUMITSU KUWANO,
Central Research Laboratories, Sankyo Co., Ltd., Shinagawa-ku, Tokyo 140, Japan

and

MAKOTO SUZUKI
School of Pharmaceutical Sciences, Meijo University, Tenpaku-ku, Nagoya 468, Japan

(*Received in Japan* 30 *May* 1980)

Abstract—Conformations of 14-membered macrolide—pikromycin, narbomycin, and their derivatives—in solution are studied based upon their NMR and CD spectra compared with the conformation of *p*-bromobenzoylpikromycin in solid state. The α,β-unsaturated CO group at the C-9 position in pikromycin, acetylpikromycin, *p*-bromobenzoylpikromycin, diacetylpikromycin, pikronolide, narbomycin and narbonolide has an *s-trans* conformation in solution of the protic solvent. While, in pikromycin, acetyl pikromycin, and *p*-bromobenzoylpikromycin, it has an *s-cis* conformation in solution of the aprotic solvent. This phenomenon has not been reported previously in macrolides, and is caused by an intramolecular H-bond between the OH group at the 12-position and the C-3 CO group in the aprotic solvent. This was confirmed from NMR, IR, and CD spectra.

The conformation of the 14-membered macrolactone is discussed with reference to "diamond lattice" conformation models A, B, C, D, and F. A new "diamond lattice" conformation model E for pikromycin in the aprotic solvents is proposed based on spectral data.

There are many reports on conformational studies on erythromycins from NMR[2] and CD[3] spectra. Celmer[4] has proposed a similar conformation for the macrolactone ring in oleandomycin. Recently, Egan *et al.*[5] reported that the conformation of the 14-membered macrolactone ring in erythronolide B, were relatively flexible. This conformational moving was confirmed by CMR spectra.[6] Previously,[1] we discussed similar conformational moving in oleandomycin and its derivatives based on the X-ray analysis of 11,4″-bis[*O*-(*p*-bromobenzoyl)]oleandomycin.

"Diamond lattice" conformation models

The application of Dale's "diamond lattice" conformation model[7] A (Diamond Model A) to 14-membered macrolide antibiotics was proposed earlier by Celmer.[8] Egan *et al.*[5,9] subsequently proposed an alternate "diamond lattice" conformation model B (Diamond Model B) to be applied to the 14-membered macrolactone of erythromycin[5,9] and lankamycin[10] antibiotics.

Recently, we proposed another "diamond lattice" conformation model F (Diamond Model F) instead of the Diamond Models A and B for 14-membered macrolactone of oleandomycin and erythromycin antibiotics based on the X-ray analysis of 11,4″-bis[*O*-(*p*-bromobenzoyl)]oleandomycin.[1]

In this paper, we would like to report the conformational flipping of 14-membered macrolactone of pikromycin derivatives, comparing the conformational moving of oleandomycin antibiotics and using the "diamond lattice" conformation models (Diamond Models). The conformational relationship between the Diamond Models A, B, and F is clearly shown by the maps of dihedral angles in Fig. 1.

In an earlier paper, we proposed the application of a "diamond lattice" conformation model C[11] (Diamond Model C) to the 14-membered macrolactone of kromycin (**7**), 10,11-dihydrokromycin, deoxykromycin, and 10,11-dihydrodeoxykromycin on the basis of the X-ray analysis of kromycin (**7**).[12] It is clear that the Diamond Model C fits the conformation of **7**, **8** and this is proved by the maps of dihedral angles shown in Fig. 2. Evidently, the shape and each dihedral angle determined by X-ray analysis (dotted line) are in accord with those estimated from the Diamond Model C (solid line).

Recently, a new "diamond lattice" conformation model D (Diamond Model D) for the 14-membered macrolactone of *p*-bromobenzoylpikromycin (**5**) was proposed based on the X-ray analysis.[13] In Fig. 3 shows that the Diamond Model D applied to **5** based on the X-ray analysis. It is clear that the shape and each dihedral angle determined by X-ray analysis (dotted line) are in accord with those estimated from the Diamond Model D (solid line).

Chemistry

Pikromycin[14] (**1**) was obtained from the fermentation broth of *Streptomyces flavochromogenese*,[15] and narbomycin (**2**), pikronolide (**9**)[16] and narbonolide

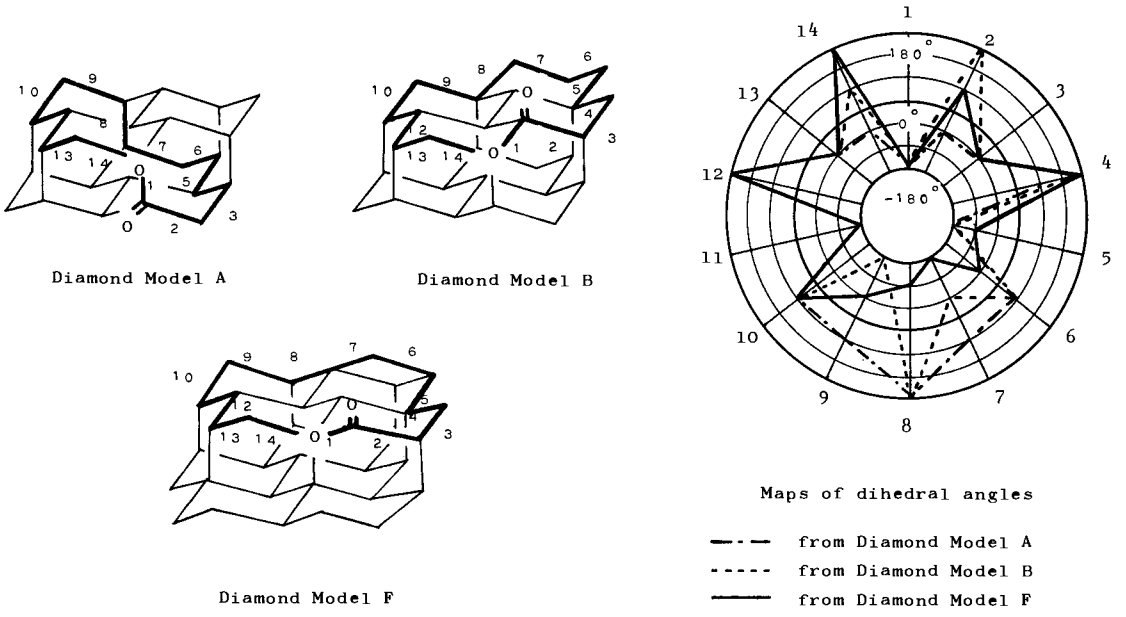


Fig. 1. Diamond model A, B, F and maps of dihedral angles (A, B, F).

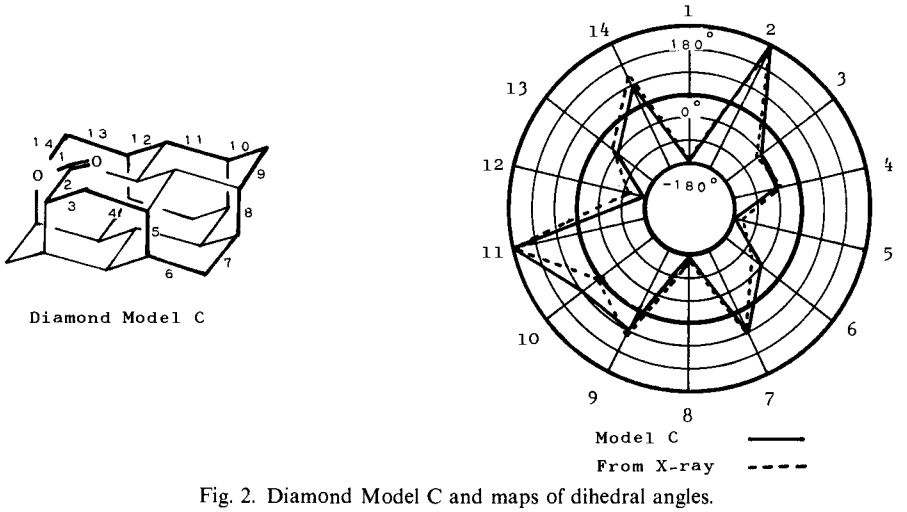


Fig. 2. Diamond Model C and maps of dihedral angles.

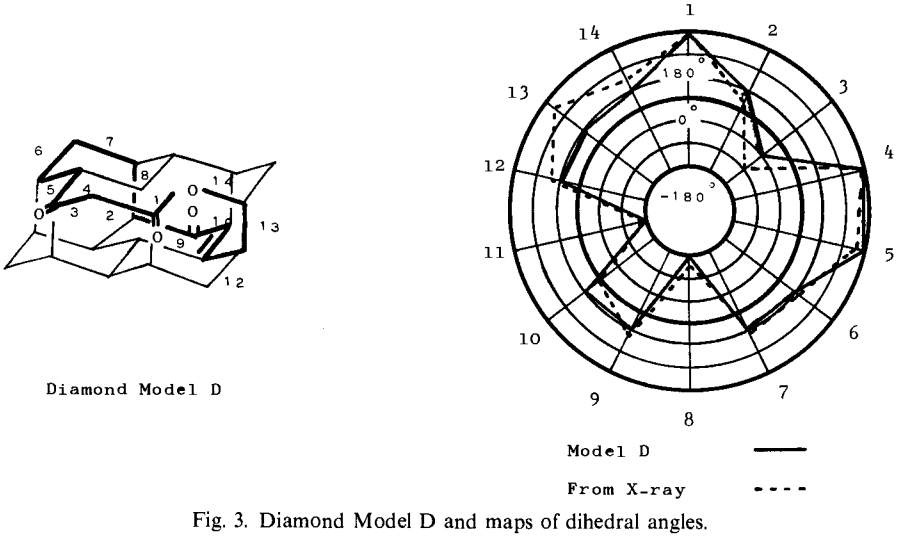
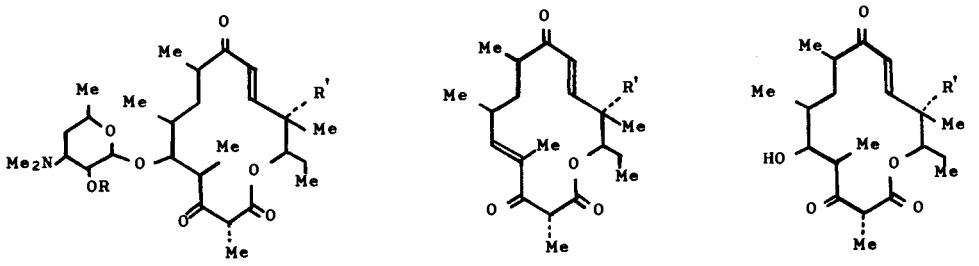


Fig. 3. Diamond Model D and maps of dihedral angles.



1	R=H	R'=OH	7	R'=OH	9	R'=OH
2	R=H	R'=H	8	R'=H	10	R'=H
3	R=$COCH_3$	R'=OH				
4	R=$COCH_3$	R'=$OCOCH_3$				
5	R=p-bromobenzoyl	R'=OH				
6	R=$COCH_3$	R'=H				

Chart 1.

(**10**)[17] were obtained from the fermentation broth of *Streptomyces venezuelae* MCRL-0376.

Acetylpikromycin (**3**) was prepared from **1** with acetic anhydride in dry benzene solution, and diacetylpikromycin (**4**) was obtained from **1** with acetic anhydride in pyridine at room temperature. Easy acetylation of the tertiary hydroxyl group at 12-position of **1** may be explained by the small steric hindrance because of the bridge-head position. For a similar reason, acetylation of a tertiary hydroxyl group was reported in steroids[18] and sugar derivatives.[19] Acetylnarbomycin (**6**) was prepared by a similar procedure to that for **4**.

Stereochemistry in solution

Fig. 4 shows the CD curves of pikromycin (**1**), acetylpikromycin (**3**), diacetylpikromycin (**4**), pikronolide (**9**), narbomycin (**2**), acetylnarbomycin (**6**), and narbonolide (**10**). The n-π^* Cotton effect owing to a carbonyl group at 3-position appeared around

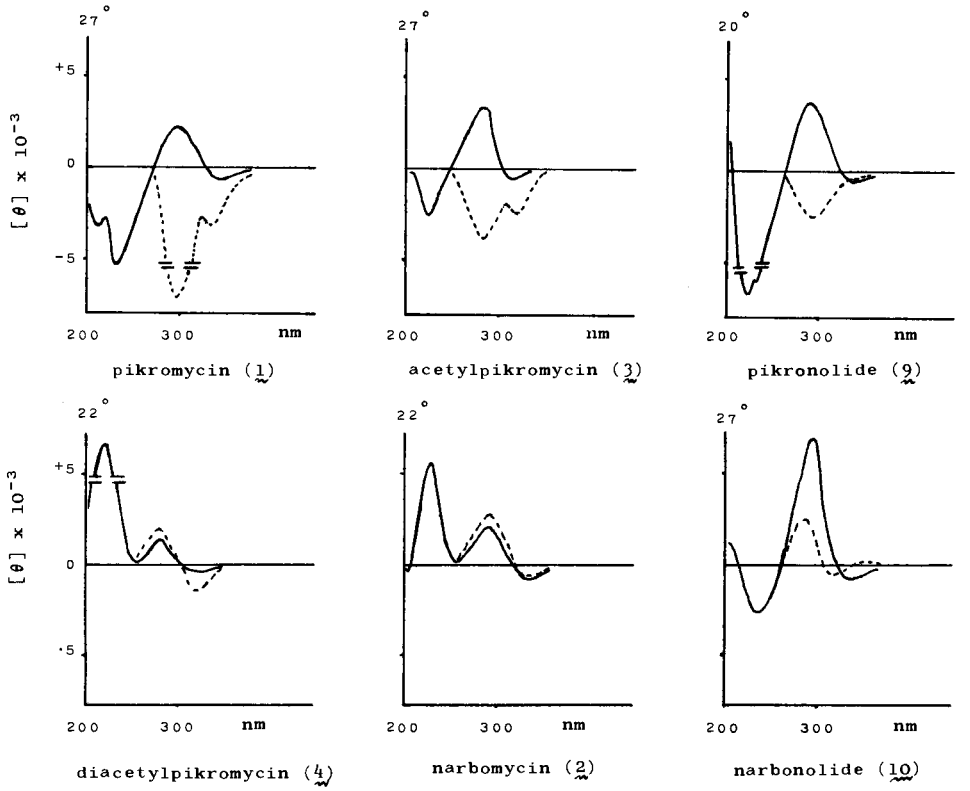


Fig. 4. CD curves in MeOH (——) and $CHCl_3$ (- - -).

280–290 nm and it should be noted that the sign of the effect changes according to different solvents in some cases.

The reversal of the sign of the n-π^* Cotton effect at about 290 nm was observed in pikromycin (**1**), acetylpikromycin (**3**), and pikronolide (**9**) by changing solvents. In methanol, the positive Cotton effect was observed with pikromycin, narbomycin and their derivatives as shown in Fig. 4. While, in chloroform or ether, the negative Cotton effect was observed with pikromycin (**1**), monoacetylpikromycin (**3**), and pikronolide (**9**). This phenomenon is clearly detected by adding methanol in ether solution as shown in Fig. 5. Low temperature CD curves of pikromycin (**1**) and narbomycin (**2**) are shown in Fig. 6. The conformation of their 14-membered macrolactone is more rigid under low temperature.

This can be explained by the intramolecular H-bonding between the CO group at 3-position and the OH group at 12-position. When the OH group is acetylated or replaced by H—namely, narbomycin and its derivatives—the same positive Cotton effects were observed at around 280–290 nm both in methanol and in chloroform. The above discussion can probably be explained by octant projection A (positive Cotton effect) and B (negative Cotton effect).

IR data of the CO group in carbon tetrachloride can be used for detecting the intramolecular H-bonding. In pikromycin (**1**), a strong absorption at 1750 cm^{-1} is assigned to a lactone CO and a strong absorption at

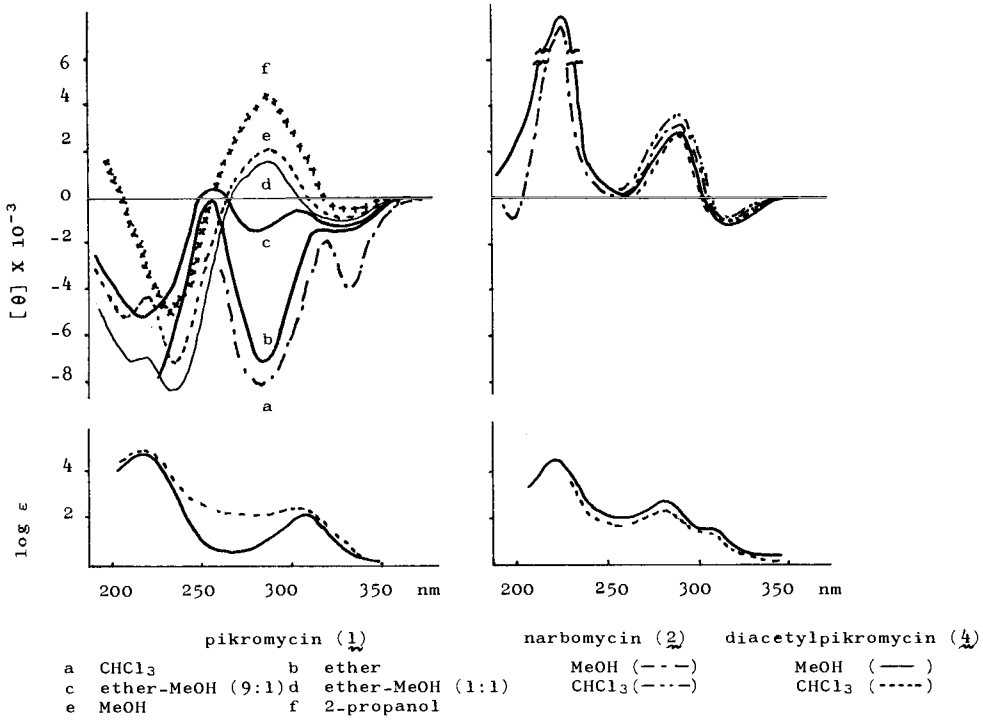


Fig. 5. CD curves of **1**, **2**, and **4** in various solvents.

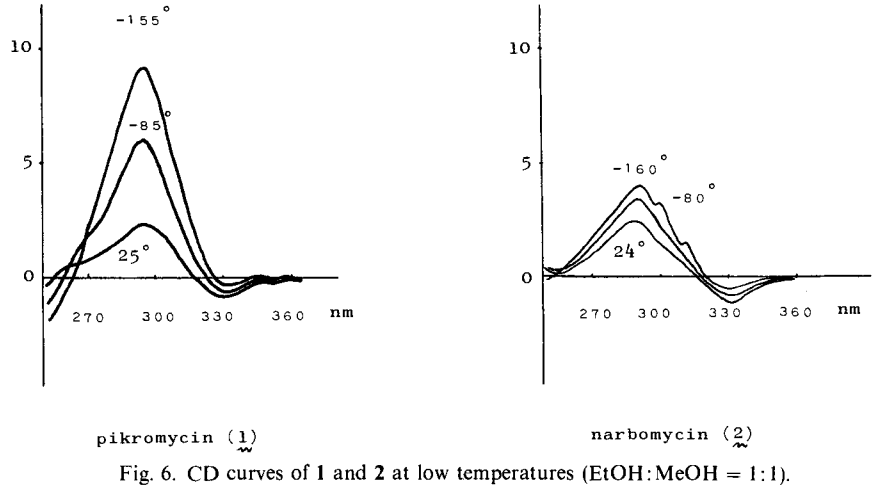


Fig. 6. CD curves of **1** and **2** at low temperatures (EtOH:MeOH = 1:1).

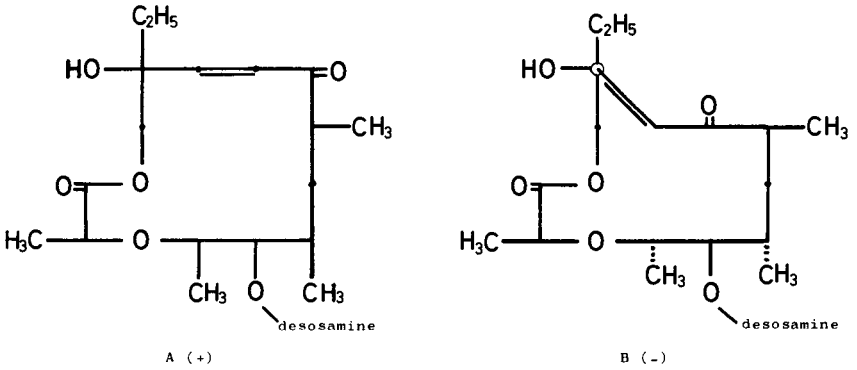


Fig. 7. Octant projections at C-3 position.

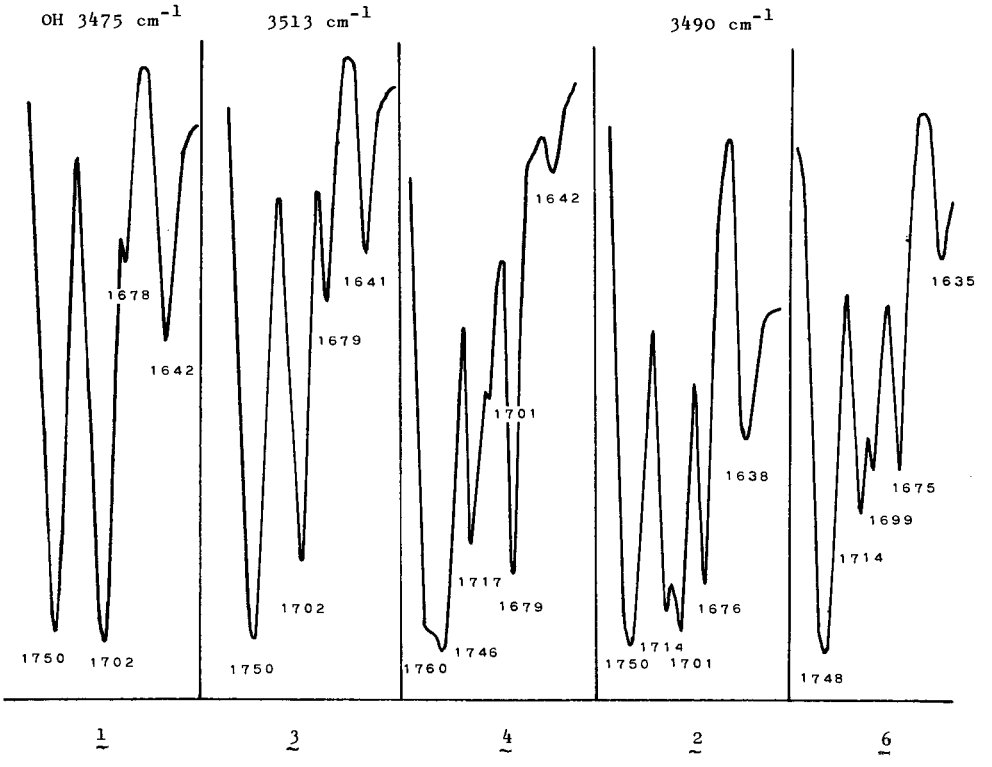


Fig. 8. IR spectra in CCl_4 solution (0.002 M) by 1 cm cell.

1702 cm^{-1} to a chelate CO at 3-position, respectively. Two bands at 1678 and 1642 cm^{-1} are assigned to an unsaturated CO group at 9-position.

A similar IR absorption band in carbon tetrachloride for the chelate carbonyl at 3-position of monoacetylpikromycin (**3**) appeared at 1702 cm^{-1}. But in diacetylpikromycin (**4**), the chelate CO band shifted about 15 cm^{-1} to a shorter wavelength and appeared at 1717 cm^{-1}. This band appeared in narbomycin and acetylnarbomycin (**6**) at 1714 cm^{-1}.

From these observations, it is concluded that an intramolecular H-bonding is formed between the CO group at 3-position and the OH group at 12-position. Medium strong bands appeared at 1678 and 1642 cm^{-1} in pikromycin (**1**), and at 1679 and 1641 cm^{-1} in acetylpikromycin (**3**), respectively, from which the conformation of the unsaturated CO group at 9-position is suggested to be the *s-cis* conformation. This hypothesis of *s-cis* conformation explains the reversal of the sign of the Cotton effect in protic solvent and aprotic solvent. In aprotic solvent, the intramolecular H-bond formation causes a part of ring flip at position 10–11 and the conformation changes from *s-trans* to *s-cis*.

This is further supported by the NMR spectra. From CMR, the Me group shows much shift by acetylation. This was also reported in erythromycin and oleandomycin derivatives.[1] The proton coupling constants of pikromycin (**1**) in aprotic solvent are $J_{4,5} = 7.0$ Hz and $J_{5,6} = 2.5$ Hz ($CDCl_3$ and C_6D_6). On the other hand, in protic solvent the values change

Table 1. Chemical schifts (δ:ppm) and coupling constants (Hz) of pikromycin (**1**) in various solvents

Solvent	$CDCl_3$	C_6D_6	CD_3OD	C_5D_5N -20°	C_5D_5N 32°	C_5D_5N 100°
4-H ($J_{4,5}$)	3.20 (7.0)	3.13 (7.0)	3.04 (5.5)	3.15 (5.6)	3.12 (6.5)	3.02 (6.5)
5-H ($J_{5,6}$)	3.95 (2.5)	3.71 (2.5)	4.01 (2.0)	4.02 (2.0)	4.34 (2.2)	4.18 (2.2)
10-H ($J_{10,11}$)	6.28 (16.0)	6.49 (16.0)	6.22 (16.0)	6.32 (16.0)	6.63 (16.0)	6.93 (16.0)
11-H ($J_{11,10}$)	6.63 (16.0)	6.84 (16.0)	6.69 (16.0)	6.71 (16.0)	7.22 (16.0)	7.02 (16.0)

to $J_{4,5} = 5.5$ Hz and $J_{5,6} = 2.0$ Hz (CD_3OD). In narbomycin (**2**) and diacetylpikromycin (**4**), the values were the same in $CDCl_3$ and CD_3OD, that is, $J_{4,5} = 6.0$ and 5.0, $J_{5,6} = 2.0$ Hz, respectively, and these values are similar to those of pikromycin (**1**) in methanol.

Observed NOE's in benzene also support the *s-cis* conformation of pikromycin (**1**) in aprotic solvent. The NOE's (Fig. 9) were observed between 4-CH_3 and 10-H ($6 \pm 2\%$), between 8-H and 10-H ($15 \pm 4\%$), and between 11-H and 12-CH_3 ($16 \pm 3\%$) in C_6D_6. Similar conclusion was obtained in $CDCl_3$ and C_5D_5N summarized in Table 2. The NOE's between 4-Me and 10-H, and between 11-H and 12-Me were confirmed by the application of the homonuclear INDOR technique. The chemical shift of 10-H (6.28 ppm) to a higher field was more than that of 11-H (6.63 ppm). These data suggested the *s-cis* conformation for the α,β-unsaturated CO group at C-9 position.

On the other hand, observed NOE between 8-H and 11-H in CD_3OD supports the *s-trans* conformation of

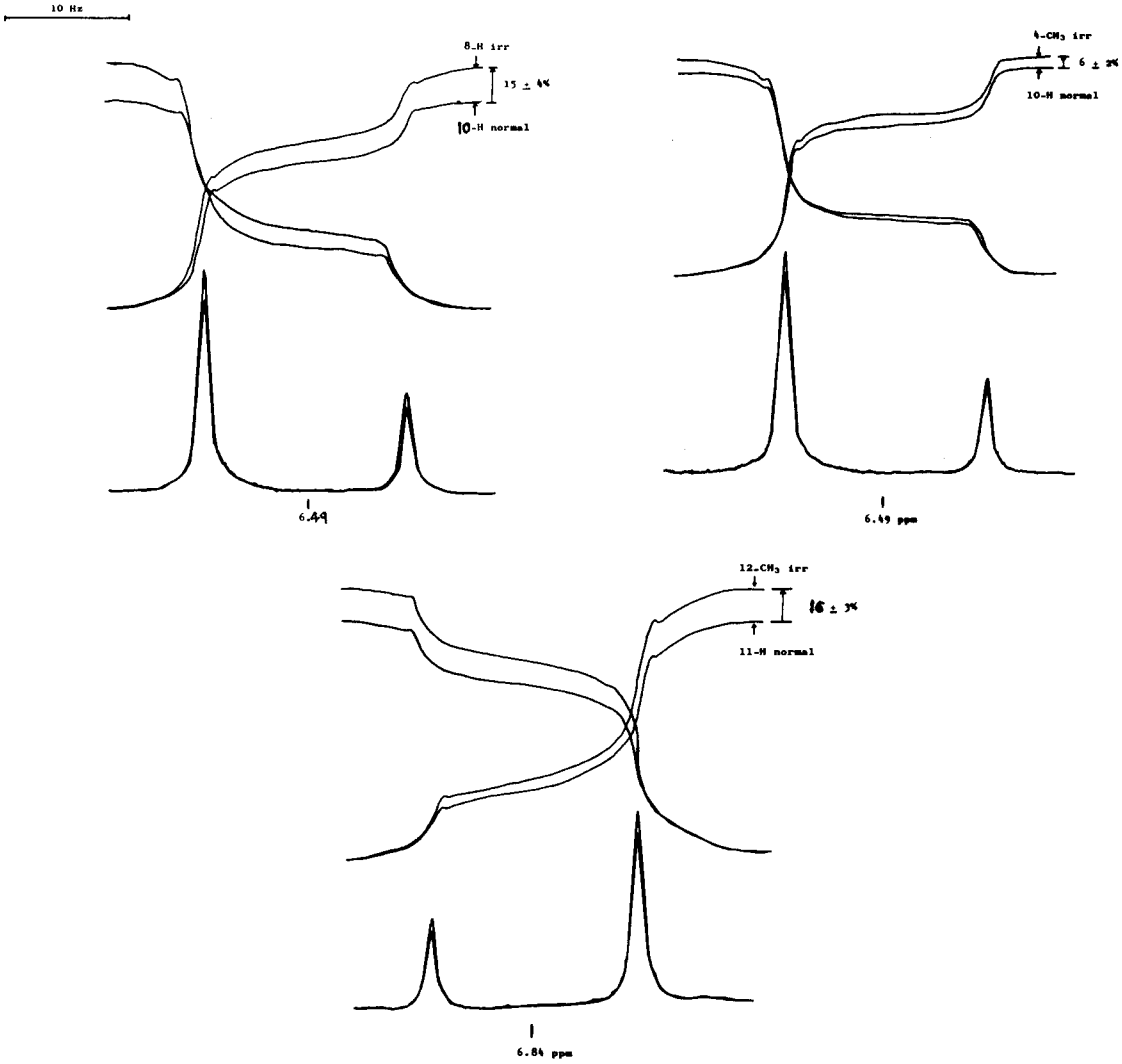
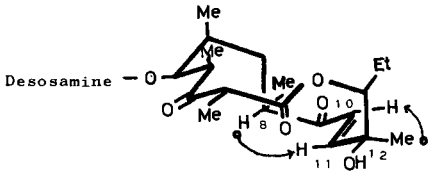
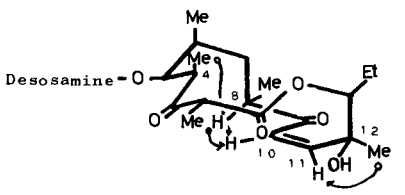


Fig. 9. NOE data of pikromycin (**1**) in C_6D_6.

Table 2. Data of NOEs in various conditions





	solvent	[8-H]→11-H	[12-Me]→10-H	solvent	[8-H]→10-H	[12-Me]→11-H	[4-Me]→10-H
pikromycin	CD_3OD	15%	12%	C_6D_6	15%	16%	6%
diacetylpikromycin	$CDCl_3$	17	20	$CDCl_3$	18	12	6
narbomycin	$CDCl_3$	-	11	C_5D_5N (-20°)	18	14	6
narbonolide	$CDCl_3$	10	15	" (32°)	15	13	6
				" (100°)	12	11	6

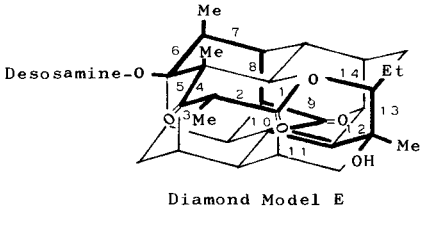
1 in protic solvent. A similar result was obtained in diacetylpikromycin (**4**; 17% between 8-H and 11-H, 20% between 12-Me and 10-H), narbomycin (**2**; 11% between 12-Me and 10-H), and narbonolide (**10**; 10% between 8-H and 11-H, 15% between 12-Me and 10-H).

The J values of **1** in C_6D_6, $J_{13,14}$ = 2 and 11 Hz at 5.12 ppm revealed that the ethyl group at C-13 position was hindered from free-rotation by the steric hindrance of the 12-OH group. This tendency was also observed in acetylpikromycin (**3**) ($J_{13,14}$ = 2.5 and 11 Hz) and pikronolide (**9**) ($J_{13,14}$ = 3 and 10 Hz). This result was confirmed from the comparison of the J values of **1**, **3**, and **9** with those of narbomycin (**2**) ($J_{13,14}$ = 6 and 8 Hz), which showed a poorly split d-doublet when irradiated at 14-CH_2 protons, and from the high-temperature NMR studies on **1** (Table 3). These data show that the steric hindance of 12-OH group affected the free rotation of the 13-Et group, but did not hinder it completely.

In conclusion, the most favorable new "diamond lattice" conformation model E (Diamond Model E) is proposed for pikromycin (**1**), acetylpikromycin (**3**), *p*-bromobenzoylpikromycin (**5**), and pikronolide (**9**) in

Table 3. NMR data of pikromycin (**1**) at 13-H in various conditions (δ:ppm; Hz)

Solv. \ Temp.	25°	50°	80°	100°	120°	149°
$CDCl_3$	5.00(11.1/2.8)	4.98(11.5/3.0)	4.98(11.2/3.0)	4.97(10.5/3.2)	–	–
C_6F_6	4.93(11.0/3.2)	4.93(11.0/3.2)	4.93(11.5/3.5)	4.93(11.5/3.5)	–	–
$CHBr_3$	–	–	–	–	– (10.0/3.0)	– (9.9/3.2)



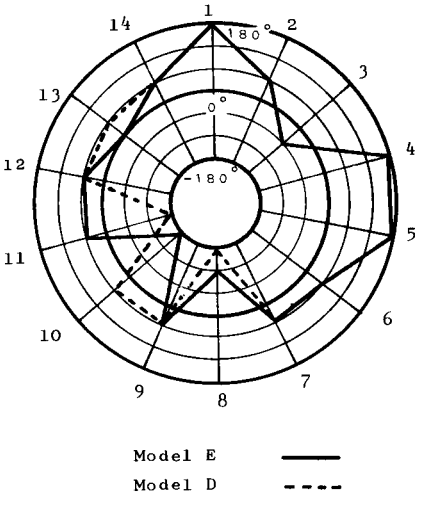


Fig. 10. Diamond Model E and maps of dihedral angles (D, E).

aprotic solvent such as chloroform, ether and pyridine. The Diamond Model E can explain NMR and CD data, and *s-cis* conformation of the α,β-unsaturated CO group at C-9 position.

EXPERIMENTAL

Temps are uncorrected. NMR spectra were measured with a Varian HA-100 and JEOL PS-100 spectrometers operating in frequency sweeps at 32° and 25°, respectively, with internal TMS- or benzene-locked mode. Chemical shifts are recorded in ppm (δ) and coupling constants are recorded in Hz. Mass spectra were determined with a JEOL 01S spectrometer by a direct inlet system at 75 eV. IR spectra were recorded with a Shimadzu IRG-1 (KBr) and with a Japan Spectroscopic Model DS-701G in CCl_4 and 1 cm cell was used for the intramolecular H- bond measurements. CD data were obtained on a Japan Spectroscopic Model J-20 recording polarimeter.

Acetylpikromycin (**3**). Soln of **1** (100 mg) in dry benzene (10 ml) and Ac_2O (1 ml) was left at room temp for 10 min. After decomposition of excess reagent, the solvent was evaporated under a reduced pressure. The residue was dissolved in ether, and washed with $NaHCO_3$aq and water. Evaporation of dried ethereal soln left **3** (92 mg) as a white powder; IR (KBr) 1750, 1702, 1679, 1641 cm^{-1} (CO); UV λ_{max}^{EtOH} 225 nm (log ε 4.02). (Found: C, 63.42; H, 8.74; N, 2.45. Calc. for $C_{30}H_{49}NO_9$: C,63.47; H, 8.70; N, 2.47%).

Diacetylpikromycin (**4**). Soln of **1** (100 mg) in pyradine and Ac_2O (1 ml) was left at room temp for 2 hr. After decomposition of excess reagent, the mixture was extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ soln left **4** (80 mg) as a white powder; IR (KBr) 1750, 1745, 1717, 1710, 1679, 1642 cm^{-1} (CO); UV λ_{max}^{EtOH} 225 nm (log ε 4.10). (Found:

Table 4. NMR data of pikromycin (**1**)

	Chemical shifts (δ ppm; J value, Hz)			
	C_6D_6	$CDCl_3$	$\Delta^{CDCl_3}_{C_6D_6}$	CD_3OD
2-H	4.01, q, $J_{2,2Me}$=7.2	3.89	-0.12	(4.07)
2-Me	1.38, d, J=7.2	1.47	0.09	1.33
4-H	3.13, dq, $J_{4,5}$=7.0; $J_{4,4Me}$=6.8	3.20	0.07	3.04
4-Me	1.20, d, J=6.8	1.31	0.11	1.30
5-H	3.71, dd, $J_{5,4}$=7.0; $J_{5,6}$=2.5	3.95	0.24	4.01
6-H	2.2, m, $J_{6,5}$=2.5; $J_{6,6Me}$=7.0	2.1		
6-Me	1.05, d, $J_{6Me,6}$=7.0	1.05	0	1.01
8-H	2.61, m, $J_{8,8Me}$=6.5	2.70	0.09	2.76
8-Me	1.24, d, J=6.5	1.10	-0.14	1.09
10-H	6.49, d, $J_{10,11}$=16.0	6.28	-0.21	6.22
11-H	6.84, d, $J_{11,10}$=16.0	6.63	-0.21	6.69
12-OH				
12-Me	1.13, s	1.33	0.20	1.33
13-H	5.12, dd, $J_{13,14}$=11 and 2	5.01	-0.11	4.87
14-H	(1.3), t, $J_{14Me,14}$=7.0	1-1.8		
14-Me	0.73, t, $J_{14Me,14}$=7.0	0.88	0.15	0.90
1'-H	4.25, d, $J_{1',2'}$=7.5	4.36	0.11	4.30
2'-H	3.17, dd, $J_{2',1'}$=7.5; $J_{2',3'}$=10.3	3.24	0.07	3.27
3'-H	2.16, m, $J_{3',2'}$=10.3; $J_{3',4'}$=4 and 12	2.48	0.32	2.61
NMe_2	1.88, s	2.28	0.40	2.33
4'-H	1.5, m			
5'-H	3.20, m, $J_{5',4'}$=2 and 10.5; $J_{5',5'Me}$=6.0	3.56	0.36	3.57
5'-Me	1.05, d, $J_{5'Me,5'}$=6.0	1.24	0.19	1.22

Table 5. NMR data of acetylpikromycin (**2a**) and diacetylpikromycin (**3**)

	Chemical shifts ($CDCl_3$, δ ppm; J value, Hz)	
	2a	**3**
2-H	3.75, q, $J_{2,2Me}$=7.2	3.81, q, $J_{2,2Me}$=7.0
2-Me	1.43, d, J=7.2	1.39, d, J=7.0
4-H	2.96, dq, $J_{4,5}$=5.5; $J_{4,4Me}$=7.0	2.80, dq, $J_{4,4Me}$=7.3; $J_{4,5}$=4.5
4-Me	1.23, d, J=7.0	1.24, d, $J_{4Me,4}$=7.3
5-H	4.18, dd, $J_{5,4}$=5.5; $J_{5,6}$=2.5	4.40 dd, $J_{5,4}$=4.5; $J_{5,6}$=2.0
6-H		2.30
6-Me	0.98, d, $J_{6Me,6}$=7.2	0.95, d, J=6.7
7-H_2		6.42
8-H	2.85	3.07
8-Me	1.11, d, $J_{8Me,8}$=6.5	1.12, d, J=6.5
10-H	6.17, d, $J_{10,11}$=17	5.86, d, $J_{10,11}$=17.0
11-H	6.56, d, $J_{11,10}$=17	6.42, d, $J_{11,10}$=17.0
12-H		
12-OH		
(OAc)		(2.10, s)
12-Me	1.34, s	1.59, s
13-H	4.99, dd, $J_{13,14}$=11 and 2	5.29, dd, $J_{13,14}$=10.5 and 3
14-H_2	1.82	
14-Me	0.88, t, $J_{14Me,14}$=7.0	0.88, t, $J_{14Me,14}$=7.0
1'-H	4.52, d, $J_{1',2'}$=7.5	4.52, d, $J_{1',2'}$=7.5
2'-H	4.82, dd, $J_{2',1'}$=7.5; $J_{2',3'}$=10.5	4.81, dd, $J_{2',1'}$=7.5; $J_{2',3'}$=10.3
2'-OH		
(OAc)		(1.98, s)
3'-H	2.85	2.75, m, $J_{3',2'}$=10.3; $J_{3',4'}$=12.3 and 4.5
NMe_2	2.34, s	2.26, s
5'-H	3.59, m, $J_{5',4'}$=1.2 and 10	3.61, m, $J_{5',4'}$=10.5 and 2.0
5'-Me	1.27, d, $J_{5'Me,5'}$=6	1.27, d, $J_{5'Me,5'}$=6.0

Table 6. NMR data of narbomycin (**5**) and narbonolide (**7a**)

Solvent	Chemical shifts (δ ppm; J value, Hz) **5** $CDCl_3$	C_6D_6	$\Delta^{CDCl_3}_{C_6D_6}$	**7a** $CDCl_3$	$\Delta^{CDCl_3}_{C_6D_6}$
2-H	3.85, q, $J_{2,2Me}$=7.0	3.69	0.16	3.71	0.25
2-Me	1.37, d, J=7.0	1.33	0.04	1.35	0.10
4-H	2.94, dq, $J_{4,5}$=6: $J_{4,4Me}$=7.4	2.94	0	2.69	0.21
4-Me	1.37, d, J=7.4	1.24	0.13	1.13	0.09
5-H	4.16, dd, $J_{5,4}$=6; $J_{5,6}$=2	4.44	-0.28	3.87	-0.02
5-OH				2.28	0.13
6-H	1.72, dd, $J_{6,5}$=2; $J_{6,6Me}$=7	ca2.1	ca-0.4		
6-Me	1.03, d, J=7	1.12	-0.09	0.94	0.03
8-H	$2._7$	2.9_4	ca-0.2	2.99	0
8-Me	1.12, d, $J_{8Me,8}$=6.5	1.44	-0.22	1.10	0.02
10-H	6.12, dd, $J_{10,11}$=16; $J_{10,12}$=1.5	6.16	-0.04	6.10	0.07
11-H	6.66, dd, $J_{11,10}$=16; $J_{11,12}$=6.3	6.72	-0.06	6.88	0.15
12-H	2.74, m, $J_{12,10}$=1.5; $J_{12,11}$=6.3; $J_{12,12Me}$=7.0	2.47	0.27	2.69	0.53
12-Me	1.10, d, $J_{12Me,12}$=7.0	0.72	0.38	1.13	0.38
13-H	4.91, m, $J_{13,12}$=3.5; $J_{13,14}$=6 and 8	4.82	0.09	5.13	0.27
$14-H_2$	1.5±0.2				
14-Me	0.91, t, $J_{14Me,14}$=7	0.69	0.22	0.92	0.27
1'-H	4.30, d, $J_{1',2'}$=6.2	4.45	-0.15		
2'-H	3.24, dd, $J_{2',1'}$=6.2; $J_{2',3'}$=10.1	3.34	-0.10		
3'-H	2.49, m, $J_{3',2'}$=10.1; $J_{3',4'}$=4 and 12	2.21	0.28		
5'-H	3.55, m, $J_{5',4'}$=2.5 and 11	3.1_8	ca0.4		
5'-Me	1.25, d, $J_{5'Me,5'}$=6.3	1.07	0.18		
2'-OH	3.1_3, s	3.34	ca-0.2		
NMe_2	2.28, s	1.88	0.40		

C, 62.80; H, 8.65; N, 2.30. Calc. for $C_{32}H_{51}NO_{10}$: C, 63.03; H, 8.43; N, 2.30%).

Acetylnarbomycin (**6**). Soln of **2** (30 mg) in pyridine (0.5 ml) and Ac_2O (0.5 ml) was left at room temp for 4 hr. After decomposition of excess reagent, the mixture was extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ soln left **6** (25 mg) as a white powder; IR (KBr) 1645 cm^{-1} (CO); UV λ_{max}^{EtOH} 225 nm (log ε 3.82); NMR ($CDCl_3$) δ 2.03 (3 H, s, OAc), 2.32 (6H, s, NMe_2), 3.82 (1 H, q, J = 7.8 Hz, 2-H), 6.01 (1 H, d, J = 16.5 Hz, 10-H), 6.62 (1 H, d-d, J = 16.5 and 6 Hz, 11-H). (Found: C, 64.99; H, 8.75; N, 2.32. Calc. for $C_{30}H_{49}NO_8$: C, 65.31; H, 8.95; N, 2.54%).

Acknowledgement—We are grateful to Prof. T. Hata and Dr. W. D. Celmer for stimulating discussions during this work. We also thank Kayaku Antibiotics Research Laboratory for supplying pikromycin. This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture (847091).

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 175 to 180, 1981
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DIVALENT LANTHANIDE DERIVATIVES IN ORGANIC SYNTHESIS—II

MECHANISM OF SmI_2 REACTIONS IN PRESENCE OF KETONES AND ORGANIC HALIDES[1,2]

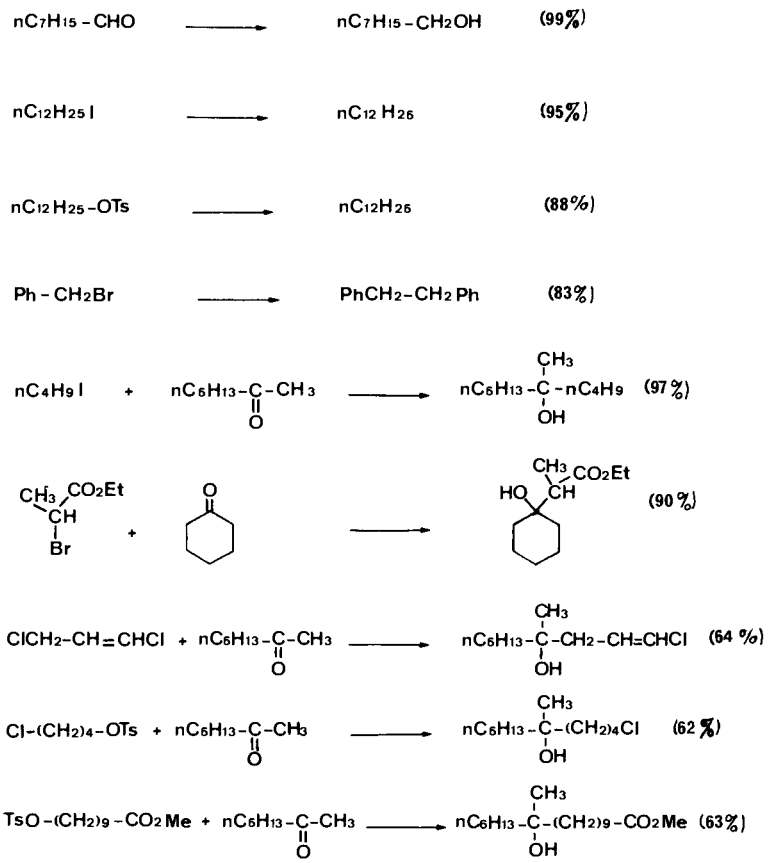
H. B. KAGAN*, J. L. NAMY and P. GIRARD
Laboratoire de Synthèse Asymétrique, associé au CNRS (LA 255),
Université de Paris Sud, 91405-Orsay Cédex, France

(*Received in France* 11 *June* 1980)

Abstract—Aprotic THF solutions of SmI_2 reduce alkyl halides or tosylates into the corresponding alkanes free of coupling products. The mechanism of this reaction involves an electron transfer from samarium to halides and hydrogen abstraction from THF. Aldehydes are selectively reduced by SmI_2 in presence of a proton donor. Ketones react with organic halides in the presence of SmI_2 giving tertiary alcohols. Mechanisms of these reactions are discussed. Some evidence including catalytic effects of $FeCl_3$ are given for electron transfers from SmI_2 towards ketones and halides.

INTRODUCTION

We recently established the usefulness of SmI_2 for mediating various organic reactions.[2] SmI_2 was easily prepared from samarium and 1,2-diiodoethane and can be stored as 10^{-1} M THF solution (THF = tetrahydrofuran). This reagent smoothly deoxygenates epoxides into olefins and sulphoxides into sulphides. SmI_2 selectively reduces aliphatic aldehyde into primary alcohol in the presence of aliphatic ketone. The reaction was performed in THF containing 2% of methanol. Aliphatic halides and tosylates were reduced into the corresponding alkanes in refluxing THF. No coupling products have been detected in this reaction. Quite the contrary dehalogenative dimerization occurs at room temperature with allylic or



Scheme 1. Some examples of SmI_2 reactions in presence of ketones and halides.[2]

benzylic halides. Grignard-type ketone addition of various organic halides are mediated by SmI_2. Tertiary alcohols are obtained after hydrolysis in high yields. Some representative examples of these reactions[2] are indicated in Scheme 1. In this paper we wish to discuss mechanisms of the reactions involving SmI_2 and ketones or/and organic halides.

DISCUSSION

Electron transfer processes from non-metal species towards organic compounds are still under wide investigation. Numerous works in the field of the organometallic reaction mechanisms have been described and several reviews are available.[3–8] In the reactions depicted in Scheme 1, SmI_2 behaves as an electron donor and appears as a new reagent able to promote various reactions which proceed by electron transfer. It is interesting to point out that SmI_2 presents a reduction potential[9] which is among the highest known for species soluble in organic medium:

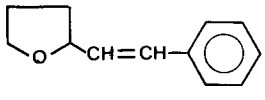
$$E_{o\ aq}Sm^{2+}/Sm^{3+} = -1.55\,V.$$

Reduction of organic halides

Two equivalents of SmI_2 convert alkyl bromides and alkyl iodides RX into the corresponding alkanes RH in refluxing THF. In these reactions we never observed the dimerization product R–R resulting from coupling of R· radicals. In iodides reduction precipitation of SmI_3 occurs. Such a conversion performed by an electron donor is generally explained either by formation of a stable organometallic species which is transformed into alkane by subsequent hydrolysis or by a mechanism involving radical and/or anionic species, which are able to abstract hydrogen from THF.[10,11]

In SmI_2 reduction experiments no carbon-metal bond was detected by titrations of the resulting solutions after Sm^{2+} colour disappearance.[12] Furthermore these solutions are unable to alkylate ketones even though it was demonstrated that $RSmI_2$ or R_2SmI does (R = phenyl, methyl).[13] Hydrolysis by D_2O of the same resulting solutions leads to a non-deuterated alkane. Thus, a mechanism involving formation of a stable organometallic species may be dismissed.

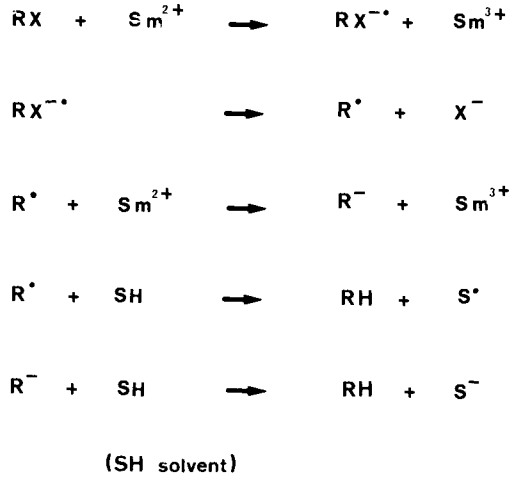
In the reaction between β-bromostyrene and SmI_2, appreciable amounts[14] of "solvent adduct" hydrocarbon **1** were obtained (22%) besides the recovered β-bromostyrene (64%). Product **1** could arise from combination of the radicals THF· and C_6H_5–CH=CH·.



1

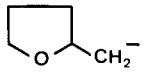
Thus, the mechanism involving radical species is the most likely for the reduction of organic halides by SmI_2 (Scheme 2).

In some circumstances transient carbanionic species are probably present in the medium. For example, reaction between tetrahydrofurfuryl bromide and SmI_2 leads to large amounts (50%) of 4-penten-1-ol



Scheme 2.

which result from the classical rearrangement[15] of the tetrahydrofurfuryl anion **2**.



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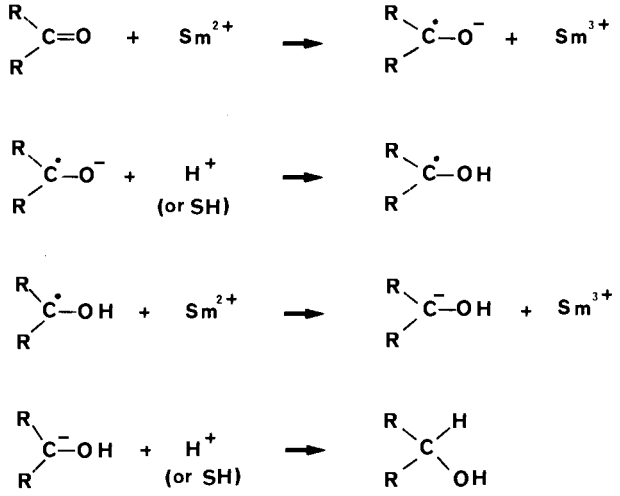
Contrary to alkyl halides, reduction of benzylic or allylic halides by one equivalent of SmI_2 lead primarily to dimerized products at room temperature. Radicals and carbanions arising from these halides are particularly stable. Moreover nucleophilic substitutions are quite easy on these substrates. In order to explain our results, we assumed that radicals, being stable enough, can diffuse outside the coordination sphere of samarium, leading to coupling products. Another hypothesis is that carbanions are sufficiently stable and abundant for further reaction with remaining halide.[16]

Alkyl tosylates are reduced into alkanes by two equivalents of SmI_2 in refluxing THF. These reactions are enhanced by small amounts of NaI. Thus, the first step is probably the conversion of tosylates into iodides,[17] followed by the reduction to alkanes. As a matter of fact, even in absence of NaI small amounts of alkyl iodides are detected among the reaction products.

Reduction of carbonyl group

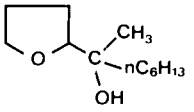
The reduction of ketones by metals dissolved in ammonia or alcohol and the related electrochemical reductions have been extensively studied. These works have been summarized.[18] The reduction of carbonyl groups by SmI_2 could be described by a scheme analogous to the classical one where SmI_2 behaves as an electron donor (Scheme 3).

The first step is the formation of a ketyl radical-anion. Two equivalents of SmI_2 per ketone and a proton donor are necessary. This mechanism is supported by the following observations. In 2-octanone reduction, in addition to the expected 2-octanol, small amounts of pinacolization products and of "solvent adduct" alcohol **3** are detected. This reveals



Scheme 3.

the existence of ketyl intermediates in the reaction medium.[19]

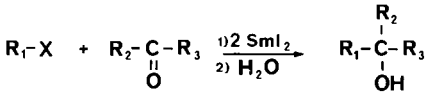


3

The reduction of octanal by SmI_2 performed in presence of CH_3OD leads mainly to the C-deuterated 1-octanol. A small amount (10%) of non-C-deuterated 1-octanol was also detected. Similar results have been obtained in the reduction of acetophenone in presence of D_2O. These experiments show that, concurrently to the proton donor methanol (or water), the solvent tetrahydrofuran has to be also considered as an hydrogen donor. Octanal was also partially reduced in aprotic SmI_2–THF solution. Subsequent hydrolysis by D_2O gave no C-deuterated I-octanol. This reveals that a ketone dianion is not the end-product before hydrolysis in the reduction reaction. Thus the Scheme 3 is the most appropriate for the reduction of carbonyl groups by SmI_2.

Condensation between a ketone and an organic halide

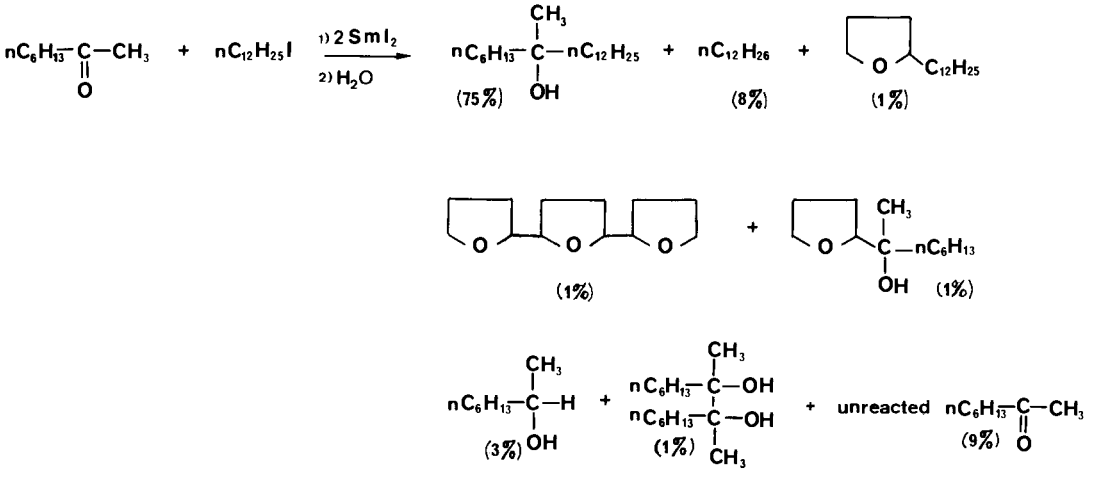
One of the most useful applications of SmI_2 was its ability to induce selective C–C bond formation between ketones and various organic derivatives RX (X = halide or tosylate).[2] Some examples of these reactions (eqn 1), which formally resemble to Grignard-type carbonyl addition, have been listed in Scheme 1.



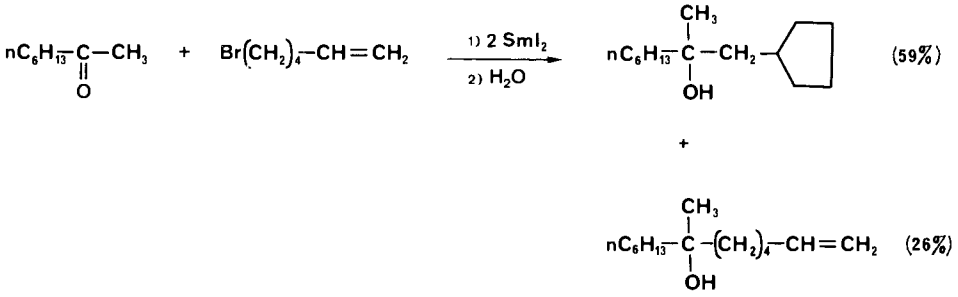
(1)

In order to obtain mechanistic informations, a complete analysis of reaction products in the alkylation of 2-octanone by 1-iodododecane in presence of two equivalents of SmI_2 was carried out with the help of a coupled gc-mass spectrometer (Scheme 4).

7-methyl-7-nonadecanol and unreacted 2-octanone are obtained in 75% and 9% yield respectively. The most abundant by-product is dodecane. The presence of THF· radicals in the reaction medium and/or THF^- carbanions is revealed by formation of small amounts of various 2-substituted THF. Ketyl radicals also are



Scheme 4.



Scheme 5.

present: pinacolization products of 2-octanone, "solvent adduct" alcohol and 2-octanol are detected.[19] Thus the main by-product is the hydrocarbon which results from the reduction of alkyl halide by SmI_2. This explains why an excess of both SmI_2 and alkyl halide allows tertiary alcohol to be obtained almost quantitatively.[2]

In the alkylations mediated by SmI_2, $R^{\cdot}$ radicals and ketyl radicals are obviously present in the reaction medium. This is supported by examination of by-products arising in these reactions, as pointed out in Scheme 4. A classical test for detection of radicals is the use of 1-bromo-5-hexene, a precursor of a hexenyl radical which is able to cyclize into methylcyclopentyl radical.[20] Reaction between 2-octanone and 1-bromo-5-hexene performed in the presence of SmI_2 is described in the Scheme 5. Since cyclopentane ring formation is clearly observed, a radical species was involved during the course of the reaction.[20]

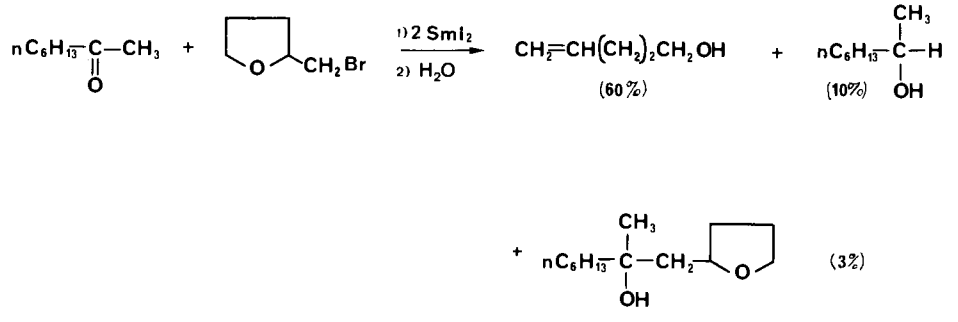
It is interesting to point out that in the absence of ketones and under conditions leading to hydrocarbons, 1-bromo-5-hexene does not lead to methylcyclopentane. In the same vein, benzylic or allylic halides react in the absence of ketones with SmI_2 to yield coupling products exclusively while only tertiary alcohols are obtained when 2-octanone is present as well; furthermore the dehalogenative dimerization is very rapid. For example benzylbromide leads to dibenzyl in 82% yield in 20 min. In the presence of 2-octanone alkylation is slower, giving as the only product the tertiary alcohol in 69% yield in 30 min. These experiments, showing that SmI_2 behaves in different ways towards allylic or benzylic halides depending on the presence of a ketone, suggest that this latter strongly complexes to SmI_2 and could be in addition a relay for electron transfer. In the reaction between SmI_2 and 1-bromo-5-hexene, in absence of ketones, we consider that $R^{\cdot}$ radicals are rapidly reduced by SmI_2 into carbanions R^-, this reaction being faster than $R^{\cdot}$ cyclization. Hexenyl anion cyclization can not occur.[15,20] Abstraction by R^- carbanion of a proton from THF molecule completes the reaction.

Optically active 2-bromooctane reacts with cyclohexanone at room temperature, in presence of SmI_2, to give a racemic tertiary alcohol. The same result is obtained using optically active ethyl 2-bromopropionate and cyclohexanone. Loss of optical activity is expected if alkyl halide was converted into a radical and/or a carbanion. These experiments exclude an alkylation mechanism involving a nucleophilic substitution of the alkyl halide by the ketone dianion **4**.

In some particular cases, alkyl anions intermediates can be formed in the reaction medium. Thus, tetrahydrofurfurylbromide reacts with SmI_2 and 2-octanone to give mainly 4-penten-1-ol, arising from rearranged tetrahydrofurfuryl anion[15] (Scheme 6).

Alkylation of ketones by alkyl tosylates was also carried out in presence of SmI_2. Such a reaction starts probably by the conversion of alkyl tosylate into alkyl iodide,[17] the alkylation of ketone occurring then through a mechanism like the one discussed above. As a proof, catalytic amounts of NaI enhance this alkylation reaction, and alkyl iodides even in absence of NaI are present in the reaction products.

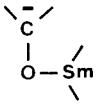
Addition of catalytic amount of ferric chloride (1% with respect to SmI_2) decreases the reaction time of the alkylation mediated by SmI_2.[2] This effect of $FeCl_3$ could be related to its ability to catalyze formation of ketyl radicals as described recently in Grignard-type



Scheme 6.

reactions[21] and/or conversion of Ln^{2+} into Ln^{3+} derivative.[22] These two effects could exist in the experiments mediated by SmI_2, where $FeCl_3$ appears as a species facilitating electron transfers.

Three mechanisms may be considered in order to rationalize experimental results: (i) the reaction occurs by successive electron transfers to alkyl halide RX producing a R^- carbanion, probably as a transient Grignard-like reagent $RSmI_2$ able to alkylate ketones; (ii) simultaneous electron transfers to alkyl halide RX and ketone give rise to a R· radical and a ketyl radical and upon coupling and subsequent hydrolysis, these two species yield alkylation product; (iii) electron transfer to the ketone leads to an alcoholate anion such as **4** and alkylation of this species by alkyl halide RX through a nucleophilic substitution yields after hydrolysis the expected alcohol.



4

More complex mechanistic schemes including intermediate species coordinated to metal may be considered. Scheme 7 takes into account all the mechanistic processes envisaged for the alkylation of ketones by organic halides in the presence of SmI_2. The above experiments show that a mechanism involving radical species is the most likely (mechanism ii). Nevertheless, according to each studied system, some of the steps indicated in the Scheme 7 may or not be involved in the mechanism of particular alkylation reaction.

As other lanthanide derivatives, SmI_2 presents a high coordination number, usually seven.[23] We believe that the alkylation reactions occur in the coordination sphere of samarium which is bonded to several molecules of THF.

In the Scheme 7 species required for these reactions are indicated between brackets, their exact stoichiometry and their solvation or association degrees being not exactly known.

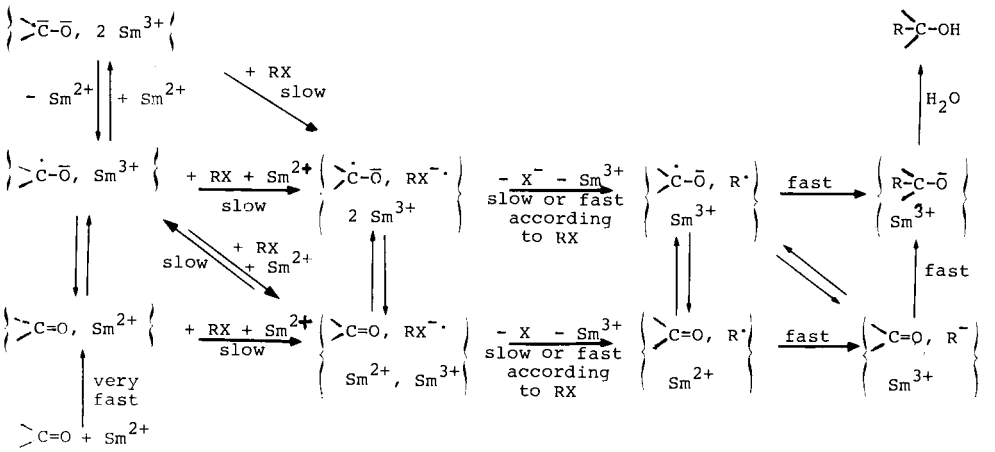
The formation of all the by-products of Scheme 4 can be explained by some of the pathways proposed in Scheme 7. THF· radicals formed by hydrogen abstraction from THF by a radical species R· (or a ketyl radical) can react with another radical R· (or a ketyl radical) leading to the "solvent adduct hydrocarbon" or to the "solvent adduct alcohol". Abstraction of hydrogen from THF converts radical R· or ketyl radical into "reduction hydrocarbon" RH or "reduction alcohol" respectively. The small amounts of "pinacolization products" arise from the dimerization of transient ketyl radicals.

Thus in the alkylation of a ketone by an alkyl halide performed in presence of SmI_2, a mechanism including radical species is the most probable, the expected tertiary alcohol resulting from the coupling of a radical R· with a ketyl radical. However other pathways depicted in Scheme 7 must not be excluded for the mechanism of some particular alkylations and more detailed studies would be necessary to improve the mechanistic schemes of SmI_2-mediated reactions.

CONCLUSION

A picture of the mechanisms involved in SmI_2-mediated reactions is now emerging. The main characteristic of this soluble reagent is its ability to transfer one electron to organic halides RX with subsequent formation of radical species R·. Electron transfer towards ketones is also possible. Thus radical chemistry is initiated by SmI_2. However the presence of highly coordinated Sm^{2+} and Sm^{3+} derivatives is determinant. It probably facilitates electron transfer and could change some of the usual reactions of radical R·. For example no coupling product R–R could be obtained from an alkyl halide RX even in absence of ketone; in such a case hydrogen abstraction from THF is the only reaction.

More mechanistic studies are necessary to widely explain the reactivity of SmI_2 which appears as a new



Scheme 7. Some tentative pathways of ketone alkylation by an alkyl halide mediated by SmI_2.

reagent able to promote many selective transformations in organic molecules. Scope of the SmI_2 reactions in organic synthesis is under investigation.

EXPERIMENTAL SECTION

Proton magnetic resonance spectra (^1H NMR) were recorded on a Perkin–Elmer Model R 32 at 90 MHz. Chemical shifts in $CDCl_3$ are reported in ppm on the δ scale relative to tetramethylsilane as internal standard. Mass spectra were obtained on a GC-MS Hewlett–Packard Model 5992 A. Gas chromatographic analyses were carried out on a Carlo Erba Model FTV 2150. Peak area integration were performed by electronic integration. Yields measured by GLC were all calculated by comparison with an internal standard. Optical rotations were measured using a Perkin–Elmer Model 241 polarimeter.

Reagents and reaction procedure

THF solutions of samarium diiodide were prepared as described in reference 2. Samarium was 40 mesh powder from Labelcomat (Belgium). THF must be deoxygenated and quite anhydrous. 1,2-diiodoethane (Merck) was purified as in reference 2. Sodium iodide and ferric chloride are dehydrated before use. Most organic compounds used are commercial samples purified by distillation or recrystallization. Tetrahydrofurfurylbromide,[24] (−) 2-bromooctane,[25] (+) ethyl 2-bromopropionate[26] and sulfonates[27] were prepared according to literature procedures.

Unless otherwise stated, all operations, the reactions between SmI_2 and various substrates such as the analysis of reaction products, were carried out in the same way as previously described.[2] Many spectra of reaction products may be compared with those of authentic samples prepared by Grignard reactions or Reformatsky reactions. Reduction experiments leading to deuterated or non-deuterated products have been analyzed with the help of a coupled GC-mass spectrometer. This apparatus has been also used for the analysis of by-products in the alkylation reaction of 2-octanone by 1-iodododecane.

1-*Phenyl*-2:2′-*tetrahydrofuryl-ethylene* (**1**). ^1H NMR 1.60–2.20 (m, 4, $J = 7$ Hz, H heterocyclic), 3.92 (m, 2, $J = 7$ Hz, H heterocyclic), 4.48 (q, 1, $J = 6$ Hz, $J' = 7$ Hz, H heterocyclic), 6.20 (d.d., 1, $J = 16$ Hz, $J' = 6$ Hz, C_6H_5–CH=C$\underline{H}$–), 6.62 (d, 1, $J = 16$ Hz, C_6H_5–C$\underline{H}$=CH–) 7.30 (m, 5, Arom); Mass spectrum *m/e* 174 (100, M^+) 146 (10), 132 (13), 131 (55), 104 (51), 103 (27), 91 (20), 77 (25).

2:2′-*Tetrahydrofuryl-octan-2-ol* (**3**). Mass spectrum *m/e* 200 (3, M^+) 185 (4), 130 (8), 129 (100), 115 (39), 71 (29), 69 (69), 55 (14).

1-*Tetrahydrofuryl-dodecane*. (Scheme 4) mass spectrum *m/e* 240 (28, M^+), 197 (39), 169 (46), 71 (100), 59, 43.

2:2′, 5′:2″-*Tertetrahydrofuran*. (Scheme 4) mass spectrum *m/e* 213 (6, MH^+) 71 (6), 59 (100), 43 (11).

2-*Methyl*-1:2′-*tetrahydrofurfuryl-octan-2-ol*. (Scheme 4) mass spectrum *m/e* 129 (10), 126 (25), 113 (61), 85 (50), 71 (41), 58 (39), 55 (100), 43 (78).

Acknowledgements—We thank Drs P. Caro and Z. Welvart for fruitful discussions and CNRS for its financial support.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 181 to 189, 1981
Printed in Great Britain

0040-4020/81/Suppl. 1-0181-09 $02.00/0
Pergamon Press Ltd.

OPTICAL ROTATORY DISPERSION STUDIES—131

DEMONSTRATION OF A CONFORMATIONAL ISOTOPE EFFECT IN DEUTERIUM SUBSTITUTED CYCLOPENTANONES†

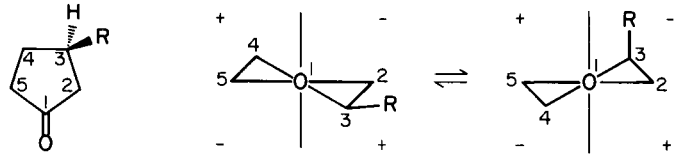
LAWRENCE Y. SING, MATTHEW LINDLEY, P. SUNDARARAMAN, GÜNTER BARTH and CARL DJERASSI*
Contribution from the Department of Chemistry, Stanford University, Stanford, CA 94305, U.S.A.

(*Received in U.S.A.* 13 *May* 1980)

Abstract—The synthesis and chiroptical properties of three chiral, deuterium-substituted cyclopentanones are reported which shed light on subtle conformational changes. Thus, the CD spectra of (3*R*)-3-deuteriocyclopentanone (**1**), (3*S*,4*S*)-3,4-dideuteriocyclopentanone (**2**) and (3*S*,4*S*)-2,2,3,4,5,5-hexadeuteriocyclopentanone (**3**) are found to undergo an increase (in the absolute sense) of the rotational strength on lowering the temperature. This change is associated with a shift in the conformational equilibrium towards the twist conformation with the deuterium in the quasi-axial position. Using literature estimates for the rotational strength of the involved twist conformation, enthalpy differences of approximately −1, −4 and −6 cal/mol were calculated for the respective conformational equilibria of **1**, **2** and **3**. Empirical force field calculations were found to be in qualitative agreement with the experimental results when weaker non-bonded interactions for deuterium were used. The gas-phase spectra of **1** and **2** are reported which reveal a surprisingly well resolved vibrational fine structure. Two superimposed main progressions with a spacing of 1250 cm^{-1} extending up to the sixth overtone are identified. It is suggested that they represent progressions in the excited state carbonyl stretch mode built upon two pseudo origins.

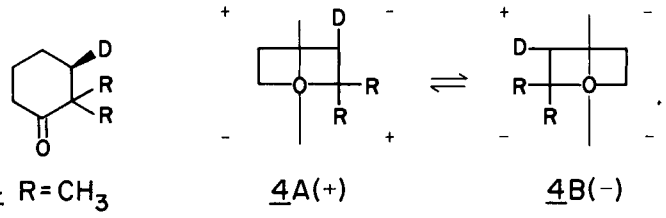
(3*R*)-3-Deuteriocyclopentanone (**1**) was the first reported[2] ketone, which owes its chirality solely to isotopic substitution and exhibits a clearly measurable Cotton effect for the CO n-π^* transition. Originally this compound had been chosen in the anticipation that it might show a particularly large rotational strength since in general chiral cyclopentanones (e.g. 3-methylcyclopentanone) exhibit much stronger Cotton effects than other alicyclic (e.g. 3-methylcyclohexanone) or aliphatic ketones.[3] More recent work in our laboratory has shown this assumption to be oversimplified, since the subsequently synthesized 6-membered ring analog, (3*S*)-deuteriocyclohexanone,[4] showed a three times larger Cotton effect amplitude. The explanation is clear: cyclopentanone exists predominantly in an equilibrium of the two possible twist conformations,[5,6] A (R=H) and B (R=H) and in contrast to the chair conformations of cyclohexanone, the twisted ring gives rise to a large rotational strength[3b,f] which is positive for A and negative for B (as predicted by the octant rule).[7]

A bulky substituent such as a Me group, will shift the conformational equilibrium towards A(R = Me, quasi-equatorial position) and consequently lead to a large (in this example positive) observed rotational strength (associated with C-3 and C-4). In contrast, when R represents deuterium, the equilibrium will be affected only very slightly resulting in the almost complete cancellation of the chiral ring contributions (due to C atoms 3 and 4 in A *vs* B). *The observed rotational strength results then predominantly from the difference between the contributions of deuterium in the quasi-axial (B) and quasi-equatorial (A) positions* and this value turns out to be smaller compared to the equivalent difference in 3-deuteriocyclohexanone.[4] In two recent communications[8,9] we have presented experimental evidence that the temperature-dependent CD spectra of various mono-deuterium substituted cyclohexanones can be used to calculate the energy difference between the conformations with the deuterium in the equatorial and axial positions, provided that through the presence of a geminal α-dimethyl group (i.e. a "chiral probe") the rotational strengths of both chair conformations become large numbers of opposite sign. This concept is demonstrated with the octant diagram representation



1 R=D A (+) B (-)

†This contribution commemorates our collaborative research in the late 1950's with R. B. Woodward which led to the development of the octant rule (Ref. 7).



of (3*R*)-2,2-dimethyl-3-deuteriocyclohexanone (**4**) whose temperature-dependent CD spectrum has been reported earlier.[8]

As pointed out above both twist conformations (**1A** or **1B**) of **1** possess large rotational strengths of opposite sign due to the ring C atoms C-3 and C-4 (which now serve as "chiral probes" similar to the gem-dimethyl group in **4**) and consequently even small temperature-induced shifts in the equilibrium position can be expected to lead to measurable changes in the observed rotational strength. Therefore, we felt encouraged to repeat the measurement of **1** at various temperatures in order to determine whether the energy difference between the conformations with the deuterium in the quasi-equatorial and quasi-axial positions can be detected through this method. In addition we report the synthesis and temperature-dependent CD spectra of (3*S*, 4*S*)-3,4-dideuteriocyclopentanone (**2**) and its perdeuterated analog (3*S*, 4*S*)-2,2,3,4,5,5-hexadeuteriocyclopentanone (**3**). A quantitative comparison of the temperature dependency of the rotational strength for compounds **1**, **2** and **3** was of particular interest since they were not expected to be of equal magnitude. Such a comparison required a precise knowledge of the enantiomeric excess of these compounds. In order to verify the previously reported[2] rotational strength of **1** we have resynthesized this compound by a different synthetic route from an intermediate of known optical purity.

Synthesis

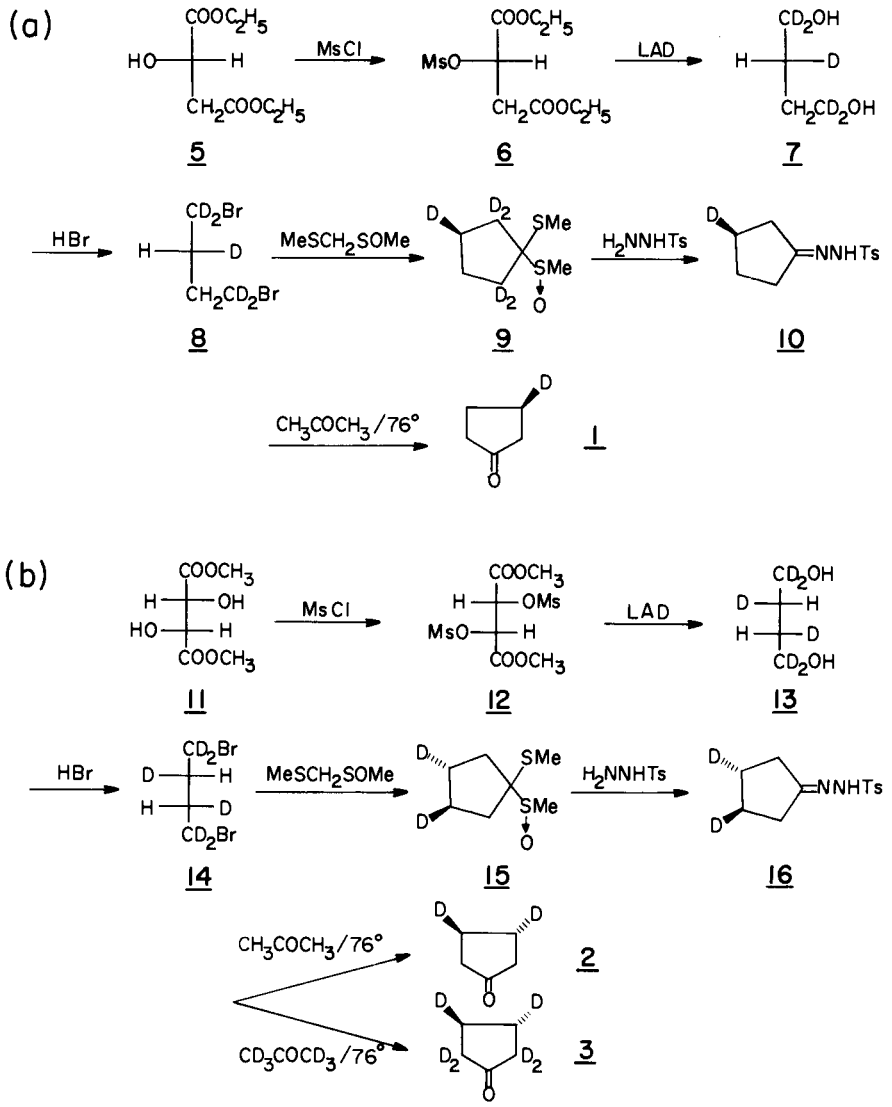
The monodeuterium substituted cyclopentanone (**1**) was synthesized according to Scheme 1a. The diethyl ester of L-malic acid (**5**) was converted via the mesylate **6** and LAD reduction to pentadeuteriobutanediol (**7**) and thence to the dibromide **8**.[10] Cyclization of **8** with methyl methylsulfonylmethylide[11] gave **9** which was transformed into the tosylhydrazone **10** and then hydrolyzed by the procedure of Maynez *et al.*[12] to **1**.

Using dimethyl-L-tartrate (**11**) as starting material, the 3,4-dideuterio analog **2** was synthesized using the same reaction steps (Scheme 1b) as outlined for the synthesis of **1**. The hexadeuterio analog **3** was obtained from **2** by perdeuteration of the CO α-positions using a D_2O-pretreated gas chromatographic column.[13] The enantiomeric excess of **1**, **2** and **3** is assumed to be equal to that of the starting material, i.e. 100%, since the LAD reduction of the mesylates **6** and **12** proceeds with nearly complete stereoselectivity and all other reaction steps in the sequence leave the chiral center(s) unaffected. It was gratifying to note that the rotational strength of **1**, as prepared by this new method, was found to be within 5% of the value reported for a sample[2] prepared by a totally different method. Compound **1** has recently[14] been synthesized also by microbiological reduction and the reported [θ]value of 62 is in close agreement with that reported in this and the previous study,[2] thereby leaving little doubt about its optical purity.

RESULTS AND DISCUSSION

The CD spectra of **1**, **2** and **3** in EPA (ether, i-pentane, ethanol 5:5:2 vv) at various temperatures together with the octant diagram representation of both twist conformations are shown in Fig. 1. In all three examples the rotational strength increases (in the absolute sense) with lowering the temperature. In order to associate these changes with a shift in the conformational equilibria of **1**, **2** and **3** as shown in Fig. 1, one has to exclude alternative possibilities like the presence of conformations other than the twist forms and/or solvent-solute interactions which also can give rise to temperature-dependent CD spectra.[15] The envelope form of cyclopentanone has been calculated[16] to be 3.22 kcal/mol higher in energy and therefore participates to the extent of less than 0.5% to the equilibrium at room temperature. Furthermore the interpretation of the microwave[5] and ^{1}H NMR[6] spectra was only consistent with the exclusive presence of the twist conformation. We also note that the main intensity changes of the CD spectra (Fig. 1) take place below *ca* 150 K; even if one assumes an energy difference as low as 1 kcal/mol between twist and envelope forms the equilibrium would already be shifted practically completely toward the twist conformations (97%) at this temperature.

In view of this evidence it appears very unlikely that the observed intensity changes are associated with a "freezing out" of the envelope conformations. The presence or absence of solvent-solute related intensity changes of the rotational strength can usually be assessed through measurements in solvents of different polarity.[15] The measurements of **1**, **2** and **3** in IPM (i-pentane, methylcyclohexane 4:1 vv), a non-polar solvent as compared to EPA, resulted in virtually identical intensity changes with temperature. However, it was observed that, while the room temperature spectra showed a well-resolved vibrational fine-structure (see spectra in i-octane in Fig. 2), the spectra at 77 K displayed no distinct vibrational structure and in addition were shifted by *ca* 10 nm to lower wavelengths. We suggest that this behavior results from a solute-solute interaction which takes place in the non-polar solvent IPM but not in EPA. Nevertheless the similarity of the temperature dependency of [R] in both solvent systems can be taken as an indication that they are not related to a solvational effect. Inspection of the octant diagram representation of the twist conformations (Fig. 1) therefore allows the qualitative conclusion that in all three examples *the twist conformation with the deuterium substituent(s) in the quasi-axial position*



Scheme 1.

increases in population on lowering the temperature. This is precisely the same conclusion obtained for the mono-deuterio substituted cyclohexanone analogs,[8,9] i.e. *the isotope of "smaller size" (deuterium) tends to preferentially occupy the position of larger strain namely the quasi-axial and axial positions in cyclopentanone and cyclohexanone respectively.*

For the quantitative determination of the energy differences one requires good estimates for the rotational strengths of both conformers.[17] Experimentally, such values are not directly available since in contrast to the cyclohexanone ring any substituent which locks the cyclopentanone ring in one or the other twist conformation will contribute by itself to the observed rotational strength. From the CD spectra of various reported cyclopentanone derivatives, Kirk[3f] has estimated the rotational strength of the twisted cyclopentanone ring to be $[R] = \pm 17$. In view of the uncertainty of such estimates we have carried out the calculations with reference values of different magnitude to give an indication of the associated range for $\Delta H°$. In addition, the contributions from the D substituents have not been included in these estimates since they remain unknown. From the results of previous studies[19–21] in the cyclohexanone series these contributions must be assumed to be very small ($[R]$ *ca* $\leq \pm 0.3$) and their neglect will not affect significantly the calculated energy differences. The results of these calculations are given in Table 1.

Comparatively few experimental data for the quasi-axial/quasi-equatorial energy differences of substituted cyclopentanones are reported in the literature and the majority of them have been determined by circular dichroism measurements.[3f] For example an energy difference of -500 cal/mol has been reported for 3-methylcyclopentanone[3f,22] and -600 cal/mol for 3-methylcyclohexanone.[23] This comparison indicates that the energy differences between axial and equatorial Me substituents are of comparable magnitude in both ring systems which also is born out by the values found by us for D (-2 to -7 cal/mol for the mono-D substituted cyclohexanones).[8,9]

The notion that D is of "smaller size" as compared to H is most likely related to the somewhat shorter C–D

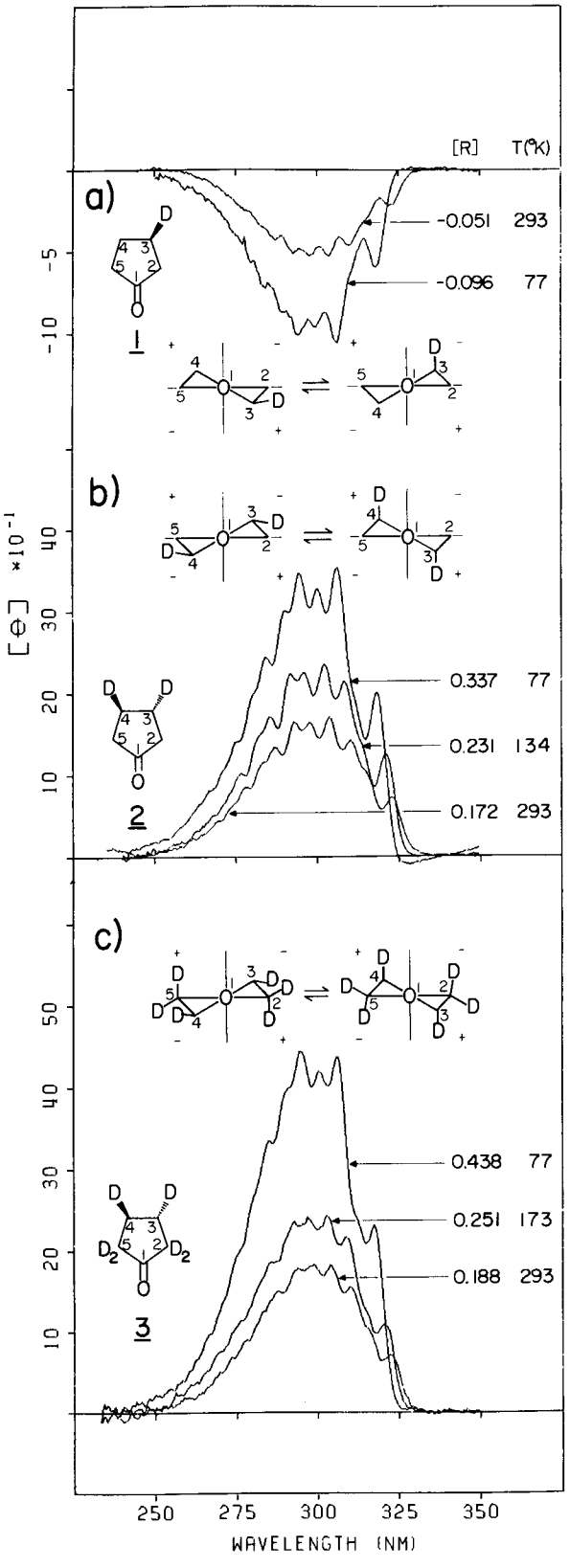


Fig. 1. Circular dichroism spectra at various temperatures and octant diagrams of both twist conformations of (a) (3*R*)-3-deuteriocyclopentanone (**1**), (b) (3*S*, 4*S*)-3,4-dideuteriocyclopentanone (**2**) and (c) (3*S*, 4*S*)-2,2,3,4,5,5-hexadeuteriocyclopentanone (**3**) in EPA (ether, i-pentane, ethanol 5:5:2 vv) as solvent. The concentrations were ca. 0.04 mol/L.

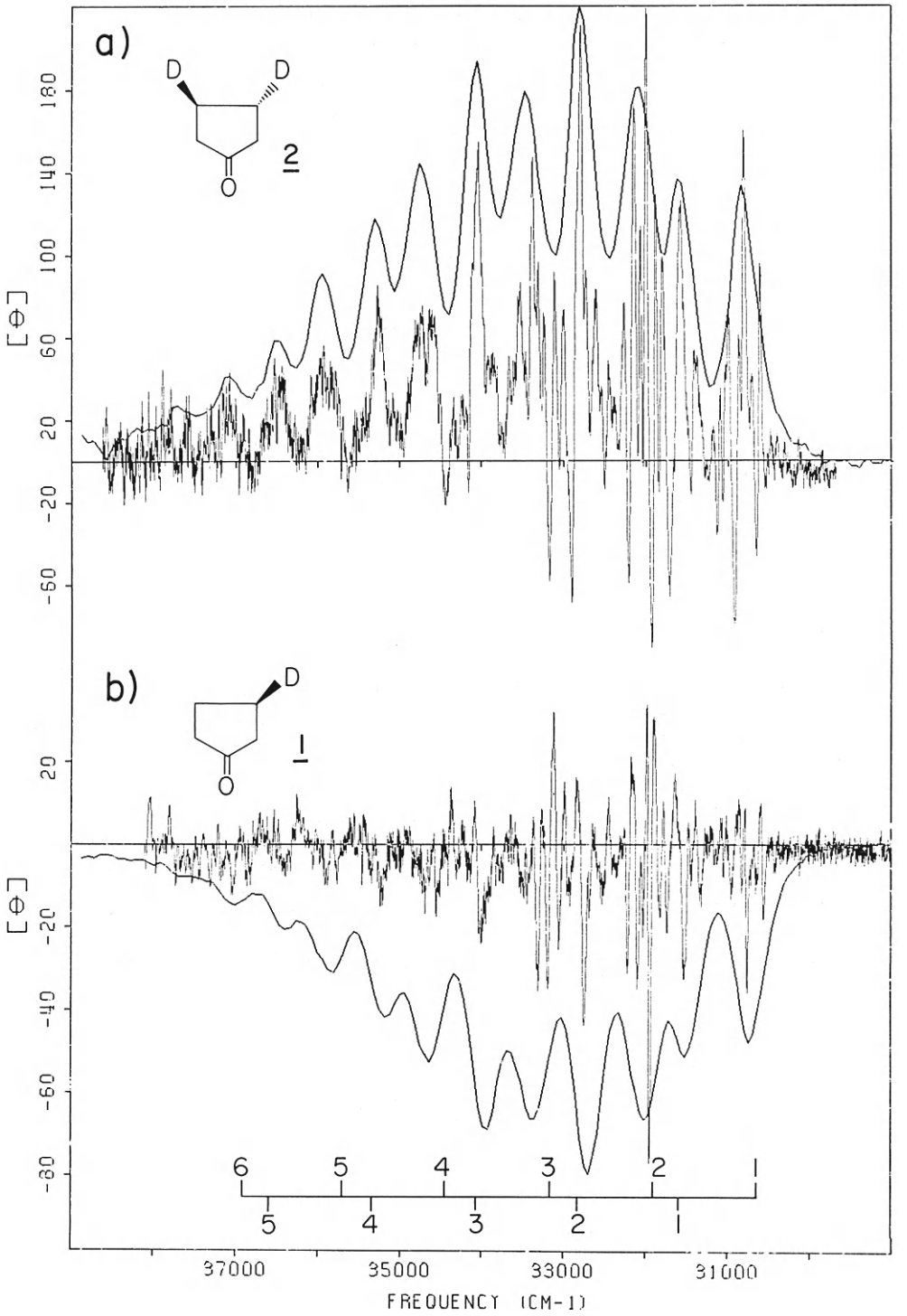


Fig. 2. Solution (in i-octane as solvent) and gas-phase spectra (at room temperature) of (a) (3*S*, 4*S*-3,4-dideuteriocyclopentanone (**2**) and (b) (3*R*)-3-deuteriocyclopentanone (**1**). The gas-phase spectra are not normalized.

bond distance (0.004 Å) and smaller vibrational amplitudes (0.01 Å) as determined through electron diffraction[24] and Raman spectroscopic[25] studies. However, from model inspections it is not immediately clear how this concept of the "size difference" between D and H can be used to explain the energy relationship of *ca* 1:4:6 as calculated for **1**, **2**, and **3** respectively (Table 1). To obtain a more quantitative idea for this steric isotope effect we have carried out empirical force field (EFF) calculations[26] on the various twist conformations with the deuterium in the quasi-equatorial and quasi-axial positions, since this method has been shown[16,27] to predict quite accurately energy differences of conformational equilibria. Although we

Table 1. Estimated energy differences for compounds **1**, **2** and **3**[1]

Estimate for [R][2] of the quasi-equatorial and quasi-axial conformers	Enthalpy differences in cal/mol for the equilibria of compounds		
	1	2	3
± 19	-0.99	-3.62	-5.51
± 17	-1.11	-4.04	-6.15
± 15	-1.26	-4.58	-6.98

1) The experimental uncertainty of the $[R]^T_{obs}$ values is approximately ±0.002. The error assocated with the linear least square fit of the data in the Arrhenius diagram was approximately 10%. The overall error associated with the ΔH^o values is therefore estimated to be 15%.
2) [R] is the reduced rotational strength.

did not expect that these calculations would reproduce the very small energy differences found experimentally, it was hoped that trends would become discernible by exaggerating the "size" difference between D and H.

The employed force field is usually broken down into bond-deformation (i.e. bond-stretch, -bend and torsional modes) and non-bond interactions.[26] The bond-stretch potential U_{st} is most frequently represented by equation 1 where the parameters A and B represent the bond force constant and equilibrium distance respectively and R_{ij} is the internuclear distance between atoms i and j.

$$U_{st}(\text{kcal/mol}) = 144*0.5*A*(R_{ij} - B)^2. \quad (1)$$

The non-bond potential U_{nb} is described by a three parameter Buckingham equation (2) where A, B and C are empirically chosen parameters.

$$U_{nb}(\text{kcal/mol}) = 144*[A*EXP(-BR_{ij}) - C/R_{ij}^6]. \quad (2)$$

Reducing the magnitude of B in eqn (1) leads to a shorter equilibrium bond length and reduction of A in 2 results in a "softer" non-bond interaction i.e. to a reduction of the potential energy for a given atomic distance R_{ij}. The chosen parameters for hydrogen and deuterium and the calculated energy differences for **1**, **2** and **3** are summarized in Table 2. As indicated above we place no particular physical significance on the

Table 2. EEF calculations[a] for the twist conformations of **1**, **2** and **3**

Assumption	Energy difference (cal/mol) between the twist conformations with the deuterium in the quasi-equatorial and quasi-axial positions (see Fig. 1)		
	1	2	3
shortening of C-D bond[b] length only	18	38	38
reduction of non-bond[c] interactions for D only	-68	-135	-135
C-D bondlength shortening plus reduction of D non-bond interactions	-51	-99	-99

a) the calculations were carried out with the program MOLBD2 described by R.H. Boyd J. Chem. Phys., 49, 2574 (1968).

b) the parameters for the bond deformation modes were taken from ref. 16 and D.H. Wertz, and N.L. Allinger, Tetrahedron, 30, 1579 (1974). The C-D stretch mode parameter B in equation (1) was set to 1.070 vs. 1.095 for the C-H bond.

c) the non-bond parameters for equation 2 were taken from S. Fitzwater and L.S. Bartell J. Amer. Chem. Soc., 98, 5107 (1976). The chosen parameters for the D interactions were: D...D; A=11.8; D...H, A=13.25; C...D, A=121.9.

absolute magnitude of the calculated values but rather wish to emphasize the relationship between them. First it is interesting to note that the reduction of the C–D bond length alone leads to a contradiction with experiment—the conformations with the D in the quasi-equatorial positions are calculated to be of lower energy. However, the use of weaker non-bond interactions leads to a qualitative agreement with experiment, i.e. the twist conformations with the D in the quasi-axial position are found to be lower in energy. It should be noted that the calculations predict that the ratio of the energy differences of **1**, **2** and **3** is 1:2:2 (rather than the observed 1:4:6), i.e. they confirm what one might have predicted intuitively: the introduction of a second D in **2** leads to a doubling of $\Delta H°$ as compared to **1** and that the perdeuteration of the α-positions in **3** has no further effect on the energy difference. Whether this discrepancy between calculation and experiment results from deficiencies in the chosen model or whether effects other than purely steric ones contribute to the stabilization of the conformation with the D in the quasi-axial positions cannot be decided at present.

Although not directly related to the conformational problem, we wish to take the opportunity to present the remarkable gas phase CD spectra of (3*R*)-deuteriocyclopentanone (**1**) and (3*S*,4*S*)-3,4-dideuteriocyclopentanone (**2**) which are shown in Fig. 2 together with their spectra in i-octane as solvent. The solution spectra appear to be analyzable in terms of two superimposed progressions with a nearly uniform spacing of 1250 cm^{-1} and origins at 30380 and 30826 cm^{-1} respectively as schematically indicated in Fig. 2. In the gas phase spectra each of these bands is resolved into a large number of vibrational sub-levels, the resolution becoming more diffuse toward the blue end of the spectrum. The vibration involved in the two main progressions is undoubtedly the carbonyl stretch mode in the excited state (totally symmetric a_1 symmetry). From the analysis of the high resolution absorption spectrum of cyclopentanone Howard–Lock and King[28] have concluded that the $n \rightarrow \pi^*$ transition gains intensity via two different vibronic pathways. One based on a hot pseudo-origin involving the ground state ring puckering mode (a_2 symmetry) and a cold pseudo-origin involving the excited state ring puckering and CO out-of-plane bend mode (b_1 symmetry). These two origins serve as starting points for the a_1 C=O stretch mode. This analysis appears to offer an explanation for the presence of two progressions in ν_{1250} as observed in the CD spectrum. That the CD spectra are considerably better resolved than the corresponding absorption spectrum (see Fig. 1 in Ref. 28) indicates that the CO stretch mode is particularly effective in inducing optical activity compared to other totally symmetric modes whose presence cause the absorption spectrum to be more diffuse. Another interesting observation is the presence of various bands of opposite sign in the gas phase spectra (Fig. 2). As Weigang[29] has pointed out, vibrational bands of opposite sign can be expected within the $n \rightarrow \pi^*$ transition depending on which higher electronic state is vibronically coupled by a particular vibration.[30] Alternatively the presence of negative bands could also result from a small frequency shift of the vibrational bands between both conformations of **1** and **2** (diagrams in Fig. 1) one having positive and the other negatively signed bands.

CONCLUSION

In conclusion, the temperature dependency of the CD spectra of **1**, **2** and **3** reveal the presence of a conformational isotope effect. The D substituent behaves as if it were of "smaller size", thereby shifting the conformational equilibrium towards the conformation where it occupies the site of larger non-bond strain i.e. the quasi-axial position in cyclopentanone. This result is consistent with that obtained previously for the deuterium substituted cyclohexanones[8,9] (where the chair conformation with the deuterium in the axial position was found to be energetically more stable) and again demonstrates the remarkable utility of chiroptical methods for quantitative studies of subtle conformational changes.

EXPERIMENTAL

Magnetic resonance spectra were determined on Varian T-60 and Bruker HXS-360 spectrometers. IR spectra were recorded on a Perkin–Elmer 700A spectrometer. Mass spectra were recorded on an AEI-MD 9 mass spectrometer and a Hewlett–Packard 7610A High Efficiency gas chromatograph interfaced through an all-glass dual-stage Watson–Bieman molecular separator to a Varian MAT-711 high resolution mass spectrometer. The CD spectra were measured with a JASCO J-40 circular dichrometer using an earlier described[31] cell for the low temperature measurements. The accessible temp range was 77–293 K, the accuracy of the temp control is estimated to be ± 5 degrees. The gas-phase spectra of **1** and **2** were measured at room temp using a 10 cm cell. The instrumental slit-width for these measurements was 18 μm, corresponding to a spectral resolution of 0.07 nm (*ca* 8 cm^{-1} in the 350–250 nm wavelength region). The wavelength scale was calibrated with a soln of holmium perchlorate[32] to an accuracy of *ca* 0.2 nm (*ca* 20 cm^{-1} in the 350–250 nm wavelength region). Elemental analyses were performed by the Microanalytical Laboratory at the Department of Chemistry of Stanford University.

(2*R*)-1,1,2,4,4-*Pentadeuteriobutane*-1,4-*diol* (**7**). To a soln of **5** in 500 mL of CH_2Cl_2 was added 20 mL Et_3N (dist. over CaH_2). The mixture was cooled to 0° and 10 mL methanesulfonyl chloride was added dropwise. The mixture was stirred at 0° for 10 min and then poured into ice and HCl and extracted with ether. The ether soln was washed to neutrality with $NaHCO_3$, dried over $MgSO_4$ and evaporated to yield 26 g (yield 100%) of **6** ^{1}H NMR ($CDCl_3$, δ ppm) 1.30 (t, 3 H, J = 7), 1.33 (t, 3 H, J = 7), 3.0 (d, 2 H, J = 6), 3.26 (s, 3 H), 4.26 (q, 2 H, J = 7), 4.30 (q, 2 H, J = 7), and 5.40 (t, 1 H, J = 6); IR (neat) 1700, 1380, 1190, 980, 940 and 740 cm^{-1}. A soln of the crude **6** (26 g, 0.1 mol) in dry THF (50 mL) was added dropwise to a stirred and ice-cooled suspension of lithium aluminum deuteride-d_4 (30 g) in dry THF (100 mL). The mixture was stirred at 0° for 2 hr, followed by 10 hr at 25° and then heated under reflux for 24 hr. Standard workup and tlc analysis of the residual oil indicated one major component which was purified by column chromatography (silica gel; EtOAc/MeOH 9:1) to give 4.5 g (50%) of **7**. ^{1}H NMR ($CDCl_3$, δ ppm) 1.66 (br s), 4.0 (br s, OH); IR (neat) 3300, 2170, and 2070 cm^{-1}.

(2*R*)-1,1,2,4,4-*Pentadeuterio*-1,4-*dibrobutane* (**8**). This compound was prepared in 80% yield by using the procedure described by Goldsworthy[10] for the nondeuterated analog. The dibromo compound **8** is a colorless liquid b.p., 110°/40 mm, ^{1}H NMR ($CDCl_3$, δ ppm) 2.08 (s); IR (neat) 2950, 2170 and 970 cm^{-1}, which was used directly in the next step.

(3*R*)-3-*Deuteriocyclopentanone* p-*toluenesulfonylhydrazone* (**10**). To a suspension of 3.44 g potassium hydride (24% content, dispersed in mineral oil) in 50 mL dry THF at $-10°$ under an atmosphere of N_2 was added 0.92 g (7.39 mmol) methyl methylsulfinylmethyl sulfide. After the mixture was stirred at $-10°$ for 1 h, 2 g of **8** was added dropwise and the mixture kept stirring at $-10°$ for 1 hr and then at room temp for 17 hr. After addition of CH_2Cl_2 (200 mL) the deposited solid was filtered off. Evaporation of the solvent left a light yellow oil, to which was added 30 mL abs EtOH and 2.27 g (9.32 mmol) p-toluenesulfonylhydrazide. The mixture was heated to reflux and 10 drops 36 N HSO_4 were added and refluxing continued for another 4 hr. After the solvent was removed under reduced pressure, the residue was washed with cold pentane and then recrystallized twice from EtOH to give 0.9 g (40%) of **10** as white needles. The mother liquor was concentrated and purified by column chromatography (silica gel; EtOAc/hexane 1:1) followed by recrystallization from EtOH to give additional 0.5 g of **10**; m.p. 186–187° (lit. m.p.[33] of the undeuterated analog 183°). ^{1}H NMR ($CDCl_3$, δ ppm) 2.43 (s, 3 H), 7.26 (d, 2 H, J = 8), 7.81 (d, 2 H, J = 8); mass spectrum, *m/z* (rel. intensity) 64(55), 65(90), 67(75), 68(100), 98(50), 99(50), 155(20), 157(30), 253 (M^+, <1).

(3*R*)-3-*Deuteriocyclopentanone* (**1**). A lit[12] procedure of regeneration of cyclopentanone from its *p*-toluenesulfonylhydrazone was adapted to give **1**. A soln of **10** (0.356 g, 1.4 mmol) in 4 mL reagent grade acetone in a sealed tube was heated at 76° for 20 hr. Upon addition of 30 mL pentane, white needles precipitated and were removed by filtration. The filtrate was carefully concentrated by distillation through a 6″ Vigreux column. The distillation was terminated as soon as the temp at the column head reached 37°, at which stage a residue of colorless liquid and white solid remained in the distillation flask. The residual liquid was decanted and purified by preparative gas chromatography (10% Carbowax 20 M on Chromosorb W, 150°) to give 70 mg of **1** as a colorless liquid (58%); mass spectrum, *m/z* (rel. intensity) 29(100), 31(27), 32(27), 33(13), 42(17), 55(11), 56(51), 85(M^+, 20); isotopic purity >99%.

Dimethyl (2*R*, 3*R*)-2,3-*dimesyloxysuccinate* (**12**). A soln of **11** (Aldrich Chemical Company, Inc.) (5 g, 28.1 mmol) in pyridine (50 mL) was stirred at $-20°$ and treated dropwise with methanesulfonyl chloride (6.88 g, 60 mmol). After stirring at $-20°$ for 3 hr, a light brown milky mixture was obtained. With stirring, the entire mixture was poured into ice (100 g) and the white ppt was filtered off, washed with water, dried *in vacuo* at room temp, and recrystallized from acetone/pentane to give 6 g of white needles (75% yield): m.p. 133–134°; ^{1}H NMR ($CDCl_3$, δ ppm) 3.25 (s, 3 H), 3.90 (s, 3 H), 5.70 (s, 1 H): IR (Nujol) 1765 cm^{-1}; $[\alpha]_{578}$ +51.1° (*c* = 1.58, acetone). Found: C, 29.12; H, 4.14. Calc. for $C_8H_{14}O_{10}S_2$: C, 28.74; H, 4.22%).

(2*S*, 3*S*)-1,1,2,3,4,4-*Hexadeuteriobutane*-1,4-*diol* (**13**). Synthesis as described for **7**. ^{1}H NMR (acetone-d_6, δ ppm): 1.58 (br s), 3.9 (br s, OH); IR (neat): 3300, 2170 and 2070 cm^{-1}. (Found C, 49.75. Calc. for $C_4H_4D_6O_2$: C, 49.96%).

(2*S*, 3*S*)-1,1,2,3,4,4-*Hexadeuterio*-1,4-*dibromobutane* (**14**). Synthesis as described for **8**. ^{1}H NMR ($CDCl_3$, δ ppm) 2.08 (s). IR (neat) 2950, 2170 and 970 cm^{-1}. Mass spectrum, *m/z* (rel. intensity) 60.08690 (100, $C_4H_2D_5$), 61.09283 (67.49, C_4HD_6), 141.01613 (94.00, $C_4H_2D_6{}^{79}Br$), 143.01379 (93.29, $C_4H_2D_6^{81}Br$), 219.93701 (1.77, $C_4H_2D_6^{79}Br_2$), 221.93578 (4.89, $C_4H_2D_6^{79}Br^{81}Br$), 223.93667 (1.77, $C_4H_2D_6^{81}Br_2$).

(3*S*, 4*S*)-3,4-*Deuteriocyclopentanone* p-*toluenesulfonylhydrazone* (**16**). Synthesis as described for **10**. ^{1}H NMR: (acetone-d_6, δ ppm) 1.65 (m, 2 H), 2.15 (m, 4 H), 2.36 (s, 3 H), 7.27 (d, J = 8 Hz, 2 H), 7.49 (d, J = 8 Hz, 2 H); IR (Nujol) 3210, 1070, and 1600 cm^{-1}; mass spectrum, *m/z* (rel. intensity) 69 (100), 71 (90), 99 (45), 124 (34), 254 (M^+, 3).

(3*S*, 4*S*)-3,4-*Dideuteriocyclopentanone* (**2**). Synthesis as described for **1**. ^{1}H NMR ($CDCl_3$, δ ppm) 2.15 (s), 2.17 (s); IR (Nujol) 1740, 2150, and 2200 cm^{-1}; mass spectrum, *m/z* (rel. intensity) 31(100), 32(73), 56(23), 57(60), 58(2), 85(1), 86(M^+, 6), 87(M^+ + 1, 1); isotopic purity >99%.

(3*S*, 4*S*)-2,2,3,4,5,5-*Hexadeuteriocyclopentanone* (**3**). Compound **3** was prepared similarly to **2** by using acetone-d_6 instead of reagent grade acetone in the regeneration from the *p*-toluenesulfonylhydrazone **16**. After purification by preparative gas chromatography, **3** was obtained as a colorless liquid (37% yield): mass spectrum, *m/z* (rel. intensity) 57(100), 87(2), 88(8), 89(24), 90(M^+, 32). The isotopic purity at the α-position is only 52% based on mass spectral analysis, which can be effectively increased to 89% by three successive passes through a D_2O pretreated gas chromatographic column[13] (10 ft 10% Carbowax 6000, with 10% KOH, pretreated with 3 × 1 mL of D_2O, oven temp 150°, t_R = 4 min). ^{1}H NMR ($CDCl_3$, δ ppm) 1.92 (s); IR ($CDCl_3$) 1739, 2130, and 2180 cm^{-1}; mass spectrum, *m/z* (rel. intensity) 31(100), 57(97), 59(30), 88(2), 89(7.5), 90(M^+, 39), 91(M^+ + 1, 2).

Acknowledgement—This work has been supported through grants from the National Science Foundation (Grant No. CHE 78-27413) and the National Institutes of Health (Grant No. GM 20276). Technical assistance by Ruth Records is gratefully acknowledged.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 191 to 200
Printed in Great Britain.

0040-4020/81/Suppl. 1-0191-10 $02.00/0
Pergamon Press Ltd.

THE DYE-SENSITIZED PHOTOOXIDATION OF IMIDAZOLES

TRAPPING OF INTERMEDIATES BY NUCLEOPHILES

HARRY H. WASSERMAN*, MARY S. WOLFF, KENNETH STILLER,
ISAO SAITO and JAMES E. PICKETT
Department of Chemistry, Yale University, New Haven, CT 06520, U.S.A.

(*Received in U.S.A.* 17 *July* 1980)

Abstract—The reactions of a series of imidazoles with singlet oxygen have been investigated. While there is evidence that 2,5-endoperoxides or zwitterionic intermediates may be initially formed, the isolated products appear to arise from the decomposition of hydroperoxides or dioxetanes. Nucleophiles such as methanol and diphenyl sulfide serve to intercept unstable intermediates. Based on the photooxidation of model 5-substituted imidazoles, a rationale is presented for the destruction of histidine residues by two equivalents of oxygen in the "photodynamic" process.

Singlet oxygen, as an electrophilic species, reacts readily with electron-rich heterocyclic compounds such as furans, oxazoles, pyrroles and imidazoles.[1,2] Among these substances, imidazoles have been of special interest because of the involvement of this system in the so-called photodynamic effect.[3] Thus, it is well known that enzymes such as insulin, lysozyme and ribonuclease are inactivated by exposure to oxygen and light in the presence of sensitizing dyes such as methylene blue, and this inactivation has been correlated with the oxidative destruction of certain amino acid residues in the polypeptide chain. More specifically, it has been postulated that the loss of activity at histidine sites can be associated with the reaction of the imidazole portion of the molecule with singlet oxygen.[4]

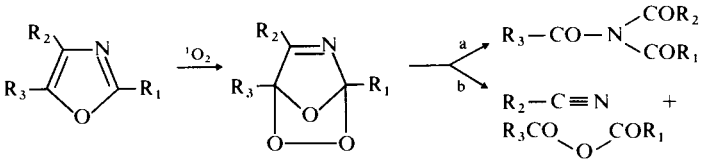
Early investigations on imidazole photooxidation were limited to 2-methylimidazole,[5] histidines,[6] and 2,4,5-triaryl derivatives.[7] More recently,[8,9] information has been provided on the structure of the initially formed peroxides in alkyl imidazole–singlet oxygen reactions. Working at low temperatures two groups have found evidence for the formation of hydroperoxides[8] and 2,5-endoperoxides[9] as unstable intermediates.

In the studies described here, we report on the photooxidation of a series of alkyl- and aryl-substituted imidazoles using methanol and methylene chloride as solvents. Methanol was used for most of the oxidation studies because it provided a polar medium for the reactions, and also served as an efficient nucleophile for reaction with initially formed peroxidic products and for addition to reactive imino intermediates. Our investigation of transient species in these oxidations has also been aided by other trapping methods. These have included the introduction of diphenyl sulfide as a scavenger for intermediate dioxetanes,[10] and the use of alkyl carboxylate side chains substituted at the 2-position of the imidazole for intramolecular interception of 2,5-endoperoxides.

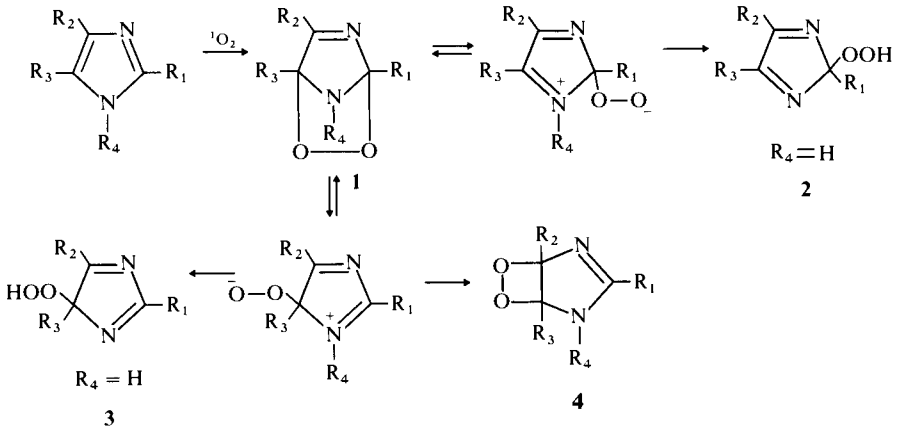
The oxidative changes taking place in the imidazoles differed markedly from those observed in the oxazole series (Scheme 1) where rearrangements to triamides (path a) or cleavage to nitriles (path b) have been reported.[1] As will be outlined in the following discussion, imidazole photooxidation products appeared to result from initial endoperoxide (**1**) formation followed by ring-opening to form hydroperoxides (**2**), (**3**) or dioxetanes (**4**). (Scheme 2). The observed reaction products may then be derived from subsequent decomposition of the peroxidic species (**2**, **3** or **4**). In general, the oxidations were carried out at room temperature using methylene blue as the sensitizing dye and a 150-watt tungsten floodlamp as a source of visible light. Oxygen was bubbled through the solutions until the starting materials were completely consumed as indicated by tlc monitoring of the reaction mixture.

Photooxidation of the parent system, imidazole, and 4-methylimidazole (**5**, R=Me) in methanol took place rapidly, along with considerable decomposition. In both cases, the isolated products, (4,5-dimethoxyimidazolidin-2-ones (**6**)) showed incorporation of one molecule of oxygen and two molecules of solvent. A likely reaction pathway is pictured in Scheme 3.

The reactions of a series of phenyl-substituted imidazoles with singlet oxygen under similar conditions are summarized in Table 1. In the case of 4,5-diphenylimidazole (entry no. 1), the reaction course parallels that outlined in Scheme 3, although the formation of dibenzoylurea indicates a second-stage process involving an additional equivalent of oxygen. This more complex type of oxidation, also shown by 5-phenylimidazole (entry no. 2), will be

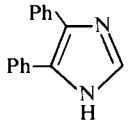
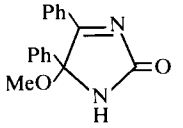
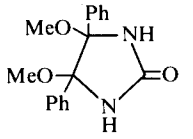
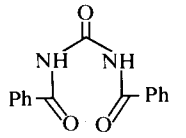
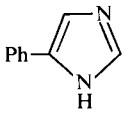
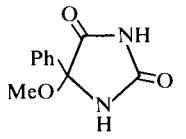
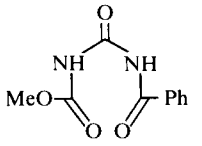
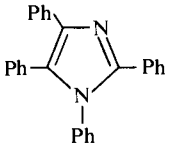
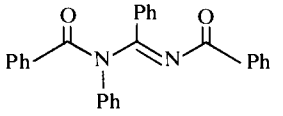
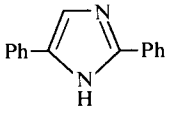
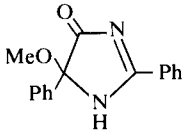


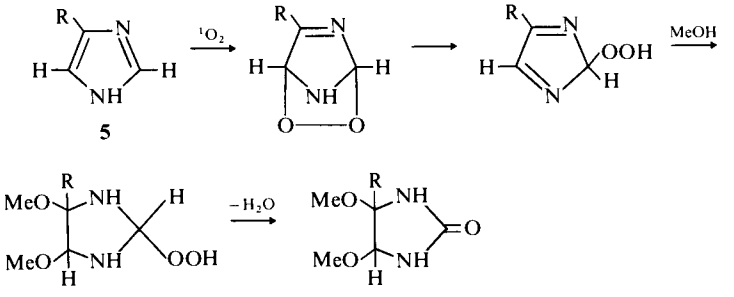
Scheme 1.



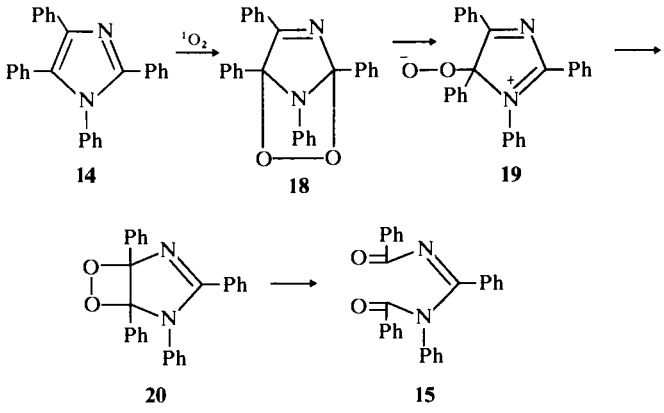
Scheme 2.

Table 1. Photooxidation of imidazoles

Imidazole	Products (Yields)			
1.  7	 8 (36%)	 9 (6%)	 10 (3%)	
2.  11	 12 (15%)	 13 (2%)		
3.  14	 15 (97%)			
4.  16	 17 (29%)			



Scheme 3.



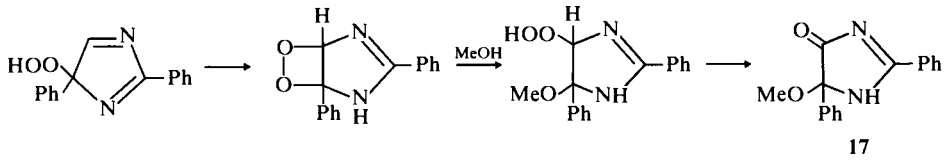
Scheme 4.

discussed in the section on histidine oxidation. Tetraphenylimidazole (**14**), on the other hand, underwent reaction to form the cleavage product (**15**). The latter most probably arises from the dioxetane (**20**), formed by the sequence shown in Scheme 4. The generation of **20** from initially formed 2,5-endoperoxide (**18**) is consistent with the recent findings of Foote *et al.* on low temperature photooxidations of imidazoles[9] and may involve the zwitterionic product (**19**) as a non-isolable intermediate. Dioxetane formation also accounts for the oxygenation at the 4- and 5-positions of 2,5-diphenylimidazole in the formation of **17** (entry no. 4) as outlined in Scheme 5.

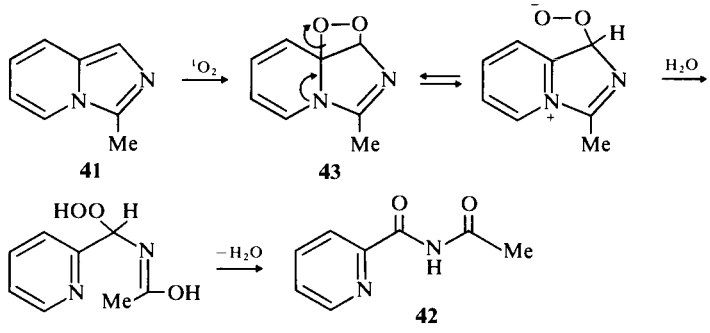
Table 2 lists a series of fused-ring imidazoles yielding photooxidation products by processes corresponding closely to those outlined above. Thus, in entries nos. 1–3, the products are formed by solvent trapping as in Scheme 3 while the reactions in entries nos. 4–9 involve dioxetane intermediates as in Scheme 4. Formation of the pyridinodiamide (**22**; entry no. 10) also appears to involve a dioxetane (**43**) as shown in Scheme 6.

The solvent effects in the photooxidation of the 2-phenyl-4,5-pentanoimidazole (entry no. 9) are of particular interest in studying the intermediate steps leading to the ring-expanded product (**39**). It appears quite probable that the 4,5-dioxetane (**44**) is a key intermediate. In methanol, the dioxetane undergoes ring-opening to the imino hydroperoxide (**45**) which readily reacts with solvent at the 5-position. Subsequent decomposition of the hydroperoxide (**46**) takes place by a Witkop-type fragmentation[11] (Scheme 7). In the non-polar medium (CH_2Cl_2) decomposition of the dioxetane by oxygen-oxygen bond rupture is the preferred reaction pathway leading to **40**.

Histidine-related photooxidations. Particular attention has been paid to the photooxidation of imidazoles because of the correlation of enzyme deactivation by air and light with the destruction of histidine residues.[3,4] Two equivalents of oxygen are required for the inactivation of each histidine residue in the polypeptide chain. In early work on the photooxidation of histidine derivatives, complex mixtures were obtained.[6] Our own investigations on the methylene blue-sensitized photooxidation of N-benzoylhistidine methyl ester (**47**) in methanol also yielded a mixture of products. Hydrolysis of this

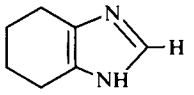
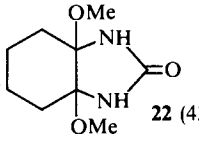
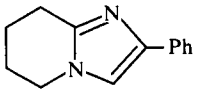
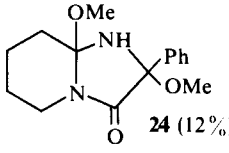
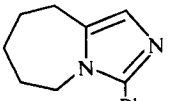
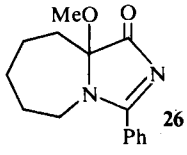
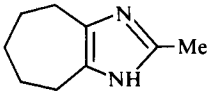
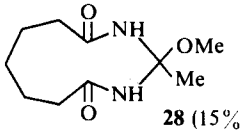
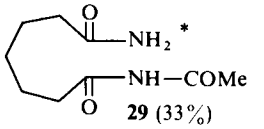
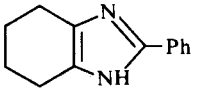
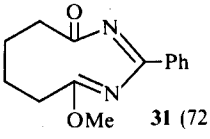
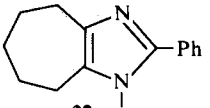
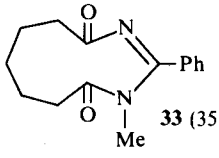
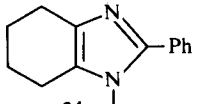
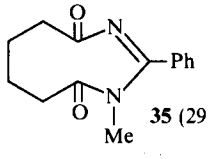
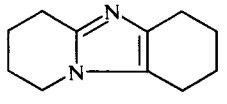
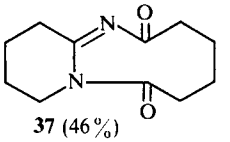
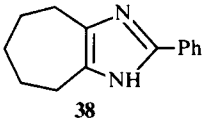
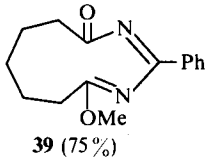
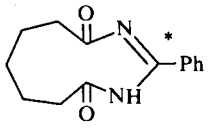
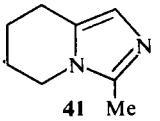
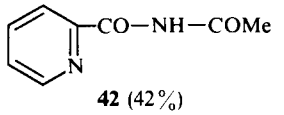


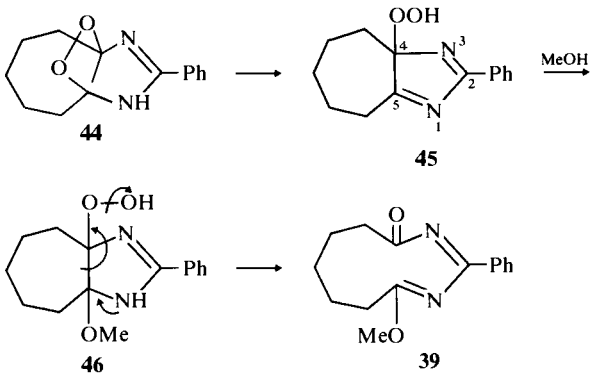
Scheme 5.



Scheme 6.

Table 2. Photooxidation of Imidazoles

	Imidazole	Solvent	Products (Yields)
1.	 **21**	MeOH	 **22** (42%)
2.	 **23**	MeOH	 **24** (12%)
3.	 **25**	MeOH	 **26** (60%)
4.	 **27**	MeOH CH_2Cl_2*	 **28** (15%)  **29** (33%)
5.	 **30**	MeOH	 **31** (72%)
6.	 **32**	CH_2Cl_2	 **33** (35%)
7.	 **34**	CH_2Cl_2	 **35** (29%)
8.	 **36**	MeOH	 **37** (46%)
9.	 **38**	MeOH CH_2Cl_2*	 **39** (75%)  **40** (61%)
10.	 **41**	MeOH	 **42** (42%)

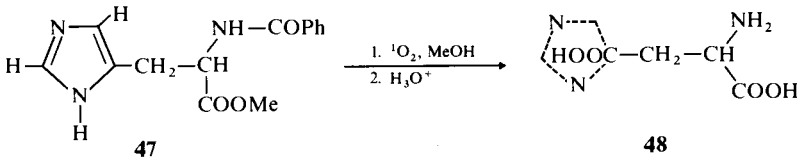


Scheme 7.

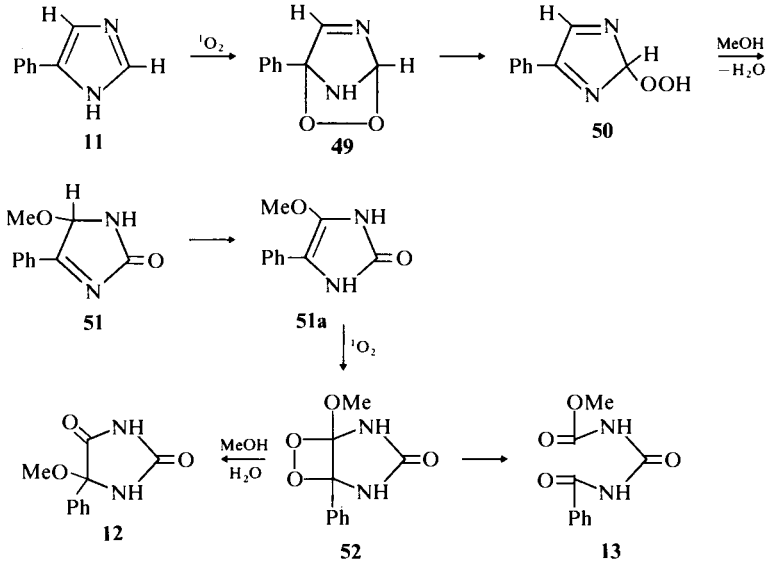
reaction mixture with 6N HCl yielded aspartic acid (**48**) in 65% yield (Scheme 8).

Evidence bearing on the mode of formation of aspartic acid in the above process and, more generally, on the oxidative cleavage of 5-substituted imidazoles by two equivalents of singlet oxygen was derived from the photooxidation of 5-phenylimidazole leading to **12** and **13** (Table 1, entry no. 2). A rationale for the more complex oxidation leading to these products is given in Scheme 9. The first equivalent of oxygen adding to **11** yields an endoperoxide (**49**) which decomposes with loss of water to the diimino derivative (**50**). Addition of methanol and dehydration then leads to the imidazolinone (**51**) which undergoes tautomerization and oxidation to **52** by a second mole of singlet oxygen. The dioxetane (**52**) may undergo cleavage to form **13**, or solvolysis in wet methanol to form **12**. Model imidazolinones undergo rupture of the double bond similar to the conversion of **51a** to **13** under similar conditions of photooxygenation as summarized in the oxidations of **53** to **54** (Table 3).

Diphenyl sulfide as a dioxetane trapping agent. Photooxidation of tetraphenylimidazole in benzene-acetone (9:1) leads, nearly quantitatively, to the dibenzoyl derivative (**15**), presumably by cleavage of the intermediate dioxetane (**55**) as shown in Scheme 10. Evidence for the intermediacy of a dioxetane was obtained by carrying out the photooxygenation in the presence of diphenyl sulfide (0.16 M). Under these conditions the rearranged lactam (**56**) appears to form by attack of the diphenyl sulfide on the oxygen–oxygen bond of the dioxetane, followed by a

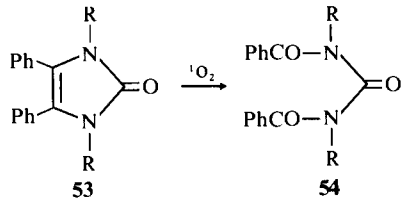


Scheme 8.



Scheme 9.

Table 3.

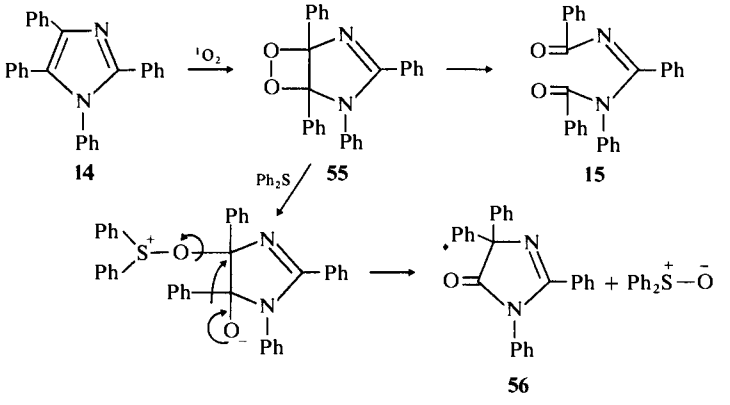


Yields of Dibenzoylureas

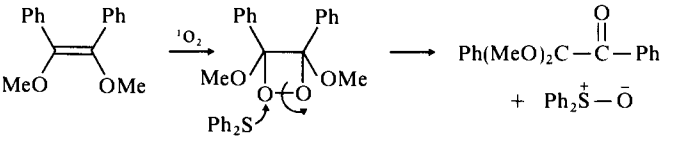
	R	MeOH	CH_2Cl_2
a.	H	55	47
b.	Me	55	70
c.	Ph	—	80

rearrangement involving a 1,2-shift of a phenyl group with release of diphenyl sulfoxide. Our studies on the action of diphenyl sulfide on stable model dioxetanes[10] have shown analogous rearrangements accompanied by the formation of diphenyl sulfoxide (Scheme 11).

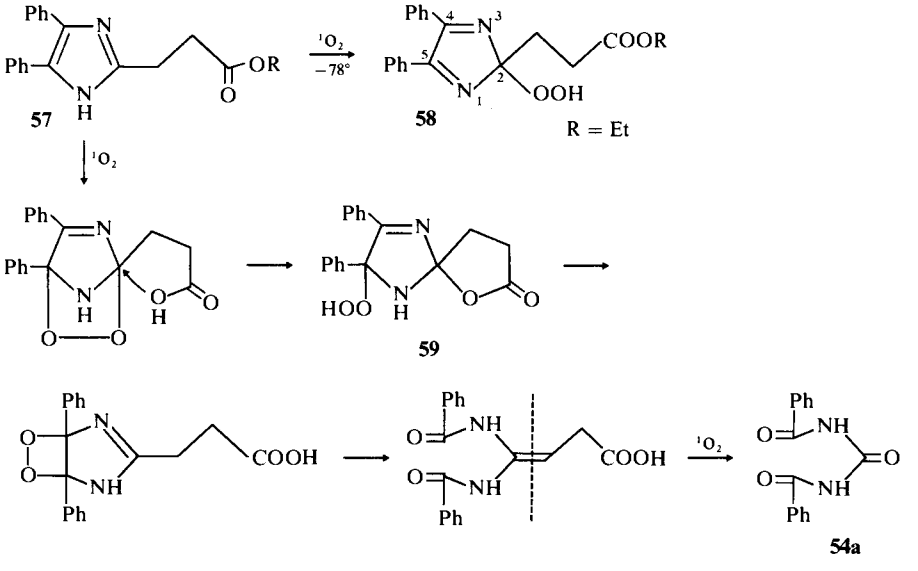
Intramolecular interception of peroxides. In order to learn more about transient products formed at early stages of imidazole photooxidation we investigated the possibility of intramolecular trapping of peroxidic intermediates. For this purpose we utilized 4,5-diphenylimidazole-2-propionic acid and its ethyl ester as substrates for singlet oxygen reactions. The ethyl ester (**57**, R=Et) reacted readily with exactly one equivalent of singlet oxygen to give a product showing typical behavior of a hydroperoxide (immediate starch-iodide coloration). This product was stable in



Scheme 10.



Scheme 11.



Scheme 12.

solution at −78° but gradually decomposed on warming above 0°. The structure of this peroxide was uniquely defined as **58** by the ^{13}C NMR spectrum which showed equivalent carbons for C-4 and C-5 and only one set of phenyl carbon resonances. The isomeric 5-hydroperoxide or any cyclic peroxide would not provide the symmetry required for the observed NMR spectrum. The acid (**57**, R=H), on the other hand, reacted with two equivalents of singlet oxygen to yield dibenzoylurea (**54a**). We suggest that in contrast to the ester case (**57**, R=Et) where the 2-hydroperoxide is formed, the carboxyl group in **57**, R=H, assists in opening the 2,5-endoperoxide yielding the 5-hydroperoxide (**59**). The further reactions of **59** leading to dibenzoylurea would then include carbon–carbon bond cleavage by a second-stage singlet oxygen-enamine reaction as outlined in Scheme 12.

EXPERIMENTAL

Methods. Mops are uncorrected. Microanalyses were performed by Dr. R. Rittner, Olin Corp., New Haven. IR spectra were run as KBr pellets on a Perkin-Elmer model 337 spectrophotometer and are calibrated to polystyrene. NMR spectra were taken on a Varian model A60-A spectrophotometer; chemical shifts are reported as δ values with TMS internal standard, using $CDCl_3$ as solvent unless otherwise indicated. UV spectra were taken on a Bausch and Lomb 550 instrument. Mass spectra were obtained on a Hitachi RMU-6 spectrometer.

The standard photooxidation reaction was carried out in a 3-neck round-bottom flask at room temp with methylene blue as sensitizer. O_2 was passed through the magnetically stirred soln during irradiation with a 150 watt tungsten lamp. The reactions were followed by tlc and were terminated when the starting material was exhausted.

Photooxidation of imidazole. A sample of 4.45 g (65 mmol) imidazole was dissolved in 4500 mL MeOH with 4 mg methylene blue. The standard photooxidation was allowed to proceed slowly in this very dilute soln for 14 days. In more concentrated soln, considerable tarring took place. After removal of the solvent *in vacuo*, the residue was dissolved in a small amount of EtOAc and chromatographed on 200 g silica gel. The column was eluted with $CHCl_3$–MeOH, 9:1. 4,5-Dimethoxyimidazolone-2 was isolated from the mixture and was crystallized from EtOAc, 977 mg, 9%, m.p. 112–114°. (Found: C, 41.09; H, 7.04; N, 19.20. Calc. for $C_5H_{10}O_3N_2$: C, 41.09; H, 6.90; N, 19.17%). IR ($CHCl_3$): 1728 cm^{-1}; NMR ($CDCl_3$): δ 3.40 (s, 6 H), 4.82 (s, 2 H), 7.5 (bs, 2 H).

Photooxidation of 4-methylimidazole (**5**). 4-Methylimidazole[12] (4.5 g, 55 mmol) was photooxidized in 3 L MeOH for 24 hr. The residue, after evaporation of the solvent, was chromatographed on 400 g silica gel. Elution with ether and with 4% MeOH–ether gave a thick oil (1.5 g) which crystallized from ether to give 0.56 g 5-methoxy-5-methylhydantoin, m.p. 120–130°, 7%. Recrystallization from ether provided an analytical sample, m.p. 132.5–134°. (Found: C, 41.70; H, 5.61; N, 19.22. Calc for $C_5H_8N_2O_3$: C, 41.67; H, 5.59; N, 19.44%); NMR: δ 1.63 (s, 3 H), 3.27 (s, 3 H), 6.00 (bs, 2 H); IR: 3220, 1780, 1725 cm^{-1}; MS: *m/e* 144 (M^+), 116, 113, 101, 73, 42, 41.

Elution with 10% MeOH–ether gave an oil (1.2 g) which solidified on standing, providing **6**, m.p. 100–109°, 13%. Recrystallization from EtOAc provided an analytical sample, m.p. 131–133°. (Found: C, 44.98; H, 7.64; N, 17.40. Calc for $C_6H_{12}N_2O_3$: C, 44.99; H, 7.55; N, 17.49%); NMR: δ 1.45 (s, 3 H), 3.26 (s, 3 H), 3.38 (s, 3 H), 4.58 (b, 1 H), 7.44 (b, 1 H), 7.15 (b, 1 H); IR: 3250, 3120, 1710 cm^{-1}; MS: *m/e* 145, 129, 60, 43. Further elution with 30% MeOH-ether provided an intractable oil (1.8 g, *ca* 18%).

Photooxidation of 4,5-diphenylimidazole (**7**). A sample of the imidazole (1.269, 5.7 mmol) was dissolved in 1800 mL MeOH with 4 mg methylene blue. The standard photooxidation was carried out for 24 hr at a temp of 32°. Following the removal of solvent *in vacuo*, the residue was dissolved in $CHCl_3$ and chromatographed on 200 g silica gel. Elution of the column with $CHCl_3$ yielded a yellow oil which was crystallized from benzene. Compound **8** was recrystallized from benzene to yield 525 mg (36%), m.p. 180–2°, lit. 179–80°.[27] The IR and UV spectra were superimposable on those of an authentic sample. (Found: C, 72.16; H, 5.20; N, 10.52. Calc for $C_{16}H_{14}O_2N_2$: C, 71.96; H, 5.52; N, 11.92%); NMR: ($CDCl_3$): δ 8.0–7.2 (m, 2 H), 7.2–7.6 (m, 8 H), 3.35 (s, 3 H); IR: (KBr): 1728 cm^{-1}; UV: $\lambda_{max}^{CHCl_3}$ (log ε 276 mμ (4.2.).

Elution of the column with $CHCl_3$ also yielded an oil whose bis-2,4-dinitrophenylhydrazone was identical with that of benzil as shown by its superimposible IR spectrum and its mixture m.p. The yield of the hydrazone was 74 mg (2%), m.p. 188–89°.

Elution of the column with $CHCl_3$–MeOH, 98:2, yielded two compounds. The first compound was recrystallized from benzene to yield 40 mg (3%) of **10**. The IR spectrum of the urea was superimposable on that of an authentic sample.[26] An analytical sample was prepared by repeated recrystallization from benzene. (Found: C, 67.15; H, 4.51; N, 10.44. Calc. for $C_{15}H_{12}O_3N_2$: C, 66.95; H, 4.48; N, 10.37%).

The second compound which was eluted from the column was recrystallized from acetone to yield 109 mg (6%) of **9** with MeOH of crystallization, m.p. 209–212°, dec., lit. 214–214°, dec.[28] The IR spectrum was superimposable on that of an authentic sample.[28] (Found: C, 68.44; H, 6.08; N, 9.39. Calc. for $C_{17}H_{18}O_3N_2$: C, 68.71; H, 6.07; N, 9.10%).

Photooxidation of 5-phenylimidazole (**11**). A sample of 5-phenylimidazole[24] (4.5 g, 31 mmol) was dissolved in 4500 mL MeOH with 4 mg methylene blue. The standard photooxidation was carried out for 32 hr. After removal of the solvent *in vacuo*, the residue was dissolved in a small amount of $CHCl_3$ and chromatographed on silica gel. The column was eluted with $CHCl_3$ and the first 600 mL were collected. This fraction was then rechromatographed on 200 g silica gel, and the column eluted with ether. Two compounds were isolated from the chromatography. The first, compound **12**, was crystallized from $CHCl_3$–ether: yield, 971 mg, 15%, m.p. 167–170°. (Found: C, 58.22; H, 4.85; N, 13.58. Calc. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59%); NMR (deuteroacetone): δ 3.1 (br, 1 H), 3.37 (s, 3 H), 7.5 (m, 5 H), 8.0 (br, 1 H); UV: λ^{MeOH} 269 (log ε 2.4), 263 (log ε 2.8), 258 (log ε 2.9), 245 (log ε 3.1) nm: IR (KBr): 1792, 1723 cm^{-1}.

The second compound **13** isolated from the chromatography, m.p. 169–172°, yield 105 mg, 2%, was recrystallized from trichloroethylene. (Found: C, 54.06; H, 4.54; N, 12.61. Calc. for $C_{10}H_{10}N_2O_4$: C, 54.19; H, 4.64; N, 12.57%); NMR ($CDCl_3$): δ 3.84 (s, 3 H), 7.55–7.65 (m, 3 H), 8.1 (m, 2 H), IR (KBr): 1797, 1703, 1668 cm^{-1}.

Photooxidation of 1,2,4,5-tetraphenylimidazole (**14**). The imidazole[29] (2.08 g, 5.6 mmol) was dissolved in 1700 mL MeOH with 5 g methylene blue. The standard photooxidation reaction was carried out for 24 hr. The MeOH was removed under reduced pressure, and the solid which resulted was recrystallized twice from MeOH yielding 2.20 g (97%) of **15**, m.p. 145–146.5°, identical with an authentic sample.[30]

Photooxidation of 2,5-diphenylimidazole (**16**). 2,5-Diphenylimidazole was prepared according to the method of Aines.[23]

A sample of 1.339 g (6.1 mmol) of imidazole was dissolved in 1400 mL MeOH with 4 mg methylene blue. The standard photooxidation was carried out for 30 hr at 32°. After removal of the solvent *in vacuo*, the residue was dissolved in a small amount of $CHCl_3$, chromatographed on 200 g silica gel, and the column was eluted with a 7:3 soln of benzene–EtOAc. The crystalline residue was recrystallized from benzene to yield 451 mg of **17** m.p. 154–157°, 29%. The analytical sample was prepared by repeated recrystallization from benzene, m.p. 156–157°. (Found: C, 72.32; H, 5.18; N, 10.68. Calc. for $C_{16}H_{14}O_2N_2$: C, 72.17; H, 5.30; N, 10.52%); NMR ($CDCl_3$):

δ 7.9–8.2 (m, 2 H), 7.2–7.8 (m, 8 H), 3.40 (s, 3 H); UV: λ^{MeOH} 258 (log ε 3.97), 238 (log ε 4.18); IR (KBr): 1763, 1617 cm^{-1}; ($CHCl_3$): 1747, 1730 cm^{-1}.

Photooxidation of tetrahydrobenzimidazole (**21**). Tetrahydrobenzimidazole was prepared by the general method of Bredereck and Theilig,[13] m.p. 147–149°, lit[14] 149–150°. Photooxidation of the imidazole (1.13 g, 0.93 mmol) for 24 hr in MeOH with NaOAc (20 mg) was followed by dissolution of the residue in $CHCl_3$ and clarification with charcoal. The soln was evaporated *in vacuo*, triturated three times with MeOH and evaporated, and crystallized as its methanolate from 4 mL MeOH to give hard cubic crystals of **22** (480 mg, m.p. 167–169°). A second crop was obtained, 300 mg, m.p. 156–160°; overall yield, 42%. A run without NaOAc gave the product in 37% yield, m.p. 113–127°. Recrystallization from EtOH–EtOAc gave pure material, m.p. 156–157°, which was further recrystallized for analysis. (Found: C, 54.13; H, 8.31; N, 14.09. Calc. for $C_9H_{16}N_2O_3$: C, 53.99; H, 8.05; N, 13.99%); NMR: δ 1.00–1.60 (b, 8 H), 3.38 (s, 3 H), 6.39 (b, 2 H); IR: 3240, 3200, 3100, 1710 cm^{-1}; MS: *m/e* 200 (M^+), 184, 168, 136.

Photooxidation of 4-phenyl-1(1,2α)pyrimidazole (**23**). The imidazole (Aldrich, 1.5 g, 7.7 mmol) was photooxidized for 18 hr in 1.5 L MeOH, and the residue after evaporation of the solvent was chromatographed on 200 g silica gel. The fraction eluted with ether crystallized to give **24**, m.p. 83–85° (0.25 g, 12%). An analytical sample was obtained by recrystallization from ether–hexane, m.p. 85–89°, long flat prisms. (Found: C, 65.97; H, 5.78; N, 10.17. Calc. for $C_{15}H_{16}N_2O_3$: C, 66.19; H, 5.92; N, 10.29%); NMR: δ 8.18 (bd, 1 H), 7.73 (m, 3 H), 7.32 (m, 3 H), 6.60 (m, 2 H), 3.71 (s, 3 H), 3.33 (s, 3 H); IR: 3440, 1740 cm^{-1}; UV: λ^{MeOH} 230 (log ε 4.5), 288 (log ε 4.2) nm; MS: *m/e* 272 (M^+), 257, 241, 226, 212, 198, 181, 169, 134, 122, 94.

Photooxidation of 2-phenyl-(1,5)imidazepine (**25**). The imidazole (1.50 g, 7.1 mmol) was photooxidized in MeOH with NaOAc (200 mg) for 8 hr. The residue, after clarification with charcoal, crystallized from EtOAc–ether to give **26**, m.p. 112–120° (1.1 g, 60%). Photooxidation without NaOAc gave the product, m.p. 95–110°, in 36% yield. Recrystallization from EtOAc provided pure **26**, m.p. 121–125°. (Found: C, 69.06; H, 7.02; N, 10.84. Calc. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 6.85; N, 10.65%); NMR: δ 7.55 (m, 5 H), 3.40–4.20 (m, 2 H), 3.15 (s, 3 H), 1.20–2.10 (b, 8 H); IR: 1730, 1603 cm^{-1}; UV: λ^{MeOH} 252 (log ε 3.8), 286 (log ε 3.5) nm; MS: *m/e* 258 (M^+), 243, 215, 127, 96.

Preparation of 2-methyl-4,5-pentanoimidazole (**27**). 2-Acetoxycycloheptanone (45 g) was refluxed in 300 mL formamide at 180–190° for 6 hr. Aqueous base was added and the resultant alkaline (pH 10) mixture was extracted with $CHCl_3$. The dried extracts were evaporated to dryness and the solid residue crystallized from $CHCl_3$-pet ether, yield: 19 g (42%), m.p. 228–236°. An analytical sample was prepared by recrystallization from EtOH–EtOAc–ether, m.p. 233°. (Found: C, 72.46; H, 9.46; N, 18.31. Calc. for $C_9H_{14}N_2$: C, 71.96; H, 9.39; N, 18.65%); NMR: δ 1.70 (b, 6 H), 2.30 (s, 3 H), 2.60 (m, 4 H), 7.93 (1 H); IR: 3500, 1603 cm^{-1}; UV: λ^{MeOH} 222 (log ε 3.8), 268 (log ε 2.4) nm; MS: *m/e* 150 (M^+), 44.

Photooxidation of 2-methyl-4,5-pentanoimidazole (**27**). The imidazole (1.25 g, 8.3 mmol) was photooxidized in 2 L MeOH for 18 hr in the presence of NaOAc (15 mg). The clarified residue was crystallized from $CHCl_3$–CCl_4 to give **28**, m.p. 142–145° (250 mg, 15%). A run without NaOAc gave 12% of product, m.p. 78–90°. Recrystallization from MeOH–EtOAc (1:10) gave pure **28**, m.p. 140–148°. (Found: C, 56.13; H, 8.78; N, 13.60. Calc. for $C_{10}H_{18}N_2O_3$: C, 56.06; H, 8.47; N, 13.06%); NMR: δ 3.40 (s, 3 H), 1.90 (s, 3 H), *ca* 2 (9–12 H); IR: 3230, 3100, 1660 cm^{-1}; UV: λ^{MeOH} 214 (log ε 3.1) nm; MS: *m/e* 214 (M^+), 199, 183, 171, 100.

Photooxidation in CH_2Cl_2 and acidic work up gave the hydrolysis product, **29**, in 33% yield, m.p. 139–142°. The same product was obtained from hydrolysis of **28**. (Found: C, 53.99; H, 8.05; N, 13.99. Calc. for $C_9H_{16}N_2O_3$: C, 54.03; H, 7.94; N, 13.53%); NMR (DMSO-d_6): δ 6.70 (b, 2-3 H), 2.50 (s, 3 H), 2.10 (b, 10 H); IR: 3410, 3350, 3270, 3210, 1730, 1640, 1620 cm^{-1}; MS: *m/e* 200 (M^+), 142, 100, 59, 43.

Preparation of 2-phenyltetrahydrobenzimidazole (*2-phenyl-4,5-butanoimidazole*, (**30**)). According to the method of Weidenhagen,[18] a soln of adipoin (15 g, Aldrich) in MeOH (500 mL) was added to a mixture of copper acetate (63 g), conc ammonia (560 mL), and benzaldehyde (20 g). The soln was heated on a steam bath for 2–3 hr and allowed to cool to room temp. The Cu- complex of the imidazole (25–30 g) was removed by filtration and freed of Cu by treatment of an alcohol suspension with gaseous H_2S. The mixture was then heated with Norit and filtered and the red-brown soln evaporated to dryness *in vacuo*. The solid (crude imidazole) was suspended in EtOAc and filtered with suction, yield 10–15 g (50–58%). Recrystallization from alcohol provided pure imidazole, m.p. 250–255°. (Found: C, 78.39; H, 7.20; N, 14.26. Calc. for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13%); IR: 3400, 1650 cm^{-1}; UV: λ^{MeOH} 210 (log ε 3.6), 294 (log ε 4.0) nm; MS: *m/e* 198 (M^+).

Photooxidation of 2-phenyltetrahydrobenzimidazole (**30**). The imidazole (0.715 g, 3.6 mmol) was photooxidized in 1 L MeOH with NaOAc (10 mg) for 15 hr. After the usual work-up, the residue was crystallized from ether as clusters of rhombic prisms, yielding **31** (0.61 g) m.p. 85.5–88°, which was twice recrystallized for analysis. The first recrystallization provided 466 mg, m.p. 86–88°. The combined mother liquors provided a second crop, 160 mg, m.p. 80–84°; overall yield, 72%. (Found: C, 69.05; H, 6.80; N, 10.85. Calc. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47%); NMR: δ 1.8–2.3 (bm, 8 H), 3.8 (s, 3 H), 7.7–7.8 (m, 5 H); IR: 1680, 1660, 1630 cm^{-1}; UV: λ^{MeOH} 209 (log ε 4.1), 246 (log ε 4.2) nm; MS: *m/e* 244 (M^+), 229, 215, 99, 59, 45.

Preparation of 1-methyl-2-phenyl-4,5-pentanoimidazole (**32**). 2-Phenyl-4,5-pentanoimidazole (3.8 g) was dissolved in dry THF, 100 mL. NaH (0.5 g) was added and the mixture heated. MeI (3 g) was added dropwise and the mixture heated for 30 min at 80°. A few drops of water were added, and the THF was evaporated *in vacuo*. The residue was dissolved in $CHCl_3$, washed with water, and evaporated. The residue was crystallized in two crops from cyclohexane by addition of EtOAc, total wt. 2.1 g, m.p. 110–116°. Recrystallization from ether provided material melting at 119–123°. (Found: C, 79.81; H, 8.02; N, 12.58. Calc. for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38%); UV: λ^{MeOH} 209 (log ε 3.9), 278 (log ε 4.1) nm.

Photooxidation of 1-methyl-2-phenyl-4,5-pentanoimidazole (**32**). The imidazole (0.50 g, 2.2 mmol) was photooxidized for 2 hr in CH_2Cl_2. The residue, after clarification in ether with charcoal, crystallized on standing at room temp for 15 hr. Crystallization from cyclohexane afforded **33** m.p. 84–87° (0.20 g, 35%), which was further recrystallized for analysis. (Found: C, 70.24; H, 7.02; N, 10.94. Calc. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84%); NMR: δ 7.7 (m, 5 H), 3.3 (s, 3 H), 2.5 (m, 4 H), 1.6 (m, 6 H); IR: 1630, 1680 cm^{-1}; UV: λ^{MeOH} 209 (log ε 4.2), 258 (log ε 4.2) nm; MS: *m/e* 258 (M^+), 243, 241, 215, 181, 161, 118.

Preparation of 1-methyl-2-phenyltetrahydrobenzimidazole (**34**). Compound **34** was prepared exactly as for **32**, m.p. 128–129° (cyclohexane). (Found: C, 79.04; H, 7.95; N, 13.39. Calc. for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20%); UV: λ^{MeOH} 209 (log ε 3.8), 278 (log ε 4.0) nm; MS: *m/e* 212 (M^+).

Photooxidation of 1-methyl-2-phenyltetrahydrobenzimidazole (**34**). The imidazole (0.39 g, 1.8 mmol) was orange photooxidized in CH_2Cl_2 for 3.5 hr. The residue crystallized on standing several days at room temp. Recrystallization from benzene–hexane afforded **35**, m.p. 101–106° (0.13 g, 29%), which was further recrystallized for analysis. (Found: C, 68.65; H, 6.82; N, 11.64. Calc. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47%); NMR: δ 7.50 (m, 5 H), 3.19 (s, 3 H), 2.95 (m, 4 H), 2.03 (m, 4 H); IR: 1710, 1670 cm^{-1}; UV: λ^{MeOH} 209 (log ε 4.0), 243 (log ε 3.9) nm; MS: *m/e* 244 (M^+), 215, 161, 118.

Photooxidation of 4,5-butano-(1,2α)pyrimidazole (**36**). 4,5-Butano(1,2α)pyrimidazole[17] (1.7 g, 10.5 mmol) was photooxidized for 15 hr in 2 L MeOH. The residue was clarified

with charcoal ($CHCl_3$), triturated with a little benzene, and filtered. The solid (0.90 g, 46%, m.p. 156–164°) was recrystallized from $CHCl_3$–pet ether to give pure **37**, m.p. 162–163.5°. The same product, m.p. 160–164°, was obtained on photooxidation in CH_2Cl_2 for 1 hr (52%). (Found: C, 64.31; H, 5.91; N, 13.36. Calc. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72%); NMR: δ 3.00 (b, 4 H), 2.00 (b, 4 H), 7.35 (qd, 2 H), 7.90 (td, 1 H), 8.72 (bd, 1 H); IR: 1690, 1640 cm^{-1}; UV: λ^{MeOH} 215 (log ε 4.0), 260 (log ε 3.6), 263 (sh, log ε 3.0), 283 (sh, log ε 3.0) nm; MS: *m/e* 204 (M^+), 176, 94.

Preparation of 2-phenyl-4,5-pentanoimidazole (**38**). The imidazole was prepared as for 2-phenyltetrahydrobenzimidazole using 2-acetoxycycloheptanone, m.p. 273–277°. (Found: C, 78.80; H, 7.83; N, 13.16. Calc. for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20%); IR: 3420, 1590 cm^{-1}; UV: λ^{MeOH} 294 (log ε 4.3), 212 (log ε 3.9) nm; MS: *m/e* 212 (M^+).

Photooxidation of 2-phenyl-4,5-pentanoimidazole (**38**). The imidazole (0.50 g, 2.36 mmol) was photooxidized in the usual manner for 2.5 hr in MeOH. An ether soln of the residue, on seeding, deposited crude **39** m.p. 71–80° (440 mg, 73%). A pure sample from ether gave m.p. 86–88°. (Found: C, 70.33; H, 6.91; N, 10.69. Calc. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84%); NMR: δ 1.6, (b, 6 H), 2.4 (b, 4 H), 3.8 (s, 3 H), 7.4 (m, 3 H), 7.8 (m, 2 H); IR: 1680, 1620 cm^{-1}; UV: λ^{MeOH} 208 (log ε 4.2), 247 (log ε 4.0) nm; MS: *m/e* 258 (M^+), 242, 229, 215, 201.

3-Phenyl-2,4-diazacyclodec-3-en-1,5-dione (**40**) was obtained from the photooxidation of **38** in CH_2Cl_2 (61%), m.p. 168–170° from EtOAc. (Found: C, 69.02; H, 6.81; N, 11.33. Calc. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47%); NMR: δ 1.6 (b, 6 H), 2.4 (b, 4 H), 7.4 (m, 3 H), 7.8 (m, 2 H); IR: 3200, 1710, 1660, 1630 cm^{-1}; UV: λ^{MeOH} 209 (log ε 4.2), 253 (log ε 4.1) nm; MS: *m/e* 244 (M^+), 215, 201, 147, 103, 104.

Hydrolysis of **39** *and* **40** *gave N-benzoylpimelamide*, m.p. 153–156° (water). (Found: C, 63.86; H, 6.85; N, 10.42. Calc. for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.92; N, 10.68%); IR: 3390, 3300, 3190, 1740, 1680, 1640 cm^{-1}; MS: *m/e* 262 (M^+), 245.

Photooxidation of 2-methylimidazo-(1,5α)pyridine (**41**). The imidazole[15] (1.7 g, 14 mmol) was photooxidized in 2 L MeOH for 4 hr. The residue, after clarification with charcoal, was crystallized from ether to give lustrous plates of **42**, m.p. 68–70° (0.90 g, 42%). Recrystallization from ether gave an analytical sample, m.p. 78–79°, lit[16] 81–82°; identical in all respects to that prepared from picolinamide and Ac_2O. (Found: C, 58.61; H, 4.89; N, 17.11. Calc. for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06%); NMR: δ 2.61 (s, 3 H), 7.60 (m, 1 H), 8.20–7.95 (m, 2 H), 8.63 (bd, 1 H), 10.15 (b, 1 H), IR: 3300, 1725, 1705, 1690, 1660 cm^{-1}; UV: λ^{MeOH} 230 (log ε 4.2), 268 (log ε 3.8) nm; MS: *m/e* 164 (M^+), 149, 106, 78, 43.

Photooxidation of the methyl ester of N-benzoylhistidine (**47**). A sample of N-benzoylhistidine[25] (110 mg, 0.4 mmol) was dissolved in 100 mL MeOH with 1 mg methylene blue. The standard photooxidation was carried out for 30 hr. After removal of the solvent *in vacuo*, the residue was hydrolyzed in 10 mL 6 N HCl. The solvent was removed *in vacuo* with mild heating (60°), and the residue analyzed using a Spinco amino acid analyzer with the following results: residual histidine, 3%; aspartic acid (**48**) 62%; two peaks in the hydroxy acid region, ~10% and ~15%.

A control experiment was run in which 100 mg of the starting material was hydrolyzed in 10 mL 6*N* HCl. The solvent was removed *in vacuo* and the residue was chromatographed as before. Only one peak corresponding to histidine was obtained.

Photooxidation of 4,5-diphenylimidazolinone (**53a**). The imidazolinone[19] (2.0 g, 8.5 mmol) was suspended in 2 L MeOH and photooxidized for 18 hr. The residue was clarified with charcoal in $CHCl_3$. The residue was triturated with ether yielding, **54a** (1.2 g, 55%).

Photooxidation of 1,3-dimethyl-4,5-diphenylimidazolinone (**53b**). The imidazolinone[20] (0.50 g, 1.9 mmol) was photooxidized in MeOH for 12 hr. The residue was crystallized from EtOAc–hexane to give **54b**, m.p. 157–159° (0.31 g, 55%). A yield of 70% was obtained using CH_2Cl_2 as solvent. Recrystallization from EtOAc provided the analytical sample, m.p. 160–161°, lit[21] m.p. 162–163°. (Found: C, 68.98;, H, 5.70; N, 9.56. Calc. for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45%); NMR: δ 1.30 (10 H), 2.9 (s, 6 H); IR: 1725, 1680, 1655 cm^{-1}; MS: *m/e* 296 (M^+), 191, 105, 77.

Photooxidation of tetraphenylimidazolinone (**53c**). The imidazolinone[22] (2.0 g, 5.2 mmol) was photooxidized in CH_2Cl_2 for 5 hr. The usual work-up gave *sym*-**54c**, 1.7 g, m.p. 160–180°, 80%. Recrystallization from alcohol afforded 1.35 g lustrous plates, m.p. 196–200°, identical with an authentic sample,[22] m.p. 197–199°, lit[22] 200°.

Photooxidation of tetraphenylimidazole (**14**) *in the presence of diphenyl sulfide*. Compound **14** (744 mg, 2 mmol) and diphenyl sulfide (2.9 g, 16 mmol) were dissolved in benzene-acetone (9:1) and photooxidized for 30 min with methylene blue as sensitizer. Two mmol of O_2 were consumed. After evaporation of the solvent and chromatography on silica gel the mixture yielded **56** (244 mg, 33%, m.p. 157–158°). (Found: C, 83.71; H, 4.97; N, 7.27. Calc. for $C_{27}H_{20}N_2O$: C, 83.48; H, 4.19; N, 7.21%); IR: 1725, 1610, 1590, 1570 cm^{-1}; MS: *m/e* 388 (M^+), 360, 269, 257, 180, 165.

Also isolated were diphenyl sulfoxide (41%) and **15** (12%).

4,5-Diphenylimidazole-2-propionic acid, ethyl ester (**57**, R=Et). Desyl bromide (27.5 g, 100 mmol), K_2CO_3 (14 g, 100 mmol), succinimide (10 g, 100 mmol), and Bu_4NBr (20 mg) were stirred and refluxed for 12 hr in 100 mL $CHCl_3$. The mixture was filtered and the solvent evaporated to yield a mass of white crystals that were filtered off and washed with a little ether (yield: 21.0 g, 75%). Without further purification this product was dissolved in 75 mL EtOH and saponified with 5.0 g (78 mmol) KOH dissolved in 50 mL hot EtOH. After refluxing for 1 hr, the mixture was cooled, acidified with conc HCl and refluxed overnight. The mixture was then cooled and filtered to give a white product which was washed with water and dried (yield 20.6 g; 81%; m.p. 135–136°). NMR: δ 1.20 (t, 3 H), 2.59 (br.s, 4 H), 4.08 (q, 2 H), 6.54 (d, 1 H), 7.33 (m, 9 H), 7.93 (br. d, 2 H); IR: 3370, 1735, 1635, 1500 cm^{-1}.

Without further purification the above product was dissolved in 100 mL glacial AcOH with 21 g ammonium acetate and refluxed 6 hr under N_2. The mixture was then poured into ice water, filtered, and the product recrystallized from 2-butanone (yield: 9.5 g; 55%) m.p. 127° (phase transition); 142–143°. NMR: δ 1.23 (t, 3 H), 2.87 (m, 4 H), 4.12 (q, 2 H), 7.30 (m, 10 H); IR: 3420, 1720, 1600, 1420, 1370, 1180 cm^{-1}; (Found: C, 74.93; H, 6.07; N, 8.91. Calc. for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74%).

Saponification of the imidazole ester with KOH and acidification gave **57** (R=H) as an amorphous solid m.p. >250°. NMR (DMSO-d_6): δ 2.82 (m, 4 H), 7.30 (m, 10 H); IR (KBr): 3300, 1720, 1600, 1440, 1380, 1185 cm^{-1}.

Photooxidation of 4,5-diphenylimidazole-2-propionic acid (**57**, R=H). The imidazole propionic acid (1.45 g, 5 mmol) was suspended in 150 mL dichloroethane and photooxidized 7 hr at 0° with methylene blue sensitizer. Ten mmol of O_2 were consumed. The mixture was washed with water and evaporated to give a gummy solid yielding 150 mg of crystalline **54a** after trituration with ether and filtration, m.p. 203.5–204.5° (lit[26] 202–203°). IR: 3181, 1759, 1678, 1600, 1524, 1491, 1279 cm^{-1}; NMR ($CDCl_3$ + DMSO-d_6): δ signals only between 7–8; MS: *m/e* 268 ($C_{15}H_{12}N_2O_3$, M.W. 268).

When the photooxidation was carried out in an NMR tube ($CDCl_3$) and the products observed directly in the NMR, only dibenzoylurea resonances were found.

Photooxidation of 4,5-diphenylimidazole-2-propionic acid ethyl ester (**57**, R=Et). The imidazole ethyl ester (320 mg, 1 mmol) was dissolved in 2 mL CH_2Cl_2 and photooxidized with Sensitox (polymer-based Rose Bengal) at −78°. The mixture was decanted and the solvent exchanged to $CDCl_3$ by repeated partial evaporation at −78° under reduced pressure. The carbon NMR was then taken at −78°: 13.7 (–CH_3), 28.3, 28.9 (methylene), 60.5 (–OCH_2–), 123.9 (C=N), 128.0, 128.7, 129.3, 131.2 (aromatics), 167.2 (NNC(OOH)R),

172.3 (C=O). When warmed above 0° the sample decomposed. In a large scale run (5 mmol) the amount of O_2 taken up in this oxidation was shown to be one molar equivalent.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 201 to 212, 1981
Printed in Great Britain

0040-4020/81/Suppl. 1-0201-12 $02.00/0
Pergamon Press Ltd.

BIOSYNTHESIS OF PSEUROTIN A

P. MOHR and CH. TAMM*
Institut für Organische Chemie der Universität Basel, St. Johanns-Ring 19,
CH-4056 Basel, Switzerland

(*Received in Germany* 15 *July* 1980)

Abstract—The ^{13}C-NMR spectra of pseurotin A (**1**), a secondary metabolite of *Pseudeurotium ovalis* Stolk, and of some derivatives were measured and interpreted. Incorporation experiments with [1,2-$^{13}C_2$]-propionate, [2-^{13}C]-malonate, [1-^{13}C]- and [2,3-$^{13}C_2$]-phenylalanine and [^{13}C–CH_3]-L-methionine showed that the building blocks of pseurotin A (**1**) are 1 unit of propionate (starter unit), 4 units of malonate, 1 unit of phenylalanine and 2 units of methionine. A biogenetic pathway is proposed. Experiments with [$^{13}C^2H_3$]-L-methionine demonstrated that both O- and C-methylation occur with retention of all three hydrogen atoms of the methyl group. Using [2-$^{13}C^2H_2$]-propionate as precursor the fate of the α-H atoms of the starter unit was studied. Finally, the incorporation rates with [2-^{13}C, ^{15}N]-phenylalanine were determined by mass spectrometry and ^{13}C NMR spectroscopy. By comparing the labelling pattern with the results obtained after the incorporation of [^{15}N]-phenylalanine it could be deduced that the ^{15}N atoms are not statistically distributed. Hence, a nitrogen-free intermediate can be excluded.

The pseurotins are a new class of secondary metabolites which have been isolated recently from cultures of *Pseudeurotium ovalis* Stolk.[1,2] They are characterized by an 1-oxa-7-aza-spirol[4.4]non-2-ene-4,6-dione skeleton. The individual members of the family differ from each other by the functionalization of the side chain attached to the bicyclic system. To our knowledge no other class of natural products containing this heterospirocyclic structure is known. Therefore an investigation of its biogenetic origin seemed to be of general interest. It appeared to us reasonable to assume that the skeleton of the pseurotins arises by condensation of a polyketide chain with the amino acid phenylalanine. We have tested this hypothesis in the case of pseurotin A (**1**) by incorporation experiments using radioactive as well as ^{13}C-labelled precursors. In order to distinguish between the various theoretically possible pathways, Na[1-^{14}C]- and [2-^{14}C]-acetate, Na[2-^{14}C]-malonate, Na[1-^{14}C]-propionate, [^{14}C-CH_3]-L-methionine, [U-^{14}C]- and [4′-^{3}H]-L-phenylalanine, [2-^{13}C]-malonic acid, [^{13}C–CH_3]-L-methionine, Na[1,2-$^{13}C_2$]-propionate, [1-^{13}C]- and [2,3-$^{13}C_2$]-D,L-phenylalanine, [$^{13}C^2H_3$]-L-methronine, Na[2-$^{13}C^2H_2$]-propronate, [^{15}N]-L-phenylalanine and [2-^{13}C, ^{15}N]-D,L-phenylalanine were administered to growing cultures of *Pseudeurotium ovalis* Stolk (strains S 2269 and S 3484†). From the signal enhancement in the ^{13}C NMR spectra of the ^{13}C-enriched pseurotin A (**1**) samples, the labelling pattern could easily be deduced. Therefore the ^{13}C NMR spectra of pseurotin A (**1**) and some of its derivatives were measured and fully interpreted.

†We thank Dr. E. Härri, Sandoz AG., Basel, for providing the strain and advice for growing the cultures.

‡According to the ^{1}H and ^{13}C NMR spectra, one of the two possible epimers is about 90% predominant. However, even from molecular models it is not easy to predict which side of the CO group is less hindered.

§This name proposed by Eugster *et al.*[4] does not correspond to the IUPAC-rules. Nevertheless it is preferred, since these compounds show no chemical relationship with the aromatic furanones.

^{13}C NMR *spectroscopy*

The structure of pseurotin A (**1**) was elucidated by spectroscopic and chemical methods as well as by the X-ray analysis of 12(S), 13(S)-dibromopseurotin A (**2**). Because the halogenation proceeds by *trans*-opening of the bromium ion and since the dibromo derivative obtained can be reconverted to the natural product by treatment with zinc in acetic acid, the Z-geometry of the double bond is proven. The proton noise decoupled ^{13}C NMR spectrum of pseurotin A (**1**) exhibited 19 signals for the 22 C atoms. The assignments as summarized in Table 1 are based essentially on the comparison with the off-resonance decoupled spectrum and with the chemical shifts of 12(S), 13(S)-dibromopseurotin A (**2**), 12,13,17-tetrahydropseurotin A (**3**), 12,13-dihydropseurotin A (**4**) and 17-dihydropseurotin A (**5**). While the dibromo derivative **2** and the epimeric mixture of 12,13,17-tetrahydropseurotin A (**3**) were prepared as previously described,[1] the selective reduction of the double bond of the side chain to form compound **4** was achieved by homogeneous catalytic hydrogenation with tris-(triphenylphosphine)–rhodium(I)–chloride in ethanol/benzene (1:1) (*cf* Scheme 1). Sodium cyanoborohydride attacked only the benzoyl-system and gave the 17-dihydropseurotin A (**5**) in quite a good yield.‡

The two Me groups are separated sufficiently from each other to be assigned without any uncertainty. The same is true for C(14) and the OMe signal at 52.2 ppm. The three peaks at 69.7, 72.8 and 75.3 ppm arising from the secondary carbinol C atoms were assigned to C(11), C(10) and C(9) respectively. The latter remains nearly unchanged in all the derivatives, while the former two are characteristically affected by the functionality in the side chain. C(11), as well as (14), is upfield shifted in compounds **1** and **5** owing to the γ-effect resulting from the interaction in the sterically less favourable Z-position.[3] C(2) and C(3) in the Δ^2-furenidone-(4) system§ are easy to distinguish as the β-atom is very strongly deshielded. The C atoms of the aromatic moiety absorb in all the compounds containing an intact benzoyl group at the same frequencies within the experimental error. The

Table 1. Assignments of the C-atoms in the ^{13}C NMR spectra

Compound	1	2	3	4	5
C(2)	167.3	167.8	168.6	167.5	168.2
C(3)	113.6	114.5	113.6	113.7	113.6
C(4)	197.9	197.4	198.2	197.7	198.2
C(5)	92.7	93.0[a]	93.4/93.0[b]	92.7	93.0
C(6)	187.7	186.7	187.9/187.7[b]	188.0	187.3
C(8)	92.4	92.9[a]	90.2/89.7[b]	92.4	89.6
C(9)	75.3	75.2	74.8	75.3	74.9
C(10)	72.8	70.2	73.2	73.4	72.8
C(11)	69.7	71.1	72.4	72.5	69.5
C(12)	129.0	62.5	32.9	33.1	128.7
C(13)	135.9	61.6	28.5	28.6	135.9
C(14)	21.8	29.2	23.2	23.3	21.9
C(15)	14.5	13.0	14.3	14.3	14.6
C(16)	5.8	5.7	5.7	5.7	5.8
C(17)	196.2	196.4	73.9/73.7[b]	196.3	73.9
C(18)	134.7	134.6	140.4/140.0[b]	134.7	140.2
C(19)/C(23)	131.3	131.3	128.4	131.3	128.7
C(20)/C(22)	129.2	129.2	128.7	129.2	128.7
C(21)	134.7	134.4	128.7	134.7	128.7
$-OCH_3$	52.2	52.4	52.4/52.2[b]	52.3	52.5

a) Assignments may be reversed

b) Epimeric mixture

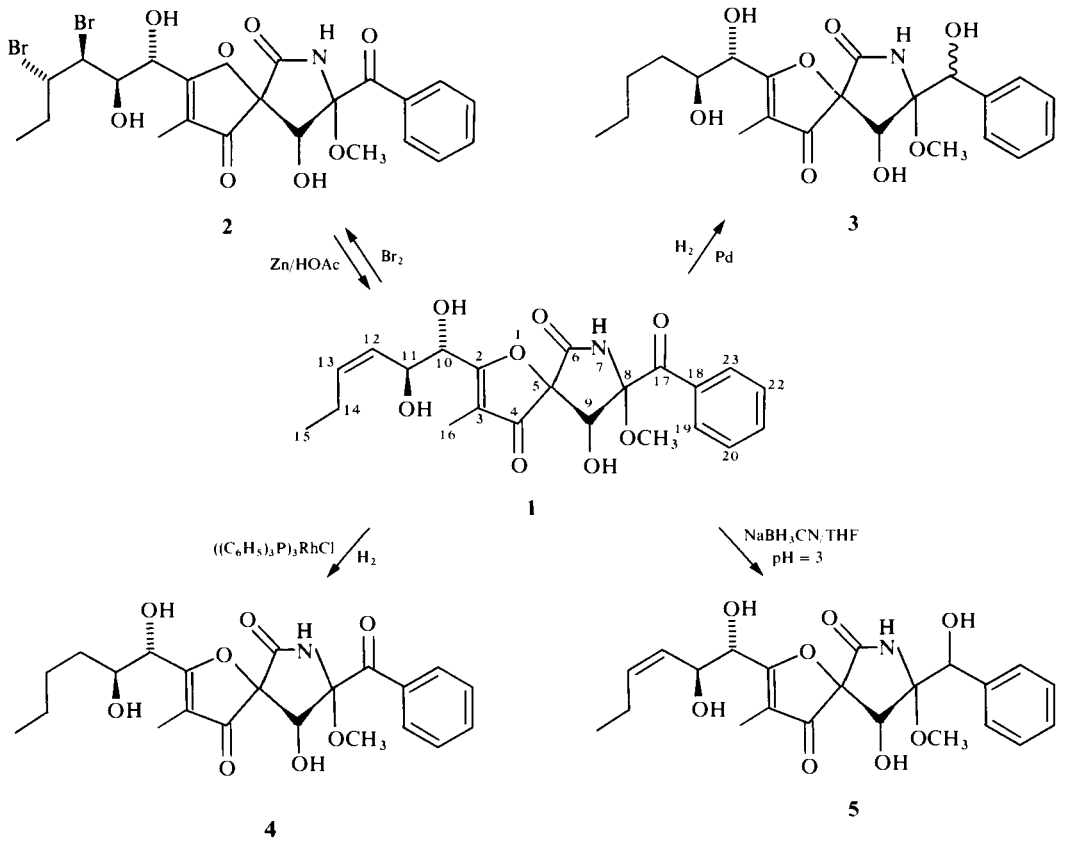
All spectra were measured in $(CD_3)_2CO$.

Table 2. Incorporation of radioactive precursors into pseurotin A (1)

Precursor	Absolute Incorporation rate (%)
Na[1-^{14}C]-acetate	0.17
Na[2-^{14}C]-acetate	0.23
Na[2-^{14}C]-acetate	0.14[a]
Na[2-^{14}C]-malonate	1.4
Na[1-^{14}C]-propionate	2.5
[^{14}C-CH_3]-L-methionine	7.2
[U-^{14}C]-L-phenylalanine	10.5[b]
[4'-^{3}H]-L-phenylalanine	8.7[b]

a) Precursors diluted with inactive material and added at the beginning.

b) The differences of the incorporation rates are probably not significant but may be due to some tritium loss in the precursor owing to its short half-life.



Scheme 1.

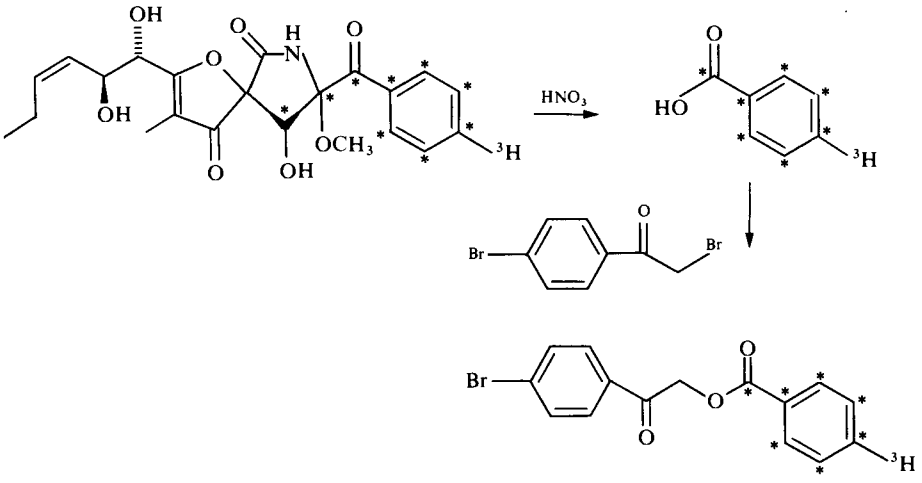
assignment of the signal at 129.0 ppm to C(12) and of 135.9 ppm to C(13) respectively is compatible with the expected values for these olefinic C atoms. This was later confirmed by the incorporation of the doubly labelled propionate. The signal for the lactam-CO-atom needs no further comment. Finally, the C(4)-atom could easily be detected, since it is little affected by the reduction of the benzoyl group. C(5) and C(8) whose resonance frequencies are separated only by 0.3 ppm could be distinguished by the incorporation of the [2,3-$^{13}C_2$]-phenylalanine. The spectra of the four other pseurotins[2] agree well with the assignments for pseurotin A (**1**).

Incorporation experiments

The strains of *Pseudeurotium ovalis* were grown on a glucose/peptone media. The production curve revealed that the pseurotin A (**1**) concentration begins to increase after two or three days. Therefore, the precursors were administered after 48 hr. The cultures were harvested after 8 days yielding 60–100 mg pseurotin A (**1**) per liter. The radioactive samples were recrystallized three times from tetrahydrofuran/-hexane in order to achieve constant radio-activity. The results obtained after addition of the potential precursors are presented in Table 2. All of them are incorporated significantly, thus confirming the origin of the pseurotins from an acetate/malonate derived polyketide and from phenylalanine. At least one of the two Me groups must be derived from methionine. Propionate could be the starter unit or—via methylmalonate—a link of the polyketide-chain. However, the incorporation rate is high enough to exclude an indirect labelling.

After the administration of [U-^{14}C]- and [4′-^{3}H]-L-phenylalanine the pseurotin A (**1**) was degraded with HNO_3 to benzoic acid whose *p*-bromophenacylester was analyzed for the determination of the labelling pattern (*cf* Scheme 2). The specific tritium activity was found to be the same as in the metabolite within the experimental error (Table 3). The result shows that phenylalanine is incorporated exclusively at C atoms Nr. 8, 9 and 17–23, provided that no decarboxylation has taken place. The $^{3}H/^{14}C$ ratio increased from 4.2 to 5.8 suggesting that the amino acid is incorporated intact and that two labelled atoms are lost during the degradation to benzoic acid.

Having established the basic biogenetic units of pseurotin A (**1**) the various precursors were also fed as ^{13}C-labelled molecules in order to elucidate the labelling pattern. The expected ^{13}C NMR signal enhancement can be estimated assuming that the absolute incorporation rates are the same in both experiments with ^{14}C and ^{13}C labelled precursors. Since the culture conditions always vary slightly, the calculation is on a theoretically weak ground. The proton noise decoupled ^{13}C NMR spectrum obtained after administering Na[1,2-$^{13}C_2$]-propionate showed for C(14) and C(13) a triplet. The adjoining ^{13}C-atoms of the precursor are incorporated as a unit and



Scheme 2.

Table 3. Degradation of pseurotin A (1) to benzoic acid

	$^3H/^{14}C$	^3H-Activity (dpm/mmol)
Pseurotin A (1)	4.2	$2.0 \cdot 10^7$
p-Bromophenacylester	5.8	$2.1 \cdot 10^7$
(calc.:	5.4[a])	

[a]) 5.4 is the expected value if the activity is distributed equally over the nine C atoms.

Table 4. Relative intensities after the incorporation of [2-^{13}C]-malonate

C-atom	Pseurotin A (1) Natural	Enriched
16	1.01	1.07
15	1.07	0.94
14	1.36	1.24
$-OCH_3$	1.00	1.00
11	1.46	1.43
10	1.50	4.46
9	1.54	1.36
8	0.42	0.33
5	0.34	0.74
3	0.32	0.72
12	1.53	4.52
20/22	6.75	2.99
19/23	6.53	2.46
18/21	2.08	1.00
13	1.63	1.28
2	0.37	0.24
6	0.42	0.32
17	0.36	0.18
4	0.20	0.15

therefore split into a doublet (J = 43 Hz), while the singlets between them are due to the natural pool. Thus the C atoms Nr. 13, 14 and 15 are derived from propionate which serves as starter unit for building the polyketide chain.

As expected the incorporation rate of radioactive malonate has been higher than that of acetate from which it is formed in a biotin dependent enzymatic reaction (*cf* Table 2). Therefore, in the ^{13}C experiment malonate was chosen as an equivalent for acetate in the chain propagation step of the polyketide formation. [2-^{13}C]-malonic acid was administered as the monosodium salt and the resulting spectrum compared with that which was obtained from natural pseurotin A (**1**) measured under identical conditions. For the unequivocal determination of the labelled positions we applied the method of Hanson[5] by normalizing the peak heights with respect to the OMe group, a C atom which is not acetate/malonate derived. In Table 4 these relative intensities are presented. C(3), C(5), C(10) and C(12) show a 3-fold signal enhancement. This result agrees with a biosynthesis via a C_{11}-polyketide. Surprisingly the signal intensities of the phenylalanine derived atoms seem to be lowered. A part of the ^{13}C activity is obviously scrambled during the biosynthesis, e.g. via citrate-cycle (*cf*[6]).

The C_1-donor methionine which had been shown to be a further biogenetic precursor was administered with the methyl group labelled by C-13. In the resulting ^{13}C NMR spectrum the intensity of both the OMe signal and the 16-Me group are increased about 15-fold. Since the unambiguous proof 15 years ago that in the biosynthesis of ergosterol exactly two of the three hydrogens of the Me group of methionine are retained during the alkylation of the side chain[7] much attention has been paid to the problem of the stereochemistry of the reaction and the different possible pathways. In order to gain more insight into the mechanism of the methylation process in pseurotin A (**1**) a sample of [$^{13}C^2H_3$]-L-methionine was synthesized from S-benzylhomocysteine and double labelled methyliodide according to known procedures[8] and administered to growing cultures of *Pseudeurotium ovalis*. Fig. 1 shows the proton noise decoupled ^{13}C NMR spectrum in the region 0–60 ppm. Both Me signals are clearly split into a septet with a coupling constant of 19.5 Hz for C(16) and 22 Hz for the O-OMe group, respectively. The resonance frequencies are both shifted upfield by 0.7 ppm. This value is also consistent with retention of all three D atoms. The OMe signal due to the natural methionine pool is superimposed by one of the seven lines, but the corresponding C(16)-peak is clearly resolved. Owing to quadrupole broadening and lacking nuclear Overhauser effect the intensities cannot be compared with those which are obtained after incorporation of mono-labelled methionine. A ^{13}C NMR spectrum, simultaneously noise decoupled of protons and deuteriums, shows two broad singlets for $^{13}CD_3$ and two narrow singlets for $^{13}CH_3$ (Fig. 2), but no further signal corresponding to a partially exchanged Me group. Accordingly, both alkylation processes proceed with retention of all three H atoms. These findings agree with the presumption that the C-methylation takes place in an early stage of the biosynthesis when the enolic double bond of the polyketide can react with S-adenosylmethionine, while the O-alkylation is probably a secondary transformation.

During the past few years much effort has been made to explore the origin and fate of the H atoms during a biosynthesis. One of the critical problems is the detection of the incorporated label. By using $^{13}C/^2H$ double labelled precursors it has become possible to observe indirectly the directly bound hydrogens. Thus "intact incorporation" can be established. The use of [$^{13}C^2H_3$]-acetate permits to localize the starter unit of a polyketide chain and to study the rate of exchange in acidic methylene groups.[9] We have extended this method to propionate in order to explore its scope and limitations in the case of the biogenesis of pseurotin A (**1**) and E (**6**). The latter compound is a minor metabolite of the same strain. It differs from pseurotin A (**1**) only by the geometry of the double bond and the state of oxidation of C(14).† If pseurotin E (**6**) is a biogenetic precursor of pseurotin A (**1**) quantitative

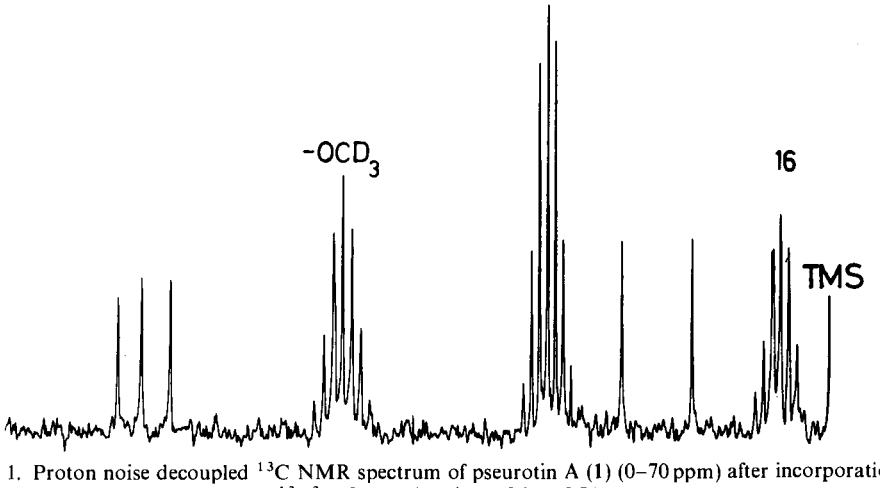


Fig. 1. Proton noise decoupled ^{13}C NMR spectrum of pseurotin A (**1**) (0–70 ppm) after incorporation of [$^{13}C^2H_3$]-L-methionine ($(CD_3)_2CO$).

†In a preliminary experiment pseurotin A (**1**) and E (**6**) gave almost the same dilution values after the incorporation of [2-^{14}C]-malonate.

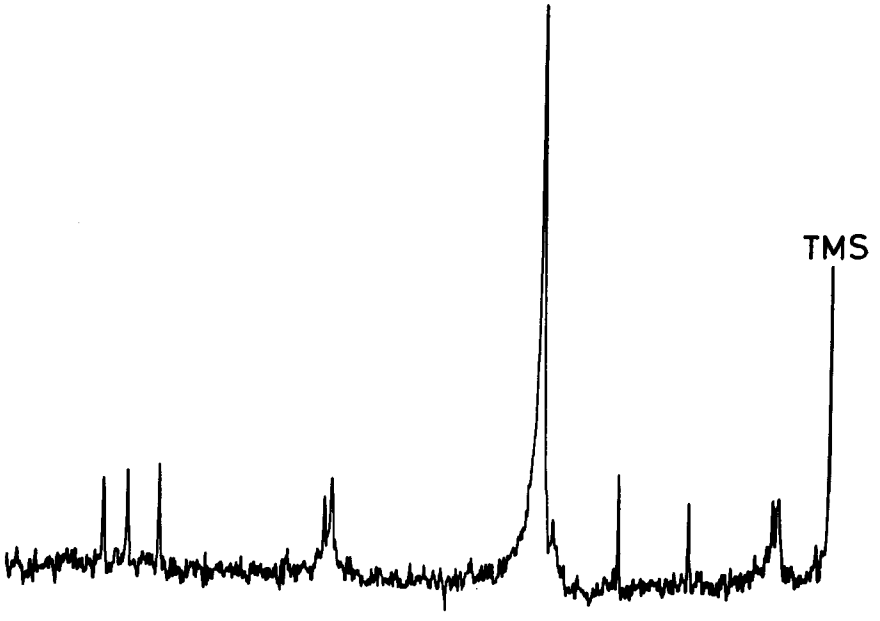


Fig. 2. Proton and deuterium noise decoupled ^{13}C NMR spectrum of pseurotin A (**1**) (0–70 ppm) after incorporation of [$^{13}C^2H_3$]-L-methionine ($(CD_3)_2CO$).

deuterium-loss is to be expected. [2-$^{13}C^2H_2$]-propionate was prepared according to Atkinson *et al.*[10] by repeated exchange of commercially available Na[2-^{13}C]-propionate in D_2O/OD^- at 160°. After six iterations a deuterium content of at least 98% was achieved. Fig. 3 shows the relevant region of the proton noise decoupled ^{13}C NMR spectrum of pseurotin A (**1**) after incorporation of this precursor. Nine clearly resolved lines appear: a quintet corresponding to the molecules which have retained both D atoms centred at 21.21 ppm; a triplet at 21.54 ppm and a singlet at 21.86 ppm for $^{13}CH_2$ whose intensity is slightly enhanced over the natural abundance. Taking into account that the fully deuterated species are lacking the nuclear Overhauser effet and that their integral is distributed over five (broadened) signals in the ratio 1:2:3:2:1 we can estimate that by far more than the half of the precursor molecules are incorporated in an intact manner. From these results it can be concluded that pseurotin E (**6**) does not act as an intermediate in the biosynthesis of pseurotin A (**1**). Either the biogenetic relationship is inverse or the pathways separate in an earlier stage. The observation that some deuterium is lost during the biosynthesis is not unexpected. Whereas it is unlikely that the propanoyl-coenzyme A or some acyl carrier derivatives are acidic enough to exchange with the hydrogens of water under physiological conditions, a rapid competitive equilibrium between propanoyl-coenzyme A and methylmalonyl-coenzyme A could explain the lower incorporation rate of deuterium as compared with ^{13}C.

For the experiments with [1-^{13}C]-D,L-phenylalanine a specimen was prepared using the Strecker-synthesis as described for radioactive samples.[11]

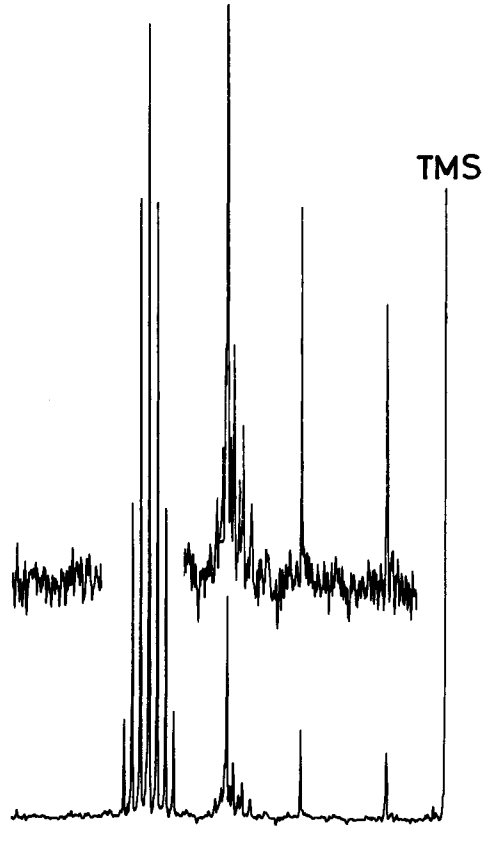
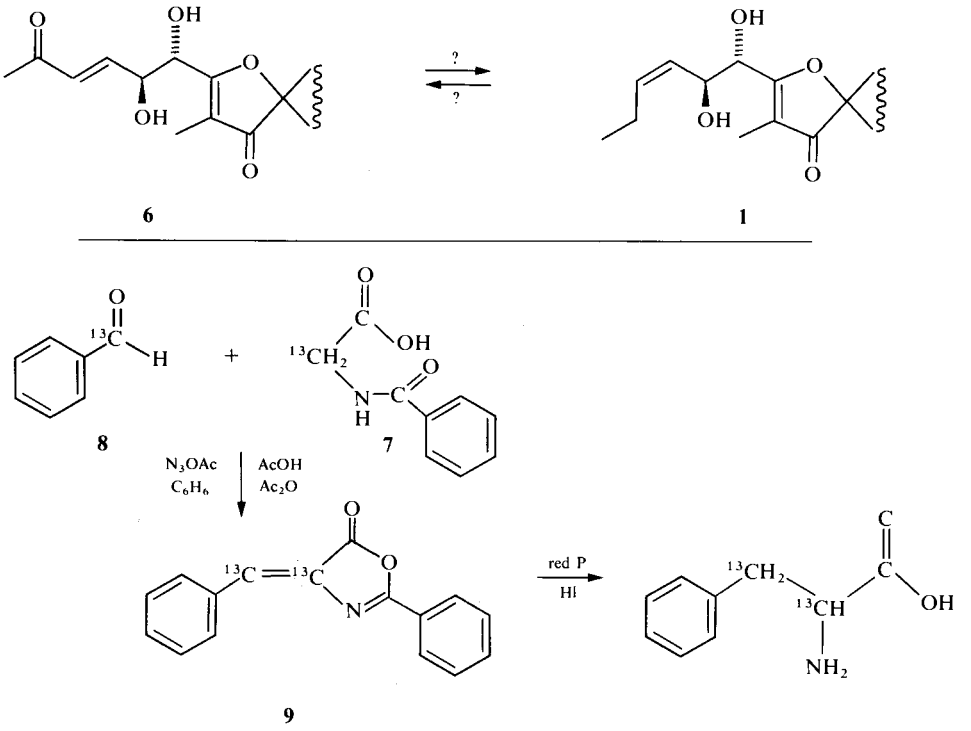


Fig. 3. Proton noise decoupled ^{13}C NMR spectrum of pseurotin A (**1**) (0–30 ppm) after incorporation of [2-$^{13}C^2H_2$]-propionate ($(CD_3)_2CO$).



Scheme 3.

Incorporation into pseurotin A (**1**) led to the expected results. The integral for C(9) is dramatically enhanced, showing that the amino acid is incorporated without decarboxylation or rearrangement. As mentioned above the double labelling technique was applied to distinguish the signals of C(5) and C(8) separated only by 0.3 ppm. For this purpose a synthesis for [2,3-$^{13}C_2$]-D,L-phenylalanine was carried out starting with commercially available Na[2-^{13}C]-acetate and [^{13}C]-benzoic acid. In the key step [2-^{13}C]-hippuric acid (**7**)[12] was condensed with [^{13}C]-benzaldehyde (**8**) obtained via the imidazolide.[13] Reductive opening of the resulting azlactone **9** yielded the desired double labelled amino acid (*cf* Scheme 3).[14] The ^{13}C NMR spectrum of the enriched pseurotin A (**1**) is shown in Fig. 4.

The adjacent carbons are incorporated as an intact unit and are therefore split into a doublet (J = 51.5 Hz). Since the resonance frequencies are separated by 2350 Hz (at 22.63 MHz) a first order spectrum is observed with the satellites lying symmetrically with respect to the middle signals. They are slightly enhanced because about 9% of the precursor molecules are each enriched with ^{13}C at C(2) and C(3), respectively. The peak at 92.4 ppm can now definitively be assigned to C(8) and the other at 92.7 ppm to C(5).

CONCLUSIONS

Using singly and doubly labelled ^{13}C precursors the biosynthetic origin of each of the 22 C atoms of pseurotin A (**1**) has been established. On the basis of these results two possible biogenetic pathways as outlined in Scheme 4 are proposed. However, neither the postulated intermediates nor the reaction sequence are based on an experimental proof. Propanoyl-coenzyme A acts as the starter unit. It is condensed in four successive cycles with malonate. The resulting C_{11}-polyketide combines with phenylalanine probably forming first the amide linkage. In the next step the lactam ring is closed to yield a tetramic acid derivative. For the construction of the spiro-center an OH group might be introduced in order to generate an electrophilic site at C(5). The C-methylation presumably occurs before the stabilization of the polyketide and its separation from the enzyme have taken place. In an alternative pathway the Δ^2-furenidone-(4) ring could be formed after the attachment of the 16-Me group at C(3). The partial reduction of the side chain is arbitrarily thought to take place in an early stage of the biosynthesis. The further reactions are likely to be secondary transformations and to occur at a late stage. They comprise oxidations at the benzylic C atom and at the nucleophilic positions C(8) and C(10) as well as the O-methylation.

The origin of the nitrogen atom

In spite of the fact that the biogenetic origin of N atoms in natural products has been studied for more than 30 years,[15] many crucial problems of the N metabolism have remained unresolved. No radioactive isotope is known which has a sufficiently long half-life suitable for biosynthetic investigations. Thus the incorporation of ^{15}N-labelled precursors is the only feasible method. The enriched metabolite can be examined either by mass spectrometry or more directly by ^{15}N NMR spectroscopy. However, the low natural abundance of ^{15}N of only 0.37% and the

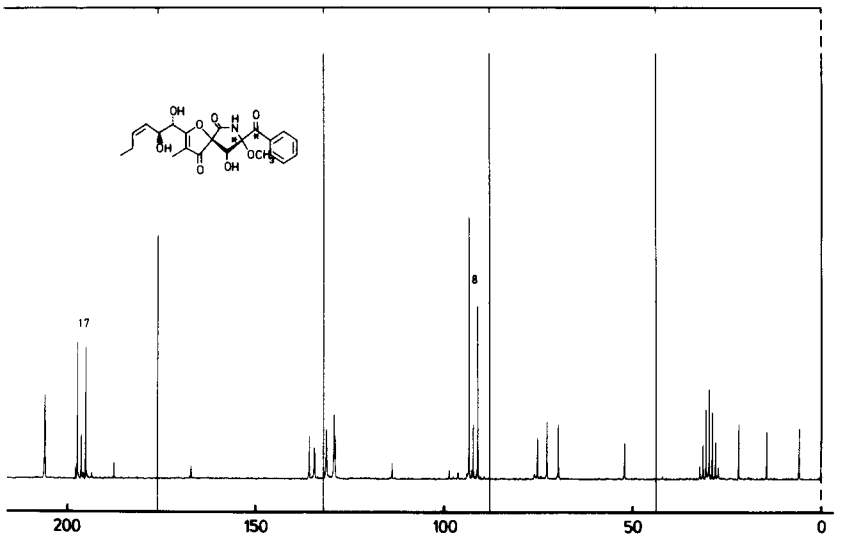
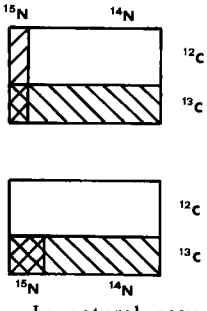


Fig. 4. Proton noise decoupled ^{13}C NMR spectrum of pseurotin A (**1**) after incorporation of [2,3-$^{13}C_2$]-D,L-phenylalanine ($(CD_3)_2CO$).

unfavourable nuclear properties are serious disadvantages. Additional difficulties for the establishment of the biogenetic network are due to the ubiquitous cellular transaminases. They convert α-amino acids reversibly into the corresponding α-keto acids. Therefore a negative incorporation experiment does not allow one to draw reliable conclusions. We now propose a novel approach to circumvent these problems to obtain some information concerning the origin of the nitrogen atoms in mould metabolites. [^{15}N]-L-phenylalanine and—in a separate experiment—equal amounts of [2-^{13}C,^{15}N]-D,L-phenylalanine, which was synthesized from commercially available double labelled glycine in a similar way as shown in Scheme 3, were administered to growing cultures of *Pseudeurotium ovalis*. From the mass spectra of both enriched specimens of pseurotin A (**1**) the rates of incorporation were determined using the fragment ion *m/z* 326 (M^+-benzoyl). The intensity of the molecular peak is too low—even after silylation with trimethylchlorosilane/hexamethyldisilazane—to supply reliable results. On the other hand both interesting atoms are certainly part of the fragment ion *m/z* 326 and since this peak is not superimposed by others this disadvantage carries little weight. The percentage of ^{15}N loss was also determined by ^{13}C NMR spectroscopy of the double labelled pseurotin A (**1**) sample.

The two experiments are based on the following reasoning. Even if transaminase activity is present in the fungal metabolism, the probabilities for the incorporation of ^{13}C and ^{15}N are not independent of each other. Although the bulk of the N isotope is certainly lost during the biosynthesis and dispersed over the whole amino acid pool, the retained ^{15}N atoms will be not exclusively but predominantly, situated next to a ^{13}C-atom unless the rate of exchange is of another order of magnitude than if the rate of the pseurotin A (**1**) biosynthesis. Only in this rather improbable case a statistical and independent incorporation of ^{13}C and ^{15}N is to be expected. This dependence should be reflected by the ratios of the isotopic peaks in the mass spectra as well as by the intensities of the ^{15}N-satellites in the ^{13}C NMR spectra. Let P13, P15 be the probabilities that atom Nr. 8 is a ^{13}C-, Nr. 7 a ^{15}N-isotope respectively. The following graphic illustration which represents the two readily calculable extremes, shows that the first isotopic peak is (relatively) smaller, the second one (relatively) higher, if the ^{15}N atoms are preferably adjacent to a ^{13}C atom.†



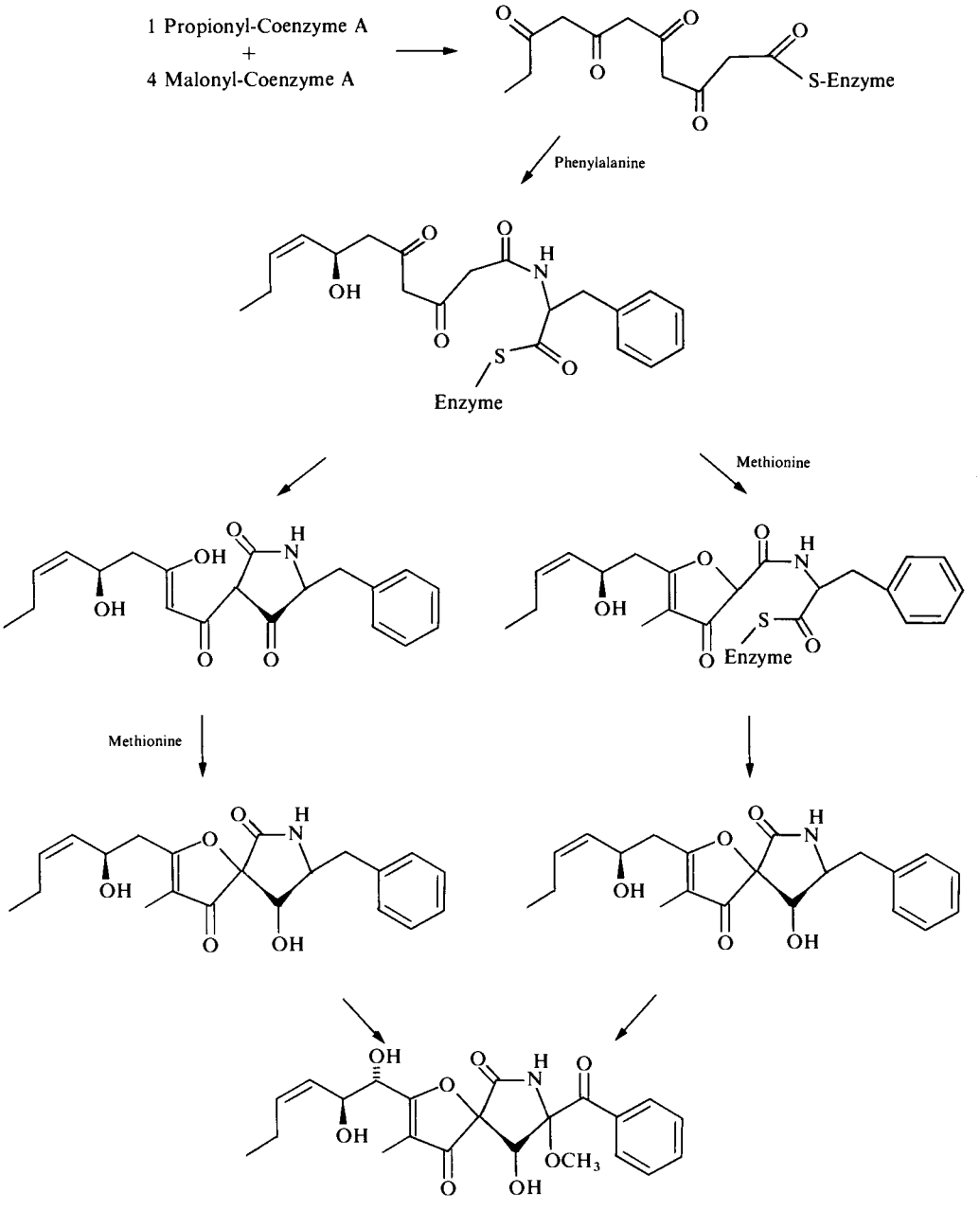
(1-P13) × (1-P15)	M^+
P13 × (1-P15) } P15 × (1-P13) }	$M^+ + 1$
P13 × P15	$M^+ + 2$
1 − P13	M^+
P13 − P15	$M^+ + 1$
P15	$M^+ + 2$

In natural pseurotin A (**1**) and in the enriched specimen obtained after administering 63 mg [^{15}N]-L-phenylalanine (95 atom %)/600 ml the ratios of the isotopic peaks were determined as follows:

326	327	
100	16.7 ± 2.13 (±0.870, 95%, 7)	natural pseurotin A (**1**)
100	20.9 ± 1.24 (±0.489, 95%, 6)	[^{15}N]-enriched pseurotin A (**1**)

Taking into account that due to the low natural abundance of ^{15}N, the isotopic pattern of the labelled molecules is nearly the same as that of the unlabelled molecules, except for one atomic mass unit shift, the

†Complete independence would be necessarily observed if a nitrogen free compound like phenylpyruvic acid or a cinnamic acid derivative was a real intermediate.



Scheme 4.

mole fraction X of ^{15}N can be calculated with a fair accuracy:

326	327	328	
39.2	6.55	1	Natural labelling pattern
$(1-X) \times 39.2$	$(1-X) \times 6.55$	$(1-X) \times 1$	$(1-X)$ Molecules are unlabelled

$(1-X) \times 39.2 : [(1-X) \times 6.55 + X\,39.2] =$ Labelling pattern of ensemble of labelled and unlabelled molecules

$= 25.6:5.34$

$\Rightarrow X = 0.04$

About 4% of all molecules are labelled at position 7. The overwhelming majority of ^{15}N is lost, the dilution is much greater than in the corresponding ^{13}C-experiments. But the incorporation rate is always higher than in similar experiments in the cytochalasan series.[16]

The results have to be compared with those obtained after the incorporation of 88 mg of [2-^{13}C, ^{15}N]-D,L-phenylalanine/800 ml (91.3 atom % ^{13}C, 99.1 atom % ^{15}N). Fig. 5 shows the relevant region of the proton noise decoupled ^{13}C NMR spectrum. The peak at 92.4 ppm is strongly enhanced, thus the main part of the label is lost as in the preceding experiment. In addition, two symmetrical ^{15}N-satellites can be observed, the left one being superimposed by the signal for the spiro centre C(5). A coupling constant of 12.5 Hz is consistent with the published data for $J_{^{13}C^{15}N}$.[17]

Their intensity is nearly 10% of the middle peak and not 4% as expected. Although comparisons of integral values of digitalized NMR spectra should be done with care, a statistical incorporation seems to be improbable. With a 50-fold signal enhancement supposed for C(8), each of the satellites should show a lower intensity than an unlabelled C atom. On the other hand, the ^{13}C-satellites of C(8)—obviously 1.1% of the central resonance—should each exhibit an intensity which is 25–30% of the intensity of the ^{15}N-satellites. But this behaviour is not observed. The two symmetrical lines separated by 90 Hz are side bands, because we know from the incorporation experiments with [2,3-^{13}C-D,L-phenylalanine that the coupling constant between C(8) and C(17) is 51.5 Hz. The coupling with C(9), a sp^3-nucleus, must be still weaker.[17] Thus the ^{15}N-satellites show nearly a ten times greater intensity than the ^{13}C-satellites which are not clearly recognized in the noise.

These observations and their interpretation are in good agreement with the results of the mass spectra. Taking into account the isotopic pattern for natural pseurotin A (**1**), one can set up two equation systems; one assuming that the probabilities for incorporation of ^{13}C and ^{15}N are fully independent, the other supposing that ^{15}N is found only next to ^{13}C:

	^{13}C and ^{15}N statistically distributed			^{15}N only next to ^{13}C			
	326	327	328	326	327	328	
Natural labelling pattern	100	16.7	2.55	100	16.7	2.55	
(1 − P13) × (1 − P15)	100	16.7	2.55	100	16.7	2.55	(1-P13)
P13 × (1-P15)		100	16.7		100	16.7	(P13-P15)
P15 × (1-P13)		100	16.7				
P15 × (1-P13)		100	16.7				
P13 × P15			100			100	P15
pattern found in the enriched metabolite	100	131.8	33.5	100	131.8	33.5	
	P13 = 0.51; P15 = 0.10				P13 = 0.56; P15 = 0.05		

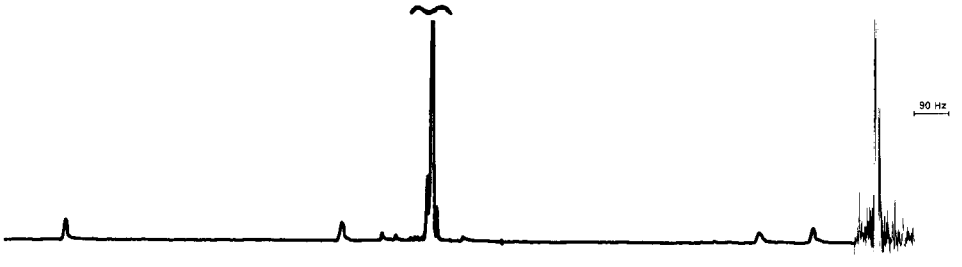


Fig. 5. Proton noise decoupled ^{13}C NMR spectrum of pseurotin A (**1**) (70–120 ppm) after incorporation of [2-^{13}C, ^{15}N]-D,L-phenylalanine ($(CD_3)_2CO$).

Both solutions are compatible with the ^{13}C NMR spectrum, but only the second one with the results obtained after incorporation of [^{15}N]-L-phenylalanine. It is impossible to explain why the ^{15}N-incorporation rate should now be more than doubled. Although the accuracy of our experiment is not ideal, because the metabolites were produced in two separate runs, a nitrogen free intermediate, which would necessarily require an independent incorporation of ^{13}C and ^{15}N, is highly improbable.

The support of these investigations by the "Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung" (Projects No. 2.629.0.76 and 2.158.0.78) and by Sandoz AG., Basel, is gratefully acknowledged.

EXPERIMENTAL

1. *General methods.* mps were determined on a Kofler block and are corrected. Optical rotations were measured on a Perkin–Elmer polarimeter, model 141. The 90 MHz ^1H NMR and 22.63 MHz ^{13}C spectra were recorded with a Bruker WH 90 spectrometer with Fourier transform in our institute (K. Aegerter). The mass spectra were measured in the Institute of Physical Chemistry, University of Basel, on an A.E.I. MS 30 instrument (R. Fink). We are indebted to Mr. G. Marbach, Sandoz AG., Basel, for radioactivity determinations and to Dr. J. C. Vederas, University of Alberta, Edmonton, Canada, for running the deuterium noise decoupled ^{13}C NMR spectrum.

Radioactive precursors were purchased from Amersham Radiochemical Centre (Buckinghamshire, England), ^{13}C- and ^{15}N-labelled compounds were obtained from Radium Chemie (Teufen, AR, Switzerland), Sharp & Dohme GmbH (München, BRD), KOR Isotopes (Cambridge, Mass., U.S.A.) and Prochem (London, England). Preparative tlc was carried out with silica gel PF 254 (Merck) and column chromatography with silica gel 70-325 mesh from E. Merck AG., Darmstadt, BRD, or with Florisil 100–200 mesh from Sigma, St. Louis, Mo, U.S.A.

2. *Production of pseurotin A* (**1**) *and E* (**6**). Inocula were prepared from slants of *Pseudeurotium ovalis* Stolk (strains S 2269 and S 3484) on agar (2% malt, 0.4% yeast extract). Cultures were grown in 500 ml Erlenmeyer flasks, each flask containing 200 ml of the following medium (g/1): glucose 20; pepton 2; yeast extract 2; KH_2PO_4 2; $MgSO_4 \cdot 7H_2O$ 2; pH 4.8–5.3 (not adjusted). All cultures were shaken for 8 days at 28° on a rotary shaker (220 rpm). Aqueous solns of the precursors (pH was adjusted if necessary) were sterilized and added aseptically after 48 hr. The mycelium and the medium were extracted with the same volume of EtOAc and the organic layer washed with water. The organic extract was dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified on a silica gel column (CH_2Cl_2/MeOH) to give 60–100 mg/1 of **1** and ≤ 8 mg/1 of **6**, respectively. The latter was isolated after tlc as unstable oil, pseurotin A (**1**) could be recrystallized from THF/hexane.

3. *Degradation to benzoic acid.* A soln of 100 mg of **1** (0.23 mmol) in 4 ml 30% HNO_3 was refluxed for 3.5 hr. The resulting benzoic acid was isolated from the mixture by steam distillation (350 ml) and neutralized with 0.05 N KOH against phenolphthalein. After evaporation the K-salt was dissolved in 2 ml H_2O and 4 ml MeOH and the pH adjusted to 6 (dil HCl). 84 mg (0.30 mmol) of *p*-bromophenacylbromide was added and the mixture boiled for 3.5 hr. The solvent was evaporated, the residue extracted with CH_2Cl_2 and the insoluble KBr filtered off. Purification by tlc (benzene/2 × development) gave 23.6 mg (0.074 mmol) of pure *p*-bromophenacylester, m.p. 116–117°, which was identical with an authentic sample.

4. 12, 13-*Dihydropseurotin A* (**4**). 144 mg (0.33 mmol) of **1** was dissolved in 20 ml benzene/EtOH (1:1) and hydrogenated in the presence of 70 mg (0.076 mmol) of tris-(triphenylphosphine)rhodium chloride for 12 hr at room temp and atmospheric pressure. The solvent was evaporated and the catalyst removed by filtering through a short column of alumina. The crude product was purified on a silica gel column (CH_2Cl_2/MeOH) to yield 83 mg (0.19 mmol) of **4**, mp. 176–179° (dec). IR (KBr): 1715, 1680, 1605; ^1H-NMR (DMSO): 0.8 (m, 3 H, C(15)): 1.2 (m, 6 H, C(14), C(13), C(12)); 1.64 (s, 3 H, C(16)); 3.25 (s, 3 H, O–CH_3); 4.39 (d, J = 8.8, 1 H, C(9)); 4.3–4.6 (m, 2 H, C(10), C(11)); 4.57 (d, J = 5.9, 1 H, C(11)–OH); 5.68 (d, J = 5.6, 1 H, C(10)–OH); 6.29 (d, J = 8.8, 1 H, C(9)–OH); 7.4–7.7 (m, 3 H, C(20)–C(22)); 8.2–8.3 (m, 2 H, C(19), C(23)); 9.94 (s, 1 H, –NH); ^{13}C–NMR ($(CD_3)_2CO$): Table 1; MS: 401 (M^+–32 (MeOH), 328 (M^+–105 (benzoyl)); 315 (base peak, M^+–32–86 (pentanal)), 105 (benzoyl), 77 ($C_6H_5^+$).

5. 17-*Dihydropseurotin A* (**5**). A few crystals of methylorange were dissolved in 10 μl H_2O and 200 μl THF. 144 mg (0.33 mmol) of **1** and 22 mg (0.35 mmol) $NaBH_3CN$ and then, drop by drop, a mixture of 30 μl H_2O and 30 μl acetylchloride in 200 μl THF were added so that the indicator kept its red colour. The reaction was followed by Hc CH_2Cl_2/MeOH). The crude product was diluted with 10 ml H_2O and extracted with three portions of 10 ml CH_2Cl_2. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. After purification on a silica gel column (CH_2Cl_2/MeOH) 73 mg (0.17 mmol) of **5** (epimeric mixture in a ratio of 9:1) and a small amount of starting material were obtained.

^1H-NMR (DMSO): 0.92 (t, J = 7, 3 H, C(15)); 1.60 (s, 3 H, C(16)); 1.9–2.2 (m, 2 H, C(14)); 3.23 (s, 3 H –OCH_3); 4.3–4.8 (m, 6 H, C(9), C(10), C(11), C(9)–OH, C(17)–OH); 4.87 (br d, 1 H, C(11)–OH); 5.4 (m, 2 H, C(12), C(13)); 5.74 (d, J = 4.4, 1 H, C(10)–OH); 7.25–7.44 (m, 5 H, C(19)–C(23)); 8.97 (s, 1 H, –NH). ^{13}C-NMR ($(CD_3)_2CO$): Table 1.

Synthesis of precursors

6. [$^{13}C^2H_3$]-L-*methionine* (*cf*[8]). S-Benzyl-L-homocysteine was prepared from commercially available D,L-homocystine via brucine salt of the N-formyl-S-benzyl-derivative according to ref. 8. The crude product showed $[\alpha]_D^{20}$ + 17.5° (*c* 1 in 1 N HCl). 0.62 g (2.75 mmol) thereof dissolved in liquid ammonia was reduced by adding small pieces of Na (~0.2 g) until the blue colour persisted for several min. The temp of the cooling bath was raised to −50° and 170 μl (365 mg, 2.65 mmol) of [$^{13}C^2H_3$]-methyliodide (90 atom % ^{13}C, 98 atom % ^2H) was introduced by a syringe directly beneath the surface of the mixture. After evaporation of the ammonia the residue was dissolved in water and treated with HI to pH 5. The filtered soln was concentrated to *ca* 2 ml, 50 ml hot EtOH was added and the mixture kept at 0° to yield 344 mg (2.25 mmol) of [$^{13}C^2H_3$]-L-methionine, which was checked on HC (n-butanol: acetic acid: water = 8:2:2). Runs with unlabelled material showed $[\alpha]_D^{20}$ − 4.5° (*c* 0.96 in H_2O).

^1H-NMR (Dioxane): 3.8 (m, 1 H, C(2)); 2.0–2.7 (m, 4 H, 2 × CH_2); no aromatic protons and no signal for $^{13}CHD_2$.

7. [1-^{13}C]-D,L-*phenylalanine* (*cf*[11]). 5.8 g (35 mmol) of 1,1-dimethoxy-2-phenylethane was refluxed in 2 ml MeOH and 2 ml 6 N HCl for 10 min. After removing the solvent carefully and quantitatively (otherwise the yields are very low) under reduced pressure the crude phenylacetaldehyde was added to a soln of 323 mg (6.03 mmol) ammonium chloride in 1 ml H_2O and cooled to 0°. This was immediately followed by the methanolic soln (10 ml) of 50 mg of labelled sodium cyanide (90 atom % ^{13}C). The residual 279 mg of $Na^{13}CN$ (total amount 329 mg (6.6 mmol) were dissolved in 4 ml 50% MeOH and added drop by drop. After standing overnight 0.7 ml 50% NaOH was added to the yellow mixture and the alcohol removed by distillation. The α-aminonitril and the polymerized aldehyde were separated from the inorganic salts by extraction with ether (2 ×). The combined ether solns were acidified with 7 ml 4 N HCl and distilled into a soln of NaOH (HCN!). The gummy residue containing the amino acid was heated with three 10 ml portions 3 N HCl. The combined extracts were evaporated to dryness and then treated with

conc HCl. After filtration the soln was concentrated to a volume of *ca* 1.5 ml; *ca* EtOH was added and the pH adjusted to 6 with alcoholic ammonia. On cooling, 330 mg (2 mmol) of [1-^{13}C]-D,L-phenylalanine separated out. The product was checked on Hc (n-butanol: acetic acid: water = 8:2:2) and used without further purification.

8. [2,3-$^{13}C_2$]-D,L-*Phenylalanine* (*cf*[12,13,14]). Starting from Na[2-^{13}C]-acetate (90 atom% ^{13}C) [2-^{13}C]-hippuric acid (**7**) was prepared according to known procedures.[12] The latter was condensed with [^{13}C]-benzaldehyde (**8**), which had been synthesized from [^{13}C]-benzoic acid (90 atom% ^{13}C) via the imidazolide,[13] in the following manner: 1.88 g (8.9 mmol) of $C_6H_5{}^{13}CHO \cdot NaHSO_3$ and 1.61 g (8.9 mmol) of **7** were dissolved in 5.1 ml Ac_2O, 0.55 ml AcOH and 11 ml benzene. 750 mg NaOAc was added and the mixture refluxed for 5 hr. After cooling the cake was transferred to a Büchner funnel, washed twice with 2 ml cold H_2O and dried. The mother liquor was chromatographed on a florisil column (CH_2Cl_2). The combined crops of **9** (1500 mg, 5.58 mmol) were directly used for the next step. 325 mg (1.2 mmol) of **9** was treated with 275 mg (7.3 mmol) red P and 1.7 ml Ac_2O. During a period of about 1 hr 1.6 ml of 50% HI was added (exothermic reaction! If the mixture solidified the cake was stirred with a glass rod). The suspension was then refluxed for 3 hr and, after cooling, filtered with suction. The filtrate and the washings (2 × 2 ml glacial AcOH) were evaporated *in vacuo*, dissolved in 20 ml H_2O and evaporated again to dryness. 20 ml ether and 20 ml H_2O were added to the residue and the mixture vigorously shaken. The aqueous layer was separated and extracted with two 10 ml portions ether. The water soln was heated on a steam bath with a trace of Na_2SO_3 to remove the dissolved ether. The volume was reduced to *ca* 2 ml and the pH adjusted to *ca* 6 with alcoholic ammonia. 150 mg (0.90 mmol) of [2,3-$^{13}C_2$]-D,L-phenylalanine could be isolated which was checked on Hc (n-butanol: acetic acid:water = 8:2:2) and incorporated without further purification. Phenylalanine from runs with unlabelled material was also examined by ^{1}H NMR.

9. [2-^{13}C,^{15}N]-D,L-*Phenylalanine* (*cf*[12,14]). According to ref. 12 210 mg (2.73 mmol) of commercially available [2-^{13}C,^{15}N]-glycine (91.3 atom% ^{13}C, 99.1 atom% ^{15}N) was treated with 422 mg (3.0 mmol) benzoyl chloride to yield 482 mg (2.66 mmol) double labelled hippuric acid (mp. 182–183°). Condensation with benzaldehyde and reductive opening of the azlactone were carried out following the procedure for [2,3-$^{13}C_2$]-D,L-phenylalanine. The resulting amino acid (159 mg, 0.95 mmol) was used without further purification.

^{13}C-NMR (D_2O/OD^-, chemical shifts refer to the signal at 131.1): 41.1 (d, $J_{^{13}C\,^{13}C}$ *ca* 35, C(3)); 58.8 (d, $J_{^{13}C\,^{15}N}$ 3, C(2) ninety-fold increased); 128.7 (*para*); 130.5 (*meta*); 131.1 (*ortho*); 139.3; C(1) (d) could not be detected.

10. *Sodium* [2-$^{13}C^2H_2$]-*propionate* (*cf*[10]). 1.45 g (15 mmol) of sodium [2-^{13}C]-propionate (91.8 atom% ^{13}C) was dissolved in 20 ml of D_2O (99.7 atom% ^{2}H) containing 5 mmol of NaOD and kept in a sealed tube at 160° for 48 hr. This process was repeated six times yielding a precursor containing at least 98 atom% ^{2}H in α-position. MS (free acid): 77 (M^+ Calc. for $CH_3{}^{13}CD_2COOH$), 60, 45. ^{13}C-NMR (D_2O/OD^-, chemical shifts refer to the signal at 30.2): 10.1 (d, $^2J_{^{13}C\,^{13}C}$ 35, C(3)); 30.2 (qui, $^2J_{^2H\,^{13}C}$ 19, C(2)D_2); 30.5 (t, $^2J_{^2H\,^{13}C}$ 19, C(2)HD, the intensity is 4.8% of that for $^{13}CD_2$); the signal for C(1) (d) was too weak to be detected.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 213 to 223, 1981
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0040-4020/81/Suppl. 1-0213-11 $02.00/0
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DIARYL TELLUROXIDES AS NEW MILD OXIDISING REAGENTS†

STEVEN V. LEY* and CLIVE A. MEERHOLZ
Department of Chemistry, Imperial College, London SW7 2AY

and

DEREK H. R. BARTON
Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France

(*Received in U.K.* 7 *August* 1980)

Abstract—Dianisyltelluroxide (**1**) has been shown to be an especially mild and selective oxidising reagent for a number of organic substrates. Phosphines can be oxidised to their corresponding oxides while thiols are converted to disulphides. Thiocarbonyl compounds can be transformed to their oxo analogues either directly by **1** or by a catalytic cycle involving the use of 1,2-dibromotetrachloroethane as a room temperature brominating agent for various Te^{II} species.

On oxidation acyl hydrazines produce hydrazides in high yield whereas aryl hydrazines afford arenes and symmetrical and unsymmetrical tellurides.

Many other readily oxidised functional groups are inert towards **1**.

Although organosulphur reagents,[1] and in more recent years organoselenium reagents,[2] have been used with success in organic synthesis very few tellurium containing compounds have found useful application.[3]

Here we report in full the use of diaryltellurium (IV) species as mild and selective oxidising reagents.[4] We have focused our efforts mainly on the use of bis(*p*-methoxyphenyl)telluroxide (**1**) for several reasons. Firstly the reagent is easily prepared by basic hydrolysis of the dichloride (**2**) which in turn was readily obtained in 83% yield by treatment of anisole with $TeCl_4$.

The telluroxide (**1**) is soluble in most organic solvents and is stable in the dark at room temperature. Also, in contrast to the unstable and unpleasant dialkyltelluroxides,[5] compound **1** and the corresponding telluride (**3**) are odourless. Lastly Te–O bonds are weaker than, either S–O or Se–O bonds.[6] The observation that the mass spectrum of **1** does not show a molecular ion but has the base peak corresponding to the telluride (**3**), exemplifies this weakness. Thus telluroxides might efficiently transfer oxygen to organic substrates.

It has recently been demonstrated that dimethylselenoxide is a better oxidant than dimethylsulphoxide for certain phosphorus containing compounds.[7] It follows therefore that the telluroxide (**1**) could be even better and that the odourless telluride (**2**), formed as a by-product, could be recovered and reoxidised to **1**.

Accordingly treatment of either tri n-butylphosphine or triphenylphosphine with **1** (1 equiv) at room temperature gave good yields of the corresponding phosphine oxides. The reaction however did not show any substantial improvement over the literature procedures.

Next we investigated the use of **1** to effect the conversion of thiocarbonyl groups to their oxo analogues. Reagents that will effect this transformation are known.[8]

A number of readily available thiocarbonyl and selenocarbonyl compounds (**4** → **14**) were treated with the telluroxide (**1**) and, with a few exceptions, were found to afford their corresponding oxo derivatives (Table 1). The product yields were generally high and elemental S (or Se) was also isolated in each case. Separation of the oxidation product from dianisyltelluride (**3**) was nearly always possible using column chromatography or plc, the exception being the trithiocarbonate (**8**).

Similar reaction of thiocamphor (**15**) with **1** gave a number of products two of which were camphor and the dithione (**16**). The oxo derivatives are undoubtedly formed by similar mechanisms to those proposed in related systems. Compound **16** is most likely derived by oxidation of the thioenol by **1** to the *bis*-vinyldisulphide which slowly undergoes a hetero-Cope reaction[9] (Scheme 1).

Reaction of phenylisothiocyanate with **1** gives diphenylurea on aqueous work up. No attempt was made to isolate the intermediate phenylisocyanate. Although the dianisyltelluroxide (**1**) is only sparingly soluble in water it can be used to convert thiourea into urea using an aqueous system.

This last observation may find application in the modification of certain nucleic acids following the discovery of 4-thiouridine in t-RNA of *E. coli*.[10] Many methods have been used to chemically transform this base.[11]

Another obvious area where new mild oxidants are required is for the conversion of thiols to disulphides.

It has been reported that diorganotellurium dialkoxides[12] and diaryl dichlorides[13] both effectively convert aromatic thiols to disulphides. The dianisyltelluroxide (**1**) should be equally effective. In this case the by-products of the reaction would be water and the inoffensive telluride (**3**) (Scheme 2).

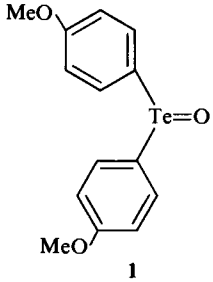
The thiols (**17** → **20**) rapidly react with **1** to give the corresponding disulphides in very high yields. The fact

†Dedicated with respect to the memory of Robert Burns Woodward.

Table 1. Oxidation of thiocarbonyl derivatives by dianisyltelluroxide (1)[a]

Starting material	Reaction time (h)	Yield of oxo-derivative (%)
4a	24	Quant
4b	0.3	93
5a	1.5	66
5b	0.25	Quant
5c	27	70
6a	63	Quant
6b	16	68
7	0.5	96
8	20	a
9	4	91
10	1	98
11	0.75	87
12	42	23
13	0.3	Quant
14	20	87

a) Inseparable from the telluride (3)



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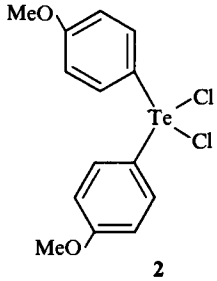

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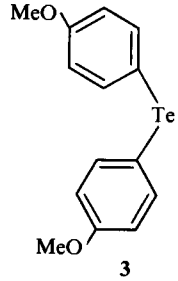

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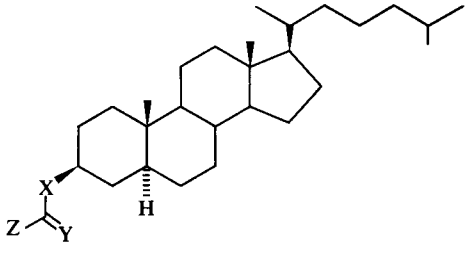
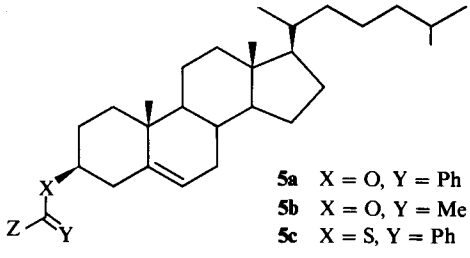


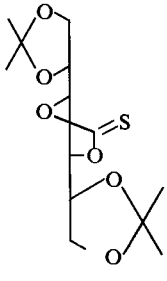
4a X = O, Y = S, Z = SMe
4b X = O, Y = Se, Z = Ph



5a X = O, Y = Ph
5b X = O, Y = Me
5c X = S, Y = Ph

$(RNH)_2C=S$

6a R = H
6b R = Ph



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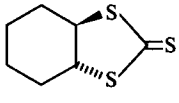

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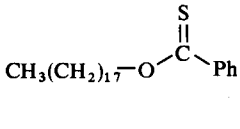

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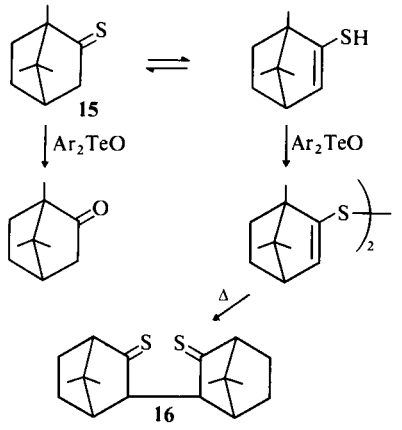
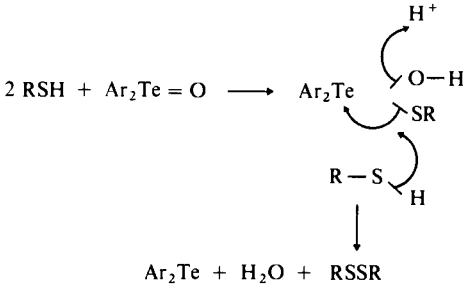


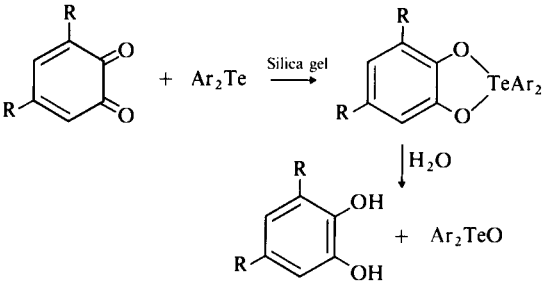
Scheme 1



Scheme 2

that **17** and **20** react to afford disulphides although other easily oxidised functional groups are present demonstrates the mildness of the new oxidant. Other useful procedures have also recently been reported.[14]

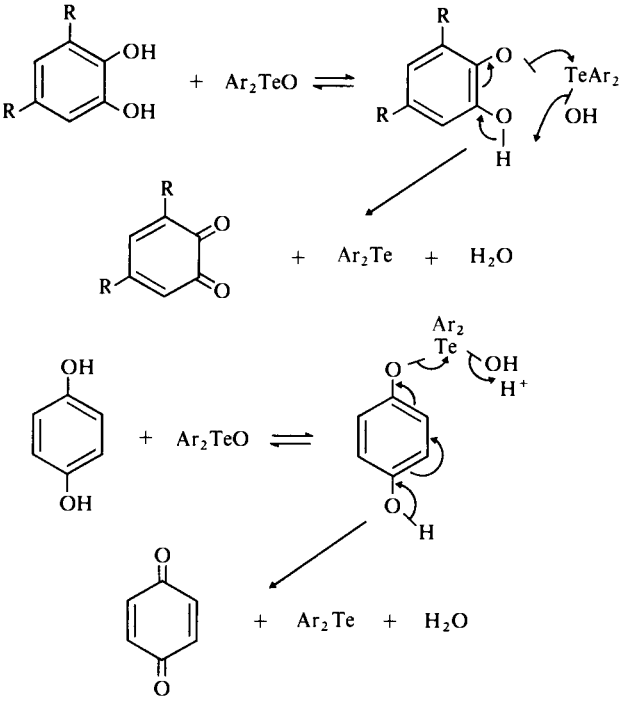
The oxidation of phenols is often a facile process. However many simple monohydroxylic phenols are not oxidised by **1**. Reaction of the hydroquinones (**21** and **22**) and the catechol (**23**) with the telluroxide (**1**) affords the corresponding quinones (**24–26**). The mechanism for these oxidations is not clear although a recent report[15] which describes the use of diphenylselenoxide as an oxidant for catechols suggests a selenurane species (**27**) as a possible intermediate. Alternative mechanisms can be proposed (Scheme 3).



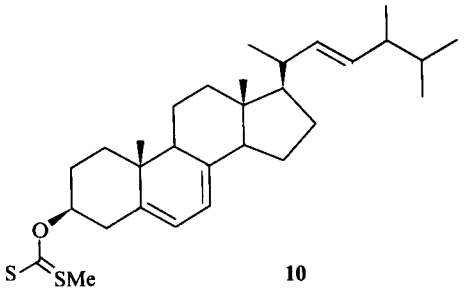
Scheme 4

Theoretically only one equivalent of telluroxide should be necessary for complete oxidation of both catechols and hydroquinones as is in fact found for the oxidation of **21** and **22**. However when the mixture from the oxidation of **23** with 1 equiv of **1** was subjected to plc little or no telluride (**3**) was obtained while the ortho quinone (**26**) was isolated together with unreacted catechol (**23**).

In contrast the ^{1}H NMR spectrum of the crude mixture showed only the presence of the telluride (**3**) and quinone. Only when an excess of telluroxide (**1**) was used could one obtain **26** in acceptable yields. Furthermore if equimolar amounts of pure quinone (**26**) and telluride (**3**) were dissolved in $CDCl_3$ the ^{1}H NMR spectrum showed only these to be present; however if this mixture was analysed by tlc quinone, catechol and trace amounts of the telluride could be detected. These observations suggest that under



Scheme 3



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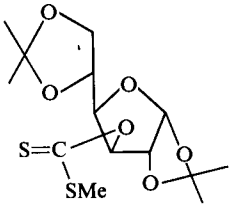

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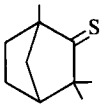

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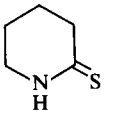

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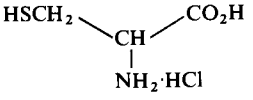

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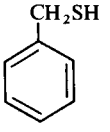

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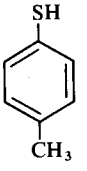

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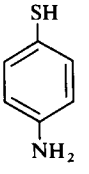

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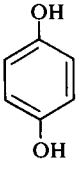

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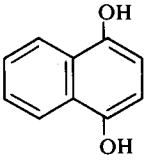

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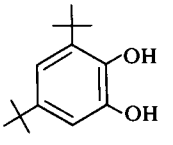

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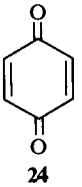

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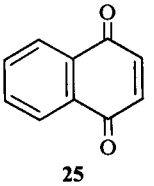

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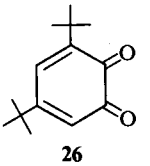

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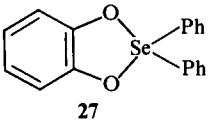

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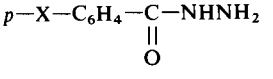
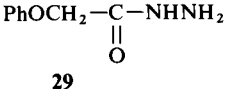


28 X = H
30 X = OMe
31 X = NO_2

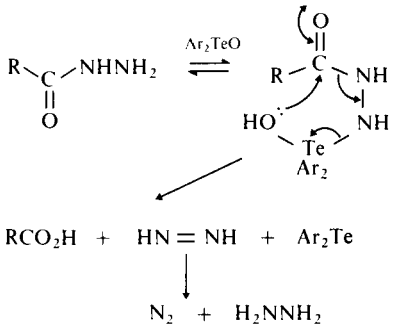


29

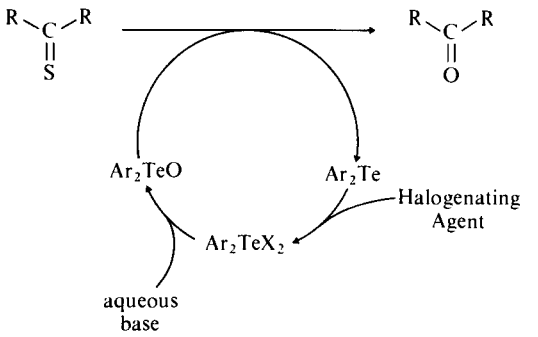
conditions of chromatography on silica gel a reverse reaction can take place (Scheme 4).

In order to further extend the scope of **1** as an oxidant we have studied its reaction with hydrazines as these oxidation reactions are of some interest.[16]

Thus reaction of the acyl hydrazines (**28** → **31**) with the telluroxide (**1**) gave the hydrazides (**32** → **35**) rapidly at room temperature. These reactions are therefore analogous to oxidation by diphenylselenoxide and benzeneseleninic anhydride. Of interest however was the additional isolation of *p*-anisic acid and *p*-nitrobenzoic acid, in low yield, from the oxidation of **30** and **31** respectively. A possible mechanism to account for these products is shown in Scheme (5). Treatment of the hydrazines (**36** → **40**) with **1** gave the parent arene, anisole and symmetrical and unsymmetrical diaryl tellurides (Table 2). The formation of the latter is interesting and deserves further study. We are not convinced that aryl radicals are involved.



Scheme 5



Scheme 6

Finally in this section the oxidation of hydrazine hydrate to diimide was attempted. Using only equivalent amounts of **1** and hydrazine hydrate in the presence of cinnammic acid (1.5 equiv) a fair amount of reduction did indeed occur, however, this potentially useful process was not investigated further.

In common with many other oxidising reagents the telluroxide (**1**) also rapidly converted N-phenylhydroxylamine into nitrosobenzene in high yield. Other examples of this oxidation were not studied.

Diazodiphenylmethane is of importance for the preparation of benzhydryl esters[17] and in heterocyclic synthesis[18] and is usually prepared by oxidation of benzophenone hydrazone.[19] Utilization of the telluroxide (**1**) as oxidant and subsequent trapping of the diazodiphenylmethane with *p*-anisic acid gave the corresponding benzhydryl ester in 77% yield.

In order to demonstrate the selectivity of the telluroxide (**1**) as an oxidant we find that it is inert to a wide variety of compounds many of which are often readily oxidised by other reagents. Those compounds which were found to be *unaffected* by **1** include, dithiolanes, enamines, aldehydes, ketones alcohols, pyrroles, indoles, amino acids, aromatic amines, mono hydroxylated aromatics, esters, hindered thiocarbamates, isonitriles, oximes, aryl hydrazones, sulphides and selenides. This impressive list we believe shows that **1** is therefore a mild and selective reagent.

Simple kinetic studies also reveal that **1** reacts approximately twice as fast with **23** than it does with **5b**, whereas the thiol (**19**) can be selectively oxidised in the presence of the catechol (**23**).

As catalytic oxidative processes are important in organic synthesis[20] we sought to establish such a process for various organotellurium species including **1**. Chosen for this study was the thiocarbonyl-carbonyl transformation for which a catalytic cycle can be represented as in Scheme 6. This cycle can obviously be entered at the telluride, telluroxide or tellurium dihalide stage and requires the telluride to be readily halogenated and subsequently converted to telluroxide by a suitable aqueous base.[4b]

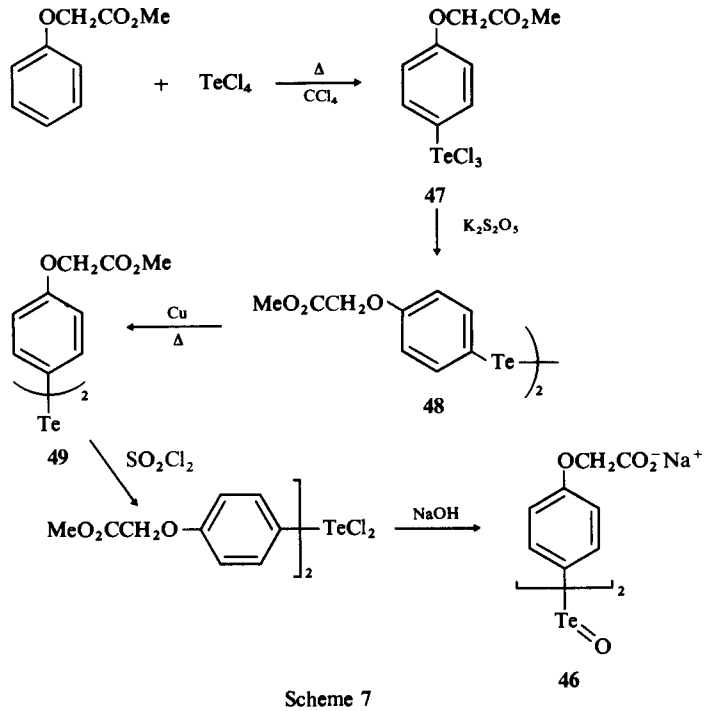
Although vicinal halides have been used before to effect halogenation of tellurides they often require high temperatures.[21] We found that the inexpensive 1,2-dibromotetrachloroethane was an excellent brominating[22] agent for tellurides at room temperature. Other reagents studied, hexachloroacetone, carbon tetrabromide, or Meldrum's acid dibromide were much less effective in the catalytic cycle. In control studies when equimolar amounts of the telluride (**3**) were mixed with the 1,2-dibromotetrachloroethane in light petroleum an 80% of the dibromide corresponding to **2** could be isolated.

In the catalytic cycle no oxidation took place in the absence of 1,2-dibromotetrachloroethane. For the reaction to work well aqueous potassium carbonate was the most satisfactory base although aqueous triethylamine could also be used.

Under optimum conditions the thiocarbonyl derivative is dissolved in chloroform together with 1.5% of the tellurium species. To this mixture was

Table 2. Oxidation of aryl hydrazines

Hydrazine Ar $NHNH_2$ Ar		Arene ArH	PRODUCTS YIELD (%) Telluride R^1TeR^2 R^1=R^2=Anisyl (3)	R^1=Aryl R^2=Anisyl
Ph	(36)	53	68	29
4-MeC_6H_4	(37)	30	59	26
2,6-(DiMe)C_6H_3	(38)	70	74	5
4-BrC_6H_4	(39)	29	49	31
4-$HO_2CC_6H_4$	(40)	26	44	–

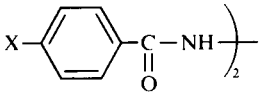


Scheme 7

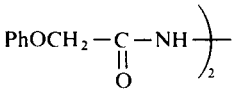
Table 3.* Oxidation of thiocarbonyl compounds at room temperature using 1,2-dibromotetrachloroethane as halogenating agent

Substrate	Eq. of halogenating agent	Eq. of tellurium species	Aqueous base	Time h	Yield %
5(a)	1.1	(3) 0.1	10% K_2CO_3	116	88
5(a)	3	(3) 0.1	10% K_2CO_3	23	90
5(a)	5	(3) 0.015	10% K_2CO_3	88	75
5(a)	5	(3) 0.015	20% K_2CO_3	20	70
5(a)	3	(3) 0.015	20% K_2CO_3	80	70
5(a)	5	(2) 0.1	20% K_2CO_3	26	87
5(a)	5	(3) 1	Et_3N	15	85
5(a)	5	(3) 0.1	Et_3N	48	41
5(a)	5	(41) 0.1	20% K_2CO_3	20	88
5(a)	5	(42) 0.1	20% K_2CO_3	2	88
5c	10	(3) 0.015	20% K_2CO_3	72	70
5c	5	(3) 0.015	20% K_2CO_3	114	70
8	5	(3) 0.015	20% K_2CO_3	72	60
13	5	(3) 0.015	20% K_2CO_3	15	Quant

* In the absence of the tellurium species no reaction was observed.



32 X = H
34 X = OMe
35 X = NO_2



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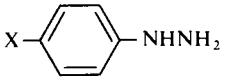
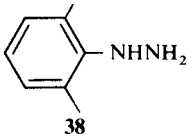


36 X = H
37 X = Me
39 X = Br
40 X = CO_2H



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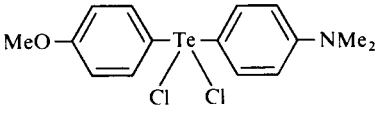

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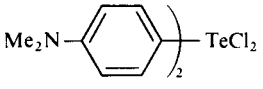

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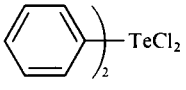

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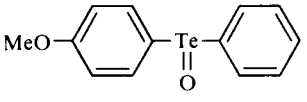

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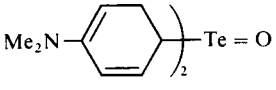


45

added an excess of 1,2-dibromotetrachloroethane and aqueous K_2CO_3 and the reaction mixture stirred vigorously until complete (Table 3).

Dipole moment studies have shown that there is appreciable mesomeric interaction of the ring π system with the Te atom in diaryl-tellurium compounds.[23] Also p_{Te}-π bonding is significant only when there are strong electron acceptor substituents on the rings. However, when powerful π-donor groups are present in the *para* positions of the rings the Te atom acts as a π-acceptor using its vacant 5d orbitals. It was therefore of interest to examine the effect of changing the aromatic substituents on the course and rate of the catalytic cycle. Thus in the table we have also compared other differently substituted dichlorides (**41**, **42** and **43**).

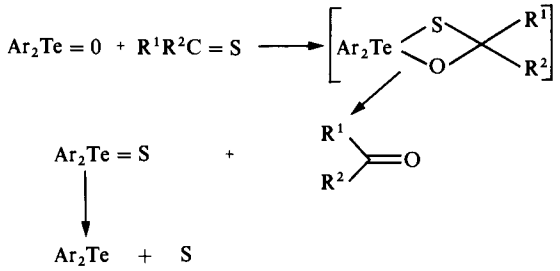
It appears that an increasing rate is observed in the series (**42** > **41** > **2** ≫ **43**). Although in separate experiments the telluroxide (**44**) reacted with the selenobenzoate (**4b**) to afford the corresponding benzoate after 1 h whereas **45** reacted with the dithiobenzoate (**5c**) at a similar rate to **1**.

In an effort to develop a potentially water soluble oxidant the telluroxide (**46**) was prepared in the following manner (Scheme 7).

Heating $TeCl_4$ in the presence of excess methylphenoxyacetate according to the method of Bergman[24] led to a very complicated mixture. However if the same reaction was repeated using carbon tetrachloride as solvent a 96% yield of the trichloride (**47**) was isolated. Treatment of **47** without further purification with potassium metabisulphite gave a 95% yield of the ditelluride (**48**). This compound was found to be unstable, tellurium being deposited on attempted crystallisation. When the crude ditelluride (**48**) was reacted with activated copper powder[25] in refluxing dioxan, a 98% yield of the telluride (**49**) was obtained which was readily crystallised from methanol. The telluroxide (**46**) was subsequently obtained by treatment of **49** with sulphuryl chloride in dry benzene followed by aqueous sodium hydroxide. Isolation of **46** was achieved by precipitation with acetone.

Preliminary results using **46** as a water soluble oxidant do not suggest that it will be very effective for transformations discussed above.

However we have shown that dianisyl telluroxide is a useful new mild, selective oxidising reagent which can be used in a catalytic cycle. We anticipate further synthetic uses of some of the Te^{IV} species described.



Scheme 8

We have not studied the mechanism of the conversion of thiocarbonyl or selenocarbonyl compounds into their carbonyl analogues. However, we made the first experiments with the idea (for thiocarbonyl derivatives) summarised in Scheme 8. Although this proposal is naive it would seem to merit further consideration.

EXPERIMENTAL

M.ps were determined using a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on Perkin–Elmer 197 and 298 spectrometers, NMR spectra were recorded using a Varian EM 360 machine. Mass spectra were recorded on a V.G. Micromass 7070 spectrometer. Solvents were purified and dried by standard techniques.

Preparation of 4,4′-dimethoxydiphenyltelluroxide (**1**). 4,4′-Dimethoxydiphenyltellurium dichloride[24] (8.00 g) was stirred at 95° in NaOH aq (100 ml, 5 %) for 1 hr. After cooling to 0° the white solid was filtered off, washed with cold water (3 × 10 ml), and dried under vacuum over P_2O_5 to give **1** (5.60 g 81 %), m.p. 187–189° (lit.[26], 190–191°), ν_{max}. (Nujol) 1585, 1575, 1490, 1460. 1401, 1380, 1295, 1247, 1180, 1172, 1109. 1068, 1026, 823, 811, and 789 cm^{-1}, δ 7.70 (4 H, d, J 9 Hz), 6.78 (4 H, d, J 9 Hz), and 3.78 (6 H, s), *m/e* 360 (M^+ absent), 344, 214 (100 %), and 199.

Oxidation of triphenylphosphine. Triphenylphosphine (262 mg) and **1** (358 mg) were dissolved in $CHCl_3$ (4 ml) (N_2). After 48 hr the $CHCl_3$ was removed under reduced pressure and the residue subjected to column chromatography (benzene–EtOAc 9 + 1) to give **3** (261 mg, 73 %) and triphenylphosphine oxide (223 mg, 80 %), m.p. 153–157° (lit.[27], m.p. 154–157°).

Oxidation of tri-n-butylphosphine. Tri-n-butylphosphine (133 mg) and **1** (236 mg) were dissolved in $CHCl_3$ (4 ml) (N_2). After 0.5 hr the $CHCl_3$ was removed under reduced pressure and column chromatography (EtOAc) of the residue gave **3** (161 mg, 71 %) and tri-n-butylphosphine oxide (140 mg, 97 %) as a colourless oil δ 1.60 (broad m) and 0.90 (broad m), *m/e* 218 (M^+), 189, 162, 161, 147, 134, 120 (100 %), and 92.

General procedure for the oxidation. All the reactions were performed at room temp under N_2 in either $CHCl_3$ or CH_2Cl_2. Approximately 10 ml of solvent was used for every 100 mg of substrate. For thiocarbonyl derivatives 1·1 equiv of **1** was used, for thiols 0·55 equiv. The mixtures were concentrated by partial evaporation of the solvent and subjected to plc or column chromatography to isolate the products. The product yields refer to chromatographic yields unless otherwise specified. The telluride (**3**) was always recovered in yields ranging from 64–96 % while S (or Se) were always recovered in near quantitative yields from the reactions with thiocarbonyl derivatives.

Oxidation of xanthate (**4a**). Compound **4a** (116 mg) after 24 hr afforded 5α-cholestan-3β-ol-methylthiocarbonate (114 mg, 100 %) m.p. 117–119. Crystallisation from EtOAc gave (80 mg, 72 %) m.p. 119.5–120.5° (lit.[28], 117°), ν_{max} ($CHCl_3$) 1700 cm^{-1}, *m/e* 462 (M^+, weak), 371, 355, 258, 256 (100 %), 192, 160 and 128.

Oxidation of selenobenzoate (**4b**). Compound **4b** (278 mg) after 0.3 hr afforded 5α-cholesten-3β-ol-benzoate (229 mg, 93 %). Crystallisation from EtOAc gave (198 mg, 80 %), m.p. 136–137° (lit.[29a], 136–137°).

Oxidation of thionbenzoate (**5a**). Compound **5a** (253 mg) after 1.5 hr afforded 5-cholestan-3β-ol-benzoate (162 mg, 66 %) m.p. 143–145°. Crystallisation from EtOAc gave (130 mg, 53 %), m.p. 144–145.5° (lit.[29b], 150–151°), ν_{max} (CCl_4) 1722 cm^{-1}.

Oxidation of thionacetate (**5b**). Compound **5b** (111 mg) after 0.25 hr afforded 5-cholesten-3β-ol-acetate (107 mg, 100 %). Crystallisation from acetone gave (90 mg, 84 %), m.p. 113–114° (lit.[29b], m.p. 114–115°).

Oxidation of dithiobenzoate (**5c**). Compound **5c** (130 mg) after 27 hr afforded 5-cholesten-3β-thiol-benzoate (88 mg, 70 %), m.p. 160–162°. Crystallisation from EtOAc gave (65 mg; 52 %), m.p. 164.5–166° (lit.[28], 167°), m/e 506 (M^+, weak), 369, and 368 (100 %).

Oxidation of thiourea (**6a**). Compound **6a** (38 mg) after 16 hr (MeOH as solvent) afforded urea (22 mg, 73 %), ν_{max} (Nujol) 1660 (broad) cm^{-1}.

Compound **6a** (38 mg) after 63 hr (water as solvent), extraction of the aqueous phase with CH_2Cl_2 and evaporation of the water at room temp under reduced pressure afforded urea (34 mg, 100 %).

Oxidation of 1,3-diphenylthiourea (**6b**). Compound **6b** (114 mg) after 16 hr (MeOH as solvent), evaporation of the MeOH under reduced pressure, trituration of the residue with benzene, and filtration afforded 1,3-diphenylurea (72 mg, 68 %), m.p. 234° (lit.[29c], 238–239°), *m/e* 212 (M^+), 119, 93 (100 %), 77, 66 and 65.

Oxidation of thioncarbonate (7). Compound 7 (145 mg) after 0.5 hr afforded the corresponding carbonate (132 mg, 96 %), m.p. 145–147° (lit.[30], 147°), *m/e* 273 (M^+ − 15) and 101 (100 %).

Oxidation of trithiocarbonate (**8**). Compound **8** (95 mg) after 20 hr afforded S (16 mg, 100 %) and a mixture of **3** and cyclohexan-1,2-*trans*-diyldithiocarbonate (228 mg), ν_{max} ($CHCl_3$, mixture) 1730 and 1640 cm^{-1}, (mixture) 7.58 (4 H, d, J 8 Hz), 6.70 (4 H, d, J 8 Hz), 3.75 (8 H, overlapping s and m), and 2.30–1.25 (8 H, m).

Oxidation of thionbenzoate (**9**). Compound **9** (97 mg) after 4 hr afforded n-octadecanylbenzoate (85 mg, 91 %), m.p. 41–42°, *m/e* 374 (M^+), 253, 252, 224, 123 (100 %), 105 and 97.

Oxidation of xanthate (**10**). Compound **10** (118 mg) after 1 hr afforded ergosteryl-3β-ol-methylthiocarbonate (111 mg, 98 %), m.p. 124° (lit.[28], 125°), ν_{max} ($CHCl_3$) 1700 cm^{-1}.

Oxidation of xanthate (**11**). Compound **11** (118 mg) after 0.75 hr afforded 3-O-(methylthiocarbonyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (98 mg, 87 %), m.p. 76–78°, *m/e* 319 (M^+ − 15), 261, 201, 195, 113, 101 (100 %), and 75.

Oxidation of thiofenchone (**12**). Compound **12** (23 mg) after 42 hr afforded fenchone (5 mg, 23 %), ν_{max} (Neat) 1965, 1930, 1875, 1742, 1465, 1385, and 1025 cm^{-1}, S (3 mg, 75 %) and **3** (39 mg, 81 %). The low yield of fenchone is caused by its volatility.

Oxidation of di-t-Butythioketone (**13**). Compound **13** (197 mg) after 0.3 hr showed (glc) a quantitative conversion into di-t-butylketone, ν_{max} 1680 cm^{-1}. Plc (petroleum–ethyl acetate 9 + 1) afforded S (36 mg, 90 %) and **3** (330 mg, 96 %).

Oxidation of thiopiperidone (**14**). Compound **14** (115 mg) after 20 hr afforded 2-piperidone (86 mg, 87 %) as a colourless oil, ν_{max} (Neat) 3400–3250 and 1650 cm^{-1} identical to an authentic sample.

Oxidation of thiocamphor (**15**). Compound **15** (168 mg) after 2 hr afforded a mixture of **2** and camphor (10 % by glc) plus a non-polar product which appeared to be a diastereomeric mixture of *bis*-vinyldisulphides (116 mg, 70 %) which slowly converted on standing to **16**, m.p. 174–177° (lit.[9], 173–174° for an optically pure sample), δ 2.50 and 2.33 (s and distored d, integral ratio 1:1) and 2.2–0.6 (m). No S could be isolated.

Oxidation of phenylisothiocyanate. Phenylisothiocyanate (121 mg) after 0.25 hr afforded 1,3-diphenylurea (50 mg, 52 %) m.p. 236–238° (lit.[29c], 238–239°), *m/e* 212 (M^+), 119, 93 (100 %), 77, 66, and 65.

Oxidation of L-*cysteine hydrochloride* (**17**). L-Cysteine hydrochloride (**17**) (157 mg), **1** (197 mg) and NaOAc (82 mg) were stirred at room temp under N_2 in de-oxygenated water (7 ml) for 1.5 hr. The heterogeneous mixture was filtered, the insoluble white solid washed with water (2 × 2 ml), EtOH (2 × 2 ml) and finally $CHCl_3$ (4 × 2 ml) to afford L-cystine (95 mg, 79 %), m.p. 260° dec (lit.,[29d] 258–261° dec), ν_{max} (KBr) 2900 broad, 2030, 1620 shoulder, 1580 broad, 1470, 1400, 1380, 1335, 1295, 1190, 1120, 1085, 1035, 960, 875, 850, 780, and 680 cm^{-1}. The filtrate was *evaporated under reduced pressure*; column chromatography of the residue afforded **3** (121 mg, 68 %).

Oxidation of thiobenzyl alcohol (**18**). Compound **18** (0.10 ml) after 0.5 hr afforded **2** (84 mg, 58 %) and dibenzyldisulphide (100 mg, 96 %). Crystallisation from EtOH gave **2** (80 mg, 77 %) m.p. 68.5–70° (lit.,[29e] 71–72° and 69–70°), δ 7.27 (10 H, s) and 3.57 (4 H, s).

Oxidation of p-*thiocresol* (**19**). Compound **19** (246 mg) after 0.1 hr afforded **3** (270 mg, 76 %) and di-*p*-tolyldisulphide (239 mg, 98 %) m.p. 44–45°. Recrystallised from EtOH gave **3** (202 mg, 83 %) m.p. 47–47.5° (lit.,[29f] 48°), δ 7.37 (4 H, d, J 8 Hz), 7.05 (4 H, d, J 8 Hz), and 2.30 (6 H, s).

Oxidation of p-*aminothiophenol* (**20**). Compound **20** (200 mg) after 1 hr afforded **2** (246 mg, 85 %) and 4,4′-diaminodiphenyldisulphide (114 mg, 58 %), m.p. 73.5–75° (lit.,[29g] 85 and 106°), δ 7.77 (4 H, d, J 8 Hz), 6.57 (4 H, d, J 8 Hz), and 3.67 (4 H, broad s).

Oxidation of 1,4-*dihydroxybenzene* (**21**). Compound **21** (55 mg) and **1** (196 mg) were dissolved in $CHCl_3$ (2 ml) at ambient temp under N_2. After 0.25 hr the mixture was subjected to plc to afford **3** (8 mg, 5 %) and **24** (35 mg, 65 %), m.p. 114–115° (lit.,[29h] 115.7°).

Oxidation of 1,4-*dihydroxynapthalene* (**22**). Similarly **22** (80 mg) with **1** (196 mg) in $CHCl_3$ (2 ml) gave the telluride (96 mg, 56 %) and **25** (77 mg, 97 %), m.p. 122–125° which on recrystallisation (EtOH) gave yellow needles (60 mg, 76 %) m.p. 125–126° (lit.,[29h] 126°), δ 8.27–7.67 (4 H, m) and 7.00 (2 H, s).

Oxidation of 2,4-*Di*-t-*butylcatechol* (**23**). Similarly **23** (111 mg) with **1** (358 mg) in $CHCl_3$ (4 ml) afforded **26** (88 mg, 80 %) as a deep red crystalline solid, m.p. 112–114° (lit.,[31] 113–114°), δ 6.92 (1 H, d, J 2 Hz), 6.18 (1 H, d, J 2 Hz), 1.29 and 1.23 (both s, combined integral 18 H). No **3** was isolated.

Oxidation of **28**. Compound **28** (68 mg) and **1** (188 mg) were dissolved in CH_2Cl_2 (3 ml) at ambient temp under N_2. After 1 hr the mixture was filtered, the ppt washed with CH_2Cl_2 (2 × 2 ml) and the filtrate evaporated under reduced pressure to yield a red oil. Column chromatography of this oil afforded **3** (151 mg, 85 %). The white ppt, after drying under vacuum afforded *sym*-**32** (35 mg, 58 %), m.p. 242–243° (lit.,[32] 241°), *m/e* 240 (M^+), 222, 105 (100 %), and 77.

Oxidation of **29**. Compound **29** (166 mg) with **1** (376 mg) in $CHCl_3$ (4 ml) after 24 hr afforded *sym*-**33** (90 mg, 67 %), m.p. 165–167°, *m/e* 300 (M^+), 179, 151, 147, 133, 118, 107, 104 (100 %), and 77.

Oxidation of **30**. Compound **30** (166 mg) with **1** (376 mg) as above afforded **3** (315 mg, 92 %), *p*-anisic acid (9 mg, 6 %) and *sym*-**34** (120 mg, 86 %) m.p. 150–168°, *m/e* 300 (M^+).

Oxidation of **31**. Compound **31** (181 mg) with **1** (386 mg) afforded the telluride (312 mg, 91 %), *p*-nitrobenzoic acid (40 mg, 24 %), and *sym*-**35** (100 mg, 67 %), m.p. 187–194°.

General procedure for the oxidation of phenylhydrazines (**36–40**). The reactions were performed at room temp with 1.1 equivs of **1** under N_2 in CH_2Cl_2, 2 ml of solvent being used for every 0.50 mmol phenylhydrazine. N_2 was always evolved with 82 % of the theoretical amount being measured in the oxidation of phenylhydrazine (**36**). The crude mixtures were analysed by glc (2 m, column, 1/8″ o.d., 10 % OV-17 on Chromosorb using a gradient temp programme) for aromatic hydrocarbons and anisole. The amounts of aromatic hydrocarbons produced were estimated by comparing peak areas to those of standard solns of benzene, toluene, *m*-xylene and bromobenzene. The mixtures were then subjected to plc to isolate the organo-tellurium products.

Oxidation of phenylhydrazine (**36**). Compound **36** (121 mg) after 0.2 hr gave benzene (53 %) **3** (262 mg, 68 %) and *phenyl-p-methoxylphenyl-telluride* (101 mg, 29 %), m.p. 61–62° (from MeOH) (lit.,[33] 60.5–61.5°), δ 7.63 (d, J 8 Hz), 7.72–7.00 (m), 6.70 (d, J 8 Hz), combined intregral 9 H, and 3.73 (3 H, s), *m/e* 314 (M^+), 184 (100 %), 168, 141, and 77 (Found: C, 50.03; H, 3.86. Calc. for $C_{13}H_{12}OTe$: C, 50.07; H, 3.88 %).

Oxidation of p-*tolylhydrazine* (**37**). Compound **37** (61 mg) after 0.2 hr gave toluene (30 %), **3** (102 mg, 59 %) and p-*methyl*-p-*methoxydiphenyltelluride* (43 mg, 26 %), m.p. 65.5–67° (from MeOH) (lit.,[34] 64–64.5°), δ 7.67 and 7.47 (both d, J 9 Hz, combined integral 4 H), 6.93 and 6.70 (both d, J 9 Hz, combined ontegral 4 H), 3.77 (3 H, s), and 2.30 (3 H, s), *m/e* 328 (M^+), 210, 198 (100 %), 183, 145, 91, 77, and 65 (Found: C, 51.62; H, 4.31. Calc. for $C_{14}H_{14}OTe$: C, 51.60; H, 4.33 %).

Oxidation of 2,6-*dimethylphenylhydrazine* (**38**). Compound **38** (68 mg) after 0.2 hr gave *m*-xylene (70 %), **3** (126 mg, 74 %) and what appears to be 2,6-dimethylphenyl-4-methoxyphenyltelluride (9 mg, 5 %) as a colourless oil, *m/e* 342 (M^+, 100 %), 234, 212, 197, 105, 104, 79, and 77.

Oxidation of p-*bromophenylhydrazine* (**39**). Compound **39** (187 mg) after 2.5 hr gave bromobenzene (29 %), **3** (166 mg, 49 %) and p-*bromo*-p′-*methoxydiphenyltelluride* (120 mg, 31 %), m.p. 55.5–57° (MeOH), δ 7.64 (2 H, d, J 9 Hz), 7.43–7.13 (2 H, m), 6.71 (2 H, d, J 9 Hz), and 3.76 (3 H, s), *m/e* 394 (M^+), 264 + 262 (100 %), 249/247, 237/235, 222, and 92 (Found: C, 39.99; H, 2.80. Calc. for $C_{13}H_{11}BrOTe$: C, 39.96; H, 2.84 %).

Oxidation of p-*hydrazinobenzoic acid* (**40**). Compound **40** (152 mg) with **1** (394 mg) after 24 hr was poured into sat. K_2CO_3 aq, the phases separated and the aqueous phase extracted with CH_2Cl_2 (2 × 10 ml). The combined organic phases were dried over $NaSO_4$ and evaporated under reduced pressure. The residue afforded **3** (151 mg, 44 %). The aqueous phase, on acidification with HCl and extraction with CH_2Cl_2 gave a yellow solid (54 mg) which on sublimation gave benzoic acid (32 mg, 26 %), m.p. 122° (lit.,[28j] 122°).

Oxidation of phenylhydroxylamine. Phenylhydroxylamine (109 mg) with the **1** (376 mg) in $CHCl_3$ (4 ml) at room temp for 0.1 hr gave **3** (150 mg, 88 %) and nitrosobenzene (96 mg, 90 %), m.p. 66–67 (lit.,[29k] 67.5–68°).

Oxidation of benzophenone hydrazone. Benzophenone hydrazone (98 mg, 0.50 mmol) and **1** (197 mg, 0.55 mmol) were stirred in $CHCl_3$ (4 ml) for 22 hr. *p*-Anisic acid (152 mg, 1 mmol) was added to the deep red soln which was briefly heated to reflux and allowed to stir at room temp for 1 hr afforded the benzhydryl ester of *p*-anisic acid (122 mg, 77 %), m.p. 95–96° (lit.,[17] 96°), *m/e* 318 (M^+), 182, 167 (100 %), 166, 165, 135, 105, 91, and 77.

Preparation of 1,2-*dibromotetrachloroethane.* A stirred soln of tetrachloroethylene (10.22 ml) and Br_2 (2.58 ml) in CCl_4 (50 ml) was irradiated with a 500W lamp for 16 hr. The solvent was removed under reduced pressure to leave a white solid (24.55, 100 %), m.p. 104° softening from 95°.

Bromination of dianisyltelluride (**3**) *using* 1,2-*dibromotetrachloroethane.* Compound **3** (70 mg) and 1,2-dibromotetrachloroethane (67 mg) were stirred in petroleum for 16 hr. Filtration of the pale yellow solid and washing with petroleum (2 × 2 ml) gave 4,4′-dimethoxydiphenyl tellurium dibromide (82 mg, 80 %). The solid was recrystallised (chloroform/petroleum) to afford yellow needles, m.p. 192–200° (lit.,[35] 198°), δ 7.95 (4 H, d, J 9 Hz), 6.92 (4 H, d, J 9 Hz), and 3.83 (6 H, s).

General procedure for the catalytic oxidation of thiocarbonyl compounds (**5a**, **8**, *and* **5c** *using* 1,2-*dibromotetrachloroethane as brominating agent.* The thiocarbonyl compound was stirred in a two phase system of CH_2Cl_2 or $CHCl_3$ and aqueous base (K_2CO_3 or Et_3N) containing an excess of the dibromide and varying amounts of dianisyltellurium compound (dianisyltelluride or dianisyl tellurium dichloride). On completion of the reaction (plc petroleum to elute unreacted dibromide followed by petroleum-EtOAc 20 + 1) the phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 2 ml). The combined CH_2Cl_2

extracts were dried over $NaSO_4$ and the solvent evaporated under reduced pressure. Column chromatography (petroleum followed by petroleum-EtOAc 20 + 1) gave unreacted dibromide and oxo-derivative. The molar proportions of reactants, quantities of solvents, reaction times and product yields are given below:

(a) **5a** (0.49 mmol), dibromide (0.53 mmol), **3** (0.05 mmol), CH_2Cl_2 (5 ml), 10% K_2CO_3 aq (5 ml), 116 hr, cholesteryl benzoate (0.42 mmol, 88%).

(b) **5a** (0.40 mmol), dibromide (1.18 mmol), **3** (0.04 mmol), CH_2Cl_2 (5 ml), 10% K_2CO_3 aq (5 ml), 23 hr, cholesteryl benzoate (0.36 mmol, 90%).

(c) **5a** (0.40 mmol), dibromide (1.98 mmol), **3** (0.006 mmol), $CHCl_3$ (2 ml), 10% K_2CO_3 aq (5 ml), 88 hr, cholesteryl benzoate (0.30 mmol, 74%).

(d) **5a** (0.40 mmol), dibromide (2.01 mmol), **3** (0.006 mmol), $CHCl_3$ (2 ml), 20% K_2CO_3 aq (5 ml), 20 hr, cholesteryl benzoate (0.29 mmol, 70%).

(e) **5a** (0.40 mmol), dibromide (1.18 mmol), **3** (0.006 mmol), $CHCl_3$ (2 ml), 20% K_2CO_3 aq (5 ml), 80 hr, cholesteryl benzoate (0.29 mmol, 70%).

(f) **5a** (0.20 mmol), dibromide (1.00 mmol), dianisyl tellurium dichloride (0.02 mmol), $CHCl_3$ (2 ml), 20% K_2CO_3 aq (2.5 ml), 26 hr, cholesteryl benzoate (0.17 mmol, 87%).

(g) **5a** (0.20 mmol), dibromide (1.00 mmol), **2** (0.20 mmol), $CHCl_3$ (2 ml), Et_3N (1.00 mmol) in water (3 ml), 15 hr, cholesteryl benzoate (0.17 mmol, 85%).

(h) **5a** (0.20 mmol), dibromide (1.00 mmol), **2** (0.002 mmol), $CHCl_3$ (2 ml), Et_3N (1.00 mmol) in water (0.50 ml), 48 hr, cholesteryl benzoate (0.08 mmol, 41%), and **4a** (0.07 mmol, 36%).

(i) **8** (0.40 mmol), dibromide (2.00 mmol), **2** (0.006 mmol), $CHCl_3$ (2 ml), 20% K_2CO_3 aq (5 ml), 72 hr, cyclohexan-1,2-*trans*-diyl-dithiocarbonate (0.24 mmol, 60%).

(j) **5c** (0.40 mmol), dibromide (4.00 mmol), **2** (0.006 mmol), $CHCl_3$ (2 ml), 20% K_2CO_3 aq (5 ml), 72 hr, 5-cholesten-3β-thiol-benzoate (0.28 mmol, 70%).

(k) **5c** (0.40 mmol), dibromide (2.00 mmol), **2** (0.006 mmol), $CHCl_3$ (2 ml), 20% K_2CO_3 aq (5 ml), 15 hr, 5-cholesten-3β-thiol-benzoate (0.28 mmol, 70%).

Oxidation of di-t-butylthioketone (**13**). Compound **13** (63 mg), dibromide (654 mg), and **3** (2 mg) were stirred in a two phase system of $CHCl_3$ (2 ml) and K_2CO_3 aq (5 ml, 20%) for 15 hr. After this time the colour of the thioketone had been completely quenched. The phases were separated, the $CHCl_3$ phase dried over $MgSO_4$ and an IR spectrum of the crude $CHCl_3$ solution showed a strong band at 1683 cm^{-1} due to di-t-butylketone.

General procedure for the oxidation of thionbenzoate (5*a*) *using catalytic amounts of* **2**,[24] **42**,[36] **41**[37] and **43**.[38] Compound **5a** (0.20 mmol), diaryl tellurium dichloride (0.02 mmol), and 1,2-dibromotetrachloroethane (1.0 mmol) were stirred at room temp in a two phase system of $CHCl_3$ (2 ml) and K_2CO_3 (2.5 ml, 20%). The reaction times and yields of cholesteryl benzoate (where determined) are given below:

(a) Using **2** after 46 hr gave a 47% benzoate.

(b) Using **42** after 2 hr gave an 88% yield of benzoate.

(c) Using **41** after 20 hr gave an 88% yield of benzoate.

(d) Using diphenyl tellurium dichloride showed a trace of starting **5a** even after 92 hr.

Preparation of 4-methoxy-4'-N,N-dimethylaminodiphenyltelluroxide (**44**). 5-Methoxyphenyl tellurium trichloride[35] (2.00 g) and N,N-dimethylaniline (1.65 ml) were stirred together at room temp in a stoppered flask. The mixture rapidly became very viscous and the minimum amount of $CHCl_3$ was added to ensure adequate stirring. After 16 hr the reaction was filtered, the residue washed with ether (3 × 5 ml) and MeOH (3 × 5 ml) and dried under vacuum to afford **41** (1.22 g, 49%). Recrystallisation from MeOH gave yellow needles, m.p. 167–169° (lit.,[37] m.p. 170–172°), δ 7.86 and 7.73 (4 H, both d, J 9 Hz), 6.90 (2 H, d, J 9 Hz), 6.62 (2 H, d, J 9 Hz), 3.78 (3 H, s), and 3.00 (6 H, s), *m/e* 357 (M^+–Cl_2), 344, 272, 254 (100%), 237, 227 and 212 (Found: C, 42,24; H, 4.04; N, 3.07; Cl, 16.43. Calc. for $C_{15}H_{17}NOTeCl_2$: C, 42.31; H, 4.02; N, 3.29; Cl, 16.55%).

The above dichloride **41** (1.22 g) was stirred in NaOHaC (20 ml, 5%) at 80° for 0.75 hr. The reaction was cooled in an ice bath, filtered, the insoluble white solid washed with water (3 × 5 ml), and dried under vacuum over P_2O_5 to afford **44** (0.886 g, 84%), m.p. 209–210.5°, δ 7.64 and 7.56 (4 H, both d, J 9 Hz), 6.93 (2 H, d, J 9 Hz), 6.69 §2 H, d, J 9 Hz), 3.80 (3 H, s), and 2.99 (6 H, s).

Reaction of telluroxide (**44**) *with selenobenzoate* (**4b**). Compound **44** (102 mg) and **3b** (139 mg) were dissolved in $CHCl_3$ (2 ml) and stirred at room temp for 1 hr under a N_2. Filtration gave Se (18 mg, 90%) and plc (petroleum-EtOAc 9 + 1) afforded 5-α-cholestan-3β-ol benzoate (120 mg, 97%) and *4-methoxy-4'-N,N-dimethylaminodiphenyltelluride* (88 mg, 99%). Recrystallisation of the telluride from MeOH gave a colourless solid, m.p. 97–98°, δ 7.62 and 7.53 (4 H, both d, J 9 Hz), 6.68 and 6.53 (4 H, overlapping d, J 9 Hz), 3.72 (3 H, s) and 2.92 (6 H, s), *m/e* 357 (M^+), 250, 227 (100%), 212 and 113 (Found: C, 50.95; H, 4.87; N, 3.78. Calc. for $C_{15}H_{17}NOTe$: C, 50.76; H, 4.83; N, 3.95%).

Preparation of 4,4'-tetramethyldiaminodiphenyltelluroxide (**45**). 4,4'-Tetramethyldiaminodiphenyltellurium dichloride was prepared as described in the lit.[36] The dichloride (800 mg) was refluxed in NaOH aq (1.0 M, 10 ml) for 0.1 hr, cooled in an ice bath and filtered. The insoluble white solid was washed with cold water (2 × 5 ml) and dried under vacuum to afford **45** (570 mg, 81%), m.p. 225–227.5°, δ 7.54 (4 H, d, J 9 Hz), 6.73 (4 H, d, J 9 Hz) and 2.99 (12 H, s), *m/e* 370 (M^+ − 16), 240 (100%), 225 and 120.

Oxidation of dithiobenzoate (**5c**) *using telluroxide* (**45**). Compound **5c** (122 mg) and **45** (100 mg) were stirred in $CHCl_3$ (3 ml) for 27 hr (N_2). Plc (petroleum–EtOAc 19 + 1) afforded 5-cholesten-3β-thiol-benzoate (77 mg, 65%). Material which was assumed to be the tetramethyldiaminotelluride decomposed rapidly on the chromatographic plate.

Preparation of 4-(methyl phenoxyacetate) tellurium trichloride (**47**). Tellurium tetrachloride (11.4 g) and methyl phenoxyacetate (21.0 g) were refluxed in CCl_4 (175 ml) for 18 hr. The reaction was cooled in an ice bath and filtered to give the crude **47** (16.1 g, 96%) which was used in the following reaction without further purification.

Preparation of 4,4'-ditelluro-bis-(methyl phenoxyacetate) (**48**). Compound **47** (16.0 g) was stirred in a two phase system of CH_2Cl_2 (200 ml) and water (200 ml). $KHSO_3$ (4 g) was added in small portions over a period of 0.1 hr and the reaction stirred for a further 1 hr at room temp. The phases were separated, the aqueous phase extracted with CH_2Cl_2 and the combined organic extracts dried over $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure gave **48** as a red oil which slowly solidified (11.1 g, 95%), m.p. 68–74°, δ 7.67 (4 H, d, J 0 Hz), 6.70 (4 H, d, J 9 Hz), 4.55 (4 H, s), and 3.77 (6 H, s), *m/e* 590 (M^+), 460 (M^+–Te), 295, 257, 166 and 79 (100%). This was used without further purification in the following step.

Preparation of 4,4'-telluro-bis-(methyl phenoxyacetate (**49**). Compound **48** (1.90 g) and activated Cu powder[25] (0.62 g) were refluxed in dry dioxan (50 ml) for 2 hr under N_2. The reaction was filtered to remove a small amount of Te. Evaporation of the filtrate and column chromatography of the residue afforded *4,4'-telluro-bis-(methyl phenoxyacetate)* (**49**) (1.46 g, 98%), m.p. 108–109° (from MeOH), ν_{max} ($CHCl_3$) 2958, 1760, 1740 (shoulder), 1585, 1570, 1485, 1440, 1294, 1175 and 1085 cm^{-1}. δ 7.55 (4 H, d, J 9 Hz), 6.78 (4 H, d, J 9 Hz), 4.56 (4 H, s), and 3.76 (6 H, s) (Found: C, 47.24; H, 3.90. Calc. for $C_{18}H_{18}O_6Te$: C, 47.21; H, 3.96%).

Formation of the telluroxide (**46**). Compound **49** (2.67 g) was dissolved in benzene (80 ml) and treated with sulphuryl chloride (0.52 ml). After 0.5 hr the benzene was evaporated under reduced pressure to leave a sticky, white solid which defied all attempts at recrystallisation, ν_{max} (Film) 1756, 1584, 1575 (shoulder), 1490, 1438, 1215, 1180, 1076, 822, and 755, δ 7.96 (4 H, d, J 9 Hz), 6.95 (4 H, d, J 9 Hz), 4.83 (4 H, s), and 3.80 (6 H, s).

Cl, 16.43. Calc. for $C_{15}H_{17}NOTeCl_2$: C, 42.31; H, 4.02; N, 3.29; Cl, 16.65%).

The above dichloride **41** (1.22 g) was stirred in NaOH aq (20 ml, 5%) at 80° for 0.75 hr. The reaction was cooled in an under vacuum afforded **46** (2.88 g, 100%), m.p. 310°, ν_{max} (Nujol) 3520, 3400–3080 (broad), 1625, 1610, 1590, 1486, 1435, 1425, 1336, 1285, 1200, 1184, 1055, 830, and 820 cm^{-1}, δ (D_2O/external TMS) 7.62 (4 H, d, J OHz), 7.03 (4 H, d, J 9 Hz), and 4.48 (4 H, s).

Acknowledgement—We thank the S.R.C. for financial support.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 225 to 231, 1981
Printed in Great Britain

0040-4020/81/Suppl. 1-0225-07 $02.00/0
Pergamon Press Ltd.

REACTIONS OF STEROIDAL 1,3-DIKETONES WITH SULFUR TETRAFLUORIDE†

H. KAUFMANN, H. FUHRER and J. KALVODA*
Research Laboratories, Pharmaceuticals Division and Central Function Research, Ciba-Geigy Ltd., Basle, Switzerland

(*Received in Germany* 28 *July* 1980)

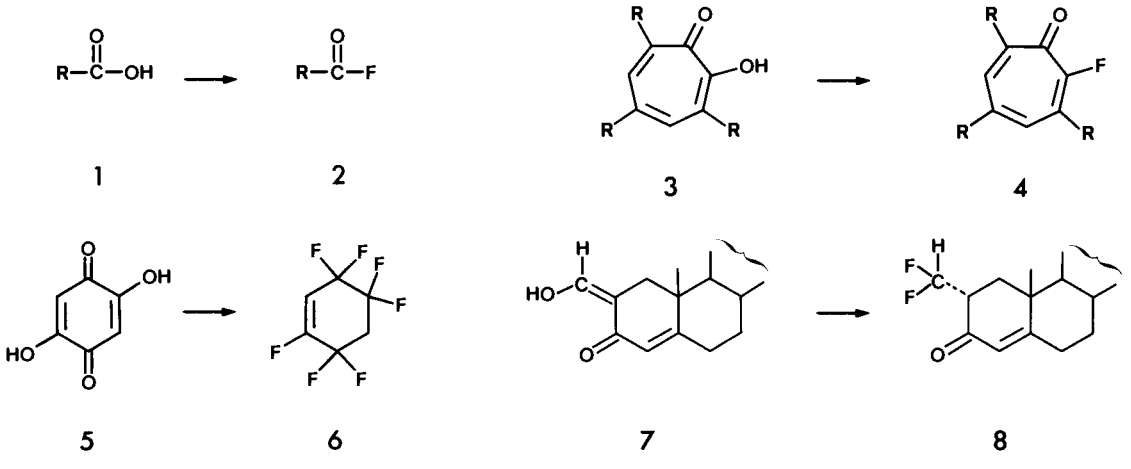
Abstract—Steroidal 1,3-diketones of type **9** and **15** have been used as substrates in the study of the reaction of enolizable β-diketones with sulfur tetrafluoride in benzene. In a smooth reaction β-fluoro-(**10**; **17**) and β-phenyl-(**11**; **18**) enones are generated. In the case of the ring-A-dione **15** in addition, the alkynyl acyl fluoride **16** is formed in 35% yield. The different products formally derive from the corresponding activated tautomeric enols. A unifying mechanism involving vinyl cation-type species **B** and **G** is discussed.

The pioneering observation of Fried *et al.*[2] concerning the enhancing effect of a 9α-F substituent on the anti-inflammatory activity of corticoids, has stimulated a world-wide search for further fluorinated analogues. Sulfur tetrafluoride[3] and its derivatives[4] hereby were often shown to be the reagents of choice for the synthesis of many novel classes of compounds in this field.[5]

Apart from the best-known reaction of sulfur tetrafluoride with CO groups, used for the generation of geminal difluoro compounds, the smooth conversion of carboxylic acids to acyl fluorides (**1** → **2**) and subsequently to trifluoromethyl derivatives, is of great preparative value. The readiness of OH groups in general to be substituted by F is believed to be dependent on their acidity. The completely enolized tropolones (**3**)[2], e.g. behave like carboxylic acids, their OH group being substituted by F (*cf* **4**),[2b] and some dihydroxy quinones of type **5** react with sulfur tetrafluoride in a similar way (→**6**).[2b] The enolized aldehyde group in **7**, on the other hand, has been converted into a difluoromethyl group (→**8**).[6]

Since steroidal β-fluoro-α,β-unsaturated ketones would constitute a class of compounds of potential biological interest, we have decided to study the reaction of the corresponding enolizable β-diketones with sulfur tetrafluoride.

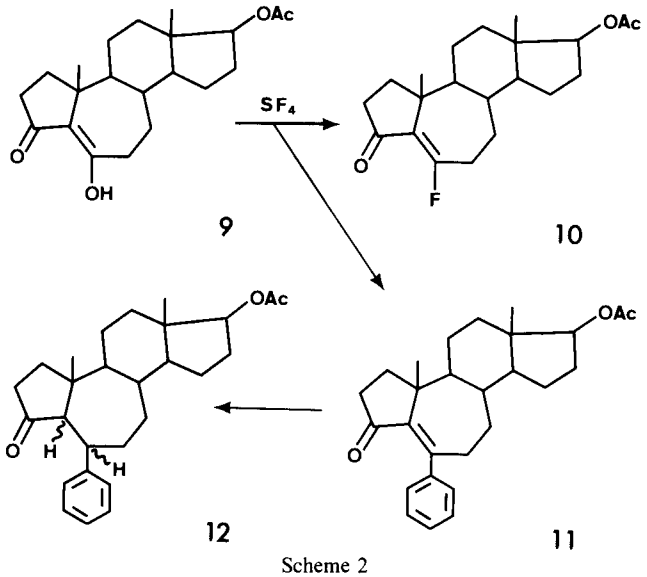
As a first substrate for the planned reactions the 10-*abeo*-steroid **9**[7] with a fixed *Z*-configuration at the enolic double bond‡ was chosen. By treating a solution



Scheme 1

†Presented in part (H.K.) at the Autumn Meeting of the Swiss Chemical Society, 9 October, 1976 in Geneva.

‡According to ^{1}H and ^{13}C NMR spectra (*cf* Table 1) the compound appears to be completely enolized, only one (=**9**) of the two possible tautomers being present in either $CDCl_3$ or DMSO solns.



Scheme 2

of compound **9** in anhydrous benzene† at room temperature for 210 min with sulfur tetrafluoride‡, two products were generated. The mixture was separated by chromatography and the structures of the individual compounds determined primarily on the basis of spectral data.

The more polar, main component of the mixture, formed in a yield of 65–70%, is an α,β-unsaturated ketone carrying a F atom in β-position to the CO group. ^{1}H-NMR, MS and UV data did not allow an unequivocal differentiation between the two possible isomeric formulas with the CO group in 3 or 5 position

Table 1. Characteristic chemical shifts in the ^{13}C–NMR spectra† of 5-substituted 17β-acetoxy-10(5 → 4)-*abeo*androst-4-en-3-ones. (Tentative assignment)

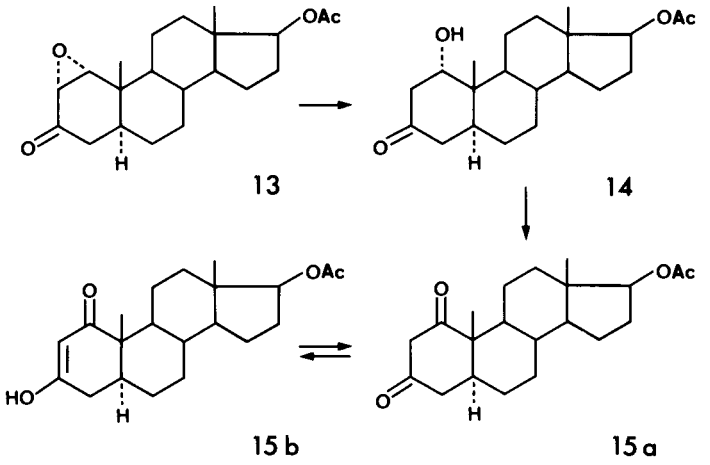
^{13}C \ Compd.	9	11	10
1	36.7	36.2	36.4
2	35.0	35.9	36.2
3	204.1	206.4	204.0
4	119.6	143.5	126.1 (J_{CF} = 2.8)
5	183.8	153.8	167.0 (J_{CF} = 288.8)
6	34.1	35.7	29.3 (J_{CF} = 26.6)
7	29.3	30.0	27.5 §
8	37.3	37.0	36.8
9	53.7	51.6	51.8
10	45.1	47.1	44.3 §
19	18.7	18.0	18.5 §

† δ in p.p.m. vs. TMS measured in $CDCl_3$; J_{CF} in Hz

§ long-range coupling

†On addition of various amounts of water-saturated benzene to the reaction mixture **11** was no longer formed while **10** was isolated in a significantly lower yield.

‡The reaction was performed at atmospheric pressure by an unconventional procedure (glassware, SF_4 bubbled through the soln).

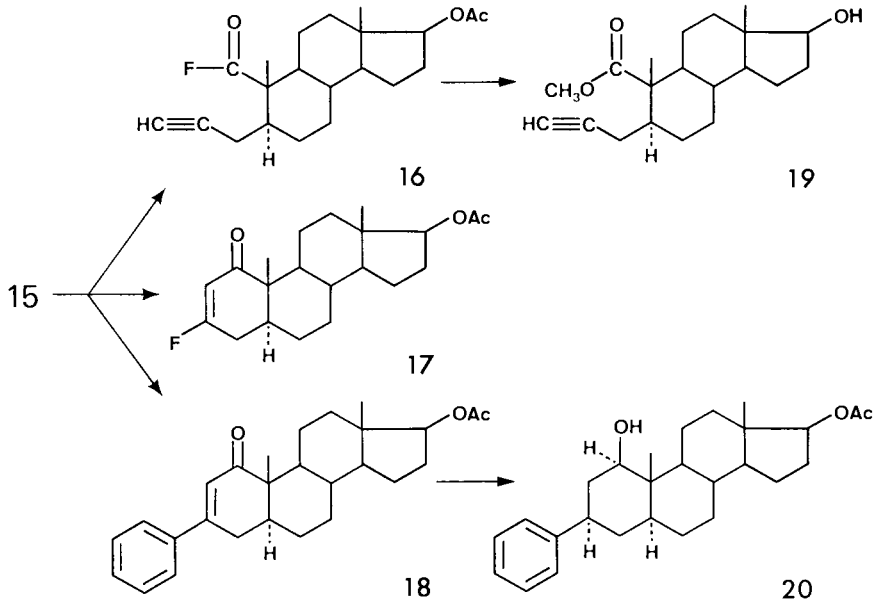


Scheme 3

respectively. The decisive arguments in favour of the desired 5-fluoro-10(5 → 4)-*abeo*androst-4-en-3-one structure **10**, were furnished by the ^{13}C-NMR spectrum (*cf* Table 1).

In the minor product (25%), a halogen-free unsaturated ketone, the OH function of **9** is formally substituted by a phenyl group. From the ^{1}H-NMR spectrum (360 MHz), in which the signal-pattern of the two C(2)-protons can be analyzed, structure **11** was deduced. This is confirmed by the ^{13}C-NMR data (Table 1), as well as by the IR spectrum of the hydrogenation product **12**, showing a single stretching band at 1730 cm^{-1}, corresponding to the overlapping absorptions of the 17-acetate and of a saturated cyclopentanone.

The high yields in the conversion of **9**→**10**, and the isolation of the interesting phenylated compound **11** stimulated the following experiments with an enolizable β-diketone containing a fixed *E*-configuration at the enolic double bond. The 17-acetoxy diketone **15**,[8]† easily available from the epoxy ketone **13** by hydrogenation to **14** and subsequent oxidation (Scheme 3), served as substrate for this second series of reactions. When compound **15** was treated with sulfur tetrafluoride under the same conditions, as described above for the keto-enol **9**, a mixture of *three* products was formed in a yield of approximately 70%. Using two different solvent-systems the mixture was separated by preparative tlc (*cf.* Scheme 4).



Scheme 4

†According to ^{1}H- and ^{13}C-NMR spectra the compound is completely enolized (*cf* structure **15b**) in DMSO, whereas in $CDCl_3$ only the diketo tautomer **15a** is observed.

Table 2. Characteristic chemical shifts in the ^{13}C–NMR spectra† of **15** and its reaction products. (Tentative assignment)

Compd. / ^{13}C	15 a	15 b	18	17	16
1	206.3	204.0	206.2	204.6	167.0 (J_{CF}=373.8)
2	56.2	102.4	129.7	108.2 (J_{CF}=10.3)	70.4
3	203.2	173.0	153.8	175.2 (J_{CF}=288.4)	81.7
4	30.3	29.8	30.3	31.4 (J_{CF}=18.3)	23.1
5	44.2	41.5	43.0	41.1 (J_{CF}=4.2)	42.7
6	27.6	27.1	28.3	27.7 (J_{CF}=9.2)	26.0
7	35.7	33.2	32.9	30.0	30.4
8	36.9	36.1	36.5	36.4	34.1
9	47.0	47.8	47.6	47.5	48.7
10	50.3	44.8	46.3	46.7	50.9 (J_{CF}=38.8)
19	11.2	11.3	10.7	10.9	9.9

† measured in $CDCl_3$ (15 b in DMSO); δ in p.p.m. vs. TMS; J_{CF} in Hz

The most lipophilic component, obtained in 30–35% yield, contains one F atom and one acetylenic group, but no unsaturated ketone. From spectral data (coupling of F with the C (10) carbon, a broad signal for the ethynylic hydrogen, a CO-band in the IR spectrum at 1820 cm^{-1}, corresponding to an acyl fluoride etc) structure **16** was deduced for the compound. In accord with this proposal, acid-catalyzed methanolysis of **16** furnished the expected methyl ester **19**.

The second product (20%) is a β-fluorinated α,β-unsaturated ketone. On account of the ^{13}C–NMR spectrum (*cf* Table 2) structure **17** is proposed for this compound. The isomer with the CO function in position 3 and the F at C(1) was not found.

Structure **18** was deduced for the last component of the original reaction mixture, a F-free phenylated compound on the ground of the spectral data and of its conversion to the tetrahydro derivative **20**. The position of the OH group in **20** was determined unambiguously by using the simple coupling pattern due to the geminal proton in the ^{1}H–NMR spectrum.

The results obtained in the reactions of sulfur tetrafluoride with compounds **9** and **15** have demonstrated that both types of β-diketones behave formally like vinylogous acids; the enolic OH group of the most stable tautomer being substituted by F (**10**, **17**). Under the specific reaction conditions used, no further fluorination of the second CO group takes place.

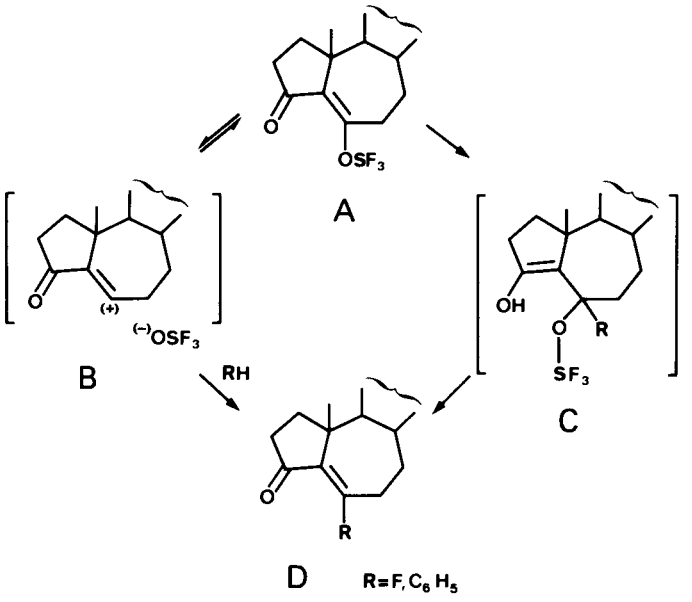
In this respect, the reaction of enolized β-diketones with SF_4 represents a short way to β-fluoro-enones. Another interesting aspect of both described cases, which might cast some light on the more detailed mechanism of the reaction of SF_4 with β-diketones is the generation of the β-phenylated ketones **11** and **18**, and of the fragmentation product **16**.

It is generally accepted[2] that the first step in the reaction of sulfur tetrafluoride with alcohols consists in the formation of an alkoxysulfur trifluoride intermediate (**a**), according to the following Scheme:

$$\geq C-OH + SF_4 \xrightarrow{-HF} \underset{\mathbf{a}}{\geq C-O-SF_3} \longrightarrow \geq C-F + SOF_2$$

S_N2- or S_Ni-type reactions have been postulated for the subsequent substitution of the OSF_3-group by F. But, as stated by Boswell *et al.*,[2a] there is most likely a continuum of mechanisms operative from S_Ni to S_N2.

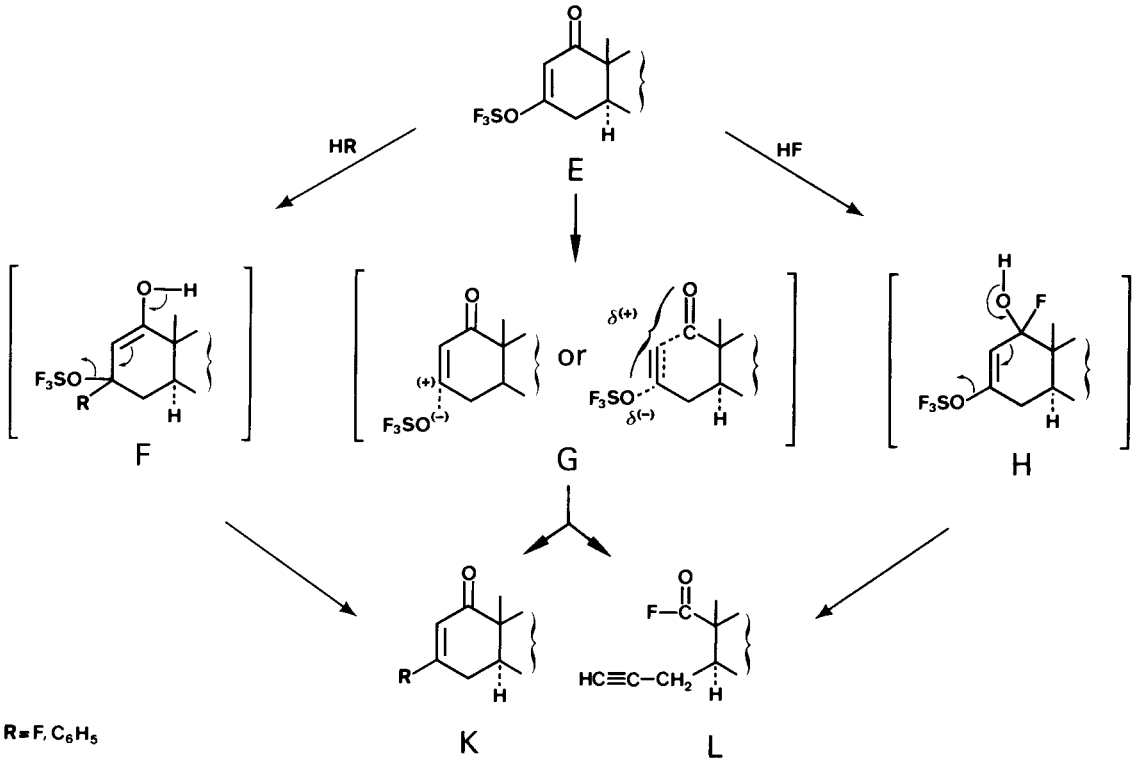
In the case of the alkoxysulfur trifluoride of type **A** (*cf* Scheme 5), most probably formed from the enol **9** in the first stage of the reaction, various "classical" mechanisms can be postulated for its transformation into 5-fluoro- and 5-phenyl-compounds **D** (*cf* **10** and **11**). A 1,4-addition of hydrofluoric acid across the α,β-unsaturated system, e.g. would generate the highly



Scheme 5

unstable enolic intermediate **C**, which would easily eliminate the elements of "hydroxysulfur trifluoride" (or one equivalent each of hydrofluoric acid and thionyl fluoride) to form the β-fluoro ketone **D** (R=F). It would be rather problematic to postulate a (HF-catalyzed) electrophilic attack on the benzene molecule by C(5) of **A**, to form the intermediate **C** ($R = C_6H_5$). Similar difficulties could arise, if one should postulate a primary interaction of sulfur tetrafluoride with the O of the CO function, followed by addition of the ate-complex to benzene.

Formally, a Friedel–Crafts-type reaction of a *vinyl cation* like **B**, would pose less problems. The F_3SO-anion should be an excellent leaving group and promote formation of such a highly reactive species. "Hot" vinyl cations[9] of this type have been postulated by Martin,[10] Schegolev,[11] Martens[12] *et al.*, as intermediates in the acyl chloride–$AlCl_3$ or acyl triflate-mediated acylations of alkynes. If these reactions were carried out in the presence of aromatic solvents, the corresponding β-aryl-α,β-unsaturated ketones have been also isolated.[11d]



Scheme 6

It would therefore seem reasonable to expect that similar vinyl cationic species, preferably as ion-pairs **B** or **G**† respectively are involved in the reactions of β-diketones described above. They could not only explain the generation of compounds of type **D** and **K**, but would also help to rationalize the fragmentation of **E** to the acyl fluoride **L**, which alternatively could be formed via the α-fluorohydrine **H** (cf. Scheme 6).

EXPERIMENTAL‡

(In collaboration with **O. Kopp**)

All the m.ps are uncorrected. Optical rotations were measured in $CHCl_3$ soln. ^{1}H-NMR spectra were obtained at 100 and/or 360 MHz with a Varian XL-100-15 and Bruker HX-360 spectrometer respectively in $CDCl_3$ soln, using TMS as internal standard; chemical shifts are reported in δ values (abbreviations: s singlet, d doublet, q quartet,§ m multiplet, **AB** AB-type signal pattern), coupling constants J in Hz. IR spectra were determined in CH_2Cl_2 on a Perkin–Elmer 540 E instrument. Mass spectra were taken on a Varian CH 7 mass spectrometer, and the UV spectra (in EtOH) on a Cary 118 Varian Spectrophotometer.

Reaction of 17β-acetoxy-5-hydroxy-10(5→4)-abeoandrost-4-en-3-one **9** *with* SF_4. A soln of **9**[7] (1,00 g) in anhyd. benzene (150 ml) was placed in a glass hydrogenation vessel connected on one side to a SF_4 cylinder, on the other side, via a reduction valve, to an aspirator (in a thoroughly ventilated hood). A gentle stream of pure SF_4 was bubbled through the soln and the progress of the reaction monitored by tlc [system: toluene–EtOAc (4:1)]. After about 180 min the gas supply was stopped and the closed vessel shaken for another 30 min. The mixture was flushed with N_2, diluted with ether-benzene, washed with ice-cold sat $NaHCO_3$aq and H_2O, dried over Na_2SO_4 and evaporated under vacuum. The crude amorphous product (1,10 g) was chromatographed on silica gel (50 g). The first fractions eluted with toluene-EtOAc (95:5) afforded 300 mg of *17β-acetoxy-5-phenyl-10(5→4)-abeoandrost-4-en-3-one* **11**, which was twice recrystallized from CH_2Cl_2-ether (211 mg)§§, m.p. 148–149°. $[\alpha]_D^{20} = -59°$ (c = 0.399); IR: 1730, 1710, 1620, 1380, 1120, 1040 cm^{-1}; NMR: 0.87 (3 H, s, CH_3-18), 1.29 (3 H, s, CH_2-19), 2.05 (3 H, s, CH_3-acetate), 2.45 + 2.64 (2 H, **AB**, CH_2–2; $J_{\alpha\beta}$ = 16.7, $J_{\alpha z} \simeq J_{\beta y} \simeq$ 11, $J_{\alpha y} \simeq J_{\beta y} \simeq$ 1.9), 4.62 (1 H, q, H–17α; $J_{\alpha\beta'}$ = 8.5, $J_{\alpha\alpha'}$ = 10.5), 7.0 + 7.25 (2 H + 3 H, m, aromatic protons); UV: λ_{max}240 (ε 5000), 253 (ε 5000), 272 (ε 5000), 360 (ε 280); MS (*m/e*): 406 (M), 391 (M–Me), 388 (M–H_2O; MI 370), 364 (M–C_2H_2O), 346 (M–AcOH), 198 (ring A + C(6) + C(7) + ∅). (Found: C, 79.80; H, 8.45%. $C_{27}H_{34}O_3$ Requires: C, 79.76; H, 8.43%).

From later fractions eluted with the same solvent crude crystalline *17α-acetoxy-5-fluoro-10(5→4)-abeoandrost-4-en-3-one* **10** (790 mg) was obtained. It was twice recristallized from CH_2Cl_2-ether (579 mg), m.p. 156–157°. $[\alpha]_D^{20} = -47°$ (c = 1.125); IR: 1720, 1645, 1032, 868 cm^{-1}; UV: λ_{max} 245 (ε 9100), 290 (sh); NMR: 0.84 (3 H, s, CH_3–18), 1.18 (3 H, s, CH_3–19), 2.03 (3 H, s, CH_3–acetate), 2.13–2.55 (5 H, m, CH_2–2 + CH_2–6 + ?); 4.16 (1 H, q, H–17α; $J_{\alpha\alpha'}$ = 10.5, $J_{\alpha\beta'}$ = 8.5). MS (*m/e*): 349 (M + H), 348 (M), 328 (M–HF, MI 309.5), 306 (M–C_2H_2O), 288 (M–AcOH), 268 (328–AcOH, MI 219), 253 (268–Me, MI 239). (Found: C, 72.28; H, 8.48; F, 5.40%. $C_{21}H_{29}O_3F$ Requires: C, 72.39; H, 8.39; F, 5.45%).

Hydrogenation of 17β-acetoxy-5-phenyl-10(5→4)-abeoandrost-4-en-3-one **11**. Compound **11** (100 mg) was dissolved in EtOH (25 ml) and hydrogenated in the usual way, using 10% Pd/C (30 mg) as catalyst. Absorbed: 5.71 ml; calculated: 5.52 ml H_2. The mixture was filtered, the solvent evaporated and the isomeric *17β-acetoxy-5ξ-phenyl-10(5→4)-abeo-4ξ-androstan-3-ones* **12** recrystalized twice from CH_2Cl_2–ether–light petroleum to yield a single compound (16 mg), m.p. 148–150°. IR: 1730, 1601, 13781, 1125, 940 cm^{-1}; MS (*m/e*) 408 (M), 393 (M–Me), 390 (M–H_2O), 348 (M–AcOH); MI 297), 330 (348–H_2O).

17β-Acetoxy-1α-hydroxy-5α-androstan-3-one **14**. 17β-Acetoxy-1α,2-epoxy-5α-androstan-3-one[8] (1.00 g) was dissolved in a mixture of THF (20 ml) and EtOH (10 ml) and hydrogenated in the presence of a 5% Pd/C-catalyst (1.00 g!). Absorbed: 70.5 ml; calculated: 64.8 ml H_2. The filtered soln was evaporated under vacuum and the crude product recrystallized from $CHCl_3$–MeOH–ether, yielding 842 mg of pure **14**, m.p. 237–241° (lit.[8]: 231–234°). $[\alpha]_D^{20} = +25°$ (c = 1,534). IR: 3600, 1730, 1715, 1230, 1110, 1030 cm^{-1}; NMR (d_5-pyridine): 0.85 (3 H, s, CH_3 18 or CH_3–19), 1.01 (3 H, s, CH_3–19 or CH_3–18), 2.01 (3 H, s, Me–acetate), 2.32 + 2.73 (2 + 2 H, m, CH_2–2 + CH_2–4), 4.21 (1 H, m, H-1β), 4.72 (1 H, q, H–17α), 6.45 (1 H, d, OH). (Found C, 72.56; H, 9.31%. $C_{21}H_{32}O_4$ Requires: C, 72.38; H, 9.26%).

17β-Acetoxy-5α-androstane-1,3-dione[8] **15**. To a cooled (0–4°) stirred soln of hydroxy ketone 14 (500 mg) in acetone (50 ml) a small excess (0.5 ml) of Kiliani's chromic acid soln[13] was added. After 20 min the residual reagent was reduced by MeOH, ice-cold H_2O was added and the resulting suspension extracted into CH_2Cl_2–ether. The organic layer was washed with sat $NaHCO_3$aq and H_2O, dried over Na_2SO_4 and evaporated under vacuum. The crude product (290 mg) was recrystallized from CH_2Cl_2–ether to give **15** (189 mg), m.p. 212–213° (lit.[8]: 210–212°). $[\alpha]_D^{20} = +93°$ (c = 0.774); IR: 1727, 1703, 1245, 1060, 1043, 1030, 1017 cm^{-1}; UV (EtOH): λ_{max} 253 (ε 13 450); (EtOH + NaOH): λ_{max} 283 (ε 24 800); NMR: 0.82 (3 H, s, CH_3–18), 1.32 (3 H, s, CH_3–19), 2.04 (3 H, s, CH_3–acetate), 2.17 (1 H, m, H–11α ?), 2.42 (α) + 2.54 (β) (2 H, AB, CH_2–4; $J_{\alpha\beta}$ = 18, $J_{\alpha\alpha'}$ = 4.5, $J_{\alpha\alpha''}$ = 1.8, $J_{\beta\alpha'}$ = 13, 3.23(α) + 3.68 (β) (2 H, AB, CH_2–2; $J_{\alpha\beta}$ = 17, $J_{\alpha\alpha'}$ = 1.8), 4.59 (1 H, q, H–17α; $J_{\alpha\alpha'}$ = 11.5, $J_{\alpha\beta'}$ = 9); NMR (DMSO): 0.75 (3 H, s, CH_3–18), 0.92 (3 H, s, CH_3–19), 1.98 (1 H, s, CH_3–acetate), 4.50 (1 H, q, H–17α; $J_{\alpha\alpha'}$ = 10, $J_{\alpha\beta'}$ = 7), 4.96 (1 H, br. s, H–2), (Found: C, 72.90; H, 8.62%. $C_{21}H_{30}O_4$ Requires: C, 72.80; H, 8.73%).

Reaction of 17α-acetoxy-5α-androstane-1,3-dione **15** *with* SF_4. Under the same conditions as described for **9**, a soln of **15** (1.00 g) in anhyd benzene (200 ml) was treated with SF_4 for 210 min. The progress of the reaction was monitored by tlc [system: toluene–EtOAc (4:1)]. The mixture was flushed with N_2, diluted with ether-benzene, washed with ice-cold $NaHCO_3$aq and H_2O, dried over Na_2SO_4 and evaporated under vacuum. The crude product (920 mg) was separated on six TL-plates [100 cm; silicagel PF 254; 1,5 mm thick; system: toluene–EtOAc (90:10)] into two zones.

The less polar zone was eluted with toluene–EtOAc mixtures to give *17β-acetoxy-1,2-seco-5α-androst-2-yn-1-oic acid fluoride* **16** (400 mg), which was crystallized from ether–light petroleum (300 mg), m.p. 93–95°. $[\alpha]_D^{20} = -11°$ (c = 1.061); IR: 3300, 2120, 1820, 1727, 1242, 1050, 1040, 1030 cm^{-1}; NMR: 0.78 (3 H, s, CH_3–18), 1.09 (3 H, s, CH_3–19), 2.01 (3 H, s, CH_3–acetate), 2.07 (1 H, m, H–C≡C), 4.58 (1 H, q, H–17α; $J_{\alpha\alpha'}$ = 11, $J_{\alpha\beta'}$ = 8); MS (*m/e*): 348 (M), 333 (M–Me), 328 (M–HF), 313 (328–Me), 300 (328–CO?), 288 (M–AcOH), 273 (288–Me; MI 259), 268 (288–HF). (Found: C, 72.69; H, 8.54%. $C_{21}H_{29}FO_3$ Requires: C, 72.39; H, 8.39%).

The second zone afforded a mixture of two compounds (320 mg) which was separated by a second preparative tlc [system: light petroleum–MeOH (95:5)–4x″ to top″].

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†The optimal stereo-electronic arrangement in **G** should favour participation of the lone electron-pairs on the CO oxygen in the stabilization of the vinyl cation.

‡The elemental analyses were carried out in our Analytical Laboratories (direction of Dr. W. Padowetz). Special determinations were performed in the Spectroscopy Laboratories (Dr. H. Hürzeler, S. Moss).

§Doublet of doublets.

§§From other fractions and from the mother liquors additional amounts of less pure product were obtained.

The slightly less polar component (242 mg) was recrystallized from CH_2Cl_2–ether–light petroleum, yielding 17α-acetoxy-3-fluoro-5α-androst-2-en-1-one **17** (185 mg) m.p. 155–156°. $[\alpha]_D^{20} = +98°$ ($c = 1.394$). IR: 1725, 1680 (sh), 1670, 1375, 1358, 1158, 1042, 1032, 1020 cm^{-1}: UV: λ_{max} 224 (ε 8900), 282 (ε 25); NMR: 0.81 (3 H, s, CH_3–18), 1.06 (3 H, s, CH_3–19), 2.03 (3 H, s, CH_3–acetate), 2.49 (2 H, m, CH_2–4), 4.58 (1 H, q, H–17α; $J_{\alpha\alpha'} = 10$, $J_{\alpha\beta'} = 8$), 5.50 (1 H, q, H–2; $J_{HF} = 14$, $J_w = 2$); MS (*m/e*): 348 (M), 333 (M–Me), 305 (M–MeCO), 288 (M–AcOH; MI 238), 273 (288–Me; MI 259). (Found: C, 72.47, H, 8.42%. $C_{21}H_{29}FO_3$ Requires: C, 72.39; H, 8.39%).

The most polar compound (116 mg) was recrystallized from CH_2Cl_2–ether–light petroleum and gave the pure *17β-acetoxy-3-phenyl-5α-androst-2-en-1-one* **18** (80 mg), m.p. 205–206°. $[\alpha]_D^{20} = +130°$ ($c = 0.496$); IR: 1725, 1615, 575, 1495, 1240, 1070, 1040, 1030, 1020 cm^{-1}; UV: λ_{max} 219 (ε 9 250), 280 (ε 18 900); NMR: 0.82 (3 H, s, CH_3–18), 1.09 (3 H, s, CH_3–19), 2.02 (3 H, s, CH_3–acetate), 2.54 (3 H, m, CH_2–4 + ?), 4.59 (1 H, s, H–17α; $J_{\alpha\alpha'} = 10$, $J_{\alpha\beta'} = 8$), 6.25 (1 H, br. s, H–2), 7.37 + 7.51 (5 H, m, aromatic protons); MS (*m/e*): 406 (M), 391 (M–Me), 388 (M–H_2O), 378 (M–28), 363 (M–MeCO), 346 (M–AcOH), 198, 185, 184. (Found: C, 79.80; H, 8.36%. $C_{27}H_{34}O_3$ Requires: C, 79.76; H, 8.43%).

Methyl 17β-hydroxy-1,2-seco-5α-androst-2-yn-1-oate **19**. A soln of **16** (100 mg) and *p*-toluenesulfonic acid (10 mg) in MeOH (10 ml) was heated under reflux for 66 hr†, the cool mixture poured into stirred ice-cold $NaHCO_3$aq and extracted twice with $CHCl_3$. The organic layers were washed with water, dried and evaporated under vacuum, yielding a mixture of three products (80 mg). This was chromatographed on silica gel (10 g) in toluene and toluene–EtOAc (90:10). The combined more polar fractions afforded after recrystallization from CH_2Cl_2–ether **19** (36 mg), m.p. 146–148°. $[\alpha]_D^{20} = +2°$ ($c = 0{,}500$); IR: 3600, 3300, 2120, 1720, 1170, 1135, 1100, 1078, 1055, 1026 cm^{-1}; NMR: 0.74 (3 H, s, CH_3–18), 1.05 (3 H, s, CH_3–19), 2.02 (1 H, m, H–C≡C–), 3.68 (1 H, q, H–17α), 3.70 (3 H, s, MeO–); MS (*m/e*): 318 (M), 303 (M–Me), 300 (M–H_2O), 286 (M–MeOH), 259 (M–$COOCH_3$), 241 (259–H_2O). (Found: C, 75.20; H, 9.52%. $C_{20}H_{30}O_3$ Requires: C, 75.43; H, 9.49%).

3β-Phenyl-5α-androstane-1β,17β-diol 17-acetate **20**. Compound **18** (200 mg) was dissolved in EtOH (50 ml) and hydrogenated in the presence of 10% Pd/C-cytalyst (60 mg!). The hydrogenation was stopped after 1.5 equiv of H_2 were absorbed. The filtrated soln was evaporated in vacuum, affording a mixture of three products, which was subsequently chromatographed [20 g silicagel; eluant: toluene and toluene–EtOAc (95:5)]. After separation of the residual crude **18** (about 10%) **20** (157 mg) was obtained, and purified by crystallization from CH_2Cl_2–ether (97 mg), m.p. 206–208°. $[\alpha]_D^{20} = -3°$ (0,346); IR: 3590, 1725, 1602, 1220, 1155, 1030, 1000 cm^{-1}; NMR: 0.81 (3 H, s, CH_3–18), 0.94 (3 H, s, CH_3–19), 2.04 (3 H, s, CH_3–acetate), 2.7 (1 H, m, H–3α), 3.62 (1 H, m, H–1α), 4.52 (1 H, q, H–17α; $J_{\alpha\alpha'} = 10$, $J_{\alpha\beta'} = 8$), 7.28 (5 H, m, aromatic protons). NMR (after addition of TAI): 4.92 (1 H, q, H–1α; $J_{\alpha\alpha'} = 5$, $J_{\alpha\beta} = 12$). (Found: C, 78.91; H, 9.23%. $C_{27}H_{38}O_3$ Requires: C, 78.98; H, 9.33%).

†The reaction was monitored by tlc [toluene-ethyl acetate (4:1)] and by IR spectroscopy. The first step consists in saponification of the 17-acetoxy group, followed by hydrolysis of the acyl fluoride.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 233 to 240, 1981
Printed in Great Britain.

0040-4020/81/Suppl. 1-0233-08 $02.00/0
Pergamon Press Ltd.

THE METABOLITES OF THE MARINE MOLLUSCS *TRIDACHIELLA DIOMEDEA* AND *TRIDACHIA CRISPATA*

CHRIS IRELAND and JOHN FAULKNER*
Scripps Institution of Oceanography, La Jolla, CA 92093, U.S.A.

(*Received in U.S.A.* 5 *June* 1980)

Abstract—Tridachione (**1**) and 9,10-deoxytridachione (**2**) were isolated from *Tridachiella diomedea* collected from the Gulf of California. The corresponding mollusc from the Caribbean, *Tridachia crispata*, contained crispatone (**13**) and crispatene (**14**). The structures of tridachione (**1**) and crispatone (**13**) were determined by X-ray crystallographic studies. The structures of 9,10-deoxytridachione (**2**) and crispatene (**14**) were elucidated from spectral data and chemical interconversions. Photolysis of 9,10-deoxytridachione (**2**) gave a single photoproduct **18** having the bicyclohexene ring system of crispatene (**14**).

Studies of the chemistry of opisthobranch molluscs have shown them to be a most interesting group of invertebrates.[1] Unlike other molluscs, opisthobranchs lack the protection of an external shell and use other forms of defense against predators. One of the most common forms of defense is the use of toxic or noxious chemicals, often derived from a dietary source.[2] The sea hares consume large quantities of algae and can store the unsavory constituents from their algal diet in a digestive gland. The nudibranchs feed on sponges and have been shown to use sponge metabolites in their defensive secretions.[3] We have been particularly interested in the chemistry of a group of sacoglossans that contain functional chloroplasts derived from siphonous marine algae.[4] These sacoglossans appear to be almost independent of an external food source as they employ the photosynthetic ability of the chloroplasts to produce primary metabolites from dissolved inorganic carbonate. Since these sacoglossans lack both physical defense mechanisms and dietary-derived chemical defense mechanisms, we suspected that they might be capable of synthesizing the constituents of a chemical defense mechanism.

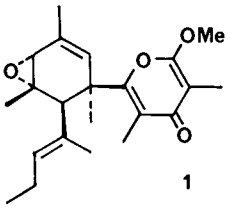
Tridachiella diomedea (Bergh),[5] commonly known as the "Mexican Dancer," was collected in shallow water (−2 m) in the Gulf of California and on the Pacific coast of Panama and El Salvador. *Tridachia crispata* (Mörch)[6] was collected in shallow water at Glover Reef, Belize and on the Caribbean coast of Panama. Despite the physically different habitats, these two sacoglossans are quite similar in appearance and behavior. In two recent communications,[7,8] we have reported the major metabolites of each sacoglossan. The metabolites were structurally dissimilar but had similar biosynthetic origins. In this paper we will describe structural elucidations and chemical reactions of the metabolites of *Tridachiella diomedea* and *Tridachia crispata*.

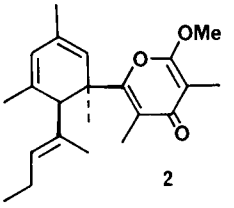
The metabolites of Tridachiella diomedea

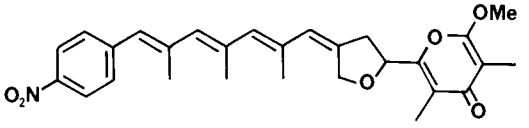
The ether soluble material from an acetone extract of homogenized *T. diomedea* was chromatographed on silica gel to obtain tridachione (**1**) (~1.0 mg/animal) and 9,10-deoxytridachione (**2**) (~0.75 mg/animal). Tridachione (**1**) had the molecular formula $C_{22}H_{30}O_4$ indicating the presence of eight unsaturation equivalents. The ^{13}C NMR spectrum contained a CO carbon signal at δ 181.1 (s) and olefinic carbon signals at 161.0 (s), 160.1 (s), 132.5 (s), 131.6 (d), 129.0 (d), 128.5 (s), 118.4 (s) and 97.8 (s); tridachione (**1**) was therefore a tricyclic molecule. The presence of a α-methoxy-β,β'-dimethyl-γ-pyrone ring system could be inferred by comparing the ^{13}C NMR spectrum with that of spectinabilin (**3**)[9] (Table 1). The signals at δ 60.5 (s) and 54.7 (d) suggested the presence of a trisubstituted epoxide ring. Thus, the third ring must be carbocyclic.

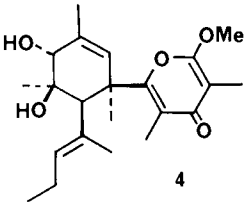
The presence of the epoxide ring was confirmed by treatment of tridachione (**1**) with aqueous acid to obtain the diol **4**. The ^1H NMR spectrum of the diol **4** was similar to that of tridachione (**1**) with the exception of the presence of a new allylic α-OH proton signal at δ 5.48 (s, 1 H) in place of the α-epoxy proton signal of tridachione. Oxidation of the epoxide functionality in tridachione (**1**) with periodic acid in ether gave a keto-aldehyde **5** (IR 1710, 1680 cm^{-1}) having the molecular formula $C_{22}H_{30}O_5$. Since cleavage of the epoxide ring did not result in loss of C atoms from the molecule, the epoxide ring must be fused to the carbocyclic ring. The ^1H NMR spectrum of the keto-aldehyde **5** contained an aldehyde signal at δ 9.41 (s, 1 H), a vinyl proton signal at 6.92 (s, 1 H) due to the β-proton on an α,β-unsaturated aldehyde and a signal at 3.86 (s, 1 H) due to a proton on the α-carbon of a β,γ-unsaturated ketone. We did not observe the expected methyl ketone signal in the 2.0 ppm region; in retrospect, we must assume that the Me group was shielded by either the pyrone ring or an olefinic bond and gave a signal in the 1.7–1.86 ppm region.

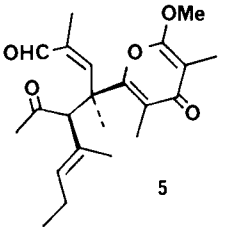
With the exception of the signals due to the 1-methylbutene side-chain [δ 0.68 (t, 3 H, J = 7 Hz), 2.05 (m, 2 H), 5.18 (t, 1 H, J = 7 Hz)], the ^1H NMR spectrum of tridachione (**1**) consisted of seven three-proton singlets and three one-proton singlets. The lack of coupling between the remaining signals in the ^1H NMR spectrum of tridachione (**1**) prevented structural elucidation by interpretation of spectral data. Fortunately, treatment of tridachione (**1**) with boron trifluoride etherate in dry ether at 0° gave a crystalline isomeric diketone **6** whose structure and relative stereochemistry were determined by a single crystal X-ray diffraction study.[7] Since the boron trifluoride catalyzed rearrangement of cyclic epoxides to ketones has been shown to be a highly stereospecific reaction involving a suprafacial proton migration,[10] the

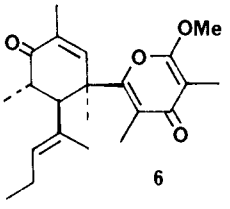








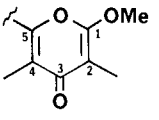




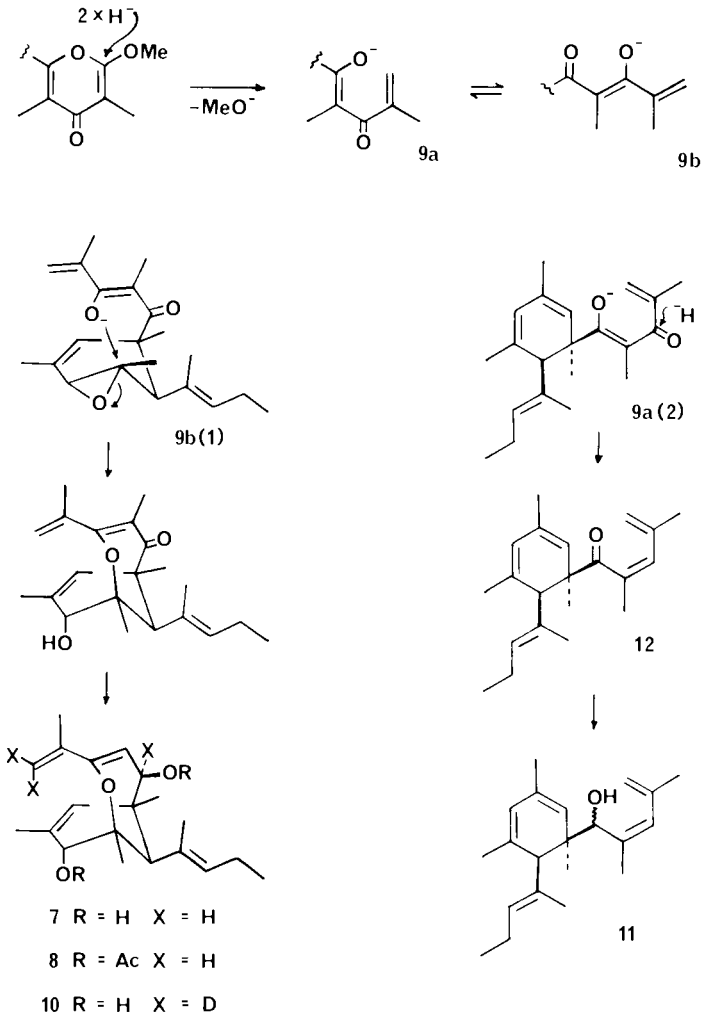
structure and stereochemistry of tridachione (**1**) were assigned as shown.

9,10-Deoxytridachione (**2**) had the molecular formula $C_{22}H_{30}O_3$. The spectral data suggested that the relationship of tridachione (**1**) to 9,10-deoxytridachione (**2**) was that of an epoxide to the corresponding olefin. In particular, the ^{1}H NMR spectrum of 9,10-deoxytridachione (**2**) contained an additional vinyl proton signal at either δ 5.56 (s, 1 H) or 5.65 (s, 1 H) and lacked an α-epoxy proton signal while the ^{13}C NMR spectrum contained two additional olefinic signals at the expense of two signals in the δ 50–65 region. The structure of 9,10-deoxytridachione (**2**) was confirmed by synthesis. Reduction of

Table 1. Comparison of the ^{13}C NMR data for the α-methoxy-γ-pyrone ring in spectinabilin (**3**), tridachione (**1**), 9,10-deoxytridachione (**2**), crispatone (**13**) and crispatene (**14**)



	3	1	2	13	14
C-1	162.1	161.0	161.7	162.2	162.0
C-2	99.1	97.8	98.8	100.0	99.2
C-3	180.6	181.8	181.8	181.1	181.2
C-4	119.9	118.4	120.0	121.0	120.1
C-5	155.2	160.1	161.1	157.7	159.9
OCH_3	55.3	57.6	59.6	55.0	54.9
CH_3-2	6.9	6.1	6.8	6.6	6.5
CH_3-4	9.4	11.6	12.2	10.5	12.7



Scheme 1. The reduction of tridachione (**1**) and 9,10-deoxytridachione (**2**) with lithium aluminum hydride.

tridachione (**1**) with zinc dust in the presence of sodium iodide and sodium acetate in acetic acid[11] gave 9,10-deoxytridachione (**2**) identical in all respects to the natural product.

The α-methoxy-β,β′-dimethyl-γ-pyrone ring system was unaffected by most reagents but could be reduced with LAH. Reduction of tridachione (**1**) with LAH in refluxing ether gave the diol **7**. The diol **7** had the molecular fomula $C_{21}H_{32}O_3$ which, together with the ^{1}H NMR data, indicated a reductive elimination of the OMe group. The ^{13}C NMR spectrum contained eight olefinic C signals including signals at δ 156.7 (s) and 99.8 (s) that could be assigned to an enol ether moiety and signals at 146.8 (s) and 108.2 (t), assigned to a terminal methylene group. The ^{13}C NMR spectrum contained additional signals at 84.5 (s), 76.8 (d) and 73.5 (d) that suggested the presence of a tertiary ether linkage and two secondary alcohols. This assignment was confirmed by the conversion of the diol **7** into the corresponding diacetate **8** using acetic anhydride in pyridine at 25°. Since the ^{13}C NMR spectrum contained eight olefinic carbons and the molecular formula demanded six unsaturation equivalents, the diol **7** must be bicyclic. The ^{1}H NMR spectrum of diol **7** contained terminal methylene proton signals at δ 4.82 (s, 1 H) and 5.07 (s, 1 H), two additional olefinic protons at 5.27 (t, 1 H, J = 7 Hz) and 5.76 (s, 1 H) and two α-OH proton signals at 3.59 (d, 1 H, J = 7 Hz) and 4.98 (s, 1 H), the latter signals being shifted to 4.80 (s, 1 H) and 6.18 (s, 1 H) in the coresponding acetate **8**. The proposed mechanism of formation of diol **7** is shown in Scheme 1. The epoxide ring was protected from hydride attack by the pyrone ring and the 1-methylbutene group. However, the enolate anion **9b** was ideally positioned for nucleophilic attack at C-10. The alternative reaction of enolate anion **9a** with the epoxide ring would have given a cross-conjugated dienol; however, the ultraviolet band at 240 nm was consistent with a conjugated dienol. In order to confirm the spectral interpretation and mechanistic assumptions, tridachione (**1**) was reduced with lithium aluminum deuteride in refluxing ether to obtain a d_3-diol **10**. As expected, the ^{1}H NMR spectrum of the d_3-diol **10** lacked the signals at δ 4.82, 4.98 and 5.07 that corresponded to the terminal methylene protons and the C-5 α-OH proton.

Reduction of 9,10-deoxytridachione (**2**) with LAH in refluxing ether gave a 1:1 mixture of two isomeric alcohols **11**. The alcohol mixture was oxidized with Jones' reagent to obtain a single conjugated dienone **12** (λ_{max} 275 nm). The production of a mixture of alcohols can be explained by assuming the reduction mechanism shown in Scheme 1. The intermediate **9** was reduced at C-3 (**9a**) rather than C-5 (**9b**) to obtain the conjugated dienone **12** as an intermediate. Reduction of dienone **12** gave both diastereoisomeric alcohols. The ^{1}H NMR spectrum of the mixture of alcohols contains two signals at δ 5.37 (s, 0.54 H) and 5.32 (s, 0.46 H) due to the proton at C-7, two signals at δ 2.51 (s, 0.46 H) and 2.48 (s, 0.54 H) due to the doubly allylic proton at C-11, the α-OH proton signal at 4.30 (s, 1 H), two terminal methylene proton signals at 4.88 (s, 1 H) and 5.03 (s, 1 H) and three additional olefinic signals at 5.55 (s, 1 H), 5.53 (s, 1 H) and 5.14 (m, 1 H). In the ^{1}H NMR spectrum of the dienone **12**, the β-vinyl proton signal was shifted downfield to δ 6.50 (s, 1 H) while the terminal methylene protons were at δ 5.37 (s, 1 H) and 5.44 (s, 1 H). The chemical shift of the β-vinyl proton signal suggested the *Z* stereochemistry about the $^3\Delta$-olefinic bond.[12]

The metabolites of Tridachia crispata

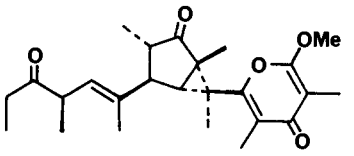
The ether-soluble material from the acetone extraction of homogenized *T. crispata* was chromatographed on silica gel to obtain crispatone (**13**) ($\sim$0.12 mg/animal) and crispatene (**14**) ($\sim$0.28 mg/animal). Crispatone (**13**) had the molecular formula $C_{25}H_{34}O_5$, which corresponds to the molecular formula of tridachione (**1**), plus an additional "propionate" unit. The IR spectrum contained two CO bands at 1725 and 1710 cm^{-1} together with the γ-pyrone bands at 1660 and 1590 cm^{-1}. The ^{13}C NMR spectrum (Table 1) and ^{1}H NMR signals at δ 1.83 (s, 3 H), 1.95 (s, 3 H) and 3.96 (s, 3 H) suggested the presence of the α-methoxy-β,β'-dimethyl-γ-pyrone ring system while the ^{1}H NMR spectrum indicated that the additional propionate unit had been added to the side chain to produce a 1,3-dimethyl-1-hexen-4-one side chain. Signals at δ 1.05 (t, 3 H, J = H z) and 2.49 (q, 2 H, J = 7 Hz) were assigned to the terminal ethyl ketone. A second methyl signal at δ 1.05 (d, 3 H, J = 7 Hz) was coupled to a methine at 3.48 (m, 1 H) which was in turn coupled to a vinyl proton at 5.38 (d, 1 H, J = 8 Hz); the chemical shift of the methine proton required that it be adjacent to the ethyl ketone. The Me group on the trisubstituted olefin gave a signal at δ 1.82 (bs, 3 H). The remaining signals in the ^{1}H NMR spectrum consisted of singlets at δ 1.20 (s, 3 H), 1.24 (s, 3 H), 1.87 (s, 1 H) and 2.40 (s, 1 H) together with a Me signal at 1.18 (d, 3 H, J = 7 Hz) coupled to a methine signal at 2.38 (q, 1 H, J = 7 Hz), assigned to a Me group on a carbon adjacent to carbonyl. These signals could not be assigned in any obvious manner to a bicyclohexanone ring system. The structure of crispatone (**13**) was therefore determined from single-crystal X-ray diffraction data.[8] The stereochemical arrangement of substituents at C-7, C-11 and C-10 resulted in a H–C(7)–C(11)–H dihedral angle of $\sim$90° and a H–C(10)–C(11)–H dihedral angle of $\sim$110°. Thus the H(C-7)–H(C-11) coupling constant was $<$0.5 c/s, resulting in a singlet at δ 1.89 for the cyclopropyl proton while the expected small H(C-11)–H(C-10) coupling would not be observed because of the almost identical chemical shifts of these protons. The ^{13}C NMR spectrum was assigned (Table 2) using J^r values to differentiate between certain signals.[13]

Crispatene (**14**) had the molecular formula $C_{25}H_{34}O_4$. The IR spectrum indicated that crispatene (**14**) contained the γ-pyrone ring (1660, 1590 cm^{-1}) and the ketone (1710 cm^{-1}) in the side chain but lacked the ketone in the 5-membered ring. The ^{13}C NMR spectrum contained signals (Table 1) that could be assigned to the α-methoxy-β,β'-dimethyl-γ-pyrone system. The ^{1}H NMR spectrum contained signals at δ 1.04 (d, 3 H, J = 7 Hz), 2.47 (m, 2 H), 1.16 (d, 3 H, J = 7 Hz), 3.45 (m, 1 H), 5.26 (d, 1 H, J = 9 Hz) and 1.61 (bs, 3 H) that were assigned to the 1,3-dimethyl-1-hexen-4-one side chain. Comparison of the spectral data of crispatene (**14**) with that of crispatone (**13**) led to the suggestion that both contained the same basic carbon skeleton but that crispatene contained a 9,10-olefinic bond. The ^{1}H NMR spectrum contained a vinyl proton signal at δ 5.39 (s, 1 H), a vinyl Me signal at 1.58 (s, 3 H), a signal at 2.80 (s, 1 H) due to the bis-allylic proton at C-11, two methyl signals at 1.11 (s, 3 H) and 1.20 (s, 3 H), and a signal at 1.41 (s, 1 H) due to the cyclopropyl proton. The lack of coupling between the C-11 and C-7 protons was expected, provided that the stereochemistry about the bicyclic ring system is the same as for crispatone (**13**). The ^{13}C NMR spectrum was assigned as shown in Table 2. The similar chemical shifts for the cyclopropyl carbon atoms suggested that both compounds had an identical substitution pattern and stereochemistry about the cyclopropyl ring.

The photochemical relationship of 9,10-*deoxytridachione* (**2**) *and crispatene* (**14**)

We proposed[7] that the metabolites of *T. diomedea*, tridachione (**1**) and 9,10-deoxytridachione (**2**) had been derived by polyketide condensation of seven "propionate" units. The metabolites of *T. crispata*, crispatone (**13**) and crispatene (**14**) could therefore be derived from eight "propionate" units. Whereas the formation of both the γ-pyrone ring and the cyclohexadiene ring in 9,10-deoxytridachione (**2**) can be explained by orthodox polyketide condensation reactions, the formation of the bicyclo[3,1,0]hexane ring in crispatene (**14**) would require either abnormal condensation reactions or a molecular rearrangement. However, molecules of the type **15** could be the precursor of both 9,10-deoxytridachione (**2**) and crispatene (**14**). A disrotatory thermal cyclization of the (6*E*, 8*Z*, 10*E*)-hexatriene or a conrotatory photochemical cyclization of the (6*E*, 8*Z*, 10*Z*)-hexatriene could give rise to 9,10-deoxytridachione (**2**)[14a] while a $[_\pi 4a + {}_\pi 2_s]$ photochemical cycloaddition reaction of the (6*E*, 8*Z*, 10*Z*)-hexatriene could produce crispatene (**14**).[14b] In the natural systems we would expect these reactions to be enzyme-mediated in order to produce optically active products. However, the possibility of photochemical reactions occurring in organisms that are known for their photosynthetic abilities is a most attractive hypothesis. We therefore attempted to show a photochemical relationship between the ring systems of 9,10-deoxytridachione (**2**) and crispatene (**14**).

The photochemical rearrangement of a 1,3-cyclohexadiene to obtain the corresponding bicyclo-[3,1,0]hex-2-ene has been described by Barton and



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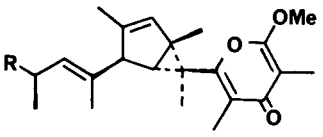
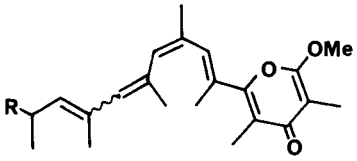


14 R = C_2H_5CO 18 R = H



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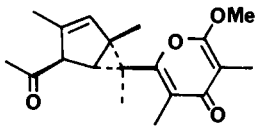

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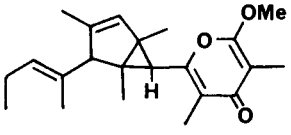

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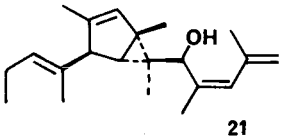

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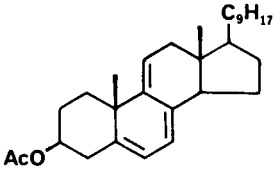

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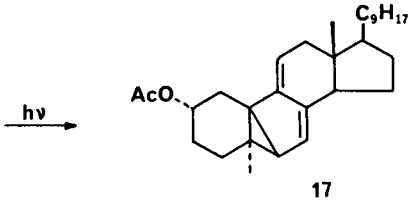

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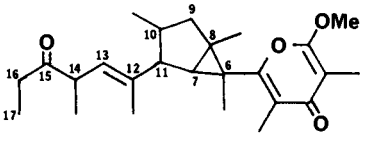
Table 2. Comparison of selected signals from the ^{13}C NMR spectra of crispatone (**13**) and crispatene (**14**).



	13	14		13	14
C-6	42.2*	40.5*	C-12	137.0	137.3
C-7	37.4	36.5	C-13	126.6	126.4
C-8	31.9*	31.7*	C-14	45.7	45.8
C-9	216.0	129.1	C-15	211.0	211.5
C-10	48.8	143.0	C-16	33.5	33.4
C-11	51.0	58.0	C-17	7.8	7.6

*These signals may be exchanged.

Kende,[15] who photolyzed dehydroergosterol acetate (**16**) in benzene solution to obtain photodehydroergosterol (**17**). Similar rearrangements in the Vitamin D series and in simple model compounds have been studied by Dauben *et al.*,[16] Ullman *et al.*,[17] and Havinga *et al.*[18] Using the conditions of Barton and Kende, a solution of 9,10-deoxytridachione (**2**) in benzene was photolyzed using a 450 watt Hanovia lamp for 3 hr to obtain a single photoproduct **18** in 85% yield. The ^{1}H NMR spectrum of the photoproduct **18** was, with the exception of signals assigned to the side chain, remarkably similar to the ^{1}H NMR spectrum of crispatene (**14**). In particular, the spectrum of the photoproduct **18** contained only two vinyl proton signals at δ 5.33 (s, 1 H) [cf. 5.39 in crispatene] and 5.30 (t, 1 H, J = 7 Hz) that were assigned to the cyclopentene and side-chain vinyl protons respectively. The bis-allylic C-11 proton at δ 2.75 (s, 1 H) and the C-7 cyclopropyl proton at 1.42 (s, 1 H) both appeared as singlets, as had the C-11 and C-7 protons in crispatone (**13**) and crispatene (**14**). The Me signals at C-6 and C-8 occurred at identical chemical shifts [δ 1.11 (s, 3 H) and 1.20 (s, 3 H)] in both the photoproduct **18** and crispatene (**14**), suggesting an identical substitution pattern and stereochemistry in both molecules. In order to confirm that the bicyclo[3,1,0]hex-2-ene ring system in photoproduct **18** was identical to that of crispatene (**14**), both molecules were carefully ozonized in ethyl acetate solution at −78°, followed by workup with zinc in acetic acid, to obtain the same major product, the methyl ketone **19**. The two samples of ketone **19** not only had identical spectral and chromatographic properties but had identical optical rotations.

Despite the biosynthetic relationship and similarities in spectral data between crispatone (**13**) and crispatene (**14**), it could be argued that the photochemical rearrangement of 9,10-deoxytridachione (**2**) had proceeded *via* a di-π-methane rearrangement to obtain structure **20**,[19] in which both the cyclopropyl proton and the bis-allylic proton signals were necessarily singlets. This structure could be ruled out by reduction of the photoproduct **18** with LAH in refluxing ether to obtain a single secondary alcohol **21** that contained a conjugated diene system (UV 228 nm). The ^{1}H NMR spectrum of alcohol **21** contained an α-OH proton signal at δ 4.40 that appeared as a singlet, with slight broadening due to allylic coupling with the olefinic proton signal at δ 5.65. Thus the carbinol functionality was unlikely to be adjacent to the cyclopropyl carbon bearing hydrogen.

An accepted mechanism for the photochemical conversion of 1,3-cyclohexadienes to bicyclo[3,1,0]hex-2-enes involves a hexatriene intermediate.[20] The expected intermediate in the photolysis of 9, 10-deoxytridachione (**2**) is the non-chiral tetraene **15** (10 *Z*, R = H), which can undergo a stereo-specific $[_\pi 4_a + {}_\pi 2_s]$ cycloaddition to give the photoproduct **18**. However, the retention of optical activity during photolysis and the absence of other products expected from the photolysis of the tetraene argue against that mechanism. We propose that the photochemical rearrangement of 9,10-deoxytridachione (**2**) has occurred through the more direct $[_\sigma 2_a + {}_\pi 2_a]$ mechanism.[14c]

Subsequent to the completion of this study, one of the authors (C.I.) showed that a related sacoglossan, *Placobranchus ocellatus*, contained both 9,10-deoxytridachione (**2**) and the photoproduct **18** and provided some preliminary data supporting the occurrence of the photochemical rearrangement *in vivo*.[21]

EXPERIMENTAL

IR spectra were recorded on a Perkin–Elmer Model 137 spectrophotometer. UV spectra were recorded on a Perkin–Elmer Model 124 double-beam spectrophotometer. Optical rotations were measured on a Perkin–Elmer Model 141 polarimeter, using a 10 cm microcell. ^{1}H NMR spectra were recorded on a Varian HR-220 NMR spectrometer, and ^{13}C spectra were recorded on a Varian CFT-20 NMR spectrometer; all chemical shifts are reported with respect to Me_4Si ($\delta = 0$). Low-resolution mass spectra were recorded on a Hewlett–Packard 5930A mass spectrometer. High-resolution mass spectra were supplied by the mass spectrometry service at UCLA. Melting points were measured on a Fisher–Johns apparatus and are uncorrected. All solvents used were either spectral grade or distilled prior to use.

Collection and extraction of Tridachiella diomedea

Specimens of *T. diomedea* were collected by hand (0 to −4 m) at Bahia Concepcion (26°43′N, 111°55′W), Bahia de Los Angeles (20°N, 113°33′W), Isla San José (24°52′N, 111°35′W) and Isla Espiritu Santo (24°31′N, 110°23′W). All specimens contained the same metabolites. The animals were stored in acetone for one week then homogenized in acetone. The resulting suspension was filtered and the acetone evaporated under vacuum to obtain an oily residue that was partitioned between ether and water. The combined ether extracts were dried over Na_2SO_4 and the solvent evaporated to obtain an oil. The oil was chromatographed on silica gel using eluants of increasing polarity from hexane through ether to EtOAc. Fractions eluted with 1:1 hexane–ether contained **2** (~0.75 mg/animal) while elution with 70% ether in hexane gave **1** (~1.0 mg/animal).

Tridachione (**1**). $[\alpha]_D$—113.3° (*c* 0.06, $CHCl_3$); IR ($CHCl_3$) 1660, 1590, 890 cm^{-1}; UV (MeOH) 257 nm (ε 6,000); ^{1}H NMR ($CDCl_3$) δ 0.68 (t, 3 H, J = 7 Hz), 1.32 (s, 3 H), 1.36 (s, 3 H), 1.60 (s, 3 H), 1.80 (s, 3 H), 2.01 (s, 3 H), 2.05 (m, 2 H), 2.07 (s, 3 H), 2.91 (s, 1 H), 3.11 (s, 1 H), 3.93 (s, 3 H), 5.18 (t, 1 H, J = 7 Hz), 6.10 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 181.1 (s), 161.0 (s), 160.1 (s), 132.5 (s), 131.6 (d), 129.0 (d), 128.5 (s), 118.4 (s), 97.8 (s), 60.5 (s), 57.6 (q), 55.3 (s), 54.7 (d), 46.7 (d), 31.2 (t), 21.8 (q), 21.5 (q), 20.2 (q), 12.9 (q), 12.0 (q), 11.6 (q), 6.1 (q); mass spectrum, *m/e*, 358 (M^+) 343, 315, 283, 254, 222, 155; HRMS, Obs: 358.2139, $C_{22}H_{30}O_4$ Requires: 358.2144.

9,10-*Deoxytridachione* (**2**). $[\alpha]_D$—194.8° (*c*, 0.27, $CHCl_3$); IR ($CHCl_3$) 1660, 1590 cm^{-1}; UV (MeOH) 257 nm (ε 12,000); ^{1}H NMR ($CDCl_3$) δ 0.69 (t, 3 H, J = 7 Hz), 1.32 (s, 3 H), 1.42 (s, 3 H), 1.69 (s, 3 H), 1.76 (s, 3 H), 1.81 (s, 3 H), 2.03 (s, 3 H), 2.71 (s, 1 H), 3.95 (s, 3 H), 5.09 (t, 1 H, J = 7 Hz), 5.56 (s, 1 H), 5.65 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 181.8, 161.7, 161.1, 134.9, 132.2, 131.0, 127.8, 124.3, 122.4, 120.0, 98.8, 59.6, 55.4, 47.6, 26.9, 22.3, 21.5, 21.1, 13.8, 13.7, 12.2, 6.8; mass spectrum, *m/e*, 342 (M^+) 327, 313, 199, 155; HRMS, Obs: 342.2199, $C_{22}H_{30}O_3$ requires 342.2195.

Collection and extraction of Tridachia crispata

Specimens of *T. crispata* were collected by hand (0 to −2 m) at Glover Reef, Belize (16°40′N, 87°45′W) and Galeta Island, Panama (9°23′N, 79°50′W). The animals were stored in acetone for one month then homogenized in acetone. The filtered extract was evaporated to obtain an oil that was partitioned between ether and water. The combined ether extracts were dried over sodium sulfate and the solvent evaporated. The resulting oil was chromatographed on silica gel. Elution with 50% ether in hexane gave fractions containing **14** (~0.28 mg/animal) followed by fractions containing **13** (~0.125 mg/animal).

Crispatone (**13**). $[\alpha]_D$—84.7° (*c* 0.03, $CHCl_3$); IR ($CHCl_3$) 1725, 1710, 1660, 1590 cm^{-1}; UV (MeOH) 257 nm (ε 5800); ^1H NMR ($CDCl_3$) δ 1.05 (t, 3 H, J = 7 Hz), 1.05 (d, 3 H, J = 7 Hz, 1.18 (d, 3 H, J = 7 Hz), 1.20 (s, 3 H), 1.24 (s, 3 H), 1.82 (s, 3 H), 1.83 (s, 3 H), 1.87 (s, 1 H), 1.95 (s, 3 H), 2.38 (q, 1 H, J = 7 Hz), 2.40 (s, 1 H), 2.49 (q, 2 H, J = 7 Hz), 3.48 (m, 1 H), 3.96 (s, 3 H), 5.38 (d, 1 H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 216.0 (s), 211.0 (s), 181.1 (s), 162.2 (s), 157.5 (s), 137.0 (s), 126.2 (d), 121.0 (s), 100.0 (s), 55.0 (q), 51.0 (d), 48.8 (d), 45.7 (d), 42.2 (s), 37.4 (d), 33.5 (t), 31.9 (s), 16.6 (q), 15.9 (q), 13.3 (2q), 11.0 (q), 10.5 (q), 7.8 (q), 6.6 (q); mass spectrum, *m/e*, 414 (M^+), 357, 304, 289, 249, 189, HRMS, Obs: 414.2392, $C_{25}H_{34}O_5$ requires 414.2406.

Crispatene (**14**). $[\alpha]_D$—92.8° (*c* 0.12, $CHCl_3$); IR ($CHCl_3$) 1710, 1660, 1590 cm^{-1}; UV (MeOH) 256 nm (ε 5700); ^1H NMR ($CDCl_3$) δ 1.04 (t, 3 H, J = 7 Hz), 1.11 (s, 3 H), 1.16 (d, 3 H, J = 7 Hz), 1.20 (s, 3 H), 1.41 (s, 1 H), 1.58 (s, 3 H), 1.61 (s, 3 H), 1.84 (s, 3 H), 1.95 (s, 3 H), 2.47 (m, 2 H), 2.80 (s, 1 H), 3.45 (m, 1 H), 3.94 (s, 3 H), 5.26 (d, 1 H, J = 8 Hz), 5.39 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 211.5 (s), 181.2 (s), 162.0 (s), 159.9 (s), 143.0 (s), 137.3 (s), 129.1 (d), 126.4 (d), 120.1 (s), 99.2 (s), 58.0 (d), 54.9 (q), 45.8 (d), 40.5 (s), 36.5 (d), 33.4 (t), 31.7 (s), 17.6 (q), 16.3 (q), 13.7 (q), 13.3 (q), 13.1 (q), 12.7 (q), 7.6 (q), 6.5 (q); mass spectrum, *m/e* 398 (M^+) 382, 341, 313; HRMS, Obs: 398.244, $C_{25}H_{34}O_4$ requires 398.246.

Diol **4**. Conc. HNO_3 (3 drops) was added to a stirred soln of **1** (30 mg, 0.8 mmol) in glacial AcOH (2 mL). Soln was stirred at 25° for 30 min then quenched by pouring into 5% $NaHCO_3$aq. The organic material was extracted with $CHCl_3$ (3 × 15 mL). The combined extracts were dried over Na_2SO_4, and the solvent evaporated to obtain **4** (30 mg, 94% theoretical): IR ($CHCl_3$) 3600, 1660, 1590 cm^{-1}; UV (MeOH) 256 nm; ^1H NMR ($CDCl_3$) δ 0.82 (t, 3 H, J = 7 Hz), 1.25 (s, 3 H), 1.30 (s, 3 H), 1.69 (s, 3 H), 1.82 (s, 3 H), 1.89 (s, 3 H), 2.07 (s, 3 H), 2.75 (s, 1 H), 3.94 (s, 3 H), 5.30 (t, 1 H, J = 7 Hz), 5.48 (s, 1 H), 6.08 (s, 1 H); mass spectrum, *m/e*, 358 ($M-H_2O$), 343, 315, 222.

Keto-aldehyde **5**. Periodic acid (50 mg, 0.22 mmol) was added to a stirred soln of **1** (29 mg, 0.08 mmol) in ether (15 mL) and the soln was boiled under reflux for 20 min. The cooled mixture was poured into water (10 mL), the ether layer separated and the aqueous phase extracted with ether (2 × 10 mL). The combined ether extracts were dried over Na_2SO_4, and the solvent evaporated to obtain **5** (27 mg, 90% theoretical): IR ($CHCl_3$) 1710, 1680, 1660, 1590 cm^{-1}; UV (MeOH) 253 nm; ^1H NMR ($CDCl_3$) δ 1.05 (t, 3 H, J = 7 Hz), 1.45 (s, 3 H), 1.70 (s, 3 H), 1.76 (s, 3 H), 1.84 (s, 3 H), 1.86 (s, 3 H), 2.02 (s, 3 H), 2.18 (m, 2 H), 3.86 (s, 1 H), 4.07 (s, 3 H), 5.66 (t, 1 H, J = 7 Hz), 6.92 (s, 1 H), 9.41 (s, 1 H); mass spectrum, *m/e*, 374 (M^+), 315, 249.

Diketone **6**. BF_3. etherate (400 μL) was added to a soln of **1** (20 mg, 0.06 mmol) in dry ether (5 mL) at 0° under N_2. After 1 min the reaction was quenched with water (1 mL). The ether phase was dried over Na_2SO_4 and the solvent evaporated to give **6** (8 mg, 40% theoretical) as crystals from hexane: mp 194–197°; IR ($CHCl_3$) 1680, 1660, 1590 cm^{-1}; UV (MeOH) 251, 240 nm; ^1H NMR ($CDCl_3$) δ 0.98 (t, 3 H, J = 7 Hz), 1.00 (d, 3 H, J = 7 Hz), 1.25 (s, 3 H), 1.57 (s, 3 H), 1.84 (s, 3 H), 1.88 (s, 3 H), 2.06 (m, 2 H), 2.07 (s, 3 H), 2.43 (d, 1 H, J = 12 Hz), 2.65 (m, 1 H), 3.82 (s, 3 H), 5.36 (t, 1 H, J = 7 Hz), 6.50 (s, 1 H); mass spectrum, *m/e* 358 (M^+), 343, 326, 271, 249, 189.

Conversion of tridachione (1) *into* 9,10-*deoxytridachione* (**2**)

A soln of **1** (30 mg, 0.082 mmol) in AcOH (min. volume) was added to a cooled soln of NaI (21 mg, 0.142 mmol) and NaOAc (7 mg, 0.085 mmol) in AcOH (10 mL) and water (500 μL) at 0°. Zn dust (21 mg, 0.32 mmol) was added to the stirred soln. After 1½ hr the mixture was filtered and the solvent removed under vacuum. The residue was partitioned between ether (3 × 20 mL) and water (10 mL) and the combined ether extracts dried over Na_2SO_4 and evaporated to obtain **2** (15 mg, 52% theoretical), identical in all respects to the natural material.

Reduction of tridachione (**1**) *with lithium aluminum hydride*

LAH (70 mg) was added to a soln of **1** (50 mg, 0.14 mmol) in anhyd ether (20 mL) and the mixture was boiled under reflux for 1 hr under N_2. The mixture was cooled and excess reagent was destroyed by sequential dropwise addition of 5% NaOHaq (2 mL; caution!) and water (5 mL). The ether layer was filtered, dried over Na_2SO_4 and the solvent evaporated to obtain **7** (23 mg, 55% theoretical): IR ($CHCl_3$) 3600 cm^{-1}; UV (MeOH) 240 nm; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 7 Hz), 1.27 (s, 3 H), 1.32 (s, 3 H), 1.50 (s, 3 H), 1.51 (s, 3 H), 1.61 (s, 3 H), 1.72 (s, 3 H), 2.05 (m, 2 H), 2.28 (s, 1 H), 3.59 (m, 1 H), 4.82 (s, 1 H), 4.98 (s, 1 H), 5.07 (s, 1 H), 5.27 (t, 1 H, J = 7 Hz), 5.76 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 156.7 (s), 146.8 (s), 135.7 (d), 134.2 (d), 132.6 (s), 131.3 (s), 108.2 (t), 99.8 (s), 84.5 (s), 76.8 (d), 73.5 (d), 61.8 (d), 46.7 (s), 21.0 (q), 20.3 (q), 19.2 (q; q; t), 14.1 (q), 13.3 (q), 8.6 (q); mass spectrum, *m/e*, 332 (M^+) 291, 189; HRMS, Obs: 332.235, $C_{21}H_{32}O_3$ requires 332.235.

Acetylation of diol **7**. A soln of **7** (9 mg, 0.027 mmol) in AC_2O (1 mL) and pyridine (1 mL) was stirred at 25° for 24 hr. The reagents were removed under vacuum and the residue was partitioned between ether (2 × 10 mL) and water (5 mL). The combined ether extracts were dried over Na_2SO_4 and the solvent evaporated to obtain **8** (8 mg, 70% theoretical): ^1H NMR ($CDCl_3$) δ 0.94 (t, 3 H, J = 7 Hz), 1.19 (s, 3 H), 1.27 (s, 3 H), 1.48 (s, 3 H), 1.57 (s, 9 H), 2.04 (s, 3 H), 2.07 (s, 3 H), 2.36 (s, 1 H), 4.80 (s, 2 H), 5.12 (s, 1 H), 5.22 (t, 1 H, J = 7 Hz), 5.83 (s, 1 H), 6.18 (s, 1 H); mass spectrum, *m/e*, 416 (M^+), 373, 357, 333, 248.

Reduction of 9,10-*deoxytridachione* (**2**) *with lithium aluminum hydride*

LAH (20 mg) was added to a soln of **2** (14 mg, 0.04 mmol) in anhyd ether (10 mL) and the mixture was boiled under reflux for 1 hr under N_2. The mixture was worked up as described previously to obtain **11** (7 mg, 58% theoretical) as a 1:1 mixture of two diastereoisomers: IR ($CHCl_3$) 3600 cm^{-1}; UV (MeOH) 230 nm; ^1H NMR ($CDCl_3$) δ 0.91 (t, 3 H, J = 7 Hz), 1.16 (s, 3 H), 1.41 (s, 3 H), 1.57 (s, 3 H), 1.63 (s, 3 H), 1.70 (s, 3 H), 1.94 (m, 2 H), 2.48 (s, 0.54 H), 2.51 (s, 0.46 H), 4.30 (s, 1 H), 4.88 (s, 1 H), 5.03 (s, 1 H), 5.14 (m, 1 H), 5.32 (s, 0.46 H), 5.37 (s, 0.54 H), 5.53 (s, 1 H), 5.55 (s, 1 H); mass spectrum, *m/e*, 300 (M^+), 282, 267, 254, 229; HRMS, Obs: 300.246, $C_{21}H_{32}O$ requires 300.247.

Oxidation of diol **11**. Jones' reagent (40 μL, 0.048 mmol) was added dropwise to a stirred soln of **11** (7 mg, 0.023 mmol) in anhyd acetone (5 mL) at 0°C. After 10 min, the excess oxidant was destroyed with i-PrOH (1–2 drops) and the solvents removed under vacuum. The residue was partitioned between ether (3 × 20 mL) and water (20 mL). The combined ether extracts were dried over Na_2SO_4 and the solvent evaporated to obtain **12** (6 mg, 85% theoretical): UV (MeOH) 275, 238 nm; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3 H, J = 7 Hz), 1.43 (s, 3 H), 1.73 (s, 9 H), 1.94 (s, 3 H), 1.98 (s, 3 H), 2.55 (s, 1 H), 5.23 (t, 1 H, J = 7 Hz), 5.37 (s, 1 H), 5.44 (s, 1 H), 5.54 (s, 1 H), 5.64 (s, 1 H); mass spectrum, *m/e*, 298 (M^+), 283.

Photolysis of 9,10-*deoxytridachione* (**2**). A soln of **2** (20 mg, 0.058 mmol) in benzene (500 mL) was placed in the well of a water-cooled photolysis apparatus (Ace Glass) and irradiated with light from a 450 W Hanovia lamp for 3 hr. Evaporation of the solvent gave an oil that was chromatographed on silica gel using ether as eluant to obtain a single photoproduct (**18**, 16 mg, 85% theoretical): ^1H NMR ($CDCl_3$) δ 0.98 (t, 3 H, J = 7 Hz), 1.11 (s, 3 H), 1.20 (s, 3 H), 1.42 (s, 1 H), 1.55 (s, 3 H), 1.57 (s, 3 H), 2.75 (s, 1 H), 3.96 (s, 3 H), 5.30 (t, 1 H, J = 7 Hz), 5.33 (s, 1 H); mass spectrum, *m/e*, 342 (M^+), 326, 313, 199; HRMS, Obs: 342.217, $C_{22}H_{30}O_3$ requires 342.219.

Ozonolysis of crispatene (**14**). A soln of O_3 in EtOAc was prepared by bubbling a mixture of O_3 in oxygen through EtOAc at −78° until a blue-colored soln resulted. This soln was added dropwise to a stirred soln of **14** (9 mg, 0.002 mmol) in EtOAc (10 mL) at −78° and the course of the reaction was

followed by tlc on silica gel. As soon as all starting material had reacted, excess O_3 was removed in a stream of N_2 and the solvent was evaporated under vacuum.

AcOH (5 mL) and Zn dust (20 mg) were added to the ozonide and the mixture was stirred at 25° for 1 hr. The mixture was diluted with ether (25 mL), filtered and the solvent removed under vacuum to obtain an oil containing one major component. The oil was chromatographed on silica gel to obtain **19** (3 mg, 41% theoretical): $[\alpha]_D + 32°$ (*c* 0.02, $CHCl_3$); IR 1710, 1660, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 3 H), 1.25 (s, 3 H), 1.60 (s, 1 H), 1.72 (s, 3 H), 1.84 (s, 3 H), 1.98 (s, 3 H), 2.17 (s, 3 H), 3.09 (s, 1 H), 3.96 (s, 3 H), 5.56 (s, 1 H); mass spectrum, *m/e*, 316 (M^+), 301, 284, 275; HRMS, Obs: 316.168, $C_{19}H_{24}O_4$ Requires: 316.167.

Ozonolysis of photoproduct **18**. A soln of **18** (4 mg, 0.01 mmol) in EtOAc (5 mL) was subjected to ozonolysis using the procedure described above to obtain **19** (1.5 mg), identical in all respects to the sample obtained from crispatene.

Reduction of photoproduct **18** *with lithium aluminum hydride*

LAH (30 mg) was added to a soln of **18** (10 mg, 0.029 mmol) in anhyd ether (20 mL) and the mixture was boiled under reflux for 1 hr. The mixture was worked up as described for a previous LAH reduction to obtain **21** (5 mg, 57% theoretical): IR ($CHCl_3$) 3600 cm^{-1}; UV (MeOH) 228 nm; ^1H NMR ($CDCl_3$) δ 0.91 (s, 3 H), 0.97 (t, 3 H, J = 7 Hz), 1.22 (s, 1 H), 1.46 (s, 3 H), 1.52 (s, 3 H), 1.57 (s, 3 H), 1.58 (s, 3 H), 2.05 (m, 2 H), 2.65 (s, 1 H), 4.40 (s, 1 H), 4.92 (s, 1 H), 5.07 (s, 1 H), 5.25 (s, 1 H), 5.25 (t, 1 H, J = 7 Hz), 5.64 (s, 1 H); mass spectrum, *m/e*, 300 (M^+), 282, 267.

Acknowledgements—We thank J. R. Lance for identifying the molluscs. Samples of *T. crispata* were collected during a cruise on R/V Alpha Helix, supported by the National Science Foundation (OCE 76-80874). The research was supported by a grant from the National Science Foundation (PCM 72-02539). The NMR Facility at U.C.S.D. was supported by a grant from the National Institutes of Health (RR-00708).

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 241 to 246, 1981
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0040-4020/81/Suppl. 1-0241-06 $02.00/0
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SYNTHESES IN THE ELLIPTICINE-OLIVACINE SERIES

A POSSIBLE BIOGENETIC MODEL†

RICHARD BESSELIÈVRE and HENRI-PHILIPPE HUSSON*

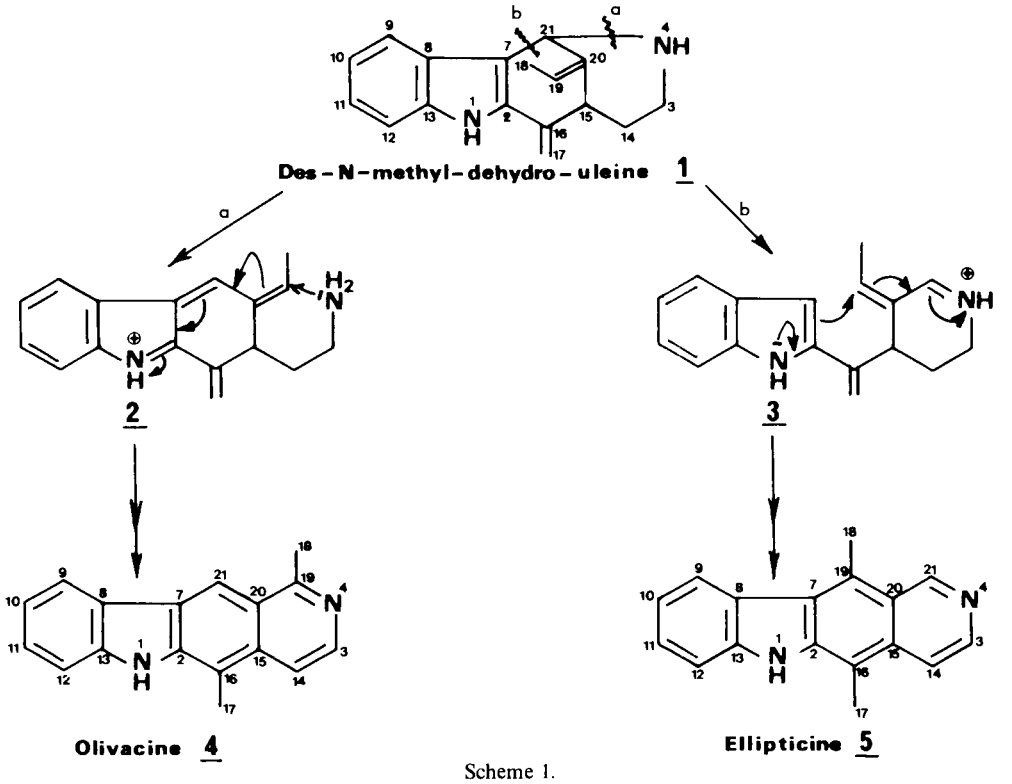
Institut de Chimie des Substances Naturelles C.N.R.S., 91190 Gif-sur-Yvette, France

Abstract—The syntheses of the antitumor alkaloids ellipticine **5** and olivacine **4** have been achieved according to a general scheme based on the acid catalysed fragmentation of desethyl-uleine **14** into the carbazole **15**. In the initial study, **15** was synthesised from 1-benzenesulfonyl-2-lithio-indole and 4-formyl pyridine in 10 steps. A notable improvement was made with the preparation in high yield of **15** in a one-pot reaction between indole and the Δ^3 piperidine **20**. The missing carbon atoms were introduced according to a Bischler reaction on **15** to yield olivacine **4** after demethylation and aromatisation. Ellipticine was obtained in the same way from **23**.

Since the structural elucidation and the first synthesis of ellipticine **5** by Woodward,[1] a great deal of work has been devoted to the synthesis of this pyrido[4,3-*b*]carbazole alkaloid[2] due to its promising antitumor activity.[3] Much less attention has been paid to the synthesis of the isomeric alkaloid olivacine **4** which has also proved to possess potential anticancer properties.[4]

In continuation of our interest in the biomimetic synthesis of alkaloids we sought a synthetic approach to ellipticine **5** and olivacine **4** inspired by a biogenetic hypothesis. These two alkaloids exhibit unexpected structural features in comparison with their parent indole alkaloids since a three carbon chain bonds the indole nucleus and the N-4 atom instead of the two carbon atoms of the tryptophan side chain.

Potier and Janot[5] proposed an attractive hypothesis for the biogenesis of these alkaloids. Conjugated iminium salts which may often be invoked for the biogenesis of indole alkaloids[6] are key intermediates in this postulate. Thus an intramolecular Mannich type reaction of the intermediate **3** (Scheme 1) allowed biomimetic syntheses of ellipticine **5**[2,7] *via* intermediates of the aforementioned type. On the other



Scheme 1.

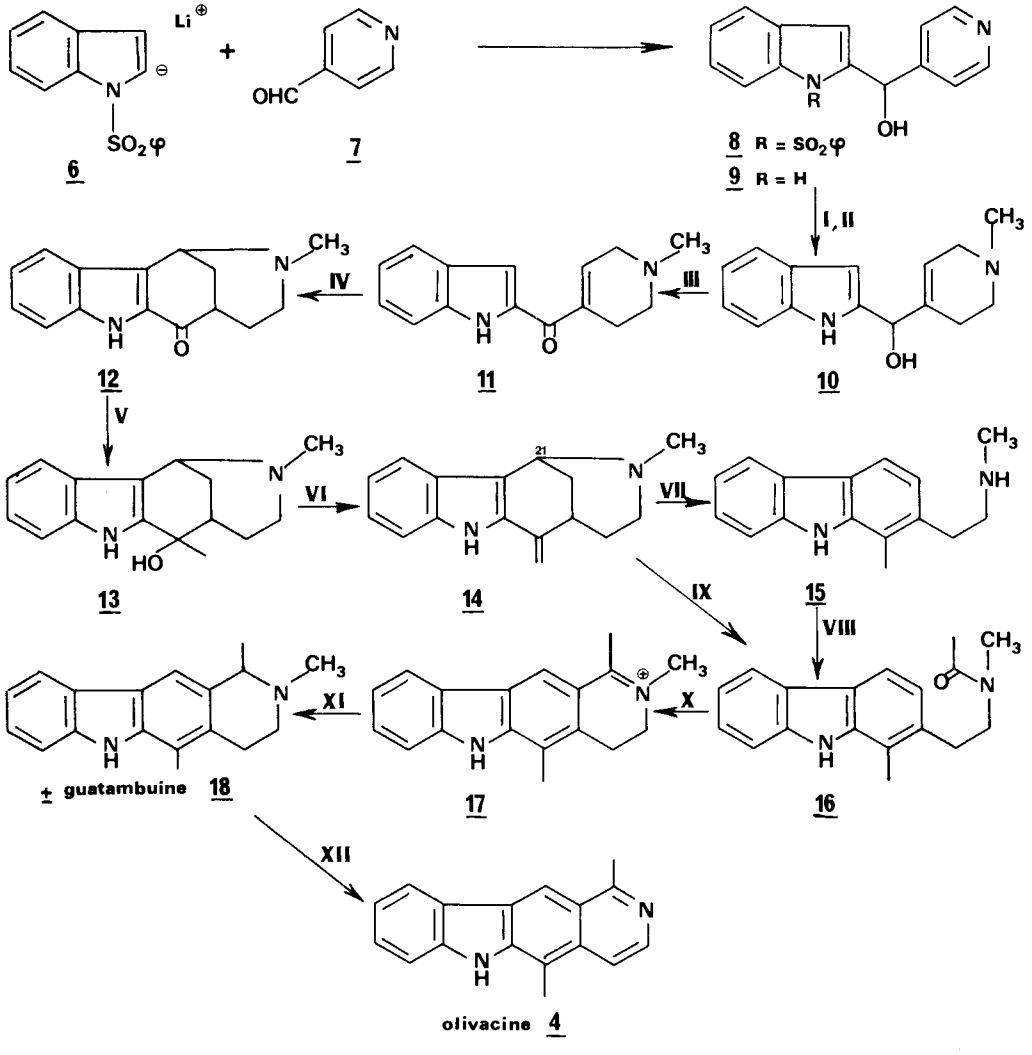
†Preliminary communication of part of this work: R. Besselièvre and H.-P. Husson, *Tetrahedron Lett* 1873 (1976). The work described comprises part of the Ph.D. Thesis of R. Besselièvre (University of Paris-Sud, 1977).

hand, the nucleophilic addition of N-4 onto the conjugated iminium ion **2** could give the olivacine skeleton.

One can imagine that intermediates **2** and **3** are formed by fragmentation of the alkaloid des-N-methyl-dehydrouleine **1**[8] according to two different pathways *a* or *b*, after protonation of N-4 or C-7 respectively (the biogenetic numbering will be used throughout this paper). Route *a* is reminiscent of the fragmentation of gramine quaternary salts previously observed.[9,10] We were able to make such a reaction on a tertiary base, in acidic medium, with the α-acylindole alkaloid ervitsine in order to make a correlation with another alkaloid.[11] Some precedent therefore did exist to favour our proposal for a possible biogenetic hypothesis for the formation of olivacine **4**.

It was our aim to prepare desethyluleine **14** (Scheme 2) to check the validity of this hypothesis and its usefulness in synthesis.

The synthetic scheme was inspired by the Joule synthesis[12] of uleine itself whose original step was the cyclisation of an α,β unsaturated ketone of type **11** into **12**. The key intermediate **9** was obtained differently on condensation of the 2-lithio derivative of benzenesulfonyl indole **6**[13] with 4-formyl pyridine **7** followed by basic hydrolysis of the protecting group.



Scheme 2.

Quaternization of the pyridine nitrogen with MeI followed by $NaBH_4$ reduction yielded the tetrahydropyridine **10**. MnO_2 oxidation of **10** gave the α, β unsaturated ketone **11** (air oxidation of **10** is also effective but slower).

Cyclisation of **11** into desethyl-dasycarpidone **12** was achieved on its boiling in 50% AcOH–H_2O for 10 hr. This reaction proceeds *via* the deconjugated iminium salt coming from the conjugated enol. The exomethylene group of **14** was efficiently introduced in two high yield steps *via* the addition of MeLi to **12** followed by dehydration with CF_3COOH. This approach is more convenient than the Wittig reaction[12] whose yield is poor. Refluxing **14** in 50% AcOH–H_2O for 24 hours afforded the carbazole **15** (Y = 90%) which was acetylated to give **16** and cyclized *via* a Bischler–Napieralski reaction in a classical manner. The N-acetyl derivative **16** could also be obtained directly from AcCl treatment of **13** or **14**. $NaBH_4$ reduction of **17** led to (±)guatambuine **18** which could also be obtained by Pictet–Spengler reaction of **15** with CH_3CHO. Demethylation and dehydrogenation of **18** in boiling decalin in the presence of 10% palladium-charcoal afforded olivacine **4**.

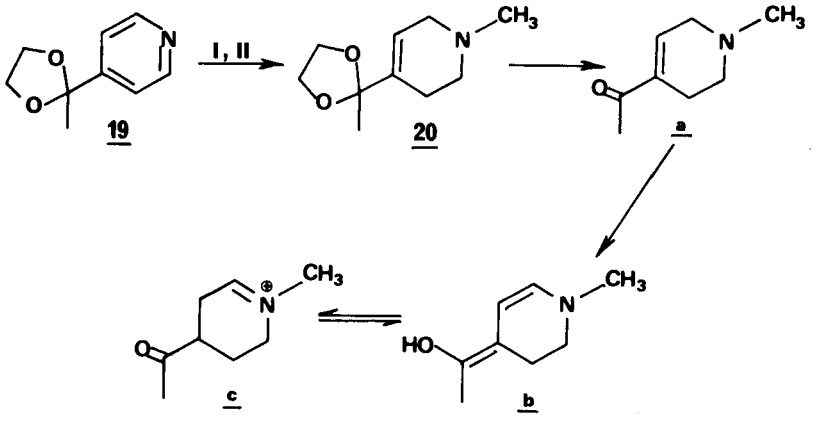
N-desmethyl-dehydrouleine **1** not being available (probably due to its sensitivity to acid treatment during extraction from the plant), it was not possible to apply the facile fragmentation reaction of **14** into **15** to the probable precursor of the guatambuine–olivacine series.

The tertiary alcohol **13** can be regarded as derived from indole and 1-methyl 4-acetyl Δ^3 piperidine *a* (Scheme 3) *via* a nucleophilic substitution on the position α to N-4 *via* an iminium ion followed by an addition on the keto group.

The piperidine **a** (Scheme 3), an equivalent of **11**, should give in acid medium **c**, which is the required intermediate for the proposed substitutions with indole. The keto group of 4-acetyl pyridine was transformed into its ethylene ketal **19**, the nitrogen was quaternarized with MeI and finally $NaBH_4$ reduction afforded **20** (overall yield 72%).

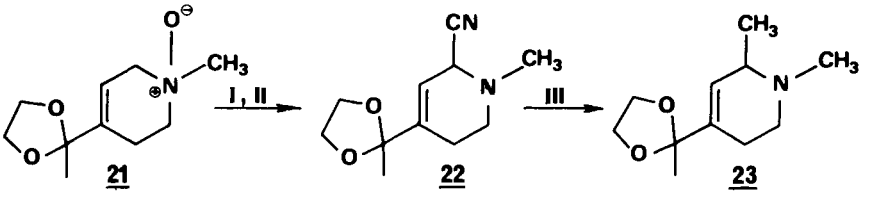
Equimolecular amounts of indole and **20** were refluxed for 56 hours in 50% AcOH–H_2O under an argon atmosphere. After work up the carbazole **15** was obtained in a one-pot reaction in 74% yield as its hydrochloride (Scheme 5).

This synthesis of **15** represents a notable improvement over the former route since there are fewer steps and the reagents are cheaper (no lithio derivative is necessary and the starting materials are commercially available). The first synthesis of 10-methoxy olivacine **28**,[14] whose structure had been



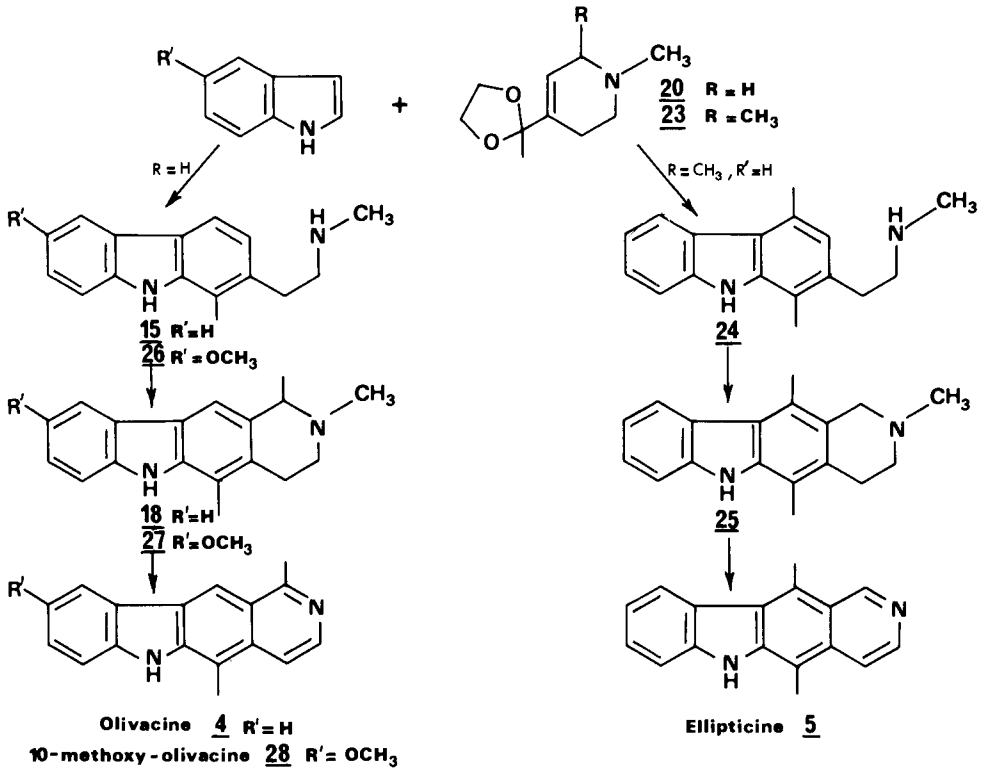
Reagents : I, CH_3I, CH_3CN ; II, $NaBH_4$, CH_3OH.

Scheme 3.



Reagents : I, $(CF_3CO)_2O$, CH_2Cl_2, 0°, 15 min. ; II, KCN, H_2O, pH4, 20 min. ; III, CH_3MgBr, THF, – 10°, 1 h.

Scheme 4.



Scheme 5.

proposed on the basis of physical data only, was achieved similarly starting from 5-OCH_3 indole (in this case the carbazole **26** was obtained in 90% yield).

The efficiency of this synthesis prompted us to adopt a similar strategy in the synthesis of ellipticine. The required Δ^3-piperidine **23** was obtained from **20** according to an original method recently developed in our laboratory[15] (Scheme 4). Trifluoroacetic anhydride treatment of the N-oxide **21** gave a conjugated iminium salt isolated as its cyano adduct **22**.

On treatment of **22** with CH_3MgBr **23** was regiospecifically prepared. Condensation of **23** with indole, in the same conditions utilized for the preparation of the carbazole **15**, gave **24** in low yield (Scheme 5). Ellipticine synthesis was achieved from **24** *via* a Pictet–Spengler cyclisation with CH_2O followed by a dehydrogenation-demethylation with 10% palladium–charcoal.

The surprisingly poor yield in comparison with the high yield of the synthesis of **15** could be explained because of a difficult Mannich reaction on the substituted intermediate iminium ion.

In conclusion we suggest a biogenetic hypothesis for the ellipticine-olivacine series and our proposal is illustrated by a model reaction in the case of olivacine.

EXPERIMENTAL

Infrared spectra (IR) were recorded in $CHCl_3$ solutions on a Perkin–Elmer 257 spectrophotometer. Infrared absorption bands are expressed in cm^{-1} using polystyrene calibration. Ultraviolet spectra (UV) were run in ethanol solution on a Bausch and Lomb Spectronic 505 spectrophotometer. ^1H nuclear magnetic resonance (NMR) spectra were recorded on a Perkin–Elmer R 12 spectrometer (60 MHz). Chemical shift data are reported in parts per million (ppm, tetramethylsilane as an internal standard, $\delta = 0$), where, s, d, dd, t, q and m designate singlet, doublet, doublet of doublets, triplet, quartet and multiplet respectively. Mass spectrometry (MS) was performed on an AEI MS 50 in the Institut de Chimie des Substances Naturelles 91190 Gif-sur-Yvette, France where the elemental analyses were also carried out. Satisfactory elemental analyses were obtained for all products described. All reactions were run under argon and freshly distilled THF was used.

1-*Benzenesulfonylindol-2-yl 4-pyridyl carbinol* **8**

1-Benzenesulfonyl-2-lithioindole **6** (2.57 g, 10 mmol) was prepared in THF[13] at $-12°$ and was added slowly *via* a syringe to a THF solution of 4-pyridine–carboxaldehyde (1.1 g, 10 mmol). The resultant yellow reaction mixture was stirred at 15° for 30 min, diluted with water and then acidified (pH2) with HCl. The excess of indole was removed by extraction with ether. The aqueous phase was made alkaline with NH_4OH and extracted with $CHCl_3$. The combined $CHCl_3$ fractions were washed with water, dried over anhydrous sodium sulfate and distilled to give the crude product (2.265 g) which was crystallized from methanol (Y: 62%): m.p. 200°; $C_{20}H_{16}N_2O_3S$.

Indol-2-yl 4-pyridyl carbinol **9**

A solution of **8** (1.5 g, 4.1 mmol) in ethanol (90 ml) water (90 ml) and 10N sodium hydroxyde (20 ml) was heated at reflux for 2 hr to give **9** which was extracted with hot $CHCl_3$ after dilution of the reaction mixture with water. Concentration of the combined $CHCl_3$ fractions resulted in crystallisation. After standing overnight at 0° 0.515 g of crystals of pure **9** were filtered off (Y: 57%): m.p. 192°; $C_{14}H_{12}O N_2$; MS *m/e* (rel intensity) 224 ($M^{+\cdot}$, 100), 206 (85).

Indol-2-yl 1,2,5,6-tetrahydro-1-methyl-4-pyridyl carbinol **10**

The derivative **10** was prepared from the methiodide of **9** by $NaBH_4$ reduction as previously described.[12]

Indol-2-yl 1,2,5,6-tetrahydro-1-methyl-4-pyridyl ketone **11**

The alcohol **10** was oxidised with MnO_2 as previously described to yield the ketone **11**.[12]

Desethyldasycarpidone **12**

Desethyldasycarpidone **12** was obtained from **11** according to the procedure of Joule *et al.*[12]

Alcohol **13**

To a 1 M solution of CH_3Li (3 ml) in THF (20 ml) at $-10°$ was added desethyldasycarpidone **12** (0.360 g, 1.5 mmol) in THF (36 ml) *via* a syringe. The reaction mixture was stirred at room temperature for 1 hr and then diluted with water and extracted according to the usual procedure. The crude product (0.410 g, Y $\simeq$ 100%) was crystalline and was not recrystallized; $C_{16}H_{20}N_2O$; MS *m/e* 256 ($M^{+\cdot}$); NMR ($CDCl_3$) 1.55 (s, CH_3), 2.21 (s, N–CH_3).

Desethyluleine **14**

The dehydration of **13** into **14** was performed in an NMR tube. To a solution of **13** (40 mg, 0.16 mmol) in $CDCl_3$ three drops of CF_3COOH were added. The reaction mixture was heated at 50°. The NMR spectra showed that after 1 hr the reaction was complete. After extraction, the crude product was crystallized from benzene (quantitative yield): m.p. 213°; $C_{16}H_{18}N_2$; MS *m/e* (rel intensity) 238 $M^{+\cdot}$, 80) 195 (60), 194 (58), 181 (100); UV nm (log ε) 225 (4.35), 303 (4.25), 3.10 (4.23); NMR ($CDCl_3$) 2.25 (s, NCH_3), 4.20 (t, 1 H, H-21), 4.95 (s, 1 H, H-17), 5.25 (s, 1 H, H-17).

Carbazole **15**

Method A. The carbazole **15** was prepared on refluxing **14** (40 mg) in 50% aqueous acetic acid for 24 hr. After extraction the crude product was crystallized as its hydrochloride from ethanol (35 mg, Y $\simeq$ 90%): m.p. > 300°; $C_{16}H_{19}N_2Cl$. Base: MS *m/e* (rel intensity): 238 ($M^{+\cdot}$, 35) 195 (100), 194 (50); UV nm (log ε) 239 (4.67), 249 (4.55), 260 (4.31), 295 (4.26) 326 (3.61), 339 (3.60); NMR ($CDCl_3$) 2.42 (s, NCH_3), 2.45 (s, CH_3).

Method B. The tetrahydropyridine **20** (1.83 g, 10 mmol) and indole (1.17 g, 10 mmol) in 50% aqueous acetic acid (50 ml) were refluxed for 56 hr. After extraction the amorphous carbazole (1.760 g, Y = 74%) was crystallized as its hydrochloride from methanol.

N-Acetyl derivative **16**

Method A. The alcohol **13** or desethyluleine **14** (0.2 mmol) were stirred in C_6H_6 solution in the presence of AcCl (0.6 mmol) and Na_2CO_3 (1 g) for 12 hr at room temperature. After extraction the derivative **16** was obtained as an amorphous solid (53 mg, Y = 95%); $C_{18}H_{20}N_2O$; MS *m/e* (rel intensity): 280 ($M^{+\cdot}$, 44) 207 (100), 194 (90); NMR ($CDCl_3$) exhibited two rotamers 1.82 and 2.04 (2s, CH_3), 2.44 and 2.49 (2s, NCH_3) 2.84 and 2.92 (2s, CH_3).

Method B. The secondary amine **15** (2.38 g, 10 mmol) was stirred for 1 hr in acetic anhydride–pyridine (1:1) (30 ml). After extraction the compound **16** was isolated in 95% yield.

(±) *Guatambuine* **18**

Method A. The amide **16** (2.80 g, 10 mmol) and $POCl_3$ (4 ml) were refluxed for 10 hr in $CHCl_3$. The yellow precipitate was then filtered off and washed with $CHCl_3$ (2.1 g). The crystals of the intermediate iminium salt **17** were dissolved in a mixture of $CHCl_3$ (30 ml) and CH_3OH (50 ml) and reduced with excess $NaBH_4$ at room temperature. After isolation by extraction (±) guatambuine **18** was crystallized from ethanol (1.9 g; Y: 72%): m.p. 250°; $C_{18}H_{20}N_2$ MS *m/e* (rel intensity) 264 ($M^{+\cdot}$, 8%) 263 (90%), 249 (100%); UV nm (log ε) 240 (4.62), 250 (4.48), 261 (4.34), 290 (3.95), 299 (4.24), 330 (3.59), 3.40 (3.56). NMR ($CDCl_3$) 1.5 (d, J = 6.5 Hz, CH_3), 2.31 (s, CH_3), 2.48 (s, NCH_3), 3.78 (q, J = 6.5 Hz, 1 H, H-19).

Method B. To a solution of the secondary amine **15** (2.38 g, 10 mmol) in methanol (100 ml) was added 10 N HCl to make the solution strongly acidic. The solution was refluxed for 7 days and acetaldehyde (2 ml) was added every day. The reaction mixture was then extracted and the crude product (starting material and guatambuine) was purified by chromatography on a silicagel column. Elution with $CHCl_3$: methanol (98:2) gave pure guatambuine (0.88 g, Y: 33%).

Olivacine **4**

A solution of (±) guatambuine **18** (0.264 g, 1 mmol) in decalin (20 ml) was refluxed with 10% palladium–charcoal (0.250 g) for 24 hr. The reaction mixture was diluted with hexane (100 ml) and extracted with CH_3OH (5 × 20 ml). The CH_3OH extract was washed with hexane and diluted with aqueous ammonia. Half of the CH_3OH was distilled. The concentrated phase was then extracted with $CHCl_3$ (3 × 40 ml). The $CHCl_3$ extracts were washed, dried and evaporated leaving a crude product purified by elution from a silicagel column. Olivacine (0.060 g, Y: 24%) was crystallized from ether–methanol: m.p. > 300°; $C_{17}H_{14}N_2$; MS *m/e* 246 ($M^{+\cdot}$). IR superimposable on that of the natural product.

4-*Acetylpyridine ethyleneketal* **19**

The ketone (60 g), toluene (1.3 l), ethylene glycol (30 g) and toluene-p-sulfonic acid (20 g) were refluxed together under a Dean-Stark head for 56 hr. Further ethylene glycol (6 × 5 g) was added in small portions every 8 hr. The toluene solution was evaporated under vacuum in the presence of N ammonia solution. The aqueous solution was then extracted with $CHCl_3$. The combined $CHCl_3$ phases were washed, dried and distilled. The residue was purified by distillation (57.5 g, Y: 70%): b.p. 113° (15 mm Hg). The liquid ketal solidified at room temperature: m.p. 50°; $C_9H_{11}NO_2$; MS *m/e* 165 ($M^{+\cdot}$); NMR ($CDCl_3$) 1.61 (s, CH_3), 3.80 and 4.08 (2m, CH_2–CH_2).

Tetrahydropyridine **20**

The pyridine **19** (57.5 g) was quaternarized with CH_3I in acetonitrile (1.4 l) and the salt (m.p. 135° from benzene) was reduced with $NaBH_4$ in methanol according to usual procedures. The tetrahydropyridine was distilled b.p. 114° (17 mm Hg); overall yield: 81%; $C_{10}H_{17}O_2N$: MS *m/e* 183 ($M^{+\cdot}$); NMR ($CDCl_3$) 1.43 (s, CH_3) 2.34 (s, N–CH_3), 3.76 (m, CH_2–CH_2), 5.82 (m, 1 H).

N-Oxide **21**

A solution of **20** (5 g, 27 mmol) in 300 ml CH_2Cl_2 containing 30% EtOH was heated with 30% hydrogen peroxide (5 ml) at reflux for 70 hr. Excess peroxide was then destroyed by the addition of 10% Pd/C, stirring at reflux for 2 hr. Once the reaction mixture was free of all traces of unreacted peroxide it was filtered through a bed of celite and concentrated to give a colorless liquid (5.4 g). NMR ($CDCl_3$): 1.45 (s, CH_3) 3.15 (s, N–CH_3) 3.90 (m, CH_2–CH_2) 5.84 (m, 1 H).

2-*Cyano* Δ3-*piperidine* **22**

The N-oxide (3.5 g, 17.5 mmol) was dissolved in CH_2Cl_2 (30 ml) and stirred under an argon atmosphere at 0°. Trifluoroacetic anhydride (2 ml) was added *via* a syringe and the solution stirred for 15 min. The resulting reaction mixture was then concentrated in vacuo and reacted with an aqueous solution of potassium cyanide (5 g) in water (30 ml). The aqueous layer was quickly adjusted to pH 4.0 by addition of trifluoracetic acid. The reaction was stirred for 20 min and extracted with CH_2Cl_2 (3 × 20 ml). The combined organic layers were washed, dried and distilled.

A colourless oil (1.65 g, Y 45%) was obtained: MS *m/e* (rel intensity) 208 ($M^{+\cdot}$, 10), 180 (15), 121 (17), 87 (100). NMR ($CDCl_3$) 1.43 (s, CH_3), 2.49 (s, NCH_3) 3.90 (m, CH_2–CH_2), 4.1 (m, 1 H, N–CH–CN), 5.9 (1 H). IR 2222 cm^{-1} (W).

Tetrahydropyridine **23**

Methylmagnesium bromide (solution 2M in ether: 3 ml) was added slowly *via* syringe to a solution of aminonitrile **22** (1.110 g, 5.3 mmol) in THF (30 ml) which was stirred at $-10°$ under an argon atmosphere. The solution was allowed to warm up slowly to room temperature ($\sim$1 hr). The reaction was then stopped by the addition of an aqueous solution of $(NH_4)_2SO_4$ and extracted with CH_2Cl_2. The residue was purified by bulb to bulb distillation b.p. 110° (2 mm, Hg) (Y: 57%) MS *m/e* (rel intensity) 197 ($M^{+\cdot}$, 6), 182 (95), 110 (100), 87 (26). NMR ($CDCl_3$) 1.12 (d, J = 6.5 Hz, CH_3) 1.40 (s, CH_3), 2.35 (s, NCH_3), 3.85 (m, CH_2–CH_2), 5.63 (s, broad, 1 H).

Carbazole **24**

The carbazole **24** was synthesised according to the procedure used to prepare **15**. The yield after purification by preparative thick layer chromatography on silicagel was 5%. MS *m/e* (rel. intensity) 2.52 ($M^{+\cdot}$, 9%) 209 (21) 196 (100). NMR ($CDCl_3$): 2.40, 2.41, 2.49 (3s, CH_3).

N-methyl-tetrahydro-ellipticine **25**

As described for the preparation of **18**, **24** was reacted with 40% formaldehyde solution (Y: 53%). m.p. 215° (methanol), MS *m/e* (rel intensity) 264 ($M^{+\cdot}$, 70), 263 (100), 249 (55), 221 (80); UV nm (log ε) 229 (4.48), 240 (4.69), 249 (4.55), 262 (4.33), 285 (3.97), 2.95 (4.26), 317 (3.40), 327 (3.59), 340 (3.57). NMR ($CDCl_3$) 2.28 (s, CH_3), 2.49 (s, CH_3), 2.63 (s, N–CH_3). This compound was identical in all respects with the natural product.

Ellipticine **5**

Ellipticine was obtained from **25** as described for olivacine **4** from (±) guatambuine **18** (Y: 36%). The product was identical with an authentic sample of ellipticine.

Carbazole **26**

The derivative **26** was prepared according to the procedure used for **15** (method B) (Y: 90%); **26** was crystallized as its acetate m.p.: 250° (water) dec. Base $C_{17}H_{20}N_2O$; MS *m/e* (rel intensity) 268 ($M^{+\cdot}$, 32), 225 (100); NMR ($CDCl_3$) 2.45 (s, NCH_3), 2.47 (s, CH_3), 3.91 (s, OCH_3).

(±)-10-*Methoxy guatambuine* **27**

The secondary amine **26** was acetylated according to the preparation of **16** (method B) (Y: 63%) m.p. 171° (methanol) MS *m/e* (rel intensity) 310 ($M^{+\cdot}$, 44) 237 (100), 224 (96). The amide was then treated as **16** (method A) to afford (±)-10-methoxy guatambuine **27** (overall yield 76%): m.p. 95° (ethanol); $C_{19}H_{22}N_2O$; MS *m/e* (rel intensity) 294 ($M^{+\cdot}$, 4), 279 (100). All physical data were in accordance with those given by Burnell and Della Casa.[14]

10-*Methoxy olivacine* **28**

The compound **27** was dehydrogenated and demethylated according to the procedure used for olivacine **4** (Y: 52%). Physical data were identical with those of the natural product.[14]

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 247 to 255, 1981
Printed in Great Britain

0040-4020/81/Suppl. 1-0247-09 $02.00/0
Pergamon Press Ltd.

CATIONIC π-CYCLISATION OF α,β-UNSATURATED CARBONYL COMPOUNDS

P. NAEGELI* and M. WETLI
Givaudan Research Company, 8600 Dübendorf, Switzerland

(*Received in Germany* 2 *July* 1980)

Abstract—Several olefinic α,β-unsaturated carbonyl compounds have been cyclized by Lewis acid and the structures of the products determined. In only one case a spirocyclisation with concomitant 1,3-hydride-shift has been observed besides intramolecular cycloaddition. In the other cases there was either no reaction or a 6-endo-trig cyclisation with further rearrangement took place.

Recently[1] we reported about the stereochemical course of a Lewis acid-catalyzed cyclisation on a γ–δ unsaturated vinylic ketone giving two spiro [4.5] decenones in equal amounts. It was shown that after an initial 6-*exo*-trig process[2] of the cationic metalloenolate species a 1,3-hydride shift led to the α,β-unsaturated product ketones (diagram 1). With the present work we intended to use the same principle for building up the spiro [5.5] undecenone skeleton related to the naturally occurring sesquiterpenes α- and β-chamigrene.

Therefore we prepared compound **7** in six steps starting from β-ionone (diagram 6) and subjected it to different protonic and Lewis acids. With stannic chloride in benzene solution at room temperature a very clean reaction ensued furnishing two products **8** and **9** in the ratio 3:7 (80% yield, diagram 2). Chromatographic separation proved to be extremely tedious in the gas phase and practically impossible on columns or thin layer plates. After reduction with LAH in diethyl ether the three alcohols formed could be purified chromatographically on aluminium oxide and

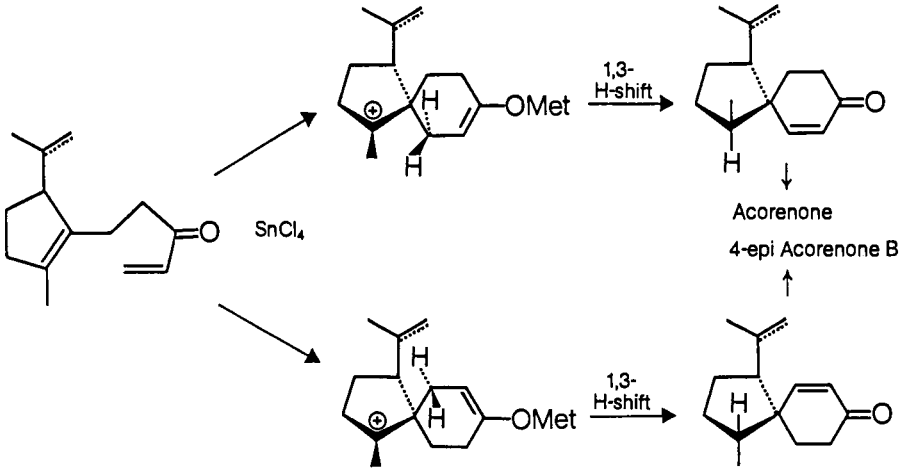

Diagram 1.

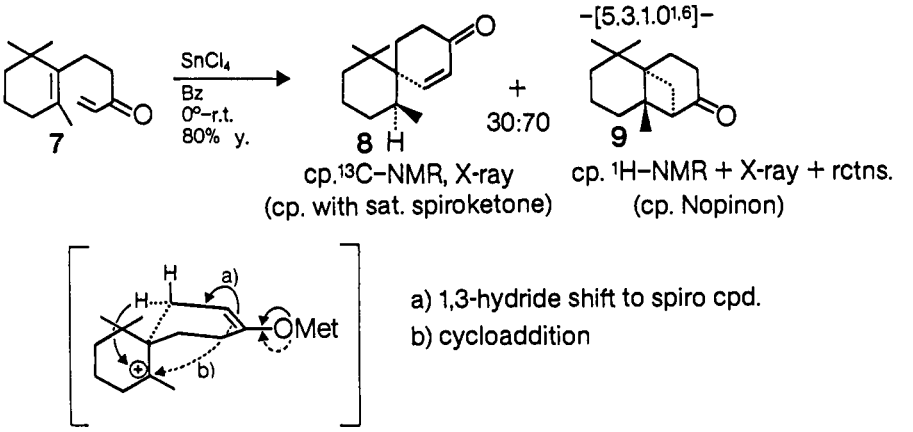

Diagram 2.

reoxidized by Jones reagent in acetone at $-10°$. Thus the alcohol first eluted gave **9** and the mixture of allylic alcohols gave **8** again (diagram 2).

The overall structure of **8** could be deduced fairly straightforward from its spectra. Besides showing a molecular ion at 206 with a parent peak at 122 *m/e* an UV absorption maximum at 236 nm ($\log \varepsilon = 4$) and a CO band at 1680 cm^{-1} in the IR suggested an isomeric α,β-unsaturated ketone in a 6- or higher membered ring. This was confirmed by the nuclear resonance frequencies of two vinylic protons appearing at $\delta = 6{,}60$ and 6,10 ppm as doublets with coupling constants of 10 c/s. In addition no Me group on a double bond was visible any more but two Me singlets at $\delta = 1{,}05$ and 0,98 ppm still appeared. The decision in favour of a spirocyclohexenone and against an anellated cycloheptenone system was done on grounds of a Me group in the PMR spectrum appearing as a doublet at $\delta = 0{,}81$ ppm with a coupling constant of 7 c/s.

Less clear was the stereochemistry about the spirocentre. We tried to find out by looking at the ^{13}C-chemical shifts of the methylene–C atoms in vicinal position to this centre. As a basis we had to look at the fully saturated spiroketone **8a** in its most stable conformation with only one axial Me group (diagram 3). By europium shift experiments it was possible to place these two triplets at $\delta = 21{,}5$ and 28,1 ppm.

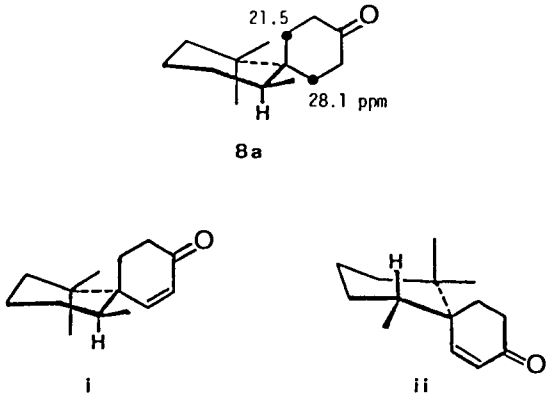

Diagram 3.

We believe that the difference in chemical shift of these two C atoms is mainly due to the different number of γ-gauche effects being exerted upon them.[1] In fact in **8a** the pointed C atom in axial position is subjected to four γ-*gauche* effects while the pointed C atom in equatorial position "feels" only three, the difference being 6,6 ppm.[1] Looking now at the original ketone **8** we determined the chemical shift for the single methylene carbon in α-position to the spirocentre to be 20.75 ppm, pointing to the influence of four γ-*gauche* effects. If we consider the two possible spiroconfigurations i and ii of the molecule in its most stable conformations, we can count again 4 γ-*gauche* effects for i and only 3 for ii. Therefore there is a preference to configuration i for ketone **8**. Because this argument gives no proof of the stereochemistry of the molecule we had an X-ray crystallographic structure determination done on the oxime derivative. The structure problem was solved by direct methods and the refinement converged at $R = 7.85\%$.[3] This determination confirmed structure **8** as shown in diagram 2 in every detail.

One tends to suggest a simultaneous 1,3-hydride shift during the described cyclisation.[1] A cyclopropane could also be formed first and reprotonated to give exactly the same stereochemistry but in view of the extreme cleanliness of the reaction it would seem to be an elusive compound.

The structure of the main product **9** had to be isomeric (molecular ion at *m/e* 206 with parent peak at 121) and tricyclic because besides a CO carbon at $\delta = 214{,}1$ ppm there was no resonance signal below 56 ppm in the ^{13}C-NMR spectrum. The IR absorption at 1700 cm^{-1} (in $CHCl_3$ soln) suggested a 6 or higher membered ketone. As with compound **8** there were no Me groups on a double bond but three tertiary Me groups visible in the proton NMR spectrum.

Structure **9** having 2 6-membered and one 4-membered ring, was preferred to two cyclopropane alternatives (with or without 1,2-shifted methyl group) because there was no indication of cyclopropane hydrogens in the proton NMR spectrum and no special absorption in the UV spectrum. A comparison with the proton NMR spectrum of nopinone showed striking similarities to **9**. In addition the chemical transformations described below beginning with the insensitivity towards acid would have made an additional structure proof obsolete. All the same an X-ray crystallographic determination of the oxime was done[3] and solved by direct methods, the refinement converging at $R = 9{,}03\%$. This work confirmed structure **9** as shown in diagram 2 in every detail.

Mechanistically the observed cycloaddition of the cationic metalloenolate intermediate is an interesting alternative to the 1,3-hydride shift or cyclopropane formation. The tricyclo-$[5.3.1.0^{1,6}]$-undecane system has been made before by an intramolecular ketene addition to an α,β-unsaturated ketone group to form a cyclobutanone.[4] As a minor product the system with the CO in the 6-membered ring was formed in an intramolecular photo-addition of an olefinic side chain to a cyclohexenone function.[5] It does not seem possible to achieve photocycloaddition of an α,β-unsaturated CO group in a side chain to a double bond in a ring as in **7**.

Ketone **9** was easily brominated in carbon tetrachloride showing a good enolisation tendency which proved a disadvantage in the addition reactions with Grignard reagents or alkyl lithium compounds. Thus the reaction with methyl lithium had to be run five times in consequence in order to get to virtually pure tertiary alcohol **10** (diagram 4). Treatment of **10** with *p*-toluenesulphonic acid in benzene at 55° formed a mixture of hydrocarbons in very good yield. Repeated column chromatography on silicagel impregnated with 15% silver nitrate allowed the separation of all six compounds formed in the dehydration reaction.

Product **13**, **12** + **16**, **17**, **14**, **15** appeared in this order on a UCON glass-capillary glc-column in the ratio indicated in diagram 4. **14** and **15** were identified with the spectra of authentic β- and α-chamigrene. The structure of the main compound **13** was deduced by analysis of its spectra and especially by comparison with the PMR spectrum of α-pinene. For hydrocarbon **12** the same as above holds. But in addition to the close spectral relations with β-pinene it could be synthesized

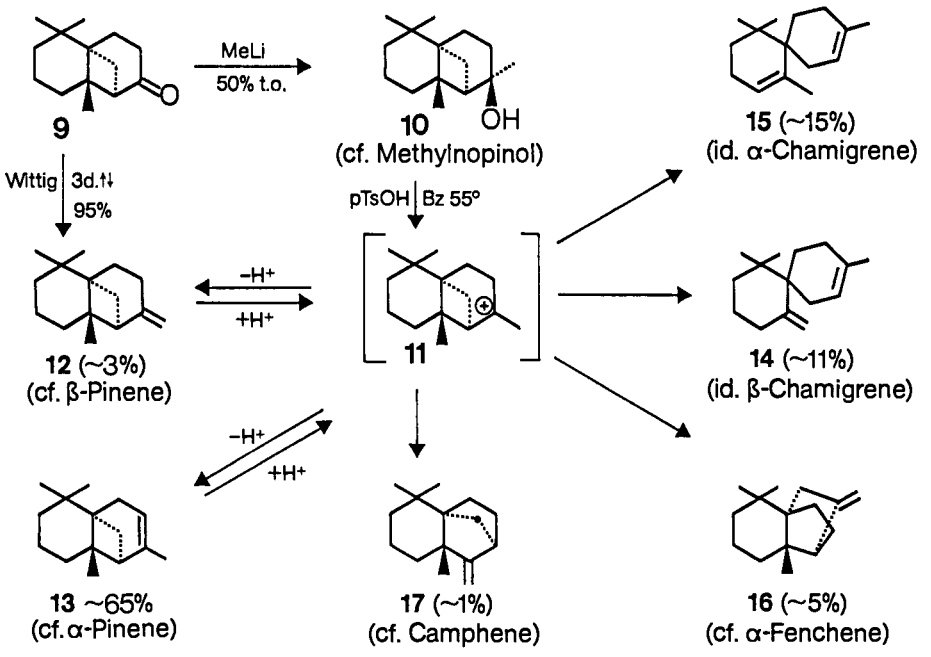

Diagram 4.

by treating tricyclic ketone **9** with methyl triphenyl phosphorane in refluxing THF and identified directly. In addition the treatment of **12** with *p*-toluenesulphonic acid in benzene gave among others **13** as main product.

Structures **16** and **17** are tentative. Because of lack of material there were no further chemical transformations made. According to their NMR-spectral data, they are both containing one methylidene group and three angular Me's. The mass spectra were clearly different from one another and also from anything known. They confirmed only molecular weight 204 and tricyclic structure of the two new hydrocarbons. The structures **16** and **17** in diagram 5 are suggested because they can be derived from cation **11** by two simple and well-known rearrangement steps. Furthermore a comparison of the PMR resonances of the two exomethylene protons of **16** with those of α-fenchene and of **17** with those of camphene showed strikingly close similarities in difference of chemical shift and especially in the coupling pattern.

The same type of cyclisation with stannic chloride was also tried on carbonyl compounds **24**, **30** and **37** (diagrams 6 and 7), hoping for spirocyclisation, in the case of **24** to build up the skeleton of the marine sesquiterpenoid spirolaurenone. We would like to add

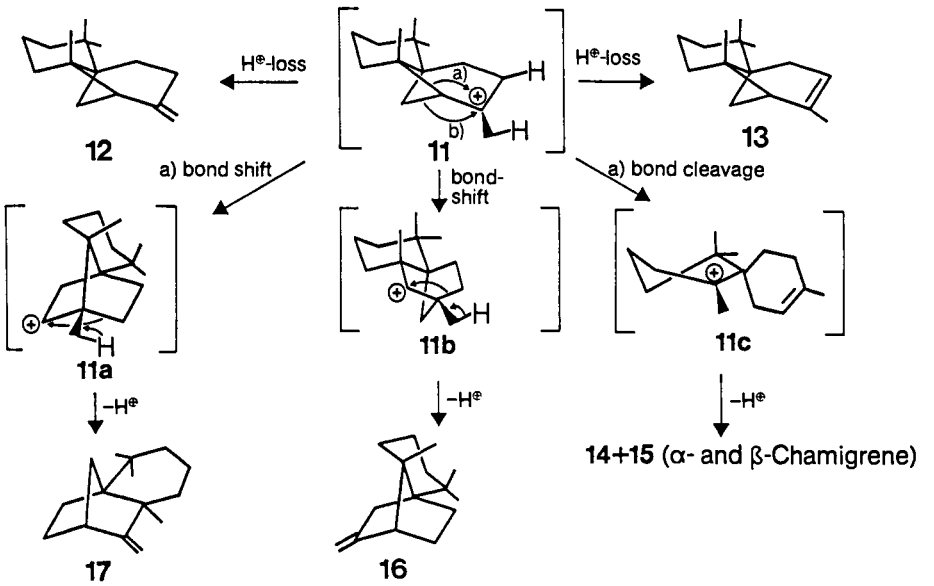

Diagram 5.

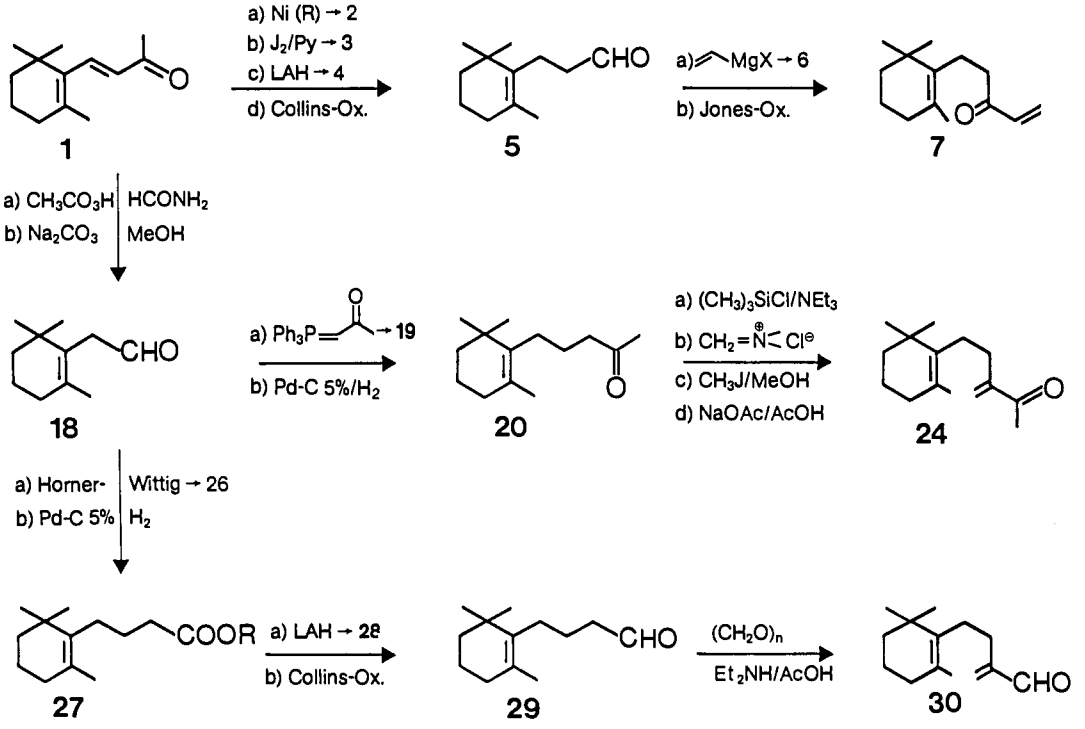

Diagram 6.

here one remark concerning the preparation of ketone **24**. The only profitable way for the Mannich type synthesis was the smooth reaction of the thermodynamically formed silyl-enol-ether of **20** with dimethyl-methylene–immonium chloride in acetonitrile and subsequent quaternization with methyl iodide and mild β-elimination of trimethylamine with the help of bicarbonate[6] or acetate. In the case of **37** (preparation see Experimental) all our attempts to cyclize this ketone by action of Lewis acids failed. There was no sign of either of the two favoured processes, the 5-*exo*-trig or the 6-*endo*-trig cyclisation[2] but rather if anything happened polymerization took place.

We subjected the aldehyde **30** to the action of stannic chloride in a benzene–toluene solvent mixture

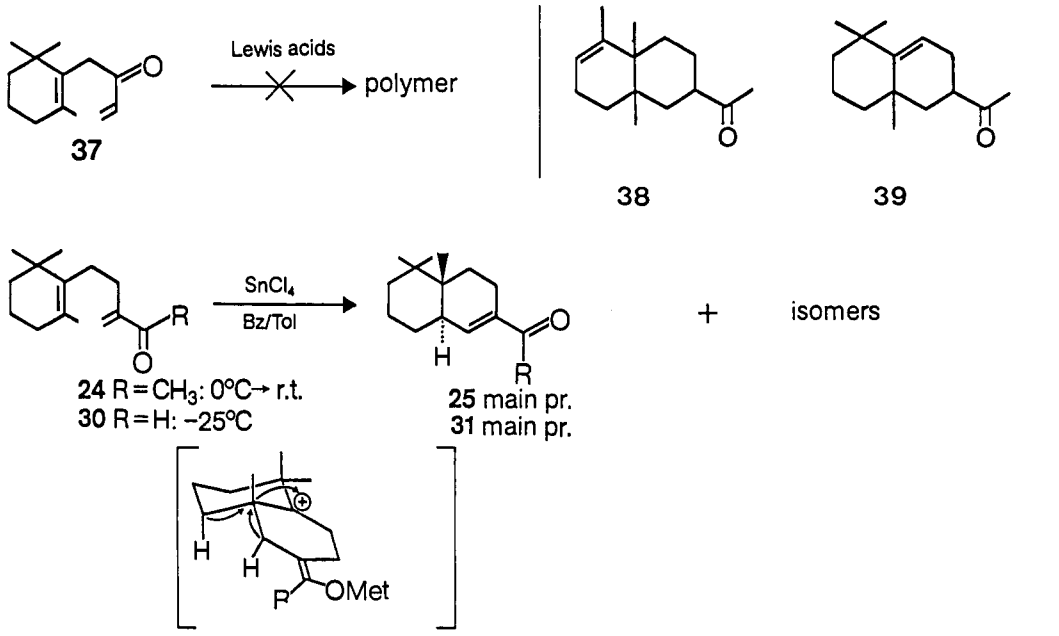

Diagram 7.

at -25 to $-20°$ for about 30 min until the starting material had virtually disappeared. The crude product contained one main product ($\sim 60\%$) that could be well separated by gaschromatographic techniques from a series of 8 to 10 minor products. According to mass, UV and IR spectra it was clearly an isomeric aldehyde with a conjugated trisubstituted double bond. The proton NMR spectrum confirmed these apparent features with resonances at $\delta = 9.40$ (sharp s) and $\delta = 6.46$ ppm (small q) each accounting for 1 proton.

Furthermore three singlets, each for three H atoms at $\delta = 0.985$ and 0.850 and 0.786 ppm accounted for three tertiary Me groups. Downfield from $\delta = 1.8$ ppm there were only three more protons accounting for the allylic positions 5 and 8. Analysis of the couplings spoke in favour of an axial proton in 5 *trans* configurated to the angular Me group in 10 as depicted in formula **31**. No evidence for a 5-*exo*-trig cyclisation to a spiro compound could be gained from spectral analysis of the more prominent minor reaction products.

The analogous cyclisation reaction of ketone **24** was slower and gave a more complex product mixture. The main product and the major by-products were separated through column-chromatography on silicagel and purified by preparative gas-chromatography.

The main cyclisation product could be assigned structure **25** on grounds of IR, UV, mass and PMR spectra being analogous to those of aldehyde **31** (Experimental). There was again no evidence whatsoever for the 5-*exo*-trig process to spiro compounds nor were there products suggesting a 1,3-hydride shift during the multistep reaction. The dominant feature in these two cases seems to be a 6-*endo*-trig-cyclisation with further rearrangements (Me shifts, proton loss and double bond isomerization). The major by-products in the above reaction were two non-conjugated methyl ketones. Both of them, according to their PMR absorptions especially, are also logic derivatives of the primarily formed cationic metal enolate i.e. either Me migration from position 1 with subsequent proton loss from carbon 2 to give **38** or simply proton loss from carbon 9 to form **39** (diagram 7).

EXPERIMENTAL

Preparation of **2**. Although being a known compound we describe a procedure that will consistently yield **2** of 90% purity in almost quantitative yield, the tetrahydroionone being the main by-product. Through careful fractional distillation under vacuum (~ 0.1 Torr) the crude **2** can be purified to a higher degree (95% or better). The catalyst after two initial hydrogenation batches not giving good quality hydrogenation, can be reused for the same purpose at least ten times. For a one-mole batch by hydrogenation at room temp and normal pressure one takes 30 ml Raney–Ni sedimented in EtOH (Fluka puriss, Buchs, Switzerland) which corresponds to about 18 g metal catalyst. After washing it with EtOAc it is combined with a soln of 200 mg 1,2-Bis(2-hydroxy-ethylthio)-ethane in 30 ml MeOH. Then this preparation is added to a soln of 192 g (1 mole) β-ionone in 1200 ml EtOAc. The hydrogen take-up is monitored and after 251 the reaction can be stopped although the hydrogenation curve is not completely horizontal. H-NMR ($CDCl_3$ plus TMS on Bruker WH 360): s(3 H) at $\delta = 2.143$; s(3 H) at $\delta = 1.568$; s(6 H) at $\delta = 0.98$; (dd(2 H, J = 8 and 8 c/s) at $\delta = 2.5$; dd(2 H, J = 8 and 8 c/s) at $\delta = 2.255$; pseudo t(2 H) at $\delta = 2.40$ (J = 6 c/s); m(2 H) at $\delta = 1.568$ and m(2 H) at $\delta = 1.416$ ppm.

Preparation of **3** was done according to lit.[7] reaching 60% crystalline acid after distillation at 0.06 Torr, 102°. Similarly **4**[7] and **5**[8] were prepared according to lit.

Preparation of **6**. 16 g (667 mmoles) Mg turnings were covered by 100 ml dry THF and a small amount of vinyl bromide added. After the reaction started the remaining 51 ml (690 mmoles) of vinyl bromide and 900 ml of THF were added in order to keep the soln at 60–65°. After additional 30 min stirring at the same temp the grey soln was kept at 35° while 41.6 g aldehyde **5** (230 mmoles) was added dropwise. The mixture was stirred at 35° for 2 more hr before it was diluted with sat NH_4Cl, extracted with ether, washed and dried in the usual way. After evaporation of the solvent the crude product was short path distilled at $\sim 75°/0{,}001$ Torr to give 45,5 g (94%) **6** (Found: C, 80.54; H, 11.62; $C_{14}H_{24}O$ requires: C, 80.71; H, 11.61%). ν_{max} (neat) 3350, 3090, 1640, 920 cm^{-1}. MS (CEC 21–110 B): M^+ 208 (16) *m/e* = 193 (5), 175 (19), 147 (4), 136 (17), 123 (100), 109 (19), 95 (41), 81 (29), 69 (25), 55 (18), 41 (16); H-NMR ($CDCl_3$ plus TMS on Varian EM 360): dq (1 H, J = 17, 10, 6 *c/s*) at $\delta = 5.92$; broad d (1 H, J = 17 c/s) at $\delta = 5.19$; broad d (1 H, J = 10 c/s) at $\delta = 5.10$; broad q (1 H, J = 6 c/s) at $\delta = 4.1$; s (3 H) at $\delta = 1.56$; s (6 H) at $\delta = 0.95$ ppm.

Preparation of **7**. 20.8 g (0,1 mole) **6** was dissolved in 700 ml acetone and kept at $-10°$. Under vigorous stirring 40 ml Jones reagent (0,106 mole CrO_3) was added dropwise and the temp finally reached 0°. After five more min further stirring the mixture was worked up with ether–water, washed to neutrality, dried and evaporated. Short path distillation at 50°/0.06 Torr gave 18.1 g pure **7** (88%); (Found: C, 81.18; H, 10.94; $C_{14}H_{22}O$ requires: C, 81.50; H, 10.75%). λ_{max} 213 nm ($\varepsilon = 9500$ in EtOH). ν_{max} (neat) 1695/1685, 1615, 1092, 985, 960 cm^{-1}. MS (CEC 21–110 B): M^+ 206 (14) *m/e* = 191 (24), 188 (27), 173 (28), 163 (3), 145 (5), 136 (55), 121 (100), 107 (19), 93 (30), 79/81 (16), 69 (14), 55 (33), 41 (19). H-NMR ($CDCl_3$ plus TMS on Bruker WH 360): $\delta = 6.36$ (1 H, dd, J = 18/10 c/s); $\delta = 6.22$ (1 H, split d, J = 18/1 c/s); $\delta = 5.82$ (1 H, split, J = 10/1 c/s); $\delta = 2.650$ (2 H, m, J = 8 c/s + +); $\delta = 2.310$ (2 H, m, J = 8 c/s + +); $\delta = 1.920$ (2 H, broad pseudo t, J = 6 c/s); $\delta = 1.590$ (3 H, s); $\delta = 1.575$ (2 H, m); $\delta = 1.428$ (2 H, m); $\delta = 0.990$ ppm (3 H, s).

Preparation of **8** *and* **9**. To 25.8 g (125 mmoles) of **7**, dissolved in 1250 ml dry benzene plus 250 ml dry ether, 275 ml of a soln of stannic chloride in benzene (0.5 molar) were added at $-5°$. After addition the soln was stirred and slowly (3–4 hr) brought to room temp and left overnight. The mixture was then poured into an excess of sat bicarbonate–ice mixture and extracted thoroughly with ether. After washing to neutral and drying, the solvent was evaporated to give 28 g of a viscous yellow oil which was short path distilled at 70–78°/0.01 Torr ($\sim 10\%$ residue). The distillate was semicrystalline and consisted of **8** and **9** in a ratio of roughly 1:2. This distillate was dissolved in 100 ml ether and added dropwise to a stirred suspension of 1.64 g (43.3 mmoles) LAH in 1 l ether at room temp. After 3 hr stirring sat NH_4Cl was carefully added. A sandy ppt formed which was separated by decantation and twice washed with ether. After washing the combined organic layer to neutrality, drying with $MgSO_4$ and evaporation 25.1 g semicrystalline product was obtained. Chromatography on the 65-fold weight silicagel (0.06–0.2 mm particle size) using hexane–ether eluted the tricyclic alcohol first (m.p. 96–98.5°) and then the spiroalcohols (with hexane ÷ ether = 50 ÷ 50). They were individually re-oxidized with Jones reagent in acetone soln at $-10°$ to give **8** and **9** again in pure state after Kugelrohr-distillation.

Data of **8**, λ_{max} 236 nm ($\varepsilon = 10000$ in EtOH). ν_{max} (neat) 1680, 1620, 1380, 1365, 970/960/940, 865, 795, 750 cm^{-1}; MS (Varian-MAT CH5): M^+ 206 (85), *m/e* = 191 (16), 171 (4), 163 (17), 149 (12), 136 (20), 122 (100), 107 (40), 94 (69), 79 (80), 69 (40), 55 (38), 41 (50), 29 (12). H-NMR ($CDCl_3$ plus TMS on Varian XL-100): d (1 H, J = 10 c/s) at $\delta = 6.60$; d (1 H, J = 10 c/s) at $\delta = 6.10$; sharply split group (2 H) at

$\delta = 2.6$–2.4; s (3 H) at $\delta = 1.05$; s (3 H) at $\delta = 0.98$; d (3 H, J = 7 c/s) at $\delta = 0.81$ ppm. ^{13}C-NMR ($CDCl_3$ plus TMS on Varian XL-100; shift experiment with $Eu(fod)_3$-d_{27}); singlets at $\delta = 199.2/44.1/38.7$ ppm; doublets at $\delta = 156.6/129.8/36.2$ ppm; triplets at $\delta = 36.7/35.8/29.6/21.8/20.75$ ppm; quartets at $\delta = 28.5/23.2/17.95$ ppm. The oxime of **8** was made with freshly prepared hydroxylamine acetate in refluxing ethanolic soln and extracted from the diluted reaction mixture with ether. Recrystallization from ether–hexane or methylene chloride–hexane mixtures gives needles having a m.p. 176–177° (Found: C, 75.91; H, 10.27; N, 6.29%; $C_{14}H_{23}ON$ requires: C, 75.97; H, 10.47; N, 6.33%).

Data of **9** (Found: C, 81.50; H, 10.98%; $C_{14}H_{22}O$ requires: C, 81.50; H, 10.75%) m.p. 145–150° (waxy crystals). ν_{max} ($CHCl_3$) 1700, 1450, 1408, 1375, 1360, 1295, 1045, 970 cm^{-1}. MS (Varian MAT CH5): M$^+$ 206 (26), *m/e* = 191 (30), 188 (77), 173 (35), 163 (16), 149 (18), 136 (78), 121 (100), 109 (55), 93 (83), 79 (74), 69 (50), 55 (64), 41 (76), 39 (36), 27 (19). H–NMR ($CDCl_3$ plus TMS on Bruker WH 360): $\delta = 2.545$ (1 H, dq, J = 18/10/7 c/s); $\delta = 2.415$ (1 H, broad dd, J = 10/6 c/s); $\delta = 2.365$ (1 H, d, J = 6 c/s); $\delta = 2.348$ (1 H, dd, J = 18/9/1.5 c/s); $\delta = 1.962$ (1 H, broad dd, J = 14/10 c/s); $\delta = 1.860$–1.660 (2 H, m); $\delta = 1.545$ (1 H, sharp d, J = 10 c/s belonging to hydrogen on cyclobutane bridge, coupling only with its geminal partner and pointing towards carbonyl side of the molecule); $\delta = 1.318$ (1 H, dm with J_1 = 13 c/s); $\delta = 0.91$ (3 H, s); $\delta = 0.845$ (3 H, s); $\delta = 0.785$ ppm (3 H, s). The best substance for spectral comparison in this case is nopinone. ^{13}C-NMR ($CDCl_3$ plus TMS on Varian XL-100; shift experiment with $Eu(fod)_3$-d_{27}): singlets at $\delta = 214.1/48.0/42.4/32.4$ ppm; doublet at $\delta = 55.8$ ppm; triplets at $\delta = 38.8/36.2/33.3/25.6/22.5/18.1$ ppm; quartets at $\delta = 25.2/23.5/20.7$ ppm. The oxime of **9** was prepared as described above and recrystallized from ether–hexane, m.p. 159–160°.

Preparation of **8a**. 618 mg (3 mmoles) of **8**, dissolved in 25 ml dry EtOAc were hydrogenated completely in presence of 0.5 g pre-hydrogenated platinum oxide (Adams catalyst) at room temp and normal pressure. After filtration over Celite and evaporation of the solvent, 610 mg fully saturated alcohol-mixture, m.p. ~65–75° was obtained. Jones oxidation in acetone at −10° gave after normal work-up 590 mg **8a** m.p. 60–62° (~95% purity). ν_{max} ($CHCl_3$) 1710, 1475/1465, 1405, 1390, 1330, 1150, 975, 960/950, 925, 895, 850, 830 cm^{-1}. MS (Varian MAT CH5): M$^+$ 208 (55), *m/e* = 193 (2), 175 (2), 165 (2), 161 (2), 150 (4), 137 (10), 123 (100), 109 (24), 95 (17), 82 (22), 69 (19), 55 (22), 41 (21), 29 (6). H-NMR ($CDCl_3$ plus TMS on Varian XL-100): $\delta = 2.48$–2.15 (4 H, m); $\delta = 0.96$ (6 H, s); $\delta = 0.99$ ppm (3 H, d, J = 7 c/s). ^{13}C-NMR ($CDCl_3$ plus TMS on Varian XL-100; shift experiment with $Eu(fod)_3$-d_{27}): singlets at $\delta = 214/38.3/38.1$ ppm; doublet at $\delta = 38.1$ ppm; triplets at $\delta = 38.9/38.7/37.3/31.0/\underline{28.1}/21.8/\underline{21.5}$ ppm; quartets at $\delta = 27.0/22.6/18.2$ ppm.

Preparation of **10**. 3.1 g (15 mmoles) of **9** were dissolved in 150 ml dry ether and a soln of 10 ml MeLi in ether (18 mmoles) was added at room temp. Stirring was continued for 30 min and then the mixture was poured into crushed ice–hexane (pH 10–11), washed to neutrality, dried and the solvents evaporated. The crude product showed 50% starting material. Therefore the same procedure was repeated five times. 2.9 g crystalline **10** resulted. (Found: C, 81.12; H, 11.89%; $C_{15}H_{26}O$ requires: C, 81.02; H, 11.79%). After recrystallization from hexane the m.p. was 110–111°. ν_{max} ($CHCl_3$) 3650, 3480, 1370/1360, 1130, 1102, 1090, 1035, 990, 975, 935, 905/900, 885/880 cm^{-1}. MS (Varian MAT CH5): M$^+$ 222 (4), *m/e* = 207 (7), 204 (100), 189 (56), 161 (35), 147/148/151 (22), 133 (43), 119 (98), 109 (65), 95 (99), 81 (55), 69 (43), 55 (41), 43 (60). H-NMR ($CDCl_3$ plus TMS on Bruker WH 360): $\delta = 2.135$ (1 H, split dd, J = 10/7/1 c/s); $\delta = 1.680$ (1 H, d, J = 7 c/s); $\delta = 0.985$ (1 H, d, J = 10 c/s); $\delta = 1.223$ (3 H, s); $\delta = 1.167$ (3 H, s); $\delta = 0.780$ (3 H, s); $\delta = 0.660$ ppm (3 H, s). ^{13}C-NMR ($CDCl_3$ plus TMS on Varian XL-100); singlets at $\delta = 74.55/47.8/39.5/32.2$ ppm; doublet at $\delta = 51.7$ ppm; triplets at $\delta = 38.8/36.8/33.0/28.2/24.4/18.1$ ppm; quartets at $\delta = 31.7/25.4/23.5/21.8$ ppm.

Preparation of **12**. 8.1 g (20 mmoles) triphenylphosphonium–iodide, suspended in 200 ml THF, was brought into contact with 10 ml (~20 mmoles) n-BuLi in hexane. The orange soln was stirred 1 hr at room temp before 4.12 g (20 mmoles) of **9** in 30 ml THF were added at −20°. Shortly after addition a ppt formed. After 24 hr at room temp analysis still showed 90% starting ketone present. Therefore the mixture was kept under reflux for another 2 days after which time the turnover was more than 90%. Pouring on ice, extraction with hexane and usual work-up gave 5 g crude oily product. This was chromatographed on 30 g silicagel. Hexane eluted 3.6 g (88%); pure **12** (Found: C, 87.81; H, 11.91%; $C_{15}H_{24}$ requires: C, 88.16; H, 11.84%); ν_{max} (neat) 3080, 1645, 1450, 1380/1370/1360, 1190, 1090, 1065, 980, 965, 875 cm^{-1}. MS (Varian MAT CH5): M$^+$ 204 (51), *m/e* = 189 (53), 175 (15), 161 (22), 148 (24), 137 (48), 133 (53), 123 (31), 119 (43), 111 (94), 105 (37), 95 (78), 93 (62), 91 (58), 81 (64), 69 (100), 55 (48), 41 (61). H-NMR ($CDCl_3$ plus TMS on Bruker WH 360): $\delta = 4.633$ (1 H, narrow m); $\delta = 4.566$ (1 H, narrow m); $\delta = 2.50$ (1 H, allyl. coupled dt, J = 17/9/2.5 c/s); $\delta = 2.27$ (1 H, ddd, J = 17/7/4 c/s); $\delta = 2.25$ (1 H, d, J = 6 c/s); $\delta = 2.20$ (1 H, dd, J = 9/6 c/s); $\delta = 1.375$ (1 H, d, J = 9 c/s); $\delta = 1.23$ (1 H, dm, J = 12 c/s); $\delta = 0.77$ (3 H, s); $\delta = 0.76$ (3 H, s); $\delta = 0.69$ ppm (3 H, s). (The best information for comparison is gained from β-pinene). ^{13}C-NMR ($CDCl_3$ plus TMS on Bruker WH 360); singlets at $\delta = 150.5/47.6/41.7/32.5$ ppm; doublet at $\delta = 49.7$ ppm; triplets at $\delta = 105.6/39.1/36.4/26.8/25.0/24.1/18.9$ ppm; quartets at $\delta = 25.5/23.4/20.6$ ppm.

Preparation of **13**, **16**, **17** (besides **12**, **14**, **15**). 2.45 g (11 mmoles) of **10** and 200 mg *p*-toluenesulfonic acid hydrate were dissolved in 65 ml dry benzene and kept at 55° bath temp for 5 hr (until no starting material was visible on glc). The water formed was pipetted out. After diluting with hexane the soln was washed to neutrality. The crude oily product was pre-purified on 8 thick layer plates (Merck) with the solvent system 25 pentane ÷ 25 hexane ÷ 50 $CHCl_3$ ÷ 5 EtOAc to yield 1.9 g (85%) of water–clear hydrocarbon mixture. Column chromatography on silicagel impregnated with 15% $AgNO_3$ (first on 100-fold weight, then again on 200-fold weight, particle size 0.06–0.2 mm) using hexane and 99 hexane ÷ 1 ether mixture and for a third column using hexane and 99 hexane ÷ 1 benzene mixture as eluant, allowed the separation in the following order: **13**, **15**, **16**, **17**, **12**, **14**.

Data of **13** (Found: C, 87.82; H, 12.07%; $C_{15}H_{24}$ requires: C, 88.16; H, 11.84%). ν_{max} (neat) 1470/1460/1455, 1380/1370/1360, 1330, 1190, 1165/1155, 1130, 1060, 1020, 980, 965, 895, 795, 785 cm^{-1}. MS (Varian MAT CH5): M$^+$ 204 (20), *m/e* = 189 (10), 175 (2), 161 (9), 147 (11), 133 (32), 119 (100), 111 (31), 105 (25), 93 (27), 81 (12), 77 (11), 69 (18), 55 (12), 41 (16), 29 (7). H-NMR ($CDCl_3$ plus TMS on Bruker WH 360): $\delta = 5.25$ (1 H, narrow m); $\delta = 2.27$ (1 H, dd, J = 8/6 c/s); $\delta = 2.09$ (1 H, dm, J = 16/~1 c/s); $\delta = 1.995$ (1 H, dm, J = 16/~1 c/s); $\delta = 1.756$ (1 H, dd, J = 6/~1 c/s); $\delta = 1.672$ (3 H, narrow m); $\delta = 1.215$ (1 H, dm, J = 12 c/s); $\delta = 1.044$ (1 H, d, J = 8 c/s); $\delta = 0.822$ (3 H, s); $\delta = 0.803$ (3 H, s); $\delta = 0.680$ ppm (3 H, s). ^{13}C-NMR ($CDCl_3$ plus TMS on Bruker WH 360): singlets at $\delta = 142.6/47.9/32.2$ ppm; doublets at $\delta = 117.3/45.1$ ppm; triplets at $\delta = 38.9/35.7/32.2/31.4/18.9$ ppm; quartets at $\delta = 24.9/23.3/22.6/19.5$ ppm. (The best information for comparison is gained from α-pinene).

Data of **16** (tentative structure, comparison in certain features with α-fenchene). H-NMR ($CDCl_3$ plus TMS on Bruker WH 360): $\delta = 4.712$ (1 H, narrow q); $\delta = 4.528$ (1 H, narrow q); $\delta = 2.545$ (1 H, broad d, J = 16 c/s); $\delta = 1.84$ (1 H, broad d, J = 16/~2 c/s); $\delta = 1.945$ (1 H, tm, allylic cpl); $\delta = 1.008$ (3 H, s); $\delta = 0.969$ (3 H, s); $\delta = 0.808$ ppm (3 H, s). MS (glc-coupling to Varian MAT 212, Finnigan–Incos data system): M$^+$ 204 (10), *m/e* = 189 (20), 175 (4), 161 (18), 148

(15), 133 (26), 119 (50), 108 (100), 93 (97), 79 (58), 69 (40), 55 (32), 41 (50).

Data of **17** (tentative structure, comparison in certain features with camphene: H-NMR ($CDCl_3$ plus TMS on Bruker WH 360): $\delta = 4.631$ (1 H, s); $\delta = 4.392$ (1 H, s); $\delta = 2.581$ (1 H, broad t, J ~ 5 c/s); $\delta = 2.072$ (2 H, d, J ~ 5 c/s) ?; $\delta = 0.969$ (3 H, s); $\delta = 0.900$ (3 H, s); $\delta = 0.883$ ppm (3 H, s). MS (glc-coupling to Varian MAT 212, Finnigan–Incos data system): M^+ 204 (55), *m/e* = 189 (36), 175 (14), 161 (36), 147 (40), 133 (100), 119 (62), 106 (87), 107 (90), 91 (95), 93 (66), 79 (63), 67 (32), 69 (28), 55 (38), 41 (57).

Preparation of **18**. This was done according to lit.[9]

Preparation of **37**.[10] 6.96 g (290 mmoles) magnesium turnings were covered with 60 ml dry THF and 1 ml vinyl bromide was added while heating the turnings in order to induce reaction. Then 600 ml THF and 21.3 ml (totally 300 mmoles) vinyl bromide was added within 15 min to keep the reaction going. After additional stirring for 30 min the grey-brownish soln was cooled to 20° and 16.63 g (100 mmoles) of **18** in 100 ml THF was added within 35 min at 30–35°. After 2 hr at 35–40° the reaction was complete and the work-up done with ice-cooled sat NH_4Cl and ether extraction. After drying and evaporating the solvent, 17.9 g (92 %) of a yellowish oil was obtained which according to IR neat (3450, 3100, 1645, 920 cm^{-1}) and H-NMR in $CDCl_3$ ($\delta = 5.98$, 1 H, dq with J = 17/10/5.5 c/s; $\delta = 4.28$, 1 H, broad q, J = 6.5 c/s; $\delta = 2.36$, 2 H, broad d, J = 7 c/s; $\delta = 1.7$, 3 H, s; $\delta = 1.07$ ppm, 6 H, s) has the structure of the expected **36**. To 15.5 g (80 mmoles) of **36**, dissolved in acetone, 32 ml Jones reagent (84.8 mmoles CrO_3) were added at −20°. After dilution with water and extraction with hexane, drying and evaporation of solvent 15 g (~90 %) of **37** remained ν_{max} (neat): 1695, 1620, 1470, 1400, 1325, 1190, 1080, 990, 965 cm^{-1}. MS (CEC21-110B): M^+ 192 (64), *m/e* = 177 (36), 159 (7), 149 (7), 137 (93), 122 (36), 107 (93), 95 (100), 81 (57), 69 (21), 55 (61), 41 (39). H-NMR ($CDCl_3$ plus TMS on Varian XL-100); $\delta = 6.40$ (2 H, m); $\delta = 5.75$ (1 H, dd, J = 8.5/2.5 c/s); $\delta = 3.32$ (2 H, s); $\delta = 2.02$ (2 H, broad dd, J = 5 c/s); $\delta = 1.52$ (3 H, s); $\delta = 0.93$ ppm (6 H, s).

Preparation of **19**[11]. To 49.8 g (0.3 mole) **18** in 750 ml benzene 96 g (0.3 mole) triphenylphosphorylidene acetone was added and the mixture stirred for 24 hr at 90° bath temp (70 % starting material still present). After addition of 500 mg benzoic acid and 24 hr stirring at the same temp a probe still showed about 20 % starting material. After addition of 66 g (210 mmoles) of the phosphorane the reaction was virtually complete after 24 hr under reflux temp. The brown soln was diluted with 3 l hexane and the ppt filtered off and re-washed with hexane and the hexane extract evaporated on a rotary evaporator (water pump) at 40°. The brown crystalline residue was dissolved in 100 ml 90 % MeOH and extracted three times with 500 ml hexane. The combined hexane extracts were again washed three times with 50 ml 90 % MeOH. All the MeOH extracts and the ppt were combined and twice extracted with hexane. After drying the total hexane soln and evaporating the solvent the yield was 54.3 g (88 %). This product had to be filtered as a hexane-soln through a layer of 55 g silicagel (0.06–0.2 mm) to assure a smooth hydrogenation. λ_{max} 227 nm (ε = 13000 EtOH). ν_{max} (neat): 1695/1680, 1625, 1360, 1258, 985 cm^{-1}. MS (CEC21–110B): M^+ 206 (60), *m/e* = 191 (54), 177 (14), 163 (12), 147 (25), 133 (58), 123 (92), 107 (98), 91 (54), 81 (40), 69 (18), 67 (17), 55 (25), 43 (100). H-NMR ($CDCl_3$ plus TMS on Varian EM 360): $\delta = 6.85$ (1 H, dt, J = 16/7 c/s); $\delta = 6.07$ (1 H, d of narrow m, J = 16 c/s); $\delta = 3.02$ (2 H, broad d, J = 5.5 c/s); $\delta = 2.28$ (3 H, s); $\delta = 1.60$ (3 H, s); $\delta = 1.02$ ppm (6 H, s).

Preparation of **20**. 12.5 g (60 mmoles) of **19** in 500 ml pentane were hydrogenated in the presence of 1.8 g 5 % Pd–C at room temp, strong stirring and normal pressure. As soon as the hydrogenation curve flattened out the soln was freed from the catalyst by filtration over Celite and evaporated to leave 12.2 g (97 %) colourless oil (b.p. 90°/0.005 Torr). ν_{max} (neat) 1710, 1358, 1170 cm^{-1}. MS (CEC21-110B): M^+ 208 (22), *m/e* = 193 (22), 175 (21), 150 (33), 135 (100), 123 (75), 107 (33), 94 (44), 81 (39), 71 (17), 67 (18), 55 (24), 43 (93). H-NMR ($CDCl_3$ plus TMS on Varian EM 360): $\delta = 2.32$ (2 H, broad t, J = 7.5 c/s); $\delta = 2.12$ (3 H, s); $\delta = 1.58$ (3 H, s); $\delta = 0.97$ ppm (6 H, s).

Preparation of **24**. 6.5 g = 7.6 ml (60 mmoles) of trimethylchlorosilane and 12.1 g = 16.6 ml (120 mmoles) Et_3N were dissolved in 20 ml DMF and 10.4 g (50 mmoles) of **20** added. A spontaneous ppt formed. The mixture was stirred at 96° for 4 days. Then it was diluted with hexane, washed with cold bicarbonate then with cold 1 N HCl and water. After drying and evaporating the solvent, 15.5 g crude material was obtained. After distillation with a Vigreux column in the presence of a little dry K_2CO_3 to yield 7.5 g (54 %) of **21**. In a 6-fold run the yield was 68 % (b.p. 70°/0.005 Torr or 96°/0.01 Torr). ν_{max} (neat): 1678, 1380, 1360/1345/1320, 1258, 1200, 1150, 1100, 1060, 1010, 850, 760 cm^{-1}. MS (CEC21-110B): M^+ 280 (tr), *m/e* = 265 (~1), 253 (tr), 190 (7), 163 (~1), 150 (4), 143 (100), 135 (6), 105 (3), 93 (~2), 73 (31), 55 (2), 41 (3). H-NMR ($CDCl_3$ plus TMS on Varian EM 360): $\delta = 4.7$ and 4.48 (~1 H total, broad m); $\delta = 4.04$ (≪1 H, narrow m); $\delta = 1.62$ (3 H, s); $\delta = 1.0$ (6 H, s); $\delta = 0.20$ ppm (9 H, s). It was evident that there was always about 15–20 % kinetically formed enolether present. 18.7 g (0.2 mole) dimethyl-methyleneimmonium chloride[12] was dissolved in 180 ml dry acetonitrile and 50.4 g (0.18 mole) of **21** added. After a slight exothermic reaction the soln became homogenous after 20 min. After 2 to 3 hr at room temp it was diluted with ether and extracted with cold 2 N Na_2CO_3. Then the ether phase was extracted with 2 N HCl. The ether phase after normal treatment left 7.6 g neutral part, mainly unreacted silylenolether. The acid aqueous phase was made alkaline with 2 N NaOH and extracted with ether to furnish 39.5 g (83 %) Mannich-base **22** after normal washing, drying and evaporating the organic solvent. ν_{max} (neat) 2800, 1715, 1465, 1380/1365, 1270, 1050, 850 cm^{-1}. H-NMR ($CDCl_3$ plus TMS on Varian EM 360): $\delta = 2.20$ (9 H, s); $\delta = 1.55$ (3 H, s); $\delta = 0.96$ ppm (6 H, s). This material is directly dissolved in 180 ml dry MeOH and 90 ml = 205 g (1.444 mole) methyl iodide are added and the mixture stirred overnight at room temp. A ppt forms. The whole mixture was evaporated to dryness and then the residue triturated with 1 l hexane for 1 hr. The mother liquor was filtered off through a sintered glass funnel or centrifuged leaving 51.2 g (84–85 %) quaternary iodide **23**/m.p. 164–167° (beginning 155°). The evaporated mother liquor contained all the substitution product (with MeOH) of the Mannich base stemming from the kinetically formed trimethylsilylenolether. All the crystalline product **23** was dissolved in 1.91 AcOH, 44 g (~540 mmoles) anhyd NaOAc added and the mixture stirred well for 5 hr at 95° bath temp. After cooling and diluting with a large amount of water, it was extracted with hexane. Normal work-up yielded 25 g (90 %) bright yellowish oily **24**. λ_{max} 221 nm (ε = 7800 cyclohexane). ν_{max} (neat) 1682, 1630, 1368, 1170, 1130, 940 cm^{-1}. MS (CEC21–110B): M^+ 220 (40), *m/e* = 205 (13), 187 (5), 177 (15), 164 (5), 151 (15), 137 (100), 123 (50), 109 (5), 95 (40), 81 (32), 69 (20), 55 (25), 43 (65). H-NMR ($CDCl_3$ plus TMS on Bruker WH 360): $\delta = 6.00$ (1 H, s); $\delta = 5.80$ (1 H, s); $\delta = 2.34$ (3 H, s); $\delta = 2.305$ (2 H, m); $\delta = 2.055$ (2 H, m); $\delta = 1.91$ (2 H, pseudo t); $\delta = 1.633$ (3 H, s); $\delta = 1.567$ (2 H, m); $\delta = 1.422$ (2 H, m); $\delta = 1.01$ ppm (6 H, s).

Preparation of **26**. 10.5 g (240 mmoles) NaH (55 % dispersion) was washed with benzene by decantation. 1 l dry benzene and 52 ml (260 mmoles) ethyl-diethylphosphonoacetate were added and then to this mixture 33.3 g (200 mmoles) of **18** was added dropwise at 10–15°. The mixture was stirred overnight at room temp before it was poured into excess cold sat NH_4Cl. Extraction with ether, washing with water, drying and evaporating the solvent yielded 48.1 g (quantit.) of **26** which should not be distilled in larger amounts because of isomerization of the double bond. ν_{max} (neat) 1720, 1650, 1370, 1325, 1270, 1160–1190, 1050, 985 cm^{-1}. MS (CEC21–110B): M^+ 235 (28), *m/e* = 221 (38), 191 (15), 175 (18), 163 (4), 147 (49), 133 (8), 123 (100), 107 (43),

91 (23), 81 (15), 79 (15), 69 (7), 55 (12), 41 (28). H-NMR ($CDCl_3$ plus TMS on Varian EM 360): $\delta = 6.91$ (1 H, dt, J = 15/6 c/s); $\delta = 5.70$ (1 H, dm, J = 15 c/s); $\delta = 4.18$ (2 H, q, J = 7 c/s); $\delta = 2.92$ (2 H, broad d, J = 6 c/s); $\delta = 1.52$ (3 H, s); $\delta = 1.26$ (3 H, t, J = 7 c/s); $\delta = 0.94$ ppm (6 H, s).

Preparation of **27**. 23.6 g (100 mmoles) of **26** in 1 l pentane were hydrogenated at room temp and under normal pressure in the presence of 500 mg 5% Pd–C. The reaction was monitored and stopped accordingly when the hydrogenation curve flattened out (~2.5 l H_2). The product was filtered over Celite, evaporated and short path distilled under vacuum to furnish a quantitative yield of **27** b.p. 74°/0.001 Torr; also ~80°/0.04 Torr. (Found: C, 75.27; H, 10.98%; $C_{15}H_{26}O_2$ requires: C, 75.58; H, 10.99%). ν_{max} (neat) 1738, 1376, 1250, 1190, 1150, 1080, 1040 cm^{-1}. MS (Varian MAT CH5): M^+ 238 (18), *m/e* = 223 (38), 193 (6), 182 (40), 177 (31), 159 (16), 149 (18), 135 (75), 123 (100), 108 (46), 95 (77), 81 (62), 69 (35), 55 (43), 41 (45), 29 (38). H-NMR ($CDCl_3$ plus TMS on Bruker WH 360): $\delta = 4.136$ (2 H, q, J = 7 c/s); $\delta = 2.311$ (2 H, t, J = 7 c/s); $\delta = 1.986$ (2 H, m); $\delta = 1.90$ (2 H, pseudo t, J = 6 c/s); $\delta = 1.683$ (2 H, m); $\delta = 1.60$ (3 H, s); $\delta \sim 1.56$ (2 H, m); $\delta = 1.41$ (2 H, m); $\delta = 1.264$ (3 H, t, J = 7 c/s); $\delta = 0.981$ ppm (6 H, s).

Preparation of **28**. 64.2 g (0.27 mole) of **27** dissolved in 400 ml dry ether were added to 10.2 g (0.27 mole) of LAH in 1.8 l ether such as to have a weak reflux. After addition the mixture was stirred for 2 hr under reflux. Then the excess reagent was destroyed carefully with sat NH_4Cl (cooling with an ice bath) in excess. The ether extract was washed to neutral, dried and the solvent evaporated to furnish 51 g crude oily product which was fractionated to give 44.5 g (84% yield) pure **28** b.p. 92/0.04 Torr. (Found: C, 79.23; H, 12.45%; $C_{13}H_{24}O$ requires: C, 79.53; H, 12.32%). ν_{max} (neat) 3350, 1480–1440, 1380, 1360, 1205, 1070, 1040, 988, 945 cm^{-1}. MS (CEC21–110B): M^+ 196 (37), *m/e* = 181 (45), 163 (16), 153 (1), 147 (1), 137 (8), 123 (100), 107 (25), 95 (41), 81 (40), 71 (24), 69 (20), 55 (27), 41 (29), 31 (11), 27 (10). H-NMR ($CDCl_3$ plus TMS on Bruker WH 360): $\delta = 3.661$ (2 H, t, J = 6.5 c/s); $\delta = 1.989$ (2 H, m); $\delta = 1.90$ (2 H, pseudo t, J = 6 c/s); $\delta = 1.583$ (3 H, s); $\delta = 0.983$ ppm (6 H, s).

Preparation of **29**. 35 ml (451 mmoles) dry pyridine and 310 ml dry CH_2Cl_2 were placed in a predried flask. 21.69 g (217 mmoles) CrO_3 (predried over P_2O_5 under vacuum) were added portionwise through a closed system. A red-brown soln formed with a dark brown ppt which was stirred at 20° for 35 min. To this was added at 0° quickly a soln of 7.09 g (36.1 mmoles) of **28** in 90 ml dry CH_2Cl_2. Additional stirring for 25 min at 0–22° was necessary before the organic soln was decanted from a dark tar-like residue. The latter was rewashed with CH_2Cl_2 three times. The combined organic phase was consecutively washed with cold 2 N NaOH, 2 N H_2SO_4, sat $NaHCO_3$ and water. Drying and evaporating the CH_2Cl_2 yielded 5.55 g (79%) golden-brown liquid which was short path distilled →5 g **29** (70%); b.p. 120°/0.06 Torr. ν_{max} (neat 2730, 1730, 1450–1480, 1418/1392/1365 cm^{-1}. MS (CEC21–110B): M^+ 194 (41), *m/e* = 179 (38), 161 (45), 150 (21), 135 (9), 123 (100), 107 (38), 100 (34), 95 (66), 81 (51), 69 (28), 67 (24), 55 (31), 41 (41), 29 (10). H-NMR ($CDCl_3$ plus TMS on Bruker WH 360): $\delta = 9.786$ (1 H, t, J = 1.5 c/s); $\delta = 2.444$ (2 H, td, J = 7/2 c/s); $\delta = 1.983$ (2 H, m); $\delta = 1.901$ (2 H, pseudo t, J = 6 c/s); $\delta = 1.689$ (2 H, m); $\delta = 1.60$ (3 H, s); $\delta = 1.569$ (2 H, m); $\delta = 1.417$ (2 H, m); $\delta = 0.983$ ppm (6 H, s).

Preparation of **30**. 13.8 g (71 mmoles) of **29** and 2.8 g (94.7 mmoles) paraformaldehyde were dissolved in a mixture of 14.3 ml (137.3 mmoles), diethylamine and 13.5 ml (236.7 mmoles) glacial AcOH. As a polymerization inhibitor 100 mg BHT were added. The mixture was stirred for 3 hr at 60°. The mixture was cooled, diluted with ether, washed with water to neutral pH and dried. Evaporation of the solvent furnished 16.3 g yellow liquid. Short path distillation (twice!) at 70°/0.05 Torr left 8.8 g distillate which was chromatographed on 100 g silicagel with pentane as eluant. 6.5 g (43%) pure **30** resulted. λ_{max} 219 nm (ε = 9500 in cyclohexane). ν_{max} (neat) 2700, 1695, 1625, 1480–1440, 1380, 1360, 1340, 1325, 1230, 1210, 1155, 945, 882, 840. MS (Varian MAT CH5): M^+ 206 (13, *m/e* = 191 (8), 188 (2), 173 (21), 163 (7), 150 (9), 137 (84), 123 (52), 107 (27), 95 (100), 81 (84), 69 (25), 67 (24), 55 (31), 41 (54), 29 (16). H-NMR ($CDCl_3$ plus TMS on Bruker WH 360): $\delta = 9.556$ (1 H, s); $\delta = 6.286$ (1 H, broad s); $\delta = 5.896$ (1 H, s); $\delta = 2.292$ (2 H, m = A_2) and $\delta = 2.097$ (2 H, m = B_2); $\delta = 1.914$ (2 H, pseudo t, J = 6 c/s); $\delta = 1.636$ (3 H, s); $\delta = 1.569$ (2 H, m); $\delta = 1.428$ (2 H, m); $\delta = 1.011$ ppm (6 H, s).

Preparation of **31**. To 2 g (9.7 mmoles) of **30** in 50 ml toluene and 60 ml benzene, 21.4 ml (10.7 mmoles) 0.5 M stannic chloride in benzene was added dropwise within 15 min at −25° to −18°. After 40 min stirring at −25° no starting material could be observed. The soln was poured into excess icecold bicarbonate (pH → 7) and the whole extracted with hexane. After normal procedure 1.9 g bright yellow oil (ν_{max} (neat) 2720, 1690, 1645 cm^{-1}) was obtained which consisted of one big peak on glc with a series of minor impurities. Preparative gas-chromatographic purification on CW-20M furnished pure **31** (500 mg). λ_{max} 228 nm (ε = 11000 in cyclohexane). ν_{max} (neat) 2720, 1695, 1645, 1475, 1450, 1400, 1380, 1305, 1220/1210, 1195, 1170, 1125, 1095, 1085, 1060, 1045, 1020, 1000, 940, 900, 875, 855, 830, 790, 770, 730 cm^{-1}. MS (CEC21–110B); shows that the aldehyde quite easily oxidizes): M^+ 206 (52), *m/e* = 191 (11), 173 (9), 163 (13), 150 (19), 137 (100), 123 (56), 107 (41), 91 (44), 79 (44), 77 (48), 69 (30), 67 (26), 55 (41), 41 (56). H-NMR ($CDCl_3$ plus TMS on Bruker WH 360): $\delta = 9.402$ (1 H, s); $\delta = 6.462$ (1 H, narrow q, J ~ 1 c/s); $\delta = 2.511$ (1 H, dm, J = 13 c/s, axial angular proton); $\delta = 2.355$ (1 H, d of broad d, J = 18/6 c/s, equat. allylic proton); $\delta = 2.085$ (1 H, m with J = 18/13/6 c/s axial allyl. proton); $\delta = 1.19$ (1 H, dm, J = 13 c/s); $\delta = 0.965$ (3 H, s); $\delta = 0.85$ (3 H, s); $\delta = 0.786$ ppm (3 H, s).

Preparation of **25**. 15.4 g (70 mmoles) of **24** in 1.5 l benzene and 300 ml dry ether was subjected to the slow addition (30 min) of 182 ml (91 mmoles) 0.5 M stannic chloride in benzene at −5°. After 27 hr at room temp (25°) the conversion was ≈95% and the bright yellow soln was poured into excess icecold bicarbonate soln (pH 8) and extracted with hexane. Normal washing, drying and evaporation of solvent furnished 15.6 g crude cyclization mixture, consisting according to glc of many ketones, but mainly of three dominant peaks. After column chromatography over 65 g silicagel (0.06–0.2 mm particle size) using hexane, hexane–ether mixtures, the elution of the different ketones took place with hexane ÷ ether = 9 ÷ 1. One fraction of 3.8 g mixture of the dominant peaks was separated further by preparative glc technique on Carbowax to yield the pure **25** as the last peak. (Found: C, 81.27; H, 10.95%; $C_{15}H_{24}O$ requires: C, 81.76; H, 10.98%). λ_{max} 230 nm (ε = 13900 in cyclohexane). ν_{max} (neat) 1670, 1645, 1480, 1455/1440, 1390/1380, 1360, 1312, 1280/1260, 1130, 1115, 1075, 1015, 948, 910/900, 880, 855 cm^{-1}. MS (CEC21–110B): M^+ 220 (77), *m/e* = 205 (26), 202 (5), 192 (3), 187 (7), 177 (24), 163 (16), 151 (100), 137 (49), 123 (33), 107 (26), 95 (26), 83 (16), 69 (12), 55 (12), 43 (58). ^{13}C–NMR ($CDCl_3$ plus TMS on Varian XL 100): singlets at δ = 197.64/137.84/36.98/35.67 ppm; doublets at δ = 145.24/-40.23 ppm; triplets at δ = 37.14/28.74/27.66/22.84/21.63 ppm; quartets at δ = 2 × 24.98/22.03/13.82 ppm,. H-NMR ($CDCl_3$ plus TMS on Bruker WH 360): $\delta = 6.531$ (1 H, narrow m): $\delta = 2.439$ (1 H, d of broad m, J = 13 c/s, axial angular proton); $\delta = 2.392$ (1 H, dd of broad m, J = 18/6 c/s, equat. allylic proton); $\delta = 2.278$ (3 H, s); $\delta = 2.117$ (1 H, very broad m, axial allyl, proton); $\delta = 1.172$ (1 H, dm, J = 13 c/s); $\delta = 0.944$ (3 H, s); $\delta = 0.839$ (3 H, s); $\delta = 0.772$ ppm (3 H, s). The second last peak from glc preparation (tentative structure **38**); ν_{max} (neat) 1710, 1470–1440, 1390/1375/1358, 1290/1275, 1210, 1182, 1170, 1090/1080, 1010, 950, 815 cm^{-1}. MS (CEC21–110B): M^+ 220 (100), *m/e* = 205 (36), 202 (10), 187 (24), 177 (48), 159 (17), 152 (21), 151 (33), 135 (19), 123 (67), 121 (76), 107 (71), 93 (45), 81 (24), 67 (17), 55 (19), 43 (57), H-NMR ($CDCl_3$ plus TMS on Bruker WH 360); $\delta = 5.267$ (1 H, unsplit m); $\delta = 2.608$ (1 H, tt, J = 12/4 c/s, axial α-proton to carbonyl): $\delta = 2.142$ (3 H, s); $\delta = 1.614$ (3 H, narrow m); $\delta = 0.908$ (3 H, s); $\delta = 0.844$ ppm (3 H, s). The third last main peak from glc

preparation (tentative structure **39**); ν_{max} (neat) 1712, 1465, 1375, 1358, 1305, 1270, 1175 cm^{-1}. MS (CEC21–110B): M^+ 220 (100), m/e = 205 (47), 202 (6), 187 (18), 177 (41), 164 (29), 161 (53), 149 (26), 137 (41), 135 (38), 121 (56), 107 (59), 105 (82), 91 (79), 85 (15), 81 (29), 69 (18), 55 (21), 43 (79). H-NMR ($CDCl_3$ plus TMS on Bruker WH 360); δ = 5.539 (1 H, dd, J = 6/3 c/s); δ = 2.528 (1 H, m, axial α-proton to carbonyl); δ = 2.178 (3 H, s); δ = 1.133 (3 H, s); δ = 1.117 (3 H, s); δ = 1.056 ppm (3 H, s).

All IR-spectra were taken on a PE-157 model and the UV-spectra measured on a Beckman DB-G instrument.

Acknowledgements—Our thanks go to Dr. E. Billeter and Mr. J. Maerki for their help in the NMR-field.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 257 to 261, 1981
Printed in Great Britain

0040-4020/81/Suppl. 1-0257-05 $02.00/0
Pergamon Press Ltd.

EPIMERIZATION AT A QUATERNARY C-SUBSTITUTED CARBON ATOM

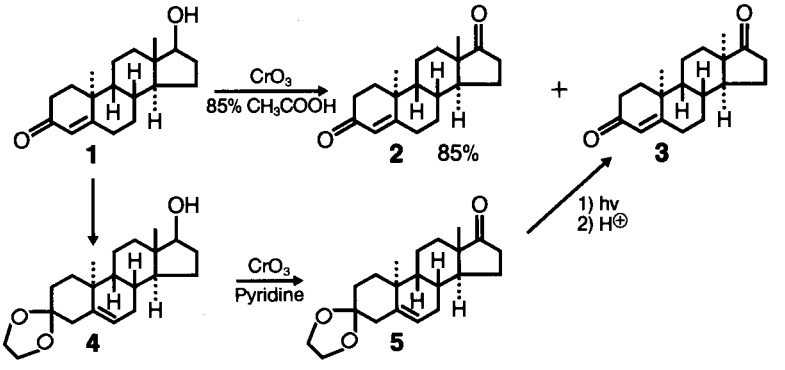
M. MÜLLER*, D. KÄGI and A. FÜRST*
Pharmaceutical Research Department, F. Hoffmann-La Roche & Co., AG, Basel, Switzerland

(*Received in Germany* 22 *July* 1980)

Abstract—Oxidation of secondary alcohols of different structures with chromic acid in aqueous acetic acid or chromic anhydride in acetic anhydride has been found to be accompanied by partial epimerization at the adjacent quaternary C-atom. In the case of compound **24**, this epimerization amounts to 45%. Reaction conditions and the structure of the alcohol influencing the extent of epimerization have been investigated. With compound **10** it has been proved that epimerization occurs prior to oxidation to the ketone. A possible reaction mechanism is discussed.

Some years ago we reported that chromic acid oxidation of the 17β-OH group of 9β,10α-testosterone led not only to the expected 9β,10α-androstenedione, but also in part to its C(13)-epimer.[a,b] At that time only the photolytic epimerisation at C(13) of 17-ketones was known. In the mean-time, epimerization at C(13) has also been observed under other conditions. Kirk *et al.*[1] and Hirschmann *et al.*[2] have reported on inversion of configuration at C(13) of D-homo-steroids by solvolysis of 17β-tosylates. Jacquesy[3] has obtained 13α-steroids by treatment of pregnane-20-ketones with hyperacids such as HF/SbF_5 or HSO_3F/SbF_3. Finally, Barton *et al.*[4] observed epimerization at C(13) by refluxing a 17-hydroxyimino-steroid in acetic anhydride and pyridine. We have investigated further our original observation and examined the course of the reaction with a series of structurally different compounds.

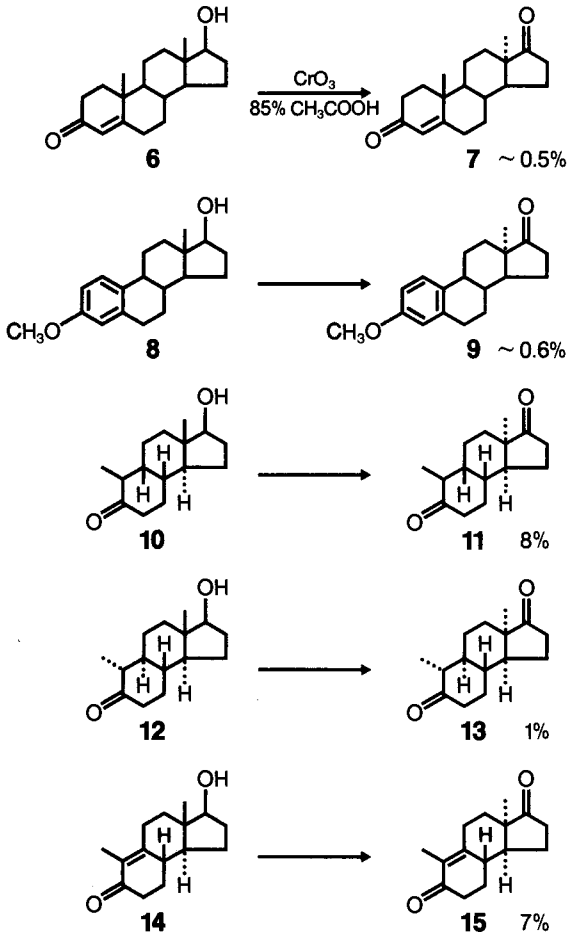
Oxidizing 9β,10α-testosterone (retrotestosterone) **1** with chromic acid in 85% aqueous acetic acid, we obtained the expected 17-ketone **2** in 85% yield. As an unexpected by-product of this oxidation 6–8% of an isomeric ketone was formed. The fact that the ORD-curve of this isomeric ketone exhibited an inverse Cotton effect compared to **2**, and that in the ^{1}H-NMR-spectrum of this compound the signal of the 18-Me group was shifted downfield by 0.11 ppm, indicated that epimerization at C(13) must have taken place. This was proved as follows: 9β,10α-testosterone **1** was transformed via **4** by oxidation with chromic anhydride in pyridine to **5**. Irradiation of **5** with a high pressure mercury lamp in ether solution, subsequent removal of the protecting group, isomerization and chromatography led to a preparation which was identical with the above by-product. Inversion of the 13-Me group by irradiation of 17-keto-steroids has



Scheme 1.

[a]5th International Symposium on the Chemistry of Natural Products, London, 8–13 July 1968, Abstracts F47, p. 354.

[b]This report is dedicated to the memory of the late Professor R. B. Woodward, who showed marked interest in our original observation communicated to him in 1968.[9]

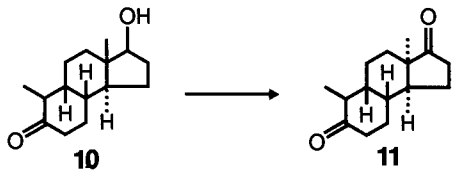


Scheme 2. Extent of isomerization (vpc determination[c]) in %.

been found by Butenandt.[5] Bots[6] has used this method to synthesize 13α-androst-4-ene-3,17-dione.

To our knowledge such an isomerization with chromic acid oxidation of a secondary alcohol has not been reported before. We therefore investigated the reaction with various tetracyclic and tricyclic compounds having the same relative position of the quaternary C-atom and the secondary OH-group as in **1**. Using exactly the same conditions (Experimental, standard procedure 1) the yield of the epimeric ketone was drastically influenced by the stereochemical and structural changes of the starting material (Scheme 2).

The influence of solvent systems frequently used for chromic acid oxidations has been tested next. Since compound **11** and its C(13)-isomer were suitable for vpc-analysis, their parent alcohol **10** has been used as starting material. Results are summarized in Scheme 3.

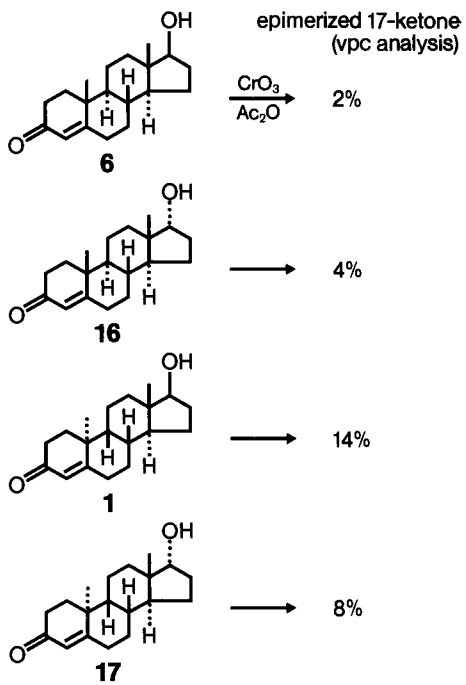


reaction conditions CrO_3 in[4)]	% inversion (vpc analysis)
85% CH_3COOH	6–8
8N H_2SO_4 acetone, O°	0
Pyridine	0
Dimethylformamide	0
Acetic anhydride	15

Scheme 3.

As acetic anhydride appeared to favour the epimerization, in the following experiments the oxidations were all carried out in this solvent.

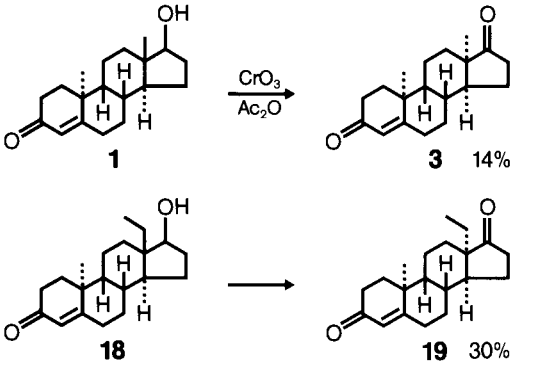
The relative configuration of the angular Me group and the OH group exerts an influence on the extent of epimerization; however, it seems to operate in different directions in the two pairs of compounds examined (Scheme 4). The nature of the angular C(13)-alkyl group markedly influenced the degree of epimerization (Scheme 5). Furthermore it is interesting to note that the tetracyclic compounds **20** and **21**[7] with C/D-*cis* configuration did not show any epimerization (Scheme 6). Finally we have investigated two pairs of racemic hydrindane alcohols. From the following results (Scheme 7) it can be concluded that in these cases the conversion of the *trans*-derivatives to the *cis*-series is favored, to the extent in one case that nearly half of the



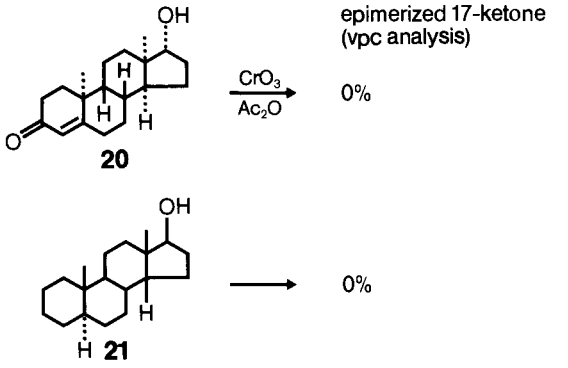
Scheme 4.

[c]With these oxidations small amounts of acidic products were always formed. For the vpc-determination only the neutral fraction was used and the percentages refer to the ratio of the abnormal and normal ketones. Retention times were compared with authentic samples.

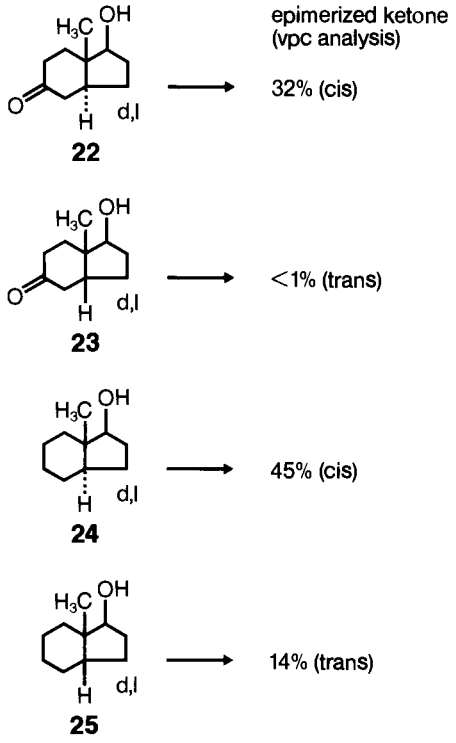
[d]Reactions were run with excess of CrO_3 at room temperature until no more starting material could be detected by tlc.



Scheme 5.



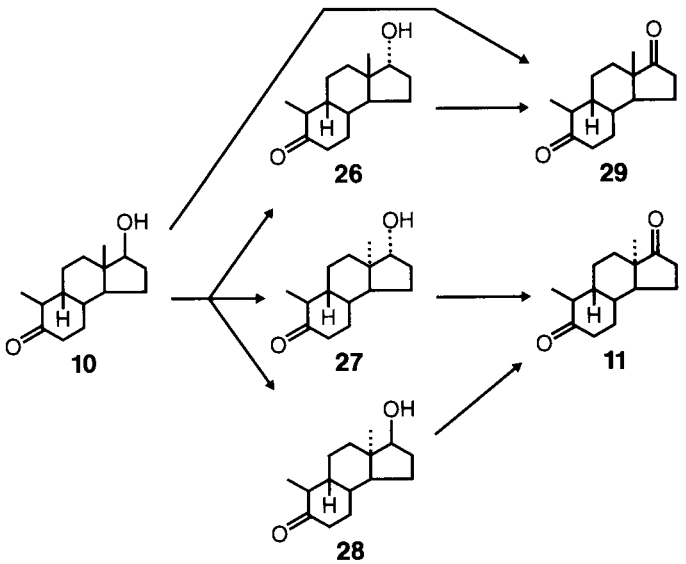
Scheme 6.



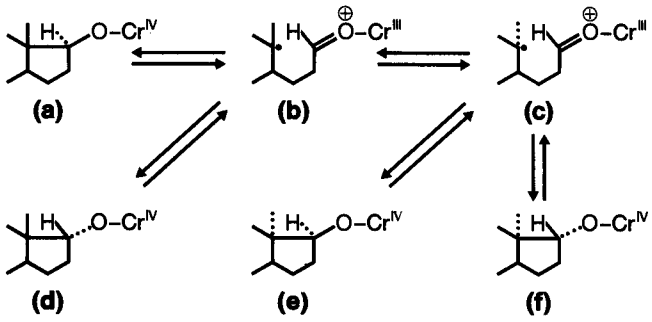
Scheme 7.

ketone obtained was epimerized. In order to elucidate the epimerization reaction, some further investigations have been made. The following has been found: (1) The epimerization is completely suppressed in the presence of manganous perchlorate while the normal oxidation to the 17-ketone is not influenced. This indicates that Cr^{IV} of Cr^{V} must be involved in the epimerization, since manganous ions reduce these chromium species very rapidly and therefore act as Cr^{IV}- or Cr^{V}-scavengers.[8] (2) The simultaneous oxidation of compound **10** and an excess of a secondary alcohol as e.g. isopropanol leads to a higher extent of epimerization. A possible explanation for this finding is that by the simultaneous oxidation of another alcohol more Cr^{IV} and/or Cr^{V} is generated. (3) Both C(13)-epimeric ketones are completely stable under the reaction conditions. (4) The extent of epimerization is unchanged when the oxidation is run in the dark, which proves that light is not involved.

The fact that epimerization has occurred before oxidation, has been proved by the following experiment: Compound **10** was oxidized in presence of



Scheme 8.



Scheme 9.

isopropanol and the reaction was stopped when about half of **10** had been oxidized to the ketone. The recovered alcoholic fraction consisted of 4 compounds in a ratio of 89:5:5:1 (vpc analysis). By careful chromatography we have been able to isolate and identify compounds as **10**, **26**, **27**. The presence of **28** could be postulated from NMR and MS data. The following scheme represents a possible mechanism of this epimerization involving a Cr^{IV}- or Cr^{V}-ester in equilibration with 2 possible oxonium radicals which are in their turn in an equilibrium with the isomerized ring-closed compounds. This mechanism, which we proposed in our preliminary report,[a] is similar to that proposed by Barton for the epimerization of 17-hydroxyimino-steroids,[4] but is different from the other observed epimerizations.[1-3]

In conclusion we would like to stress, that one has to take into account that oxidations of secondary alcohols with chromic anhydride in acetic acid or acetic anhydride can lead to epimerized products.

EXPERIMENTAL

For column chromatography Silicagel of 0.06–0.2 mesh (Merck) was used. Tlc on Merck-plates, Silicagel F254; identification by spraying with 50% *p*-toluenesulfonic acid. All m.ps are uncorrected. $[\alpha]_D$-values were taken from the ORD spectra, which have been measured in 0.1% dioxane soln (max = maximum; min = minimum). UV spectra were measured in optically pure EtOH on a Cary 14, λ_{max}-values are indicated in nm, ε-values in parenthesis. IR spectra in KBr on a Beckman IR 9 (only typical and intensive bands (in cm^{-1}) are reported). ^{1}H-NMR spectra have been measured in $CDCl_3$ on a Varian A 60, chemical shifts are in ppm relative to internal TMS; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, J = coupling constant in c/s. MS spectra have been recorded on a MS 9 (AEI, Manchester), after the mass numbers, peak intensities are given in % relative to the highest peak.

1. *Oxidation with* CrO_3 *in* 85% *aqueous acetic acid*

Standard procedure. To 4 mmoles of the secondary alcohol in 10 ml 85% aqueous AcOH was added a soln of 400 mg of CrO_3 in 10 ml 85% AcOH. The mixture was stirred for 3 hr at room temp. 1 ml MeOH was added, the mixture stirred for 10 more min, then it was poured on ice-water and extracted with ether. The ether extract was washed twice with 5% NaOHaq, then with water until neutral and finally it was dried with Na_2SO_4 and evaporated to dryness. The crude product was analyzed by vpc comparison with authentic samples, where possible. New products were fully characterized by IR, NMR, MS and ORD spectra.

2. *Oxidation with* CrO_3 *in acetic anhydride*

Standard procedure. To 4 mmoles of the secondary alcohol dissolved in 10 ml Ac_2O a soln of 400 mg CrO_3 in 10 ml Ac_2O was added with stirring during 30 min at room temp. The mixture was then stirred for another hr. The mixture was worked up as under (1) and the crude product was analysed by vpc.

The following new compounds were isolated and characterized:

9β,10α,13α-*androst*-4-*ene*-3,17-*dione* (**3**). The crude oxidation product was chromatographed on aluminium oxide (act. II) with benzene-hexane (1:1). The first fractions containing pure 3 (tlc) were combined and recrystallized from dichloromethane-isopropyl ether. M.p. 90–91°. $[\alpha]_D = -176°$. ORD.: $\alpha_{(302)} = -840°$ (min), $\alpha_{(306)} = -800°$ (max), $\alpha_{(312)} = -960°$ (min), $\alpha_{(326)} = -830°$ (min), $\alpha_{(335)} = -430°$ (max), $\alpha_{(342)} = -720°$ (min), $\alpha_{(348)} = -550°$ (max), $\alpha_{(357)} = -1053°$ (min), $\alpha_{(365)} = -898°$ (max), $\alpha_{(374)} = -1075°$ (min). UV: 240 (16300). IR: 2920, 2890, 2830, 1731, 1664, 1609, 1450, 1265, 1230, 1180. ^{1}H-NMR: 1.14 (s, CH_3–C(13)), 1.28 (s, CH_3–C(10)), 5.77 (s, H–C(4)). MS: 286 (16, M), 271 (3), 244 (9), 163 (19), 162 (13), 150 (33), 124 (100), 107 (34), 97 (43), 79 (32). (Found: C 79.47; H, 9.05. $C_{19}H_{26}O_2$ (286.40) Calc. for C, 79.68; H, 9.15%).

Synthesis of compound **3** *from* 3,3-*ethylenedioxy*-9β,10α-*androst*-5-*en*-17-*one* (**5**). A soln of 2.0 g **5** in 200 ml ether was irradiated at 16° with a mercury high pressure lamp for 3 hr. The soln was evaporated to dryness, the residue dissolved in a soln of 2 g *p*-toluenesulfonic acid in 50 ml EtOH and 5 ml water. The mixture was kept 4 hr at 25°, poured on ice–water and extracted with ether. The ether-extract yielded after washing with water and drying with Na_2SO_4 1.95 g crude product, which was chromatographed on aluminium oxide (act.II). By tlc uniform fractions were combined and recrystallized from ether–hexane. The product obtained, m.p. 90°, was identical with the compound isolated above.

Des-A-9β,13α-*androstane*-5,17-*dione* (**11**). The crude oxidation product from **10** was chromatographed on Silicagel with ether-cyclohexane (1:1). The first fractions contained pure **11**. Recrystallized from ether-hexane, it melted at 105–106°. $[\alpha]_D = -96°$. ORD: $\alpha_{(230)} = 1820°$, $\alpha_{(280)} = -1030°$, $\alpha_{(305)} = +600°$ (max), $\alpha_{(325)} = -600°$ (min), $\alpha_{(380)} = -246°$. IR: 2950, 2880, 1725, 1702, 1458, 1410, 1375, 1090, 1015. ^{1}H-NMR: 1.03 (d, J = 6.3, CH_3–C(10)), 1.10 (s, CH_3–C(13)). MS: 234 (21, M), 219 (6), 216 (9), 190 (16), 162 (85), 136 (39), 121 (56), 110 (61), 97 (95), 55 (86), 41 (100). (Found: C, 76.85; H, 9.34. Calc. for $C_{15}H_{22}O_2$ (234.35) C, 76.88; H, 9.46%).

Synthesis of compound **11** *from* 5,5-*ethylenedioxy-des-A*-9β-*androstan*-17-*one*. By irradiation of 5,5-ethylenedioxy-des-A-9β-androstan-17-one[15] as described for **3**, compound **11** was isolated in about 15% yield.

Des-A-13α-androst-9-en-5,17-dione (**15**). The crude oxidation product from **14** was chromatographed twice on Silicagel with ether–hexane (1:1). The first fractions contained **15**. The tlc-pure fractions were combined and recrystallized from acetone-hexane. m.p. 115–116°. $[\alpha]_D = -126°$. ORD: $\alpha_{(250)} = -2500°$, $\alpha_{(265)} = +2000°$ (max), $\alpha_{(313)} = -2020°$ (min), $\alpha_{(318)} = -1830°$ (max), $\alpha_{(324)} = -2330°$ (min), $\alpha_{(370)} = -602°$. UV: 249 (15500). IR: 2900, 2860, 1732, 1651, 1628, 1444, 1205, 1138, 1080. ^{1}H-NMR: 1.06 (s, CH_3–C(13)), 1.81 (d, J = 2.5, CH_3–C(10)). MS: 232 (15, M), 175 (10), 161 (8), 136 (100), 119 (15), 105 (19), 97 (91). (Found: C, 77.17; H, 8.62. Calc. for $C_{15}H_{20}O_2$ (232.33): C, 77.55; H, 8.68%).

The same compound was obtained by irradiation of 5,5-ethylenedioxy-des-A-androst-9-(11)-en-17-one, acid hydrolysis and chromatography on Silicagel (as described for **3**) in about 30% yield.

9β,10α,17α-Testosterone (**17**).[e] This compound has been synthesized by acetolysis of 9β,10α-testosterone-*p*-toluenesufonate with KOAc in AcOH (18 hr reflux), chromatographic purification of the 17α-acetate and subsequent hydrolysis with K_2CO_3 in MeOH. m.p. 217–219°, $[\alpha]_D = +66°$. UV: 241 (16400).

9β,10α,13α,17α-Testosterone (**20**). To a soln of **3** in 100 ml MeOH was added a soln of 3 g $NaBH_4$ in 160 ml MeOH and 20 ml water. The mixture was stirred for 2 hr, then poured on ice–water and extracted with CH_2Cl_2. The organic extract was washed with water, dried with Na_2SO_4 and evaporated to dryness. The residue was dissolved in 100 ml of $CHCl_3$ and stirred for 2 hr with 15 g of MnO_2. The mixture was filtered and evaporated to dryness. The residue was recrystallized twice from ether to give 1.9 g pure **20**. M.p. 116—118°. $[\alpha]_D = -70°$. ORD: $\alpha_{(270)} = +1080°$, $\alpha_{(290)} = +830°$, $\alpha_{(320)} = +1190°$ (max), $\alpha_{(284)} = +770°$ (min), $\alpha_{(357)} = -1002°$ (min), $\alpha_{(364)} = -822°$ (max), $\alpha_{(373)} = -1100°$ (min). UV: 242 (15900). IR: 3400, 2920, 2840, 1655, 1620, 1460, 1442, 1315, 1230, 1107, 1080. ^{1}H-NMR: 1.08 (s, CH_3–C(13)), 1.23 (s, CH_3–C(10)), 3.78 (m, H–C(17)), 5.76 (d, J = 1.5, H–C(4)). (Found: C, 79.29; H, 9.85. Calc. for $C_{19}H_{28}O_2$ (288.41): C, 79.12; H, 9.79%).

Isolation of 17α-hydroxy-des-A-9β-androstan-5-one (**26**) *and 17α-hydroxy-des-A-9β,13α-androstan-5-one* (**27**). To a soln of 30 g of **10** and 3.8 ml isopropanol in 170 ml Ac_2O was added within 45 min a soln of 6.4 g CrO_3 in 120 ml Ac_2O. The mixture was stirred for another 30 min and then worked up as described in the standard procedure. The crude oxidation product was chromatographed on 3 kg Silicagel. With CH_2Cl_2–Me_2CO (96:4) 17.2 g of a mixture of **11** and **29** were eluated. The CH_2Cl_2–Me_2CO (9:1 and 4:1) eluates yielded 9.5 g of an alcoholic fraction which consisted by VPC–MS-analysis of four isomeric compounds (mass 236) in a ratio of 89:5:5:1. This mixture was rechromatographed with CH_2Cl_2. The first fractions yielded pure **27**, m.p. 124–125° (ether–hexane). $[\alpha]_D = -50°$. ORD: $\alpha_{(230)} = -1461°$, $\alpha_{(267)} = -1787°$ (min), $\alpha_{(312)} = +886°$ (max), $\alpha_{(362)} = 0°$. IR: 3510, 2920, 1703, 1658, 1410, 1373, 1122, 1077, 1030. ^{1}H-NMR: 1.01 (s, CH_3–C(13)), 1.03 (d, J = 6.5, CH_3–C(10)), 4.16 (~tr, J = 7, H–C(17)). MS: 236 (20, M), 218 (26), 177 (36), 161 (24), 135 (25), 124 (44), 108 (71), 95 (51), 81 (55), 67 (55), 55 (90), 41 (100). (Found: C, 76.08; H, 10.15. Calc. for $C_{15}H_{24}O_2$ (236.37): C, 76.22; H, 10.24%).

The further eluates yielded mixtures of **10** and **27**; then the following fractions gave 5.8 g of pure **10**. Finally the CH_2Cl_2–Me_2CO (1:1) eluates yielded pure **26**, m.p. 69–70° (ether–hexane). $[\alpha]_D = -49°$. ORD: $\alpha_{(230)} = -1105°$, $\alpha_{(264)} = -1205°$ (min), $\alpha_{(313)} = +436°$ (max), $\alpha_{(436)} = -73°$. IR: 3624, 2960, 1709, 1455, 1380, 1040. ^{1}H-NMR: 0.77 (s, CH_3–C(13)), 1.03 (d, J = 6.5, CH_3–C(10)), 3.85 (d, J = 5.6, H–C(17)). MS: 236 (47, M), 218 (16), 81 (55), 55 (91), 41 (100). (Found: C, 76.33; H, 10.17%. Calc. for $C_{15}H_{24}O_2$ (236.37): C, 76.23; H, 10.24%).

The fourth isomer presumed to be **28** could not be isolated from the chromatogram.

Compound **26** gave by Jones-oxidation the dione **29**, and oxidation of **27** yielded **11**.

Compound **27** was also obtained by $NaBH_4$-reduction of the 5-ketal of **11** and subsequent acid hydrolysis. The following compounds necessary as starting materials or for vpc comparisons were synthesized according to the indicated literature: Compound 7[6,f] **9**,[9] **1**,[10] **2**,[10] **16**,[11] **18**,[12,f] **19**,[12,f] **21**,[7,g] **22**,[13,h] **23**,[13,h] **24**,[14] **25**,[14] **10** and des-A-9β-androstane-5,17-dione:[15] **12** and des-A-10α-androstane-5,17-dione:[16] **14** and des-A-androst-9-ene-5,17-dione.[17]

Acknowledgements—For determination and interpretation of spectra we thank Dr. M. Grosjean (UV., IR), Dr. K. Noack (ORD.), Dr. W. Arnold and Dr. G. Englert (NMR.), W. Meister and Dr. W. Vetter (MS.), W. Walther and Dr. M. Vecchi (GC.) and Dr. A. Dirscherl for microanalyses. We also thank Prof. A. Eschenmoser, ETH Zürich, and Prof. G. Ourisson, Université de Strasbourg, for helpful discussions.

[e]We thank Dr. P. Keller, Pharm. Research Dept., F. Hoffmann-La Roche & Cie Ltd., Basel, for synthesizing this compound.

[f]This compound has been obtained from Mr. P. Westerhof, Philips-Duphar, Weesp, Holland.

[g]We thank Prof. Y. Mazur, The Weizmann Institute of Science, Rehovoth, Israel, for making available this substance.

[h]Compound **22** and **23** and the corresponding diones have been obtained from Dr. Z. Hajos, Chem. Res. Dept., Hoffmann-La Roche Inc., Nutley, N.J., USA.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 263 to 267, 1981
Printed in Great Britain.

0040-4020/81/Suppl. 1-0263-05 $02.00/0
Pergamon Press Ltd.

PHENYLSELENYLATION OF ARACHIDONIC ACID AS A ROUTE TO INTERMEDIATES FOR LEUKOTRIENE SYNTHESIS

ISOMERIZATION OF CONJUGATED DIENES DURING SELENOXIDE ELIMINATION

JACK E. BALDWIN*, NEVILLE V. REED, and ERIC J. THOMAS
The Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, England

(*Received in UK* 28 *August* 1980)

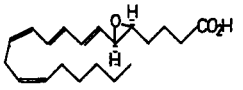
Abstract—Methyl (5*SR*, 6*SR*)-5-hydroxy-6-phenylselenyleicosa-*cis,cis,cis*-8,11,14-trienoate (**8**), available in two steps from arachidonic acid, undergoes oxidative deselenylation to give selectively either methyl (5*SR*)-5-hydroxyeicosa-*trans,trans,cis,cis*-6,8,11,14-tetraenoate (**5**) or its *cis*-8 isomer (**6**), depending upon the reaction conditions.

Recently there has been considerable interest in a series of metabolites derived from arachidonic acid called leukotrienes.[1] In particular, the epoxide leukotriene A **1**, has been implicated in the biosynthesis of several "slow reacting substances" (SRS's),[2–4] important agonists in asthma and other forms of hypersensitivity,[5] and the methyl ester of epoxide **1** has been used as an intermediate in chemical syntheses of leukotrienes C **2**,[4–6] and D **3**.[7] Several total syntheses of epoxide **1** have been reported,[4,6,8] and a conversion of arachidonic acid into epoxide **1**, *via* hydroperoxide **4**, has been described.[9] Because of our interest in oxidation of arachidonic acid, we decided to develop a chemical conversion of arachidonic acid into compounds of the leukotriene type. We wish to report some of our early results in this field, namely stereoselective syntheses of (±)-methyl 5-hydroxyeicosa-*trans,trans,cis,cis*-6,8,11,14-tetraenoate **5** and its 8-*cis* isomer **6**.

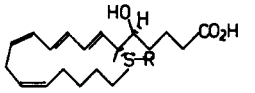
RESULTS AND DISCUSSION

The formation of 5- and 6-membered lactones by intramolecular phenylselenolactonization of unsaturated carboxylic acids is known to be an efficient reaction.[10] We therefore decided to study phenylselenolactonization of arachidonic acid as a method of functionalizing selectively the 5,6-double-bond.

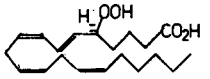
Treatment of arachidonic acid with phenylselenenyl chloride in dichloromethane at −78° proceeded smoothly and gave lactone **7**, isolated as an oil, and purified by chromatography on silica. The structure shown, which was consistent with all the spectroscopic data, was assigned by analogy with the literature assuming a *trans* addition across the originally *cis* double-bond. The completely selective functionalization of the 5,6-double bond is in accordance with the recently reported iodolactonization of arachidonic acid.[11] The lactone **7** was then hydrolysed using



(1)

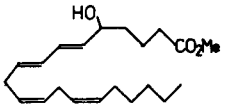


(2) R = $-CH_2-CH(NHCONHCH_2CO_2H)-NHCOCH_2CH_2CH(NH_2)CO_2H$

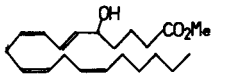


(4)

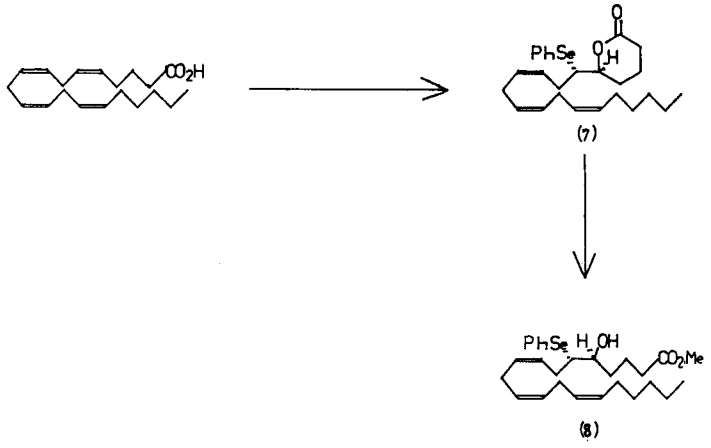
(3) R = $-CH_2-CH(NH_2)-CONHCH_2CO_2H$



(5)



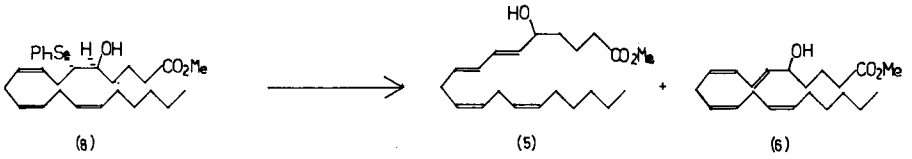
(6)



lithium hydroxide in tetrahydrofuran–water, and the free acid immediately esterified using diazomethane to give ester **8** (80%), also an oil.

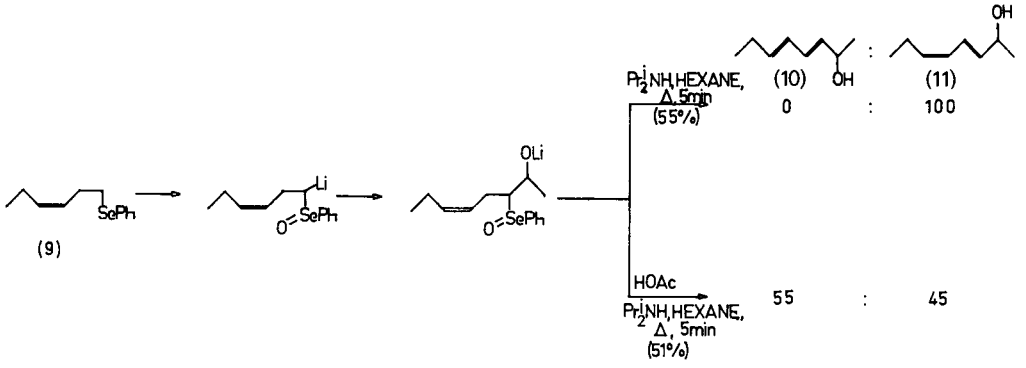
Oxidative removal of the phenylselenyl moiety from ester **8** was studied using several sets of conditions, and the results are summarized in Scheme 1.[12,13] For example treatment of ester **8** with excess sodium periodate in buffered ($NaHCO_3$) aqueous methanol at 25° for 24 hr, gave an oil which showed two closely moving spots on tlc (CH_2Cl_2-EtOAc 9:1, R_f's 0.37, 0.32). These two products were separated by column chromatography, and were identified as the hydroxy-*trans,trans*-eicosatetraenoate **5**, 60%, R_f 0.32, and its *cis*-8 isomer **6**, 15%, R_f 0.37. Similar results were obtained using excess hydrogen peroxide in aqueous methanol sodium bicarbonate, and with one equivalent of *m*-chloroperoxybenzoic acid in tetrahydrofuran at −78°, followed by addition to aqueous acetic acid and treatment with di-isopropylamine in refluxing hexane.

The structures of the products were established rigorously by spectroscopic methods. For the major product, the slower moving on tlc, ^1H NMR spin decoupling (300 MHz) showed the presence of two conjugated *trans* double-bonds, coupling constants of 15 Hz being observed across each double-bond. The position of the OH group was established by the mass spectral fragmentation of the t-butyldimethylsilyl ether, and was shown to be adjacent to the conjugated diene by spin-decoupling. Since ^1H NMR showed a total of four double-bonds, and two methylene groups each flanked by two double-bonds, the whole structure was effectively established. The *cis* geometry was assigned to the isolated double-bonds, since they had not been involved in any of the chemical transformations from arachidonic acid, and was supported by the presence of a band in the IR spectrum at 720 cm^{-1}. Isolated *cis* double-bonds are not usually affected by selenoxide elimination.[14] The minor product was similarly rigorously identified. In this case



REACTION CONDITIONS	(5) : (6)	TOTAL YIELD %
$NaIO_4$, MeOH, H_2O, $NaHCO_3$, 25°, 24h	85 : 15	75
H_2O_2, MeOH, H_2O, $NaHCO_3$, 25° 24h	85 : 15	70
MCPBA, THF, -78°; H_2O, AcOH, 0°; Pr^i_2NH, HEXANE, REFLUX	90 : 10	60
H_2O_2, THF, H_2O, KOH, 25°, 18h, CH_2N_2, Et_2O	20 : 80	60

Scheme 1.



Scheme 2.

^{1}H NMR indicated the presence of a *trans* double-bond (J 15 Hz) adjacent to the OH group, and conjugated with a *cis* double-bond (J 10.5 Hz). The *cis,trans* conjugated diene unit was also supported by IR bands at 980 and 950 cm^{-1}.[15] After our work on these compounds was complete, a synthesis of the *cis,trans*-diene **6** was reported.[16] The spectroscopic data reported for compound **6** are entirely in agreement with our own.

Therefore under these standard conditions, the oxidative elimination of the phenylselenyl moiety from hydroxyselenide **8** has been accompanied by geometrical isomerization of the *cis*-8 double-bond, which is not directly involved in the selenoxide elimination itself. No such isomerisations have been reported in recent papers, or in recent reviews, of selenoxide eliminations.[12] However we have observed a second example in a simpler system. Thus sequential treatment of *cis*-hex-3-en-1-yl phenyl selenide **9** with *m*-chloroperoxybenzoic acid, lithium di-isopropylamide, and acetaldehyde at −78°, followed by addition of the reaction mixture to aqueous acetic acid at 0°, and heating under reflux in hexane containing di-isopropylamine (Scheme 2), gave a mixture containing *trans,trans*-octa-3,5-dien-2-ol **10** and *trans,cis*-octa-3,5-dien-2-ol **11** in which the *trans,trans*-isomer **10** was the major component, **10**:**11** = 55:45.[17]

The cause of these isomerizations was not immediately apparent. However in the second example, if the aqueous acetic acid quench was omitted, and the basic solution from the selenoxide reaction with acetaldehyde, added directly to refluxing hexane containing di-isopropylamine, no isomerization was observed, and the *trans,cis*-isomer **11** was the only product isolated (55% after chromatography). Thus isomerization had not occurred under these strongly basic conditions (Scheme 2). To check this point, the long-chain hydroxyselenide **8** was treated with excess hydrogen peroxide in the presence of four equivalents of potassium hydroxide. Under these conditions, after re-esterification with diazomethane, a mixture of elimination products was obtained, in which the 8-*cis* isomer **6**, was the major component, **5**:**6** = 20:80 (Scheme 1).

Therefore the hydroxyselenide **8** can be used to prepare either the *trans,trans*-conjugated alcohol **5**, or its 8-*cis* isomer **6**. Oxidative elimination under neutral conditions ($NaHCO_3$), leads to the *trans,trans*-isomer **5** predominantly (60% isolated yield), whereas addition of base (KOH) reduces isomerization, and leads to the selective formation of the *trans,cis*-isomer **6**.

The details of the mechanism of this isomerization were not studied. However treatment of a mixture of hydroxyselenide **8** and the *trans,cis*-octa-3,5-dien-2-ol **11** with sodium periodate in buffered aqueous methanol, caused isomerization of the octadienol to its *trans,trans*-isomer **10**, 80% isomerization. Little isomerization was observed if hydroxyselenide **8** was omitted from this mixture. Possibly the side-product of the selenoxide elimination, phenyl selenenic acid is reversibly adding to the diene unit before being trapped by excess oxidant or amine, and so is responsible for the isomerization. Sulphoxide elimination is known to be reversible, but attempts to show that selenoxide elimination was reversible using D-labelling were not conclusive.[13b] However this point was not studied further.

Studies are in progress to assess the utility of the methyl 5-hydroxyeicosatetraenoates (**5** and **6**) as intermediates for leukotriene synthesis.

EXPERIMENTAL

NMR spectra (300 MHz) were obtained using a Bruker WH 300 spectrometer. UV spectra were measured on a Perkin–Elmer 555 spectrometer, and the IR spectra on a Perkin–Elmer 297 spectrometer. Hopkins and Williams silica gel MFC without binder was used for column chromatography and analytical tlc was on Merck $H_{254/366}$ silica gel. Solvents were purified and dried using standard procedures. Se-containing compounds exhibited the characteristic isotopic family in their mass spectra [^{74}Se(1), ^{76}Se(10), ^{77}Se(9), ^{78}Se(27), ^{80}Se(57), ^{82}Se(11)] but only peaks due to most abundant isotope (^{80}Se) are reported. Low resolution mass spectra were obtained using chemical ionisation techniques (methane as reagent gas), and accurate mass data obtained using field ionization, both measured on a VG micromass ZAB 1F spectrometer.

Phenylselenolactonization of arachidonic acid

Penylselenenyl chloride (3.29 g, 17.2 mmol) was added to a stirred soln of arachidonic acid (5 g, 16.4 mmol) in anhyd CH_2Cl_2 (30 ml) under dry N_2 at −78°. After the red solid had dissolved, the soln was concentrated *in vacuo*, and the oily residue chromatographed on silica (250 g) being eluted with CH_2Cl_2, to give the *lactone* 7 (5.178 g), a colourless oil homogeneous by tlc, R_f (CH_2Cl_2) 0.4; ν_{max} 3010, 2960, 2940, 2860, 1740, 1600, 1580, 1235, 745, and 700 cm^{-1}, δ ($CDCl_3$) 0.89 (3 H, t, J = 5.8 Hz, $CH_2C\underline{H}_3$), 1.3 (6 H, m, 3 × CH_2), 1.72–2.1 (6 H, m, 3 × CH_2), 2.35–2.9 (8 H, m, 4 × CH_2), 3.28

(1 H, m, CHSePh), 4.49 (1 H, m, CHO), 6.3–6.59 (6 H, m, vinyl H), 7.29 (3 H, m, aromatic H), and 7.59 (2 H, m, aromatic H); *m/z* 461 [(M + H)$^+$, 45%] and 303 [(*M* + H)$^+$ + PhSeH, 100%]. (Found: *m/z* 460.1883 $C_{26}H_{36}O_2Se$ requires: M$^+$ 460.1880).

Methyl(5SR, 6SR)-5-*Hydroxy*-6-*phenylselenyleicosa*-cis,cis,cis-8,11,14-*trienoate* (**8**)

Lithium hydroxide (25 ml of an 0.1 N aqueous soln) was added to **7** (1 g, 2.17 mmol) in aqueous THF (25 ml, 1:1), and the soln stirred at 25° for 1 hr. Acidification then extraction into CH_2Cl_2 (2 × 20 ml), was followed by immediate treatment of the CH_2Cl_2 extracts with ethereal diazomethane. Drying ($MgSO_4$) and concentration *in vacuo* gave an oil which was chromatographed on silica to give *methyl* (5*SR*, 6*SR*) 5-*hydroxy*-6-*phenylselenyleicosa*-cis,cis,cis-8,11,14-*trienoate* **8** (860 mg), a colourless oil, homogeneous by tlc, R_f (CH_2Cl_2) 0.24, ν_{max} 3500, 3020, 2960, 2930, 2860, 1740, 1580, 1200, 745, and 700 cm^{-1}, δ ($CDCl_3$) 0.89 (3 H, t, J = 6 Hz, CH_2CH_3), 1.2–1.44 (6 H, m, 3 × CH_2), 1.55–1.88 (4 H, m, 2 × CH_2), 2.06 (2 H, m, CH_2), 2.23–2.48 (4 H, m, one exch. with D_2O, OH), 2.59 (1 H, m), 2.79 (4 H, m, 2 × CH_2), 3.17 (1 H, m, CHOH), 3.55–3.69 (4 H, m, CH_3 + CH), 5.26–5.57 (6 H, m, vinylic H), 7.27 (3 H, m, aromatic H), and 7.57 (2 H, m, aromatic H); *m/z* 493 [M + H)$^+$, 7%] and 317 [(M + H)$^+$–PhSeH, 100%]. (Found: *m/z* 492.2141 $C_{27}H_{40}O_3Se$ requires: M$^+$ 492.2142).

Oxidative elimination of phenylselenium from hydroxyselenide (**8**)

(a) *Using sodium periodate-sodium bicarbonate.* $NaHCO_3$ (252 mg, 3 mmol) in water (5 ml) was added to **8** (0.4 g, 0.81 mmol) in MeOH (40 ml) at 0°, and sodium periodate (0.52 g, 2.43 mmol) in water (7 ml) added dropwise. The mixture was stirred at 25° for 24 hr before being diluted with ether (20 ml), and water (20 ml), and the organic layer separated, washed with water (2 × 20 ml), brine (2 × 20 ml), and dried ($MgSO_4$). Concentration *in vacuo* gave an oil which was shown by tlc to consist of two major components (CH_2Cl_2–EtOAc, 9:1). These two compounds were separated by chromatography on silica. The first product off the column was identified as (±)-*methyl* 5-*hydroxyeicosa*-trans,cis-,cis,cis-6,8,11,14-*tetraenoate* **6** (50 mg) a colourless oil homogeneous by tlc, R_f 0.37, ν_{max} (CS_2) 3600, 3010, 2950, 2920, 2850, 1740, 1200, 980, 950 and 720 cm^{-1}, λ_{max} (MeOH) 232 nm (ε 29, 600), δ ($CDCl_3$) 0.89 (3 H, t, J = 6.5 Hz, CH_2CH_3), 1.33 (6 H,, m, 3 × CH_2), 1.51–1.83 (5 H, m, 2 × CH_2 + OH), 2.05 (2 H, m, CH_2), 2.36 (2 H, t, J = 6.25 Hz, CH_2), 2.83 (2 H, t, J = 5 Hz, CH_2), 2.96 (2 H, t, J = 5 Hz, CH_2), 3.68 (3 H, s, OCH_3), 4.19 (1 H, m, CHOH), 5.4 (5 H, m, vinylic H), 5.7 (1 H, dd, J = 6, 15 Hz, H (6)), 6.0 (1 H, m, H(8)), and 6.53 (1 H, dd, J = 10.5, 15 Hz, H(7)); *m/z* 334 ((M + 1)$^+$, 9%), 317 (M + H)$^+$–H_2O, 100%), 303 (M + H)$^+$–CH_3OH, 17%) (Found: *m/z* 334.2505. $C_{21}H_{34}O_3$ requires: M$^+$ 334.2508). The second product off the column was identified as (±)-*methyl* 5-*hydroxyeicosa*-trans,trans,cis,cis-6,8,11,14,-*tetraenoate* **5** (150 mg), a colourless oil, homogeneous by tlc, R_f 0.32, ν_{max} (CS_2) 3600, 3010, 2950, 2920, 2850, 1740, 1200, 985, and 720 cm^{-1}, λ_{max} (MeOH) 230 nm (ε 28, 400), δ ($CDCl_3$) 0.91 (3 H, t, J = 6.25 Hz, CH_2CH_3), 1.31 (6 H, m, 3 × CH_2), 1.46–1.8 (5 H, m, 2 × CH_2 + OH), 2.06 (2 H, m, CH_2), 2.36 (2 H, m, CH_2), 2.78 (2 H, t, J = 5 Hz, CH_2), 2.95 (2 H, t, J = 5 Hz, CH_2), 3.68 (3 H, s, OCH_3), 4.13 (1 H, m, H(5)), 5.4 (4 H, m, vinylic H), 5.6 (1 H, dd, J = 7.5, 15 Hz, H(6)), 5.68 (1 H, dt, J = 15.5 Hz, H(9)), 6.04 (1 H, dd, J = 10, 15 Hz, H(8)), and 6.18 (1 H, dd, J = 10, 15 Hz,, H(7)); *m/z* 335 [(M + H)$^+$, 9%] and 317 [(M + H)$^+$–H_2O, 100%]. (Found: 334.513 $C_{21}H_{34}O_3$ requires: M$^+$ 334.2508).

The t-butyldimethyl silyl ether were prepared by the method of Corey and Ventateswarln, and showed the characteristic cleavage product in the mass spectrum at 245 corresponding to the $Me_3C—\overset{Me}{\underset{Me}{Si}}—O—CH\ (CH_2)_3\ CO_2Me$ fragement.[18]

(b) *Using hydrogen peroxide–sodium bicarbonate.* $NaHCO_3$ (84 mg, 1 mmol) in water (3 ml) was added to **8** (44 mg, 0.089 mmol) in MeOH (10 ml) and 30% H_2O_2 (1 cm^3, 11.4 mmol) added dropwise. The reaction was stirred at room temp for 18 hr, then worked up in the normal way to yield a similar mixture of **6** 4 mg, and **5** 17 mg.

(c) *Using* m-*chloroperoxybenzoic acid–diisopropylamine.* m-Chloroperoxybenzoic acid (18.6 mg, 0.108 mmol) in THF (1 ml) was added to **8** (50 mg, 0.108 mmol) in THF (5 ml) at −78° under anhyd N_2. The mixture was stirred for 60 min, then warmed to 0°, AcOH (0.05 ml) and water (0.05 ml) added, and the resulting suspension added to diisopropylamine (21.8 mg, 0.216 mmol) in hexane (10 ml) at reflux.

After 5 min, the reaction was cooled, then worked up in the normal way to give **6** 3 mg, and **5** 20 mg.

(d) *Using hydrogen peroxide–potassium hydroxide.* KOH (24 mg, 0.43 mmol) was added to a stirred soln of **8** (50 mg, 0.108 mmol) in THF-water (5 ml, 10:1), followed by 30% H_2O_2 (5 ml, 15 mmol). The mixture was stirred at 25° for 18 hr, water (10 ml) added, and the mixture acidified to pH 5 using 0.1 N HCl, and extracted into ether (3 × 30 ml). The ether extract was treated with excess diazomethane, dried ($MgSO_4$), and concentrated *in vacuo* to give an oil. Column chromatography on silica (5 g), eluting with CH_2Cl_2–EtOAc (9:1) gave the 8-*cis*-eicosatetraenoate **6** (18 mg) and the 8-*trans*-isomer **5** (4.5 mg).

cis-*Hex*-3-*en*-1-*yl phenyl selenide* (**9**). Methanesulphonyl chloride (1.26 g, 11 mmol) was added dropwise over a period of 20 min to a soln of *cis*-hex-3-en-1-ol (1 g, 10 mmol) in pyridine (40 ml). The mixture was allowed to warm to room temp, stirred for 6 hr, then diluted with ether (30 ml) and water (50 ml). The organic layer was separated, washed with water (3 × 50 ml), 0.5 N aq. HCl (3 × 50 ml), sat $NaHCO_3$aq (3 × 50 ml), and brine (3 × 50 ml), then dried ($MgSO_4$). Concentration *in vacuo* gave an oil which was chromatographed on silica (20 g) to give *cis*-hex-3-en-1-yl mesylate, a colourless oil, homogeneous by tlc, R_f 0.58 (CH_2Cl_2), ν_{max} 1340, 1170, and 740 cm^{-1}, δ ($CDCl_3$) (60 MHz) 1.0 (3 H, t, J = 6 Hz, CH_2CH_3), 1.7–2.8 (4 H, m, 2 × CH_2), 2.95 (3 H, s, SO_2CH_3), 4.25 (2 H, t, J = 5 H_2, $CH_2OSO_2CH_3$), and 5.0–5.8 (2 H, m, vinylic H).

cis-Hex-3-en-1-yl mesylate (892 mg) in EtOH (50 ml) was added to a colourless soln of sodium phenylselenide (prepared by the addition of sodium borohydride (84.8 mg, 2.23 mmol) to a stirred soln of diphenyl diselenide (634 mg, 2.03 mmol) in anhyd EtOH (40 ml) under N_2) under a dry N_2 atmosphere, and the mixture stirred for 18 hr. Dilution with ether (30 ml) and water (50 ml), gave an organic phase which was separated, washed with water (3 × 40 ml), brine (3 × 40 ml), and dried ($MgSO_4$). Concentration *in vacuo* and distillation gave a yellow oil identified as cis-*hex*-3-*en*-1-*yl phenyl selenide* **9** (854 mg), b.p. 134–136°/0.5 mm Hg, ν_{max} 1590 and 740 cm^{-1}, δ ($CDCl_3$) 1.0 (3 H_1 t, J = 6 Hz, CH_2CH_3), 2.05 (2 H, m, CH_2), 2.55 (2 H, m, CH_2), 2.93 (2 H, t, J = 8 Hz, CH_2SePh), 5.3–5.55 (2 H, m, vinylic H), 7.2 (3 H, m, aromatic H), and 7.53 (2 H, m, aromatic H); *m/z* 240 (M$^+$, 27%) and 158 (M$^+$ + H-PhSe, 50%).

Preparation of octa-3,5-*dien*-2-*ols* (**10** *and* **11**) *from* cis-*hex*-3-*en*-1-*yl phenyl selenide* (**9**).

(a) *Under standard conditions.*[17] *m*-Chloroperoxybenzoic acid (180.5 mg, 1.04 mmol) in THF (1 ml) was added to a soln of *cis*-hex-3-en-1-yl phenyl selenide (250 mg, 1.04 mmol) in THF at −78° under anhyd N_2. After 45 min, a soln of lithium di-isopropylamide in THF (2.3 ml of a 1 N soln) was added, the mixture stirred for 5 min, and a soln of freshly distilled acetaldehyde (48.5 mg, 1.1 mmol) in THF (1 ml) added. Stirring was continued for 30 min, the soln warmed to 0°, AcOH (0.2 ml) and water (0.2 ml) in THF (1 ml) added, and then the mixture added to di-isopropylamine (0.15 ml, 1.05 mmol) in hexane (10 ml) at reflux. The mixture was heated under reflux for 5 min, cooled, diluted with 5% Na_2CO_3aq (50 ml), washed with 0.1 N HClaq (3 × 30 ml), $NaHCO_3$aq (3 × 30 ml), and brine (3 × 30 ml), and then

dried ($MgSO_4$). Concentration *in vacuo* gave an oil, which was chromatographed on silica (10 g), being eluted with CH_2Cl_2, to give a mixture of *trans,trans-* and *trans,cis*-octa-3,5-dien-2-ols **10** and **11** (65 mg). These components could not be separated by chromatography. However comparison with the pure materials (see below) showed the ratio to be **10**:**11** = 55:45.

(b) *Omitting acetic acid step.* The procedure described in (a) above was repeated except that the addition of aqueous AcOH was omitted. Work-up as described above gave a colourless oil which was purified by column chromatography and identified as trans,cis-*octa*-3,5-*dien*-2-*ol* **11** (73 mg), R_f 0.22 (CH_2Cl_2)) λ_{max} 3400 (broad), 1640, 990, 950, and 740 cm^{-1}, ($CDCl_3$) 1.0 (3 H, t, J = 6.25 Hz, $CH_2C\underline{H}_3$), 1.27 (3 H, d, J = 6.25 Hz, $CHOHC\underline{H}_3$), 1.9 (1 H, s, exch. with D_2O, OH), 2.03–2.1 (2 H, m, $C\underline{H}_2CH_3$), 4.3 (1 H, m, $C\underline{H}OH$), 5.4 (1 H, m, H(6)), 5.68 (1 H, t, J = 15 Hz, H(3)), 5.93 (1 H, dd, J = 10.5, 12 Hz, H(5)), and 6.45 (1 H, dd, J = 10.5, 15 Hz, H(4)), λ_{max} (MeOH) 233 nm (ε 27, 240). (Found *m/z*: M^+ 126.1048, $C_8H_{14}O$ requires $\underline{M}^+$ 126.1048).

(c) *Oxidative elimination of phenylselenium from hydroxyselenide* (**8**) *in the presence of* trans,cis-*octa*-3,5 *dien*-2-*ol* (**11**). The oxidation procedure of **8** using sodium periodate-sodium hydrogen carbonate was repeated but in the presence of *trans,cis*-octa-3,5-dien-2-ol (10 mg). Normal work up procedure was used except for chromatography with CH_2Cl_2 only as solvent. Oxidative removal of the phenylselenyl group had occurred to give a mixture (as above), but the recovered dienol had isomerised (80%) and was identified as trans,trans-*octa*-3,5- *dien*-2-*ol* (6 mg), R_f 0.22 (CH_2Cl_2), ν_{max} 3400, 1650, 990, δ ($CDCl_3$) 1.0 (3 H, t, J = 6.25 Hz, $CH_2C\underline{H}_3$), 1.25 (3 H, d, J = 6.25 Hz, CHOH $C\underline{H}_3$), 1.9 (1 H, s exch. D_2O, OH), (2.05–2.15 (2 H, m, $C\underline{H}_2CH_3$), 4.38 (1 H, m, $C\underline{H}OH$), 5.66 (1 H, dd, H_3), 5.76 (1 H, m, H_6), 6.0 (1 H, t, H5), 6.18 (1 H, dd, H4), λ_{max} (MeOH) 231 nm (ε 25, 350). (Found: *m/z*: M^+ 126.1048, $C_8H_{14}O$, required: H^+ 126.1048).

Acknowledgements—We thank the SRC and Glaxo Group Research Ltd., for a CASE Award (to N.V.R.) and Dr. W. Leimgruber (Hofmann La Roche, Nutley, U.S.A.) for a generous gift of arachidonic acid. We also thank Dr. R. F. Newton for helpful discussion, Lady Richards and Mrs. McGuiness for ^1H NMR spectra, Dr. R. T. Aplin for mass spectra, and finally the SRC for a research grant for the purchase of a ZAB 1F spectrometer and associated data systems.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 269 to 274, 1981
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0040-4020/81/Suppl. 1-0269-06 $02.00/0
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SYNTHETIC APPROACHES TO POLYHYDROXYAGAROFURANS†

J. W. HUFFMAN* and G. F. HILLENBRAND

Department of Chemistry and Geology, Clemson University, Clemson, SC 29631, U.S.A.

(*Received in U.S.A.* 14 *July* 1980)

Abstract—In a synthetic approach to the polyhydroxyagarofurans found throughout the family Celastraceae, the Robinson annulation of hydroxycarvone with ethyl vinyl ketone has been repeated. In contrast to the reported results 10-epieudesma-4,11-diene-3,9-dione is the major product (43%) of the annulation and eudesma-4,11-diene-3,9-dione is a minor product (24%). The structure and stereochemistry of these isomers was determined by conversion to eudesmane derivatives of known structure and stereochemistry. The requisite isomer from the annulation, 10-epieudesma-4,11-diene-3,9-dione, was converted to 9-keto-α-agarofuran by epoxidation with *m*-chloroperoxybenzoic followed by reduction to a stereoisomeric mixture of 10-epieudesm-4-en-3,9,11-triols. Oxidation of this mixture with Jones reagent afforded the ketoagarofuran. This annulation and agarofuran synthesis has also been carried out using hydroxy-carvone and methyl vinyl ketone to afford 14-nor-9-keto-α-agarofuran.

The family Celastraceae is well known as a source of the tumor inhibitory compounds of the maytansine[1] and triptolide[2] groups; however, in addition to these substances, many of the plants of this family produce polyhydroxy sesquiterpenes based on the agarofuran ring system. These polyhydroxyagarofurans range in structural complexity from the relatively simple triol, isocelorbicol (**1**),[3] through compounds bearing nine hydroxyl groups, such as euonyminol.[4] Many of these polyols occur in nature as ester alkaloids, usually derived from nicotinic acid or substituted nicotinic acids.[5]

In an approach to the synthesis of these sesquiterpenes, we envisioned carrying out one of the established agarofuran syntheses,[6] modified to use as starting material a 9-oxygenated-10-epieudesmane derivative (e.g. 10-epieudesma-4,11-diene-3,9-dione (**2**). Based on the known stereochemical outcome of the Robinson annulation reaction,[7] dione **2** would be predicted to be the major product from the reaction of 2-methyl-5-isopropenylcyclohexane-1,3-dione (hydroxycarvone) with ethyl vinyl ketone. However, some years ago Lacoume and Zalkow reported that the alkylation of hydroxycarvone with ethyl vinyl ketone affords a triketone (**3**) which on cyclization with pyrrolidine gives ketol **4**. Dehydration of this ketol gives dione **5**, with the normal eudesmane configuration at C-10.[8] The stereochemistry of dione **5** was established by its conversion to eudesm-4-ene (**6**).[8]

Although these workers reported that the alkylation of hydroxycarvone produced exclusively triketone **3**, this seemed unlikely in view of the known stereochemistry of the alkylation of cyclohexanone enolates,[7] and a reinvestigation of Lacoume and Zalkow's annulation was undertaken. The starting material for this sequence, hydroxycarvone (2-methyl-5-isopropenyl-1,3-cyclohexanedione) was prepared many years ago by Treibs in low yield by the vigorous alkaline peroxide oxidation of carvone.[9] The procedure was modified by Lacoume and Zalkow, but the yields were still low and variable (25–40%).[10] We have further modified this preparation by isolating the epoxide formed by mild alkaline peroxide oxidation of carvone and carrying out the rearrangement to the diketone with warm base in a subsequent step. This procedure consistently affords yields of 60–70% of once recrystallized material. Alkylation of hydroxy-carvone under the reported conditions[8,10] gave material which appeared to be homogeneous (glc, tlc) and agreed in its spectral properties with those described by Lacoume.[10] Subsequent determination of the NMR spectrum under optimum conditions resolved the quaternary methyl singlet at δ 1.20 into a pair of singlets at δ 1.20 and 1.21, indicating that this material was actually a mixture. One component of this mixture is trione **3** and the other is presumably its epimer at the quaternary center (**7**). Cyclization of this mixture of triketones with pyrrolidine–acetic acid,[10] afforded in 32% yield a 3:1 mixture of ketol **4** and diketone **5**, both of which agreed in their spectral and physical properties with those of material prepared by Lacoume and Zalkow.[11]

On the assumption that the low yield of cyclized material and the failure to isolate or detect any products with the 10-epieudesmane stereochemistry was caused by a facile reverse Michael reaction of trione **7** under the weakly basic reaction conditions, the cyclization was repeated under mildly acidic conditions. Prolonged treatment of the mixture of triones with aluminum-t-butoxide in benzene[12] gave in low yield a mixture of three compounds, enone **5**, an isomer, subsequently shown to be enone **2**, and a ketol isomeric with ketol **4**. On the basis of its spectral properties and subsequent conversion to enone **2** on heating with p-toluenesulfonic acid in benzene, the isomeric ketol was assigned structure **8**. It was ultimately found possible to effect the conversion of the mixture of triketones **3** and **7** cleanly and in good yield to a mixture of enones **2** and **5** in a ratio of ca. 2:1 with *p*-toluenesulfonic acid in benzene. Although this cyclization method afforded the 10-epieudesmane derivative (**2**) as the major product, some effort was made to improve both the yield and stereoselectivity of

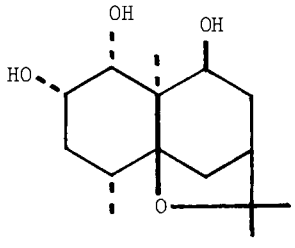
†Dedicated to the memory of Professor Robert Burns Woodward.

the initial alkylation. The use of methanolic potassium hydroxide as a catalyst increased the yield somewhat, however, neither this procedure nor the use of sodium hydride in the presence of excess hydroxycarvone caused a significant change in the ratio of stereoisomers obtained from the alkylation. As predicted, and in contrast to the published work of Lacoume and Zalkow,[8] the Robinson annulation of hydroxycarvone follows the normal stereochemical path and affords the 10-epieudesmane derivative as the major product. The earlier workers were apparently misled by the near identity of the physical and spectral properties of triones **3** and **7** combined with the failure of trione **7** to cyclize to the 10-epieudesmane (**2**) on heating with pyrrolidine–acetic acid.

Although there seemed to be no reason to question Lacoume and Zalkow's assignment of stereochemistry to dione **5**, there was some question at this stage regarding the two diones we had obtained from the acid catalyzed cyclization of the mixture of triones **3** and **7**. These diones have virtually identical IR and NMR spectra, the m.p.s of their dinitrophenylhydrazones are nearly the same and in our hands the m.p. of the monothioketal of enone **5** differs markedly from that reported.[8] In the absence of a comparison samples of enone **5** or a derivative, and prior to investigating synthetic routes to the agarofuran ring system, the stereochemical assignments of enone **2** and **5** were confirmed by their conversion to 10-epieudesm-4-ene (**9**) and eudesm-4-ene (**6**), respectively.

Enone **5** was converted to eudesm-4-en-9-one (**10**) by essentially the method described by Lacoume and Zalkow;[8] however, a number of attempts to repeat the reported desulfurization of the thioketal of ketone **10** afforded complex mixtures. Ketone **10** was, however, smoothly converted to eudesmene **6** by Wolff–Kishner reduction.

The conversion of enone **2** to 10-epieudesm-4-ene (**9**) followed essentially the same route as that used for the conversion of enone **5** to olefin **6**: selective



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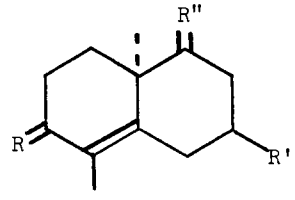
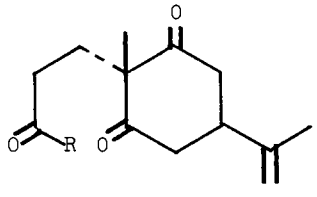
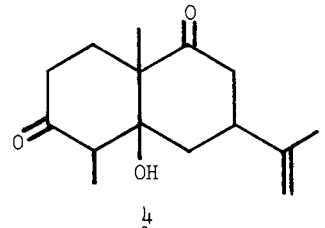


2 R,R"=O,R'=$CH_3CH=CH_2$
9 R,R"=H_2, R'=$(CH_3)_2CH$
11 R,R"=O, R'=$(CH_3)_2CH$
12 R=SCH_2CH_2S, R'=$(CH_3)_2CH$,R"=O
13 R=H_2,R'=$(CH_3)_2CH$, R"=O



3 R=C_2H_5
17 R=CH_3



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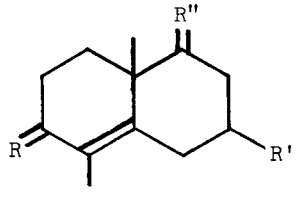
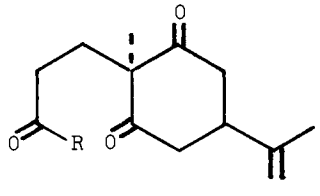
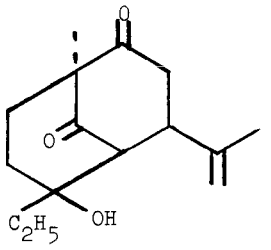


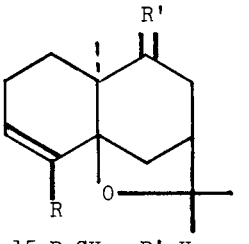
5 R,R"=O, R'=$CH_3CH=CH_2$
6 R,R"=H, R'=$(CH_3)_2CH$
10 R=H_2, R'=$(CH_3)_2CH$,R"=O
14 R=H, OH, R"=$(CH_3)_2COH$, R"=H_2



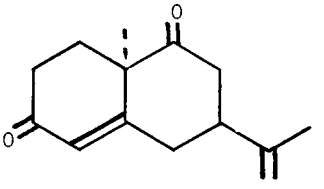
7 R=C_2H_5
18 R=CH_3



8



15 R=CH_3, R'=H_2
16 R=CH_3, R'=O
20 R=H, R'=O



19

reduction to enone **11**, using Wilkinson's catalyst, conversion to monothioketal **12**, desulfurization of which afforded 10-epieudesm-4-en-9-one (**13**). Wolff–Kishner reduction of ketone **13** afforded 10-epieudesm-4-ene (**9**), identical to a sample prepared by an established method.[13]

Having confirmed that enone **2** has the requisite 10-epieudesmane structure, efforts to effect its conversion to an agarofuran derivative were initiated. The original synthetic design envisioned a modification of Büchi's agarofuran synthesis which leads to a 2-ketoagarofuran *via* the photooxygenation of 2,4-diene system. This route would provide the functionality necessary for the introduction of the 1α,2α-diol system characteristic of the vast majority of the polyhydroxyagarofurans isolated to date. The initial step of this proposed sequence was to be the preparation of the 2,4-diene derived from enone **2** by the lithium disiopropylamide induced decomposition of the corresponding tosylhydrazone.[14] Although this sequence was effective for the conversion of enone **5** to the corresponding 2,4-diene,[15] it failed in the case of enone **2**.

Several years ago we made the fortuitous observation that Jones oxidation of 3,11-dihydroxyeudesm-4-ene (**14**, epimers at C-3) gave α-agarofuran (**15**) in good yield.[6d] Accordingly, treatment of enone **2** with *m*-chloroperbenzoic acid afforded a mixture of epimeric 11,12-oxides, which on reduction with lithium aluminum hydride gave a mixture of stereoisomeric 3,9,11-triols. Jones oxidation of this mixture of triols proceeded smoothly to produce 9-keto-α-agarofuran (**16**) in 47% yield from enone **2** and an overall yield of 15% from hydroxycarvone.

In our synthetic design, the 4α-(axial) Me group, which is present in virtually all naturally occurring polyhydroxyagarofurans, is to be introduced by reduction of the unsaturation present in the ring-A of a suitably functionalized conversion product of agarofuran **16**. In anticipation of potential problems in obtaining stereoselectivity at this center, it was felt that as an alternative approach the addition of the 4α-Me group via a suitable organometallic reagent at some later stage in the synthesis might prove more satisfactory. Accordingly, the 14-nor analogue of 9-keto-α-agarofuran was prepared by a synthetic route essentially identical to that used for the synthesis of ketone **16**: Alkylation of hydroxycarvone with methyl vinyl ketone afforded a mixture of triones **17** and **18**, which on cyclization with *p*-toluenesulfonic acid gave a mixture of the 14-nor analogues of enones **3** and **5**. From this mixture 14-nor-10-epieudesma-4,11-diene-3,9-dione (**19**) was obtained as a crystalline solid and the stereochemistry at C-10 was tentatively assigned on the basis of the similarity of the NMR spectra of this compound to that of enone **2**. This assignment was confirmed by conversion to 14-nor-9-keto-α-agarofuran (**20**) by the route used for the preparation of ketone **16**. Although no difficulty in preparing ketone **16** was encountered, the overall yield from enone **19** was low and various modifications in this sequence have resulted in no significant improvement.

9-Keto-α-agarofuran (**16**) and its 14-nor analogue (**20**) are both reasonable substrates for the synthesis of various members of the polyhydroxyagarofuran group of sesquiterpenes. The synthetic routes described provide methods for preparing these potentially useful synthetic intermediates in sufficient quantity for their use as starting materials for the synthesis of isocelorbicol (**1**) and other representative members of this group of natural products.

EXPERIMENTAL

Microanalyses were performed by Atlantic Microlab, Atlanta, Georgia. IR Spectra were routinely measured as liquid films or as solns in CCl_4. NMR spectra were carried out in $CDCl_3$ and were recorded at 60 MHz using a Varian A60A spectrometer; signals are reported in parts per million

relative to TMS (δ). M.ps were obtained using a Kofler hot stage and are uncorrected. Mass spectra were determined at 70 eV using a Hewlett–Packard 5985B spectrometer.

2-Methyl-5-isopropenyl-1,3-cyclohexanedione (hydroxycarvone)

To a soln of 40.0 g (0.266 mol) *l*-carvone in 40 ml MeOH, previously cooled to 0° in an ice–salt bath, was added with stirring a soln of 32.0 g (0.570 mol) KOH in 40 ml water and 120 ml MeOH. To the resulting mixture at −5° was added in one portion, 30 ml 30% H_2O_2, previously cooled to −13°. The temp rose to 15° after 10 min. Another 35 ml portion of 30% H_2O_2 was added after 25 min, by which time the temp had fallen to −3°. The mixture was stirred at or slightly below 0° for 1 hr during which time an oily layer separated and 200 ml water were added. The mixture was extracted with four portions of benzene, the organic layers were combined, washed with water, and bring, dried and the solvent removed to give 43.9 g of pale yellow epoxide, which was sufficiently pure for further use; IR (CCl_4), 1708 cm^{-1}, NMR δ 1.35 (s, 3 H, CH_3), 1.68 (d, 3 H, J = 1 Hz, CH_3C=), 3.35 (dd, 1 H, J = 3 Hz, 1 Hz, –CHOC), (m, 2 H, H_2C=C). To 1 *l* of 1N NaOH at room temp was added 43.9 g (0.264 mole) of crude epoxide and the heterogeneous mixture was heated on a steam bath and occasionally swirled until dissolution occurred (approximately 1 hr). The soln was cooled to room temp and acidified with 20% HCl aq. The resulting slurry was cooled to 0° and the ppt filtered off. The crude wet ppt was dissolved in 1.5 *l* EtOAc and the bulk of the water was removed by azeotropic distillation. On cooling there was obtained 29.3 g (60%) hydroxycarvone, m.p. 184–186° (Reported, 187–189°[10]). Concentration of the mother liquor afforded an additional 3.8 g (9%) material of similar purity; IR 1730, 1710, 1610 cm^{-1}; NMR δ 1.77 (s, 3 H, CH_3), 1.85 (d, 3 H, J = 1 Hz, CH_3C=), 2.61 (m, 5 H, CH_2–C=O, CH), 5.05 (q, 4 H, J = 1.5 Hz, H_2C=).

Alkylation of 2-methyl-5-isopropenyl-1,3-cyclohexane-dione with ethyl vinyl ketone

A. To a stirred soln of 5.00 g (0.03 mol) hydroxycarvone in 50 ml benzene containing 4 ml pyridine and maintained under N_2 was added 4.00 g (0.047 mol) ethyl vinyl ketone in 5 ml benzene. The mixture was heated at reflux for 19 hr, cooled and extracted with ether. The ethereal extracts were washed with dil HCl aq, sat $NaHCO_3$ aq and water. After drying the solvent was removed leaving a brown oil which on distillation (bp 120–150°, air bath, 0.05 mm) afforded 3.33 g (55% based on 0.023 mols hydroxycarvone consumed) of a mixture of **3** and **7**; IR, 1705, 1695 cm^{-1}; NMR δ 1.03 (t, J = 7 Hz, 3 H, CH_3CH_2), 1.20, 1.21 (s, 3 H total, CH_3 for each isomer) 1.86 (m, 3 H, CH_3–C=), 2.96 (m, 4 H, CH_2COCH_2), 4.95 (m, 2 H, CH_2=C). Acidification of the basic extracts afforded 1.15 g of recovered hydroxycarvone.

B. To a stirred suspension of 2.76 g NaH (57% dispersion in mineral oil, washed thrice with dry hexanes) in 200 ml dry THF and maintained under N_2 was added 21.8 g (0.03 mol) hydroxycarvone and an additional 50 ml THF and the mixture stirred at ambient temp for 10 min. A soln of 5.50 g (0.065 mol) ethyl vinyl ketone in 75 ml dry THF was added dropwise. The mixture was stirred and heated at reflux for 18 hr, cooled, and 100 ml of 1.0 N HCl was added dropwise, followed by 200 ml water. The THF was removed with warming at reduced pressure and the aqueous suspension made alkaline by the cautious addition of solid KOH. The product was isolated as described in Part A to give 9.85 g (61% based on ethyl vinyl ketone) of a mixture of **3** and **7**, the spectral properties of which were identical to those described in part A.

C. To a soln of 54.4 g (0.328 mol) hydroxycarvone in 225 ml MeOH was added 25.0 g (0.290 mol) ethyl vinyl ketone and 12.5 ml of 11.7% (w/v) methanolic KOH. The mixture was stirred and heated at reflux 5.5 hr, cooled, and poured into 1000 ml water. The product was isolated as described above to give 53.6 g (74%) of a mixture of **3** and **7**, the spectral properties of which were identical to those described in part A.

Cyclization of triketones 3 and 7

A. *With pyrrolidine-acetic acid.* To 1.00 g (0.004 mol) of the mixture of the epimeric triketones in 50 ml dry THF was added, with stirring and under N_2, 0.37 ml pyrrolidine, followed by the dropwise addition of 0.26 ml AcOH in 25 ml dry THF. The mixture was heated at reflux under N_2 for 4 hr, cooled, poured into ether and extracted with dil KOH aq. The organic layer was washed with successive portions of dil HCl and $NaHCO_3$, dried and the solvent removed to give 0.70 g partially crystalline material. Crystallization from hexanes afforded 0.24 g (24%) of **4**, m.p. 129–130° (lit m.p. 129–130°[8]). The IR and NMR spectra were identical to those of material prepared by Lacoume and Zalkow.[11]

The mother liquors were concentrated to dryness, the residue taken up in ether–hexanes (1:9) and chromatographed on Woelm silica gel. Elution with ether-hexanes afforded 0.070 g (8%) of **5** as a colorless oil, the IR and NMR of which were identical to those of the material prepared by Lacoume and Zalkow. The 2,4-dinitrophenyl hydrazone had m.p. 205–206° (reported: 207–208°[8]). Dehydration of **4** afforded **5** as described by Lacoume and Zalkow.[8]

B. *With aluminum t-butoxide.* A soln of 10.00 g (0.40 mol) of **3** and **7** in 250 ml dry benzene containing 12.3 g (0.050 mol) aluminum t-butoxide was heated at reflux under N_2 for 80 hr. The cooled mixture was poured into 800 ml 1N HCl, the aqueous layer drawn off and extracted with ether. The organic extracts were combined, extracted with three portions of sat $NaHCO_3$ aq, washed with brine, dried and the solvent removed at reduced pressure to give 6.01 g brown oil which was dissolved in ether-hexanes (1:7) and chromatographed on Woelm silica gel. Elution with ether–hexanes mixtures afforded first 1.22 g (12%) of **5** followed by 1.46 g (15%) of (**2**); IR 1720, 1675, 1610 cm^{-1}; NMR δ 1.40 (s, 3 H, CH_3), 1.75 (s, 6 H, CH_3C=C), 4.56, 4.75 (m, 2 H, CH_2=C). The 2,4-dinitrophenylhydrazone formed red crystals from EtOAc cyclohexane, m.p. 200–202° (Found: C, 61.02; H, 5.92; N, 13.52. Calc. for $C_{21}H_{24}N_4O_5$: C, 61.16; H, 5.87, N, 13.58%).

The final ether–hexanes fractions afforded 0.493 (5%) bridged ketol as white crystals, m.p. 106–107° from hexanes: IR 1745, 1645 cm^{-1}; NMR δ 1.05 (s, 3 H, CH_3), 1.05 (t, J = 6 Hz, 3 H, $C\underline{H}_3CH_2$), 1.75 (s, 3 H, CH_3 C=C), 4.75, 4.92 (m, 2 H, CH_2=C). (Found: C, 72.04, H, 8.87. Calc. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%). Acidification of the original bicarbonate extracts afforded 1.80 g of hydroxycarvone.

C. *With p-toluenesulfonic acid.* To a soln of 24.6 g (0.098 mols) of **3** and **7** in 1250 ml benzene was added 1.51 g *p*-toluenesolfonic acid. The mixture was stirred and heated at reflux under N_2 with the continuous removal of water for 72 hr. The products were isolated as described in part B, to give 6.00 g (24%) of **5** and 10.40 (43%) of **2**.

10-Epieudesma-4,11-diene-3,9-dione (**2**)

A soln of 0.83 g (0.033 mol) of bridged ketol **8** in 125 ml benzene containing 0.10 g *p*-toluenesulfonic acid was heated at reflux with the continuous removal of water for 5 hr. The mixture was cooled, washed with sat $NaHCO_3$ aq, dried and the solvent removed to give 0.77 g (100%) of **2** as a brown oil, the spectral properties of which were identical to those described above.

Eudesm-4-en-9-one (**10**)

This material was prepared from (**5**) following the method outlined by Lacoume and Zalkow.[8] The spectral data for all the intermediates and **10** agreed with those reported, as did their physical properties, with the exception of the monothioketal of eudesm-4-en-3,9-dione which in our hands has m.p. 64–65° (lit. m.p. 74–75°[8]) after repeated recrystallization from pentane.

Eudesm-4-ene (**6**)

To a soln of 0.047 g (0.00017 mol) semicarbazone of eudesm-4-en-9-one in 2 ml diethylene glycol was added

0.050 g KOH and two drops hydrazine hydrate. The mixture was heated with stirring and the solvent slowly distilled off until a vapor temp of 185° was attained, and then heated at reflux for 4.25 hr. The mixture was cooled and extracted with two portions hexanes. The hexane extracts were combined, washed with sat $NaHCO_3$ aq, dried and the solvent removed to give a brown oil which was dissolved in hexanes and chromatographed on Woelm silica gel to give 0.017 g (49 %) of **6** as a colorless oil. The spectral properties agreed with those reported by Lacoume and Zalkow, and were markedly different from those of **9**.

10-*Epieudesm*-4-*ene*-3,9-*dione* (**11**)

To a soln of 0.814 g (0.00351 mol) of **2** in 40 ml benzene was added 0.401 g tris (triphenylphosphine) rhodium (1) chloride. The reaction flask was purged with H_2 for 20 min, sealed and stirred under H_2 for 25 hr. The mixture was filtered through a column of alumina and the solvent removed to give a yellow oil. Distillation (159–165°, air bath, 0.01 mm) gave 0.597 g (73 %) of **11** as a colorless oil, IR, 1715, 1660, 1605 cm^{-1}; NMR δ 0.89 (d, J = 5.5 Hz, $C\underline{H}_3CH$); 1.37 (s, 3 H, CH_3), 1.75 (s, 3 H, $CH_3C{=}C$). The 2,4-dinitrophenylhydrazone was obtained as red crystals from EtOAc-cyclohexane, m.p. 184–186° (Found: C, 60.90; H, 6.36; N, 13.49. Calc. for $C_{21}H_{26}N_4O_5$: C, 60.85; H, 6.32; N, 13.51 %).

Monothioketal of 10-*epieudesma*-4-*ene*-3,9-*dione* (**12**)

To a stirred soln of 0.305 g (0.0013 mol) of **11** in 2 ml AcOH, under N_2, was added successively 0.122 g (0.0013 mol) ethanedithiol in 1 ml AcOH and 0.117 g *p*-toluenesulfonic acid in 1 ml AcOH. The mixture was stirred under N_2 for 14 hr, poured into water and extracted with three portions ether. The etheral extracts were combined, washed with 10 % NaOH aq and sat $NaHCO_3$ aq, dried and the solvent removed to give a pale yellow semi-solid. This material was dissolved in ether–hexanes (1:24) and chromatographed on Woelm silica gel. Elution with ether–hexanes afforded 0.325 g (81 %) crystalline thioketal, m.p. 107–108° after recrystallization from hexanes; IR 1720 cm^{-1}; NMR δ 0.90 (d, J = 5.5 Hz, 3 H, $C\underline{H}_3CH$); 0.94 (d, J = 5.5 Hz, $C\underline{H}_3CH$); 1.24 (s, 3 H, CH_3); 1.97 (s, 3 H, $CH_3C{=}$); 3.32 (br s, 4 H, $S(CH_2)_2S$). (Found: C, 65.79; H, 8.45. Calc. for $C_{17}H_{26}OS_2$: C, 65.76; H, 8.44 %).

10-*Epieudesm*-4-*en*-9-*one* (**13**)

To a soln of 0.192 g (0.00062 mol) of **12** in 30 ml EtOH was added 4.0 ml (settled volume) Raney Ni suspended in 30 ml EtOH. The mixture was heated, with stirring, under N_2 for 30-hr, cooled, filtered through Celite and concentrated to afford 0.183 g yellow oil. The crude material was dissolved in ether-hexanes (1:9 and chromatographed on Woelm silica gel. Elution with the same solvent system afforded 0.106 g (78 %) of **13** as a colorless oil, b.p. 70–80° (air bath, 0.025 mm); IR (CCl_4) 1715 cm^{-1}; NMR δ 0.98 (m, 6 H, $(CH_3)_2CH$); 1.22 (s, 3 H, CH_3); 1.68 (br s, 3 H, $CH_3C{=}$). (Found: C, 81.57; H, 11.00 Calc. for $C_{15}H_{24}O$: 81.76; H, 10.98 %).

10-*Epieudesm*-4-*ene* (**9**)

To a soln of 0.033 g (0.00015 mol) of **13** in 3 ml triethylene glycol was added 0.493 g hydrazine hydrate and 0.125 g hydrazine hydrochloride. The mixture was heated to 130°, with stirring, and maintained at that temp for 2.5 hr. The mixture was cooled slightly, 0.184 g of solid KOH was added, and the temp increased to 210° for 2.5 hr. After cooling, 5 ml water was added and the mixture extracted with two portions water and sat $NaHCO_3$ aq, dried and the solvent removed at reduced pressure to give a pale yellow oil. This oil was taken up in hexanes and filtered through Woelm silica gel to give 0.025 g (77 %) of **9**, which was identical in all respects (IR, NMR, glc) to a sample prepared by an alternative route.[13]

9-*Keto*-α-*agarofuran* (**16**)

To a stirred soln of 5.87 g (0.0253 mol) of **2** in 260 ml dry $CHCl_3$ was added 5.73 g *m*-chloroperbenzoic acid (80 %). The mixture was stirred under N_2 for 30 hr, washed successively with two portions of 10 % Na_2SO_3 aq, three portions of 10 % NaOH aq, water and brine. After drying the solvent was removed to give 5.84 g of a mixture of epimeric epoxides which was used in the succeeding step without purification: NMR δ 1.31 (s, 3 H, $CH_3C{-}C$ (O)), 1.39 (s, 3 H, CH_3) 1.81 (s, 3 H, $CH_3C{=}C$).

To a stirred suspension of 2.66 g LAH in 200 ml dry ether at 0° under N_2 was added dropwise 5.84 g crude epoxide mixture in 100 ml dry ether. The reaction was stirred at 0° for 8 hr, warmed to room temp and stirred an additional 18 hr. After cooling to −10°, 2.7 ml water was added cautiously, followed by 2.7 ml 15 % NaOH aq and 8.1 ml water. The ppt was filtered off and washed thoroughly with THF. Removal of the solvents afforded 6.0 g of a mixture of triols as a colorless glass, the IR of which showed no CO absorption. The crude mixture of triols was dissolved in 200 ml permanganate stable acetone and 11.0 ml Jones reagent was added dropwise with stirring. The mixture was stirred at ambient temp for 2.5 hr, poured into water and extracted with ether. The etheral extracts were washed with water, sat $NaHCO_3$ aq and brine, dried and the solvent removed at reduced pressure to give a yellow oil. This oil was dissolved in ether–hexanes (1:1) and chromatographed on Woelm silica gel. Elution with the same solvent pair gave 2.80 g (47 %) of **16** as a nearly colorless oil, homogeneous to tlc, which crystallized on standing. A small portion was crystallized from pentane, m.p. 73–74°; IR 1750 cm^{-1}; NMR δ 1.04 (s, 3 H, CH_3), 1.19, 1.26 (s, 3 H each), $(CH_3)_2C{-}O$), 1.77 (br s, 3 H, $CH_3C{=}$); 5.55 (m, 1 H, $HC{=}C$). (Found, C, 76.84; H, 9.47. Calc. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46 %).

Alkylation of 2-*methyl*-5-*isopropenyl*-1,3-*cyclohexanedione with methyl vinyl ketone*

The alkylation of hydroxycarvone with methyl vinyl ketone was effected using methanolic KOH as described above for the preparation of **3** and **7**. From 25.4 g (0.153 mol) diketone and 9.07 g (0.129 mol) methyl vinyl ketone there was obtained 26.5 g (87 %) of a mixture of **13** and **18** of sufficient purity for subsequent reactions. A small sample of the product triketones was distilled (b.p. 150°, air bath, 0.05 mm), to give a colorless oil. IR (CCl_4) 1725, 1700, 1645 cm^{-1}, NMR δ 1.20, 1.22 (s, total 3 H, CH_3 for each isomer), 1.76 (br s, 3 H, CH=), 2.07 (s, 3 H, CH_3CO), mass spectrum *m/e* (rel intensity), 236.2 (28), 179.2 (30), 178.2 (19, 125.1 (21), 123.1 (21), 110.1 (24), 109.1 (40), 95.1 (100).

14-*Noreudesma*-4,11-*diene*-3,9-*dione and* 14-*nor*-10-*epieudesma*-4,11-*diene*-3,9-*dione* (**19**)

Treatment of 26.50 g (0.112 mol) of **17** and **18** with *p*-toluenesulfonic acid in benzene as described above, followed by chromatography on Woelm silica gel and elution with EtOAc–cyclohexane (3:7) afforded 2.06 g (9 %) 14-noreudesma-4,11-diene-3,9-dione as a colorless liquid (b.p. 150–155°, air bath, 0.05 mm); IR 1718, 1680, 1642, 1620 cm^{-1}; NMR δ 1.47 (s, 3 H, CH_3), 1.78 (br s, 3 H, $CH_3C{=}$), 4.79 (m, 2 H, $H_2C{=}$), 5.81 (br s = CHCO). (Found: C, 76.82; H, 8.35. Calc. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31 %).

Continued elution with EtOAc-cyclohexane afforded 8.00 g of a mixture of ketones followed by 9.50 g (39 %) of **19** as crystals from hexanes, m.p. 93–95°; IR (CCl_4) 1715, 1676, 1638, 1620 cm^{-1}; NMR δ 1.48 (s, 3 H, CH_3), 1.65 (br s, 3 H, $CH_3C{=}$), 4.46, 4.68 (m, 1 H each, $H_2C{=}$), 5.67 (m, 1 H = CHCO). (Found: C, 77.03; H, 8.35. Calc. for $C_{14}H_{18}O_2$: 77.03; H, 8.31 %).

14-*Nor*-9-*keto*-α-*agarofuran* (**20**)

The conversion of 14-nor-10-epieudesma-4,11-diene-3,9-dione to **20** was carried out as described for the preparation of **16**. From 5.52 g (0.025 mol) of **19**, after chromatography on Woelm silica gel and elution with ether–hexanes (1:7), there was obtained 0.835 g (15%) of **20** as crystals from pentane, m.p. 93–94°; IR 1716 cm^{-1}; NMR δ 1.04 (s, 3 H, CH_3), 1.17, 1.21 (s, 3 H, each, $(CH_3)_2CO$), 5.41 (d, J = 10 Hz, CH–C̲H̲=CH–), 5.81 (dd, J = 10 Hz, J = 3 Hz, CH_2C̲H̲=CH). (Found: C, 76.33; H, 9.16, Calc. for $C_{14}H_{20}O_2$: C, 76.33, H, 9.15%).

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 275 to 279, 1981
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0040-4020/81/Suppl. 1-0275-05 $02.00/0
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IZUMENOLIDE—A NOVEL β-LACTAMASE INHIBITOR PRODUCED BY *MICROMONOSPORA*—III

THE STRUCTURE OF IZUMENOLIDE

WILLIAM L. PARKER*, MARLENE L. RATHNUM and PHILLIP T. FUNKE
The Squibb Institute for Medical Research, P.O. Box 4000, Princeton, NJ 08540, U.S.A.

(*Received in USA* 11 *July* 1980)

Abstract—Izumenolide, a β-lactamase inhibitor isolated from fermentations of *Micromonospora chalcea* subsp. *izumensis*, was shown by spectroscopic methods and chemical degradation to be a novel macrolide having structure **1**.

The β-lactam antibiotics constitute one of the major weapons against diverse bacterial infections by virtue of their potent antimicrobial activity and low toxicity. However, resistance arising from production of β-lactamases protects many otherwise susceptible pathogens. Hence, there has been a continuing search for agents to specifically inhibit these enzymes and thus serve as adjuncts in the therapeutic attack on β-lactamase producing organisms. This has recently led to the discovery and characterization of clavulanic acid and the olivanic acids, streptomycete-produced inhibitors that are themselves β-lactams. A review of the inhibition of β-lactamases has recently been published.[1]

We wish to report the structure of izumenolide (**1**), a potent inhibitor of β-lactamases that is not itself a β-lactam. The discovery, production by fermentation, isolation, preliminary chemical characterization, and biological characterization of izumenolide are being published elsewhere.[2,3]

RESULTS AND DISCUSSION

The isolation of **1** involved extraction into butanol at pH 2, back extraction into water at pH 7, precipitation from water by the addition of $Ca(NO_3)_2$, and regeneration of the Na salt. Thin-layer chromatography of the purest material obtained showed one major component and two minor components. Although efforts to further purify izumenolide on a preparative scale were not successful, this material was of adequate purity to determine the structure of the major component.

It is clear from the isolation scheme that **1** is acidic. Electrophoresis verified this, showing a high, constant mobility in the pH range 9.3 to 3.3, and undiminished mobility at the latter pH indicated that **1** is a strong acid.

The molecular weight of izumenolide was estimated by ultracentrifugation of the ammonium salt.[4] Values of 900 and 1300 were obtained in water and methanol, respectively. Failure of the inhibitor to dialyze through a membrane with a molecular-weight cutoff of 12,000 was inconsistent with this molecular weight range, but anomalous dialysis behavior of this sort has also been observed for the enzyme inhibitor, panosialin,[5] which has some gross chemical similarities to izumenolide. Elemental analysis of the sodium and ammonium salts of **1** showed that sulfur is a constituent of izumenolide and led, in conjunction with the molecular weight, to an approximate empirical formula of $C_{38-53}H_{69-103}O_{14-19}S_{3-4}M_{3-4}$ ($M{=}Na^+$ or NH_4^+).

The IR spectrum (strong peak at 1230 cm^{-1}) and the strongly acidic nature of **1** indicated that it may be a sulfate ester and this was confirmed by acid hydrolysis. Izumenolide is fairly stable to acid at room temperature, giving no change in 1 N HCl after 24 hr; however, all activity is lost after heating at 100° for 5 min. Heating at 100° in 6 N HCl for 1 hr gave inorganic sulfate, isolated as the barium salt, in good yield based on the elemental analysis.

The other functionality present in izumenolide was largely established by spectroscopic methods on the intact agent. An α,β-unsaturated ester with the *E*-configuration was indicated by peaks in the IR spectrum at 1711 and 1646 cm^{-1}, by a max at 214 nm in the UV spectrum, and by absorption in the ^{1}H-NMR spectrum at 5.77 (d, J = 15.7 Hz) and 6.83 ppm (d, t, J = 15.5, 6.8 Hz) and in the ^{13}C-NMR spectrum (Table 1) at 122.5, 151.0 and 167.9. Comparison of the intensity of the UV absorption of the sodium salt ($E^{1\%}_{1cm}$ = 95) to that of methyl crotonate (UV max at 212 nm, log ε 4.16) indicated a molecular weight for **1** (*ca* 1500) that is somewhat higher than the values obtained by ultracentrifugation and distinctly higher than that corresponding to the structure ultimately derived (Na salt: MW 941). An additional double bond in **1** was indicated by peaks in the ^{1}H-NMR spectrum at 5.38 ppm and in the ^{13}C-NMR spectrum at 125.5 and 132.5 ppm. The position of this double bond was established by ozonolysis (Me_2S work-up[6]) giving acetaldehyde, isolated as the dinitrophenylhydrazone. The *E*-configuration was assigned from the chemical shifts of the olefinic carbons and from the chemical shift (18.2 ppm) of the terminal Me group (expected at 18 ppm in the *E*-olefin and at 13 ppm in the *Z*-olefin).[7]

Izumenolide is rather stable to base, but gives the chromatographically homogeneous substance **2** after 5 hr at 100° in 1 N NaOH. The ^{13}C-NMR spectrum of **2** has a peak at 68.5 ppm assigned to a hydroxylated carbon that correlates with a peak at 73.3 ppm in the spectrum of **1**. A carboxylate group (IR: 1570 and 1420 cm^{-1}) is also present in **2**, establishing that the

Table 1. ^{13}C-NMR spectrum of izumenolide (a)

Chemical Shift (b)	Assignment (c)	Chemical Shift	Assignment
(12.7)	40'	40.2 t	16,30
18.1 q	40	73.2 d	29
25.8 t } 26.0 t }	13,19,27,33	78.0 d	15,17,31
		122.5 d	2
(27.7)	37'	(124.5)	39'
29.1	5	125.5 d	39
30.2	6,36	(131.6)	38'
30.7	7~12,20~26,34~35	132.5 d	38
(33.1)	4'''	150.7 d	3
33.5	4,37	(151.0)	3'''
35.5 } 35.9 }	14,18,28,32	167.9 s	1
		(172.5)s	1''

(a) Ammonium salt in CD_3OD. (b) Chemical shifts are in ppm downfield from TMS. CD_3OD (49.0 ppm) was used as an internal reference. Multiplicities were determined by single-frequency off-resonance decoupling. Weak peaks due to minor components are in parentheses. (c) The numbering system is shown in structure 1. Primed numbers are assigned to the 38,39-Z isomer, the double primed number to the 2,3-dihydro component, and the triple primed numbers to the base hydrolysis product.

ester function in **1** is lactonic. A peak at 78.0 ppm in the spectrum of **1**, attributed to the sulfated carbons, is unchanged in the spectrum of **2**. The ^{13}C-NMR spectrum of izumenolide contains a weak peak at 151.0 ppm, that may be due to a trace of **2** produced during isolation. In addition to the peaks discussed above, the ^{13}C-NMR and ^{1}H-NMR spectra of izumenolide have intense peaks at 30.7 and 1.23 ppm, respectively, indicative of substantial $-(CH_2)_n-$ regions.

The exact nature of the carbon skeleton of **1** was determined by the degradative sequence shown in Chart 1. Hydrogenation of **1** yielded a derivative (**3**) that retained β-lactamase-inhibiting activity. Since tlc of **3** showed minor components with the same mobilities as those that contaminate **1**, these minor components are not double-bond isomers or analogs with more or less unsaturation. It was thought that treatment of **3** with $LiEt_3BH$ might reductively remove the sulfate esters by analogy with the corresponding reduction of sulfonate esters;[8,9] they were, however, inert (no reaction after one week) under the conditions used. Only slow reductive opening of the lactone to the diol **4** occurred.[10] Acid hydrolysis of **4**, followed by tosylation of the resulting alcohol **5**, gave the pentatosylate **6**. Treatment of **6** with $LiEt_3BH$[8] then gave a crystalline hydrocarbon that was easily identified as n-tetracontane (**7**) from the mass spectrum and by comparison with authentic material. The empirical formula of **1** (Na-salt) is thus established as $C_{40}H_{71}O_{14}S_3Na_3$. Agreement with the elemental analysis[2] is surprisingly good, considering the

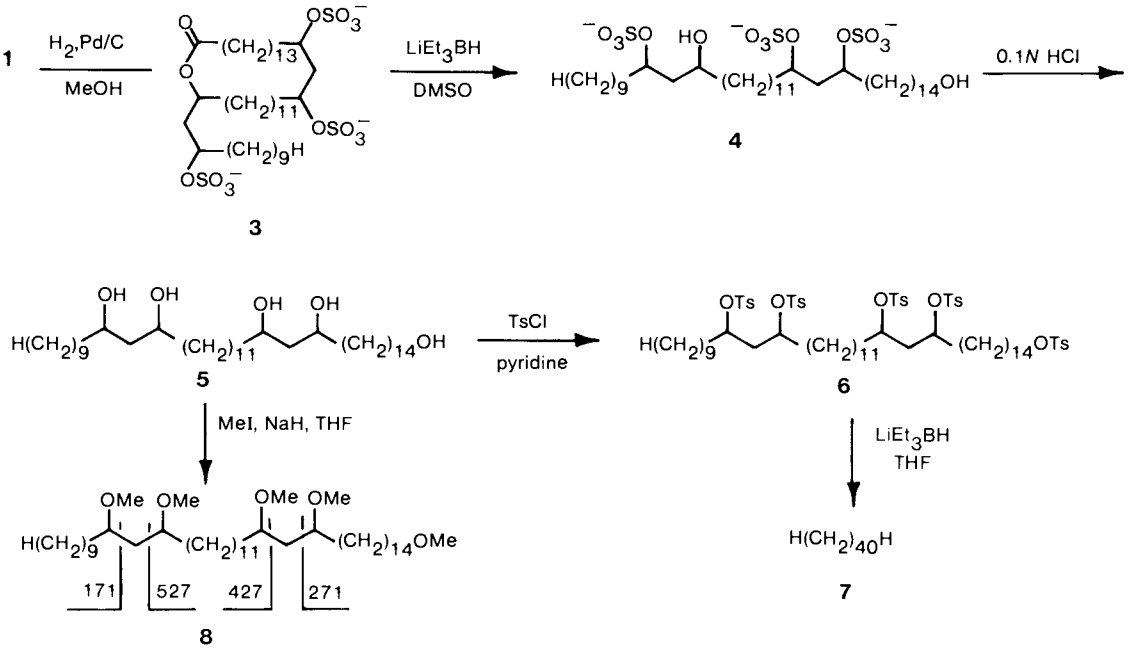
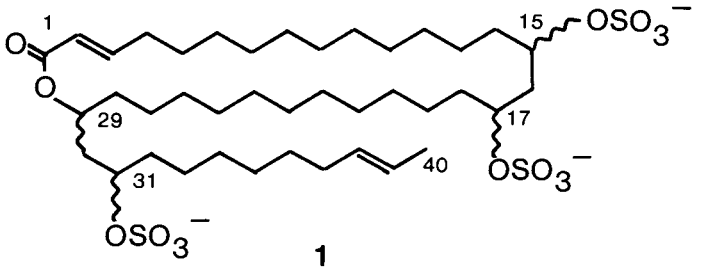


Chart 1.



extraneous components observed by tlc and the brevity of the isolation scheme.

Methylation of the pentaol **5** with methyl iodide gave pentamethyl ether **8**. The mass spectrum of this compound served to locate the oxygenated carbons in **1**. Major fragments were observed at *m/z* 171, 271, 427, and 527; these uniquely establish oxygenation at C-15, C-17, C-29, and C-31 (in addition to C-1) as shown in structure **8**.

The position of closure of the lactone was established by the sequence in Chart 2. Methylation of the diol trisulfate **4** gave the dimethylether trisulfate **9**. Hydrolysis to the dimethylether triol **10**, followed by tosylation and reduction of the resulting tosylate **11** with $LiEt_3BH$, gave the dimethyl ether **12**. Mass spectral fragments at *m/z* 199 and 467, as shown in structure **12**, established oxygenation at C-29 (in addition to C-1). Izumenolide is thus a 30-membered lactone and the full structure, exclusive of configuration of C-15, C-17, C-29 and C-31, is as shown by structure **1**.

The sequence shown in Chart 3 was also applied to izumenolide. Hydrolytic removal of the sulfate groups from the base hydrolysis product **2** gave a tetraol that was converted to the trimethylsilyl derivative **13** and examined by mass spectroscopy. Fragmentation to give ions with *m/z* 227, 399, 599 and 771 is consistent with the structure proposed for **1**. However, additional ions are observed at *m/z* 401 and 773. These apparently arise from a component in which the C-2, C-3 linkage is saturated. This is consistent with the UV spectrum of izumenolide which gave absorption at 212 nm that was somewhat weaker than that expected for an α,β-unsaturated ester. The ^{13}C-NMR spectrum of izumenolide has a weak peak at 172.5 ppm that is reasonably assigned to the lactone carbonyl of 2,3-dihydro izumenolide.

The ^{13}C-NMR spectrum of izumenolide also indicates that there is a minor component in which the 38,39-double bond has the *Z*-configuration. Weak peaks at 27.7, 131.6, 124.5 and 12.7 ppm are assigned, respectively, to C-37, C-38, C-39 and C-40 in this

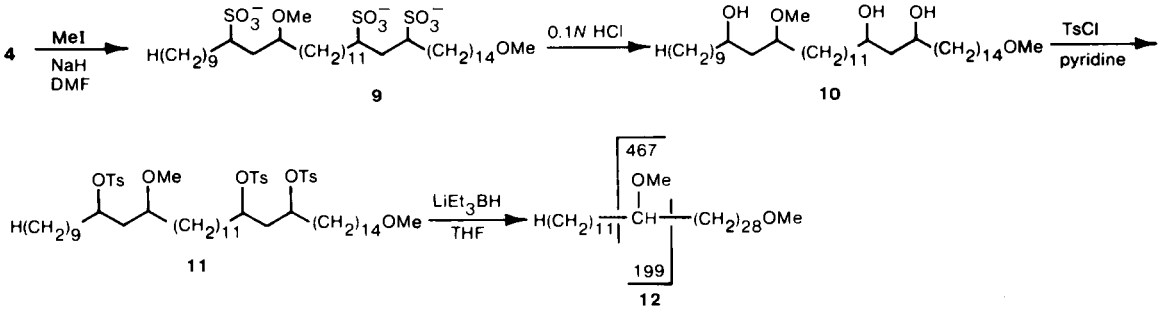
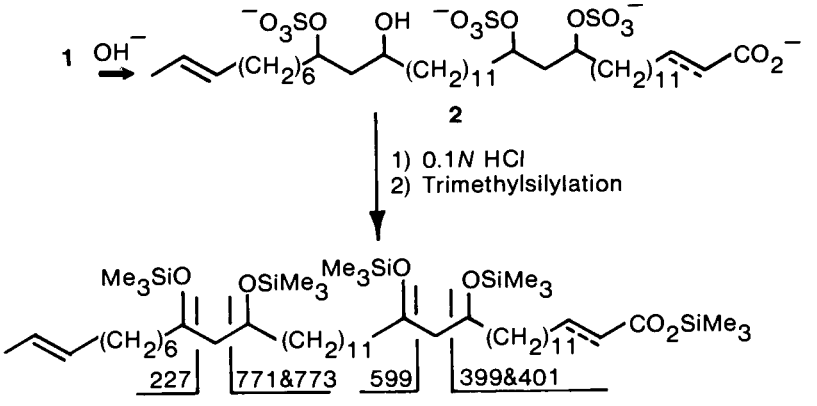


Chart 2.



13a α, β-unsaturated
13b α, β-saturated

Chart 3.

isomer.[7] The spectrum also has weak peaks at 33.1 and 151.0 ppm that could be due to C-4 and C-3 of base-hydrolysis product **2**, known (tlc and IR spectrum) to contaminate izumenolide to a small extent (as one might expect, considering the isolation).

As mentioned above, the 2,3-dihydro and the 38,39-*Z* components (and presumed combinations) would not be expected to be chromatographically distinct in the system used (Experimental, hydrogenation of **1**). Since intermediates in the degradation were chromatographically purified, and minor components discarded, it is not possible to provide any informed speculation about the minor components that are chromatographically distinct.

To the best of our knowledge, izumenolide is the first macrolide reported to have sulfate ester groups. The structure is unusually simple, having no branching in the carbon skeleton. The substitution pattern, in which only odd-numbered carbons are oxygenated, is consistent with straight-forward biosynthesis from acetate.

It was observed in the course of the degradation that the β-lactamase inhibitory activity was completely retained by the hydrogenation product **3**, and was partially retained by the other degradation products (**2**, **4** and **9**) in which the sulfate esters were still intact. This is further discussed in Ref. 3.

EXPERIMENTAL

NMR spectra were recorded on Varian Associates XL-100-15 and Jeol Ltd. FX60Q spectrometers; chemical shifts are given in ppm (δ) downfield from internal Me_4Si or $Me_3SiCD_2CD_2CO_2Na$. Mass spectra were determined on an AEI MS-902 double-focusing mass spectrometer.

Tlc was done on Merck silica gel 60 plates eluting with 2-BuOH–HOAc–H_2O, 3:1:1 (System A); $CHCl_3$–MeOH, 9:1 (System B); or as specified. Phosphomolybdic acid-H_2SO_4 was used for detection unless noted otherwise. The various sulfate esters were used as their sodium salts unless otherwise specified.

Acid hydrolysis of **1**. An 11.3-mg sample of **1** was dissolved in 0.5 mL of MeOH and 0.5 mL of 6 N HCl and the soln heated in an open tube at 100° for 1 hr. The resulting mixture was concentrated to dryness and the residue distributed in n-BuOH–NH_4OHaq. The aqueous phase was acidified with excess conc HCl and treated with $Ba(OH)_2$, giving 7.4 mg of $BaSO_4$ (calculated: 7.9 mg).

Base hydrolysis of **1**. A soln of 105 mg of **1** in 2 mL 1 N NaOH was heated under N_2 in a sealed tube at 100° for 5 hr. The resulting soln was neutralized (H_2SO_4), saturated with Na_2SO_4 and extracted with several portions of n-PrOH that had been equilibrated with warm, sat Na_2SO_4aq. The extract was concentrated *in vacuo* and the residue triturated with MeOH. The mixture was filtered and the filtrate mixed with EtOAc and concentrated *in vacuo*, giving 101 mg of **2**: IR (KBr) 1570 and 1420 ($-CO_2^-$) and 1230 cm^{-1} ($-OSO_3^-$), tlc (System A) R_f 0.47; ^{13}C-NMR (ND_4^+ salt in CD_3OD) δ 169.9 (C-1), 151.1 (C-3), 132.5 (C-38), 125.4 (C-39), 122.3 (C-2), 78.0 (C-15, C-17 & C-31), 68.4 (C-29), 18.1 (C-40), 12.8 [w, (Z)–CH=CH–$\underline{C}H_3$]. (Found: C, 48.97; H, 7.42; S, 9.94; Na, 9.46. Calc. for $C_{40}H_{72}O_{15}S_3Na_4$: C, 48.97; H, 7.40; S, 9.80; Na, 9.37%).

Hydrogenation of **1**. A soln of 0.95 g of **1** in MeOH was treated at 1 atm with H_2 and 10% Pd/C in three 0.5-g portions, resulting in the uptake of 41 mL of H_2 (exclusive of that taken up by the catalyst). (Calc. 45 mL for an equivalent wt. of 470.6). The mixture was filtered washing with water and the filtrate concentrated *in vacuo*. The residue was converted to a dry powder by dissolving in MeOH, adding MeCN, and concentrating *in vacuo*, giving 0.82 g of **3** (Na salt): tlc (System A) R_f 0.11 (tr), 0.14 (s), 0.18 (w).

A sample of **3** was converted to the ammonium salt by passage in MeOH-H_2O (1:1) through a column of Dowex 50W-X2 (NH_4^+). The ammonium salt was converted to a dry, deliquescent powder as above: UV (water) weak end absorption; ^{13}C-NMR (CD_3OD) δ 175.2 (C-1), 78.0 (C-15, C-17 & C-31), 72.9 (C-29), 14.5 (C-40). (Found: C, 50.74; H, 9.01; N, 5.01; S, 10.58, Ash 1.34. Calc. for $C_{40}H_{87}N_3O_{14}S_3$: C, 51.64; H, 9.43; N, 4.52; S, 10.34%).

Lithium triethylborohydride reduction of **3**. A carefully dried 165-mg sample of **3** was dissolved under Ar in 3.3 mL of dry DMSO, and 2 mL of 1 M $LiEt_3BH$ in THF was added. After 72 hr at room temp, sat Na_2SO_4aq was added. The product was extracted into n-PrOH and the extract concentrated to dryness. The residue was triturated with MeOH and the resulting filtrate mixed with MeCN and concentrated *in vacuo*, giving 225 mg of solid. This was dissolved in water and applied to a 80-ml column of Amberlite XAD-2 in water. The column was washed with water and then the product was eluted with MeOH. The MeOH eluate was concentrated *in vacuo* and the residue converted to a powder by concentration of a MeOH–EtOAc mixture. This gave 130 mg of **4** as a deliquescent powder: tlc (System A) indistinguishable from that of **2**; IR (KBr) 1236 cm^{-1} ($-OSO_3^-$). (Found: C, 50.70; H, 8.67; S, 8.52; Na, 8.34. Calc. for $C_{40}H_{79}O_{14}S_3Na$: C, 50.61; H, 8.39; S, 10.13; Na, 7.27%).

The product was converted to the ammonium salt as described for **3**: ^{13}C-NMR (CD_3OD) δ 78.0 (C-15, C-17 & C-31), 68.5 (C-29), 63.0 (C-1), 14.5 (C-40).

Acid hydrolysis of **4**. A soln of 88.5 mg of the ammonium salt of **4** in 10 mL 0.1 N HCl was heated on a steam bath for 90 min. The resulting mixture was cooled and extracted with several portions of the lower phase of MeOH–$CHCl_3$–H_2O, 1:1:1. The extract was concentrated *in vacuo* and the residue (58 mg) dissolved in $CHCl_3$–MeOH (9:1) and filtered (hot) through a 1-mL column of silica gel to remove polar impurities. Concentration of the effluent gave 42.5 mg of **5**: tlc (System B) 0.33 (w), 0.39 (w), 0.45 (s), 0.53 (w); mass spectrum of trimethylsilylated derivative, *m/z* 912 (M^+–Me_3SiOH).

Tosylation of **5**. A soln of 42.5 mg of **5** and 191 mg TsCl in 1 mL dry pyridine was left at 5° for 17 hr. Work up and tlc (*vide infra*) showed incomplete reaction. The product was retreated as above but for 15 hr at room temp. The resulting soln was diluted with water and extracted with ether. The extract was washed with sat $NaHCO_3$aq, water, sat NaClaq, dried ($MgSO_4$) and concentrated *in vacuo*, giving 45 mg residue. This was purified by preparative tlc on silica gel, eluting with $CHCl_3$. The major fluorescence-quenching band, R_f 0.5 ~ 0.6, was collected giving 17.9 mg of **6** as a colorless oil: IR ($CHCl_3$) 3030, 3010 & 1600 (Ar), 1360 & 1176 cm^{-1} ($ROSO_2Ar$); ^{1}H-NMR ($CDCl_3$) δ 7.77 & 7.33 (10 H, AB quartet, J = 8.3 Hz, ArH), 4.51 (4 H, quintet, J = 5.8 Hz, H–C–OSO_2Ar), 4.02 (2 H, t, J = 6.4 Hz, $-CH_2OSO_2Ar$).

Lithium triethylborohydride reduction of **6**. The pentatosylate **6** was dissolved under Ar in 0.5 mL of 1 M $LiEt_3BH$ in THF, giving a clear soln that gelled in a few min. After 19 hr at room temp, MeOH was added followed by water. The mixture was extracted with $CHCl_3$ and the extract concentrated *in vacuo*. The residue in hot heptane was filtered through a small column of silica gel. Concentration of the effluent gave 5.4 mg of **7** as a crystalline solid: m.p. 80.0 ~ 81.0°; mmp with n-tetracontane 80 ~ 81.5°; IR (neat crystalline film) and mass spectra indistinguishable from those of n-tetracontane.

Methylation of **5**. A mixture of 28 mg of **5**, 228 mg of NaH, and 0.5 mL of MeI in 5 mL of THF was stirred at room temp under N_2 for 21 hr. Excess NaH was destroyed with MeOH and the mixture was concentrated *in vacuo*. The residue was mixed with water, acidified with HCl, and extracted with the lower phase of $CHCl_3$–MeOH–H_2O (1:1:1). The extract was concentrated and the residue purified by preparative tlc on silica gel, eluting with $CHCl_3$–EtOAc (19:1). The major

band (detected with rhodamine B, R_f 0.6 ~ 0.7) was collected and gave 14.6 mg of **8** as a colorless oil: IR (neat film) 2829 (–OMe), 1096 cm^{-1} (C–O–C); ^{1}H–NMR ($CDCl_3$) δ 3.34 (s), 3.33 (s), 3.31 (s) (–OMe); mass spectrum *m/z* 712 (M^+).

Methylation of **4**. A mixture of 53 mg of **4** (dried *in vacuo* at 70° for ½hr), 390 mg of NaH, and 0.5 mL of MeI in 5 mL of DMF (dried with type 4A molecular sieves) was stirred under Ar at room temp for 43 hr. Water and CH_2Cl_2 were added and the mixture neutralized with H_2SO_4 and concentrated *in vacuo* to remove excess MeI. The aqueous soln was washed with CH_2Cl_2, filtered, concentrated to remove traces of CH_2Cl_2, and applied to a 1.5 × 26-cm column of Diaion HP20AG in water. The column was washed with water until the effluent contained no detectable sulfate and then with MeOH. Concentration of the methanolic eluate gave 45 mg of **9**: IR (KBr) 1232 ($ROSO_3^-$); tlc (System A) R_f 0.31 (tr), 0.38 (w), 0.44 (tr), 0.47 (s).

Acid hydrolysis of **9**. Crude **9** (45 mg) was hydrolyzed in 0.1 N HCl and the product extracted as described for **5**, giving 28 mg of **10** as a white solid: tlc (System B) R_f 0.52 (w), 0.56 (w), 0.59 (m), 0.64 (m), 0.76 (s).

Tosylation of **10**. A soln of 28 mg of crude **10** and 107 mg of TsCl in 0.5 mL pyridine was left under Ar for 16 hr at room temp. The soln was cooled on ice, treated with a little water and after a few min mixed with 1 N HCl and extracted with ether. The extract was washed with 1 N HCl, sat $NaHCO_3$aq, sat NaClaq, dried ($MgSO_4$) and concentrated *in vacuo*, giving 36 mg residue. This was chromatographed on a Whatman PLK5F silica gel plate, eluting with $CHCl_3$. A fluorescence-quenching band, R_f 0.47 ~ 0.67, was collected, giving 20 mg. Rechromatography on a Merck silica gel 60 plate, eluting with benzene-ether, 19:1 (R_f 0.14 ~ 0.26) gave 15.6 mg of **11**: tlc (same system) R_f 0.25 (s), 0.30 (m), 0.33 (m), 0.37 (w), 0.45 (tr); IR (neat film) 1365, 1191, 1179 cm^{-1} ($ROSO_2Ar$); ^{1}H-NMR ($CDCl_3$) δ 7.76 & 7.33 (AB quartet, J = 8.5 Hz, ArH), 4.50 (m, H–C–OSO_2Ar), 3.32 & 3.22 (–OMe), 2.44 (ArMe), 1.24 [–$(CH_2)_n$–], 0.88 (RMe).

Lithium triethylborohydride reduction of **11**. A soln of 15.6 mg of **11** in 0.5 mL 1 M $LiEt_3BH$ in THF was kept under Ar at room temp for 64 hr. Water was added and the product was isolated with $CHCl_3$ to give 10.2 mg solid: tlc (benzene), R_f 0.02 (tr), 0.05 (tr), 0.27 (s), 0.47 (tr), 0.67 (m). Preparative tlc in this system and collection of a band with R_f 0.17 ~ 0.29 (detected with rhodamine B) gave 5.1 mg of **12** as a waxy, crystalline solid, m.p. 60 ~ 62°: tlc (benzene) R_f 0.29; ^{1}H-NMR ($CDCl_3$) δ 3.33 & 3.32 (–OMe), 1.26 [–$(CH_2)_n$–], 0.87 (RMe); IR (neat solid from melt) 1098 cm^{-1} (C–O–C); mass spectrum *m/z* 622 (M^+). (Found: C, 80.94; H, 13.77. Calc. for $C_{42}H_{86}O_2$: C, 80.95; H, 13.91%).

Acid hydrolysis of **2** *and trimethylsilylation of the hydrolysate*. A soln of 13.2 mg of **2** in 5 mL 0.1 N HCl was heated at 100° for 1.5 hr and the resulting mixture extracted with MeOH–$CHCl_3$ (1:1). Concentration of the extract gave 7.7 mg of solid: tlc (System A) R_f 0.42. Treatment with a mixture of bis-O,N-(trimethylsilyl)trifluoroacetamide and trimethylsilylimidazole gave the trimethylsilyl derivative **13**: mass spectrum *m/z* (relative intensity) 1012 (8), 1014 (7) (M^+ of **13a** and **13b**, respectively).

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 281 to 287, 1981
Printed in Great Britain

0040-4020/81/Suppl. 1-0281-07 $02.00/0
Pergamon Press Ltd.

STEREOCONTROLLED PREPARATION OF PRECURSORS TO ALL PRIMARY PROSTAGLANDINS FROM BUTADIENE†

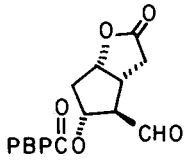
LEO A. PAQUETTE* and GARY D. CROUSE
Evans Chemical Laboratories, The Ohio State University,
Columbus, OH 43210, U.S.A.

(*Received in USA* 19 *June* 1980)

Abstract—Four key precursors to the primary prostaglandins have been prepared in efficient fashion from butadiene. In addition to its simplicity, the new approach capitalizes on the pivotal role of a single precursor molecule, allows for early resolution, and results in placement of four contiguous chiral centers about a cyclopentane ring without initial benefit of a stereodirecting group. Butadiene is cyclodimerized to *cis*^{2}-1,5-cyclooctadiene which is transformed in four steps to *cis*^{3}-1,4,7-cyclononatriene. Monoepoxidation and base-promoted ring opening of this medium ring hydrocarbon gives *cis*^{3}-2,4,7-cyclononatrien-1-ol which isomerizes exclusively to aldehyde **8** in the presence of potassium hydride at room temperature. The derived carboxylic acid is easily resolved and iodolactonized to **2**, the key intermediate from which **1**, **19**, **21**, and **22** are readily obtainable in few laboratory steps.

The important biological role of many prostanoids and the high interest in their medicinal potential are underscored by the voluminous literature on prostaglandin synthesis.[1] Of the several synthons which have evolved as suited to the stereoselective construction of this class of compounds, the aldehydo lactone **1** first prepared independently by the Corey[2] and Sutherland groups[3] has been accorded special attention. This intermediate can be functionalized with requisite sidechains by conventional Wittig chemistry and converted to the so-called primary prostaglandins with relative ease. We describe herein a new synthetic approach to this same group of compounds which is based upon the successful construction of iodolactone **2** from butadiene.[4] The scheme enjoys the economic advantage of being based on an inexpensive raw material and depends in its key step on the overriding of thermally favored [1,5] hydrogen sigmatropy by kinetically accelerated anionic [3,3] carbon sigmatropy. Further, the stereochemical requirement that four contiguous chiral centers be developed about the cyclopentane nucleus of this new synthon is achieved simply without the benefit of a stereodirecting group. The early stage at which optical resolution is accomplished is also noteworthy.

The cyclodimerization of butadiene to *cis*^{2}-1,5-cyclooctadiene (**3**) is performed today on commercial scale[5,6] and requires no comment here. The heating of **3** with sodium trichloroacetate in dimethoxyethane followed by dechlorination with lithium in t-butyl alcohol-tetrahydrofuran affords *cis*-bicyclo-[6.1.0]non-4-ene (**4**). The conversion of **4** to *cis*^{3}-1,4,7-



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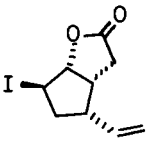

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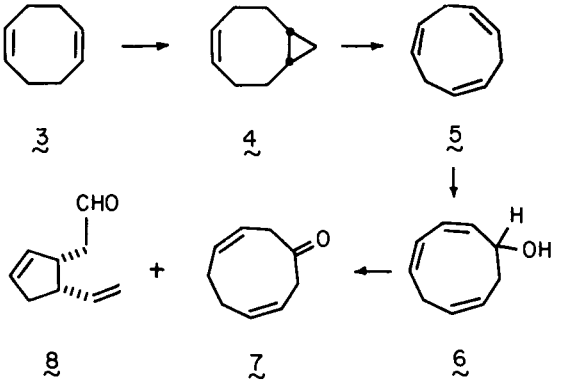


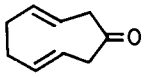
3 **4** **5** **6** **7** **8**

cyclononatriene (**5**) was readily accomplished in 60% overall yield by appropriate modification of Detty's procedure[7] (see Experimental). Selective monoepoxidation of **5** and lithium diisopropylamide-promoted ring opening led efficiently to *cis*^{3}-2,4,7-cyclononatrien-1-ol (**6**).[8,9]

When heated with benzene solvent in sealed vessels at 160°, **6** underwent chemical change in accord with conventional first-order kinetics. However, the desired aldehyde **8** comprised only 20% of the reaction mixture, the major component (80%) being dienone **7**. The assignment of a structure to **7** is based chiefly upon its IR and NMR spectral properties. In particular, the substance exhibits a carbonyl stretching frequency at 1700 cm^{-1}, a combination of four olefinic (δ 6.0–5.35), four α-carbonyl (3.08), and four methylene protons (2.34–2.1), and a symmetry simplified ^{13}C spectrum (five lines). The isomeric trans,trans dienone **9** has recently been prepared via organometallic intermediates by Baker and Copeland.[10] When subjected to thermal activation at temperatures above 160°, **7** was smoothly transformed into *cis*-3,4-divinylcyclopentanone (**10**).

The complication of kinetically favored [1,5] hydrogen migration within **6** was resolved by making recourse to an anionic process. In agreement with earlier precedent,[11,12] treatment of **6** with 1.2 equiv of oil-free potassium hydride in anhydrous ether or

†Dedicated in fond memory of Prof. Robert B. Woodward.



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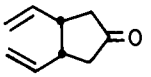

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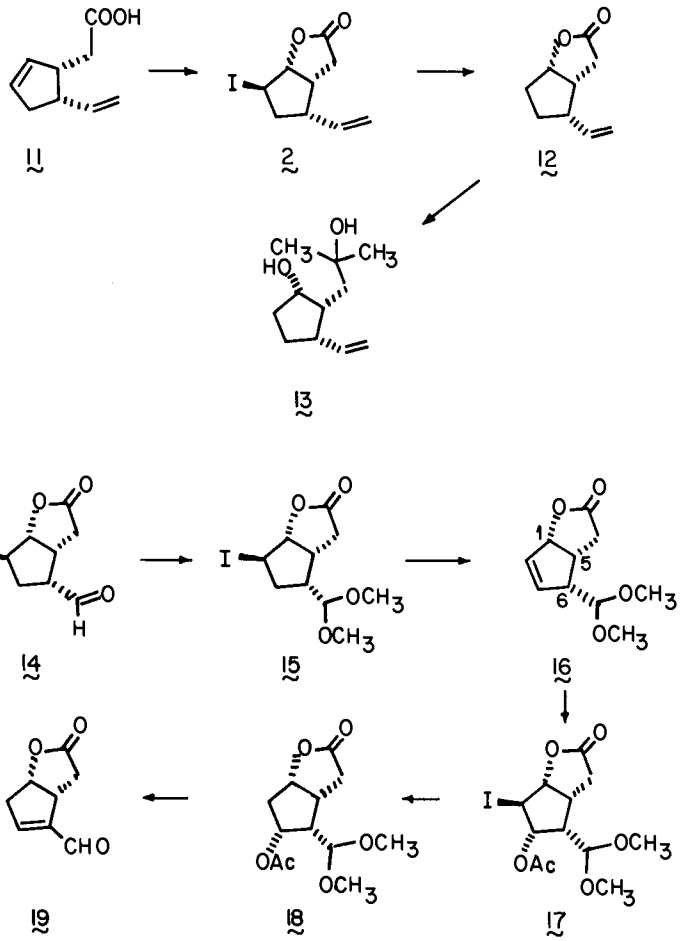
tetrahydrofuran at room temperature was adequate to promote quantitative conversion to **8**, homogeneous by tlc and vpc analysis. As a result of the boat conformation of the oxy-Cope transition state within $\mathbf{6}^{-}$–K^{+}, the sidechains in **8** must be cis. Consequently, the chiral center attached to the vinyl group must later be epimerized. That such a transformation can indeed be accomplished (see below) is considered confirmatory of the indicated stereochemistry.

The clean conversion of the potassium alkoxide of **6** to **8** is especially noteworthy because it represents the first example where the process kinetically favored under thermolysis conditions does not continue to be preferred following a substituent change from –OH to $-O^{\ominus}K^{\oplus}$. Detailed kinetic studies have now shown[4] that the general effect of alkoxide anion substitution on neighboring C–H and C–C bond reactivity is substantially accelerative, although appreciably less so for [1,5]~H (10^5–10^6) than for [3,3]~C sigmatropy (10^{10}–10^{11}). In view of this large rate differential, the neutral [1,5]~H shift is certain to be overridden under oxy anionic conditions, precisely as required by our strategy.

When oxidized with silver oxide in alkaline solution,[13] **8** was transformed into the oily carboxylic acid **11** whose resolution was efficiently achieved with *endo*-bornylamine.[14] Several recrystallizations of the diastereomeric salt from acetone gave colorless crystals having $[\alpha]_D^{23}$ + 120°. The free acid recovered from this material exhibited $[\alpha]_D^{23}$ + 157°. For the purpose of determining the level of enantiomeric enrichment, **11*** was cyclized to **2***, $[\alpha]_D^{23}$ – 21.8°, using standard iodolactonization methodology[15,16] and subsequently reduced with tri-n-butytlin hydride. The regiospecific formation of **2** stems chiefly from the kinetic advantages of γ- vs δ-lactone ring formation. Reaction of lactone **12***, $[\alpha]_D^{23}$ – 3.2°, with excess methyllithium provided diol **13*** which was directly subjected to $Eu(tfc)_3$ analysis ($CDCl_3$ soln).[17] Whereas racemic **13** shows four cleanly separated singlets attributable to the presence of two diastereotopic methyl groups in each enantiomer, the optically active diol exhibited only two singlets in that region of the spectrum. Resolution was therefore considered to be ≥98% complete. That the desired antipode of **11*** was in hand is to be demonstrated subsequently.

The ozonolysis of **2** at –78° in dichloromethane solution containing 5 equiv of methanol, followed by reductive workup with dimethyl sulfide, provided aldehyde **14**. Despite the hindered environment of its carboxaldehyde group, this molecule exhibited some



11 2 12 13 14 15 16 17 18 19

resistance to epimerization (see below). Consequently, the ketalization of **14** with trimethyl orthoformate and *p*-toluenesulfonic acid was examined. The nicely crystalline product (**15**) was smoothly dehydroiodinated with diazobicycloundecene (DBU) in refluxing tetrahydrofuran to give double bond isomer **16** as the only characterizable product (91 %). The ^{1}H NMR spectrum of **16** (in $CDCl_3$) is characterized by a pseudosinglet olefinic absorption of area 2 at δ 5.98, a multiplet centered at 5.4 for H_1, and a doublet (J = 7 Hz) at 4.2 for the acetal proton. The signal due to H_6 coincides with that of another proton and appears as a complex multiplet in the region 3.3–3.0. The extensive coupling with H_6 contrasts with that observed in the epimeric series (see **22**) and presumably arises as a consequence of its dihedral angle relationship to H_5 and long range coupling to H_1 and *exo*-H_4 (near W-plan arrangements). Although **16** did not respond well to the usual Prevost conditions or to various selenium reagents, success was realized with IOAc in acetic acid under anhydrous conditions.[18] When the workup was also performed with the exclusion of water, a crystalline iodo acetate was isolated in 65 % yield. In view of the endo orientation of the acetal substituent and the V-shaped geometry of the bicyclic lactone nucleus, iodonium ion formation on the exo face was considered a certainty. Less well resolved was the question concerning the regioselectivity of the ring opening, rearside approach to C_7 and C_8 appearing almost equally congested. Nonetheless, the only product which could be detected was assigned structure **17** on spectral grounds and particularly the strength of the ensuing conclusive chemical evidence.

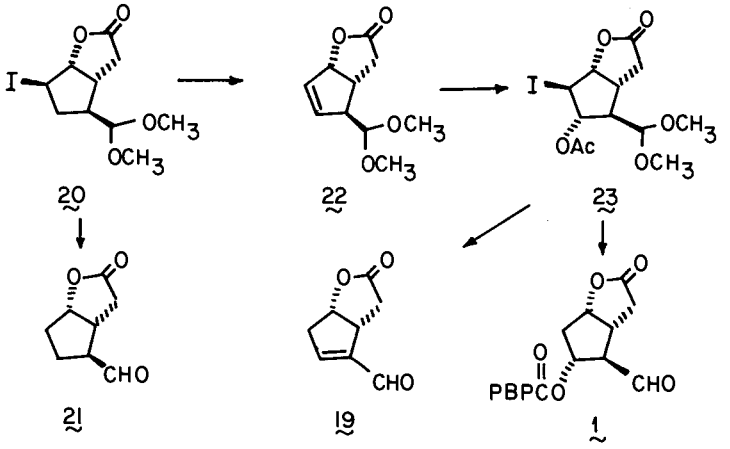
Reductive deiodination of **17** with tri-n-butyltin hydride in toluene at 80°[10] proceeded efficiently to give **18**. When treated at room temperature with concentrated hydrochloric acid in 2% isopropyl alcohol-chloroform solution, **18** underwent not only hydrolysis of its ketal, but particularly facile (antiplanar) β-elimination of acetic acid as well. Since the well known aldehyde **19**[20,21] was produced, the acetate group in **17** and **18** is required to be bonded to C_7.

Initial attempts to epimerize **14** under acidic (*p*-TsOH; 1 N HCl) or mildly alkaline conditions (K_2CO_3/MeOH; $NaHCO_3$) led to no reaction or to modest conversions that proceeded entirely too slowly. Stronger bases such as sodium methoxide expectedly attacked the lactone ring as well. The two-phase acidic conditions originally devised by Brown *et al.*[19] proved moderately satisfactory, but were abandoned when discovered to be capricious with regard to the extent of equilibration and the production of an unknown byproduct (up to 20 %). Optimum results were achieved with *p*-chloroaniline in a mixed solvent system consisting of isopropyl alcohol and acetic acid (*ca* 7:1). Subsequent direct ketalization routinely afforded **20** in 85–90 % overall yield.

The important aldehyde **21** was obtained by tri-n-butyltin hydride reduction of **15** or **20** and subsequent hydrolysis as above under two-phase conditions. A shorter alternative route to **21** consisted of reductive dehalogenation of **2** and ozonolysis of **12** followed by acidic epimerization.

When treated with DBU, **20** was more rapidly (8 hr, 20°) converted to **22** than was **15** to **16** (5 hr, 66°), this rate difference reflecting the diminished steric shielding surrounding *endo*-H_7 in the epimerized acetal. Further, **22** could be transformed into **23** through application of predescribed conditions. In contrast to the stable crystalline **17**, **23** was obtained as a heat- and light-sensitive oil which proved difficult to purify. Reductive deiodination of this intermediate furnished a *trans*-locked β-acetoxy acetal which was efficiently converted to **19**. Usefully, the same deiodination product was easily transformed to **1** in three well-precedented laboratory manipulations.

That the appropriate enantiomer of **11*** had been earlier obtained was established by conversion of a sample of the enantiomerically pure acid to **19***. The optical rotation observed for our material (248°) proved to be in excellent agreement with the $[\alpha]_D$ of an authentic pure sample.[22] In light of the prior elaboration of several 11-desoxy prostaglandins from **21**,[23,24] a formal total synthesis of these substances is achieved. Also, the ready availability of **22** opens a direct access route to the A prostaglandins.[25] Since **19** is an established precursor of the C prostaglandins[20] and thromboxane B_2,[21] and the successful elaboration of F prostaglandins from **1** has been described previously,[26,27] the present scheme provides a



preparatively useful route to a wide selection of prostanoid hormones from the simplest of achiral conjugated dienes.

EXPERIMENTAL

PMR spectra were obtained with a Varian EM-360 spectrometer; apparent splittings are given in all cases. ^{13}C NMR spectra were recorded on a Bruker WP-80 spectrometer and infrared spectra were determined on a Perkin–Elmer Model 467 instrument. Mass spectra were recorded on an AEI-MS9 spectrometer at an ionization potential of 70 eV. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

cis-9,9-Dichlorobicyclo[6.1.0]*non-4-ene*. A mixture of 325 g (2.98 mol) *cis*^{2}-1,5-cyclooctadiene, 111 g (0.599 mol) sodium trichloroacetate and 175 ml 1,2-dimethoxyethane was slowly heated with stirring to 100° in a thermostated oil bath. During the first 2 hr, considerable CO_2 was evolved and a dark brown color developed. After 20 hr, the cooled mixture was filtered through a pad of diatomaceous earth. The residue was washed with 500 ml ether and the combined filtrates were distilled through a 20 cm Vigreux column. The pressure within the distillation apparatus was gradually reduced to 10 mm and the product was collected at 95–110°. There was obtained 82 g (71%) colorless liquid of sufficient purity for use in the next step.

cis-Bicyclo[6.1.0]*non-4-ene* (**4**). Li wire (16% g, 2.33 g-at) was cut into small pieces, washed free of oil with pentane, and added to 500 ml dry THF. A soln containing 67.9 g (0.354 mol) *cis*-9,9-dichlorobicyclo[6.1.0]non-4-ene, 65.7 g (0.89 mol) t-BuOH, and 400 ml THF was slowly added dropwise with intermittent cooling from an ice-bath to maintain a gentle reflux rate. Upon completion of the addition, the mixture was heated at reflux for 2 hr, cooled, and filtered through a glass wool plug. To the filtrate was added 2 l of pentane and this soln was washed with water (4 × 500 ml) and saturated brine (300 ml) prior to drying over $MgSO_4$. The solvents were removed by distillation through a 20 cm Vigreux column at atmospheric pressure. The residue was distilled under reduced pressure to yield 40 g (93%) hydrocarbon as a colorless liquid, b.p. 78–81° (25 mm); ^1H NMR (δ, $CDCl_3$) 5.58 (m, 2 H), 2.16 (m, 6 H), 0.53 (m, 5 H), and −0.10 (m, 1 H).[7]

cis^3-1,4,7-*Cyclononatriene* (**5**), A soln of 30.9 g (0.253 mol) of **4** in 250 ml CCl_4 was stirred magnetically at 0° (ice-bath cooling) while a 25% (v/v) soln of Br_2 in CCl_4 was added dropwise until the red color just persisted. The mixture was concentrated on a rotary evaporator to give a pale yellow oil which partially crystallized upon standing.

To a soln of this dibromide in 300 ml DMF was added 116.3 g (1.74 mol) anhyd Li_2CO_3, 43.0 g (1.66 mol) anhyd LiF, and some powdered soft glass. With magnetic stirring, this mixture was heated at 100° for 12 hr in a thermostated oil bath, then cooled and poured into 2 l of ice and water. The product was extracted into hexane (5 × 400 ml), washed with water (4 × 300 ml) and brine, dried, and concentrated at atmospheric pressure by distillation of solvent through a 20 cm Vigreux column. The resulting oil was heated at its reflux temp (170°) for 0.5 hr and crystallized from MeOH to give 18.4 g (60%) of **5**, m.p. 50–51°.[28–30]

cis^3-1,4,7-*Cyclononatriene oxide*. A stirred soln of **5** (1.5 g, 12.5 mmol) in 30 ml ether was cooled to 0° while monoperphthalic acid (20.5 ml of 0.62 N) in ether was added dropwise from an addition funnel. The soln was stored overnight in a refrigerator, washed with $NaHCO_3$aq, dried, and evaporated to leave 1.4 g (90%) of a crystalline residue, m.p. 40–42°, consisting of an 18:1:1 mixture of monoepoxide, diepoxide, and unreacted **5**. Recrystallization from pentane gave colorless crystalline monoepoxide, m.p. 50.5–51.5°, but this procedure was not necessary and the unpurified product could be used directly.

2,4,7-*Cyclonoatrien-1-ol* (**6**). Diisopropylamine (27.8 g, 0.276 mol) was added dropwise to a cold (0°) soln of n-BuLi (185 ml of 1.5 N in hexane, 0.276 mol) in 100 ml of anhyd THF under N_2 during 30 min. After an additional 0.5 hr, a soln of the monoepoxide (25 g unpurified, 0.184 mol) in 50 ml of the same solvent was introduced dropwise over 1 hr. After 4 hr, 100 ml of 10% NH_4Claq was added to the dark brown mixture which was diluted with ether (300 ml) and extracted successively with three 100 ml portions NH_4Claq and once with brine (100 ml) prior to drying and solvent evaporation. Distillation of the residue gave **6** as a clear liquid, b.p. 55–60° (0.07 mm), which solidified on standing: 20 g (80%), homogeneous by tlc (1:1 hexane–ether). The ^1H NMR and IR spectra of this alcohol were identical to those reported earlier.[8,9]

Pyrolysis of **6**. A base-washed glass ampoule was charged with 100 mg (0.73 mmol) of **6** and 250 mg benzene. The soln was degassed, sealed *in vacuo*, and heated at 170° in a furnace for 2 hr. The products were isolated by preparative VPC (0.25 in. × 5 ft 10% SE-30, 105°) and identified as **7** (70%), **8** (20%), and **10** (10%, time-dependent; increases at the expense of **7** at longer reaction times).

For **7**. IR (neat, cm^{-1}) 3020, 2940, 2860, 1700, and 1640; ^1H NMR (δ, $CDCl_3$) 6.0–5.35 (m, 4 H), 3.08 (d, J = 7.5 Hz, 4 H), and 2.34–2.1 (m, 4 H); ^{13}C NMR (ppm, $CDCl_3$) 210.50, 133.24, 124.56, 26.37, and 26.07; *m/e* calc. 136.0888, obs 136.0892. (Found: C, 79.35; H, 8.92. Calc. for $C_9H_{12}O$; C, 79.42; H, 8.83%).

For **10**. IR (neat, cm^{-1}) 3080, 1745, 1635, 990, and 910; ^1H NMR (δ, $CDCl_3$) 6.15–5.55 (series of m, 4 H), 5.3–4.75 (m, 2 H), 3.3–2.75 (m, 2 H), and 2.5–2.1 (m, 2 H); ^{13}C NMR (ppm, $CDCl_3$) 217.2, 137.4, 116.1, 44.0, 42.7. (Found: C, 79.24; H, 8.86. Calc. for $C_9H_{12}O$: C, 79.42; H, 8.83%).

Pyrolysis of **7**. A soln of **7** (50 mg, 0.36 mmol) in 200 mg benzene contained in a base-washed glass ampoule was degassed. The vessel was sealed *in vacuo* and heated in a furnace at 210° for 4 hr. The sole product (47 mg, 94%), which was isolated by medium pressure liquid chromatography on silica gel (elution with 2% EtOAc in hexane), exhibited spectra identical to that of **10** described above.

cis-(4-Vinyl-3-cyclopentenyl)acetaldehyde (**8**). KH (15.0 g of a 23.6% suspension, 88 mmol) was placed in a 250 ml 3-necked round bottom flask, blanketed with N_2, and washed free of oil with anhyd ether (2 × 50 ml). Additional dry ether (75 ml) was added and the slurry was stirred at 0° while **6** (10.0 g, 73.5 mmol) dissolved in 75 ml of the same solvent was introduced dropwise. After completion of the addition, the soln was allowed to warm to room temp and stirred for 4 hr. The reddish-brown mixture was rapidly poured into a stirred mixture of 10% NH_4Claq (100 ml) and ice (50 g). The organic phase was separated, washed with sat $NaHCO_3$aq (50 ml) and brine (50 ml), dried, and concentrated. The light brown oil (9.9 g), homogeneous by tlc and vpc, was extensively decomposed on attempted distillation and therefore was oxidized directly. An analytical sample was isolated by preparative vpc (5 ft × 0.25 in. 5% SE-30, 100°); IR (neat, cm^{-1}) 1720 and 1620; ^1H NMR (δ, $CDCl_3$) 9.78 (t, J = 1 Hz, 1 H), 6.0–5.35 (m, 3 H), 5.2–4.75 (m, 2 H), and 3.5–2.0 (series of m, 6 H); ^{13}C NMR (ppm, $CDCl_3$) 202.14, 139.21, 133.39, 130.60, 115.73, 45.33, 45.09, 43.03, and 37.26; *m/e* calc. 136.0888, obs 136.0892. (Found: C, 79.54; H, 8.96. Calc. for $C_9H_{12}O$: C, 79.42; H, 8.83%).

cis-(4-Vinyl-3-cyclopentenyl)acetic acid (**11**). Aq_2O (8.52 g, 36.8 mmol, prepared *in situ* by the method of Campaigne,[13] was stirred with 30 ml water in a cooled 100 ml flask. To this suspension was added a soln of **8** (2.00 g, 14.7 mmol) in 2 ml of ether. The cooled reaction mixture was rapidly stirred for 30 min and the brown-black solid was removed by filtration and washed with several portions hot water. The cooled filtrate was sequentially extracted with ether, acidified, and reextracted with CH_2Cl_2 (3 × 30 ml). The latter solns were combined, dried, and evaporated to give 1.5 g (70%) of **11** as a pale yellow oil which could be purified by Kugelrohr distillation at 100° and 0.1 torr; IR (neat, cm^{-1}) 3100, 1710,

1630, 1430, 940, and 910; ^{1}H NMR (δ, $CDCl_3$) 14.3 (s, 1 H), 6.0–5.7 (m, 3 H), 5.10 (dd, J = 7 and 1 Hz, 1 H), 4.96 (s, 1 H), 3.2–2.9 (m, 2 H), and 2.7–2.0 (m, 4 H).

A sample of **11** was hydrogenated over Pd-C and treated with diazomethane to give the perhydro methyl ester. This substance was purified by preparative vpc for analysis; *m/e* calc. 170.1307, obs 170.1312. (Found: C, 70.38; H, 10.55. Calc. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66%).

Resolution of **11**. The carboxylic acid was dissolved in acetone and treated with an equivalent amount of *endo*-bornylamine. The ppt was recrystallized seven times from acetone to give crystals, m.p. 108–109°, exhibiting $[\alpha]_D^{23}$ + 120° (*c* 1.66, C_2H_5OH). Acidification of this salt gave **11*** as a colorless oil, $[\alpha]_D^{23}$ + 157° (*c* 3.52, C_2H_5OH).

Iodolactonization of **11**. To a stirred soln of **11** (1.0 g, 6.58 mmol) in 53 ml 0.5 N $NaHCO_3$ was slowly added a soln containing I_2 (1.67 g, 6.6 mmol) and KI (4.02 g, 24.2 mmol) in water (50 ml) until the reddish color persisted. After 2 hr, the mixture was extracted with CH_2Cl_2 (4 × 50 ml) and the combined organic phases were washed with 5% $Na_2S_2O_3$aq (2 × 30 ml), water (50 ml), and brine (30 ml) prior to drying. Removal of solvent left a yellowish liquid which was filtered through a small column of silica gel (CH_2Cl_2 elution) and recrystallized from hexane-EtOAc (9:1): There was obtained 1.5 g (85%) of **2** as a colorless crystalline solid, m.p. 71–71.5°; IR (nujol, cm^{-1}) 3030, 2990, 1790, 1640, 1185, and 1005; ^{1}H NMR (δ, $CDCl_3$), 5.9–5.4 (m, 1 H), 5.2–4.8 (m, 3 H), 3.9–3.6 (m, 1 H), 3.4–2.8 (m, 2 H), 2.4–2.1 (m, 2 H), and 2.0–1.6 (m, 2 H); *m/e* calc. 277.9806, obs 277.9813. (Found: C, 38.94; H, 4.01. Calc. for $C_9H_{11}IO_2$: C, 38.87; H, 3.99%).

Analogous treatment of **11***, $[\alpha]_D^{23}$ + 157°, gave **2***, m.p. 80–81°, $[\alpha]_D^{23}$ − 21.8° (*c* 1.82, C_2H_5OH).

endo-6-Vinyl-3-oxo-2-oxabicyclo[3.3.0]*octane* (**12**). A soln of **2** (300 mg, 1.08 mmol) and tri-n-butyltin hydride (350 mg, 1.21 mmol) in 10 ml dry toluene was heated at 80° under N_2 with stirring for 20 hr, cooled, and concentrated on a rotary evaporator. The residue was taken up in EtOAc (25 ml) and stirred for 4 hr with a soln of KF (0.25 g) in water (25 ml). The ppt was removed by filtration and the organic phase was separated, dried, and evaporated. Preparative tlc purification of the resulting oil on silica gel (elution with pentane–EtOAc 2:1) gave **12** as a colorless oil, 100 mg (62%), which was purified for analysis by preparative vpc (5 ft × 0.25 in. 5% SE-30, 130°C); IR (neat, cm^{-1}) 3080, 1775, 1640, 1180, 995, and 910; ^{1}H NMR (δ, $CDCl_3$) 5.95–5.6 (m, 1 H), 5.16–4.95 (m, 3 H), 3.15–2.38 (series of m, 4 H), and 2.2–1.5 (series of m, 4 H); *m/e* 152.0838, obs. 152.0841. (Found: C, 70.99; H, 7.92. Calc. for $C_9H_{12}O_2$: C, 71.07; H, 7.89%).

Analogous treatment of **2*** afforded **12***, $[\alpha]_D^{23}$ − 3.2° (*c* 1.91, C_2H_5OH).

Reaction of **12** *with methyllithium*. To a cold (−78°) magnetically stirred soln of **12** (100 mg, 0.72 mmol) in 10 ml anhyd ether was added dropwise 2 ml 1.4 N MeLi in ether (2.8 mmol). The mixture was stirred at −78° for 1 hr, treated slowly with water (2 ml), and warmed to room temp. The organic phase was separated, washed with brine (10 ml), dried, and evaporated. The resulting clear liquid which crystallized on standing (82 mg, 68%) was recrystallized from petroleum ether–ether (4:1) to give **13** as colorless needles, m.p. 75–76°; IR (nujol, cm^{-1}) 3300, 1635, 1145, 1065, 995, and 920; ^{1}H NMR (δ, $CDCl_3$) 6.12–5.82 (m, 1 H), 4.95 (s, 1 H), 4.83 (dd, J = 6 and 3 Hz, 1 H), 4.32 (m, 1 H), 3.9–2.9 (br mound, 2 H), 2.7–2.4 (br m, 1 H), 2.2–1.4 (series of m, 7 H), 1.3 (s, 3 H), and 1.26 (s, 3 H). (Found: C, 71.71; H, 11.15. Calc. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94%).

Comparable treatment of **12*** afforded **13***, m.p. 84–85°, $[\alpha]_D^{23}$ + 40° (*c* 1.21, EtOH).

Europium shift experiments with **13**. Generally, a 10 mg sample of the diol in 200 μl $CDCl_3$ was treated with 13-20 mg (27–40 mol-eq) tris(trifluoromethylcamphorato)europium and the ^{1}H NMR spectra of these solns were recorded (60 MHz) at 250 Hz sweep width. With the racemic sample, four Me signals emerged from the original two and appeared at δ 4.0, 3.8, 2.7, and 2.5, sufficiently well separated for accurate integration (1:1:1:1 ratio). The optically active diol showed only the two signals at 4.0 and 2.7 (1:1 ratio).

endo-5-(*Dimethoxymethyl*)-exo-8-*iodo*-3-*oxo*-2-*oxabicyclo*[3.3.0]*octane* (**15**). O_3 was bubbled through a cold (−78°) soln of **2** (5.0 g, 17.9 mmol) in 50 ml CH_2Cl_2 and 10 ml MeOH until a blue color appeared. The excess O_3 was purged with O_2 for 30 min and Me_2S (1.5 g, 24.2 mmol) together with *p*-toluenesulfonic acid (100 mg, 0.6 mmol) were added. This mixture was stirred at 0° for 20 hr, at which point trimethyl orthoformate (17.0 g, 0.16 mol) was introduced. After being stirred for an additional 20 hr at room temp, the mixture was shaken with sat $NaHCO_3$aq (2 × 25 ml), dried, and evaporated. There was obtained 4.6 g (79%) of **15** as a pale yellow crystalline solid. Recrystallization of this material from EtOAc-hexane gave colorless needles, m.p. 72–73°; IR (nujol, cm^{-1}) 1790; ^{1}H NMR (δ, $CDCl_3$) 5.2 (d, J = 6 Hz, 1 H), 4.6–4.3 (m, 2 H), 3.35 (s, 3 H), 3.3–2.5 (series of m, 4 H), and 2.2–1.9 (m, 2 H); *m/e* calc. 326.0015, obs 326.0020. (Found: C, 36.73; H, 4.63. Calc. for $C_{10}H_{15}IO_4$: C, 36.84; H, 4.60%).

Comparable treatment of **2*** (40% ee) gave **15***, m.p. 91.5–94°, $[\alpha]_D^{23}$ − 16.5° (*c*, 1.38, C_2H_5OH).

endo-5-(*Dimethoxymethyl*)-3-*oxo*-2-*oxabicyclo*[3.3.0]*oct*-7-*ene* (**16**). A magnetically stirred soln of **15** (3.24 g, 10 mmol) and DBU (1.9 g, 12.5 mmol) in 50 ml of anhyd THF was heated at 60° for 5 hr. After cooling, CH_2Cl_2 (100 ml) was added and the soln was washed with 5% NH_4Claq (2 × 50 ml) and brine prior to drying and concentration. Chromatography on Florisil (CH_2Cl_2 elution) provided 1.8 g (91%) of **16** as a clear oil; IR (neat, cm^{-1}) 1785 and 1620; ^{1}H NMR (δ, $CDCl_3$) 5.98 (pseudosinglet, 2 H), 5.4 (m, 1 H), 4.2 (d, J = 7 Hz, 1 H), 3.4 (s, 3 H), 3.36 (s, 3 H), 3.3–2.85 (m, 2 H), and 2.7–2.4 (m, 2 H). (Found: C, 60.46; H, 7.06. Calc. for $C_{10}H_{14}O_4$: C, 60.63; H, 7.07%).

endo-5-(*Dimethoxymethyl*)-endo-6-*acetoxy*-exo-7-*iodo*-3-*oxo*-2-*oxabicyclo*[3.3.0]*octane* (**17**). Unsaturated **16** (500 mg, 2.5 mmol) dissolved in 1 ml AcOH was added via syringe to a soln of I_2 (641 mg, 2.52 mmol) and AqOAc (460 mg, 2.75 mmol) in AcOH (15 ml) and the suspension was stirred under a N_2 for 20 hr. The ppt was separated by filtration and the filtrate was evaporated to leave a yellow semi-solid which was recrystallized from EtOAc–hexane. Purified **17** was obtained as a yellowish solid (610 mg, 63%), m.p. 106° dec; IR (nujol, cm^{-1}) 1785 and 1750; ^{1}H NMR (δ, $CDCl_3$) 5.52 (t, J = 5 Hz, 1 H), 4.80 (t, J = 3 Hz, 1 H), 4.42 (d, J = 3 Hz, 1 H), 4.22 (dd, J = 5 and 3 Hz, 1 H), 3.40 (2, 3 H), 3.36 (s, 3 H), 3.3–2.2 (series of m, 4 H), and 2.22 (s, 3 H).

The $[\alpha]_D^{23}$ of **17*** of 40% ee was determined to be −90.7° (*c* 1.09, $CHCl_3$).

endo-5-(*Dimethoxymethyl*)-endo-6-*acetoxy*-2-*oxo*-2-*oxabicyclo*[3.3.0]*octane* (**18**). A magnetically stirred soln containing 620 mg (1.61 mmol) of **17** and 500 mg (1.72 mmol) tri-n-butyltin hydride in 10 ml toluene was heated at 80° under N_2 for 20 hr. Following the evaporation of solvent, the residue was taken up in EtOAc (25 ml) and stirred overnight with a soln of KF (1 g) in water (25 ml). The ppt was separated by filtration and the organic phase was removed and dried. Evaporation of solvent gave 370 mg (89%) of **18** after preparative tlc on silica gel (EtOAc elution); IR (neat, cm^{-1}) 1785, 1740, 1150, 1130, and 1060; ^{1}H NMR (δ, $CDCl_3$) 5.35 (dd, J = 14 and 8 Hz, 1 H), 4.98 (t of d, J = 7 and 2 Hz, 1 H), 4.42 (d, J = 6 Hz, 1 H), 3.4 (s, 3 H), 3.36 (s, 3 H), 3.2–2.9 (m, 1 H), 2.8–1.8 (series of m, 5 H), and 2.02 (s, 3 H); *m/e* calc. 258.1103, obs 258.1108.

Hydrolysis-elimination of **18**. A sample of **18** (117 mg, 0.45 mmol) was dissolved in 5 ml $CHCl_3$ containing 10 drops i-PrOH. Conc HCl (2 ml) was added and the soln was stirred vigorously for 1 hr prior to the addition of brine (10 ml). The organic phase was separated, washed with sat $NaHCO_3$aq (10 ml) and NaCl aq (10 ml), dried, and evaporated. There was obtained 48 mg (70%) of **19**, m.p. 69–72° after sublimation. The ^{1}H spectrum was superimposable upon that of an authentic sample.[20,21]

Similar treatment of the acetate derived from optically active **11***, $[\alpha]_D^{23}$ + 114°, furnished **19***, m.p. 73–74°, $[\alpha]_D^{23}$ + 236° (*c* 1.06, C_2H_5OH).

exo-5-(*Dimethoxymethyl*)-exo-7-*iodo*-3-*oxo*-2-*oxabicyclo*-[3.3.0]*octane* (**20**). A soln of **2** (3.2 g, 11.4 mmol) in CH_2Cl_2 (25 ml) and MeOH (5 ml) was ozonized in the predescribed manner and subsequently treated with Me_2S (100 mg, 14.4 mmol) at 0° for 24 hr. The mixture was washed with water (2 × 20 ml) and brine (20 ml), dried, and concentrated to leave a glassy syrup. The epi-aldehyde was taken up in i-PrOH (30 ml) and AcOH (5 ml) and this soln was stirred under N_2 while *p*-chloroaniline (1.75 g, 13.7 mmol) was added in one portion. After 24 hr, the brownish liquid was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (30 ml) and stirred with 30 ml of 2 N HCl for 30 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (30 ml). The combined organic layers were washed with 2 N HCl (25 ml) and brine (25 ml) before drying. Trimethyl orthoformate (10 g, 94 mmol) and *p*-toluenesulfonic acid (100 mg) were added to the stirred soln. After 6 hr, the mixture was washed with 10% $NaHCO_3$aq (30 ml), dried, and concentrated to give 3.3 g (88%) of **20**. The analytical sample was prepared by medium-pressure liquid chromatography on silica gel (elution with hexane-EtOAc, 3:1); IR (neat, cm^{-1}) 2940, 2830, 1782, 1150, 1060, 955, and 885; ^1H NMR (δ, $CDCl_3$) 5.1 (dd, J = 6 and 3 Hz, 1 H), 4.42 (d, J = 6 Hz, 1 H), 4.15 (d or t, J = 7 and 3 Hz, 1 H), 3.38 (s, 3H), 3.33 (s, 3 H), and 3.1–2.0. (Found: C, 37.18; H, 4.81. Calc. for $C_{10}H_{15}IO_4$: C, 36.84; H, 4.63%).

exo-3-*Oxo*-2-*oxabicyclo*[3.3.0]*octylcarboxaldehyde* (**21**)

A. From **12**. A soln of **12** (800 mg, 5.2 mmol) in 30 ml CH_2Cl_2–MeOH (4:1) was ozonized at −78°. Me_2S (500 mg, 8 mmol) was added and the soln was stirred at 0° for 24 hr. Solvent evaporation left a residue which was taken up in 20 ml $CHCl_3$ containing 2% i-PrOH. Conc HCl was added and the soln was stirred for 1 hr at room temp before brine (20 ml) was added and the phases were separated. The organic layer was washed again with brine (20 ml), dried, and concentrated to furnish 670 mg (83%) of **21**. The spectra of this product were superimposable upon those of authentic material.[23]

B. From **15**. A soln of **15** (500 mg, 1.23 mmol) and tri-n-butyltin hydride (400 mg, 1.37 mmol) in 15 ml dry toluene was heated at 80° for 18 hr and worked up in the manner described to yield 200 mg (83%) acetal; IR (neat, cm^{-1}) 2840, 1780, 1060, and 170; ^1H NMR (δ, $CDCl_3$) 5.0 (t, J = 3 Hz, 1 H), 4.3 (d, J = 4 Hz, 1 H), 3.35 (s, 6 H), 3.0 (m, 1 H), and 2.8–1.4 series of m, 7 H); *m/e* calcd 200.1048, obs 200.1053.

This product (200 mg, 0.10 mmol) in 5 ml dioxane was stirred with 5 ml 2 N HCl for 8 hr at 20°. CH_2Cl_2 (10 ml) was added and the organic phase was separated. The aqueous layer was reextracted with CH_2Cl_2 (10 ml) and the combined organic phase was washed with 10% $NAHCO_3$aq (10 ml) and brine (10 ml). Drying and solvent evaporation afforded 145 mg (95%) of **21**.

exo-5-(*Dimethoxymethyl*)-3-*oxo*-2-*oxabicyclo*[3.3.0]*oct*-7-*ene* (**22**). A soln of **20** (3.4 g, 10.5 mmol) and DBU (2.4 g, 15.6 mmol) in 30 ml anhyd THF was stirred vigorously at room temp for 8 hr, then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 ml), 1 N HCl (25 ml) was added, and the soln was stirred for 30 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (30 ml). The combined CH_2Cl_2 layers were washed with 10% NaCl aq, dried, and concentrated. The resulting dark brown viscous liquid (2.0 g) was chromatographed on Florisil (elution with hexane–EtOAc, 4:1) to give 1.8 g (86%) of **22** as a colorless oil; IR (neat, cm^{-1}) 3060, 1785, 1620, 1150, and 1060; ^1H NMR (δ, $CDCl_3$) 6.0 (narrow m, 2 H), 5.65–5.35 (m, 1 H), 4.12 (d, J = 6 Hz, 1 H), 3.38 (t, J = 6 Hz, 1 H), 3.38 (s, 3 H), and 3.2–2.2 (series of m, 4 H). (Found: C, 60.58; H, 7.09. Calc. for $C_{10}H_{14}O_4$: C, 60.62; H, 7.07%).

exo-5-(*Dimethoxymethyl*)-endo-6-*acetoxy*-exo-7-*iodo*-3-*oxo*-2-*oxabicyclo*[3.3.0]*octane* (**23**). Treatment of 1.0 g (5.0 mmol) with AqOAc (900 mg, 5.4 mmol) and I_2 (1.3 g, 5.1 mmol) in 25 ml AcOH in the predescribed manner gave a yellowish oil which was purified by Florisil chromatography (elution with hexane–ether, 4:1). There was obtained 1.65 g (86%) of **23** as a gummy solid, m.p. 80°; IR (neat, cm^{-1}) 2950, 2840, 1785, and 1750; ^1H NMR (δ, $CDCl_3$) 5.36 (t, J = 5 Hz, 1 H), 5.3–4.9 (m, 1 H), 4.52 (d, J = 6.5 Hz, 1 H), 4.45–4.2 (m, 1 H), 3.45 (s, 3 H), 3.38 (s, 3 H), 3.25–2.2 (series of m, 4 H), and 2.08 (s, 3 H). (Found: C, 37.30; H, 4.44. Calc. for $C_{12}H_{17}IO_6$: C, 37.53; H, 4.43%).

The optically active **23*** exhibited a m.p. of 90° dec.

3-*Oxo*-2-*oxabicyclo*[3.3.0]*oct*-6-*enyl*-6-*carboxaldehyde* (**19**). A soln of **23** (300 mg, 0.78 mmol) and tri-n-butyltin hydride (250 mg, 0.86 mmol) in 10 ml benzene was heated at reflux under N_2 for 12 hr. The solvent was evaporated and the resulting oil was dissolved in EtOAc (25 ml) and stirred vigorously with 25 ml of 5% KF. After 5 hr, the mixture was filtered and the separated organic phase was washed with brine and dried. Concentration left the acetate as a pale yellow oil which was purified by preparative layer chromatography on silica gel (elution with EtOAc-hexane, 1:1): 173 mg (86%); IR (neat, cm^{-1}) 1785 and 1760; ^1H NMR (δ, $CDCl_3$) 5.3–4.9 (m, 2 H), 4.27 (d, J = 5 Hz, 1 H), 3.42 (s, 3 H), 3.40 (s, 3 H), 3.1–2.1 (series of m, 6 H), and 2.0 (s, 3 H); *m/e* calc. 258.1103, obs 258.1107.

A soln of the acetate (175 mg, 0.68 mmol) in 5 ml of $CHCl_3$–2% i-PrOH and conc HCl was stirred vigorously for 4 hr prior to the addition of brine (10 ml) and CH_2Cl_2 (25 ml). The separated organic phase was washed with brine, dried, and evaporated to give a yellowish oil, sublimation of which at 60° and 1 torr furnished 75 mg (73%) of **19** as a colorless crystalline solid, m.p. 72°. The ^1H NMR spectrum of this material was superimposable upon that of an authentic sample[27] and the material isolated as above.

endo-7-(*p-Phenylbenzoyloxy*)-3-*oxo*-2-*oxabicyclo*-[3.3.0]*octane*-exo-6-*carboxaldehyde* (**1**). To a soln of the preceding acetate (170 mg, 0.65 mmol) in 10 ml MeOH was added K_2CO_3 (91 mg, 0.66 mmol) and the mixture was stirred at room temp for 2 hr. AcOH (40 μl, 0.7 mmol) was introduced and the filtered soln was concentrated to yield a semisolid. This residue was taken up in pyridine (5 ml) and treated with *p*-phenylbenzoyl chloride (175 mg, 0.80 mmol) and 4-dimethylaminopyridine (20 mg, 0.16 mmol). After being stirred for 36 hr, the mixture was evaporated and the residue was purified by prep tlc on silica gel (elution with 90% EtOAc in hexane). There was obtained 160 mg (61%) of the ester acetal, whose ^1H NMR spectrum was superimposable upon that of an authentic sample.[19]

Hydrolysis of this product by the method of Brown *et al.*[19] afforded **1** in 80% yield.

Acknowledgements—The authors are indebted to the National Institutes of Health for financial support through grant AI-11490 and to Professor E. J. Corey, Dr. Norman A. Nelson, and Dr. Edward D. Brown for ^1H NMR spectra, certain physical constants, and (in the last instance) an authentic sample of **1**.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 289 to 302, 1981
Printed in Great Britain.

0040-4020/81/Suppl. 1-0289-14 $02.00/0
Pergamon Press Ltd.

ORGANOMETALLIC COMPOUNDS IN ORGANIC SYNTHESIS—XI

THE STRATEGY OF LATERAL CONTROL OF REACTIVITY: TRICARBONYLCYCLOHEXADIENEIRON COMPLEXES AND THEIR ORGANIC SYNTHETIC EQUIVALENTS

ARTHUR J. BIRCH*, B. M. RATNAYAKE BANDARA, KEVIN CHAMBERLAIN, BRIAN CHAUNCY, PETER DAHLER, ANTHONY I. DAY, IAN D. JENKINS, LAWRENCE F. KELLY, THONG-CHAK KHOR, GUY KRETSCHMER, ANDRIS J. LIEPA, ACHARAN S. NARULA, WARWICK D. RAVERTY, EZIO RIZZARDO, CHARLES SELL, G. RICHARD STEPHENSON, DAVID J. THOMPSON and DAVID H. WILLIAMSON
Research School of Chemistry, Australian National University P. O. Box 4, Canberra, A.C.T. 2600, Australia

(*Received in UK* 3 *September* 1980).

Abstract—The concept is discussed of superimposed lateral control of reactivity, stereochemistry and structures, by attachment of complexed metal atoms to olefinic systems. This differs from classical endogenous control of synthesis by classical anionoid and cationoid groups in the skeleton, and its application has many theoretical and practical advantages. It is illustrated by considerations of reactions of substituted tricarbonylcyclohexa-1,3-dieneiron derivatives; notably the derived dienyliron salts, which are defined as equivalents of specifically substituted aryl cations or as cyclohex-2-enone cations, dependent on the structures and reaction sequences. The effects are noted of classical substituents on the positions and on the rates of reactivity of some complexed dienyl cations; both regio- and stereospecificities are dependent on the nature of the anion involved and the conditions. Probable mechanisms are discussed. Other effects of lateral control include those on the classical reactivities of attached groups (such as hydrolysis of CO_2Me) and on adjacent groups, such as stereochemistry of reduction of the 3-carbonyl in the ergosterone complex. Some useful new C–C bond-forming reactions made possible by the approach are noted.

STRATEGIES OF ORGANIC SYNTHESIS

To achieve appropriate reactivities for the junction of component molecules, classical organic synthesis requires the presence of appropriately reactive groups. This requirement leaves structural remnants in the new skeleton, often not the structures desired which must then be attained by further manipulations. This strategy may be termed endogenous control of reactivity and steric selectivity; reactions are frequently not completely regio- or stereospecific. It was pointed out in the first discussion of the strategy now termed convergent synthesis,[1] that a major problem is to modify appropriately the structures resulting from the initial reactivity requirements. Increasing functionality in target molecules accentuates the problem, since groups required for synthetic activation are frequently identical in type with those required as substituents, which implies the use of competitive reactions or roundabout protection methods.

Many of these problems can, in principle, be overcome in appropriate structures by superimposing the required control of activation and stereochemistry in the form of laterally attached groups consisting of complexed transition metal atoms. The fundamental activation needed can then be independent of a requirement for classical anionoid and cationoid substituents in the skeleton, the presence of which may, however, be important in influencing the regiospecificities of reaction. Steric control, due to molecular shape as is possible with classical globular molecules,[2] or of an entirely different type resulting from the reactivities superimposed by the complexing group itself, is unusual in relation to most classical processes in being frequently complete. Superimposed control can be exercised to bring about reactions on the same, or the opposed, side to the metal according to the mechanism and to kinetic or thermodynamic control of products.

In order to permit the use in synthesis of such principles, previous work in these laboratories,[3,4] has been concerned with preparations and reactions of some $Fe(CO)_3$ complexes, a series which we now discuss as illustrative but not exclusive examples of the application of the strategy. The type of thinking expressed is general to olefin π-complexes, but particular applications require close considerations of the appropriate metals and ligands.

We call this strategy "lateral control of reactivity, stereochemistry and structure". The use of such groups is analogous to that of external scaffolding in erecting a building. It also has affinities with the ideas of enzyme chemistry, although the exact processes are very different. The concept can be extended, in slightly different terms, to the classical coordination complexes and the effects in them of a metal atom on the reactivities of the organic complexing group.

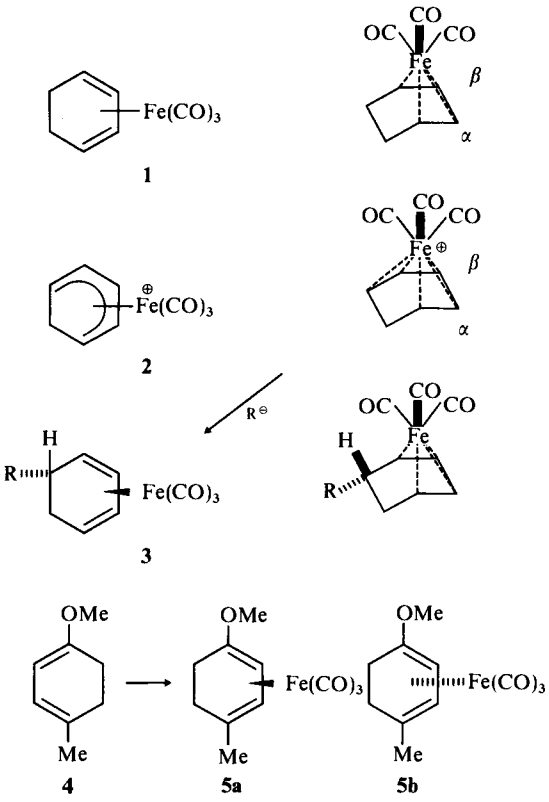
Characteristics of cyclohexa-1,3-diene or dienyl $Fe(CO)_3$ *complexes*

A general characteristic of $Fe(CO)_3$ π-complexes with cyclohexa-1,3-dienes such as **1** is that the metal is joined simultaneously to a number of carbons, four in the neutral diene complexes and five in the cationic

complexes (**2**), the complexed portion of the molecule being globular in type with a β-face of the ring (carrying the metal) and an α-(opposed) face. Reaction capabilities differ completely between the two ring faces. Also, because of the obligatory C–Fe bonding, the carbons involved are necessarily cisoid. This is inevitable inside a ring but is also true of open-chain compounds, and, for example, also prevents externalisation of complexed unsaturation from a ring, giving another dimension of synthetic control of structures. Addition and removal of the complexing group in one step[3] contrasts with classical methods in that four directed bonds are formed and broken simultaneously in the η^4–η^5 series or two in the η^2–η^3 series.

An outstanding feature of induced reactivity conferred by complexing is the ability to form cations of the η^5 type **2**. Cationoid processes can therefore be carried out independently of any need for the presence of classical cationoid groups such as carbonyl. Such cations can indeed contain typical anionoid groups such as OMe. These formal equivalents of stabilised mesomeric carbocations usually react in kinetically controlled processes with anionoid (nucleophilic) reagents solely on the α-face, with the partial exception of some hydride reductions noted later, resulting in the steric control of the newly formed centre, e.g. as in **3**.

Control can extend to the production of a newly fully resolved chiral centre if the cation is optically resolved.[5,47] All complexes of unsymmetrically substituted dienes such as **5a**, **5b** and the derived cations unless symmetrical, are capable of existing as enantiomers whether or not the diene itself is chiral. This permits in principle one solution of an old problem: to use one resolved centre to induce another, of known configuration, and then to remove the first.



The stereospecificity of formation of a new C–C or other bond, in a reaction involving an asymmetric cation of known configuration, results in enantiospecific generation of a new centre, of known configuration, resolved to the extent that the initial cation is resolved. Removal of metal and attached groups from the neutral product then abolishes the inducing asymmetry. This applies to any sterically defined process including formation of C–H or C–D when an asymmetric centre results. In the following account, an asterisk (*) with a formula number indicates an absolute configuration[5] rather than one component of a racemic mixture.

Availability of complexes

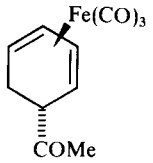
In order to utilise these and other characteristics in organic (as distinct from organometallic) synthesis, it is necessary to be able: (1) to add and to remove the lateral complexing group efficiently; (2) to prepare efficiently and in states of purity a wide range of complexes with specific substitutions; (3) to examine and understand the regio- and stereospecificities of reactions in relation to mechanisms involving structures of complexes and reagents, and conditions. A number of aspects of these topics have already been discussed[3] and will not be pursued further here except to note that no cation is mentioned in this review unless it can be obtained in a state of purity. Reagents of choice for removal of $Fe(CO)_3$ are $Me_3NO \cdot 2H_2O$[6] or $CuCl_2$.[7]

In considering synthetic strategies, it is necessary to distinguish in practice between the use of the complexes as reagents and to perform steps in later stages of a long sequence. The dominant factor in the first type of usage is ease of formation, and in the second case is yield. In particular, unconjugated dienes from Birch reductions of aromatic compounds can be used directly for simple preparations, but often mixtures or poor yields result which require to be separated or isomerised. For high yields of defined products, after a long synthetic sequence, it would be desirable to form a complex from a preformed specifically substituted conjugated diene.

Kinetic and thermodynamic control of products

To define the regio- and stereospecificity of reactions it must be established whether products are determined by a rate, or an equilibrium (or partial equilibrium) position. Equilibration can be attained either by reversals of the addition to a cation, or by enolisations of groups such as CHCOR or $CHCO_2Me$ in a η^4 complex. An example of the latter seems to be the Friedel–Crafts acetylation of the cyclohexadiene complex, originally thought[8] to give the 5α-COMe (**6**). Repetition of the work[9] shows initially the formation of the 5β-COMe (**7**) isomerisable with base into the known 5α-COMe (**6**). The yield in the acylation with the $Fe(CO)_3$ complex is about 45%, but by use of the less electron-withdrawing $Fe(CO)_2PPh_3$ the acetylated product is formed in 75% yield.[9] This is one pointer to possible synthetic control by manipulating the metal ligands appropriately.

Examples of equilibration by reversal are shown with anions like OMe[10,28] or OH.[11] The ratio 40α:60β (**8**, **9**) for the 5-OMe cyclohexadiene complex is surprising and possibly indicates stabilisation of β-OMe by orbital interaction, of an unknown character,



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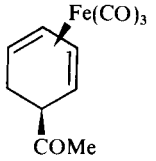

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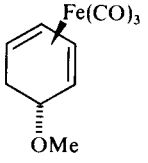

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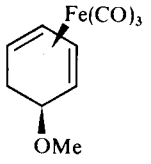

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rather than the expression of simple classical hindrance.[9] Reversal of 5α- C–C formation in some products of reaction of carbon nucleophiles with cations is known by means of sulphuric acid[12] but this process regenerates the cation and does not produce a steric isomer equilibrium. We assume for new C–C or C–H formation in reactions with cations that the products are kinetically controlled; for other more reversible nucleophiles the results may depend on conditions which have not been closely examined except in the case quoted.[10] Kinetic control (apparently α-) is possible in such cases, but depends on the use of irreversible experimental conditions. It is not clear at present that reversal will affect regio as well as stereospecificities, but it would be expected.

Regiochemistry

Electrophilic reactions on substituted cyclohexadiene complexes in relation to directive effects have been little examined.

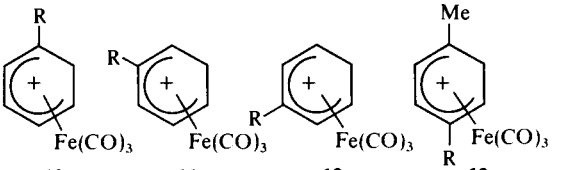
The substituted complexed cations are formally, stabilised specifically protonated benzenes which, unlike these parents, do not readily undergo deprotonation but react at C-1 or C-5 with anionoid (nucleophilic) reagents. In contrast to some larger rings[13] or derivatives of other metals,[14] in the cyclohexadienyl $Fe(CO)_3$ cation series reaction does not occur on C-2, C-3 or C-4, although if it is regarded as a mesomeric carbonium ion reaction at C-3 is formally possible. The stability of the complexed cations is attributable to charge delocalisation over the orbitals of a 3-dimensional π-system, and the relative reactivities of the two termini of the carbon system must be due to modifications by the substituents of the entire molecular orbital system. Substituents therefore do not necessarily show in any simple form the electronic effects of classical organic chemistry. Whilst this must be borne in mind, the addition of nucleophiles to a large number of organometallic cations has been surveyed and the conclusion made that the addition of hard nucleophiles to 18-electron cations may be considered charge, rather than orbitally controlled.[15] A rough correlation does seem to exist between ^{13}C NMR shifts and selectivities[16] which may provide useful indications of trends. Also, experimental selectivity between the termini depends not only on the nature and position of the substituent, but on the type of the reagent and the conditions as noted below. One readily interpretable classical effect of substitution is steric inhibition by a substituent on a position to which electronic effects would normally direct reaction.

The cation cannot be regarded as a classical carbonium ion, since a significant part of the charge is located on Fe.[17] Also the siting of a counter anion, and possible conformations of polar CO groups may have at present unknown effects on charge localisation in reactions. "Free" cations of this type must also differ from those based on classical polarisations of groups like carbonyl, in requiring little activation energy, at least in reactions with anions. The more reactive the anion the less should be the selectivity induced by substitution in the cation. Results quoted below agree qualitatively with the proposition that the weaker the acid corresponding to the anion used the less selective is that anion. However, complications in both regio- and stereoselectivity may result from changing mechanisms; if, for example, a reagent interacts first with the $Fe(CO)_3$ and is then transferred to the carbon system, as with hydride via a formyl complex.[18]

Problems of regio-control depend on the nature of the substituents. With 1-CO_2Me (**10**, R = CO_2Me) or 2-OMe (**11**, R = OMe) the 5-product results[3,4] except when very reactive anions are used.[19,20] However, with a weakly directive group like 2-Me (**11**, R = Me) selectivity is dependent on the nature of the reagent: allylsilanes,[21] 1,2-bis TMS 1-cycloalkenes[22] and aromatic amines[23] are known to react exclusively at C-5. With $NaBH_4$ in MeCN, selectivity is low, and attempts to increase this by lowering temperatures, surprisingly, resulted in decreased selectivity. The ratios of 1-Me:2-Me product are: 0.70 (82°); 0.79 (25°); 0.96 (−5°); 1.08 (−40°).

Improvements in selectivity may be affected by simple modifications of structures. In the case of borohydride reduction in acetonitrile of the 2-isopropoxy-5-methyl cation (**13**, R = O-*i*-Pr), undesired reaction at the 1-terminus is reduced but not completely suppressed [6%, compared to 10% for the corresponding 2-methoxy cation (**13**, R = OMe)[24]].

For synthetic uses it is desirable to know something of changes in rate of cation reactions due to substitution. The effects of the substituents OMe, Me, CO_2Me on overall reaction rates of the tricarbonylcyclohexadienyliron cation with acetylacetone under standard[25] conditions (40° ± 0.1°) in homogeneous solution in MeCN (or $MeNO_2$ in instances noted) have been examined under pseudo first order conditions by quantitative disappearance of the infrared peak at $\nu = 2110\,cm^{-1}$ due to $Fe(CO)_3^{\oplus}$. Previous preparative work, confirmed by tlc with the products here, indicates only one product from the unsymmetrical cations, representing addition to the 5-position. The rates relative to the unsubstituted cation **2**, 1.00 (MeCN) or 1.10 ($MeNO_2$) are: symmetrical: 3-Me (**12**, R = Me) 0.83; 3-OMe (**12**, R = OMe) 1.24 ($MeNO_2$); 3-OMe-1,5-Me_2, (**14**), 0.006 ($MeNO_2$), unsymmetrical: 1-CO_2Me, (**10**, R = CO_2Me) 12.13 or



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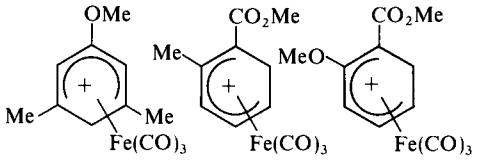


14 15 16

10.55 ($MeNO_2$); 1-CO_2Me-2-Me, (**15**), 6.59 or 7.31 ($MeNO_2$); 1-CO_2Me-2-OMe, (**16**), 1.62; 2-OMe, (**11**, R = OMe) 0.09; 2-Me, (**11**, R = Me) 0.38.[26]

A comparison between symmetrical and unsymmetrical cations requires recognition of the existence of two possible reactive positions in the first series and one in the second. The rates can be qualitatively explained partly by probable electronic effects of substituents: donation stabilising the cation and slowing reaction rates (2- or 3-Me, and particularly 2-OMe) (which must affect the 1-position much more than the 5-position) and electron withdrawal (1-CO_2Me) increasing rates. The 3-OMe marginally increases rates possibly through its inductive effect. In the disubstituted cases, expected effects of competition are seen. Steric effects must also be involved, particularly in the slow rate of the 1,5-Me_2-3-OMe (**14**) cation where addition must take place in a substituted position if it occurs at all. Because of the low rate the product could not be identified: it might be that of deprotonation. Whatever the product, the presence of the terminal Me is highly inhibitory of addition. Such steric effects have already been qualitatively noted.[27] Comparison of rates $MeCN:MeNO_2$ are not representative of a reproducible trend, but the difference, at maximum, is about 10%.

Stereochemistry

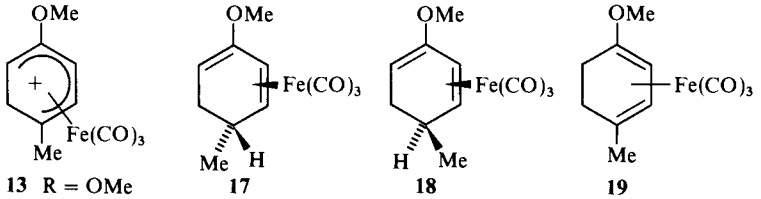
There is evidence[10,28] for reversible interaction of $Fe(CO)_3^{\oplus}$ with $RO^{\ominus}$, but no indication of direct transfer to the carbon system. The first evidence of substantial kinetic β-attack on a cation was the formation of some **17** by borohydride reduction of **13** (R = OMe), together with the expected **18** and **19**. A possible explanation[18] is partial attack on carbonyl to give a formyl complex, with transfer of hydride direct to the carbon system. To see to what extent the result depends on the reagent this was changed using the symmetrical cation **14**. With $NaBH_4$ the $\alpha:\beta$ ratio (**20**, **21**) is 88:12; $LiBH_4$ 79:21; K(*s*-Bu)$_3$BH 56:44; $LiEt_3BH$ 24:76 [all in THF/MeCN (2:1, 0°)]. The result agrees with observations[18] that trialkylborohydrides favour attack of metal carbonyls on the CO.

Steric control

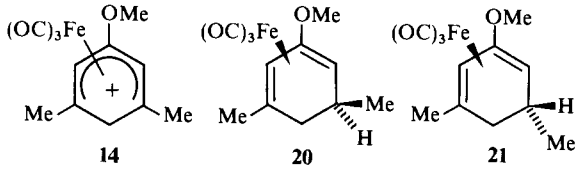
X-Ray studies of products in several key cases[29] confirm that kinetic α-attack occurs on the carbon system of cations. Expectation that this is general is extended to other cases on the basis of usual formation of only one product in C–C forming reactions, and of the internal consistency with results from this assumption in explaining other reactions of the products requiring proton migrations (on the β-face),[3] and attack of Ph_3C^+ to remove hydride (on the experimentally supported assumption that this is on the α-face and is inhibited by adjacent α-substituents).[12] Furthermore, production of the known α-isomer **22** of the phellandrene complex, by an alkylation of the cation **11** (R = Me) is unaccompanied by any formation of the known β-complex which could have been readily detected. Acid-catalysed isomerisation of **22** yields **23** by β-face shift of hydrogen.[4,9]

The course of hydride addition is more complex and is discussed in more detail below, but in the unsubstituted case[30] the deuterium introduced by BD_4^- is selectively removed by the trityl cation and is therefore on the α-face.

In any case it is very important in relation to potential applications to define whether a neutral



13 R = OMe 17 18 19



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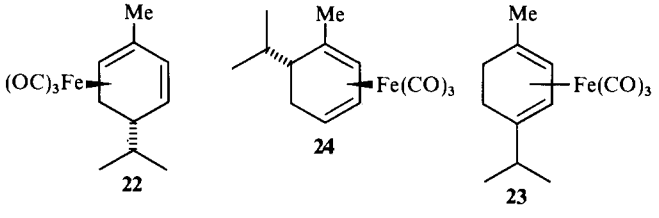

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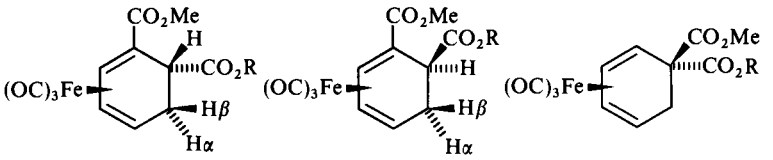
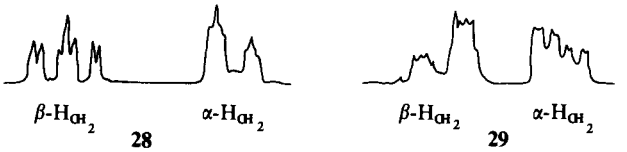


25 26 27

CH_2-splitting patterns

α-substituted complex (25) β-substituted complex (26)



28 29

with $Eu(fod\text{-}d_9)_3$

complex has an α- or a β-substituent. This may be reasonably definable on the basis of expectations: for example since rearrangements involve H-migration on the β-face, a centre bearing a substituent should be generated with this on the α-face. However, in cases such as esters where competing directive factors are involved,[4] it is particularly important to have clear evidence, and in the examples **25** (R = Me) and **26** this was provided by X-ray crystallography. Rapid spectral methods are clearly more desirable.

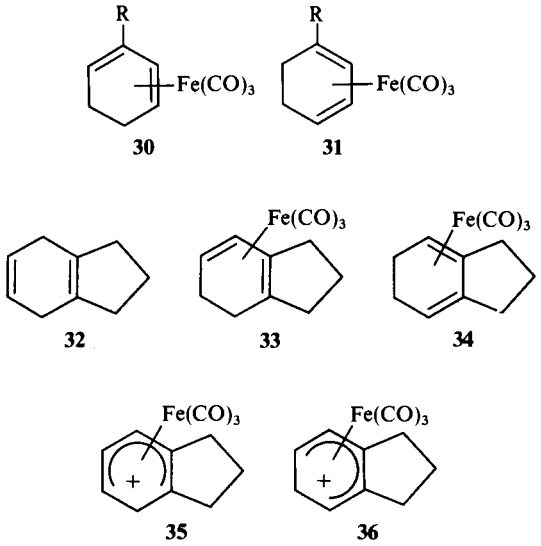
^{1}H NMR spectroscopy can be used to distinguish an α- from a β-substituent, particularly if an isomeric pair is available. Protons on a β-face resonate at lower field than the corresponding α-protons.[10,31] If only one isomer is available its steric configuration can often be assigned by examining the splitting pattern of an adjacent CH_2.[32] The types of pattern observed for CH_2 splitting are illustrated by those of the isomeric diesters **25** and **26**, the structures of which have been defined by X-ray.[33] In some cases it is necessary to add lanthanide shift reagents to resolve the pattern: in the case of **26** $Eu(fod\text{-}d_9)_3$ is present.

A range of complexes with groups such as NR_2, OR, SR, SeR, phenyl and CN have been examined by NMR[34] and the splitting patterns obtained for CH_2 enable the stereochemical assignment of the substituent in 5-position.

Lateral control of the structure of a complexed system

Lateral attachment of a complexed metal atom has several consequences in permitting control of the nature of the complexed diene. If the complex results from olefinic migration processes, e.g. based on 1,4-dihydrobenzenes, the nature of the kinetic product depends on the mechanism of the migration process, including the β-migration of H which results in any sp^3-substituent being α. The nature of the C-metal bonding requires a cisoid unsaturated system. The ability to bring about acid-catalysed equilibration between isomeric substituted complexes further can lead to a new dominant product. A series of defined dienes can thus be made available through the complexes.

The thermodynamic stability, as related to substitution, is not the same for the complex as for the diene. With alkyl complexes the group is found predominantly in the 2-position **30**,[35] and with

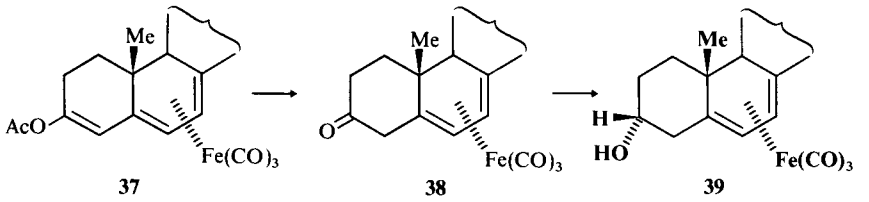


30 31 32 33 34 35 36

CO_2Me in the 1-position (**31**, R = CO_2Me).[13,36] Also, attempts to equilibrate free cyclohexadienes result often in dehydrogenation, disproportionation or formation of transoid dienes. For example, attempts to make the uncomplexed hydrocarbon of **33** from the readily available **32** failed.[37] Reaction of the latter with $Fe(CO)_5$ under controlled conditions gave exclusively **33** from which $Fe(CO)_3$ can be removed to yield the required diene for further use in a diterpene synthesis.[37] Acid-catalysed isomerisation of **33** led to **34.** Removal of hydride from **33** gave **35** and from **34** the isomeric **36**.[38] These conversions are one example of a set of processes leading controllably to isomeric complexes, dienes and cations.

Lateral control of classical reactivities

Attachment of $Fe(CO)_3$ to a diene can usefully alter the classical reactions of organic groups carried on the system towards conventional reagents both in rate and stereochemistry. An example of the latter is the conversion of the less hindered α-side of the ergosterol nucleus into the more hindered side, enabling hydride attack of a 3-carbonyl from the β-side. We described this work at the Chemical Society Anniversary Meeting in April 1976, and shortly afterwards the same



result was published by another group.[39] We merely note here (Experimental) that the use of the enol acetate of ergosterone (**37**) is superior to the published method, since the required 3-carbonyl (**38**) can be recovered by mild hydrolysis rather than oxidation of 3-OH, a procedure to be avoided where possible with $Fe(CO)_3$ complexes susceptible to oxidation. Hindered hydride reduction then occurs mainly from the β-face (**39**).

The classical way to alter the rate of hydrolysis of CO_2R is to alter the nature of the alkyl group. Lateral control in appropriate cases can alter, reversibly, the nature of the acid portion instead. In particular a 1-CO_2Me of a cyclohexa-1,3-diene $Fe(CO)_3$ complex is found to be very resistant to alkaline hydrolysis, and an adjacent β-CO_2Me (**26**) is apparently highly hindered, although the situation is complicated by base-catalysed isomerisation to α-CO_2Me, which is then hydrolysed to **25** (R = H).

The half hydrolyses formulated above **26** (R = Me) to **25** (R = H) and **27** (R = Me) to **27** (R = H) are readily accomplished in excellent yields without taking any particular precautions related to conditions.[40] In the ^1H NMR of **27** (R = H) it is the high-field Me of **27** (R = Me) which has disappeared and which correlates with the steric configuration.[40]

Lateral protection

Lateral complexing of olefins, by altering the properties of the unsaturated system can act either as reversible protection to inhibit classical reactivities, or to induce alternative reactivities. An example is provided by thebaine, which readily yields a diene–$Fe(CO)_3$ complex[41] in which the characteristic reactions of the diene are abolished; for example N-demethylation can be brought about, to give, after removal of $Fe(CO)_3$ N-desmethylthebaine.[42] Otherwise unknown rearrangements of the skeleton can result from the complexing.[41]

Synthetic equivalents

The concept of synthetic equivalents[43] is inherent in the known reactivities of molecules, but in practice its expression is a graphic way to bring to the attention of the synthetic chemist the potentialities of a defined sequence based on a particular type of structure. The equivalence formulae are particularly useful in demonstrating the potentials of lateral control, since this is imposed on the classical anionoid and cationoid reactivities of substituents, in terms of which the synthetic chemist usually thinks, in a way which renders these modifying rather than central to reactivity, and therefore a new way of expressing the equivalent reactivity is desirable.

If extended too far the notation would lose much of its usefulness, and we have arbitrarily confined it to sequences of not more than three steps, excluding removal of the complexing group. The discussion is here limited to η^5 cations in the $Fe(CO)_3$ series, and the related dienones below, but it could be extended not only to neutral complexes, but to other metal complexes including the η^2–η^3 series. The (+)-charges (Tables 1 and 2) mark the actual positions of reactivity, and also have the designated steric consequence, which may be of significance after removal of the iron, dependent on the symmetry of the organic part.

The "equivalent" depends on the sequence of reactions, so the same starting material (e.g. **11**, R = OMe) can be regarded as several alternative equivalents. The sequences here are shown as (A) and (B): (A) reaction with an anionoid reagent (nucleophile) to give **40** followed by dehydrogenation with $Fe(CO)_3$ removal results in the equivalent of an aryl cation **41** (Table 1); and (B) removal of $Fe(CO)_3$ leads from **40** to a cyclohexadiene which in the OMe series is the equivalent of a cyclohex-2-enone (**42**) into which it is convertible by acid hydrolysis (Table 2). The equivalence of **43** can be extended further to **44** on the basis of classical organic reactions of nucleophilic

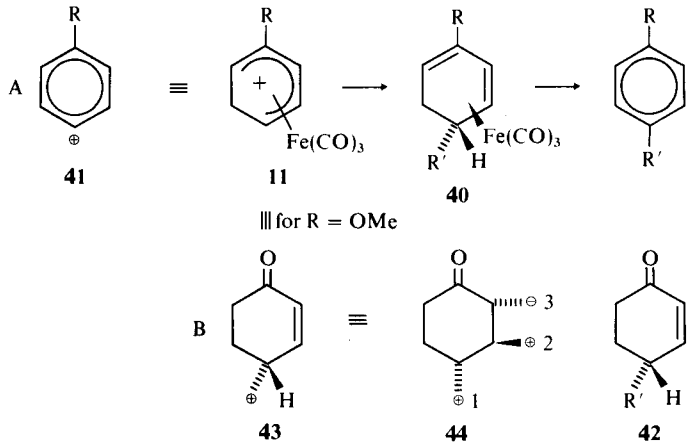
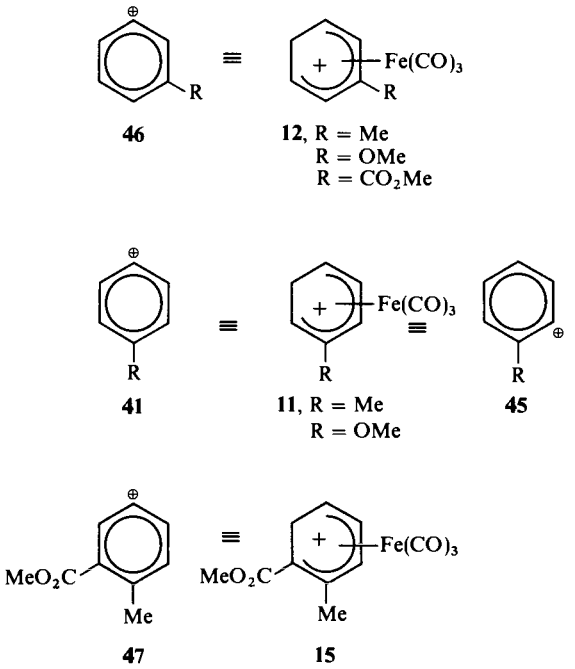


Table 1. Examples of aryl cation equivalents



addition to the first produced enone and subsequent regiospecific electrophilic reaction with the resulting anion. This equivalent would also be expected to have the dominant stereochemistry indicated (**44**). It is necessary in such equivalence formulae to conduct reactions in the numbered sequence.

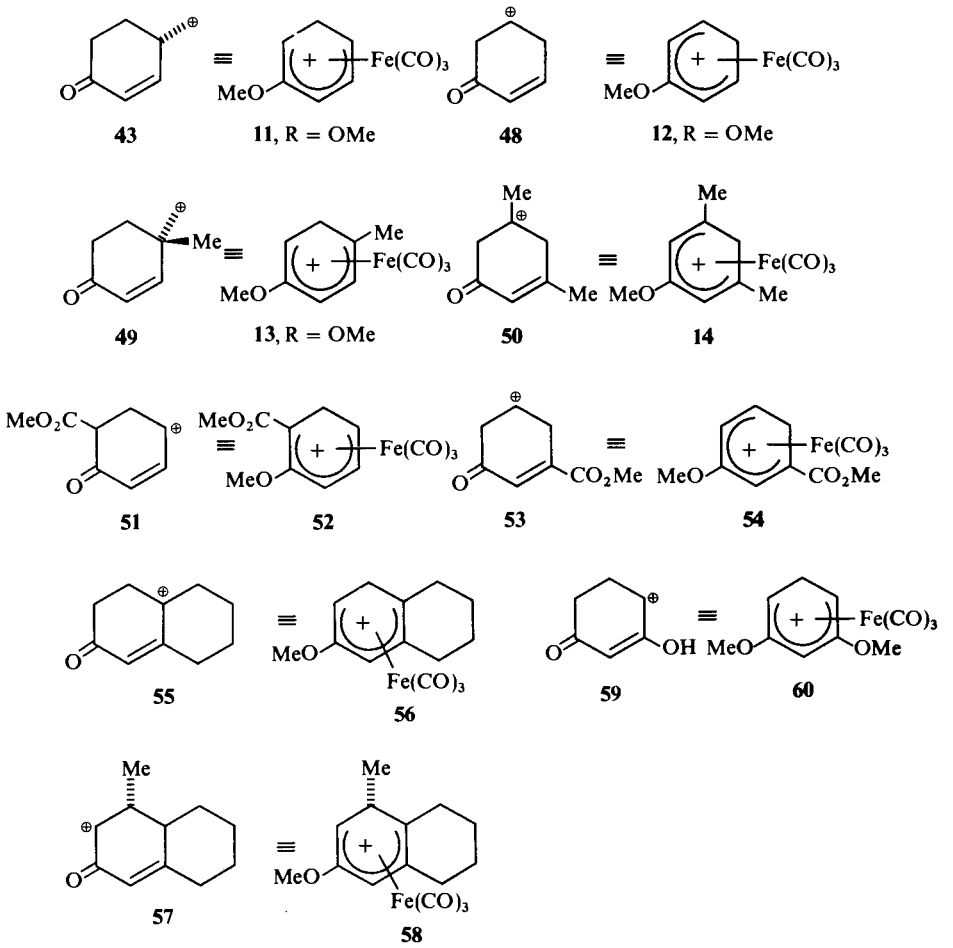
One example of the designated steric significance of the positive charge is that optical activity of the cation will lead to production of the unsaturated ketone product as one defined enantiomer, of known absolute configuration if that of the cation is known.

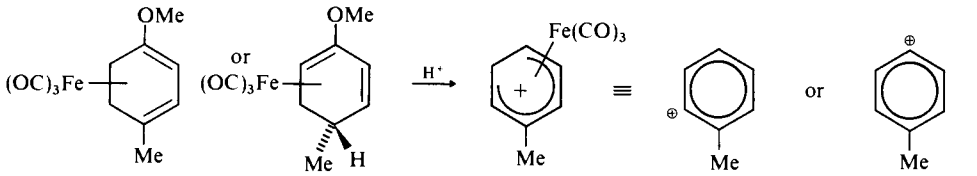
In some cases the notion of equivalence can usefully be extended back by one stage to the neutral precursors of cations, e.g. **17** or **19** can be regarded as **11** (R = Me) and hence as **45** or **41** (R = Me).

Deuterium can also be considered as a substituent of similar equivalents in conjunction with specific methods[3] for its introduction.

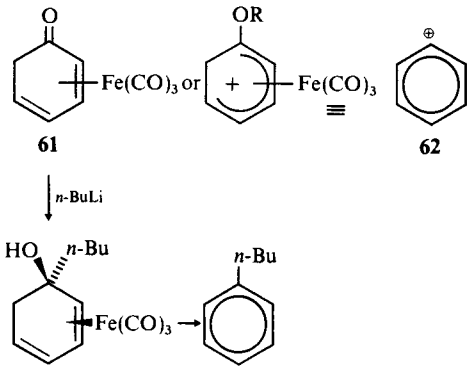
Another set of direct aromatic equivalents is defined by the substituted cyclohexadienone complexes of type **61**. These can be reacted in the carbonyl form with $BrZnCH_2CO_2Et$,[44] or with LiR under defined experimental conditions. Removal of $Fe(CO)_3$ then results in a substituted benzene by dehydration. For example, the cyclohexadienone complex itself with n-BuLi yields n-butylbenzene.[45] For reactivity purposes

Table 2. Examples of cyclohexenone cation equivalents





19 17 11, R = Me 45, R = Me 41, R = Me



61 62 63

they behave as ketonic tautomers of phenols, although carbonyl reactions are sluggish.

Reversal of classical polarities

The ability to formulate equivalents in the 2-OMe series as a cation in the 2- or 4-position to a CO reverses the classical activation associated with a CO group or a OMe group. 2-Enolate anions are well known; the classical electron-donating effect of OMe in a diene leads in Diels–Alder processes to the equivalent of a 4-anion of cyclohex-2-enone (**64**).[2] The equivalence notation shows very clearly in this case the difference induced by complexing. The notation also clearly indicates what cation equivalents are at present missing from the series (e.g. a pure equivalent of a cyclohexenone 6-cation).

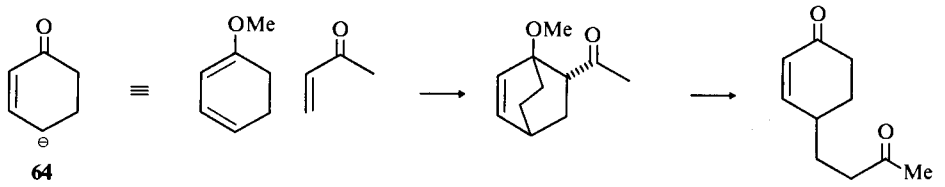
C–C *forming reactions*

The naked nature of the cations confers a wide ability to form C–X (X = N, O, S, C etc) under very mild experimental conditions. The outcomes most interesting for synthetic purposes are new methods of forming C–C. Hitherto, the laboratory use of the equivalents in synthetic action has been necessarily mainly confined to examining the basic features of the processes they undergo, but the topic is now at a point where it should be possible to participate in complex syntheses, with the increasing definitions of ways to make specifically substituted pure complexes, and the increasing understanding of the reactions. We have recently reported experimental advances which convert what were to some extent paper processes into practical ones. These involve the expansion of the range of participating anionoid (nucleophilic) reagents and the use of advantageous experimental techniques discussed below.

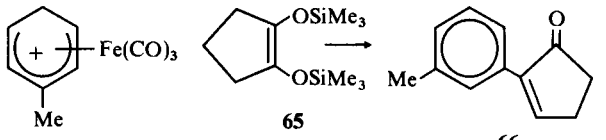
Previous work has already noted reactions with anions such as cyanide, malonate, β-diketone enolates, or even with the conjugate acids of such enols, including ketones, which seem to react as the stable enol.[3] Enamines have been shown to react as expected,[46] but recently TMS enol ethers, which can result from either kinetic or thermodynamic enolisation have been found to react with retention of regiospecificity.[47] Such enol ethers can be derived from ketones, aldehydes, esters, or lactones and if treated with aryl cation equivalents, efficient arylations in the 2-position of such CO precursors can be achieved.[48]

Initial difficulties with attempted alkylations using lithium alkyls, when decomposition resulted in ether solvents,[49] have been overcome. Alkylations of cations in CH_2Cl_2 at low temperature give yields >80%, including t-BuLi.[20] It seems no longer necessary to use Zn or Cd reagents.[49]

The reactions of TMS enol ethers are rapid and require no catalyst. One example below is that of a model reaction being developed for aromatic analogues of prostaglandins. The 3-Me cation PF_6 **12** (R = Me) reacts with the bis-TMS ether (**65**), required in excess, followed by acid treatment, dehydrogenation with removal of $Fe(CO)_3$ to give **66**. This novel approach to 2-arylcyclopentenones, which effectively defines an equivalent of a cyclopent-2-enone 2-anion,



64



12, R = Me 65 66

depends also on the unusual ease of the dehydration possibly due to enolisation and oxyallyl cation formation.[50]

Allylsilanes or allyltin reagents also react readily, notably involving only the initial double bond terminus.[21,51]

Substitutions of a number of aromatic rings occur when these are sufficiently reactive,[52] including anilines.[23,53] This can be used as a carbazole synthesis,[23] e.g. alkylation of the unsubstituted salt **2** with *p*-toluidine gives a mixture of **67** and **68**. 3-Methylcarbazole (**69**) is obtained by oxidation of the major product (**67**).

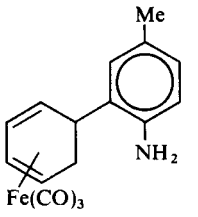
Difficulties connected with applications in synthesis

Some desirable, rather highly substituted, complexes are not readily available, either because available unconjugated dienes are isomerised to conjugated ones in unwanted directions during or before complexation, or because the required conjugated dienes themselves are not at present available. Formations of appropriately substituted cations also encounter structural limitations, for example the trityl cation does not abstract hydride from an α-alkylated position or one adjacent to it.[12,54] However, the range of methods available for cation formation includes acid-catalysed removal of α-CO_2H,[55] or of OR in consequence of migration.[35a]

Reactions do not always proceed as simple models would indicate, and effects of multiple substituents still require examination. Some obvious steric effects are observed; for example the 2-OMe cation (**11**, R = OMe) normally reacts in the 5- and not in the 1-position, but a 5-Me tends to inhibit reaction there relative to C-1 in borohydride reductions.[12] Deprotonation of an alkyl group at a terminal position of a cation is also sometimes dominant over addition,[56] yielding a conjugated triene complex.

Much further work is needed on the production, in pure form, of strategically substituted cation salts, including the use of other metals and complexing groups.

The importance of availability of optically active salts has been emphasised. These are often not readily available, but a classical resolution of the 1-CO_2H (**10**, R = CO_2H) has been achieved,[57] and presumably other acids could be resolved and the CO_2H used to lead to other substituted groups. Optically active natural dienes such as (−)phellandrene or (−)carvone can lead to optically active complexes by stereoselective isomerisations,[4] but appropriate dienes are rarely available. A very attractive method would be to have the ability to transfer $Fe(CO)_3$ chirally from an optically active donor, such as the complex of an α,β-unsaturated ketone,[58] to any unsymmetrically substituted diene, irrespective of the nature of its substituents. This method was found to be partially successful; for example the complexes of (+)-pulegone (**70**) yield an active complex (**5**)* when reacted with 1-methoxy-4-methyl-cyclohexa-1,3-diene (**4**), which has



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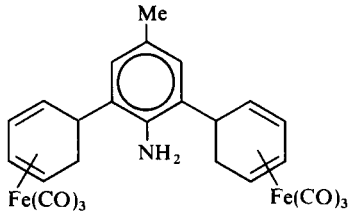

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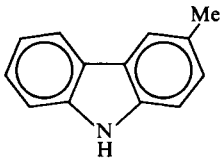

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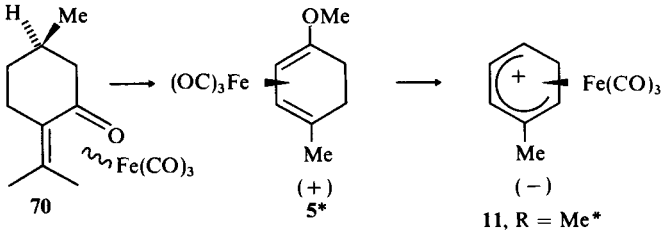

70 (+) 5* (−) 11, R = Me*

however too low an enantiomeric excess (about 10%) to be synthetically useful, although it can be used to demonstrate absolute configurations[5] and the feasibility of enantiospecific processes. **5*** was converted to optically active 2-Me salt (**11**, R = Me)*. The $Fe(CO)_3$ complex of 16-dehydropregnenolone acetate, gives a higher excess (up to about 30%) and of the opposite absolute configuration.[58] Work is in progress to develop more specific donors.

Reactions of the optically active OMe complex with acid generate the expected[35a] cation by OMe loss, which have apparently an undiminished degree of resolution.[5]

EXPERIMENTAL

This section contains at the end some details related to the previous discussions, but its aim is chiefly to provide some characteristic experimental examples which can be more generally extrapolated. The conditions noted are good ones, without necessarily being optimal.

The examples given include the use of aromatic precursors through metal-ammonia reductions; complexation with or without isomerisation; the action of acid both as an isomerising agent and a generator of cations; the use of TMS enol ethers both in complexation and as reagents; asymmetric complexation; reactions of cations with some characteristic nucleophilic (anionoid) reagents including an aromatic amine, and the production of a *m*-substituted aryl cyclopentenone by an alkylation process.

M.p.s were determined on a Reichert hot stage apparatus and are uncorrected. IR spectra were recorded using a Pye-Unicam SP 800 spectrophotometer. 100 MHz ^{1}H-NMR spectra were measured on Varian HA 100 and JEOL Minimar spectrometers (Me_4Si as the internal standard). Mass spectra were measured on an A.E.I. MS 902 mass spectrometer, $[\alpha]_D$ measurements were made on NPL Automatic Polarimeter 143C. Solvents used, unless otherwise stated, were reagent grade.

Metal ammonia reductions of aromatic precursors

The following is an example of the procedure which we routinely employ for reduction of a variety of aromatic substrates to yield precursors.

Anisole (216 g, 2 mol), t-BuOH (500 ml), diethyl ether (500 ml) were placed in a 5 l conical flask. About 2 l of liquid ammonia were transferred directly from an inverted cylinder into the reaction flask, which is swirled several times during the addition to mix the reactants. Li wire (*ca* 5 cm lengths) was added to the magnetically stirred mixture, as rapidly as the foaming allows, until a permanent blue colour was maintained for 30 min. About 5 g-atom of Li was usually required for the reduction. Towards the end of the reaction, the wall of the conical flask was washed with ether to return any unreacted material to the flask. MeOH (or solid NH_4Cl) was cautiously added to destroy the blue colour. The ammonia was allowed to evaporate overnight. Cold water (1 l) and petroleum ether (b.p. 30–40°, 1 l) were added to the remaining liquid. The organic phase was separated and washed with water (5 × 1 l) to remove t-BuOH and ammonia, followed by drying over anhyd. K_2CO_3. Evaporation of solvent, followed by distillation gave 1-methoxy-1,4-cyclohexadiene (176 g, 80%) b.p. 50°/35 mm (lit.[59] 40°/20 mm). Similarly 3-methyl-, 3-methoxy-, and 4-methoxyanisole gave 75–77% yields of the respective dihydroanisole derivatives.

Acid catalyzed isomerisation of kinetically to thermodynamically favoured complexes; synthesis of bicyclo-[4.3.0]nona-2,6(1)-diene

Bicyclo[4.3.0]*nona*-3,6(1)-*diene* (**32**). Indene (11.6 g, 0.10 mol) was reduced with Li (3 g, 0.43 mol) following the procedure described above to give the title product (10.9 g, 91%) as a colourless liquid b.p. 59–60°/14 mm (lit.[60] 59–59.5°/11 mm). IR (neat): 1650, 915, 660 cm^{-1}. NMR ($CDCl_3$): δ 1.67–2.53 (6 H, m, 7-H, 8-H, 9-H); 2.63 (4 H, s, 2-H, 5-H); 5.71 (2 H, s, 3-H and 4-H).

Tricarbonyl[(1,2,3,6-η)-*bicyclo*[4.3.0]*nona*-2,6(1)-*diene*]-*iron*(0) (**33**). The hydrocarbon **32** (5 g, 0.04 mol) and $Fe_2(CO)_9$ (18 g) were heated in refluxing acetone (50 ml) under N_2 for 3 hr. Cyclohexane was then added and the volume reduced to approximately 20 ml, by evaporation *in vacuo* at 25°. The residue was filtered through a short column of alumina and washed through with petroleum ether. After the solvent had been removed the residue was freed of uncomplexed material by heating to 50° at 0.1 mm for 30 min which gave pure complex **33** (3.6 g, 32%) as a yellow oil. IR (neat): 2045, 1955 cm^{-1}. NMR ($CDCl_3$): δ 1.4–2.8 (10 H, m, $-CH_2-$); 2.94 (1 H, m, 3-H); 5.27 (1 H, d, J = 7 Hz, 2-H). MS: 260 (M^+), 232, 204, 176, 174. (Found: 260.0138 (M^+). $C_{12}H_{12}FeO_3$ requires: M 260.0136.

Tricarbonyl[(1,2,5,6-η)-*bicyclo*[4.3.0]*nona*-1,5-*diene*] *iron* (0) (**34**). The complex **33** (300 mg, 1.2 mmol) was dissolved in conc H_2SO_4 (1 ml) and stirred under N_2 for 1.5 hr. A satd $NaHCO_3$aq was cautiously added to the mixture until effervescence ceased, the neutral soln was then extracted with hexane (3 × 10 ml), the extract dried over $MgSO_4$ and freed of solvent to give the complex (222 mg, 74%) as a yellow oil. IR (neat): 2040, 1955 cm^{-1}. NMR ($CDCl_3$): δ 1.36–2.92 (10 H, m, $-CH_2-$); 3.30 (2 H, broad s, 2-H, 5-H). MS: 260 (M^+), 232, 204, 176, 174. (Found: 260.0141 (M^+). $C_{12}H_{12}FeO_3$ requires: M 260.0136).

Bicyclo[4.3.0]*nona*-2,6(1)-*diene*. The Fe-complex **33** (100 mg) was added dropwise to $FeCl_3 \cdot 6H_2O$ (2 g) in acetone (5 ml) at 0° and the soln stirred for 30 min. The soln was then partitioned between ether and water, the ether phase washed with water, dried and freed of solvent to yield 37 mg (80%) of pure product. IR (neat): 3030, 2920, 2870, 2820, 1442, 1008 and 758 cm^{-1}. NMR ($CDCl_3$): δ 1.90 (2 H, tt, J = 6 Hz, 8-H); 2.08–2.56 (8 H, m, 9-H, 7-H, 5-H, 4-H); 5.59 (1 H, dt, J = 3 Hz, 10 Hz, 3-H); 5.89 (1 H, d, J = 10 Hz, 2-H). UV(hexane): λ_{max} 294 (ε 680 sh), 277 (2000 sh), 274 (2100 sh), 269 (2200 sh) and 260 nm (2000 sh). (Found: C, 89.7 H, 10.1. C_9H_{12} requires: C, 89.9 H, 10.1).

Conjugation of a 1,4- *to a* 1,3-*diene prior to complexation; an improved procedure for the synthesis of tricarbonyl* [(2,3,4,5-η)-2,4-*cyclohexadien*-1-*one*]*iron* (**61**).

1,4-Dimethoxy-1,4-cyclohexadiene (11 g) was stirred in degassed refluent $CHCl_3$ (EtOH-free, 100 ml) containing Wilkinson's catalyst (0.12 g) during 2 hr. The cooled soln was filtered through alumina and the solvent removed to leave a colourless oil (11 g) which was shown to consist of the conjugated and non-conjugated 1,4-dimethoxycyclohexadienes (ratio 3:1 respectively) together with some aromatic material (< 10%). NMR for the conjugated isomer in the mixture ($CDCl_3$): δ 2.40 (4 H, br s, 5-H, 6-H); 3.60 (6 H, s, OMe); 4.90 (2 H, s, 2-H, 3-H).

This mixture (11 g) was heated in the presence of filtered $Fe(CO)_5$ (25 ml) and di-n-butyl ether (freshly filtered through basic alumina) at a bath temp of 135–145° for 18 hr. After cooling, the soln was filtered through Celite and solvent removed, together with excess $Fe(CO)_5$, under aspirator pressure (12 mm, 70°). Chromatography on silica with petroleum ether gave a single band which was collected and distilled to give tricarbonyl[(1,2,3,4-η)-1,4-dimethoxy-1,3-cyclohexadiene]iron b.p. 90°/10^{-3} mm as a low melting solid (7.13 g, 48% based on conjugated diene). IR (CCl_4): 2055, 1960 cm^{-1}. NMR (CCl_4): δ 1.70–2.35 (4 H, m, 5-H, 6-H); 3.40 (6 H, s, OMe); 5.02 (2 H, s, 2-H, 3-H). MS: 280 (M^+) 252, 224, 196. (Found: C, 47.29 H, 4.28. Calc for $C_{11}H_{12}FeO_5$: C, 47.18 H, 4.32%).

Conc H_2SO_4 (4 ml) was poured onto the foregoing complex (1.5 g) at *ca* 0° and the resulting slurry was stirred for 1 hr. Addition of dry ether caused a gum to separate which was triturated with ether until the washings were colourless. The gum was then dissolved in water and gently warmed (50°, 0.5 hr) to hydrolyse any 1-MeO salt. Extraction with ether

followed by usual work-up gave **61** (1.2 g, 80%) identified by comparison of its spectral properties with those of the known compound.[11] Addition of NH_4PF_6 (1 g) to the aqueous washings caused a yellow solid to precipitate which was collected and readily identified as the known[59] 2-MeO cation **11** (R = OMe) (0.17 g, 8%).

Preparation of tricarbonylcyclohexadienyliron salts from unsaturated ketones via trimethylsiloxydienes; complexation and acid cleavage

Trimethylsiloxy-1,3-cyclohexadienes. These were prepared according to the procedure reported in the literature[61] except that the solvent system used was 1:1 ether/THF.

2-Trimethylsiloxy-1,3-cyclohexadiene was prepared from commercially available 2-cyclohexen-1-one in 67% yield; b.p. 55–56°/0.9 mm (lit.[61] 56–58°/6.0 mm). NMR ($CDCl_3$): δ 0.20 (9 H, s, $OSiMe_3$); 2.1–2.3 (4 H, m, $-(CH_2)_2-$); 4.8–5.0 (1 H, m, 1-H); 5.6–6.1 (2 H, m, 3-H and 4-H).

1-Trimethylsiloxy-1,3-cyclohexadiene was prepared from 3-cyclohexen-1-one[62] in 66% yield; b.p. 54–56°/0.70 mm. NMR ($CDCl_3$): δ 0.24 (9 H, s, $OSiMe_3$); 2.29 (4 H, m, $-(CH_2)_2-$); 5.15 (1 H, d, J = 5 Hz, 2-H); 5.3–5.6 (1 H, m, 4-H); 5.8–6.0 (1 H, m, 3-H). (Found: 168.0972 (M^+). $C_9H_{16}OSi$ requires: M 168.0970).

1-Methyl-3-trimethylsiloxy-1,3-cyclohexadiene was prepared from commercially available 3-methyl-2-cyclohexen-1-one in 80% yield; b.p. 57–59°/0.60 mm (lit.[61] 51–53°/1.0 mm). NMR ($CDCl_3$): δ 0.19 (9 H, s, $OSiMe_3$); 1.85 (3 H, s, Me); 2.0–2.4 (4 H, m, $-(CH_2)_2-$); 4.76 (1 H, m, 4-H); 5.47 (1 H, t, 2-H).

2-Methyl-3-trimethylsiloxy-1,3-cyclohexadiene was prepared from 2-methyl-2-cyclohexen-1-one[63] in 74% yield; b.p. 62–64°/0.74 mm. NMR ($CDCl_3$): δ 0.22 (9 H, s, $OSiMe_3$); 1.76 (3 H, broad s, Me); 2.14 (4 H, m, $-(CH_2)_2-$); 4.94 (1 H, t, J = 4 Hz, 4-H); 5.63 (1 H, m, 1-H). (Found: 182.1128 (M^+). $C_{10}H_{18}OSi$ requires: M 181.1127).

Complexation of trimethylsiloxy-1,3-cyclohexadienes. 2-Trimethylsiloxy-1,3-cyclohexadiene (2.0 g, 12 mmol) was refluxed with $Fe(CO)_5$, (3.1 ml, 24 mmol, filtered through cotton wool) in 20 ml di-n-butyl ether at 140° under argon atmosphere for 12 hr. The mixture was allowed to cool to room temp before it was filtered under argon through a pad of Celite, which was washed with ether. The very air-sensitive green to yellow solution obtained was placed under vacuum (not water aspirator) to remove the solvent. The residual greenish yellow to brown liquid was distilled to give tricarbonyl[(1,2,3,4-η)-2-trimethylsiloxy-1,3-cyclohexadiene]-iron (2.83 g, 77%); b.p. 49–52°/0.007 mm. IR (neat): 1965, 2050 cm^{-1}. NMR ($CDCl_3$): δ 0.31 (9 H, s, $OSiMe_3$); 1.3–2.1 (4 H, m, $-(CH_2)_2-$); 2.74 (1 H, dt, 4-H); 3.37 (1 H, q, 1-H); 5.22 (1 H, dd, $J_{1,3}$ = 2 Hz, $J_{3,4}$ = 7 Hz, 3-H). (Found: 308.0140 (M^+). $C_{12}H_{16}FeO_4Si$ requires: M 308.0167).

The other complexes in the series, all very air-sensitive, were prepared using the same procedure. *Tricarbonyl[(1,2,3,4-η)-1-trimethylsiloxy-1,3-cyclohexadiene]iron,* yield 52%; b.p. 74–76°/0.05 mm. IR (neat): 1960, 2040 cm^{-1}. NMR ($CDCl_3$): δ 0.21 (9 H, s, $OSiMe_3$); 1.3–2.3 (4 H, m, $-(CH_2)_2-$); 2.6–3.0 (1 H, m, 4-H); 4.8–5.3 (2 H, m, 2-H and 3-H). (Found: 308.0167 (M^+). $C_{12}H_{16}FeO_4Si$ requires: M 308.0167).

Tricarbonyl[(1,2,3,4-η)-1-methyl-3-trimethylsiloxy-1,3-cyclohexadiene]iron, yield 41%; b.p. 57–59°/0.007 mm. NMR ($CDCl_3$): δ 0.20 (9 H, s, $OSiMe_3$); 1.5–2.0 (4 H, m, $-(CH_2)_2-$); 2.07 (3 H, s, Me); 2.88 (1 H, q, 4-H); 5.13 (1 H, d, 2-H). (Found: 322.0326 (M^+). $C_{13}H_{18}FeO_4Si$ requires: M 322.0323).

Tricarbonyl[(1,2,3,4-η)-2-methyl-3-trimethylsioxy-1,3-cyclohexadiene]iron, yield 28%; b.p. 55–58°/0.01 mm. NMR ($CDCl_3$): δ 0.29 (9 H, s, $OSiMe_3$); 1.3–1.7 (4 H, m, $-(CH_2)_2-$); 2.11 (3 H, s, Me); 2.69 (1 H, t, 1-H or 4-H); 3.05 (1 H, t, 1-H or 4-H). MS: 322 (M^+), 294. (Found: 294.0373 (M^+-CO). $C_{12}H_{18}FeO_3Si$ requires: M 294.0374).

Acid cleavage of tricarbonyl(trimethylsiloxycyclohexadiene)-iron complexes to form cations. The procedure used was that described below for tricarbonyl(methoxycyclohexadiene)-iron complexes. The cationic complexes, isolated as the PF_6 salts, were readily identified by their characteristic proton NMR spectra.

Tricarbonyl(2-trimethylsiloxy-1,3-cyclohexadiene)iron and tricarbonyl(1-trimethylsiloxy-1,3-cyclohexadiene)iron both gave **2** (75% in each case). Tricarbonyl(1-methyl-3-trimethylsiloxy-1,3-cyclohexadiene)iron gave **12** (R = Me) (75%). Tricarbonyl(2-methyl-3-trimethylsiloxy-1,3-cyclohexadiene)iron gave **11** (R = Me) (70%).

Preparation of tricarbonylcyclohexadienyliron salts via demethoxylation of tricarbonyl 1- and 2-methoxycyclohexadieneiron

180 ml of conc H_2SO_4 in a round-bottom flask, equipped with a magnetic bar, was cooled to 0°. 1 ml of formic acid was added dropwise to the acid. To this slightly foaming acid mixture was then added the complex **30/31** (R = OMe[59]) (45 g, 0.18 mol) dropwise at a rate that maintained the reaction temp below 5°. The colour of the mixture was never permitted to be darker than amber. If the colour of the mixture became too dark, addition was stopped to allow it to return to a lighter colour. The addition usually took 60–90 min. The dropping funnel and other glassware used in the transfer of the complex were washed with nitromethane, and the washings added to the mixture. Stirring was continued for another 30 min. The amber liquid was then poured into a mixture of 1 kg of ice and 60 g of NH_4PF_6 in a 21 beaker with vigorous stirring. The residual liquid in the reaction flask was washed into the beaker with water. The yellow ppt formed was filtered, washed several times with water followed by ether. The air-dried salt was dissolved in about 300 ml nitromethane. The resultant soln was filtered directly into 1.21 of ether. The ppt **2**, after vacuum drying, amounted to 60–62 g (92–95%).

Addition of nucleophiles to cations

Reaction of a cation with an oxygen nucleophile: Tricarbonyl[(1,2,3,4-η)-2-methyl-5α-(2-propoxy)-1,3-cyclohexadiene]iron (0) (**40**), R = Me, R^1 = O-*i*-Pr). To a stirred suspension of tricarbonyl[(1,2,3,4,5-η)-2-methyl-2,4-cyclohexadien-1-yl]iron (1 +) PF_6 (1 −) **11** (R = Me)[35a] (500 mg, 1.32 mmol) and 2-propanol (0.5 ml) in dry CH_2Cl_2 (25 ml) was added ethyldiisopropylamine (200 mg) at room temp. When a clear yellow soln was observed (*ca* 15 min), the solvent was removed under reduced pressure. The residue was extracted with petroleum ether (b.p. 30–40°), and the concentrated soln was passed through a short column of basic alumina (act. 4). Removal of solvent gave a yellow oil (297 mg, 77%). IR (neat): 2035, 1965 cm^{-1}. NMR ($CDCl_3$): δ 1.07 (6 H, two d, J = 6 Hz, diastereotopic $CHMe_2$; 1.50 (1 H, m, J = 15 Hz, 6α-H); 2.12–2.28 (4 H, m, overlapped with the singlet at δ 2.12, 6β-H, 2-Me); 2.88 (2 H, m, 1-H, 4-H); 3.53 (1 H, hept, J = 6 Hz, $CHMe_2$; 3.92 (1 H, dt, J = 10.4 Hz, 5β-H); 5.33 (1 H, d, J = 6 Hz, 3-H). (Found: 292.0343 (M^+) $C_{13}H_{16}FeO_4$ requires: M 292.0398).

Alkylation of aromatic amines; carbazole formation

Tricarbonyl [(1,2,3,4-η)-5-(2′-amino-5′methylphenyl)1,3-cyclohexadiene]iron (0). A soln of PF_6 salt **2** (1.17 g, 3.2 mmol) in MeCN (50 ml) was added dropwise to a soln of *p*-toluidine (0.75 g, 7.0 mmol) in MeCN (20 ml) at reflux over a period of 30 min. After a further 30 min the solvent was evaporated and excess *p*-toluidine removed from the residue by sublimation (45°/0.5 mm). The brown residue was extracted with boiling hexane (4 × 20 ml). The title product was obtained from the combined extracts, after concentration, as yellow needles (0.6 g, 59%), m.p. 86–87°. IR (cyclohexane): 2055, 1983 cm^{-1}. NMR ($CDCl_3$): δ 1.44 (1 H, dm, 6α-H); 2.18 (3 H, s, Me); 2.30 (1 H, dq, 6β-H); 3.12 (2 H, m, 1-H, 4-H); 3.22 (2 H, broad, NH_2); 3.31 (1 H, dt, 5β-H); 5.45 (2 H, m, 2-H, 3-H); 6.32 (1 H, d, J = 8 Hz, 3′-H); 6.66 (1 H, dd, J = 8 Hz, 2 Hz, 4′-H); 6.71 (1 H, d, J = 2 Hz, 6′-H).

MS: 325 (M^+), 297, 269, 241. (Found: C, 59.46 H, 4.88 N, 4.23. $C_{16}H_{15}FeNO_3$ requires: C, 59.10 H, 4.65 N, 4.31%). The residue was separated by prep. tlc (silica, ether/hexane, 3:7) to give the title product (0.16 g, 15%) and the double alkylation product **68** (0.68 g, 9%), m.p. 165–167°. IR (cyclohexane): 2055, 1983 cm^{-1}. NMR ($CDCl_3$): δ 1.49 (2 H, d, 6α-H); 2.17 (3 H, s, Me); 2.30 (2 H, dq, 6β-H); 3.10 (4 H, m, 1-H, 4-H); 3.24 (2 H, broad, NH_2); 3.30 (2 H, dt, 5β-H); 5.46 (4 H, m, 2-H, 3-H); 6.65 (2 H, s, aromatic protons). MS: 543 (M^+), 515, 487, 459, 431, 403, 375. (Found: C, 55.39 H, 4.03 N, 2.90. $C_{25}H_{21}Fe_2NO_6$ requires: C, 55.28 H, 3.90 N, 2.58%).

3-Methylcarbazole (**69**). I_2 (0.35 g; 2.8 mmol) was added in one portion to a soln of **67** (0.25 g, 0.8 mmol) in pyridine (5 ml). Gas was evolved. The soln was warmed to 90° and heated for 1 hr. After addition of sodium dithionite (0.1 g) to the cooled soln the suspension was poured into aq. citric acid (50 ml; 10%) and extracted with ether (4 × 20 ml). The extracts were washed with sat NaCl (20 ml) and dried over $MgSO_4$. The title product was isolated by prep. tlc (silica, ether/hexane, 1:5) as colourless plates (0.1 g, 69%). IR (mull): 3400, 807, 753, 748, 729 cm^{-1}. A sample was recrystallised from CCl_4 and sublimed (100–120°/10^{-3} mm) as plates, m.p. 206–207° (lit.[64] 207–208°). MS: 181 (M^+). UV (EtOH): λ_{max} 236 nm. (Found: C, 86.16 H, 6.22 N, 7.75. $C_{13}H_{11}N$ requires: C, 86.15 H, 6.12 N, 7.73).

Alkylation with LiR; Reaction of t-butyl lithium with tricarbonyl[(1,2,3,4,5-η)-2-methoxy-2,4-cyclohexadien-1-yl]-iron(1+) PF_6(1−) **11** (R = OMe). To a suspension of **11** (R = OMe)[59] (2.0 g, 5.08 mmol), in CH_2Cl_2 (30 ml) at −78°, was added t-BuLi (4 ml of 1.52 M soln in pentane/hexane, 20% excess) dropwise. The mixture was stirred at this temp for 1 hr, after which the cooling bath was removed and 1 ml of 2 M HCl added with stirring. On reaching room temp, the mixture was washed with dil HClaq, water and $NaHCO_3$aq. After drying over K_2CO_3, the solvent was removed. The crude product was chromatographed on basic alumina (act. 4) with petroleum ether to give 1.25 g (80%) of a yellow liquid. The NMR is consistent with the presence of a 60:40 mixture of 2 isomeric compounds, (a) tricarbonyl[(1,2,3,4-η)-5-t-butyl-2-methoxy-1,3-cyclohexadiene]iron: NMR ($CDCl_3$): δ 0.73, (9 H, s, t-Bu); 3.30 (1 H, m, 1-H); 3.61 (3 H, s, OMe); 5.17 (1 H, dd, 3-H); (b) tricarbonyl[(1,2,3,4-η)-6-t-butyl-1-methoxy-1,3-cyclohexadiene]iron: NMR ($CDCl_3$): δ 0.83, (9 H, s, t-Bu); 3.40 (3 H, s, OMe); 4.98 (1 H, dd, 3-H); 5.56 (1 H, d, 2-H). The region δ 1.12–2.80 contains a series of multiplets which integrate for 4-H, 5-H and 6-H of the two isomers. MS: 306 (M^+), 278, 250, 248, 220. (Found: 306.0552 (M^+). $C_{14}H_{18}FeO_4$ requires: M 306.0554).

Alkylation with allylsilane

A stirred mixture containing **11** (R = Me)[35a] (0.5 g) and allyltrimethylsilane (2 ml) in dry CH_2Cl_2 was refluxed in an atmosphere of N_2 during 36 hr. The clear soln was evaporated and the resulting oil chromatographed on silica with petroleum ether. Distillation of the yellow oil offered tricarbonyl [2-methyl-5-(2-propenyl)-1,3-cyclohexadiene]-iron, which according to ^1H NMR was >95% of one regioisomer, b.p. 90°/10^{-3} mm (Kugelrohr). IR (CCl_4): 2050, 1975, 1640 cm^{-1}. NMR (CCl_4): δ 1.24 (1 H, m, H-6); 1.90 (3 H, m, H-6, CH_2=CH–CH_2); 2.04 (1 H, m, H-5); 2.08 (3 H, s, Me); 2.90 (2 H, m, H-1, H-4); 5.16 (1 H, dd, J = 6, 2 Hz, H-3); 5.82–4.76 (3 H, m, CH_2=CH); MS: 274 (M^+), 246, 218, 190, 188. (Found: C, 56.82 H, 5.09. $C_{15}H_{14}O_3Fe$ requires C, 56.97 H, 5.15%).

Synthetic equivalents

Formation of a 5-substituted cyclohex-2-enone; alkylation of tricarbonyl-3-methoxycyclohexadienyliron (1+). The 3-MeO cation **12** (R = OMe)[21] (2 g) was heated at 80° in EtOH (25 ml) containing cyclopentanone (3 ml). After about 0.5 hr a homogeneous soln was obtained which was then cooled, poured into water and extracted with ether. The organic phase was collected, dried ($MgSO_4$) and evaporated to leave a yellow oil. Chromatography on silica (petroleum ether/ether, 9:1) gave tricarbonyl [(1,2,3,4-η)-2-methoxy-6-(2′-oxocyclopentyl)1,3-cyclohexadiene]iron as a yellow oil (1.5 g, 90%). IR (CCl_4): 2045, 1975, 1738 cm^{-1}. NMR (CCl_4): δ 1.90–2.50 (10 H, m, cyclohexanone ring protons, 5-H, 6-H); 2.60 (1 H, m, 4-H); 3.12 (½H, overlapping dd, J = 4 and 2 Hx, diasteromeric 1-H); 3.35 (½ H, overlapping dd, J = 4 and 2 Hz, diastereomeric 1-H); 3.55 (3 H, s, OMe); 5.06 (1 H, dd, J = 6, 2 Hz, 3-H). Irradiation at δ 5.06 caused the resonances at both 3.12 and 3.35 to collapse into doublets (J = 4 Hz). MS: 332 (M^+). (Found: C, 54.14 H, 4.96. $C_{15}H_{16}FeO_5$ requires: C, 54.24 H, 4.86%).

To a stirred soln of this complex (1.3 g) in acetone at 0° was added Jones' reagent dropwise until evolution of gas ceased. The soln was poured into water and extracted with ether. After drying, the organic phase was evaporated to leave a colourless oil which was chromatographed on silica (petroleum ether/ether, 1:1) to give pure 5-(2′-oxocyclopentyl)-cyclohex-2-en-1-one as an oil (0.5 g, 57%). IR (CCl_4): 1740, 1690 cm^{-1}. NMR ($CDCl_3$): δ 1.3–2.6 (12 H, m, remaining ring protons); 5.88 (1 H, d, J = 10 Hz, 2-H); 6.84 (1 H, m, 3-H). (Found: 178.0992 (M^+). $C_{11}H_{14}O_2$ requires: M 178.0994).

Alkylation involving formation of a m-substituted 2-arylcyclopentenone; 2-(3′-methylphenyl)-1-oxo-2-cyclopentene (**66**). Compound **65**[65] (1 ml; excess) was added to a stirred suspension of **12** (R = Me)[35a] (500 mg, 1.3 mmol) in dry MeCN (4 ml) at −25°. After 15 min the solvent was evaporated. The residue was dissolved in MeOH (10 ml); conc. HCl (5 drops) was added and the soln stirred at rt for 42 hr. The mixture was poured into water (50 ml) and extracted with ether (3 × 40 ml). The extracts were combined, washed with water (3 × 40 ml) and dried over $MgSO_4$. Evaporation gave a brown gum which was eluted through a short column of alumina with $CHCl_3$. This crude material was dissolved in toluene (40 ml) and heated at reflux with 10% Pd–C (200 mg) for 60 hr. Filtration, evaporation and tlc (silica, hexane/ether, 1:1) gave **66** (64 mg, 28% based on **12** (R = Me). Recrystallisation from MeOH gave needles, m.p. 51–53°. IR (mull): 1715 cm^{-1}. NMR ($CDCl_3$): δ 2.38 (3 H, s, Me); 2.64 (4 H, m, two CH_2); 7.1–7.6 (4 H, m, aromatic H); 7.78 (1 H, t, vinyl H). MS: 172 (M^+). (Found: C, 83.37 H, 6.96. $C_{12}H_{12}O$ requires: C, 83.69 H, 7.02%).

Optically active complexes

Preparation of optically active tricarbonyl[(1,2,3,4,5-η)-2-methyl-2,4-cyclohexadien-1-yl]iron(1+)_ hexafluorophosphate(1−) **11** (R = Me)*1-*Methoxy-4-methyl-1,3-cyclohexadiene* (**4**). 1-methoxy-4-methyl-1,4-cyclohexadiene (17 g, 0.14 mol) was heated at reflux with Wilkinson's catalyst (30 mg) in EtOH–free $CHCl_3$ (150 ml) for 3 hr. After cooling and evaporation, the residue was filtered through basic alumina with benzene. Evaporation gave a 10:3 mixture of 1,3- and 1,4-dienes as a pale yellow oil. This material was used without further purification; in the following complexation with pulegone-$Fe(CO)_3$ (**70**) allowance was made for the presence of 1,4-diene in considering the weight of 1,3-diene used.

Asymmetric complexation of 1-methoxy-4-methyl-1,3-cyclohexadiene. (+)-Pulegone ($[\alpha]_D^{20}$ + 22°) (3.7 g, 24 mmol) was added to $Fe_2(CO)_9$ (10 g, 27 mmol) suspended in degassed petroleum ether (b.p. 40–60°; 150 ml). The mixture was warmed very gently to reflux, with efficient stirring. The reaction mixture darkened to a deep red and the $Fe_2(CO)_9$ was consumed. After 5 hr, **4** (4 g, 32 mmol) was added and heating at reflux continued for 11 days; the progress of the reaction was followed by tlc (silica, benzene/hexane, 1:1). The solvent was removed on a rotary evaporator and the volatile products were distilled from the residue (30–80°/10^{-3} mm, Kugelrohr). The distillate was chromatographed in two portions on silica(benzene/hexane) and the yellow fractions combined and distilled (60°/10^{-3} mm, Kugelrohr) to give **5*** (6.71 g, 78%). ($[\alpha]_D^{20}$ + 13°, c = 9, $CHCl_3$). (Found: C, 50.06 H, 4.58. $C_{11}H_{12}FeO_4$ requires: C, 50.03 H, 4.58%).

Treatment with conc. H_2SO_4. The product **5*** (3.36 g, 12.7 mmol) was stirred at 5° with conc H_2SO_4 (2 ml). After 20 min the resulting thick paste was triturated with dry ether

(4 × 20 ml) and then dissolved in water (20 ml). NH_4PF_6 (2.1 g, 12.9 mmol) was added and the yellow ppt was collected by filtration, washed with water and ether, and air-dried. Pure **11** (R = Me)* (4.22 g, 88%) ($[\alpha_D^{20}] - 2.5°$, $c = 9$, MeCN), obtained by reprecipitation from MeCN by addition of dry ether, was dried over KOH pellets.

Alkylation with a Cd-*derivative; optically active* (−)-*tricarbonyl*[(1,2,3,4-η)-5α-*isopropyl*-2-*methyl*-1,3-*cyclohexadiene*]*iron*(0) (**22**)*. An excess of di-isopropyl cadmium in THF was added to a stirred soln of **11** (R = Me)* ($[\alpha]_D^{20} - 2.5°$, $c = 9$, MeCN) (0.41 g) in MeCN (4 ml) at −24°. After 7 min NH_4Claq (5 ml, 10%) was added and the THF removed on a rotary evaporator. Water (20 ml) was added, and the product was extracted with pentane (4 × 30 ml), the combined organic phases dried, concentrated and eluted through a short column of silica with hexane. Removal of solvent gave 0.23 g (76%) of a 7:3 mixture of the isomers (**22*** and **24**) which was separated by chromatography on silica/$AgNO_3$ (15%) with hexane. **22*** eluted first and was isolated as a yellow oil ($[\alpha]_D^{20} - 1.4°$, $c = 7$, $CHCl_3$). IR (cyclohexane): 2040, 1970, 1964 cm^{-1}. NMR ($CDCl_3$): δ 0.77 (3 H, d, J = 6 Hz, Me); 0.81 (3 H, d, J = 6 Hz, Me); 1.32 (2 H, m); 1.86 (2 H, m); 2.05 (3 H, s, Me); 2.86 (1 H, dd, J = 6.3 Hz, 4-H); 2.99 (1 H, m, 1-H); 5.20 (1 H, dd, J = 6.2 Hz, 3-H) MS: 276 (M^+), 248, 220, 218. (Found: C, 56.61 H, 5.64. $C_{13}H_{16}FeO_3$ requires: C, 56.55 H, 5.84%). Further elution gave **24**. IR (cyclohexane): 2038, 1969, 1963 cm^{-1}. NMR ($CDCl_3$): δ 0.57 (3 H, d, J = 6.5 Hz, Me); 0.82 (3 H, d, J = 6.5 Hz, Me); 1.36 (1 H, m, 1′-H); 1.50 (3 H, s, Me); 1.82 (1 H, dt); 1.95 (1 H, m); 2.24 (1 H, dt); 2.86 (1 H, m, 4-H); 5.07 (1 H, m, 3-H); 5.24 (1 H, m, 2-H).

Reductions

Reduction of tricarbonyl[(1,2,3,4,5-η)-1,5-*dimethyl*-3-*methoxy*-2,4-*cyclohexadien*-1-*yl*]*iron*(1+) *PF*$_6$ (1−) (**14**). General procedure. To a magnetically stirred soln of the **14**[12] (106 mg, 0.25 mmol) in 5 ml of 2: 1 THF/MeCN, at 0° under N_2, was added, by syringe, 1.0 ml of a 1 M soln of lithium triethylborohydride in THF. The mixture was stirred at 0° for 30 min, quenched by the dropwise addition of 0.6 ml water and partitioned between ether and water. The ether phase was washed well with water, dried and evaporated. Filtration of the crude product through a small amount of alumina yielded 48 mg (65%) of a 76:24 mixture of **21**[12] and the corresponding **20**.

Pure **20** could be obtained from mixtures of **20** and **21** by selective demethoxylation of **21** (conc H_2SO_4, 0°) and subsequent purification of the ether soluble residue by tlc (silica). IR (cyclohexane): 1980, 1972 cm^{-1}. NMR ($CDCl_3$): δ 1.00 (3 H, d, 5-Me); 1.24–2.32 (3 H, m, 5-H, and 6-H); 1.62 (3 H, s, 1-Me); 3.16 (1 H, t, J = 1.5 Hz, 4-H); 3.59 (3 H, s, OMe); 4.98 (1 H, s, 2-H). MS: 278 (M^+), 250, 222, 220, 182, 178, 162. (Found: 278.0246 (M^+). $C_{12}H_{14}FeO_4$ requires: M 278.0241).

Temperature dependence of $NaBH_4$ *reduction of* **11** (R = Me).[35a] $NaBH_4$ (50 mg, excess) was added in one portion to a soln of the title salt[35a] (100 mg, 0.26 mmol) in dry MeCN (3 ml) at reflux, 25°, −5° or −40°. After 20 min the mixture was filtered, evaporated, and the residue was taken up in pentane (30 ml). The soln was filtered through a small pad of alumina, washed with water (2 × 10 ml), dried over $MgSO_4$ and evaporated to give the neutral complexes (33–34 mg, 50%) as a yellow oil. The ratio of **31** (R = Me)[11,35a] and **30** (R = Me)[11,35a] was determined by glc analysis (2% OV17 on Gas Chrome Q) at 60–120°. **30** (R = Me) elutes before **31** (R = Me). Each reduction was repeated twice, and each sample was analysed twice by glc. The mean of these four values (±2–3%) is given in the theoretical section.

Alteration of reactivity of a conjugated group.

Alkaline hydrolysis of tricarbonyl[(1,2,3,4-η)-1,6-*dimethoxycarbonyl*-1,3-*cyclohexadiene*]*iron* (0) **25**, (R = Me).[32] An ice-cooled methanolic soln (30 ml) of the title diester (100 mg, 0.3 mmol) and NaOHaq (15 ml, 20%) was stirred at 5–10° for 2 hr. Water (100 ml) was added and the resulting soln was washed with petroleum ether. The aqueous soln was acidified with ice-cooled HCl (20%) and extracted with ether (4 × 25 ml). The combined ether extract was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to give a yellow solid residue (71 mg, 74%), (**26**, R = H) which was recrystallised from chloroform/petroleum ether (b.p. 40–60°), m.p. (dec >150°). IR ($CHCl_3$): 3500–2300 (br. CO_2H); 2035, 1987, 1700 (CO) cm^{-1}. NMR ($CDCl_3$): δ 1.91 (1 H, m, 5α-H); 2.40 (1 H, m, $J_{5\alpha,5\beta}$ = 15.5 Hz, 5α-H); 3.23 (1 H, m, $J_{2,4}$ = 1 Hz, $J_{4,5\alpha}$ = 2.8 Hz, $J_{4,5\beta}$ = 15.5 Hz, 4-H); 3.46 (1 H, dd, $J_{6,5\beta}$ = 12 Hz, $J_{6,5\alpha}$ = 3.7 Hz, 6-H); 3.67 (3 H, s, CO_2Me); 5.43 (1 H, dd, $J_{3,4}$ = 4.5 Hz, $J_{3,5}$ = 0.9 Hz, 3-H); 6.21 (1 H, d, $J_{2,3}$ = 4.5 Hz, 2-H); 10.21 (1 H, s, CO_2H). MS: 322 (M^+), 294, 266, 238. (Found: C, 44.58 H, 3.33. $C_{12}H_{10}FeO_7$ requires: C, 44.75 H, 3.13%).

Tricarbonyl[(1,2,3,4-η)-5α-*carboxy*-5β-*methoxycarbonyl*-1,3-*cyclohexadiene*]*iron* (0) (**27**, R = H). An analogous treatment of **27** (R = Me)[32] (300 mg, 0.89 mmol) gave **27** (R = H) (241 mg, 84%). The title compound was crystallised from $CHCl_3$ and petroleum ether (b.p. 40–60°) as unstable yellow crystals, m.p. 98–99°. IR ($CHCl_3$): 3400–2400 (br, CO_2H); 2045, 1980, 1720 cm^{-1} (CO). NMR ($CDCl_3$): δ 2.20–2.56 (2 H, m, 6-H); 3.20 (1 H, m, 1-H); 3.32 (1 H, dd, $J_{3,4}$ = 6 Hz, $J_{2,4}$ = 2 Hz, 4-H); 3.78 (3 H, s, CO_2Me); 5.38 (2 H, m, 2-H, 3-H); 11.2 (1 H, s, CO_2H). MS: 322 (M^+), 294, 266, 238. (Found: C, 44.74 H, 3.20. $C_{12}H_{10}FeO_7$ requires: C, 44.75 H, 3.13%).

Steric hindrance of a classical reduction in the ergosterol series

Tricarbonyl(*ergosta*-3,5,7,22-*tetraen*-3-*ol*-*acetate*)*iron* (**37**). To a soln of the ergosta-3,5,7,22-tetraen-3-ol-acetate[66] (0.872 g, 2 mmol) in anhydrous benzene (15 ml) was added $Fe_3(CO)_{12}$ (2.05 g, 4 mmol) and the mixture was stirred and heated at reflux under N_2 for 20 hr. After filtration through Celite and evaporation of the solvent, the residue was chromatographed on silica (30 g). Elution with benzene/petroleum ether (1:1) removed traces of unreacted $Fe_3(CO)_{12}$. The *tricarbonyl* (*ergosta*-3,5,7,22-*tetraen*-3-*ol*-*acetate*)*iron* (**37**) was eluted with benzene and recrystallised 6-H or 7-H, 22-H, 23-H); 5.37 (1 H, d, J = 2 Hz, 4-H). UV: λ_{max} 253 (ε 2200) and 207 nm (ε 27000). (Found: C, 69.2 H, 7.7. $C_{33}H_{44}FeO_5$ requires: C, 68.8 H, 7.7%).

Tricarbonyl(*ergosta*-5,7,22-*trien*-3-*one*)*iron* (**38**). A mixture of **37** (0.576 g, 1 mmol), $KHCO_3$ (0.2 g, 2 mmol) and MeOH (20 ml) was stirred and heated at reflux under N_2 for 0.5 hr. After cooling to room temp the product was collected, washed with water/MeOH (1:1), dried *in vacuo* and recrystallised from EtOH to give bright yellow needles (0.96 g, 83%), m.p. 148–150°. IR: 2025, 1960, 1940, 1750, 1660 cm^{-1}. NMR: δ 2.07 (3 H, s); 4.96 (1 H, d, J = 4 Hz, 6-H or 7-H); 5.14 (3 H, m, 6-H or 7-H, 22-H, 23-H); 5.37 (1 H, d, J = 2 Hz, 4-H). UV: λ_{max} 253 (ε 2200) and 207 nm (ε 27000). (Found: C, 69.2 H, 7.7. $C_{33}H_{44}FeO_5$ requires: C, 68.8 H, 7.7%).

carbonyl(ergosta-5,7,22-trien-3-one)iron (0.49 g, 92%), m.p. 181–182° (in a tube sealed *in vacuo*) (lit.[39] 145–147° dec). On a Kofler block in air these crystals begin to darken at approximately 145° but do not melt. IR: 2020, 1945, 1710 cm^{-1}. NMR: δ 4.84 (1 H, d, J = 4 Hz, 6-H or 7-H); 5.16 (3 H, m, 6-H or 7-H and 22-H, 23-H). MS: 534 (M^+). UV: 240 (18300) and 213 nm (ε 20200). No max at 252 nm in $CHCl_3$ [lit.[39] UV: ($CHCl_3$) 252 nm (ε 10800)]. (Found: C, 69.4 H, 7.8. Calc for $C_{31}H_{42}FeO_4$: C, 69.7 H, 7.9%).

Reduction of tricarbonyl(*ergosta*-5,7,22-*trien*-3-*one*)*iron* **38** *to* **39**. A stirred soln of the ketone complex **38** (0.25 g) in purified THF (15 ml) under N_2, was cooled in an ice bath and treated with lithium tri-t-butoxyaluminium hydride (0.5 g). After keeping the mixture at 5° overnight it was worked up by addition of $(NH_4)_2SO_4$aq and extraction with benzene. The benzene soln was filtered through silica and the product was recrystallised from MeOH to give **39** as yellow needles (0.21 g, 84%), m.p. 124–126° (lit.[39] 120°). IR: 3610, 3560, 2020, 1945 cm^{-1}. NMR: δ 4.04 (1 H, m, 3-H); 4.80 (1 H, d, J = 4 Hz, 6-H or 7-H); 5.16 (3 H, m, 6-H or 7-H and 22-H, 23-H). MS:

536 (M^+). UV: 239 (19800) and 209 nm (ε 23700). (Found: C, 69.2 H, 8.4. Calc for $C_{31}H_{44}FeO_4$: C, 69.4 H, 8.3%). Tlc and NMR of the total reduction mixture indicated the presence of only traces of the more polar 3β-OH epimer.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 303 to 317, 1981
Printed in Great Britain

0040-4020/81/Suppl. 1-0303-15 $02.00/0
Pergamon Press Ltd.

SYNTHESIS OF ISOPRENOID NATURAL PRODUCTS FROM β-KETO ESTERS

F. W. SUM and LARRY WEILER*

Department of Chemistry, University of British Columbia, Vancouver, British Columbia V6T 1Y6, Canada

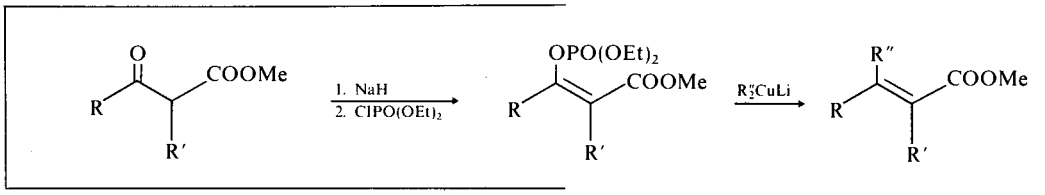
(*Received in U.S.A.* 8 *May* 1980)

Abstract—The anions of β-keto esters were reacted with diethyl phosphorochloridate to yield the corresponding enol phosphate. These enol phosphates were coupled with lithium dimethylcuprate to give the resulting β-methyl α,β-unsaturated ester stereoselectively and in good yield. When combined with the γ-alkylation of the β-keto ester dianions this overall sequence results in the stereoselective and regioselective incorporation of an isoprene moiety in a synthetic sequence. This transformation has been applied in the synthesis of (*E*,*E*)-10-hydroxy-3,7-dimethyldeca-2,6-dienoic acid (butterfly compound), *Latia* luciferin, and mokupalide.

General and facile synthetic methods for the stereoselective formation of substituted alkenes play an important role in the arsenal of modern organic chemistry. The wide-spread occurrence of olefinic units in many classes of natural products is a major impetus to the development of these methods. The activity of many physiologically active alkenes is dramatically dependent on the configuration of the olefinic bonds in these substances. Hence, access to stereochemically pure synthetic alkenes is of prime importance for investigations in these areas. In addition, the synthesis of many natural products rely heavily on the chemist's ability to stereoselectively generate olefinic intermediates for subsequent conversion into the target molecules.

Mono- and disubstituted alkenes are relatively easy to prepare, and control over the geometry of the latter does not impose much difficulty. However, the general and stereoselective synthesis of tri- and tetrasubstituted alkenes is challenging and has been the goal of many synthetic endeavours. There are useful solutions to this problem involving additions to acetylenes,[1] cleavage of rings,[2] sigmatropic rearrangements,[3] allylic rearrangements,[4] or additions to carbonyl compounds.[5] While these methods have their own particular synthetic values, they often have certain limitations.

About ten years ago we developed a simple and efficient method to generate the dianion of β-keto esters[6a] and trap the dianion at the γ-carbon with a variety of electrophiles—eqn (1).[6] In the ensuing decade there were many applications of this methodology to the synthesis of natural products.[7] Recently we have developed a new stereoselective method to prepare alkenes from β-keto esters—eqn (2).[8] This method also has its limitations.[8] However in combination with the γ-electrophilic substitution illustrated in eqn (1), it should prove to be very useful in a number of applications. For example, using the sequence of eqns (1) and (2) we are able to stereoselectively introduce the isoprene unit **1** into a synthetic pathway. The utility of this particular methodology is demonstrated in the three natural products syntheses discussed herein.



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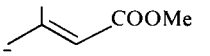
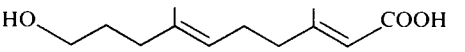


1

A. *Butterfly compound.* (*E*,*E*)-10-Hydroxy-3,7-dimethyldeca-2,6-dienoic acid (**2**).[9]

The major components in the hairpencil secretion of male danaid butterflies have been isolated and identified as a family of long chain unsaturated acids



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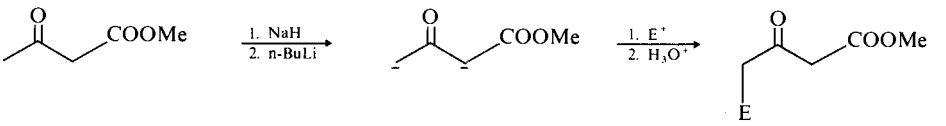
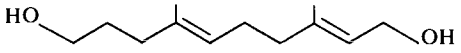


(1)

and alcohols.[10] Among them, the diol **3**[11] from the queen butterfly (*Danaus gilippus*), and the hydroxy acid **2**[12] and diacid **4**[13] from the monarch butterfly (*Danaus plexippus*) represent three closely related compounds whose exact functions still remain unknown. Since it is a formidable task to acquire even minute quantities of these substances from the natural source, further investigations of these compounds calls for their laboratory preparation.



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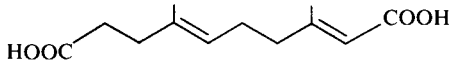

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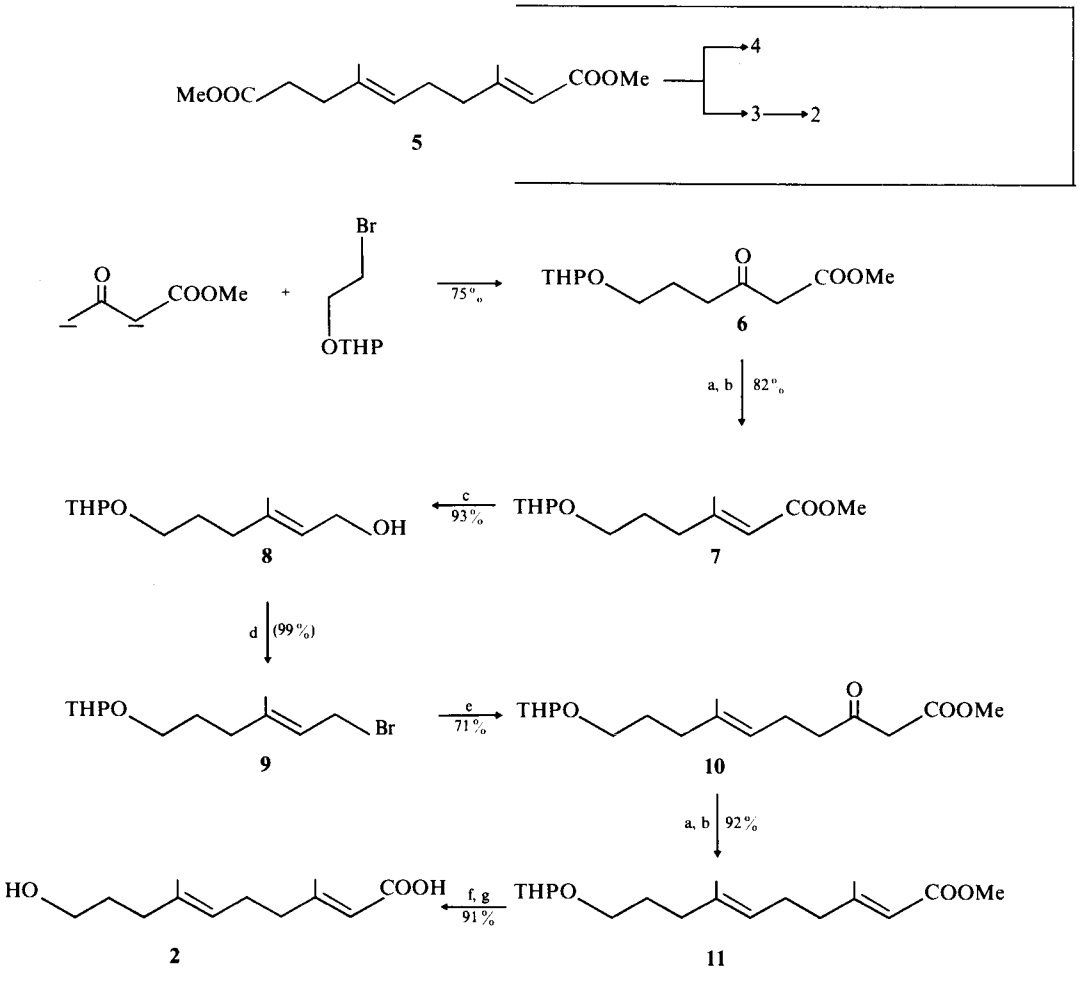
Partial syntheses of diol **3**[11] and diacid **4**[13] from (*E*,*E*)-farnesol have been reported. In a later publication, Meinwald, Johnson and coworkers[14] jointly reported an improved route to **3** and **4** via the common intermediate, diester **5** prepared by a five-step sequence from acrolein dimethyl acetal. One drawback in the synthesis of **5** was the low stereoselectivity observed in a Wittig-type reaction. Hydroxy acid **2** was also synthesized from **3** by a two-step transformation which involved a selective silver oxide oxidation. Katzenellenbogen and Christy[15] accomplished a stereoselective synthesis of diol **3** from geraniol, using the [3,3]-sigmatropic rearrangement of an allyl siloxyvinyl ether intermediate as the key step.

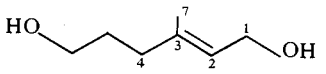
By employing the alkene synthesis developed earlier,[8] we were able to synthesize hydroxy acid **2** as shown in Scheme 1. Hydroxy acid **2** may be regarded as a precursor to both diol **3** and diacid **4**. In fact, Meinwald *et al.* have shown that **2** can be converted into diacid **4**[13] by the Cornforth oxidation and into diol **3**[12] by reduction with LAH.

The tetrahydropyranyl ether of 2-bromoethanol was allowed to react with two equivalents of the dianion of methyl acetoacetate to give **6** in 75% yield. A lower yield (*ca* 50%) of the desired product **6** and a significant amount (*ca* 30%) of recovered alkylating agent were observed when equivalent amounts of the two reactants were used. The β-keto ester **6** was then converted into its enol phosphate and treated with lithium dimethylcurprate at $-47°$ to produce the *E*-α,β-ethylenic ester **7** in 82% yield. Subsequent reduction of the ester with lithium aluminum hydride



Scheme 1. Synthesis of butterfly compound **2**. [a]NaH, $ClPO(OEt)_2$; [b]2eq $LiMe_2Cu$; [c]$LiAlH_4$; [d]LiBr, n-BuLi, $MeSO_2Cl$; [e]$CH_2COCHCOOMe$; [f]OH^-; [g]H_3O^+.

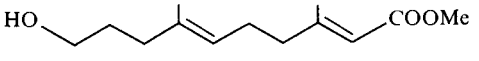
afforded the allylic alcohol **8** in excellent yield. The ^{13}C NMR of diol **12**, derived from cleavage (*p*-toluenesulfonic acid, methanol) of the tetrahydropyranyl ether protecting group in **8**, showed absorptions at δ 16.2 and 35.8 ppm, ascribable to C_7



12

and C_4 respectively. These chemical shifts were consistent with the data reported for such carbons in similar allylic alcohols with the *E* geometry[16] and provided additional evidence for the *E* configuration of the olefinic bond in ester **7**.

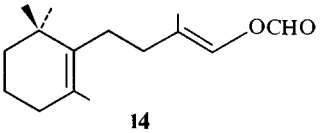
Incorporation of the second isoprene moiety was effected by conversion of alcohol **8** into the corresponding bromide **9**, followed by repetition of the foregoing reaction sequence of dianion alkylation, enol phosphate formation and lithium dimethylcuprate coupling. Several bromination methods were found unsatisfactory for the preparation of bromide **9**. However, the difficulty was circumvented by adopting Corey's procedure[17] which involved treating a mixture of alcohol **8** and lithium bromide in ether with n-butyllithium and methanesulfonyl chloride at −78° and allowing the solution to warm to room temperature. The bromide **9**, owing to its unstable nature, was used immediately to alkylate an excess of the dianion of methyl acetoacetate. β-Keto ester **10** was thus obtained in 70% yield overall from alcohol **8**. Transformation of **10** into the dienic ester **11** was accomplished in 92% yield by utilizing the enol phosphate and cuprate coupling sequence. To complete the synthesis, ester **11** was hydrolyzed with aqueous base, and then treated with aqueous acid to give the desired hydroxy acid **2** in 91% yield. The spectral data of **2** were in excellent agreement with those reported for the natural compound.[12] As a final corroboration of the structural assignments, the tetrahydropyranyl ether protecting group in **11** was cleaved (*p*-toluenesulfonic acid, methanol) to give alcohol **13** whose spectroscopic and chromatographic properties were found to be identical with those of an authentic sample.[12]



13

This synthesis of **2** demonstrates the synthetic utility of β-keto esters and their enol phosphates in the stereoselective synthesis of trisubstituted alkenes. Twice in this synthesis the isoprene equivalent **1** was stereoselectively added to an electrophile.

B. *Latia luciferin* **14**.[18]



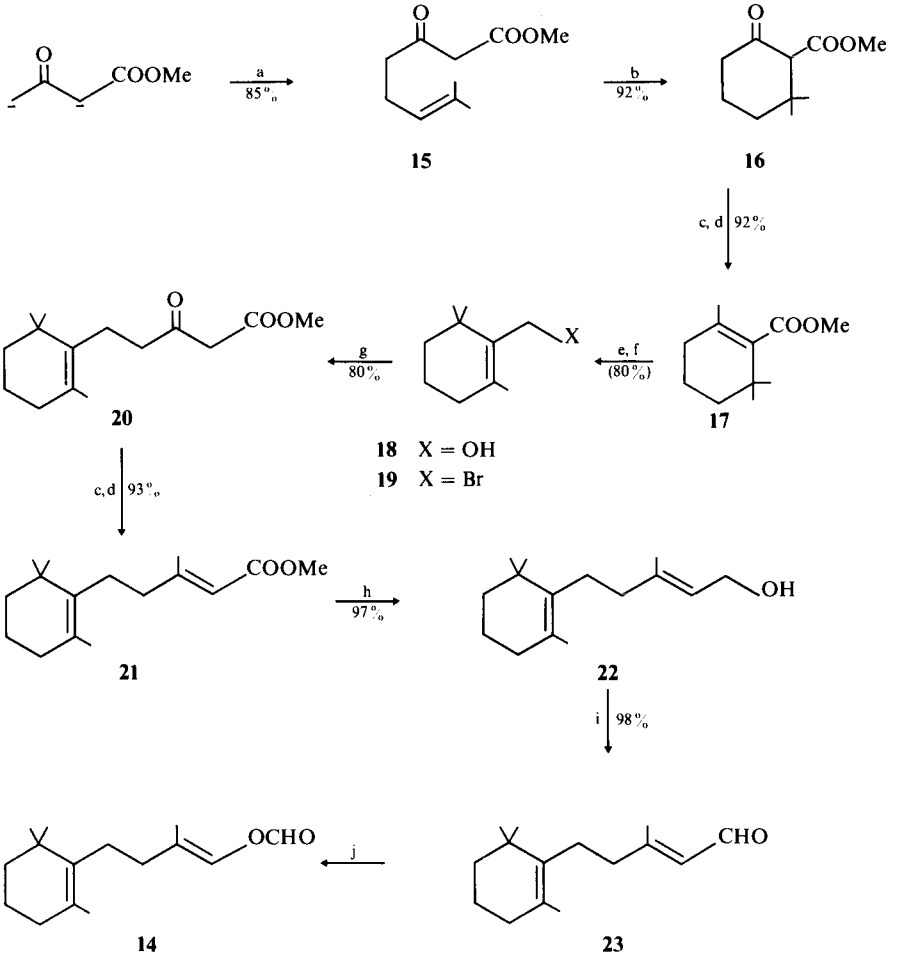
14

Latia luciferin **14** is a specific substrate of the bioluminescence enzyme in the fresh water limpet *Latia neriloides*.[19] The side-chain olefin in natural luciferin has been shown to have the *E* geometry. Nonstereoselective syntheses of *Latia* luciferin, starting from β-ionone, have been reported by two groups.[20] Magnus and Roy accomplished a third synthesis of luciferin via an intermediary α,β-epoxysilane derived from dihydro-β-ionone.[21] The last route was much improved in terms of stereoselectivity over the previous methods—only *ca* 10% of the *Z* isomer was produced.

A stereoselective synthesis of luciferin **14** was achieved, as shown in Scheme 2. Methyl β-cyclogerante (**17**) was prepared as follows. The dianion of methyl acetoacetate was alkylated with dimethylallyl bromide to give **15**[7d] in 85% yield. Exposure of **15** to stannic chloride[7c] produced the cyclic β-keto ester **16** which, upon successive treatment with sodium hydride, diethyl chlorophosphate, and lithium dimethylcuprate afforded **17** in 92% yield.

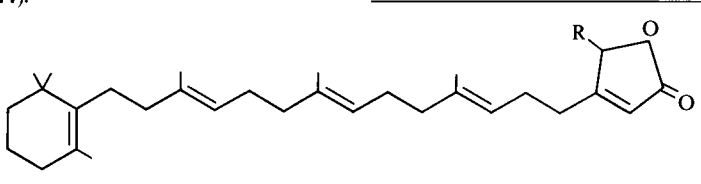
Ester **17** was reduced to alcohol **18**[22] almost quantitatively with lithium aluminum hydride. Several methods were tried to convert the hydroxy group in **18** into a leaving group appropriate for dianion alkylation. While many procedures failed to give satisfactory and reproducible results, it was found that the bromide **19** could be easily prepared, in 80% yield, by treating **18** with concentrated hydrobromic acid and n-pentane in a two-phase system at 0°.[23] The product so obtained was essentially pure according to spectroscopic analysis. Due to its thermal instability, bromide **19** was used immediately after preparation to alkylate the dianion of methyl acetoacetate to give **20**[7c] in *ca* 80% yield. Conversion of **20** into its enol phosphate, followed by reaction with lithium dimethylcuprate at −78° afforded the *E*-α,β-unsaturated ester **21** in 93% yield. No detectable amount of the *Z* isomer was observed by ^{1}H NMR and tlc analyses.

Diisobutylaluminum hydride reduction of **21** furnished the corresponding alcohol **22** which was then oxidized, with active manganese dioxide[24] in hexane, to the α,β-unsaturated aldehyde **23** in good yield. The spectral data of **23** were identical with those reported[20b] for the *E* isomer of this compound. Since aldehyde **23** has been stereoselectively transformed into the formate **14** using anhydrous hydrogen peroxide and selenium dioxide[20b] this synthesis of **23** completed our approach to *Latia* luciferin **14**.



Scheme 2. Synthesis of *Latia* luciferin **14**. [a]Me_2CCHCH_2Br; [b]$SnCl_4$; [c]NaH, $ClPO(OEt)_2$; [d]$LiMe_2Cu$; [e]$LiAlH_4$; [f]HBr; [g]$\bar{C}H_2CO\bar{C}HCOOMe$; [h]DIBAL; [i]$MnO_2$; [j]Reference 20b.

C. *Mokupalide* (**24**).[25]

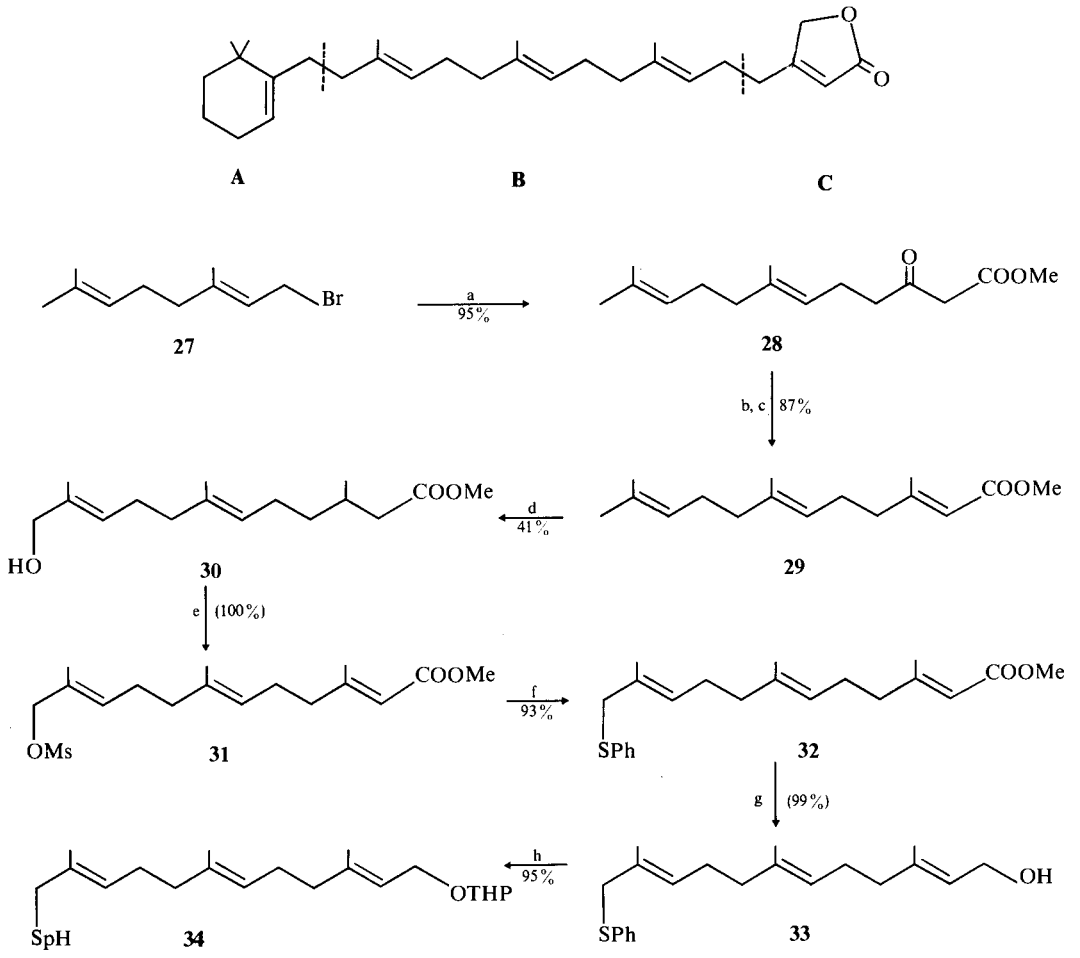


24, R = H
25, R = OH
26, R = OAc

Recently, Scheuer and Yunker isolated three novel hexaprenoids which were named mokupalide, hydroxymokupalide and acetoxymokupalide from a Pacific marine sponge.[26] The mokupalides were shown to have structures **24–26** which contain an unusual array of six isoprene units joined together in a head-to-tail fashion. Our interest in exploring the synthetic utility of the newly developed β-keto ester chemistry prompted our effort to prepare mokupalide (**24**).

A brief examination of structure **24** revealed three major synthetic objectives, viz., construction of the cyclohexene moiety, stereoselective synthesis of the three olefinic linkages with *E* geometry, and incorporation of the butenolide end group. Accordingly, the target molecule was envisioned to be composed of three units, A, B and C, as shown below. The design of our synthetic route centred upon the separate syntheses of these individual units which were assembled at appropriate stages then connected in a convergent synthesis.

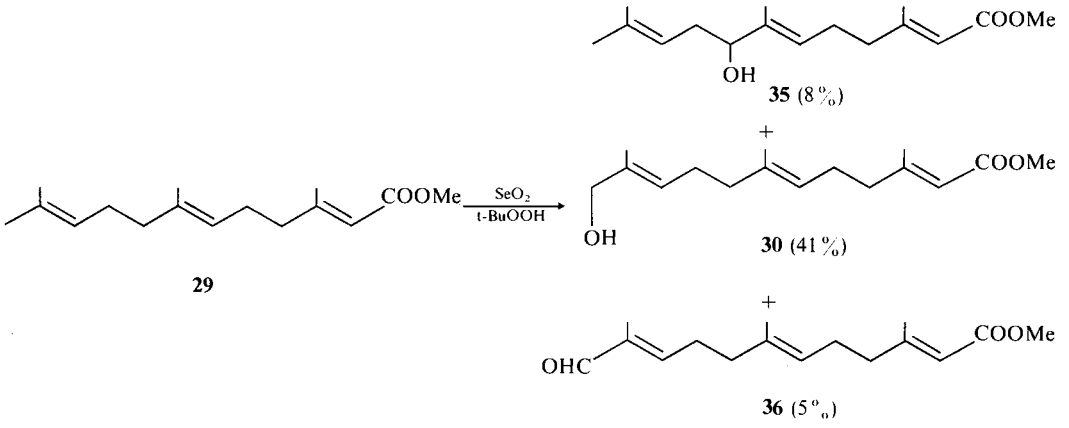
Bromide **19** (Scheme 2) served as the synthetic equivalent of subunit A. The thioether **34** is the functionalized derivative of subunit B which we



Scheme 3. Synthesis of Thioether **34**. [a]$\overline{C}H_2CO\overline{C}HCOOMe$; [b]NaH, $ClPO(OEt)_2$; [c]$LiMe_2Cu$; [d]t-BuOOH, SeO_2; [e]$MeSO_2Cl$, Et_3N; [f]PhSLi; [g]DIBAL; [h]DHP, TsOH.

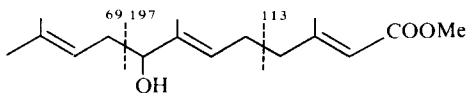
desired and a stereoselective synthesis of **34** is illustrated in Scheme 3. The dianion of methyl acetoacetate was treated with geranyl bromide (**27**) to give the alkylation product **28** in 95% yield. The β-keto ester **28** was stereoselectively converted into the *Z*-enol phosphate which was then coupled with lithium dimethylcuprate to afford (*E*,*E*)-methyl farnesoate (**29**). The above sequence invariably proceeded in greater than 85% yield and with greater than 98% stereoselectivity.

The oxidation of **29** with selenium dioxide in refluxing ethanol[27] gave unsatisfactory results. A modified procedure, developed by Umbreit and Sharpless[28] involving t-butyl hydroperoxide and a catalytic, or stoichiometric, amount of selenium dioxide was then employed. It was hoped that the mild reaction conditions of this modification might alleviate the complications encountered in using excess selenium dioxide and refluxing ethanol. Indeed, by treating **29** with selenium dioxide (0.5 eq) and 70% *t*-



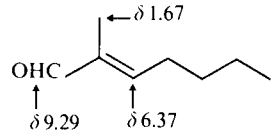
butyl hydroperoxide **29** (2 eq) in dichloromethane (4.5 hr, 10°), the allylic alcohol **30** was obtained in 41% yield along with the regioisomer **35** (8%), the aldehyde **36** (5%) and recovered **29** (19%). Careful monitoring of the reaction conditions was crucial for good results, as higher temperatures and prolonged reaction times led to significant formation of the aldehyde product and less efficient conversion into the desired alcohol **30**.

The regiochemistry of the hydroxy group in structures **30** and **35** was established by analysis of their ^{1}H NMR and mass spectral data. The ^{1}H NMR spectrum of **30** (in CCl_4) showed absorptions at δ 1.60 (s, 3 H), 3.83 (s, 2 H) and 5.25 (m, 1 H) which were ascribed to protons at C-13, C-12 and C-10 respectively. Comparison of these data with those reported for the analogous allylic alcohols *E*- and *Z*-**37**[30] (chemical shifts indicated were measured in CCl_4) confirmed the *E* geometry of the C-10 olefinic bond in **30**. Prominent mass fragments at *m/e* 181 and 149 (181–CH_4O) in the mass spectrum of **30** also supported the assigned terminal alcohol structure. Alcohol **35** exhibited a one-proton triplet (J = 7 Hz) at δ 3.93 and a one-proton multiplet at δ 5.3 in its ^{1}H NMR spectrum, which were consistent with absorptions expected for protons at C-8 and C-6 in the suggested structure. The position of the hydroxyl group in **35** was further substantiated by mass spectroscopy which showed major mass peaks at *m/e* 197, 165 (197–CH_4O) and 113, corresponding to the fragmentations illustrated below. The structure of



35

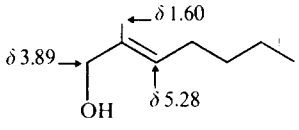
aldehyde **36** was ascertained by comparing its ^{1}H NMR absorptions at δ 1.73 (s, 3 H), 6.37 (m, 1 H) and 9.3 (d, 1 H), attributed to the C-13, C-10 and C-12 protons, with those recorded for structure **38**.[30,31]



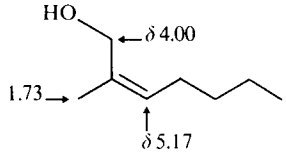
38

The allylic alcohol **30** was converted[32] into the corresponding mesylate **31**, which was immediately treated with lithium thiophenoxide in tetrahydrofuran to give sulfide **32** in 93% overall yield. The ester function in **32** was reduced with diisobutylaluminum hydride and the resulting alcohol **33** was protected as the tetrahydropyranyl ether furnishing **34** in 95% yield.

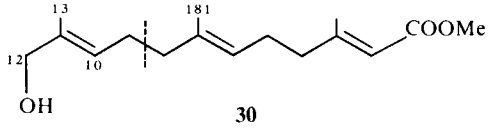
The two compounds **19** and **34**, representing the subunits A and B were assembled as shown in Scheme 4. The anion of **34**, generated by n-butyllithium in the presence of DABCO[33,34] (THF, −23°), was alkylated with bromide **19** to produce the α-alkylation product **39** in 75% yield. Biellmann and Ducep have shown that lithium in ethylamine was superior to other methods (Raney nickel, calcium-hexamine, and lithium in ammonia) for the reductive desulfurization of an allylic sulfide in polyene molecules.[34] However, it is quite inconvenient to utilize this method in small scale reactions. A nickel catalyst, prepared from nickel (II) chloride and sodium borohydride, has been developed by Truce and Roberts to desulfurize thioketals.[35] This so-called nickel boride reagent was later applied to reductively cleave benzylthioenol ethers.[36] The facility in the preparation and handling of this reagent stimulated us to test its effectiveness in the desulfurization of the allylic sulfide **39**. Indeed, when **39** was exposed to excess nickel boride in ethanol, the desulfurized compound **40** was obtained



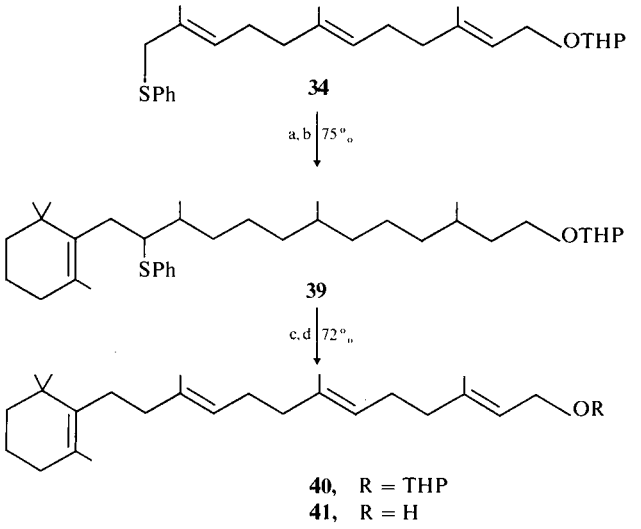
E-**37**



Z-**37**



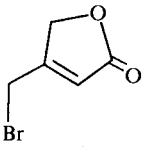
30



Scheme 4. [a]n-BuLi, DABCO; [b]**19**; [c]$NiCl_2$, $NaBH_4$; [d]TsOH, MeOH.

in *ca* 72% yield. The hydroxy group was subsequently deprotected to give alcohol **41**.

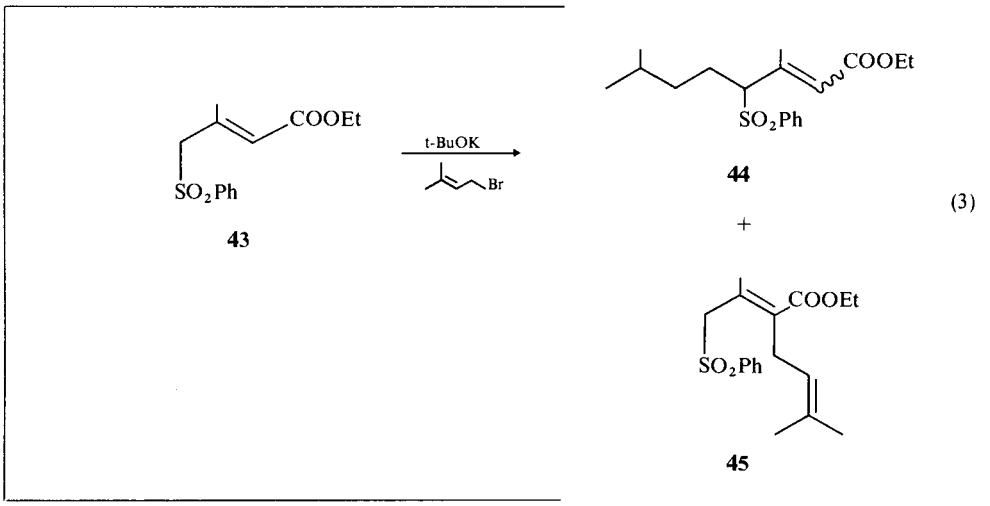
An α′-substituted 3-methyl-2-butenolide is the synthetic equivalent to subunit C. Recently Martin *et al.*[37] have reported a facile synthesis of 3-bromomethyl-2-butenolide (**42**). In a preliminary



42

attempt to assemble the mokupalide skeleton the carbanion of the phenylthioether derived from **41** (–OH → SPh) was treated with the bromo butenolide **42**. Only starting materials were recovered from this reaction. Presumably, proton exchange between the butenolide and the thioether carbanion occurred faster than the desired alkylation. On the basis of this result, it appeared more feasible to use the butenolide as the nucleophile and a derivative of **41** as the alkylating agent in the assembling process.

Julia and Arnould achieved the γ-alkylation of the α,β-unsaturated ester **43** with 1-bromo-3-methyl-2-butene, in tetrahydrofuran, using potassium t-butoxide as base (eqn 3).[38] The γ- and α-alkylation products, **44** (a mixture of *E* and *Z* isomers) and **45**, were obtained in a ratio of 89:11. More recently, the anions of γ-phenylsulfonyl-α,β-unsaturated ketones were reported to undergo selective γ-alkylations with alkyl halides in polar solvent systems.[39] The sulfonyl butenolide **46** was therefore chosen to introduce the butenolide end group C in the final coupling step. Treatment of bromide **42** with sodium benzenesulfinate in dimethylformamide (DMF) at ambient temperature afforded the sulfone **46** in 85% yield. Alkylation of the anion derived from **46** and sodium hydride[39a] (or potassium t-butoxide[39b]) in DMF (or t-butyl alcohol) invariably gave significant quantities of the dialkylated product **48** (eqn 4). This complication

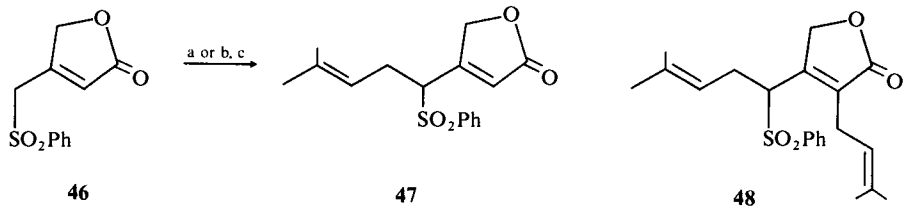


(3)

was alleviated by employing an excess of the sulfonyl anion in the alkylation. With such modification, a markedly improved yield of the desired product **47** was attained. This use of excess **46** is not detrimental when the alkylating agent is the more hard won reagent (as in the application below).

80% yield of mokupalide (**24**). The IR, ^{1}H NMR and mass spectral data of this synthetic product were identical with those of the natural compound.[26]

The above synthesis represents the first synthesis of mokupalide **24** and provides a route which possibly can lead to hydroxymokupalide **25**, and hence

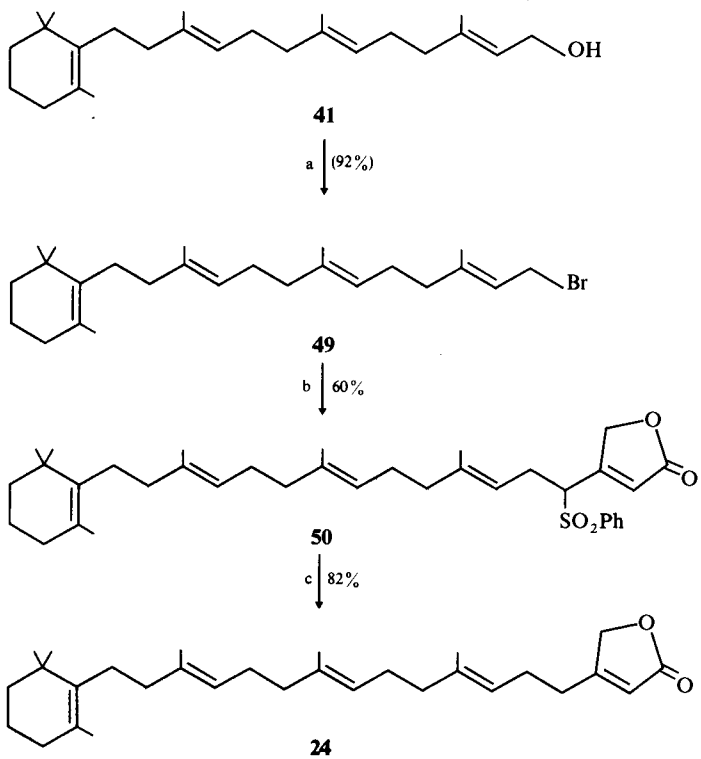


(4)

[a]t-BuOK, t-BuOH; [b]NaH, DMF (or THF-HMIA); [c]Me_2CCHCH_2Br

Scheme 5 illustrates the final steps in the synthesis of mokupalide (**24**). Alcohol **41** was converted into the bromide **49** by successive treatment with lithium bromide, n-butyllithium and methanesulfonyl chloride.[17] This unstable bromide was immediately alkylated with an excess of the anion of sulfone **46** in DMF at room temperature to produce the coupled compound **50** in 60% yield from alcohol **41**. The sulfonyl group in **50** was removed reductively with 6% sodium amalgam in methanol[40] to give a greater than acetoxymokupalide **26**, via functionalization of the butenolide moiety.[41]

In summary the enol phosphate–dimethylcuprate alkene synthesis is shown to be applicable to the synthesis of acyclic and cyclic alkenes which may be tri- or tetrasubstituted. The method is stereoselective (we have subsequently found that the method can be stereospecific[42]) and when combined with the alkylation of β-keto ester dianions[6] provides a useful route to isoprenoid compounds.



Scheme 5. Final stages of the synthesis of mokupalide (**24**). [a]LiBr, n-BuLi, MsCl; [b]anion of **46**; [c]Na-Hg, MeOH

EXPERIMENTAL

All temps are stated in degree centigrade. Kugelrohr distillations were performed by means of a Büchi Kugelrohr thermostat. Infrared spectra were recorded in $CHCl_3$ soln (unless otherwise noted), on Perkin–Elmer Model 700 or 710B spectrophotometers, and were calibrated with the 1601 cm^{-1} band of polystyrene. PMR spectra were recorded on Varian Model T-60, HA-100 or XL-100 spectrometers, in $CDCl_3$ soln unless otherwise specified. Chemical shifts are reported in the δ scale using TMS as an internal standard. The multiplicity, coupling constants (if observable) and integrated peak area are indicated in parenthesis after each signal. Low resolution mass spectra were recorded on an Atlas CH-4B mass spectrometer, and high resolution mass measurements were obtained using an AEI MS-9 or MS-50 mass spectrometer. All instruments were operated at an ionizing potential of 70 eV. All mass measurements are reported in atomic mass units. Elemental microanalyses were performed by Mr. Peter Borda, University of British Columbia. The silica gel used was supplied by E. Merck. Silica Gel PF-254 was used for both analytical and preparative tlc, whilst the grade 100–200 mesh ASTM was used for column chromatography. All solvent systems are expressed in ratios by volume (v/v). Vapor phase chromatographic (vpc) analyses were conducted on a Hewlett–Packard Model 5830-A chromatograph using 6 ft. × 1/8 in. columns of 3% OV-17 or 3% OV-101.

The petroleum ether used has the boiling range 30–60°. Dry ethyl ether and THF were obtained by distillation from LAH. CH_2Cl_2 and methanesulfonyl chloride were dried by distilling from P_2O_5. Dry DMF and hexamethyl phosphoramide (HMPA) were obtained by refluxing over calcium hydride, followed by distillation under reduced pressure. Triethylamine was purified and dried by distilling from barium oxide. The anhyd stannic chloride used was reagent grade material purchased from Fisher Scientific Company Ltd. Diethyl chlorophosphate supplied by Aldrich Chemical Company, Inc. was used directly without purification and was handled under dry N_2 at all times. MeLi (in ether), n-BuLi (in hexane) and sec-BuLi (in cyclohexane) were obtained from Aldrich Chemical Company, Inc., while EtLi (in benzene) and t-BuLi (in pentane) were supplied by Alfa Division, Ventron Corporation. The alkyllithium solns were standardized by titration against a 1.0 M soln of t-BuOH in benzene, using 1,10-phenanthroline as indicator. Sodium hydride (from Alfa Division, Ventron Corporation) was weighed as a 50% dispersion in mineral oil and was washed with dry ether to remove the oil prior to use.

General procedure for the preparation of the Z-enol phosphate of β-keto esters

To a stirred suspension of NaH (1.1 eq) in dry ethyl ether, kept under a dry N_2 and cooled in an ice-bath, was added a soln of the β-keto ester (1.0 eq) in ethyl ether. After 15–20 min at 0° (or 10 min at room temp), 1.1 eq of diethyl chlorophosphate was introduced and stirring was continued for 1–2 hr at 0° (or room temp). Progress of the reaction could be easily monitored by tlc. Although the β-keto ester enolate was usually found to react within 30 min at 0°, the reaction was allowed to proceed for a longer period of time to ensure completeness of the transformation. The enol phosphate was isolated from the mixture by either of the following work-up procedures:

(a) For less than 5 mmol scale preparations, the reaction mixture was stirred with excess solid ammonium chloride for 20 min, filtered through celite, and the filtrate was concentrated in vacuo.

(b) For larger than 5 mmol scale preparations, the mixture was quenched with aqueous ammonium chloride and diluted with ethyl ether. The ether soln was then washed with sat $NaHCO_3$ aq, dried over $MgSO_4$ and evaporated under reduced pressure.

The crude enol phosphate so obtained was essentially pure by spectroscopic and chromatographic analyses, and was used directly in reactions with lithium dialkylcuprates.

General procedures for the generation and work-up of lithium dimethylcuprate reactions.

Two equivs of MeLi (in ethyl ether) was added dropwise to a stirred suspension of 1 eq of cuprous iodide (purified according to Kauffman's procedure[43]) in dry ethyl ether at 0° and under a dry N_2. The resulting light tan soln was used for coupling reaction at the appropriate temp.

The mixture was worked up by pouring it into an ice-cold mixture of 50% aqueous ammonium chloride and concd ammonium hydroxide (*ca* 5:1), and the aqueous phase was extracted with ethyl ether. The combined ether extracts were washed with brine, dried over $MgSO_4$ and then concentrated under reduced pressure.

A. *Butterfly compound* (**2**)

Methyl 3-oxo-6-(2-tetrahydropyranyloxy)hexanoate (**6**). A soln of the dianion of methyl acetoacetate was generated [6b] from 6.96 g (60 mmol) of methyl acetoacetate, 3.02 g (63 mmol) NaH (50%) and 37.5 mL (60 mmol) n-BuLi (1.6 M) in 130 mL dry THF. To this soln, cooled in an ice-bath, was added 6.27 g (30 mmol) 2-bromoethanol tetrahydropyranyl ether (prepared from 2-bromoethanol[44]). The resulting yellow suspension was stirred for 2 hr at 0° and then poured into 200 mL ice-cold satd NH_4Cl aq. The aqueous phase was extracted with 2 × 200 mL ethyl ether and the combined organic soln was washed with brine and dried over Na_2SO_4. The crude product obtained after removal of solvents was Kugelrohr distilled to yield 5.46 g (75%) of **6** as a colorless oil: b.p. 116–118°/0.1 Torr; IR 1745, 1715, 1655, 1630, 1440 and 1030 cm^{-1}; ^1H NMR δ 1.2–2.2 (m, 8 H), 2.63 (t, J = 7 Hz, 2 H), 3.45 (s, 2 H), 3.2–4.1 (m, 4 H), 3.71 (s, 3 H), and 4.5 (m, 1 H); mass spectrum *m/e* (rel intensity) 244 (2), 190 (4), 159 (8), 143 (65), 142 (65), 111 (89), 101 (38), 85 (99), 84 (67), 83 (32), 69 (100), 55 (71) and 41 (40). (Found: C, 58.80; H, 8.27. Calc. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25%.)

Methyl Z-3-(diethylphosphoryloxy)-6-(2-tetrahydropyranyloxy)hex-2-enoate. The enol phosphate was prepared from 12.96 g (53.0 mmol) of **6**, 2.80 g (58.3 mmol) NaH, and 8.43 mL (58.3 mmol) diethyl chlorophosphate in ether at 0° as outlined above. The yield of crude product, suitable for the coupling step, was quantitative and this product had the following spectral data. IR 1725, 1670, 1280 and 1030 cm^{-1}; ^1H NMR δ 1.36 (t, J = 7 Hz, 6 H), 1.2–2.2 (m, 8 H), 2.53 (br t, J = 7 Hz, 2 H), 3.2–4.0 (m, 4 H), 3.65 (s, 3 H), 4.22 (qn, J = 7 Hz, 4 H), 4.50 (m, 1 H) and 5.33 (s, 1 H); mass spectrum *m/e* (rel intensity) 380 (0.1), 349 (2), 296 (5), 279 (6), 251 (8), 219 (10), 155 (100), 142 (42), 127 (18), 111 (25), 99 (20) and 85 (17).

High Resolution Mass Measurement Calc. for $C_{15}H_{26}O_7P$ (P^+–OCH_3): 349.1416. Found: 349.1443.

Methyl E-3-methyl-6-(2-tetrahydropyranyloxy)-hex-2-enoate (**7**). To a soln of lithim dimethylcuprate (8.4 mmol) in ethyl ether, cooled to −47°, was added 1.6 g (4.2 mmol) of the above enol phosphate (dissolved in 2 mL ether). The resulting reddish purple mixture was stirred at −47° for 2 hr and then worked up according to the above general procedure. The crude product (1.02 g, *ca* 100% yield) obtained was 97% pure **7** by vpc analysis (3% OV-17 column, 150°). Preparative tlc (silica gel, 8:1 CCl_4-ethyl ether) of 90 mg of the crude product yielded 74 mg (82%) of **7** (pure by vpc) as a colorless liquid; bp (Kugelrohr distillation) 110–112°/0.1 Torr; IR 1715, 1650, 1155 and 1030 cm^{-1}; ^1H NMR δ 1.2–2.4 (m, 10 H), 2.13 (br s, 3 H), 3.0–4.0 (m, 4 H), 3.63 (s, 3 H), 4.50 (m, 1 H) and 5.63 (m, 1 H); mass spectrum *m/e* (rel intensity) 242 (0.1), 158 (20), 141 (8), 127 (9), 112 (6), 109 (8), 85 (100), 81 (10) and 41 (10). (Found: C, 64.23; H, 9.24. Calc. for $C_{13}H_{22}O_4$: C, 64.44; H, 9.12%.)

E-3-Methyl-6-(2-tetrahydropyranyloxy)hex-2-en-1-ol (**8**). A soln of 3.63 g (15 mmol) of **7** in dry ethyl ether (10 mL) was added dropwise to a suspension of 374 mg (9.4 mmol) LAH in

60 mL of anhyd ethyl ether at room temp with constant stirring. The mixture, kept under N_2, was heated under reflux for 1 hr. About 4 mL of 5% NaOH aq was then introduced and stirring was continued for 45 min. The resulting suspension was filtered through anhyd Na_2SO_4 and the residue was eluted with more ethyl ether. The combined filtrate was concentrated under reduced pressure to give 3.16 g (98%) of crude **8** which was very pure by tlc (silica gel, 1:1 CCl_4–ethyl ether) and spectroscopic analyses. Purification of the crude product by Kugelrohr distillation furnished 2.98 g (93%) of **8**: colorless oil; b.p. 98–100°/0.05 Torr; IR 3670, 3500 and 1670 cm^{-1}; ^1H NMR δ 1.2–2.3 (m, 11 H), 1.67 (s, 3 H), 3.1–3.9 (m, 4 H), 4.09 (d, J = 7 Hz, 2 H), 4.50 (m, 1 H) and 5.38 (br t, J = 7 Hz, 1 H); mass spectrum *m/e* (rel intensity) 214 (0.5), 196 (1), 130 (5), 112 (6), 101 (10), 97 (11), 85 (100), 84 (20), 69 (10), 67 (14), 57 (15), 55 (15), 43 (14) and 41 (25).

High resolution mass measurement Calc. for $C_{12}H_{22}O_3$: 214.1569. Found: 214.1579.

E-1-Bromo-3-methyl-6-(2-tetrahydropyranyloxy)-2-hexene (**9**). A mixture of **8** (1.50 g, 7.0 mmol) and anhyd LiBr (1.97 g, 23 mmol) in dry ethyl ether (70 mL) was cooled to −78° and kept under N_2. To this stirred mixture was added 4.4 mL (7.0 mmol) n-BuLi (1.6 M in hexene), followed (after 20 min) by 0.57 mL (7.4 mmol) methanesulfonyl chloride. The resulting mixture was warmed to −10° over 1 hr, maintained at −10° for 0.5 hr and then stirred for 6 hr without the cooling bath. The final suspension was poured into 30 mL ice-cold 5% $NaHCO_3$ aq and the aqueous phase was separated and extracted with 30 mL ethyl ether. The combined ether soln was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude **9** (1.91 g, 99%), obtained as a slightly tan oil, showed satisfactory spectral data: IR 1660, 1120, and 1030 cm^{-1}; ^1H NMR δ 1.1–2.4 (m, 10 H), 1.72 (s, 3 H), 3.1–3.9 (m, 4 H), 3.95 (d, J = 8 Hz, 2 H), 4.52 (m, 1 H), and 5.5 (br t, J = 8 Hz, 1 H); mass spectrum *m/e* (rel intensity) 122 (P–C_5H_9O–Br, 11), 98 (13), 97 (100), 85 (33), 84 (77), 83 (38), 71 (12), 69 (13), 67 (16), 56 (24), 55 (93), 54 (21), 43 (45) and 41 (34). Since **9** was sensitive to distillation and chromatographic purification conditions (the crude material decomposed quite rapidly on standing at room temp) no satisfactory analytical data could be obtained.

Methyl E-7-methyl-3-oxo-10-(2-tetrahydropyranyloxy)dec-6-enoate (**10**). A soln of the dianion of methyl acetoacetate (2.44 g, 21 mmol) in dry THF (50 mL) was prepared[6b] and to this was added 1.91 g (6.9 mmol) of crude **9** at 0°. The resulting yellow suspension was stirred for 2 hr at 0° and then worked up in the same way as for **6**. Kugelrohr distillation of the crude product obtained gave 1.53 g (71%) of the alkylation product **10**: b.p. 120–122°/0.04 Torr; IR 1745 and 1715 cm^{-1}; ^1H NMR δ 1.2–2.7 (m, 14 H), 1.63 (s, 3 H), 3.1–3.9 (m, 4 H), 3.4 (s, 2 H), 3.71 (s, 3 H), 4.52 (m, 1 H), and 5.05 (m, 1 H); mass spectrum *m/e* (rel intensity) 312 (0.8), 248 (10), 228 (7), 220 (5), 210 (4), 206 (4), 192 (7), 170 (5), 164 (5), 155 (14), 152 (5), 149 (5), 143 (15), 130 (6), 127 (7), 101 (9), 95 (11), 94 (15), 85 (83). 84 (83), 83 (40), 69 (20), 67 (14), 56 (35), 55 (100), 54 (32), 43 (35), and 41 (35). (Found: C, 65.38; H, 9.20. Calc. for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03%.)

Methyl (E,E)-*3,7-dimethyl-10-(2-tetrahydropyranyloxy)-deca-2,6-dienoate* (**11**). The enol phosphate of **10** (230 mg, 0.74 mmol) was prepared as above in 5 mL dry ethyl ether and added through a two-way needle into an ether soln of lithium dimethylcuprate (1.5 mmol), cooled to −78°. The resulting orange-yellow suspension was stirred for 0.5 hr at −78° and then for 2 hr at −47° (mixture turned purple after 20 min at −47°). The mixture was worked up in the above manner to give 260 mg crude product, which upon preparative tlc (silica gel, 4:1 CCl_4-ethyl ether) afforded 210 mg (92%) of **11** as a colorless liquid: bp (Kugelrohr distillation) 108–110°/0.04 Torr; IR 1710 and 1650 cm^{-1}; ^1H NMR δ 1.1–2.5 (m, 14 H), 1.61 (s, 3 H), 2.14 (d, J = 1.4 Hz, 3 H), 3.1–4.0 (m, 4 H), 3.64 (s, 3 H), 4.52 (m, 1 H), 5.05 (m, 1 H) and 5.61 (m, 1 H); mass spectrum *m/e* (rel intensity) 310 (0.6), 279 (0.7), 278 (0.7), 227 (4), 226 (11), 196 (5), 195 (6), 194 (4), 149 (5), 121 (4), 114 (18), 95 (43), 85 (100), 84 (12), 83 (14), 67 (12), 55 (16), 43 (11) and 41 (14). (Found: C, 69.80; H, 9.92. Calc. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74%.)

(E,E)-*10-Hydroxy-3,7-dimethyldeca-2,6-dienoic acid* (**2**). To a soln of 42 mg (0.14 mmol) of **11** in MeOH (2 mL) was added 1 mL 5% NaOH aq. After stirring for 3 hr at 60°, the MeOH was evaporated under reduced pressure and the aqueous soln was acidified with 5% HCl. Dioxane was introduced (*ca* 2 mL) until a homogeneous soln was formed, which was stirred for 1 hr at room temp. The resulting mixture was saturated with NaCl and extracted with ethyl ether. The ether soln was dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was partitioned between 10% $NaHCO_3$ aq and $CHCl_3$. Acidification of the bicarbonate phase with conc HCl, followed by extraction with ethyl ether, and drying ($NaSO_4$) and evaporation of the ether extracts furnished 26 mg (91%) of **2**. The spectra data of this synthetic material were in excellent agreement with those reported previously for the natural compound[12]: IR 3600, 3400–2600 (broad), 1690 and 1640 cm^{-1}; ^1H NMR δ 1.2–2.4 (m, 8 H), 1.6 (s, 3 H), 2.15 (s, 3 H), 3.58 (t, J = 6 Hz, 2 H), 5.05 (m, 1 H), 5.62 (m, 1 H) and 6.73 (br s, 2 H, exchangeable with D_2O); mass spectrum *m/e* (rel intensity) 212 (2), 195 (10), 194 (13), 166 (11), 135 (10), 125 (12), 113 (14), 111 (15), 100 (18), 97 (17), 96 (16), 95 (94), 85 (100), 69 (16), 67 (24), 55 (26), 43 (52) and 41 (27).

High resolution mass measurement Calc. for $C_{12}H_{20}O_3$: 212.1412. Found: 212.1429.

E-*3-Methyl-1,6-hex-2-enediol* (**12**). A soln of 0.200 g (0.9 mmol) of **8** and 0.010 g *p*-toluenesulfonic acid is 10 mL dry MeOH were stirred at room temp for 3 hr under N_2. The MeOH was evaporated and the residue was dissolved in ethyl ether. The etheral soln was washed with 10% $NaHCO_3$ aq and dried over $MgSO_4$. Evaporation of the organic solvent gave 0.105 g of product which was essentially pure by tlc: ^{13}CNMR δ 16.20, 30.58, 35.80, 59.24, 62.38, 123.91 and 139.01.

Methyl (E,E)-*10-hydroxy-3,7-dimethyldeca-2,6-dienoate* (**13**). The x-ester **11** (200 mg, 0.64 mmol) and 10 mg *p*-toluenesulfonic acid were dissolved in 10 mL dry MeOH and stirred for 2 hr at room temp. The soln was then concentrated under reduced pressure and the residue was diluted with ethyl ether, washed with sat $NaHCO_3$ aq and dried over $MgSO_4$. Evaporation *in vacuo* yielded 143 mg (99%) of **13** which was identical with an authentic sample[12] by vpc (3% OV-17 column, 150°) as well as tlc (silica gel, 1:1 CCl_4-ethyl ether) analyses. The spectral properties of **13** were in excellent agreement with those of the authentic material: IR (CH_2Cl_2) 3670, 1715, 1650, 1220 and 1150 cm^{-1}; ^1H NMR δ 1.2–2.4 (m, 9 H), 1.61 (s, 3 H), 2.14 (d, J = 1.4 Hz, 3 H), 3.56 (t, J = 6 Hz, 2 H), 3.64 (s, 3 H), 5.06 (m, 1 H) and 5.60 (br s, 1 H); mass spectrum *m/e* (rel intensity) 226 (6), 208 (3), 196 (10), 195 (10), 194 (8), 167 (11), 166 (10), 114 (50), 95 (100), 85 (29), 83 (22), 82 (18), 69 (24), 67 (30), 55 (29), 43 (16) and 41 (28).

B. *Latia luciferin* 14

Methyl 7-methyl-3-oxooct-6-enoate (**15**). A soln of the dianion of methyl acetoacetate in dry THF (200 mL), prepared[6b] from 11.6 g (0.10 mol) methyl acetoacetate, 5.28 g (0.11 mol) NaH (50% oil) and 65.6 mL (0.105 mol) n-BuLi (1.6 M), was treated with 11.6 mL (0.10 mol) 1-bromo-3-methyl-2-butene at 0°. The mixture was stirred for 1 hr 45 min at 0° and then worked up as described in the preparation of **6** to give 18.6 g crude product. Distillation through a Vigreux column afforded 15.7 g (85%) of **15**: b.p. 67–68°/0.1 Torr; IR 1745, 1718 and 1640 cm^{-1}; ^1H NMR δ 1.6 (s, 3 H), 1.65 (s, 3 H), 1.95–2.73 (m, 4 H), 3.40 (s, 2 H), 3.70 (s, 3 H) and 5.0 (m, 1 H); mass spectrum *m/e* (rel intensity) 184 (13), 169 (10), 166 (15), 153 (10), 149 (24), 129 (19), 116 (27), 111 (38), 110 (35), 109 (20), 101 (42), 95 (48), 83 (36), 82 (75), 74 (100), 69 (98), 67 (64), 59 (35), 55 (45), 43 (48) and 41 (99). (Found: C, 65.35; H, 8.96. Calc. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75%.)

Methyl 2,2-dimethyl-6-oxocyclohexanecarboxylate (**16**). To a soln of 9.0 mL (77 mmol) anhyd stannic chloride in dry CH_2Cl_2 (200 mL), kept under dry N_2 and cooled in an ice-bath, was added 12.9 g (70 mmol) of **15** dissolved in 15 mL dry

CH_2Cl_2. The resulting soln was stirred at room temp for 18 hr and then poured into 100 mL ice-cold water. The aqueous phase was extracted with 3 × 150 mL ethyl ether, and the combined extracts were washed with 50% brine until neutral and dried over $MgSO_4$. Removal of solvents under reduced pressure gave rise to 12.9 g crude product which contained essentially pure **16** according to its spectral and chromatographic data. Distillation of the crude material afforded 11.9 g (92%) of **16**: b.p. 64–66°/0.1 Torr; IR 1750 (shoulder), 1730 and 1710 cm^{-1}; ^1H NMR δ 1.02 (s, 3 H), 1.08 (s, 3 H), 1.2–2.1 (m, 4 H), 2.1–2.7 (m, 2 H), 3.13 (s, 1 H) and 3.65 (s, 3 H); mass spectrum *m/e* (rel intensity) 184 (26), 169 (20), 153 (38), 141 (19), 137 (53), 111 (58), 100 (68), 83 (85), 74 (74), 69 (79), 55 (100), 43 (96) and 41 (87). (Found: C, 65.00; H, 8.55. Calc. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75%.)

Methyl 2-(diethylphosphoryloxy)-6,6-dimethylcyclohexenecarboxylate. This enol phosphate was prepared according to the above procedure in quantitative yield from 5.52 g (30 mmol) of **16**, 1.58 g (33 mmol) NaH, and 4.8 mL (33 mmol) diethyl chlorophosphate in ether at 0°. The crude product was suitable for the coupling step and it had the following spectral data: IR 1725, 1680, 1280 and 1030 cm^{-1}; ^1H NMR δ 1.15 (s, 6 H), 1.2–1.9 (m, 4 H), 1.32 (t, J = 7 Hz, 6 H), 2.4 (m, 2 H), 3.70 (s, 3 H) and 4.10 (qn, J = 7 Hz, 4 H); mass spectrum *m/e* (rel. intensity) 320 (7), 288 (100), 273 (28), 260 (25), 245 (17), 232 (24), 217 (28), 137 (10), 128 (8) and 99 (10).

High resolution mass measurement Calc. for $C_{14}H_{25}O_6P$: 320.1389. Found: 320.1403.

Methyl 2,6,6-trimethylcyclohexenecarboxylate (**17**). A soln of 9.3 g (30 mmol) of the above enol phosphate in dry ethyl ether (5 mL) was added to a stirred soln of lithium dimethylcuprate (60 mmol) in ethyl ether (150 mL) at 0°. The resulting dark purple mixture was maintained at 0° for 5 hr and then worked up according to the above procedure. The crude product (5.95 g) was distilled (Kugelrohr) to give 5.03 g (92%) of **17** as a colorless liquid: b.p. 81–83°/3.5 Torr; IR 1710, 1660 (weak) and 1070 cm^{-1}; ^1H NMR δ 1.08 (s, 6 H), 1.2–2.1 (m, 6 H), 1.64 (s, 3 H) and 3.69 (s, 3 H); mass spectrum *m/e* (rel intensity) 182 (36), 167 (80), 151 (25), 135 (100), 123 (67), 107 (48), 81 (9), 79 (10) and 77 (8). (Found: C, 72.20; H, 9.87. Calc. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95%.)

β-Cyclogeraniol (**18**). To a stirred suspension of LAH (95%; 44 mg, 1.1 mol) in anhyd ethyl ether (4 mL) was added dropwise an ether soln of **17** (182 mg, 1.0 mmol) at room temp. The resulting mixture was brought to reflux under dry N_2 for 2 hr and then cooled in an ice-bath, followed by quenching with 0.4 mL of 5% NaOH aq. Stirring was continued for 30 min at room temp and the resulting suspension was filtered through anhyd $MgSO_4$. The residue was washed several times with ethyl ether and the combined filtrate was evaporated under reduced pressure to give 151 mg (98%) of **18** which was homogeneous on tlc (silica gel, 5:1 CCl_4–ethyl ether) and was 99% pure by vpc (3% OV-101 column) analysis. An analytical sample of **18** was obtained by Kugelrohr distillation of the crude material: b.p. 55–57°/0.2 Torr; m.p. 41°; IR 3670, 3500 and 1650 (weak) cm^{-1}; ^1H NMR δ 1.05 (s, 6 H), 1.3–1.7 (m, 4 H), 1.73 (s, 3 H), 1.8–2.1 (m, 2 H) and 4.10 (s, 2 H); mass spectrum *m/e* (rel intensity) 154 (28), 139 (21), 136 (32), 123 (43), 121 (100), 105 (13), 93 (30), 79 (22) and 41 (16). (Found: C, 77.72; H, 11.91. Calc. for $C_{10}H_{18}O$: C, 77.87; H, 11.76%.)

1-Bromomethyl-2,6,6-trimethyl-1-cyclohexene (**19**). A prechilled soln of 48% HBr (50 mL) was added to 1.22 g (7.0 mmol) of **18** with cooling in an ice-bath'. The mixture, kept under N_2, was stirred for 10 min then 30 mL n-pentane was introduced. Stirring was continued for 3 hr at 0°. The two-phase mixture was then poured into ice-cold water, and the aqueous layer was extracted with n-pentane. The combined extracts were washed with sat $NaHCO_3$ aq and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product **19** (1.40 g, 82%) so obtained was homogeneous by tlc analysis (silica gel, 6:1 CCl_4–ethyl ether) and had satisfactory spectral data: pale yellow oil; IR 1645 cm^{-1}; ^1H NMR δ 1.1 (s, 6 H), 1.3–1.7 (m, 4 H), 1.72 (s, 3 H), 2.0 (m, 2 H) and 4.02 (s, 2 H); mass spectrum *m/e* (rel intensity) 137 (P^+–Br, 18), 136 (P^+–HBr, 49), 121 (100), 107 (21), 93 (30) and 79 (17).

Methyl 3-oxo-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-pentanoate (**20**). The dianion of methyl acetoacetate (102 mg, 0.88 mmole) was generated in THF.[6b] To this dianion soln, cooled in an ice-bath, was added 174 mg (0.80 mmol) of the crude bromide **19**. The resulting yellow suspension was stirred for 1 hr 45 min at 0° and then worked up in the usual manner (see **6**). The crude product (181 mg) was chromatographed on silica gel with 5:1 petroleum ether–ethyl ether to afford 160 mg (80%) of **20** as a colorless liquid: IR 1745, 1715, 1655 and 1635 cm^{-1}; ^1H NMR δ 0.97 (s, 6 H), 1.3–1.7 (m, 4 H), 1.55 (s, 3 H), 1.7–2.8 (m, 6 H), 3.40 (s, 2 H) and 3.68 (s, 3 H); mass spectrum *m/e* (rel intensity) 252 (33), 234 (47), 221 (33), 220 (94), 163 (51), 159 (82), 145 (94), 137 (6), 136 (93), 129 (53), 123 (90), 121 (100), 119 (50), 107 (82), 105 (75), 95 (91), 93 (94), 91 (77), 81 (90), 79 (86), 69 (58), 67 (61), 59 (50), 55 (90), 43 (72) and 41 (98).

High resolution mass measurement Calc. for $C_{15}H_{24}O_3$: 252.1726. Found: 252.1726.

Methyl E-3-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)pent-2-enoate (**21**). The *Z*-enol phosphate of **20** (72 mg, 0.28 mmol) in ethyl ether was prepared in the same manner as described above. This enol phosphate soln was syringed into a soln of lithium dimethylcuprate (0.56 mmol) in dry ethyl ether (3 mL), cooled at −78°. The resulting purple mixture was stirred at −78° for 2 hr and then warmed to −47° over 2 hr. The mixture was worked up according to the above procedure to give 110 mg of crude product which, after preparative tlc (silica gel, 20:1 CCl_4–ethyl ether) purification, furnished 65 mg (93%) of **21**: colorless liquid; b.p. (Kugelrohr distillation) 86–88°/0.02 Torr; IR 1715 and 1650 cm^{-1}; ^1H NMR δ 1.0 (s, 6 H), 1.2–1.7 (m, 4 H), 1.57 (s, 3 H), 1.7–2.1 (m, 2 H), 2.13 (d, J = 1.5 Hz, 3 H), 2.17 (br s, 4 H), 3.63 (s, 3 H) and 5.61 (br s, 1 H); mass spectrum *m/e* (rel intensity) 250 (10), 219 (4), 176 (5), 138 (13), 137 (100), 121 (9), 114 (40), 95 (30), 81 (15) and 41 (10). (Found: C, 76.80; H, 10.40. Calc. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47%.)

E-3-Methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)pent-2-en-1-ol (**22**). To a soln of 43 mg (0.17 mmol) of **21** in dry hexane (2 mL) was added 0.36 mL (0.36 mmol) diisobutylaluminum hydride (1 M in hexane) at −78°. The mixture was stirred under N_2 for 2 hr at the same temp, followed by quenching with satd NH_4Cl aq. After warming up to room temp, the resulting cloudy suspension was acidified with 10% HCl until the aqueous layer turned clear. The aqueous phase was extracted with ethyl ether and the ether soln was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude product (38 mg, 100%) obtained was homogeneous by tlc (silica gel, 5:1 petroleum ether–ethyl ether) analysis and showed essentially pure **22** in the ^1H NMR spectrum. Preparative tlc of the crude product gave an analytical sample of **22** (36.5 mg, 97%): colorless oil; b.p. (Kugelrohr distillation) 93–95°/0.05 Torr; IR 3650, 3500 and 1670 cm^{-1}; ^1H NMR δ 1.0 (s, 6 H), 1.2–2.2 (m, 6 H), 1.6 (s, 3 H), 1.7 (s, 3 H), 2.06 (br s, 4 H), 4.1 (br d, J = 7 Hz, 2 H) and 5.37 (br t, J = 7 Hz, 1 H); mass spectrum *m/e* (rel intensity) 222 (6), 204 (14), 191 (11), 189 (12), 149 (25), 138 (27), 137 (96), 136 (72), 123 (40), 121 (66), 119 (42), 109 (48), 107 (56), 105 (53), 95 (100), 93 (79), 91 (73), 81 (98), 79 (79), 77 (65), 69 (78), 67 (84), 65 (40), 57 (74), 55 (86), 53 (51), 44 (93), 43 (77) and 41 (98). (Found: C, 81.00; H, 11.72. Calc. for $C_{15}H_{26}O$: C, 81.02; H, 11.79%.)

E-3-Methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-pentenal (**23**). To a stirred suspension of 340 mg active MnO_2[24a] in dry hexane was added 32 mg (0.14 mmol) of alcohol **22** at 0°. Stirring was continued for 1.5 hr at 0° and 0.5 hr at room temp. The mixture was then filtered through celite and the residue was eluted with n-pentane. The combined filtrate was evaporated under reduced pressure to give 31 mg (98%) crude **23** which was homogeneous by tlc analysis (silica gel, 10:1 petroleum ether–ethyl ether) and

showed the following spectral data:[20] IR 1670 and 1635 cm^{-1}; ^1H NMR δ 1.02 (s, 6 H), 1.2–1.7 (m, 4 H), 1.6 (s, 3 H), 1.7–2.1 (m, 2 H), 2.2 (br s, 7 H), 5.83 (br d, J = 7 Hz, 1 H) and 9.13 (d, J = 7 Hz, 1 H); mass spectrum *m/e* (rel intensity) 220 (1), 219 (2), 191 (5), 177 (10), 153 (17), 139 (16), 137 (56), 135 (34), 125 (22), 123 (45), 121 (39), 119 (23), 111 (42), 109 (63), 107 (50), 95 (73), 93 (55), 91 (46), 81 (64), 79 (50), 77 (39), 71 (51), 69 (71), 67 (66), 55 (74), 43 (100) and 41 (75).

C. *Mokupalide* (**24**)

Methyl (6E)-7,11-*dimethyl*-3-*oxododeca*-6,10-*dienoate* (**28**). The dianion of methyl acetoacetate (6.96 g, 60 mmol) in THF (100 mL) was prepared[6b] and treated with **27** (10.85 g, 50 mmol) at 0° and the yellow suspension formed was stirred for 1 hr at the same temp. Work-up of the reaction mixture by the above procedure led to 12.8 g of crude product, which was purified by Kugelrohr distillation to give 11.97 g (95% based on geranyl bromide used) of **28** as a colorless liquid: b.p. 90–92°/0.02 Torr; IR 1745, 1715, 1650 and 1630 cm^{-1}; ^1H NMR δ 1.62 (s, 6 H), 1.67 (s, 3 H), 1.97 (br s, 4 H), 2.0–2.7 (m, 4 H), 3.38 (s, 2 H), 3.70 (s, 3 H) and 5.02 (m, 2 H); mass spectrum *m/e* (rel intensity) 252 (25), 234 (18), 209 (13), 191 (16), 151 (17), 137 (16), 136 (53), 129 (29), 123 (27), 121 (28), 116 (24), 110 (17), 109 (100), 107 (18), 105 (26), 101 (36), 95 (28), 93 (25), 81 (47), 69 (86), 55 (22) and 41 (53).

High resolution mass measurement Calc for $C_{15}H_{24}O_3$: 252.1725. Found: 252.1740.

Methyl (2Z,6E)-3-(*Diethylphosphoryloxy*)-7,11-*dimethyldodeca*-2,6-10-*trienoate*. The enol phosphate of **28** was prepared from 7.56 g (30 mmol) of **28** in quantitative yield. The crude product had the following spectral data: IR 1725, 1670, 1280 and 1030 cm^{-1}; ^1H NMR δ 1.35 (t, J = 7 Hz, 6 H), 1.60 (s, 6 H), 1.67 (s, 3 H), 1.7–2.3 (m, 6 H), 2.4 (m, 2 H), 3.65 (s, 3 H), 4.23 (qn, J = 7 Hz, 4 H), 5.0 (m, 2 H) and 5.30 (s, 1 H); mass spectrum *m/e* (rel intensity) 388 (12), 357 (5), 343 (3), 319 (4), 287 (18), 252 (25), 234 (20), 220 (28), 202 (13), 192 (14), 155 (100), 127 (50) and 99 (63).

High resolution mass measurement Calc. for $C_{19}H_{33}O_6P$: 388.2015. Found: 388.2024.

Methyl (2E,6E)-3,7,11-*trimethyldodeca*-2,6,10-*trienoate* (**29**). To an ether (30 mL) soln of lithium dimethylcuprate (10 mmol), cooled at −78°, was added 1.94 g (5.0 mmol) of the above enol phosphate in 2 mL ethyl ether. The resulting orange-yellow suspension was stirred at −78° for 2 hr (mixture turned reddish brown at this stage) and then at −47° for 1 hr (mixture turned dark purple). The mixture was worked up as above to give 1.23 g of crude product. Vpc analysis (3% OV-17 column, 160°) indicated a 93% purity of the desired (*E,E*)-isomer. Preparative tlc (silica gel, 50.3 CCl_4-ethyl ether) of 108 mg crude material afforded 96 mg (87%) of **29**: b.p. (Kugelrohr distillation) 96–98°/0.02 Torr; IR 1715, 1650 and 1155 cm^{-1}; ^1H NMR δ 1.60 (s, 6 H), 1.67 (s, 3 H), 1.8–2.3 (m, 8 H), 2.15 (d, J = 1.5 Hz, 3 H), 3.65 (s, 3 H), 5.0 (m, 2 H), and 5.62 (br s, 1 H); mass spectrum *m/e* (rel intensity) 250 (35), 219 (17), 207 (20), 137 (30), 136 (32), 114 (54), 81 (43), 69 (100) and 41 (53).

High resolution mass measurement Calc. for $C_{16}H_{26}O_2$: 250.1933. Found: 250.1929.

Methyl (E,E,E)-12-*hydroxy*-3,7,11-*trimethyldodeca*-2,6,10-*trienoate* (**30**). A suspension of 5.58 g (50 mmol) selenium dioxide (99.4%) in CH_2Cl_2 (250 mL) was stirred with 28.7 mL (200 mmol) of 70% t-butylhydroperoxide for 30 min at room temp in the dark. The resulting soln was cooled to 10°, followed by the addition of 25.0 g (100 mmol) of **29**. The mixture was stirred for 4.5 hr at 10° and then diluted with 150 mL CH_2Cl_2. The organic soln was washed with 10% $NaHCO_3$ aq, dried over $MgSO_4$ and evaporated under reduced pressure. The crude material obtained was chromatographed on silica gel (100–200 mesh) with 3:1 petroleum ether–ethyl ether to give the following components, in order of elution: (a) starting material **29** (4.75 g, 19%);

(b) Compound **36** (1.33 g, 5%): colorless oil; IR 1690 and 1650 cm^{-1}; ^1H NMR δ 1.62 (s, 3 H), 1.73 (s, 3 H), 2.15 (s, 3 H), 2.0–2.4 (m, 8 H), 3.64 (s, 3 H), 5.07 (m, 1 H), 5.60 (m, 1 H), 6.37 (m, 1 H) and 9.30 (d, J = 1 Hz, 1 H); mass spectrum *m/e* (rel intensity) 264 (4), 233 (6), 232 (6), 181 (18), 165 (19), 157 (28), 155 (28), 151 (27), 141 (32), 127 (53), 125 (62), 121 (51), 114 (100), 113 (31), 97 (65), 95 (99), 83 (44), 69 (32) and 55 (54). High resolution mass measurement Calc. for $C_{16}H_{24}O_3$: 264.1726. Found: 264.1728.

(c) Compound **35** (2.13 g, 8%): colorless oil; IR 3600, 1710 and 1650 cm^{-1}; ^1H NMR δ 1.63 (s, 6 H), 1.70 (s, 3 H), 2.17 (s, 3 H), 1.9–2.6 (m, 7 H), 3.63 (s, 3 H), 3.93 (t, J = 7 Hz, 1 H), 5.03 (m, 1 H), 5.3 (m, 1 H) and 5.60 (m, 1 H); mass spectrum *m/e* (rel intensity) 266 (1), 248 (2), 235 (2), 197 (24), 166 (14), 165 (100), 147 (7), 138 (5) metastable peak = $(165)^2/197$, 137 (11), 135 (9), 118 (14), 113 (10), 108 (21), 106 (17), 94 (12), 92 (17), 90 (9), 83 (16), 70 (29), 69 (18), 55 (23), 43 (16) and 41 (30). High resolution mass measurement Calc. for $C_{16}H_{26}O_3$: 266.1882. Found: 266.1870.

(d) **30** (10.91 g, 41%): colorless oil; IR 3550, 1715 and 1650 cm^{-1}; ^1H NMR δ 1.60 (s, 3 H), 1.63 (s, 3 H), 1.8–2.3 (m, 9 H), 2.13 (d, J = 1.2 Hz, 3 H), 3.63 (s, 3 H), 3.94 (s, 2 H), 5.05 (m, 1 H), 5.30 (m, 1 H) and 5.60 (m, 1 H); ^1H NMR (in CCl_4) δ 1.60 (s, 6 H), 1.18–2.3 (m, 8 H), 2.09 (d, J = 1.2 Hz, 3 H), 3.15 (br s, 1 H, exchangeable with D_2O), 3.58 (s, 3 H), 3.83 (s, 2 H), 4.95 (m, 1 H), 5.25 (m, 1 H) and 5.51 (m, 1 H); mass spectrum *m/e* (rel intensity) 266 (4), 248 (7), 234 (12), 181 (31), 164 (30), 149 (38), 135 (50), 125 (40), 123 (28), 121 (100), 114 (87), 109 (43), 107 (66), 105 (36), 97 (31), 95 (68), 93 (90), 81 (63), 69 (50), 67 (50), 55 (68), 43 (62) and 41 (60). High resolution mass measurement Calc. for $C_{16}H_{26}O_3$: 266.1882. Found: 266.1861.

Methyl (E,E,E)-12-*methanesulfonyloxy*-3-7,11-*trimethyldodeca*-2,6-10-*trienoate* (**31**). To a soln of 1.09 g (4.1 mmol) of **30** in dry CH_2Cl_2 (35 mL), cooled at −10° and kept under N_2, was added successively 0.86 mL (6.2 mmol) of anhyd Et_3N and 0.35 mL (4.5 mmol) methanesulfonyl chloride.[32] The resulting suspension was stirred for 2.5 hr at −10°, and then poured into 15 mL ice-cold water. The organic layer was separated, washed with ice-cold 5% HCl aq, sat $NaHCO_3$ aq and brine, and dried over $MgSO_4$. Removal of solvent under reduced pressure yielded 1.41 g (100%) of crude **31** as a pale yellow oil which was homogeneous by tlc analysis (silica gel, 5:1 CCl_4-ethyl ether), and showed satisfactory spectral data: IR 1710, 1650, 1360, 1170 and 1150 cm^{-1}; ^1H NMR δ 1.59 (s, 3 H), 1.70 (s, 3 H), 2.13 (d, J = 1.2 Hz, 3 H), 1.9–2.3 (m, 8 H), 2.95 (s, 3 H), 3.65 (s, 3 H), 4.54 (s, 2 H), 5.03 (m, 1 H), 5.2–5.7 (m, 2 H); mass spectrum *m/e* (rel intensity) 344 (2), 248 (34), 217 (10), 189 (12), 136 (19), 135 (100), 134 (35), 133 (22), 121 (36), 119 (38), 114 (51), 109 (24), 107 (83), 105 (35), 96 (33), 93 (76), 91 (31), 81 (32), 79 (47), 67 (25), 55 (44), 43 (26) and 41 (34).

High resolution mass measurement Calc. for $C_{17}H_{28}O_5S$: 344.1658. Found: 344.1669.

Methyl (E,E,E)-3,7,11-*trimethyl*-12-*phenylthiododeca*-2,6,10-*trienoate* (**32**). A soln of benzenethiol (0.46 mL, 4.5 mmol) in dry THF (15 mL) was allowed to react with 2.58 mL (4.5 mmol) MeLi (1.75 M in ether) for 20 min at 0°, under dry N_2. To the resultant lithium thiophenoxide soln was added 1.35 g (3.9 mmol) of **31** and the mixture was stirred for 4 hr at 0°. The mixture was then diluted with ethyl ether and water. The organic soln was separated, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The ^1H NMR spectrum of the crude product so obtained (1.44 g) showed essentially pure **32**. Preparative tlc (silica gel, 6:1 CCl_4–ethyl ether) purification of 62 mg of the crude material gave 56 mg (93%) of **32** as a colorless liquid: IR 1710, 1650, 1585, 1440 and 1150 cm^{-1}; ^1H NMR δ 1.56 (s, 3 H), 1.72 (s, 3 H), 1.8–2.3 (m, 8 H), 2.14 (d, J = 1.6 Hz, 3 H), 3.45 (s, 2 H), 3.63 (s, 3 H), 5.07 (m, 2 H), 5.60 (m, 1 H) and 6.9–7.4 (m, 5 H); mass spectrum *m/e* (rel intensity) 359 (25), 358 (100), 249 (10), 218 (17), 217 (14), 189 (25), 177 (46), 176 (57), 149 (16), 135 (66), 121 (43), 109 (40), 107 (33), 95 (18), 93 (24), 81 (25), 79 (16), 69 (18), 67 (22), 55 (26), 43 (20) and 41 (29).

High resolution mass measurement Calc. for $C_{22}H_{30}O_2S$: 358.1966. Found: 358.1956.

(E,E,E)-3,7,11-*Trimethyl*-12-*phenylthiododeca*-2,6,10-*trien*-1-*ol* (**33**). To a soln of 1.18 g (3.3 mmol) of **32** in dry ethyl ether (45 mL), cooled at −23° and kept under N_2, was added 9.9 mL (9.9 mmol) diisobutylaluminum hydride (1 M in hexane). The resulting mixture was stirred for 1 hr 50 min at −23° and then quenched with 2 mL MeOH. The cooling bath was removed, and after 20 min, the mixture was treated with 10% HCl aq until the aqueous layer turned clear. The ether soln was separated, washed with brine, and dried over $MgSO_4$. Evaporation of solvents under reduced pressure afforded 1.08 g (99%) crude **33**. Satisfactory elemental microanalysis was obtained on a tlc purified (silica gel, 4:1 CCl_4–ethyl ether) sample: colorless oil; b.p. (Kugelrohr distillation) 145–147°/0.1 Torr; IR 3650, 3500, 1665, 1585 and 1440 cm^{-1}; ^1H NMR δ 1.55 (s, 3 H), 1.66 (s, 3 H), 1.71 (s, 3 H), 1.8–2.3 (m, 9 H), 3.45 (s, 2 H), 4.09 (d, J = 7 Hz, 2 H), 4.8–5.5 (m, 3 H) and 6.9–7.4 (m, 5 H); mass spectrum *m/e* (rel intensity) 330 (29), 312 (10), 221 (32), 220 (19), 203 (46), 177 (100), 176 (28), 163 (30), 147 (30), 135 (88), 134 (63), 121 (54), 110 (67), 109 (89), 107 (78), 95 (42), 93 (72), 81 (73), 69 (55), 68 (45), 67 (70), 55 (60), 43 (45) and 41 (75). (Found: C, 76.64; H, 9.21. Calc. for $C_{21}H_{30}OS$: C, 76.31; H, 9.15%.)

(E, E, E)-1-(2-*Tetrahydropyranyloxy*)-3,7,11-*trimethyl*-12-*phenylthio*-2,6,10-*dodecatriene* (**34**). A mixture of 1.03 g (3.1 mmol) crude **33**, 391 mg (4.65 mmol) dihydropyran and a catalytic amount (10 mg) of *p*-toluenesulfonic acid in dry CH_2Cl_2 (45 mL) was stirred for 2 hr at room temp. The resulting soln was diluted with ethyl ether, washed with 10% $NaHCO_3$ aq, and dried over Na_2SO_4. Removal of solvents under reduced pressure gave 1.29 g of crude material, which after column chromatography (silica gel 100–200 mesh, 6:1 petroleum ether–ethyl ether) furnished 1.23 g (95% yield from **32**) of **34**: colorless liquid; IR 1670, 1585, and 1440 cm^{-1}; ^1H NMR δ 1.56 (s, 3 H), 1.67 (s, 3 H), 1.72 (s, 3 H), 1.3–1.8 (m, 6 H), 1.8–2.2 (m, 8 H), 3.44 (s, 2 H), 3.5–4.2 (m, 4 H), 4.56 (m, 1 H), 5.1 (m, 3 H) and 6.97–7.33 (m, 5 H); mass spectrum *m/e* (rel intensity) 414 (10), 329 (10), 202 (20), 176 (23), 134 (28), 123 (15), 121 (15), 110 (21), 109 (25), 107 (22), 93 (16), 86 (21), 85 (100), 81 (23), 69 (18), 67 (37), 57 (36), 55 (32), 43 (40) and 41 (42).

High resolution mass measurement Calc. for $C_{26}H_{38}O_2S$: 414.2593. Found: 414.2582.

(E,E,E)-13-(2-*Tetrahydropranyloxy*)-3,7,11-*trimethyl*-1-(2,6,6-*trimethyl*-1-*cyclohexen*-1-*yl*)-2-*phenylthio*-3,7,11-*tridecatriene* (**39**). A soln of 1.66 g (4.0 mmol) of **34** and 448 mg (4.0 mmol) diazabicyclo[2.2.2]octane in dry THF (25 mL) was kept under N_2 and cooled to −23°. To this was added 3.75 mL (6.0 mmol) n-BuLi (1.6 M in hexane) and the resulting orange soln was stirred for 3 hr at −23°. A soln of **19** (1.30 g, 60 mmol) in dry THF (2 mL) was then introduced. The light yellow suspension formed was stirred at −23° for 3 hr and warmed to 0° over 50 min. The reaction was worked up by quenching with 20 ml water and extracting the aqueous phase with 2 × 25 mL ethyl ether. The ether extracts were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to give 2.78 g crude material, which showed one major spot (besides a fast moving component) on tlc. Purification of 100 mg of the crude product by preparative tlc (silica gel, 10:1 petroleum ether–ethyl ether) afforded 59 mg (75%) of **39** as a colorless oil: IR 1670, 1585 and 1440 cm^{-1}; ^1H NMR δ 0.98 (s, 3 H), 1.05 (s, 3 H), 1.51 (s, 3 H), 1.66 (br s, 9 H), 1.2–2.4 (m, 22 H), 3.4–4.2 (m, 5 H), 4.57 (m, 1 H), 4.75–5.47 (m, 3 H) and 6.93–7.33 (m, 5 H); mass spectrum *m/e* (rel intensity) 550 (0.5), 449 (2), 440 (3), 413 (5), 355 (11), 338 (14), 329 (16), 311 (46), 270 (15), 255 (15), 243 (26), 219 (32), 203 (75), 202 (72), 189 (61), 187 (60), 177 (69), 175 (64), 173 (59), 163 (71), 161 (74), 159 (70), 149 (73), 147 (79), 145 (74), 135 (87), 123 (84), 119 (81), 110 (93), 109 (96), 107 (80), 105 (80), 95 (84), 93 (81), 91 (79), 85 (96), 84 (94), 69 (88), 67 (85), 57 (89), 55 (96), 43 (100) and 41 (88).

High resolution mass measurement Calc. for $C_{36}H_{54}O_2S$: 550.3844. Found: 550.3839.

(E,E,E)-13-(2-*Tetrahydropyranyloxy*)-3,7,11-*trimethyl*-1-(2,6,6-*trimethyl*-1-*cyclohexen*-1-*yl*)-3,7,11-*tridecatriene* (**40**). To a soln of nickel (II) chloride hexahydrate (29.13 g, 122 mmol) in 400 mL abs EtOH, cooled in an ice-bath, was added simultaneously a soln of **39** (1.76 g, 3.2 mmol) in EtOH (40 mL) and a soln of $NaBH_4$ (3.95 g, 100 mmol) in water with vigorous stirring.[35,36] The addition was completed over 20 min, and the resulting black suspension was removed from the cooling bath and stirred for 26 hr at room temp. The mixture was then filtered through celite and the ppt was washed with EtOH. The combined filtrate was evaporated under reduced pressure and the residue was dissolved in ethyl ether. The ether soln was washed with brine and dried over $MgSO_4$. The crude product obtained after removal of solvents was chromatographed on a silica gel (100–200 mesh) column with 20:1 petroleum ether–ethyl ether to give 1.02 g (72%) of **40** as a colorless oil: IR 1670 and 1450 cm^{-1}; ^1H NMR δ 1.0 (s, 6H), 1.2–2.3 (m, 36H), 3.4–4.2 (m, 4H), 4.57 (m, 1 H) and 4.8–5.5 (m, 3 H); mass spectrum *m/e* (rel intensity) 442 (4), 358 (5), 357 (4), 340 (15), 203 (10), 189 (8), 177 (7), 161 (6), 147 (8), 137 (73), 135 (12), 123 (14), 121 (18), 119 (11), 109 (14), 107 (15), 95 (36), 93 (18), 85 (100), 81 (35), 69 (13), 67 (15), 57 (17), 55 (16) and 41 (17).

High resolution mass measurement Calc. for $C_{30}H_{50}O_2$: 442.3811. Found: 442.3796.

(E, E, E)-13-*Hydroxy*-3,7,11-*trimethyl*-1-(2,6,6-*trimethyl*-1-*cyclohexen*-1-*yl*)-3,7,11-*tridecatriene* (**41**). A soln of **40** (486 mg, 1.1 mmol) and *p*-toluenesulfonic acid (20 mg) in 60 mL MeOH-THF (5:1) was stirred for 24 hr at room temp. The soln was then concentrated under reduced pressure to *ca* 1 mL, diluted with ethyl ether, and washed with sat $NaHCO_3$ aq. After drying over $MgSO_4$ and removal of solvents, the residue was evaporated *in vacuo* to afford 395 mg (quantitative yield) of **41**, which was homogeneous by tlc (silica gel) analysis: colorless liquid; IR 3650, 3500, 1670 and 1450 cm^{-1}; ^1H NMR δ 0.98 (s, 6 H), 1.2–2.3 (m, 30 H), 4.1 (d, J = 7 Hz, 2 H) and 4.8–5.5 (m, 3 H); mass spectrum *m/e* (rel intensity) 358 (12), 340 (10), 204 (13), 203 (9), 189 (9), 177 (12), 161 (8), 147 (11), 138 (15), 137 (100), 136 (15), 135 (16), 133 (16), 123 (20), 121 (24), 119 (14), 109 (16), 107 (16), 95 (23), 81 (25), 69 (14), 55 (16) and 41 (15).

High resolution mass measurement Calc. for $C_{25}H_{42}O$: 358.3235. Found: 358.3220.

3-*Phenylsulfonylmethyl*-2-*butenolide* (**46**). Anhyd sodium benzenesulfinate (1.15 g, 7.0 mmol) and 1.03 g (5.8 mmol) 3-bromomethyl-2-butenolide[37] were dissolved in 10 mL dry DMF. The orange-brown soln formed was stirred for 2 hr at room temp under dry N_2. The mixture was worked up by adding 20 mL water and extracting the soln with 4 × 30 mL of $CHCl_3$-n-pentane (1:1). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Removal of residual DMF *in vacuo* gave 1.35 g crude **46** (solid) which was essentially pure by tlc (silica gel) and ^1H NMR analyses. Recrystallization from CH_2Cl_2–ethyl ether–n-pentane yielded 1.18 g (85%) of **46** as colorless flakes: m.p. 125°; IR 1795, 1760, 1650, 1335, 1175 and 1160 cm^{-1}; ^1H NMR δ 4.17 (s, 2 H), 4.87 (br s, 2 H), 5.83 (br s, 1 H) and 7.4–7.9 (m, 5 H); mass spectrum *m/e* (rel intensity) 238 (54), 141 (100), 126 (15), 125 (28), 97 (29), 77 (99), 68 (16), 67 (16) and 51 (27). (Found: C, 55.31; H, 4.14; S, 13.22. Calc. for $C_{11}H_{10}O_4S$: C, 55.45; H, 4.23; S, 13.46%.)

(E,E,E)-13-*Bromo*-3,7,11-*trimethyl*-1-(2,6,6-*trimethyl*-1-*cyclo-hexen*-1-*yl*)-3,7,11-*tridecatriene* (**49**). To a mixture of **41** (425 mg, 1.2 mmol) and anhyd LiBr (413 mg, 4.76 mmol) in 25 mL dry ethyl ether, cooled at −78° and kept under N_2, was added 0.86 mL (1.3 mmol) n-BuLi (1.52 M in hexane) with stirring. After 30 min at the same temp, 0.10 mL (1.3 mmol) methanesulfonyl chloride was introduced.[17] The mixture was warmed to −10° over 1 hr, maintained at −10° for 30 min and then at room temp for 6 hr. The resulting suspension was poured into ice-cold water and the aqueous phase was extracted with 2 × 50 mL ethyl ether-n-pentane (1:1). The combined organic soln was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude **49** (463 mg, 92%) obtained was used directly in the next alkylation step without any purification. Satisfactory

spectral data were observed for this crude material (a slightly tan oil): IR 1665, 1455, 1380 and 1180 cm^{-1}; ^1H NMR δ 0.98 (s, 6 H), 1.2–2.3 (m, 30 H), 3.95 (d, J = 8 Hz, 2 H) and 4.7–5.57 (m, 3 H); mass spectrum *m/e* (rel intensity) 422 (7), 420 (7), 341 (6), 340 (8), 204 (15), 203 (9), 189 (10), 177 (12), 149 (10), 147 (10), 138 (15), 137 (100), 136 (15), 135 (13), 123 (18), 121 (21), 119 (13), 109 (16), 107 (18), 105 (12), 95 (36), 81 (24), 69 (13), 67 (13), 55 (15) and 41 (13).

High resolution mass measurement Calc. for $C_{25}H_{41}{}^{81}Br$ and $C_{25}H_{41}{}^{79}Br$: 422.2371 and 420.2391. Found: 422.2399 and 420.2391.

3-(E,E,E)-4,8,12-*Trimethyl*-14-(2,6,6-*trimethyl*-1-*cyclohexen*-1-*yl*)-1-*phenylsulfonyl*-3,7,11-*tetradecatrien*-1-*yl*]-2-*butenolide* (**50**). To a stirred suspension of 144 mg (3.0 mmol) NaH (50%) in dry DMF (20 mL) was added 714 mg (3.0 mmol) of **46** (dissolved in 1 mL of DMF) at 0°, under N_2. The cooling bath was removed, and an orange-yellow soln was formed after 30 min. To this soln was introduced 460 mg (*ca* 1.2 mmol) crude **49** and the resulting mixture was stirred for 4 hr at room temp. The reaction was quenched with 40 mL ice-cold 5% HCl and the mixture was extracted with 3 × 60 mL ethyl ether-petroleum ether (1:1). The combined extracts were washed with 2 × 40 mL 50% brine, dried over $MgSO_4$, and evaporated under reduced pressure to give 572 mg crude product. Purification of 100 mg crude material by preparative tlc (silica gel, 2:3 petroleum ether–ethyl ether) afforded 72 mg (60% yield from alcohol **41**) of **50** as a thick, colorless oil: IR 1792, 1760, 1640, 1330 and 1150 cm^{-1}; ^1H NMR δ 1.0 (s, 6 H), 1.1–2.2 (m, 30 H), 2.7 (m, 2 H), 4.0 (m, 1 H), 4.8 (d, J = 1.5 Hz, 2 H), 4.6–5.2 (m, 3 H), 5.8 (m, 1 H) and 7.3–7.9 (m, 5 H); mass spectrum *m/e* (rel intensity) 578 (15), 441 (3), 435 (2), 300 (10), 244 (18), 237 (47), 188 (19), 176 (21), 164 (19), 163 (19), 148 (18), 146 (20), 136 (100), 135 (38), 134 (33), 132 (24), 122 (34), 120 (45), 118 (36), 108 (37), 106 (40), 104 (30), 94 (60), 81 (95), 69 (97), 57 (40), 55 (51) and 41 (89).

High resolution mass measurement Calc. for $C_{36}H_{50}O_4S$: 578.3430. Found: 578.3435.

Mokupalide (**24**). A mixture of **50** (29 mg, 0.050 mmol) and disodium hydrogen phosphate (28 mg, 0.20 mmol) was dissolved in 5 mL dry MeOH. To this soln, cooled at −10° and kept under N_2, was added 75 mg (0.20 mmol) of 6% $NaHg^{45}$ in one portion. The resulting mixture was stirred for 20 min at −10°, followed by quenching with satd NH_4Cl aq and extraction with ethyl ether. The combined extracts were washed with satd $NaHCO_3$ aq, dried over $MgSO_4$ and then concentrated under reduced pressure. The crude residue obtained was chromatographed on silica gel with 1:1 petroleum ether–ethyl ether to furnish 18 mg (82%) of **24**[26]: IR 1790, 1755, 1645 and 1450 cm^{-1}; ^1H NMR δ 0.99 (s, 6 H), 1.1–2.2 (m, 32 H), 2.4 (m, 2 H), 4.65 (d, J = 1.5 Hz, 2 H), 5.05 (m, 3 H) and 5.78 (m, 1 H); mass spectrum *m/e* (rel intensity) 438 (23), 423 (5), 395 (3), 296 (5), 278 (4), 245 (5), 217 (5), 204 (12), 189 (11), 177 (24), 161 (13), 149 (28), 137 (100), 136 (36), 135 (36), 133 (28), 123 (32), 121 (52), 119 (27), 110 (29), 108 (37), 98 (46), 95 (65), 93 (41), 91 (25), 81 (83), 79 (31), 69 (65), 67 (32), 57 (40), 55 (54), 43 (28) and 41 (52).

High resolution mass measurement Calc. for $C_{30}H_{46}O_2$: 438.3497. Found: 438.3519.

3-(4-*Methyl*-1-*phenylsulfonyl*-3-*penten*-1-*yl*)-2-*butenolide* (**47**). Compound **46** (48 mg, 0.20 mmol) was alkylated with 1-bromo-3-methyl-2-butene (15 mg, 0.10 mmol) in the manner described in the preparation of **50**. Preparative tlc (silica gel, 5:1 ethyl ether-petroleum ether) of the crude product (27 mg) gave 22 mg (72% yield based on the bromide used) of **47** as colorless flakes (crystallized from petroleum ether–ethyl ether): m.p. 96°; IR 1792, 1760, 1640, 1595, 1455, 1330 and 1150 cm^{-1}; ^1H NMR δ 1.57 (s, 3 H), 1.63 (s, 3 H), 2.7 (m, 2 H), 4.0 (m, 1 H), 4.80 (br s, 2 H), 4.6–5.0 (m, 1 H), 5.8 (m, 1 H) and 7.3–7.9 (m, 5 H); mass spectrum *m/e* (rel intensity) 306 (8), 238 (15), 181 (8), 165 (100), 164 (100), 137 (12), 136 (13), 121 (33), 120 (24), 119 (27), 109 (17), 107 (23), 105 (44), 93 (28), 91 (30), 77 (36), 69 (29) and 41 (38). (Found: C, 62.65; H, 5.97; S, 10.38. Calc. for $C_{16}H_{18}O_4S$: C, 62.73; H, 5.92; S, 10.46%.)

When approximately 1:1 ratios of **46** and 1-bromo-3-methyl-2-butene were used in the alkylation under various conditions (t-BuOK, t-BuOH; NaH, THF-HMPA; or NaH, DMF), the monoalkylation product **47** was obtained in 40–50% yields, along with dialkylation product **48**.

Acknowledgement—We are grateful to Prof. J. Meinwald and Dr. C. Semmelhack for samples and spectra of the butterfly compounds, and to Prof. P. Scheuer and Dr. M. Yunker for samples and spectra of mokupalide. We are grateful to the Natural Sciences and Engineering Research Council of Canada for financial support.

This paper is dedicated to the fond memory of R. B. Woodward—teacher, leader, motivator and patron.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 319 to 327, 1981
Printed in Great Britain

0040-4020/81/Suppl. 1-0319-09 $02.00/0
Pergamon Press Ltd.

TOTAL SYNTHESIS OF APHIDICOLIN*

JOHN E. MCMURRY, ALEX ANDRUS, GARY M. KSANDER, JOHN H. MUSSER and MARK A. JOHNSON

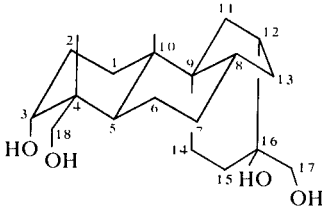
Baker Laboratory, Department of Chemistry, Cornell University, Ithaca, NY 14853‡

(*Received in U.S.A.* 7 *July* 1980)

Abstract—A total synthesis of the antiviral antitumor diterpenoid, aphidicolin (**1**), is reported. The synthesis starts from the known Δ^4-4,10-dimethyloctalin-3,9-dione (**5**) and requires 15 steps. The two key steps are the Claisen rearrangement of cyclopentenol vinyl ether **16** to unsaturated aldehyde **17**, and the carbonylation of unsaturated tosylate **20** to ketone **21**. The Claisen rearrangement gives largely cyclopentadiene elimination product under most conditions. We found, however, that thermolysis *in the presence of potassium t-pentoxide* gives the desired Claisen product **17** in 60% yield. The second key step is carbonylation of **20** with Collman's reagent, disodium tetracarbonylferrate. This reaction, which has not previously been used in natural products synthesis, takes place in 30% yield, and finishes the construction of the aphidicolin skeleton. (±) Aphidicolin was identical with an authentic sample by IR, ^{1}H and ^{13}C NMR, and GC/MS.

Aphidicolin (**1**) is a diterpenoid tetraol produced by the mold *Cephalosporium aphidicola*, Petch.[1] Rather surprisingly in view of its simple functionality, aphidicolin exhibits striking biological activity. For example, it shows marked activity against herpesvirus, both *in vitro* and in the rabbit eye.[2,3] More recent testing carried out by the National Cancer Institute has revealed that aphidicolin also possesses considerable anti-tumor activity in the C6 mouse colon and B16 mouse melanosarcoma screens.[4]

Although its precise mechanism of action is not known, aphidicolin appears to be a reversible enzyme inhibitor of DNA polymerase-α.[5] Models of aphidicolin reveal the striking fact that all four hydroxyls can very nearly touch the same flat surface. This observation is probably connected with the biological activity of aphidicolin, although it appears that not all of the hydroxyls are required for activity. Structure-activity studies[2] indicate that the non-rigid hydroxyls at C17 and C18 are probably less important than the two rigid hydroxyls at C3 and C16.



1

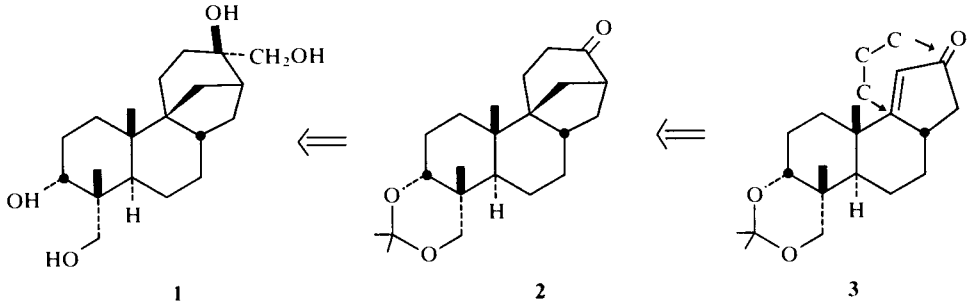
In view of the biological activity and unique carbon skeleton of aphidicolin, we undertook its total synthesis.[6,7] In this paper, we present the details of our work.

The challenges to synthesis offered by aphidicolin are several. There is, for example, the stereochemical problem presented by the A ring. Although the 3α-hydroxy-4α-hydroxymethyl-4β-methyl substitution pattern seems familiar at first glance, it is in fact unique. No other terpenoid natural product has this stereochemistry. Another and more severe stereochemical problem is that posed by the spiro center, C9. Not only is this spiro center chiral, it is also next to another quaternary carbon, C10. The presence of these two adjacent chiral quaternary centers makes this region of aphidicolin quite crowded and thus a likely source of trouble during any projected synthesis.

In planning our work, we decided to first solve the A-ring problem and then attempt to introduce spiro stereochemistry at C9 in the final stages of the synthesis. It occurred to us that cyclopentenone **3** should be a particularly valuable intermediate, and **3** thus became our initial target. The cyclopentenone ring of **3** will become the cyclopentane ring (carbons 8, 9, 11, 12, 13) of aphidicolin, and the molecule is nicely functionalized to allow addition of the required 3-carbon piece across the ends of the enone system. There is a great variety of ways by which enones can be further elaborated, and cyclopentenone **3** should allow us some flexibility of approach should our first choice of route from **3** → **2** not succeed. Once the 3-carbon piece has been added and keto-acetonide **2** obtained, the final steps from **2** to aphidicolin are known.

We began the synthesis of cyclopentenone **3** starting from 2-methyl-1,3-cyclohexanedione, and Scheme 1 shows our initial work. Robinson annulation with 1-penten-3-one gave the known[8] enedione **5** which could be selectively protected by ketalization of the saturated carbonyl. Reductive hydroxymethylation[9] then gave ketol **8**. Although we were ultimately able to achieve an overall yield of approximately 90% for the transformation from **6** to **8**, great experimental care is required in this step. Reduction of enone **6** with lithium in liquid ammonia, followed by enolate trapping with chlorotrimethylsilane, proceeded smoothly to give **7**. Regeneration of the specific enolate followed by its reaction with formaldehyde, however, must be done under exacting conditions (Experimental). Thus, it is critical that all glassware be washed with aqueous ammonia and thoroughly dried prior to use. It is also critical that the enolate be generated in tetrahydrofuran (THF) solvent, that dry

*Dedicated to the memory of Prof. R. B. Woodward.
‡This work was carried out at the University of California, Santa Cruz, CA 95064, U.S.A.

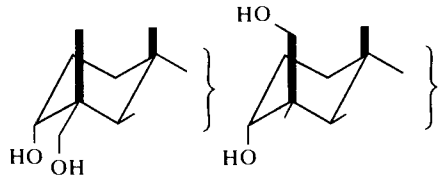


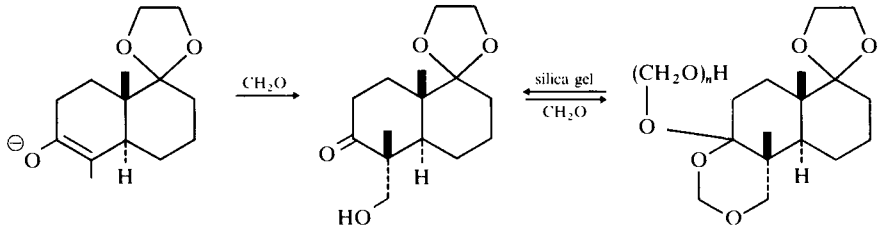
gaseous formaldehyde be introduced, that the formaldehyde be prepared by thermal depolymerization of paraformaldehyde at a temperature not exceeding 140°, and that the gaseous formaldehyde be passed through an ice-cooled trap to remove trace protic impurities (methanol, formic acid) prior to its introduction into the reaction. Even with these precautions, we were initially disappointed to find that the crude product contained no CO group and appeared grossly impure by ^{1}H NMR analysis. We discovered, however, that if the crude hydroxymethylated product is stirred over silica gel in benzene solution, a high yield of pure product **8** is obtained. Presumably, the explanation of this observation is that excess formaldehyde adds to **8** and begins oligomerizing to a host of products. Silica gel treatment unzips the formaldehyde oligomers and regenerates the desired material.

Although crystalline hydroxy ketone **8**, m.p. 105°, could be isolated if desired, it proved more convenient to subject the crude product to reduction with lithium tri-sec-butyl borohydride.[10] This reduction occurred smoothly and in quantitative yield. Interestingly, however, if the reduction was attempted with *potassium* tri-sec-butyl borohydride, only reverse aldolization and loss of formaldehyde occurred.

Diol **9** was next converted into the crystalline keto-acetonide, **10**, by treatment with acetone in dichloromethane in the presence of *p*-toluenesulfonic acid catalyst. Under these conditions, acetonide formation on the 1,3 diol portion, and *trans*-ketalization of the ethylene ketal onto acetone occur concurrently. Keto-acetonide **10** can thus be prepared in 66% overall yield from the known enedione **5**.

The sequence of reactions from enedione **5** to keto-acetonide **10** provides a single product in high yield. Based on the known[11] stereochemistry of reductive alkylation of substances similar to **5**, and on the known ability of tri-sec-butyl borohydride to produce axial alcohols,[10] we felt that **10** should have the correct stereochemistry at all four chiral centers in the aphidicolin A-ring. Corroboratory evidence comes from two sources, one spectroscopic and one chemical. Spectroscopically, compound **10** is nearly identical to the relevant portion of aphidicolin in both the ^{1}H and ^{13}C NMR spectra. Chemically, we viewed the ready formation of the acetonide grouping as evidence for the correct stereochemistry. Had reductive hydroxymethylation occurred from the β-face and hydride reduction occurred normally, acetonide formation would be quite difficult.





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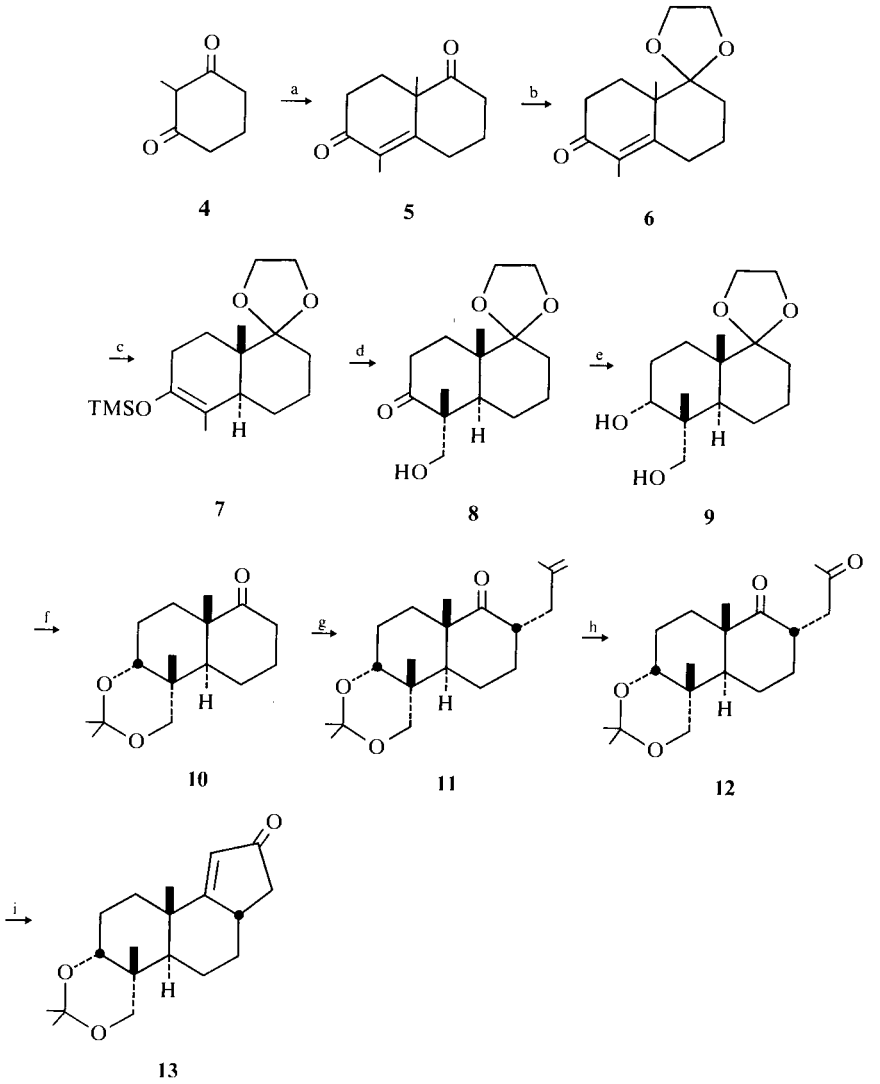
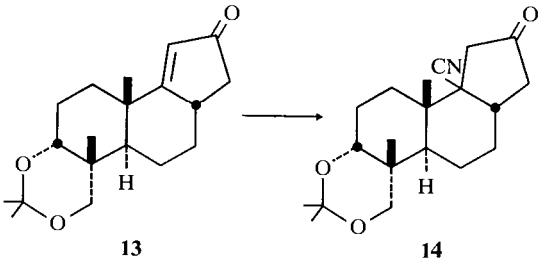
The synthesis of cyclopentenone **3** was completed by alkylation of **10** with methallyl iodide, followed by oxidative cleavage of the side chain double bond and aldol cyclization. The alkylation step proceeded with the desired stereochemistry and generated the fifth necessary chiral center as shown by equilibration experiments (equatorial side chain). Double bond oxidation, **11** → **12**, proceeded without incident using the standard OsO_4–$NaIO_4$ method but the aldol cyclization, **12** → **13**, proved troublesome. Normal protic conditions (NaOH, ethanol) are not effective in this transformation, but we found that sodium t-pentoxide in refluxing benzene provides the key intermediate **13** as white crystals, m.p. 136°, in 88%



Scheme 1. (a) $CH_2{=}CHCOCH_2CH_3$ pyrrolidine, PhH, 75%. (b) $HOCH_2CH_2OH$, p-TsOH, benzene, 80%. (c) Li, NH_3, THF, and then $(CH_3)_3SiCl$, $(CH_3CH_2)_3N$, 97%. (d) CH_3Li, THF, and then CH_2O. (e) Li(sec-Bu)$_3$BH, THF. (f) CH_3COCH_3, p-TsOH,CH_2Cl_2, 85% from **7**. (g) 1.2 equiv. of LICA, THF, and then methallyl iodide, 89%. (h) Trace of OsO_4, $NaIO_4$, H_2O, dioxane, 86%. (i) NaH, trace of t-amyl alcohol, benzene, reflux, 95%.

yield. All of the transformations to this point are summarized in Scheme 1.

Our initial attempts to use the cyclopentenone functionality for elaboration of the remaining ring centered around the use of conjugate addition reactions. We soon found, however, that the great degree of steric crowding at the enone β-carbon (C9) precluded all chances for success. Thus, sodio-dimethylmalonate, sodionitromethane, lithium diallylcuprate, and lithium divinylcuprate all failed to give any of the desired conjugate addition product on attempted reaction with enone **13**. Conjugate addition of cyanide could be effected in 40% yield using the Nagata procedure,[12] but we were unable to make further use of the nitrile product. Attempted Wittig reaction of keto-nitrile **14** with ethylidenetriphenylphosphorane caused elimination of HCN and simply regenerated enone **13**, while $LiAlH_4$ was without obvious effect on the nitrile function of **14** at 60° in THF.



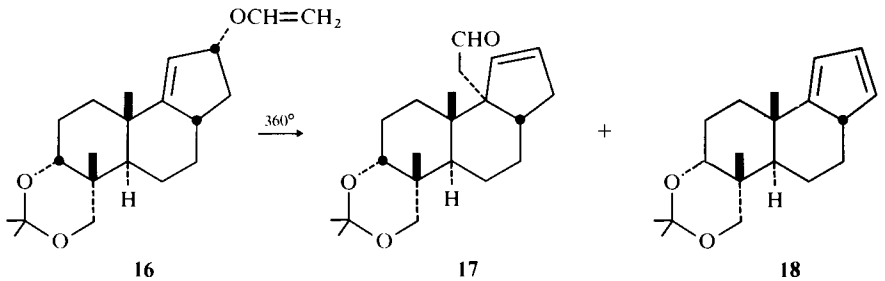
Stymied in our attempts at *inter*molecular additions to **13**, we next turned to *intra*molecular methods, and our successful route is shown in Scheme 2. Molecular models show clearly that the top face of the carbonyl

group is less hindered to nucleophilic attack than is the bottom face. Thus, $LiAlH_4$ reduction of **13** yields a single crystalline alcohol, m.p. 140–142°, to which we assign structure **15**. This is precisely the stereochemistry needed at the spiro center, C9, if the chirality can be transferred from C12 to C9 by a concerted intramolecular rearrangement. We therefore prepared vinyl ether **16** and began a study of its thermal behavior.

Initial attempts at effecting the Claisen rearrangement **16** → **17** were unsuccessful; a mixture of cyclopentadienes (**18**) resulting from elimination of acetaldehyde is the sole reaction product under most conditions, either gas phase or solution phase. After much experimentation, however, we found that gas phase pyrolysis of allyl vinyl ether **16** at 360° in a nitrogen-swept quartz flow system which had been carefully base-washed and silanized, resulted in a 20% yield of the desired unsaturated aldehyde **17**.

cyclopentadiene **18** was simply being formed by a thermal and uncatalyzed reverse ene reaction. Alternatively, however, it was also possible that traces of acid remained on the walls of the flow pyrolysis tube, resulting in an acid-catalyzed elimination of vinyl alcohol *via* a carbocation process.

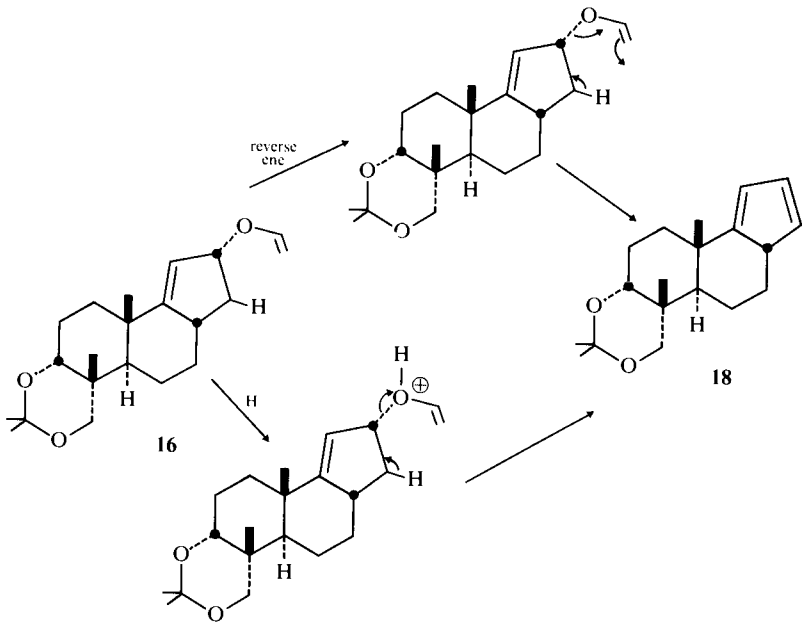
If the elimination occurs through the pericyclic mechanism, we have no handle by which to control it. If, however, the carbocation mechanism is operative, we should be able to repress it by carrying out the Claisen rearrangement *in the presence of strong base.* We therefore carried out the pyrolysis of **16** for 2 hr at 220° in toluene solution containing a small amount (approx. 0.03% by weight) sodium t-pentoxide, and were pleased to obtain a 60% yield of the desired aldehyde **16**. The yield of the Claisen rearrangement is dramatically increased by carrying out the reaction in the presence of strong base. Although we have not extended our study of this phenomenon to other

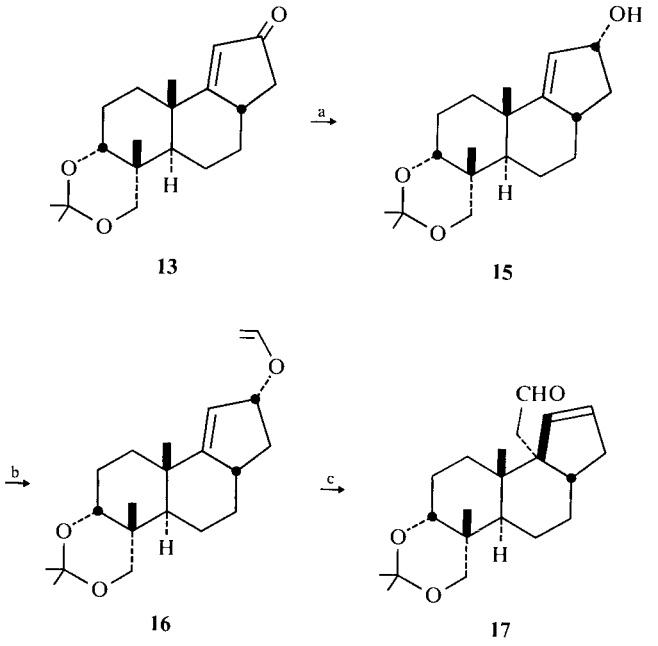


In considering how this yield might be improved, it occurred to us that cyclopentadiene by-product might be formed in either of two ways. Considering the care with which we had washed and neutralized our flow pyrolysis system, it appeared likely to us that

systems, there is no reason to expect that the effect of base would not be generally applicable in Claisen rearrangements.

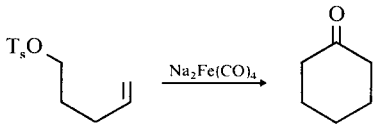
With the Claisen rearrangement successfully concluded, the stereochemical problems of aphidicolin





Scheme 2. (a) $LiAlH_4$, ether, 95%. (b) $CH_3CH_2OCH{=}CH_2$, $Hg(OAc)_2$, 90%. (c) 0.03% NaO-t-pentyl, Toluene, 220°, 60%.

had been solved, and it remained only to knit together the final ring. From the beginning of this work, we had intended to construct this final ring by making use of a novel organometallic reaction which had been heretofore unused in natural products synthesis. Mérour has shown[13] that disodium tetracarbonylferrate ("Collman's reagent") reacts with five- and six-carbon olefinic tosylates to yield cycloalkanones. For example, 1-tosyloxy-5-pentene undergoes carbonylation to yield cyclohexanone. Although the

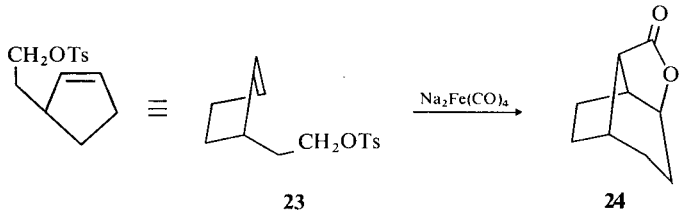


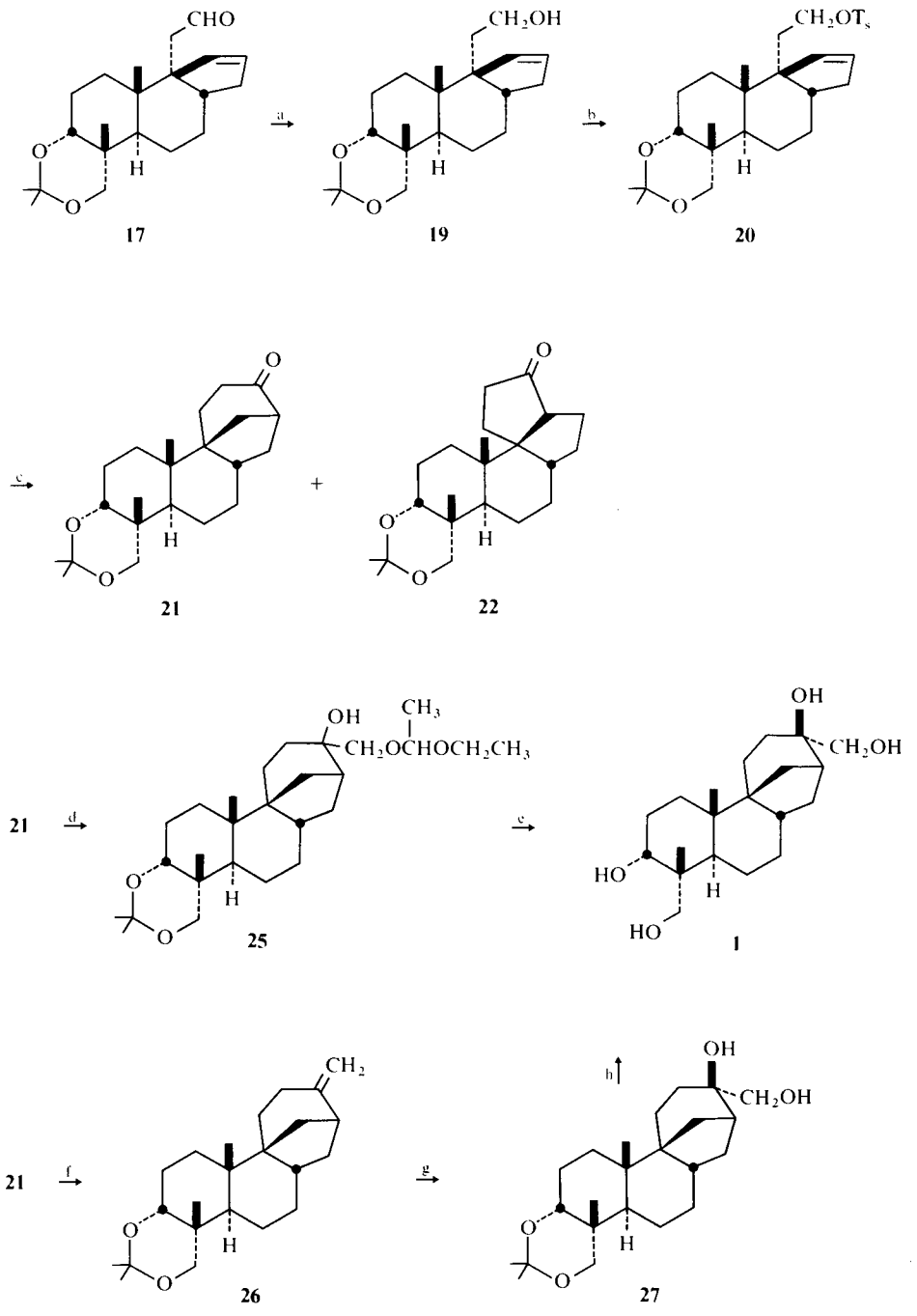
effects of substitution had been little studied, no bicyclo[3.2.1]octanone had been prepared, and no case approaching the complexity of aphidicolin had been attempted, we nevertheless sought to use the Mérour carbonylation reaction for our purposes. The route is shown in Scheme 3.

Aldehyde **17** was reduced with $LiAlH_4$, and alcohol **19** was tosylated. Olefinic tosylate **20** contains the functional groups necessary for Mérour carbonylation to occur, though one might hesitate to predict whether cyclopentanone **22** or cyclohexanone **21** might be formed. In fact, a 55% yield of a 1:1 mixture of **21** and **22** results. This mixture can be readily separated by column chromatography to yield the crystalline keto-acetonide **21**, m.p. 138–139°. The synthetic ketone **21** thus obtained was identical with an authentic sample[14] by IR, ^{1}H NMR, ^{13}C NMR, and GC/MS.

In retrospect, we were quite fortunate that the carbonylation **20** → **21** occurred as desired, since subsequent work in our laboratory has shown that olefinic tosylate **23**, which might be thought a simple model case, does *not* proceed as desired. Rather, two equivalents of carbon monoxide are incorporated, yielding a substance to which we have assigned structure **24**. While model studies have their proper place in synthesis, results such as this underscore the fact that negative results in a model system must be viewed skeptically.

Completion of the synthesis was accomplished in several ways. The original workers[1] chose a multi-step sequence involving epoxide formation, alkaline hydrolysis, and acetonide formation, at which point aphidicolin bis-acetonide and its C16 epimer could be chromatographically separated. We chose first to look





Scheme 3. (a) $LiAlH_4$, THF, 93%. (b) *p*-TsCl, pyridine, 95%. (c) $Na_2Fe(CO)_4$, N-methylpiperidone, 30%. (d) $LiCH_2OCH(CH_3)OCH_2CH_3$, 63%. (e) H_3O^+. (f) $CH_2{=}P(Ph)_3$. (g) OsO_4, pyridine, then $NaHSO_3$. (h) H_3O^+, 36% from **20**.

at alternate possibilities. Still has demonstrated[15] that 1-ethoxyethoxy-methyllithium adds to ketones to give products which can be hydrolyzed to 1,2-diols. In the present instance, addition of this reagent to keto-acetonide **21**, followed by acidic hydrolysis, gave largely the wrong isomer in contrast to reported results.[7b] Alternatively, Wittig reaction of **21** with methylenetriphenylphosphorane gave olefin **26** which, on treatment with OsO_4 in pyridine, provided diol **27** as an approximately 60:40 mixture. This mixture was hydrolyzed with aqueous acid to aphidicolin **1** and its C16 epimer. These transformations are summarized in Scheme 3.

Separation of the mixture could be accomplished either by fractional crystallization, or by conversion of the mixture into di-acetonides followed by column chromatographic separation and acid hydrolysis. (±) Aphidicolin, m.p. 218–220°, was indistinguishable from an authentic sample[14] by IR, ^{1}H NMR, ^{13}C NMR, and GC/MS.

EXPERIMENTAL

NMR spectra were obtained in $CDCl_3$ soln on JEOL FX-60 or FX-100 instruments. IR spectra were recorded on a Perkin–Elmer 337, and GC/MS data were recorded on a Finnigan 4000 instrument using a 6 ft OV-17 column. M.ps were obtained on a Hoover–Thomas apparatus and are uncorrected. Combustion analyses were carried out in-house.

Enedione 5. In a N_2 swept, one liter round bottom flask, was dissolved 2-methyl-1,3-cyclohexanedione (34.1 gm, 0.27 moles) in 160 ml benzene. The solution was azeotroped at reflux to remove water with a Dean–Stark apparatus for 1 hr. After cooling, ethyl vinyl ketone (25.0 gm, 0.30 moles) and triethylamine (17 ml, 12.34 gm, 0.122 moles) were added. The soln was refluxed for 5 hr. After cooling, most of the benzene was removed at reduced pressure. Another 100 ml benzene was added and concentration was repeated. A final 160 ml benzene was added, followed by pyrrolidine (5.2 ml, 4.4 gm, 0.062 moles). The dark brown soln was refluxed with a Dean–Stark apparatus for 15 hr. Approximately 3.6 ml of the theoretical amount of 4.5 ml water was separated. After cooling, the soln was diluted with ether and washed with 5% HCl, 5% NaOH and NaCl solns. Drying over $MgSO_4$ and filtration was followed by concentration to give an orange, viscous oil. Kugelrohr distillation gave a pale yellow oil which solidified upon standing in the refrigerator. Recrystallization from hexanes and ether gave white crystals of **5** (38.74 gm, 0.201 moles, 75%): b.p.$_{0.5\,mm}$ 140°, m.p. 38–39° (lit.[8] m.p. 39–40°; NMR: $\delta(CDCl_3)$ 1.80 (s, 3 H), 1.43 (s, 3 H); IR: (neat) 2950, 1710, 1670, 1610 cm^{-1}.

Ketal 6. In a round bottom flask swept with N_2 was placed **5** (10.58 gm, 0.055 moles), ethylene glycol (40 ml, 44 gm, 0.71 moles), 200 ml benzene, and several crystals of *p*-toluenesulfonic acid. The soln was azeotroped at reflux in a Dean–Stark apparatus for 4 hr. Analysis by tlc and IR showed the disappearance of starting material. After cooling, most of the benzene was removed under reduced pressure. Dilution with ether was followed by washing with 5% NaOH and sat NaCl aq. After drying over $MgSO_4$ and filtration, the solvent was removed by rotary evaporation. The viscous yellow oil was dissolved in 5 ml pentane and placed in the refrigerator overnight, which yielded **6** as white crystals (10.35 gm, 0.0438 moles, 80%) m.p. 57–59°; IR: (neat) 2950, 1670, 1615 cm^{-1}; ^1H NMR: $(CDCl_3)$ δ 3.93 (s, 4 H), 1.77 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR: $(CDCl_3)$ δ 197.8, 159.6, 129.4, 112.2, 64.8, 64.5, 49.8, 38.9, 35.2, 32.2, 27.5, 27.0, 18.1. (Found: C, 71.37; H, 8.63. Calc. for $C_{14}H_{20}O_3$: C, 71.12; H, 8.53%).

Trimethylsilyl enol ether 7. A one liter, 3-neck round bottom flask was fitted with a N_2 inlet, dry ice/acetone condenser, and glass side arm connected to a second one liter flask. From this second flask was distilled 600 ml dry ammonia from Na balls. After distillation was complete, the side arm was replaced with a rubber septum. Li (1.72 gm, 0.248 moles) was added in pieces. After stirring 20 min, 50 ml dry THF was added. A soln of **6** (19.51 gm, 0.0825 moles), t-BuOH (5 ml, 4 gm, 0.054 moles) and 100 ml dry THF was slowly added *via* syringe. After stirring 15 min, 2 ml piperylene was added to quench the excess Li. The soln changed color from deep blue to yellow. Ammonia was distilled off by gentle warming under a flow of N_2. Most of the THF was removed under reduced pressure. Another 100 ml THF was added and the soln was cooled to 0°. A mixture of chlorotrimethylsilane (25 ml, 21.5 gm, 0.198 moles) and triethylamine (25 ml, 18.1 gm, 0.179 moles) was added rapidly *via* syringe. After stirring at 0° for 20 min, the soln was diluted with ether and washed with cold $NaHCO_3$ aq and NaCl aq. Drying over $MgSO_4$ was followed by concentration under reduced pressure and chromatography on silica gel (ether: hexanes, 1:10). After solvent removal, **7** was obtained as a pale, yellow oil (24.86 gm, 0.0804 moles, 97%); IR: (neat) 2950, 1675 cm^{-1}: ^1H NMR: $(CDCl_3)$ δ 3.90 (s, 4 H), 0.95 (s, 3 H), 0.17 (s, 9 H); ^{13}C NMR: (acetone d6) δ 143, 113, 79, 66, 44, 42, 31, 29, 28.5, 25, 24.5, 16, 15, 2 (3).

Keto alcohol **8**. All glassware for this reaction was soaked in 20% NH_4OH aq overnight and thoroughly dried in the oven. The setup was assembled hot with a constant stream of N_2. To a 500 ml 3-neck round bottom flask, was added 250 ml of dry THF and MeLi (1.6 M in ether, 20 ml, 0.032 moles). After cooling to 0°, **7** (8.45 gm, 0.027 moles) in 100 ml dry THF was slowly added *via* syringe. Stirring at 0° for 45 min, was followed by cooling to −78°. Gaseous formaldehyde was introduced by depolymerizing paraformaldehyde (dried overnight under vacuum) at 120–145°, and sweeping it with N_2 through a −20° trap and under the surface of the soln. Bubbling in this manner continued for 45 min. Some polymerization of formaldehyde occurred at the inlet. The cold soln was poured into NH_4Cl aq and diluted with ether. The aqueous phase was separated. The organic phase was washed with NaCl aq and dried over $MgSO_4$. Solvent removal gave an oil suitable for the next reaction without additional purification. The product solidified upon standing. Recrystallization from ether/hexanes gave **8**, mp 105°; IR: $(CHCl_3)$ 3450, 2950, 2890, 1690 cm^{-1}; ^1H NMR: $(CDCl_3)$ δ 3.90 (s, 4 H), 3.46, 3.54 (AB quartet, 2 H, $J = 5$ Hz), 1.30 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR: $(CDCl_3)$ δ 218.1, 112.5, 66.4, 65.0, 64.6, 52.1, 42.7, 42.2, 35.0, 30.0, 29.4, 22.5, 21.1, 16.7, 16.0. (Found: C, 67.47; H, 9.13. Calc. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.01%).

Diol **9**. A dry, one liter round bottom flask was swept with N_2 and filled with 200 ml of dry THF and lithium tri-sec-butyl borohydride (1 M in THF, 57 ml, 0.057 moles). The flask was cooled to −78°. The crude **8** was dissolved in 100 ml dry THF and was slowly added *via* syringe. After stirring at −78° for 1 hr, the temp was raised to 0° for an additional hr. MeOH, 5 ml, was added as a quench. NaOH aq (35 ml, 10%) was added, followed by H_2O_2 aq (80 ml, 30%). Stirring at room temp was continued for 16 hr. After dilution with ether, the soln was washed with water and NaCl aq. Drying over $MgSO_4$ and solvent removal under reduced pressure gave **9** as a viscous oil, suitable for use in the subsequent reaction: IR: $(CHCl_3)$ 3350, 2950 cm^{-1}; ^1H NMR: $(CDCl_3)$ δ 3.93 (s, 4 H), 3.5 (m, 3 H), 1.27 (s, 3 H), 0.75 (s, 3 H).

Keto-acetonide **10**. The crude **9** was refluxed with 200 ml CH_2Cl_2, 100 ml acetone, and several crystals *p*-toluenesulfonic acid. After 6 hr, the soln was cooled and most of the solvent was removed by rotary evaporation. Dilution with ether was followed by washing with $NaHCO_3$ aq and NaCl aq. After drying over $MgSO_4$ the solvent was removed to leave a white solid. Compound **10** was recrystallized from ether/hexanes (6.17 gm, 0.0229 moles, 85% from **7**): m.p. 103–104°; IR: $(CHCl_3)$ 2950, 1705 cm^{-1}; ^1H NMR: $(CDCl_3)$ δ 3.63 (t, 1 H, $J = 3$ Hz), 3.27, 3.65 (AB quartet, 2 H, $J = 12$ Hz), 1.38 (s, 3 H), 1.35 (s, 3 H), 1.17 (s, 3 H), 0.82 (s, 3 H); ^{13}C NMR: $(CDCl_3)$ δ 215.0, 98.1, 72.6, 68.0, 48.1, 40.5, 37.5, 35.8, 29.3, 26.1, 25.8, 23.1, 20.1, 19.0, 17.8. (Found: C, 72.32; H, 9.95. Calc. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84%).

Alkylated keto-acetonide **11**. Freshly distilled isopropylcyclohexylamine (0.821 gm, 5.81 mmoles) and 10 ml dry THF was placed in a dry, 2 necked round bottom flask swept with N_2. After cooling to 0°, BuLi (2.3 *M* in hexane, 2.3 ml, 5.32 mmoles) was added *via* syringe. Stirring was continued for 20 min before **10** (1.287 gm, 4.84 mmoles) in 8 ml THF was added *via* syringe. The yellow soln was stirred at 0° for 30 min, then cooled to −78° and then warmed to 0° for 2 hr. The soln was poured onto sat NH_4Cl aq and diluted with ether. The aqueous phase was separated. The organic phase was washed with 0.1 N HCl, $NaHCO_3$ aq, and NaCl aq. After drying over $MgSO_4$ and filtration, the solvents were removed under reduced pressure. Chromatography on silica gel gave a white solid after removing the solvent. Recrystallization from ether/hexanes gave crystalline **11** (1.380 gm, 4.30 mmoles, 89%): m.p. 93–96°; IR: $(CHCl_3)$ 2950, 1700, 1650 cm^{-1}; ^1H NMR: $(CDCl_3)$ δ 4.70 (m, 2 H), 3.67 (t, 1 H, $J = 2$ Hz), 3.30, 3.67 (AB quartet, 2 H, $J = 12$ Hz), 1.70 (s, 3 H), 1.42 (s, 3 H), 1.38 (s, 3 H), 1.12 (s, 3 H), 0.80 (s, 3 H); ^{13}C NMR: $(CDCl_3)$ δ 213.7, 142.9, 110.9, 97.5, 72.1, 67.3, 47.6, 42.2, 41.0, 37.2, 35.3, 32.5, 29.0, 22.7, 22.0, 19.9, 18.6, 18.4, 17.0.

Diketo-acetonide **12**. Compound **11** (2.163 gm, 6.75 mmoles) was dissolved in 38 ml freshly distilled dioxane and 19 ml

water. Osmium tetroxide (0.069 gm, 0.27 mmoles) in 2 ml benzene was added and the soln turned black. After 20 min, sodium metaperiodate (3.608 gm, 16.87 mmoles) was added and the soln was vigorously stirred at room temp for 4 hr. After dilution with ether, the suspension was filtered and washed with sat NaCl aq. Drying over $MgSO_4$, filtration, and solvent removal under reduced pressure gave a black oil, which was chromatographed on silica gel to give an off-white solid. Recrystallization from ether/hexanes gave crystalline **12** (1.88 gm, 5.81 mmoles, 86%): m.p. 104–105°; IR: ($CHCl_3$) 2950, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.63 (t, 1 H, $J = 2$ Hz), 3.27, 3.60 (AB quartet, 2 H, $J = 12.5$ *Hz*), 2.80 (d, 1 H, $J = 8$ *Hz*), 2.20 (s, 3 H), 1.38 (s, 3 H), 1.33 (s, 3 H), 1.20 (s, 3 H), 0.82 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 213.3, 206.5, 97.5, 72.0, 67.3, 47.3, 42.5, 40.7, 40.6, 35.1, 31.8, 29.6, 28.6, 25.2, 22.2, 19.5, 18.4 (2), 16.6.

Tricyclic enone **13**. NaH (1.01 gm, 57% oil dispersion, 0.024 moles) was placed in a dry 2-necked round bottom flask, swept with N_2. Three portions of hexanes were used to wash out the oil. The last traces of hexanes were removed under reduced pressure. Benzene (300 ml) and 1 ml of t-pentyl alcohol were added. After stirring for 20 min, **12** (6.283 gm, 0.0195 moles) was added all at once. The mixture was heated at reflux for 2.5 hr. After cooling, the mixture was poured onto cold sat NH_4Cl aq. The aqueous phase was removed and the organic phase was washed with NaCl aq. Drying over $MgSO_4$ filtration, and removal of solvent under reduced pressure gave a yellow semi-solid. By trituration with ether/hexanes, **13** was obtained as white crystals (5.67 gm, 0.0186 moles, 95%): m.p. 136°; IR ($CHCl_3$) 2950, 1700, 1680, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.70 (s, 1 H), 3.67 (t, 1 H, $J = 2$ Hz), 3.25, 3.62 (AB quartet, 2 H, $J = 12$), 2.42 (d, 1 H, $J = 6$ Hz), 1.38 (s, 3 H), 1.35 (s, 3 H), 1.18 (s, 3 H), 0.78 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 208.5, 193.1, 121.6, 97.7, 72.2, 67.6, 41.8, 40.3, 40.1, 38.5, 37.3, 34.7, 29.2, 28.6, 22.7, 19.6, 19.1, 18.1, 16.5; (Found: C, 74.44; H, 9.23. Calc. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27%).

Allylic alcohol **15**. $LiAlH_4$ (0.125 gm, 3.28 mmoles) was suspended in 80 ml dry ether. The N_2 swept flask was cooled to −20°. **13** (2.00 gm, 6.57 mmoles) in 40 ml dry ether was slowly dripped in *via* syringe. After 30 min, 0.2 ml water, 0.2 ml 15% NaOH, and 0.6 ml water was added. When a white ppt had formed, about a gram of $MgSO_4$ was added. The mixture was filtered through celite. Solvent removal under reduced pressure gave a white solid. The allylic alcohol was recrystallized from ether/hexanes to give **15**; (1.903 gm, 6.21 mmoles, 95%): m.p. 139–152°; IR (KBr) 3300, 2950, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.20 (s, 1 H), 4.75 (br s, 1 H), 3.63 (t, 1 H, $J = 2$ Hz), 3.23, 3.63 (AB quartet, 2 H, $J = 12$ Hz), 1.38 (s, 6 H), 1.05 (s, 3 H), 0.75 (s, 3 H); ^{13}C NMR (acetone d6) δ 160.5, 121.2, 76.9, 73.5, 68.6, 42.2, 41.9, 41.6, 37.6, 31.0, 30.5, 29.8 (2), 29.2, 24.4, 21.5, 21.3, 19.5, 17.7. (Found: C, 74.64; H, 9.92. Calc. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.8%).

Allyl vinyl ether **16**. Alcohol **15** (2.606 gm, 8.50 mmoles), freshly recrystallized mercuric acetate (2.980 gm, 9.35 mmoles), and sodium acetate (0.05 gm, 0.61 mmoles) were placed in a dry round bottom flask, into which was distilled 120 ml ethyl vinyl ether (twice distilled from Na). The soln was refluxed gently for 16 hr, then cooled, and most of the solvent was removed under pressure. After dilution with ether, the soln was washed with $NaHCO_3$ aq and NaCl aq. The organic phase was dried over $MgSO_4$, filtered, concentrated and chromatographed rapidly through a short column of silica gel. Solvent removal gave a white solid. Recrystallization from hexanes gave crystalline **16** (2.54 gm, 7.64 mmoles, 90%): m.p. 55–58°; IR ($CHCl_3$) 3075, 2950, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.38 (dd, AB$\underline{X}$. 1 H, $J = 7, 14$ Hz), 5.27 (s, 1 H), 4.88 (t, 1 H, $J = 7$ Hz), 3.92–4.35 (m, 2 H, $J = 1.5$ Hz, 7.14), 3.63 (t, 1 H, $J = 2$ *Hz*), 3.23, 3.62 (AB quartet, 2 H, $J = 12$ Hz), 1.38 (s, 6 H), 1.07 (s, 3 H), 0.77 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 162,4, 150.5, 115.3, 98.0, 87.4, 83.2, 72.4, 67.8, 40.5, 37.3, 37.1, 35.6, 35.0, 34.8, 29.5, 28.4, 23.0, 20.3, 18.6, 16.9.

Olefin-aldehyde **17**. A thick walled, 50 ml, high pressure glass tube was soaked in 20% NH_4OH aq overnight and then dried overnight in the oven. Upon cooling, the tube was rinsed twice with several milliliters of bis-trimethylsilyl acetamide. The tube was then charged with **16** (0.280 gm, 0.842 mmoles), about 5 mg sublimed sodium t-pentoxide and 20 ml toluene, which had been passed through alumina and distilled from calcium hydride. The tube was immersed in liquid N_2 and allowed to warm under vacuum. This freeze-pump-thaw cycle was repeated three times. The tube was sealed under vacuum with cooling of the contents. The tube was placed in a preheated oven at 220° for 2 hr. After cooling, the tube was scored and broken open. The clear contents were filtered and concentrated under pressure. The oil was chromatographed on silica gel to give a clear oil. Trituration from ether/hexanes gave the crystalline **17** (0.168 gm, 0.50 mmoles, 60%): m.p. 127°; IR ($CHCl_3$) 3030, 2950, 2750, 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.69 (t, 1 H, $J = 3$ Hz), 6.17 (d, 1 H, $J = 6$ *Hz*), 5.88 (d, 1 H, $J = 6$ Hz), 3.62 (t, 1 H, J = 2 Hz), 3.20, 3.63 (AB quartet, 2 H, $J = 12$ Hz), 1.40 (s, 6 H), 1.02 (s, 3 H), 0.70 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 202.3, 136.1, 131.0, 97.0, 72.2, 67.3, 56.8, 44.7, 42.3, 38.2, 36.2, 33.5, 32.5, 28.6, 23.6, 22.7, 20.9, 17.8, 17.2, 15.5. (Found: C, 76.22; H, 9.81; Calc. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70%).

Hydroxy olefin **19**. $LiAlH_4$ (0.082 gm, 2.18 mmoles) was suspended in 10 ml dry THF in a dry, N_2 swept, 2 necked round bottom flask, cooled to −20°. The **17** (0.724 gm, 2.18 mmoles) in 4 ml dry THF was rapidly dripped in *via* syringe. After 30 min, the reaction was quenched with 0.1 ml water, 0.1 ml 15% NaOH aq, and 0.2 ml water. After a white ppt formed, about 0.5 gm $MgSO_4$ was added. The mixture was filtered and solvent was removed under reduced pressure to give a white solid. Recrystallization from ether/hexanes gave crystalline **19** (0.679 gm, 2.03 mmoles, 93%): m.p. 146–148°; IR ($CHCl_3$) 3450, 2950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.80 (s, collapsed AB, 2 H), 3.1–3.7 (m, 5 H), 2.03 (s, 2 H), 1.42 (s, 6 H), 0.95 (s, 3 H), 0.70 (s, 3 H); ^{13}C NMR ($CHCl_3$) δ 137.3, 131.5, 98.0, 73.5, 68.5, 62.2, 56.5, 45.9, 39.8, 35.4, 34.5, 33.7, 31.7, 29.5, 27.5, 24.6, 23.7, 22.0, 19.1, 18.0, 16.7. (Found: C, 74.92; H, 10.17. Calc. for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25%).

Olefin-tosylate **20**. Freshly recrystallized, dry *p*-toluenesulfonyl chloride (0.122 gm, 0.641 mmoles), **19** (0.195 gm, 0.583 mmoles), pyridine (0.184 gm, 2.33 mmoles), and 3 ml CH_2Cl_2 were stored in a refrigerator at −10° for 36 hr. Dilution with ether was followed by washing with cold 0.1N HCl, $NaHCO_3$ aq, and NaCl aq. After drying over $MgSO_4$, filtration, and solvent removal under reduced pressure, a yellow oil remained. Trituration with hexanes gave colorless crystals of **20** (0.260 gm, 0.554 mmoles, 95%): m.p. 123–125°; IR ($CHCl_3$) 2950, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68, 7.26 (AB quartet, 2 H), 3.90 (t, 2 H, $J = 8$ Hz), 3.58 (t, 1 H, $J = 2$ Hz), 3.17, 3.62 (AB quartet, 2 H, $J = 12$ Hz), 2.37 (s, 3 H), 1.36 (s, 6 H), 0.87 (s, 3 H), 0.65 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.7, 136.3, 133.7, 132.6, 129.8, 127.8, 98.5, 72.8, 70.1, 67.8, 55.8, 45.3, 38.7, 34.5, 33.6, 32.8, 28.9, 26.3 (2), 23.9, 23.1, 21.1, 20.6, 18.2, 17.3, 15.8.

Nor-aphidicolin keto acetonide **21**. The olefin-tosylate **20** (0.124 gm, 0.26 mmoles) was placed in a dry round bottom flask and passed into a glove box. Inside the glove box, 12 ml N-methyl-2-piperidone was distilled from calcium hydride into the flask. Disodium iron tetracarbonyl/dioxane complex (0.308 gm, 0.89 mmoles) was added. The tan mixture turned dark brown as it was stirred inside the glove box for 14 hr. The reaction was quenched with 0.5 ml AcOH, after the flask was removed from the glove box. After dilution with ether, the soln was washed with 0.1N HCl and NaCl aq. The purple soln was passed through alumina, then dried over $MgSO_4$. After filtration, the solvent was removed to give a dark oil. Chromatograohy on silica gel separated the two ketones; **22** eluted first, followed closely by **21**. Each was isolated by solvent removal under reduced pressure and recrystallized from ether/hexanes; **22** (0.023 gm, 0.065 mmoles, 25%): m.p. 139–141°; **21** (0.027 gm, 0.076 mmoles, 30%): m.p. 138–139°. Ketone **21**: IR ($CHCl_3$) 2950, 1710, 1210, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.65 (t, 1 H, $J = 2$ Hz), 3.23, 3.63 (AB quartet, 2 H, $J = 12$ Hz), 1.42 (s, 6 H), 1.08 (s, 3 H), 0.75 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 215.0, 97.7, 73.1, 68.1, 48.7, 47.8,

41.0, 39.2, 34.3 (2), 32.9, 32.5, 31.1, 29.5, 26.6, 265.6, 23.5, 21.4, 20.9, 18.7, 16.9, 15.8; (70 eV) 332, 331, 271, 243; *Anal.* Calc. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 75.82; H, 9.80. **22**: IR ($CHCl_3$) 2950, 1730, 1450, 1375 cm^{-1}. ^1H NMR ($CHCl_3$) δ 3.63 (t, 1 H, $J = 2$ Hz), 3.27, 3.65 (AB quartet, 2 H, $J = 12$ Hz), 1.43 (s, 6 H), 1.00 (s, 3 H), 0.73 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 222.7, 97.6, 72.9, 68.1, 60.6, 52.2, 43.9, 39.2, 36.6, 33.9, 33.2, 29.3, 28.5, 27.7, 26.2, 24.6, 22.8, 22.4, 20.0, 16.5, 15.7.

Methylene-acetonide **26**. Methyltriphenylphosphonium bromide (0.062 gm, 0.173 mmoles) was dried under vacuum for 1 hr. To the 2 necked, round bottom flask was added 2 ml dry ether. BuLi (2.4 *M* in hexane, 0.065 ml, 0.156 mmoles) was added *via* syringe. The yellow liquid was stirred for 2 hr at room temp. **21** (0.020 gm, 0.058 mmoles) in one ml dry ether was added *via* syringe. Stirring under N_2 for 24 hr was continued. The white soln was filtered and solvent removed under reduced pressure to give 24 mg of a white solid. Tlc showed a mixture of triphenylphosphinoxide and **26**. The crude product was used directly in the subsequent reaction. ^1H NMR ($CDCl_3$) δ 4.40 (br s, 2 H), 3.60 (t, 1 H, $J = 2$ Hz), 3.18, 3.63 (AB quartet, 2 H, $J = 12$ Hz), 1.40 (s, 6 H), 0.98 (s, 3 H), 0.72 (s, 3 H).

Diol-acetonide **27**. Crude **26** (about 25 mg) was dissolved in 1 ml pyridine. Osmium tetraoxide (0.022 gm, 0.087 mmoles) in 0.3 ml benzene was added. The black soln was stirred at room temp under N_2 for 1 hr. A soln of 0.5 ml pyridine and 0.5 ml 5% $NaHSO_3$ was added. The color of the soln lightened. After 30 min, another 0.5 ml 5% $NaHSO_3$ was added. Stirring continued for another hr to give an orange soln. Dilution with ether was followed by washing with 0.1 N HCl and NaCl aq. The aqueous phase was reextracted with ether. The combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give 29 mg crude, solid **27**; ^1H NMR ($CDCl_3$) δ 3.64 (t, 1 H, $J = 2$ Hz), 3.57 (m, 2 H), 3.20, 3.60 (AB quartet, 2 H, $J = 12$ Hz), 1.40 (s, 6 H), 1.16 (s, 3 H), 0.73 (s, 3 H).

Aphidicolin and 16-epi aphidicolin. The crude **27** (29 mg) was dissolved in 3 ml THF, 0.5 ml MeOH, and 1 ml 5% HCl and stirred for 8 hr. The mixture was extracted with six portions of CH_2Cl_2, dried over $MgSO_4$, and filtered. Solvent removal under reduced pressure gave 18 mg of a white solid. Trituration with ether/hexanes/methanol gave crystalline 16-epi aphidicolin (6 mg, 0.018 mmoles, 31% from **21**, 3 steps): m.p. 233–235°. The mother liquor was concentrated and stored in the refrigerator overnight. White crystals were isolated by removing the solvent by micropipet. Thorough drying under vacuum gave **1** (7 mg, 0.021 mmoles, 36% from ketone **20**, 3 steps): m.p. 218–220°; tlc: (ether/hexanes/-methanol: 4/1/0.3, 3 developments), natural aphidicolin, synthetic aphidicolin, $R_f = 0.51$, 16-epi aphidicolin, $R_f = 0.48$; aphidicolin: ^1H NMR (pyridine d5) δ 4.8–6.1 (br, 4 H, –OH), 3.87 (br s, 1 H), 3.72 (s, 2 H), 3.58; 3.88 (AB quartet, 2 H, $J = 10$ Hz), 1.10 (s, 3 H), 0.78 (s, 3 H); MS (70 eV) 334, 333, 320, 308, 307, 290, 289, 275, 271, 260, 259. (Found: C, 71.28; H, 10.01. Calc. for $C_{20}H_{34}O_4$: C, 70.97; H, 10.12%). 16-Epi aphidicolin: ^1H NMR (pyridine d5) δ 4.9–6.1 (br, 4 H, –OH), 3.95 (br s, 1 H), 3.90 (s, 2 H), 3.66, 3.82 (AB quartet, 2 H, $J = 10$ Hz), 0.99 (s, 3 H), 0.78 (s, 3 H); MS: (70 eV) 334, 333, 320, 308, 307, 290, 289, 275, 271, 260, 259.

Acknowledgements—We thank Dr. Barrie Nesp, Imperial Chemical Industries for his help in supplying comparison samples of aphidicolin and derived materials. This work was supported by the National Institutes of Health through grant AI 14127. The NMR and GC/MS instruments used in this work were partially funded by chemical instrumentation grants from the National Science Foundation. We thank Mr. Eric Papiashvili for expert assistance in carrying out the spectroscopic analyses.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 329 to 344, 1981
Printed in Great Britain

0040-4020/81/Suppl. 1-0329-16 $02.00/0
Pergamon Press Ltd.

CONSTITUTIONAL AND CONFIGURATIONAL ASPECTS OF THE THERMAL REORGANIZATION OF 1-CYANO-2-VINYLCYCLOBUTANE (I)

W. VON E. DOERING* and A. R. MASTROCOLA

Department of Chemistry, Harvard University, Cambridge, MA 02138, U.S.A.

(*Received in U.S.A.* 21 *July* 1980)

Abstract—Kinetics and Arrhenius parameters have been determined for three processes: automerization, ring expansion and cycloreversion, occurring in the thermal reorganization of racemic *cis* and *trans*-I. Through the reorganization of optically active materials, automerization is trisected into enantiomerization and two epimeric diastereomerizations, and ring expansion is dissected into processes leading to enantiomeric 4-cyanocyclohexenes (II). Evidence pointing to concertedness being undiscernible, the system of reorganizations is classified as not obviously concerted and discussed in terms of relative propensities of groups to rotate internally. Comparison with similar cyclopropane systems reveals no qualitative differences (beyond cycloreversion) and only one substantial quantitative difference; that is, an enhanced tendency in the cyclobutane toward ring expansion.

In order better to understand the role of internal rotation in thermal rearrangements of small rings, the behaviour of *cis* and *trans* 1-cyano-2-vinylcyclobutane (*cis*- and *trans*-I; Fig. 1)[1] is investigated. The purpose is to compare 3- and 4-membered rings in diastereomerization and enantiomerization (Fig. 1) and in ring expansions, to cyclopentene and cyclohexene, respectively (Fig. 2).

In studies of 1-cyano-2-isopropenylcyclopropane (Fig. 1: $H_m = CH_3$, cyclopropane *vice* cyclobutane; Table 5, *vide infra*), relative rotational propensities have been recognized as the key factor.[2] From the proof of Onsager that the product of specific rate constants in one sense is equal to the product in the opposite sense in a multicomponent system at equilibrium,[3] it follows specifically in the case in Fig. 1 that $k_1k_4k_1k_4 = k_2k_3k_2k_3$ whence the ratio $k_4/k_3 = k_2/k_1$. This ratio (R_A) defines the relative propensity of A to rotate internally in preference to B and is independent of starting material (k_4/k_3 from *cis* and

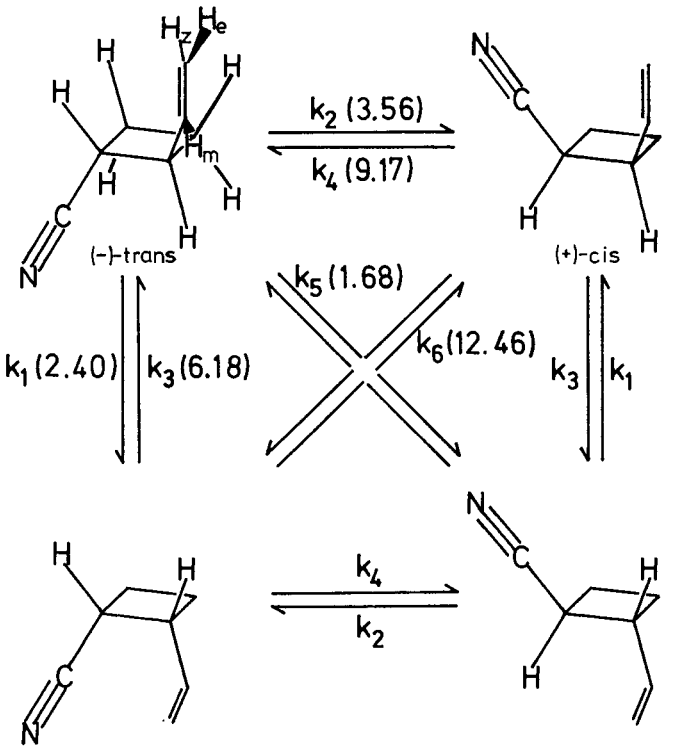


Fig. 1. Diastereomerization and enantiomerization (automerization) in 1-cyano-2-vinylcyclobutane (I) (specific rate constants at 217.8°, $10^{-6}\,sec^{-1}$).

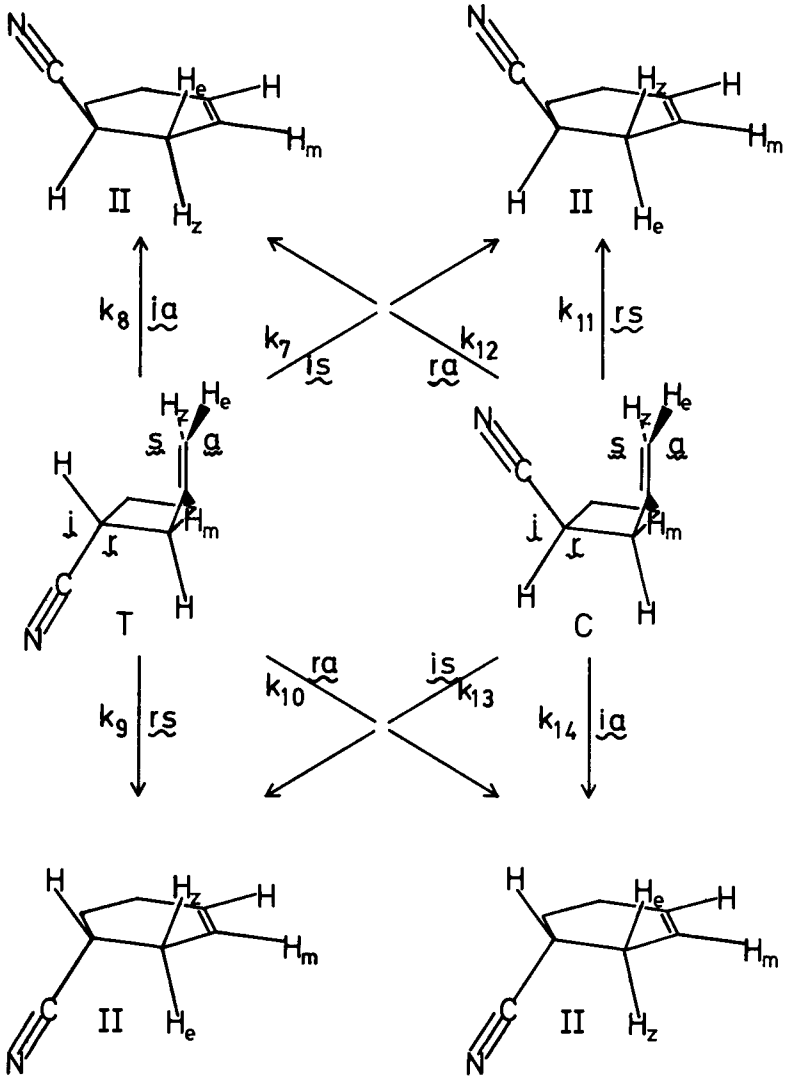


Fig. 2. The scheme of Mazzocchi and Tamburin[6] for the stereochemical elucidation of ring expansion is illustrated with 1-cyano-2-vinylcyclobutane (I). Values of specific rate constants at 217.8° follow: $(k_7 + k_8) = k_{TIi} = 2.90$, $(k_9 + k_{10}) = k_{TIr} = 2.07$; $(k_{11} + k_{12}) = k_{CIr} = 4.47$ and $(k_{13} + k_{14}) = K_{CIi} = 2.12 \times 10^{-6}\,sec^{-1}$.

k_2/k_1 from *trans*). In 1-cyano-2-isopropenylcyclopropane at 217.8°, rotation of A (cyano) is favored over rotation of B (isopropenyl) by a factor of 2.20.

Ring expansion in this cyclopropane series (Fig. 2: $H_m = CH_3$, cyclopropane → cyclopentene; Table 5, *vide infra*) is barely competitive: 2.50% from the *trans* isomer, 1.17% from the *cis* isomer. Because the terminal CH_2 moiety of the vinyl group is unsubstituted, stereochemical analysis is limited to inversional (**i**) and retentional (**r**) components and cannot inform the suprafacial (**s**) and antarafacial (**a**) components. Determined from the *trans* isomer, the ratio, **i**/**r**, is 2.4; from the *cis* isomer, **i**/**r** = 0.67.[4]

Related to this work are examples of Berson *et al.*[5] of cyclobutanes *cis*- and *trans*-1,2-disubstituted by *cis*- and *trans*-propenyl groups (Fig. 2: H_e or $H_z = CH_3$; $CH_3CH{=}CH-$ vice CN). Designed to probe other aspects of the multifaceted mechanistic problem, the two more thoroughly studied examples contain sufficient symmetry to confer achirality on the *cis* diastereomers and therefore have an R_A factor equal trivially to 1.00. However insufficient to realization of the full potential in the Mazzocchi–Tamburin design,[6] shown in Fig. 2, they permit elucidation of the stereochemistry of the ring expansion from the *trans* isomer. Such a limitation does not apply to the *cis* and *trans* 1-*cis*-propenyl-2-*trans*-propenylcyclobutanes, examples which, quite understandably, remain incompletely investigated.

The present work, too, falls short of a theoretically full elucidation owing to lack of labelling in the vinyl group. It does permit evaluation of an R_A factor, which reasonably can be compared with that of the closely related cyclopropane,[2] and it does allow determination of the inversional (**i**) and retentional (**r**) (but not the suprafacial (**s**) and antarafacial (**a**)) components of

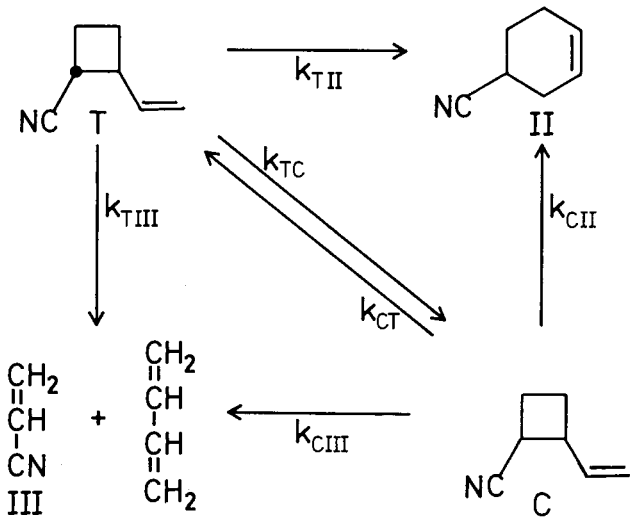


Fig. 3. These competitive constitutional reorganizations constitute the minimal kinetic set for *racemic* 1-cyano-2-vinylcyclobutane. With reference to Fig. 1, $(k_1 + k_2) = k_{TC}$ and $(k_3 + k_4) = k_{CT}$; and with reference to figure 2, $(k_7 + k_8 + k_9 + k_{10}) = k_{TII}$ and $(k_{11} + k_{12} + k_{13} + k_{14}) = k_{CII}$.

the ring expansion of both the *cis* and *trans* diastereomers for comparison with their close cyclopropane relatives.[4]

Although full Mazzocchi–Tamburin design has by now been realized in the cyclopropane series by Doering and Barsa,[7] in the cyclobutane series a similarly complete treatment awaits the completion of current studies of *cis*- and *trans*-1-cyano-*trans*-propenylcyclobutane (also labelled stereospecifically with deuterium in the 3 and 4 positions to permit resolution of the internal rotational components of cycloreversion[8]).

Kinetics of thermal reactions of racemic cis *and* trans-1-*cyano-2-vinylcyclobutane*

cis-I and *trans*-I are prepared by the photosensitized cycloaddition of butadiene and acrylonitrile according to the method of Dilling and Kroening.[9] When heated in the gas-phase at 217.8°, *cis*-I and *trans*-I undergo the reactions outlined in Fig. 3 with a mass balance >98% of theory.

Within the limits of detection (~0.2%), 3-cyanocyclohexene, which might have resulted from breaking the C_2–C_3 bond, is not formed. 4-Cyanocyclohexene (II) is recovered unchanged on being heated to 217.8° for 12 hr.

Various factors which might have influenced the rearrangements of I are collected in Table 1. Because changing from Pyrex, an acidic glass, to Corning 0120, a basic lead-potash glass, makes no difference, surface catalysis is not indicated. The lack of change between experiments at 700 mm and 1 mm total pressure indicates that results pertain to the high-pressure region, as would be expected according to RRKM

Table 1. Thermal rearrangement of 1 under a variety of conditions for 4 hr at 217.8°

Conditions	Products						
	cis-I		trans-I		II		III
	yield,%	opt.pur.,%	yield,%	opt.pur.,%	yield,%	opt.pur.,%	yield,%
700 mm/Pyrex[a]	64.7	69.3	15.9	13.7	8.3	23.5	11.1
700 mm/0120[a,c]	64.6	----	14.9	----	8.0	----	12.5
1 mm/Pyrex[a]	69.1	68.1	16.3	13.4	8.3	23.9	6.3
CH_3CN (10% sol.)[a]	60.7	81.1	10.1	9.4	12.7	13.2	16.4
700 mm/Pyrex[b]	6.2	14.6	81.2	94.4	6.7	14.4	5.9
700 mm/0120[b,c]	5.9	----	81.2	----	6.6	----	6.2
CH_3CN (10% sol.)[b]	5.2	10.1	78.2	95.9	10.0	2.1	6.9
C_6H_6 (10% sol.)[b]	5.4	9.1	77.5	93.6	10.9	6.8	5.1

[a] Starting material is (+)-cis-I. When not 100% of optical purity, results are corrected. [b] Starting material is (+)-trans-I. Similarly corrected. [c] Corning 0120, lead-potash glass.

Table 2. Specific rate constants for the six thermal reorganizations of *cis*- and *trans*-I

k_i [a]	T°C	217.8° [b]	207.1° [b]	191.7° [c]	178.4° [d]
k_{TC}		5.96 ± 0.1 *5.87 ± 0.07*	2.28 ± 0.1 *2.25 ± 0.06*	4.54 ± 0.3 *4.45 ± 0.23*	11.92 ± 0.3 *12.01 ± 1.05*
k_{TII} [e]		4.95 ± 0.1 *4.93 ± 0.06*	1.89 ± 0.1 *1.87 ± 0.03*	4.52 ± 0.6 *3.88 ± 0.21*	10.31 ± 0.2 *10.48 ± 0.90*
k_{TIII}		4.16 ± 0.4 *4.16 ± 0.32*	1.58 ± 0.1 *1.57 ± 0.03*	3.00 ± 0.2 *2.99 ± 0.09*	7.35 ± 0.5 *7.43 ± 0.29*
k_{CT}		15.29 ± 0.2 *15.12 ± 0.28*	6.29 ± 0.1 *6.18 ± 0.10*	12.86 ± 0.6 *12.71 ± 0.66*	34.5 ± 0.3 *34.12 ± 0.26*
k_{CII}		6.60 ± 0.1 *6.51 ± 0.11*	2.66 ± 0.1 *2.64 ± 0.05*	5.32 ± 0.4 *5.26 ± 0.31*	14.19 ± 0.2 *14.10 ± 0.16*
k_{CIII}		8.64 ± 0.5 *8.55 ± 0.99*	3.44 ± 0.3 *3.39 ± 0.25*	6.49 ± 0.8 *6.40 ± 0.59*	15.70 ± 0.5 *15.59 ± 0.42*

[a] The six specific rate constants outlined in Figure 3. [b] k_i in units of 10^{-6} sec^{-1}. [c] k_i in units of 10^{-7} sec^{-1}. [d] k_i in units of 10^{-8} sec^{-1}. [e] Values in italics obtained by Glenn Graham.[15]

theory for molecules of this many atoms. The same conclusion may be drawn from the results in benzene. Acetonitrile as solvent reveals little effect on the rates of rearrangement or influence on product distribution and configurational characteristics. There is possibly a little less diastereomerization relative to ring enlargement and cleavage, but no sufficiently dramatic effect to suspect a change from homolytic to heterolytic mechanism of the type so convincingly demonstrated by Chmurny and Cram in more appropriately substituted cyclopropanes.[10]

The possibility that *trans*-I and II might be formed from *cis*-I by subsequent condensation of the primary decomposition products, acrylonitrile (III) and butadiene,[9] can be rejected. First, *trans*-I is produced from *cis*-I (and *vice versa*) in far too high an amount to be accommodated by the condensation, which leads to II, *cis*-I and *trans*-I in the ratios, 200:1:1, respectively.[11] Second, a quantitative estimate of the rate of condensation is too low to account for the amount of II formed from *cis*-I or *trans*-I. A single, specific rate constant, available for the Diels–Alder condensation of acrylonitrile and butadiene ($k_{ab} = 9 \times 10^{-6}$ l/m.s. at 120°), can be coupled with an estimated† $E_a = 20600$ cal/mol to generate an estimated set of parameters, $\log k_{ab} = 6.40 - 20600/RT\ln 10$ and thence an estimated $k_{ab} = 1.72 \times 10^{-3}$ l/ms. at 217.8°. If the longest run with *cis*-I at the highest temperature (14400 sec at 217.8°) is taken and the assumption is made that the 11.1 % of III and butadiene present at the end of the reaction had prevailed from the beginning, no more than 2.1 % of the total amount of II could have arisen by a secondary Diels–Alder condensation.†

For determination of specific rate constants, reactions are effected in Pyrex ampoules with benzonitrile added as an internal standard for the subsequent gc analyses. The data are collected in Table 6. Specific rate constants are computed by numerical integration until, by trial and error, differences between experimental and calculated concentrations of all components at each time have been minimized. The function minimized ($\bar{\sigma}$) corresponds to the standard deviation (σ) in linear regression, but does not have the same statistical significance, since best fits are being sought for curved lines. The following set of differential equations corresponds to the scheme in Figure 3 and is the model for the extraction of specific rate constants:

$$d[T]/dt = -(k_{TC} + k_{TII} + k_{TIII})[T] + k_{CT}[C]$$

$$d[C]/dt = -(k_{CT} + k_{CII} + k_{CIII})[C] + k_{TC}[T]$$

$$d[II]/dt = k_{TII}[T] + k_{CII}[C]$$

$$d[III]/dt = k_{TIII}[T] + k_{CIII}[C]$$

For each of the four components, we have plotted $\bar{\sigma}_j$ vs each of the six specific rate constants, k_i. From the resultant "sensitivity" curves, an optimum value of k_i is easily identified. Uncertainty in k_i is arbitrarily taken as those + and − increments which lead to a doubling of the best $\bar{\sigma}_j$. The resultant ± values are certainly not standard deviation in the normal sense, but they should at least indicate relative uncertanties among k_i.[1] Optimized values for the six specific rate constants at four temperatures are recorded in Table 2.

The widely ignored problem of extracting uncertainties for systems of many specific rate

†Activation parameters for condensation of acrylonitrile–isoprene have been determined: $\log k = 6.75 + 19000/RT\ln 10$;[12] the difference in E_a between acrolein–isoprene ($\log k = 6.16 + 18700/RT\ln 10$) and acrolein–butadiene ($\log k = 6.01 + 19700/RT\ln 10$) is ~1000 cal/mol;[13] the ratio of k (acrolein)/k(acrylonitrile) = 7.9 in reactions with butadiene at 120° corresponds to $\Delta\Delta G^{\neq} \sim 1600$ cal/mol.[14]

†The ~6 mg of *cis*-I (m.w. 125.1) in an 8-ml ampoule in these runs corresponds to ~6.0×10^{-3} mol/liter. Setting the concentrations of III and butadiene at 11.1 % of this value, it can be calculated from the rate equation that 8.06×10^{-6} mol/liter of Diels–Alder condensation product would have been formed. This amounts to 2.1 % of that actually produced.

constants from the sum of the squares of the residual differences between calculated and observed concentrations has been examined by Glenn Graham.[15] The results of his application of the Simplex method to optimization of rate constants and of the theory of prediction error estimates to extract the associated standard deviations are also given in Table 2.

Arrhenius parameters are derived in the usual manner by least squares linear regression from the data in Table 2 and are collected in Table 3. The value of the equilibrium constant, $K = k_{CT}/k_{TC}$, is consistent with the small effective van der Waals circumference of the cyano group.[16] The interaction appears to originate in the enthalpy term: $\log K = (-0.126 \pm 0.18) + (1250 \pm 400)/RT\ln 10$.

Rates of disappearance of *trans*-I (k_T) and of *cis*-I (k_C) are given by the following expressions:

$$\log k_T = (14.82 \pm 0.16) - (44100 \pm 330)/RT\ln 10$$

$$\Delta H^{\pm} = 43.2\,\text{kcal/mol};\ \Delta S^{\pm} = 6.4\,\text{e.u.}$$

$$\log k_C = (14.91 \pm 0.39) - (43600 \pm 830)/RT\ln 10$$

$$\Delta H^{\pm} = 42.7\,\text{kcal/mol};\ \Delta S^{\pm} = 6.8\,\text{e.u.}$$

Question of concertedness

Three features of the kinetic results from racemic *cis*- and *trans*-1 are worthy of note. First, the two sets of three disparate reactions in Fig. 3, one each from *cis* and *trans*, encompass a narrow range of energies of activation (2.65 kcal/mol) and a narrow range of preexponential factors (1.23 in log A). Within each of the two sets of the ratio of the fastest to the slowest process is no greater than 2.3. Between the two sets the ratio of related rate constants is also small, but that is no more than a reflection of the remarkably small steric influence exercised by the cyano group.[16] Clearly, no extraordinary, fortuitously compensating effect on the entropy of activation conceals a process of widely differing enthalpy of activation.

Second, these thermal reorganizations can be related to the cycloreversion of unsubstituted cyclobutane by considering their respective enthalpies of activation, all of which are clustered between 41.9 and 44.6 kcal/mol. The best value[17] for cyclobutane we owe to Vreeland and Swinehart,[18] who deduce the rate expression, $\log k = 15.85 - 63200/RT\ln 10$, whence $\Delta H^{\neq} = 61.7$ kcal/mol and $\Delta S^{\neq} = 10.2$ e.u. If compensations for substitution of H by cyano[19] and vinyl[20] are made by subtraction of their stabilizing effects on the carbon free radical, 8 and 15 kcal/mol, respectively, a predicted value for the enthalpy of activation of 38.7 kcal/mol is derived. This model implies no greater a degree of concertedness than that contained in the reference reaction, cycloreversion of cyclobutane. Although it, is widely accepted that cycloaddition/reversion is not concerted, strong support for this hypothesis is provided in a recent stereochemical study by Doering and Guyton of labelled acrylonitrile.[8] Consistently, the energy criterion of concert—that the experimental enthalpy of activation be lower, by an amount outside the estimated limits of uncertainty, than an enthalpy of activation, experimental or calculated as the case may be, associated with an appropriate non-concerted model—offers no encouragement for assigning either this reaction or its two relatives to the concerted class.

The third feature to note is the apparent absence of feedback of thermochemical information in the products to the respective transition states for their formation. Why are these thermal reorganizations so insensitive to the substantial thermochemical and constitutional differences among the three types of products? Heats of formation are known for acrylonitrile and butadiene,[21] but not for *cis*-I, *trans*-I or II. Although there are ample data supporting an increment, 32.87 kcal/mol, for the replacement of primary H in RH by CN,[22] there is only a single value for the replacement of secondary H by CN. We take that value, the difference between isopropylnitrile and propane, 31.01 kcal/mol,[21] as the basis for deriving the heat of formation of 4-cyanocyclohexene (II) from that of cyclohexene. The heat of formation of *trans*-I is estimated by adding to that of cyclobutane this increment for the replacement of secondary hydrogen by secondary nitrile and an increment for the replacement of secondary hydrogen by secondary

Table 3. Arrhenius parameters for the six thermal reorganizations of *cis*- and *trans*-1

k_i [a]	$\log A_i \pm s$	$\Delta S_i^{\neq}$	$E_{a_i} \pm s$	$\Delta H_i^{\neq}$
k_{TC}	14.41 ± 0.31	4.48	44.09 ± 0.66	43.15
k_{TII}	13.88 ± 0.38	2.08	43.08 ± 0.82	42.14
k_{TIII}	14.88 ± 0.31	6.66	45.50 ± 0.66	44.56
k_{CT}	14.27 ± 0.38	3.87	42.85 ± 0.82	41.91
k_{CII}	14.15 ± 0.38	3.29	43.39 ± 0.82	42.46
k_{CIII}	15.11 ± 0.42	7.71	45.28 ± 0.90	44.34

[a] $\log k_i = \log A_i - E_{a_i}/RT\ 10^{-3}\ln 10$; E_{a_i} and $\Delta H_i^{\neq}$ in kcal/mol; $\Delta S_i^{\neq}$ in cal/deg.

vinyl, 18.65 kcal/mol.† The heat of formation of *cis*-I is that of *trans*-I corrected by the experimental difference revealed in the temperature dependence of their equilibrium constant; i.e. 1.25 kcal/mol (*vide supra*).

The customary enthalpy diagram is then constructed in order to facilitate visualization of relations among heats of formation of stable molecules and interconnecting transition states (Fig. 4). Several features emerge.

Thermodynamically, ring enlargement is enthalpically favored by 26.5–27.7 kcal/mol over automerization, its closest competitor, and might be expected to generate II exclusively but, in fact, falls far short of doing so. In contrast, cycloreversion, also an operationally competitive process, is disfavored enthalpically by a significant amount, 13 ± 0.5 kcal/mol. To be sure, the thermodynamically controlled position of equilibrium is not unfavorable in the temperature range studied (178.4–217.8°), nor is it expected to be, because a favorable change in entropy of translation, a not unreasonable estimate of which is $\Delta S \sim 30$ e.u., could contribute 14 ± 0.5-kcal/mol. The third process, automerization, is essentially thermoneutral, because the full strain of the cyclobutane ring is reincorporated. It, too, competes effectively with the two other types.

Surely, the insouciance of rates to the inherent thermodynamic advantages and disadvantages of products must count as a striking aspect of these thermal reorganizations. This phenomenon appears to be a fundamental characteristic of the not obviously concerted class of reorganizations. Although more examples must be acquired if this presently tentative impression is to be transformed into a reliable empirical generalization, even now it must command close attention.

A conceptual device sufficient for blocking transmission of thermochemical information is the interposition of a hypothetical intermediate, the formation of which is rate-determining. More generally, it is necessary only that the reactions not be concerted, that the transition states, in the framework of orbital symmetry, either not be representable as resonance hybrids of educt and product or, if so representable, achieve no energy lowering thereby.

The Diels–Alder condensation of acrylonitrile and butadiene adds to the energy diagram a reaction widely regarded as concerted. While Arrhenius parameters for this reaction are not available, they can be estimated in reasonably reliable fashion and are given by the equation, $\log k_{ab} = 6.40 - 20600/RT\ln 10$ (*vide supra*). It is reassuring to note consistency with the reactions of butadiene with itself to give vinylcyclohexene $[\log k = 5.89 \pm 0.14) - (23060 \pm 290)/RT\ln 10]$[23] and with ethylene to give cyclohexene $[\log k = (10.46 \pm 0.29) - (27500 \pm 800)/RT\ln 10]$.[24]

The transition state of the Diels–Alder reaction of acrylonitrile and butadiene may thus be placed 8–11 kcal/mol below the other transition states of Fig. 4. This Diels–Alder reaction is thereby safely concerted by the criterion that the activation enthalpy be lower than that of a non-concerted model.

More nearly direct experimental confirmation of the degree of concert may be derived from the data of Dilling and Kroening,[9] who find ratios of 4-cyanocyclohexene to *cis*- and *trans*-I of 370 and 475, respectively, in the condensation of acrylonitrile and butadiene at 150° (no solvent). These ratios correspond to $\Delta\Delta G^{\neq}$ of 5.0 and 5.2 kcal/mol, respectively. Lack of data at other temperatures, however, prevents dissection into $\Delta\Delta S^{\neq}$ and $\Delta\Delta H^{\neq}$ or quantitative comparison with the value of $\Delta\Delta H^{\neq}$ indicated in Fig. 4 from the decomposition of *cis*- and *trans*-I.

Parenthetically, note that the corresponding lowering in the Diels–Alder dimerization of butadiene amounts to 3–4 kcal/mol.[23] Presumably, the greater radical-stabilizing effect of vinyl *vis-à-vis* cyano (15 vs 8 kcal/mol, respectively)[19] opposed by a slightly greater conjugative interaction in butadiene *vis-à-vis* acrylonitrile (3.5 vs 2.5 kcal/mol, respectively) suffices to account for the smaller, just barely recognizable degree of concert: 8–11 kcal/mol (concert with acrylonitrile) less 7 kcal/mol plus 1 kcal/mol equals 2–5 kcal/mol (concert with butadiene).

Qualities usually associated with concerted reactions—regiospecificity rather than multiplicity of products, lowered activation enthalpy *vis-à-vis* that predicted of a non-concerted model—are not evident in the thermal reorganizations of *cis*- and *trans*-I. Although their non-concerted nature should not be considered proved—if the non-existence of a quality be at all a fit subject for disproof—at least none of the reactions falls obviously into the concerted category. To assign this set of constitutionally disparate thermal reorganizations to the class of not obviously concerted transformations seems apt.

Optical activity in cis- *and* trans-*I*

Introduction of optical activity offers a further look into the thermal behaviour of *cis*- and *trans*-I. Although it sheds no light on cycloreversion, it illuminates the process of ring expansion, if only partially because optical activity must be coupled with additional constitutional labelling in the vinyl groups. (Fig. 2, $H_e = CH_3$, for example). However, the *cis* diastereomer, which is achiral in the published examples,[5] is chiral here. Having optical activity in both *cis*-I and *trans*-I promises the same degree of insight into automerization as has been obtained in closely related cyclopropanes.[2] For the first time, internal rotational propensity can be determined in a cyclobutane ring and compared with its counterpart in a cyclopropane ring. What can be expected of optical activity as a tracer is shown in Fig. 1 for automerization and in Fig. 2 for ring expansion. Owing to the equality of H_e and H_z, the number of distinguishable rate constants is reduced by a factor of 2: thus, $(k_7 + k_8) = k_{TIIi}$; $(k_9 + k_{10}) = k_{TIIr}$; $(k_{11} + k_{12}) = k_{CIIr}$ and $(k_{13} + k_{14}) = k_{CIIi}$.

The preparation of optically active *cis*-I and *trans*-I begins with the readily available *trans*-1,2-cyclobutanedicarboxylic acid[25] and proceeds to the corresponding monomethyl ester by way of the dimethyl ester.[26] Reduction by the action of diborane[26] followed by oxidation with the triethyl-

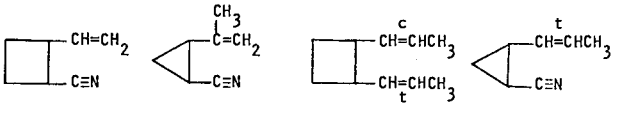
†The average of four differences in heats of formation obtained from the following pairs: 3-methylbut-1-ene–propane, 3-methylpent-1-ene–butane, vinylcyclopentane–cyclopentane and vinylcyclohexane–cyclohexane.[21]

Table 4. Specific rate constants at 217.8° of the reactions of (−)-*trans*-I and (+)-*cis*-I

(-)-trans-I		(+)-cis-I	
k_1 [a]	2.40 ± 0.02 [a,b]	k_3	6.18 ± 0.06
k_2	3.56 ± 0.05	k_4	9.17 ± 0.09
k_5	1.68 ± 0.28	k_6	12.46 ± 0.18
k_{TII_i} [c]	2.90 ± 0.03	k_{CII_i}	2.12 ± 0.06
k_{TII_r}	2.07 ± 0.02	k_{CII_r}	4.47 ± 0.06
k_{TIII}	4.17 ± 0.41	k_{CIII}	8.66 ± 0.55

[a] Error shown is ± $2\bar{\sigma}$ where $\bar{\sigma}$ is the square root of the sums of the squares of the deviations divided by n − 1. [b] Specific rate constants in units of 10^{-6} sec^{-1}. [c] See figure 2 in which $K_7 + k_8 = k_{TII_i}$, $k_9 + k_{10} = k_{TII_r}$, $k_{13} + k_{14} = k_{CII_i}$, $k_{11} + k_{12} = k_{CII_r}$.

Table 5. Comparison of thermal rearrangements among 1-cyano-2-vinylcyclobutane (this work), 1-*cis*-propenyl-2-*trans*-propenylcyclobutane,[5] 1-cyano-2-isopropenylcyclopropane,[4] and 1-cyano-2-*trans*-propenylcyclopropane[7]



k_1 [a,b]	2.40	3.16	7.20 [f]	5.69
R_A [c]	1.48	2.20		2.36
K [d]	2.58	2.67	9.31	1.47
k_5	1.68	7.03	5.30	9.84
k_6	12.46	9.20		10.73
k_7 (is)	} 2.90 [e]	0.31 [e]	6.58	0.231
k_8 (ia)			0.04	0.097
k_9 (rs)	} 2.07 [e]	0.13 [e]	6.29	0.048
k_{10} (ra)			0.32	0.057
k_{13} (is)	} 2.12 [e]	0.55 [e]		0.29
k_{14} (ia)			5.4 [g] 29.0 [h]	0.27
k_{11} (rs)	} 4.47 [e]	0.84 [e]		0.57
k_{12} (ra)				0.18
T°C	217.8°	217.8°	146.5°	207.1°

[a] All rate constants in units of 10^{-6} sec^{-1}. [b] Rate constants are defined in figures 1 and 2. [c] $R_A = k_2/k_1 = k_4/k_3$. [d] $K = k_3/k_1 = k_4/k_2$. [e] With reference to figure 2, $k_{TII_i} = k_7 + k_8$; $k_{TII_r} = k_9 + k_{10}$; $k_{CII_i} = k_{13} + k_{14}$; $k_{CII_r} = k_{11} + k_{12}$. [f] Because starting material is racemic, this rate constant is not k_1, but $k_1 + k_2$. [g] $k_{12} + k_{13}$ (ra + is): trans-V. [h] $k_{11} + k_{14}$ (rs + ia): cis-V.

amine-dimethylsulfoxide-sulfur trioxide system[27] affords the aldehydic ester, condensation of which with methylene triphenylphosphorane[28] produces a 9:1 mixture of *trans*- and *cis*-1-carbomethoxy-2-vinylcyclobutane. From the mixture of *trans* and *cis* carboxylic acid obtained upon hydrolysis, recrystallization of the quinine salt from ethanol and water affords the (−)-*trans* enantiomer.

Although a constant specific rotation is attained after six recrystallizations, a better check on optical purity is obtained by oxidation and methylation to (1R:2R)-(−)-*trans*-1,2-biscarbomethoxycyclobutane which is of known optical purity and absolute configuration.[5]

Conversion to (1R:2S)-(−)-*trans*-I is accomplished by sequential treatment with ethyl chloroformate,

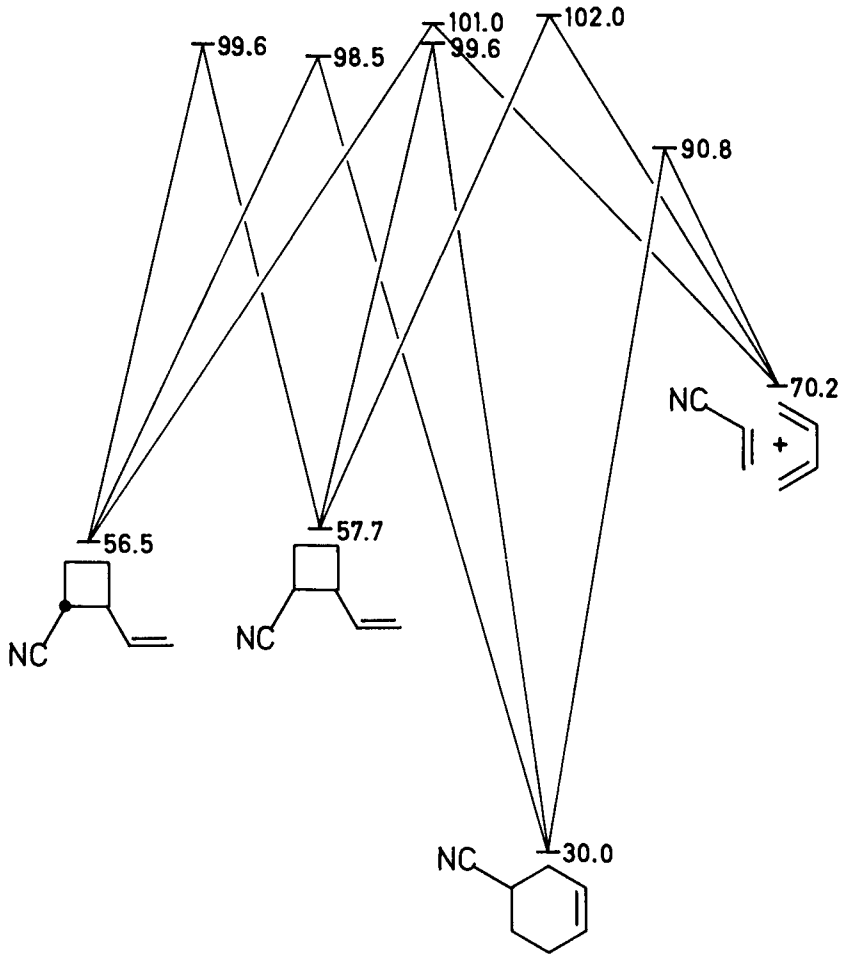


Fig. 4. Enthalpy diagram in kcal/mol (+) for reorganizations on the acrylonitrile-butadiene surface.

ammonia, and *p*-toluene sulfonylchloride in pyridine.[4] Owing to the unlikelihood of racemization in these reactions, the product, (−)-*trans*-I, is assumed to have the same degree of optical purity as the acid from which it is made.

Preparation of the *cis*-diastereomer of known optical purity and known configurational relation to (1R:2S)-(−)-*trans*-I is accomplished by establishment of equilibrium through the action of potassium t-butylate in dimethyl sulfoxide. Because recovered (−)-*trans*-I shows no decrease in specific rotation, and hydrogen α to cyano is known to be jeopardized under these conditions, it follows that (+)-*cis*-I and (−)-*trans*-I have the same configuration of the vinyl group and that (+)-*cis*-I is (1S:2S).

In order to complete the groundwork for the study, the maximum rotation of 4-cyanocyclohexene (II) and its configuration relative to I are required. The absolute configuration and maximum rotation of (S)-cyclohexene-4-carboxylic acid is already known by its chemical correlation to 4-vinylcyclohexene[29] and by the chemical correlation of 4-vinylcyclohexene to 3-methylcyclohexanone.[5] It thus remains only to convert (S)-(−)-cyclohexene-4-carboxylic acid to the corresponding nitrile, (S)-(−)-II by a conventional method. The absolute configurations are shown in Figs. 1 and 2, while maximum specific rotations are collected in Table 7.

Diastereomerization can be dissected into specific rate constants for the formation of each enantiomer: k_{TC} and k_{CT} of Fig. 3 into k_1 and k_2, and k_3 and k_4, respectively, of Fig. 1. Ring expansion can be dissected in similar fashion: k_{TII} and k_{CII} of Fig. 3 into k_{TIIi} and k_{TIIr}, and k_{CIIi} and k_{CIIr}, respectively, of Fig. 2. Additionally, enantiomerizations corresponding to the otherwise concealed reactions, k_5 and k_6, of Fig. 1 can be determined.

Quantitative evaluation of these rate constants is based on differential equations which represent cycloreversion and the transformations in Figs. 1 and 2 and define the concentrations of (+) and (−)-*cis* and *trans*-I, (+) and (−)-II and acrylonitrile (III). The experimental data are collected in Table 8. Note that treatment of optically active II at 217.8° for 12 hr occasions neither constitutional nor optical change. Approximate values of the specific rate constants for diastereomerization are obtained by graphical extrapolation to zero time of the fraction of retained optical activity at five different points and partitioning the specific rate constant for diastereomerization of

Table 6. Thermal reorganizations of I in Pyrex ampoules in the gas-phase[a]

Temp.[b] (°C)	Time (sec)	Trans-I[c] (%)	Cis-I[c] (%)	II[c] (%)	III[c] (%)	Recovery[d] (%)
217.8°[e]	2700	96.37 ± 0.23	1.49 ± 0.00	1.28 ± 0.01	0.86 ± 0.06	99.0
217.8°	5400	92.62 ± 0.48	2.83 ± 0.00	2.57 ± 0.02	1.96 ± 0.13	99.3
217.8°	8100	88.67 ± 0.19	4.01 ± 0.02	3.87 ± 0.02	3.43 ± 0.23	100.0
217.8°	10800	85.39 ± 0.24	5.04 ± 0.01	5.15 ± 0.02	4.41 ± 0.41	99.4
217.8°	14400	81.19 ± 0.24	6.17 ± 0.01	6.74 ± 0.02	5.90 ± 0.34	99.0
207.1°[f]	5400	96.96 ± 0.04	1.20 ± 0.01	0.97 ± 0.00	0.85 ± 0.05	100.0
207.1°	10800	93.98 ± 0.04	2.31 ± 0.02	1.95 ± 0.02	1.74 ± 0.04	99.0
207.1°	16200	91.37 ± 0.09	3.09 ± 0.01	2.95 ± 0.01	2.56 ± 0.10	99.9
207.1°	23400	87.80 ± 0.11	4.31 ± 0.02	4.27 ± 0.01	3.60 ± 0.12	100.0
207.1°	27000	86.12 ± 0.10	4.82 ± 0.02	4.90 ± 0.03	4.13 ± 0.10	99.9
191.7°[g]	21600	97.59 ± 0.03	0.91 ± 0.01	0.82 ± 0.01	0.66 ± 0.02	99.1
191.7°	43200	95.45 ± 0.06	1.71 ± 0.01	1.57 ± 0.01	1.25 ± 0.07	99.3
191.7°	64800	93.35 ± 0.06	2.45 ± 0.01	2.32 ± 0.01	1.86 ± 0.06	100.0
191.7°	86400	90.63 ± 0.19	3.37 ± 0.02	3.33 ± 0.02	2.61 ± 0.14	100.0
191.7°	108000	88.49 ± 0.11	4.09 ± 0.01	4.17 ± 0.00	3.20 ± 0.13	99.7
178.4°[h]	129600	96.36 ± 0.04	1.43 ± 0.00	1.30 ± 0.00	0.95 ± 0.04	99.5
178.4°	259200	92.82 ± 0.08	2.69 ± 0.02	2.57 ± 0.00	1.91 ± 0.10	99.7
178.4°	388800	89.56 ± 0.13	3.92 ± 0.02	3.94 ± 0.02	2.57 ± 0.17	99.4
178.4°	518400	86.44 ± 0.32	4.79 ± 0.06	5.09 ± 0.05	3.66 ± 0.37	100.0
178.4°	648000	83.08 ± 0.15	5.71 ± 0.02	6.40 ± 0.02	4.78 ± 0.19	99.5
217.8°[e]	2700	3.77 ± 0.01	92.99 ± 0.19	1.66 ± 0.01	1.57 ± 0.08	99.7
217.8°	5400	7.25 ± 0.01	85.57 ± 0.08	3.34 ± 0.02	3.85 ± 0.38	99.7
217.8°	8100	10.30 ± 0.02	78.82 ± 0.16	4.92 ± 0.04	5.95 ± 0.58	97.0
217.8°	10800	13.06 ± 0.20	72.06 ± 0.18	6.40 ± 0.03	8.46 ± 0.79	98.0
217.8°	14400	15.93 ± 0.03	64.70 ± 0.13	8.32 ± 0.00	11.05 ± 0.64	98.1
207.1°[f]	5400	3.05 ± 0.01	93.89 ± 0.03	1.31 ± 0.01	1.73 ± 0.03	99.7
207.1°	10800	6.17 ± 0.07	88.08 ± 0.33	2.74 ± 0.02	2.98 ± 0.43	99.5
207.1°	16200	8.70 ± 0.04	82.02 ± 0.33	4.01 ± 0.01	5.25 ± 0.36	100.0
207.1°	21600	11.19 ± 0.02	76.74 ± 0.41	5.32 ± 0.01	6.73 ± 0.44	100.0
207.1°	27000	13.18 ± 0.05	72.10 ± 0.16	6.46 ± 0.00	8.24 ± 0.15	99.8
191.7°[g]	21600	2.63 ± 0.00	95.02 ± 0.04	1.09 ± 0.01	1.25 ± 0.04	99.0
191.7°	43200	5.12 ± 0.01	90.22 ± 0.08	2.09 ± 0.01	2.54 ± 0.09	100.0
191.7°	64800	6.94 ± 0.03	86.45 ± 0.16	3.08 ± 0.03	3.51 ± 0.20	100.0
191.7°	86400	9.64 ± 0.02	80.63 ± 0.06	4.38 ± 0.02	5.33 ± 0.08	100.0
191.7°	108000	11.57 ± 0.03	76.52 ± 0.11	5.38 ± 0.05	6.49 ± 0.17	100.0
178.4°[h]	86400	2.81 ± 0.02	94.70 ± 0.15	1.17 ± 0.02	1.32 ± 0.11	100.0
178.4°	172800	5.43 ± 0.00	89.15 ± 0.05	2.33 ± 0.02	2.72 ± 0.06	100.0
178.4°	259200	7.85 ± 0.01	84.89 ± 0.22	3.46 ± 0.01	3.76 ± 0.23	100.0
178.4°	352800	10.31 ± 0.02	79.94 ± 0.23	4.69 ± 0.01	5.03 ± 0.20	100.0
178.4°	439200	12.25 ± 0.03	75.74 ± 0.39	5.72 ± 0.02	6.21 ± 0.45	100.0

[a]The upper set of data refers to trans-I as starting material; the lower set to cis-I. [b]Temperature control is afforded by suspending sealed ampoules in the vapors above liquids boiling under reflux. [c]Per cent of each isomer is the average of three GLC determinations and is reported ± σ, the standard deviation. [d]Total recovery is based on benzonitrile as the internal standard during the reaction. [e]Naphthalene. [f]Tetrahydronaphthalene. [g]Mixture of cis- and trans-decahydronaphthalene. [h]p-Cymene.

racemic material accordingly. Approximate values for k_5 and k_6 are obtained from plots of ln α versus time.

The refinement is effected as before by successively changing the value of each k until the deviations of experimental and calculated concentrations are minimized; then repeating the entire process to obtain the optimized values given in Table 4.

The "single" rotational processes define two thermodynamic quantities: the relative propensity of the cyano group to rotate *vis-à-vis* the vinyl group, $R_A = k_2/k_1 = k_4/k_3 = 1.48$; and the relative stability of the *trans* and *cis* diastereomers in terms of their equilibrium constant, $K = k_3/k_1 = k_4/k_2 = 2.58$. Three functions, R_A, K and k_1, for example, serve to determine the other three rate constants about the periphery of Fig. 1: $k_2 = R_A k_1$, $k_3 = Kk_1$ and $k_4 = R_A K k_1$.

The "double" rotational processes, k_6 and k_5, relate to enantiomerization of *cis*-I and *trans*-I, respectively. They are kinetically independent of the "single" rotational processes and do not result from two-step processes such as $k_1k_4 = k_2k_3$. The expressions, $2k_6/(k_3 + k_4)$ and $2k_5/(k_1 + k_2)$, reflect the relative proportion of the "double" to "single" processes in *cis*-I and *trans*-I, respectively, 2 being the factor by which the "single" process is statistically favored. The values of these expressions, 1.62 from *cis*-I and 0.56 from *trans*-I, reveal a significant favoring of the "double" rotational process in *cis*-I.

In the framework of conventional diradical hypothesis, distribution among products is determined by the relative rates of internal rot(ation) and clos(ure). When $k_{rot} \gg k_{clos}$, a "freely" rotating diradical, having one or two of its radical centers

prochiral leads to complete racemization. The extent of involvement of such an achiral, common intermediate is appropriately analyzed by the scheme in Fig. 5. A fraction, f_{nr}, of n(on)-r(andom) reaction, *not* proceeding by way of the common intermediate, is given by the expressions, $(k_2 - k_1)/(k_2 + k_1)$ and $(k_4 - k_3)/(k_4 + k_3)$, each of which reduces to $(R_A - 1)/(R_A + 1)$. The fraction of r(andomly) generated racemic product, f_r, being $(1 - f_{nr})$, it follows that $f_r = 2/(R_A + 1)$. Thus an upper limit to participation by a common, achiral intermediate in the present instance is 81%.

Another approach to fixing an upper limit to the possible involvement of an achiral common intermediate starts from the corollary that there are two products-in-common, (−)-*cis*-I and (+)-*trans*-I, which must be formed in identical ratio regardless of whether (−)-*trans*-I or (+)-*cis*-I is the starting material (see Fig. 5). Were the entire process via a common intermediate,

$$\frac{(-)\text{-}cis\text{-I}}{(+)\text{-}trans\text{-I}} = \frac{\beta k_t}{\alpha k_t} = \frac{k_1}{k_5} \text{ from } (-)\text{-}trans\text{-I and}$$

$$\frac{(-)\text{-cis-I}}{(+)\text{-}trans\text{-I}} = \frac{\beta k_c}{\alpha k_c} = \frac{k_6}{k_3} \text{ from } (+)\text{-}cis\text{-I and } \frac{k_1 k_3}{k_5 k_6} = 1.$$

To the extent that $(k_1k_3)/k_5k_6$ is not equal to 1, k_1/k_5 may be $<$ or $>k_6/k_3$. In the present example, $(k_1/k_5) < (k_6/k_3)$, β/α may have any values within the restriction $k_1/k_5 \leq \beta/\alpha \leq k_6/k_3$, and $(k_1k_3)/k_5k_6 < 1$ and may be set equal to $a = (a_5)(a_6)$, where a, a_5 and $a_6 \leqq 1$. Thus $(k_1/a_5k_5)(k_3/a_6k_6) = 1$ and the portions of k_5 and k_6 which may *not* involve a common intermediate are $(1 - a_5)k_5$ and $(1 - a_6)k_6$, respectively. There is no experimental basis for distribution of the non-random, non-racemic component between k_5 and k_6—values of a_5 and a_6 *ad libitum* are acceptable, within the restrictions above. Specifically, $1.43 < \beta/\alpha < 2.02$ and $a = a_5a_6 = 0.709$. From (−)-*trans*-I and (+)-*cis*-I, the lower limits for contribution *not* via the common intermediate are given by the expressions, respectively,

$$\frac{(k_2 - k_1) + (1 - a_5)k_5}{k_1 + k_2 + k_5} \text{ and } \frac{(k_4 - k_3) + (1 - a_6)k_6}{k_3 + k_4 + k_6}.$$

If a_6 is set equal to 0.709, at least 23.8% of the reaction of (+)-*cis*-I and 15.2% of the reaction from (−)-*trans*-I are *not* by way of a common intermediate; similarly, if a_5 is set equal to 0.709, the corresponding values are 10.8% and 21.6%, respectively.

Involvement of a common intermediate in ring expansion is limited to 83% in the case of (−)-*trans*-I and 64% in the case of (+)-*cis*-I. The remainder in (−)-*trans*-I represents a 13.2% excess of reaction by *inversion*, suprafacial and antarafacial being indistinguishable. In striking contrast, in the case of (+)-*cis*-I the not-in-common remainder represents a 35.6% excess of reaction by *retention*. Woodward–Hoffmann rules confer "allowed" status on both the **is** and **ra** processes but offer no assistance in relating a choice between them to differences in configuration of starting material.[30]

The need for elucidation of the **s**–**a** component is pressing. Until work in progress on the *trans*-propenyl analogue of I be complete, attention is recalled to the study by Berson and Dervan of optically active *trans*-1-*cis*-propenyl-2-*trans*-propenylcyclobutane (*trans*-IV) (see Fig. 2 and replace cyano by *cis*-propenyl $[H_z = CH_3]$ and vinyl by *trans*-propenyl $[H_e = CH_3]$). There are two products of ring expansion: *trans*-3-methyl-4-*cis*-propenylcyclohexene (*trans*-V; 52.3% of theory) produced 95.4% in the **is** stereochemistry and 4.6% in the **ra** stereochemistry, both being Woodward–Hoffmann "allowed" processes; and *cis*-3-methyl-4-*cis*-propenylcyclohexene (*cis*-V; 7.7% of theory), 99.4% in the **rs** stereochemistry and 0.6% in the **ia**, neither of which is "allowed". Two conclusions emerge: there is no choice between **i** and **r**, their ratio being $[\mathbf{i}/\mathbf{r}]_{t\,IV} = 1.01$; there is strong preference for **s** over **a**, their ratio being $[\mathbf{s}/\mathbf{a}]_{tIV} = 36$.

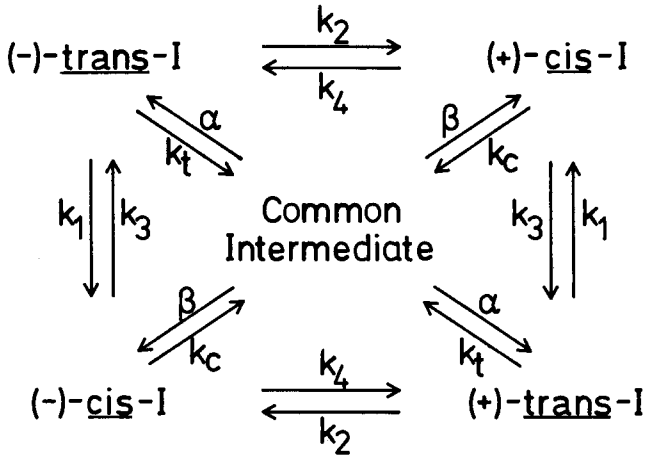


Fig. 5. A scheme for configurational reorganizations of 1-cyano-2-vinylcyclobutane (k_1, k_2, k_3, k_4 as in Fig. 1) in terms of an achiral, common intermediate, in which α and β denote the coefficients partitioning between *trans*-I and *cis*-I, respectively.

Table 7. The maximum specific rotations and absolute configurations

	$[\alpha]_D$	$[\alpha]_{578}$	$[\alpha]_{546}$	$[\alpha]_{436}$	$[\alpha]_{365}$
(1R:2R)-(-)-trans-1,2-Cyclobutane-dicarboxylic Acid	-158° [a]	-165.4°	-188.4°	-325.8°	-522.7°
(1R:2R)-(-)-Dimethyl-trans-1,2-cyclobutanedicarboxylate	-148.7° [b]	-154.3°	-176.3°	-303.5°	-483.9°
(1R:2S)-(-)-Methyl-trans-2-vinyl-cyclobutanecarboxylate	-132.2° [c]	-137.6°	-157.4°	-277.1°	-453.6°
(1R:2S)-(-)-trans-1-Cyano-2-vinylcyclobutane	-175.0° [d]	-181.4°	-206.9°	-361.0°	-578.5°
(1S:2S)-(+)-cis-1-Cyano-2-vinylcyclobutane	+56.9° [d]	+59.0°	+67.8°	+122.9°	+205.7°
(S)-(-)-Cyclohexene-4-carboxylic acid	-108.5° [b]	-113.5°	-129.9°	---	-357°
(S)-(-)-4-Cyanocyclohexene	-112.8° [d]	-115.9°	-132.6°	-232.1°	-374.6°

All [α] measured at 25° ± 3.0° in the following solvents: [a] H_2O, [b] CCl_4, [c] CH_3CH_2OH, [d] Cyclohexane.

Comparison of the behavior of the cyclobutanes with comparably substituted cyclopropanes is instructive. The experimental data from this work and that of Berson and Dervan are summarized in Table 5 alongside the comparable data on 1-cyano-2-isopropenylcyclopropane[4] and 1-cyano-2-*trans*-propenylcyclopropane.[7]†

It is impressive how much more effectively the cyclobutane engages in ring expansion. Thus, in neglect of cycloreversion which is not available to cyclopropane, (−)-*trans*-1 and (+)-*cis*-I, respectively, reveal 39.4% and 19.2% of the sum of automerization and ring expansion to be ring expansion, while 1-cyano-2-isopropenylcyclopropane and 1-cyano-2-*trans*-propenylcyclopropane reveal 2.5 and 3.7% and 1.5 and 3.3%, respectively. If it be granted that the rate-determining transition state for ring expansion reflect incipiently the *cis* configuration of the eventual cyclic

Table 8. Specific rotations of the products of the thermal rearrangement of (+)-*cis*-I (upper set) and (+)-*trans*-I (lower set) at 217.8°

Time (min)	Starting Material		Diastereomer Product		Cyclohexene	
	(+)-cis-I		(-)-trans-I		(-)-II	
	$[\alpha]_{578}$ [a]	$[\alpha]_{365}$	$[\alpha]_{578}$	$[\alpha]_{365}$	$[\alpha]_{578}$	$[\alpha]_{365}$
45	47.6°	163.6°	-29.6°	-93.7°	-34.6° [b]	-110.3° [b]
90	44.5° [c]	143.0° [c]	-28.8° [c]	-88.9° [c]	-27.1° [b,c]	-101.2° [b,c]
135	41.4°	142.4°	-27.5°	-86.5°	-30.9° [b]	-98.4° [b]
180	39.0°	133.2°	-26.6°	-84.1°	-31.0° [b]	-98.4° [b]
240	35.3°	121.4°	-25.2°	-79.0°	-27.4° [b]	-88.5° [b]
	(+)-trans-I		(-)-cis-I		(+)-II	
	$[\alpha]_{578}$ [a]	$[\alpha]_{365}$	$[\alpha]_{578}$	$[\alpha]_{365}$	$[\alpha]_{578}$	$[\alpha]_{365}$
90	164.3°	518.0°	-10.06°	-35.12°	+17.10° [b]	+55.6° [b]
135	166.3° [c]	521.2° [c]	-10.26° [c]	-34.15° [c]	+16.54° [c]	+55.4° [c]
180	160.2°	505.7°	-9.47° [b]	-32.28° [b]	+16.85°	+54.8°
240	158.6°	500.6°	-8.53°	-30.12°	+16.52°	+53.8°

[a] Rotations were determined at 25° ± 3°C in spectrograde cyclohexane and are reported as the average of two determinations unless noted otherwise.
[b] Rotation determined once only. [c] Rotations corrected to starting material of 100% of optical purity.

†Although the major results of the latter study are given in the table, we prefer to limit discussion at this time simply to a comparison with present results.

olefin, this difference may be an indication that the transformation of a cisoid conformation in starting material to a *cis* configuration in product is opposed sterically more strongly in cyclopropanes than it is in cyclobutanes. "Steric blockade" to ring enlargement by a single *cis*-propenyl[7] and to Cope rearrangement by two *cis*-propenyl groups is well established,[5,31] but has not been studied in such a manner that any difference between the 3- and 4-membered ring in response to the effect might have been elucidated.

The stereochemistry of the ring enlargement reveals a striking dependence of the ratio of inversion to retention [**i**/**r**] on configuration of starting material. From (−)-*trans*-I, $[\mathbf{i}/\mathbf{r}]_T = 1.40$, whereas from (+)-*cis*-I, $[\mathbf{i}/\mathbf{r}]_C = 0.47$; that is, *inversion* is favored from *trans*, whereas *retention* is favored from *cis*. This phenomenon finds its parallel in the cyclopropane analogs. In Sachdev's work, for example, $[\mathbf{i}/\mathbf{r}]_T = 2.3$ and $[\mathbf{i}/\mathbf{r}]_C = 0.65$;[4] while in Barsa's work, $[\mathbf{i}/\mathbf{r}]_T = 3.1$ and $[\mathbf{i}/\mathbf{r}]_C = 0.73$.[7] Although by any reasonable estimate of error, little significance can be attached to the difference between 2.3 and 3.1, both values are doubtlessly substantially greater than one.

Since the behavior of optically active *cis*-IV has not been examined by Berson and Dervan,[5] it cannot be determined whether the contrast between *cis* and *trans* diastereomers seen here and in the analogous cyclopropanes extends to their system. This situation is the more regrettable, given the care and thoroughness with which the behavior of the *trans* diastereomer was pursued. Nonetheless, informative, if fragmentary, conclusions may be drawn from their studies of racemic *cis*-IV.

On one side, were theoretical prejudice to lie in the direction of making *cis*-IV as similar to *trans*-IV as possible, it would be desirable to make the ratio in ring expansion of **a**/**s** as small as possible. (Recall that in the reactions of *trans*-IV to *cis*-V and *trans*-V, $[\mathbf{a}/\mathbf{s}]_{TIV\to CV} = 0.006$ and $[\mathbf{a}/\mathbf{s}]_{TIV\to TV} = 0.049$). This would be done by ascribing the entire generation of *cis*-V to the **is** process and of *trans*-V to the **rs** process, with the consequence that the ratio, $[\mathbf{i}/\mathbf{r}]_{CIV} = 0.186$, which is much smaller than is found for *trans*-IV ($[\mathbf{i}/\mathbf{r}]_{TIV} = 1.006$) or even the cyclopropanes noted in Table 5.

On the other side, if theoretical speculation were to run in the direction of making $[\mathbf{i}/\mathbf{r}]_{CIV} \geqq 1.00$ so that the behaviour of *cis*-IV would be more in line with that of *trans*-IV, the production of *cis*-V would be ascribed entirely to the **is** process ($k_{Cis} = 5.4 \times 10^{-6}\,sec^{-1}$), while portions of $k_{Cia} \geqq 11.8 \times 10^{-6}\,sec^{-1}$ and $k_{Crs} \leqq 17.2 \times 10^{-6}\,sec^{-1}$ would need to be assigned to the production of *trans*-V. The inevitable consequence would be the raising of the ratio, $[\mathbf{a}/\mathbf{s}]_{CV\to TV}$, to a value, 0.686, which is far higher than either value from *trans*-IV noted above. It might thus be possible to predict that optically active *cis*-IV would be found to depart strikingly from the pattern shown by the *trans*-diastereomer.

The conclusion the authors[5] draw from their experience with *trans*-IV is repeated here: "For the present, a simpler and hence preferable interpretation would describe the major reactions, **si** and **sr** as concerted processes, **si** allowed,[30] but only slightly over **sr**, which is forbidden."[32] Analogously, an interpretation would describe the *minor* reaction (*cis*-IV → *cis*-V) as an undetermined admixture of concerted, allowed processes, **is** and **ra**, and the *major* reaction as a combination of concerted, forbidden processes, **ia** and **rs**. Such efforts to analyze the stereochemistry of not obviously concerted thermal reorganizations in terms of conservation of orbital symmetry and control by subjacent orbitals constitute a valid part of current diagnostic procedure, however futile they may seem when they fail to provide insight of explicative or predictive value.

The theoretical conceptual scheme of a continuum between strongly concerted reactions, operational criteria for the recognition of which exist, and not concerted reactions, operational criteria for the positive identification of which may be inaccessible, leaves an area of *not obviously concerted* reactions, some or all of which may in reality be non-concerted. In these instances, alternate hypotheses need to be explored. Such appears to be the case here, where efforts to understand each member of the set of constitutional changes in terms of a concerted model succeeds with the Diels–Alder-like change, but fails with the cycloaddition/reversions, automerizations and ring expansions.

Key factors in the configurational and constitutional aspects of the not obviously concerted automerizations and ring enlargements are self-evidently (1) intramolecular bond-breaking, (2) internal rotation and (3) reforming of bonds. While the hypothesis of a common intermediary diradical serves as a good basis for predicting the enthalpies of activation, it is not of much help in the interpretation and prediction of internal rotations.

We continue to explore the R_A factor as a help in rationalizing and predicting the stereochemical consequences of internal rotations. The small size of the preference when expressed as $\Delta\Delta G^{\neq}$ or $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ should serve as a warning against expecting dramatic success. Nonetheless, were the R_A factor of 1,48, which reflects a small preference of the cyano group to rotate in the automerization of *cis*-I and *trans*-I, to be reflected in the ring expansion, it could lead to the preferential rotation of the cyano group, and in such a sense as to turn the cyano group away from the center of the ring. In the *trans* diastereomer, such a motion would present the **i** face of the cyano carbon radical to the **s** face of the relatively passive, cisoid allylic radical, while, in the instance of the *cis* diastereomer, the **r** face would be presented (Fig. 6).

Although an application of the R_A factor to ring expansion is consistent with the reversal of the ratio of inversion to retention seen in shifting from *trans*-I ($[\mathbf{i}/\mathbf{r}]_T = 1.40$) to *cis*-I ($[\mathbf{i}/\mathbf{r}]_C = 0.47$), it is offered less as an explanation of the major result then as an illustration of an alternate way of thinking about preferences among rotational possibilities. At the moment, it does not seem fruitful to wonder about the role of double rotational processes or about the effect worked on R_A by the non-equilibrium cisoid conformation required of the vinyl group participating in ring expansion.

In this work, a close similarity between four- and three-membered rings in automerization and ring expansion has been established. Because criteria of concertedness are not satisfied, these reactions are classified as not obviously concerted thermal reorganizations. Consistently, their properties do not respond well to analysis by theories of concerted

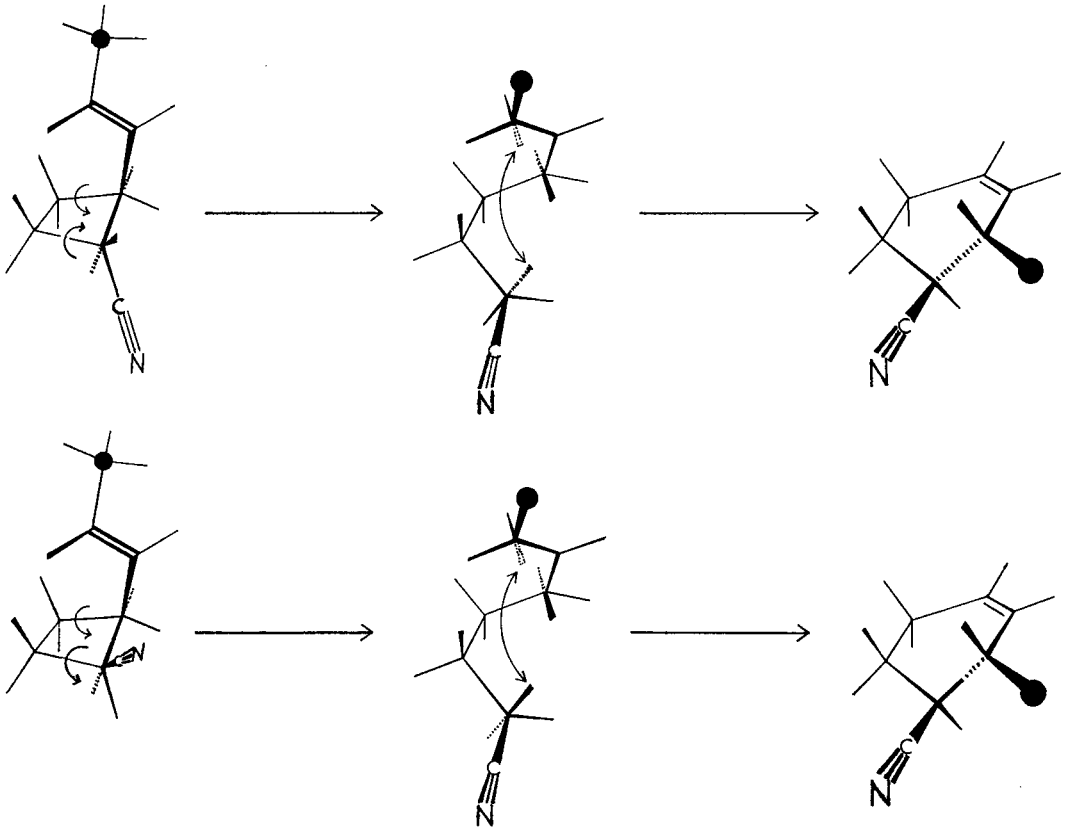


Fig. 6. Conformational depiction of the constitutional reorganization of (1R:2S)-(−)-*trans*-I (upper) and (1S:2S)-(+)-*cis*-I (lower) in their configurationally favored mode to (S)-(−)-4-cyanocyclohexene (II).

processes, but appear to call for a more useful understanding of internal rotations and their role in transition states.

EXPERIMENTAL

General. Optical rotations are determined on a Perkin–Elmer 141 digital readout polarimeter and are reported as specific rotations, the concentration being expressed in grams per 100 ml of the designated solvent. Observed rotations may be found in dissertation.[1] Volumetric errors are estimated to be ±1.0% "Ethanol" is abs EtOH, CCl_4 and cyclohexane are spectrograde.

Spectroscopic information is obtained in the following ways:

NMR: Varian T-60 spectrometer reported in ppm downfield from TMS (δ); IR: Perkin–Elmer 337 grating spectrophotometer; mass spectra: AEI Model MS-9 double focussing mass spectrometer. M and bps are uncorrected. Microanalyses are by Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Perkin–Elmer 990 gas chromatograph with a flame ionization detector and Autolab 6300 digital integrator is used for quantitative analyses. Purification and separation of larger quantities is accomplished on Aerograph A90-P and A90-P3 gas chromatographs.

The following columns are used frequently in the sequel. A: 6′ × 0.25″ o.d., 20% Carbowax 20M on 60/80 mesh non-acid-washed Chromosorb P; B: 5 m × 0.25″, 20% General Electric methyl silicone gum rubber (SE-30) on 60/80 mesh Chromosorb P washed with NaOH in methanol; C: 5 m × 0.25″, 20% 1,2,3-tris-(2-cyanoethoxy)-propane (TCEP) on 60/80 mesh non-acid-washed Chromosrb P; D: 3 m × 0.25″, 20% Carbowax 20 M on 50/60 mesh Anakrom-acid, base-washed and silanized (ABS); E: 300′ × 0.01″, Carbowax 20 M capillary.

Racemic trans- *and* cis-1-*cyano*-2-*vinylcyclobutane* (I). These materials were prepared following the general procedure of Dilling.[9] Into a 420 ml photolysis flask with immersion-well and two side-arms, one fitted with a calcium sulfate drying tube and the other with a gas inlet tube, were placed 171 ml (2.6 mol) freshly distilled acrylonitrile and 44.4 ml (0.26 mol) 2,3-butanedione. The flask was placed into a one-gallon Dewar flask containing dry-ice and acetone; the lamp housing was cooled with MeOH circulating through a dry-ice-acetone bath; butadiene-1,3 (Matheson Instrument Grade) (226 ml, 2.6 mol) was then distilled into the cooled flask and the mixture was irradiated with light from a 450-w, high-pressure Hanovia lamp filtered through Pyrex. The progress of the photolysis was followed by glpc (A: 125°, He 60 ml/min). After irradiation for two 8 hr periods, excess butadiene was allowed to evaporate at rt and excess acrylonitrile and butanedione were removed by evaporation at rt and 10 mm. The distilled residue (b.p. 42°/2 mm) was separated into its components by preparative glpc (A: 125°, He 60 ml/min):

trans-I: ret. time 8.5 min; 880 mg; NMR (CCl_4) 2.2 (m, 4 H), 2.8 (m, 1 H), 3.2 (m, 1 H), 5.0 and 5.2 (m, 2 H), 5.9 (m, 1 H); IR (CCl_4) 2240 (C≡N), 3100 cm^{-1} (=CH).

cis-I: ret. time 12 min; 800 mg; NMR (CCl_4) 2.3 (m, 4 H), 3.3 (m, 2 H), 5.0, 5.1 and 5.3 (m, 2 H), 6.0 (m, 1 H); IR (CCl_4) 2235 (C≡N), 3075 cm^{-1} (=CH).

4-Cyanocyclohexene (II): ret. time 15.5 min; 400 mg; NMR (CCl_4) 2.2 (m, 5 H), 2.8 (m, 2 H), 5.7 (d, 2 H); IR (CCl_4) 2240 cm^{-1} (C≡N).

The NMR spectra agree with those reported.[9]

Methyl trans- *and* cis-2-*vinylcyclobutane*-1-*carboxylate*. These compounds were prepared by the same general procedure used for the preparation of the corresponding nitriles. Freshly distilled methyl acrylate (194 ml, 2.26 mol), 2,3-butanedione (19.2 ml, 0.226 mol), and 2.26 mol of butadiene were irradiated for 40 hr in 10 hr periods. The progress of the photolysis was followed by analysis of aliquots by glpc (B: 140°, He 60 ml/min). After excess butadiene, methyl acrylate, and butanedione had been removed, a small amount of the distilled (b.p. 32°/0.8 mm) residue was separated by preparative glpc under the same conditions used for analysis:

Methyl *trans*-2-vinylcyclobutane-1-carboxylate: ret. time 26 min; NMR (CCl_4) 2.0 (m, 4 H), 3.0 (m, 2 H), 3.6 (s, 3 H), 5.1, 5.2, 4.9 (m, 2 H), 5.9 (m, 1 H); IR (CCl_4) 1740 cm^{-1} (C=O); mass spectrum *m/e*: calc. for $C_8H_{12}O_2$: 140.0837, found: 140.0844.

Methyl *cis*-2-vinylcyclobutane-1-carboxylate: ret. time 28 min; NMR (CCl_4) 2.1 (m, 4 H), 3.2 (m, 2 H), 3.6 (s, 3 H), 4.9 and 5.1 (m, 2 H), 5.9 (m, 1 H); IR (CCl_4) 1740 cm^{-1} (C=O); *m/e*: calc. for $C_8H_{12}O_2$: 140.0837, found: 140.0840.

Methyl cyclohexene-4-carboxylate: ret. time 45 min; NMR (CCl_4) 2.2 (m, 7 H), 3.7 (s, 3 H), 5.7 (s, 2 H); IR (CCl_4) 1740 cm^{-1}.

Methyl trans-2-*vinylcyclobutane*-1-*carboxylate*. An alternate preparation proceeded from *trans*-cyclobutane-1,2-carboxylic acid (Aldrich Chemical Co.) by way of the dimethyl ester and the monomethyl ester according to Schroff, Stewart, Uhm and Wheeler.[26] Reduction to methyl *trans*-2-hydroxymethylcyclobutane-1-carboxylate also followed their procedure but modified according to Brown and Subba Rao.[33]

Oxidation to *trans*-2-carbomethoxycyclobutanecarboxaldehyde was effected by dimethyl sulfoxide according to Parikh and Doering.[27] Into a flame-dried, 1-l three-necked flask which was attached to a 250-ml flask by a 90°-bend, glass connector and was fitted with N_2 inlet, drying tube, and magnetic stirrer were placed 166 ml of dry Et_3N, 23.8 g (0.165 mol) of methyl *trans*-2-hydroxymethylcyclobutane-1-carboxylate and 166 ml of dry DMSO. After addition of a slurry of Et_3N–SO_3 (69.5 g, 0.495 mol) in 50 ml of DMSO, the mixture was stirred overnight, acidified with 3 N HCl and extracted with CH_2Cl_2. The extracts were washed with H_2O, sat $NaHCO_3$ aq and dried ($MgSO_4$). Distillation afforded 10.97 g (47 %) of the aldehyde ester: b.p. 63°/3 mm; IR (CCl_4) 1745 cm^{-1} (ester C=O), 1735 (shoulder, aldehyde C=O); NMR (CCl_4) 2.2 (m, 4 H), 3.35 (m, 2 H), 3.75 (s, 3 H), 10.0 (s, 1 H); 2,4-dinitrophenylhydrazone, m.p. 139°. (Found: C, 48.3; H, 4.5, N, 17.5 %.) Calc. for $C_{13}H_{14}N_4O_6$: C, 48.5; H, 4.4; N, 17.4 %).

Conversion to methyl *trans*-2-vinylcyclobutane-1-carboxylate followed the procedure of Greenwald, Chaykovsky and Corey.[28] Better yields were obtained using an excess of Wittig reagent: NaH (1.83 g of a 57 % mineral oil dispersion; 0.039 mol) and methyl triphenylphosphonium bromide (14.28 g, 0.040 mol) in 40 ml DMSO. After 15 min of stirring at rt, 2.90 g (0.026 mol) *trans*-2-carbomethoxycyclobutane-1-carboxyaldehyde was added and stirring was continued at rt overnight. Isolation followed the published procedure: yield 2.39 g (62.5 %). Analysis by glpc (C: 110°, He 60 ml/min) revealed a 9:1 mixture of methyl *trans*-2-vinylcyclobutane-1-carboxylate (ret. time 29.5 min) and the *cis* isomer (ret. time 33 min), identical to previously synthesized samples.

Resolution of trans-2-*vinylcyclobutane*-1-*carboxylic acid*. Saponification of the crude (9:1) *trans* ester (reflux for 12 hr in 80 ml 80 % eq. MeOH containing 8 g (0.14 mol) KOH) afforded 9.5 g (78 %) of crude acid, which could be purified by distillation: b.p. 55°/0.05 mm; NMR (CCl_4) 2.1 (m, 4 H), 3.1 (m, 2 H), 5.1 (m, 2 H), 6.0 (m, 1 H), 12.5 (s, 1 H); IR (CCl_4) 1700 cm^{-1} (C=O); mass spectrum *m/e*: Calc. for $C_7H_{10}O_2$: 126.0681, found: 126.0688.

The crude acid (14.5 g, 0.115 mol) and quinine (37.26 g, 0.115 mol) were dissolved in 50 ml abs EtOH, treated with 400 ml water and heated to boiling, enough abs EtOH having been added to redissolve all solid material. Colorless needles deposited on standing at rt overnight. Since the crude *trans*-acid contained 5–10 % of the *cis*-acid, the progress of the resolution was followed by recovering samples of acid from the salt, esterifying with ethereal diazomethane, separating pure *trans* ester by glpc (C: 120°, He 60 ml/min) and measuring its rotation.

After one recrystallization of the salt, methyl *trans*-2-vinylcyclobutane-1-carboxylate had $[\alpha]^{27}_{578}$ + 59.9°, $[\alpha]^{27}_{365}$ + 196.4° (*c* 1.6033, EtOH); after second recrystallization: $[\alpha]^{25}_{578}$ + 107.8°, $[\alpha]^{25}_{365}$ + 352.5° (*c* 1.1337, EtOH); after third recrystallization (16.73 g of salt): $[\alpha]^{25}_{578}$ + 127.5°, $[\alpha]^{25}_{365}$ + 417.0° (*c* 0.7386, EtOH); after three further recrystallizations: $[\alpha]^{27}_{578}$ + 135.2°, $[\alpha]^{27}_{365}$ + 441.8° (*c* 0.9134, EtOH). One more recrystallization of the salt gave methyl ester $[\alpha]^{27}_{578}$ + 132.3°, $[\alpha]^{27}_{365}$ + 434.6° (*c* 0.2901, EtOH). After the 6th and 7th recrystallization of the salt, the resulting *trans* methyl ester was free of *cis* isomer.

From the mother liquor of the first recrystallization, methyl ester was obtained consisting of 10 % *cis* isomer and 90 % *trans* ester, $[\alpha]^{27}_{578}$ − 118.7°, $[\alpha]^{27}_{365}$ − 387.4° (*c* 0.9510, EtOH).

(−)-trans-1-*Cyano*-2-*vinylclobutane* [(−)-trans-I]. Conversion of 4.26 g (0.034 mol) of (+)-*trans*-carboxylic acid [corresponding methyl ester: $[\alpha]^{27}_{578}$ + 137.5°, $[\alpha]^{27}_{365}$ + 417.0° (*c* 0.7386, EtOH)] by the procedure of Doering and Sachdev[2] afforded 2.93 g (75 %) of colorless (+)-*trans*-2-vinylcyclobutane-1-carboxamide: m.p. 85° after recrystallization from CH_2Cl_2–pet. ether; NMR ($CDCl_3$) 2.2 (m, 4 H), 3.2 (m, 2 H), 5.0 (m, 1 H), 5.3 (m, 1 H), 6.2 (m, 1 H); IR ($CDCl_3$) 3530 cm^{-1} (NH), 3400 (N–H), 1675 (C=O); $[\alpha]_{578}$ + 107.5°, $[\alpha]_{365}$ + 393.9° (*c* 2.706, $CHCl_3$). A racemic sample, m.p. 102–103°, had a mass spectrometric mol wt: *m/e*: Calcd. for $C_7H_{11}NO$: 125.08406, Found: 125.08404.

Following the procedure of Doering and Sachdev,[4] 1.44 g (11.5 mol) of (−)-carboxamide [from (−)-*trans* methyl ester: $[\alpha]^{27}_{578}$ − 118.7°, $[\alpha]^{27}_{365}$ − 387.4° (*c* 0.9510, EtOH)] was converted to crude nitrile, which was separated into two components by preparative glpc (D: 120°, He 60 ml/min): (−)-*trans*-1-cyano-2-vinylcyclobutane [(−)-*trans*-I]: ret. time 16 min; 592 mg; $[\alpha]^{27}_{578}$ − 157.0°, $[\alpha]^{27}_{365}$ − 497.0° (*c* 0.3235, cyclohexane); NMR and IR identical to those of a sample prepared above; (−)-*cis*-1-cyano-2-vinylcyclobutane [(−)-*cis*-I]: ret. time 24 min; 68 mg; $[\alpha]^{27}_{578}$ − 9.3°, $[\alpha]^{27}_{365}$ − 30.8° (*c* 1.0578, cyclohexane; NMR and IR identical to those of sample prepared above).

That the glpc procedure caused no racemization was determined in separate experiments with (+)-*trans*-I, $[\alpha]^{25}_{578}$ + 156.2°, $[\alpha]^{25}_{365}$ + 493.0° (*c* 1.2681, cyclohexane), before glpc and $[\alpha]^{25}_{578}$ + 155.8°, $[\alpha]^{25}_{365}$ + 490.9° (*c* 0.9825, cyclohexane) after glpc; and with (+)-*cis*-I, $[\alpha]^{25}_{578}$ + 50.8°, $[\alpha]^{25}_{365}$ + 174.7° (*c* 0.7480, cyclohexane) after glpc.

Epimerization of trans- *and* cis-*I*. Following the procedure of Doering and Sachdev,[2] 22 mg *trans*-I in 0.2 ml of dry DMSO at 30° was treated with 10 mg t-BuOK for 10 min. Quenching with 1 ml water and extraction with pentane followed by glpc (E: 130°, He 35 psi) revealed *trans*-I (76.31 %) and *cis*-I (23.68 %); K = 0.310. Repetition of the experiment with *cis*-I gave *trans*-I (75.64 %) and *cis*-I (24.36 %); K = 0.322.

In a separate experiment with *trans*-I, *cis*-I was recovered by glpc (D: 120°, He 60 ml/min): NMR (CCl_4) 2.3 (m, 4 H), 3.3 (m, 2 H), 5.0, 5.2, 5.4 (m, 2 H), 6.0 (m, 1 H); IR (CCl_4) 2240 cm^{-1} (C≡N).

(+)-*cis*-1-Cyano-2-vinylcyclobutane [(+)-*cis*-I]. An 881-mg sample of (−)-*trans*-I ($[\alpha]^{27}_{578}$ − 157.0°, $[\alpha]^{27}_{365}$ − 497.0° (*c* 0.3235, cyclohexane)) was epimerized by the procedure above. Separation by preparative glpc (D: 120°, He 60 ml/min) afforded (+)-*cis*-I, $[\alpha]^{22}_{578}$ + 51.0°, $[\alpha]^{22}_{365}$ + 175.2° (*c* 1.0623, cyclohexane) after being rechromatographed once, and recovered (−)-*trans*-I, $[\alpha]^{22}_{578}$ − 156.6°, $[\alpha]^{22}_{365}$ − 493.7° (*c* 0.7318, cyclohexane).

(S)-(−)-4-*Cyanocyclohexene*. Following the procedure used above for 1-cyano-2-vinylcyclobutane, a 1.26-g (10 mmol) sample of (S)-(−)-4-cyclohexene-1-carboxylic

acid ($[\alpha]^{25}_{578}$ − 88.99°, $[\alpha]^{25}_{365}$ − 279.6° (*c* 0.7192, CCl_4), 78.4% optically pure) was treated with 1.01 g (10 mmol) Et_3N and 1.35 ml ethyl chloroformate followed by ammonia. The resulting amide (239 mg, 1.9 mmol) on treatment with 363 mg (1.9 mmol) of *p*-toluenesulfonyl chloride then afforded nitrile, $[\alpha]^{25}_{578}$ − 90.9°, $[\alpha]^{25}_{365}$ − 293.2° (*c* 0.8117, cyclohexane). The rotation of optically pure 4-cyanocyclohexene (obtained by correction for the 78.4% optical purity of starting acid) is $[\alpha]^{25}_{578}$ − 115.9°, $[\alpha]^{25}_{365}$ − 374.6°.

Dimethyl (1R:2R)-(−)-trans-*cyclobutane*-1,2-*dicarboxylate.* Treatment of 0.0432 g (0.3 mmol) of (1*R*:2*R*)-(−)-cyclobutane-1,2-dicarboxylic acid ($[\alpha]^{25}_{D}$ − 155.0°, $[\alpha]^{25}_{578}$ − 162.1°, $[\alpha]^{25}_{365}$ − 512.4° (*c* 1.1847, H_2O), 98.10% optically pure) with ethereal diazomethane, followed by washing with sat $NaHCO_3$ and water led to 0.04128 g (80%) of the dimethyl ester: $[\alpha]^{25}_{D}$ − 146.0°, $[\alpha]^{25}_{578}$ − 151.4°, $[\alpha]^{25}_{365}$ − 474.9° (*c* 0.7200, CCl_4). The maximum rotation of the diester at only one wavelength has been reported[5] ($[\alpha]^{25}_{D}$147°) and agrees with our value of $[\alpha]^{25}_{D}$ − 148.7°, $[\alpha]^{25}_{578}$ − 154.3°, $[\alpha]^{25}_{365}$ − 483.9°.

Conversion of methyl (1R:2S)-(−)-trans-2-*vinylcyclobutane*-1-*carboxylate to dimethyl* (1R:2R)-(−)-trans-*cyclobutane*-1,2-*dicarboxylate.* To 0.07784 g of vinyl ester (0.556 mol) ($[\alpha]^{25}_{D}$ − 114.0°, $[\alpha]^{25}_{578}$ − 118.7°, $[\alpha]^{25}_{365}$ − 391.3° (*c* 0.3065), EtOH) in 20 ml of 80% aqueous t-BuOH kept at pH 8 by the addition of solid K_2CO_3, 0.984 g (4.60 mmol) of sodium metaperiodate and 10 mg $KMnO_4$ in 27.8 ml water was added with stirring.[34] After the mixture had been stirred for 10 min, removal of t-BuOH under reduced pressure gave a residue which was dissolved in 10 ml water and acidified with 10% HCl. The dried ($MgSO_4$) ether extract thereof was esterified (diazomethane). Preparative glpc (D: 150°, He 100 ml/min) of the crude ester gave 0.05114 g (53.5%) of dimethyl cyclobutane-1,2-dicarboxylate ($[\alpha]^{25}_{D}$ − 128.3°, $[\alpha]^{25}_{578}$ − 133.1°, $[\alpha]^{25}_{365}$ − 417.9° (*c* 0.5545, CCl_4), 86.3% optically pure). Based on the maximum rotation of the diester, the maximum rotation of vinyl carboxylate is $[\alpha]^{25}_{D}$ − 132.2°, $[\alpha]^{25}_{578}$ − 137.6°, $[\alpha]^{25}_{365}$ − 453.6°.

General procedure for thermal rearrangements. Thermal rearrangements were performed in Pyrex ampoules which had been soaked in NH_4OH overnight, rinsed with distilled water until the washings were neutral, then rinsed with acetone and dried. Immediately before use, the ampoules were flame-dried with nitrogen-purging. Two sizes were used: A: 15 cm × 1 cm 0.d. with 10 cm × 0.6 cm 0.d. stem (~8 ml volume when sealed) and B: 20.5 cm × 1.2 cm 0.d. with 11 cm × 0.7 cm 0.d. stem (~16 ml volume when sealed). Samples of nitrile were introduced via microsyringe; ampoules were sealed under 10^{-4} mm pressure and suspended in the vapors of a boiling solvent bath by a Cu wire fastened to a hook at the end of the ampoule. The temp of the vapors was measured with an iron-constantan thermocouple and a Leeds and Northrup No. 8686 millivolt potentiometer.

Kinetics of the thermal rearrangement of racemic trans-*I and* cis-*I.* The rates of reaction of *trans*-I and *cis*-I were determined at the bps of four solvents: naphthalene (217.8°), tetrahydronaphthalene (207.1°), a constant boiling mixture of *cis*- and *trans*-decalin (191.7°), and *p*-cymene (178.4°). An equal volume of purified benzonitrile was admixed to serve as internal standard. About 12 μl of the nitrile–benzonitrile mixture was introduced into each of six ampoules, size A. Five of the ampoules were suspended at once in the vapor bath, to be removed one each at the end of specified intervals. Prior to analysis, ampoules were opened by cooling their stems in liquid N_2 just before being broken off and given an injection of 100 μl of *m*-xylene. Products were analyzed by glpc (E: 130°, He 35 psi) on the Perkin–Elmer 990. Relative areas were determined with the aid of an Autolab 6300 digital integrator. Response factors for *cis*-I, *trans*-I, 4-cyanocyclohexene and acrylonitrile were determined relative to benzonitrile (ret. time 47.5 min, response factor: 1.000): *cis*-I (25.5 min), 0.957; *trans*-I (34.0 min), 0.928; II (41.5 min), 0.949; and III (10.2 min), 0.722. The data are summarized in Table 6.

Rate constants for the conversion of *cis*-I and *trans*-I to individual products were extracted on the basis of the simultaneous differential equations derived from the kinetic scheme of Fig. 3. Solution of the equations was effected by numerical integration using trial values of k_1 through k_6, comparing the calculated concentrations with the experimental ones, and varying the rate constants systematically until the best agreement of calculated and experimental concentrations was obtained. A computer program for numerical integration by the method of Runge–Kutta, written by Prof. M. Saunders, Yale University, for the PDP-10, was modified by Mr. David Dixon for use on the PDP 11/45, to include an iterative variation of rate constants and the computation of error described below.

For each of *trans*-I, *cis*-I, II and III, agreement of the experimental and observed concentrations (c_i) over time is expressed as

$$\bar{\sigma}_{c_i} = \left(\sum_{1}^{n} [c_i(\text{calc}) - c_i(\text{exp})]^2/n - 1\right)^{1/2}$$

where c_i is the concentration of the *i*th component and n is the number of experimental points. A specified rate constant is then varied by a given fraction (e.g. $k_{t,c}$ becomes $k_{t,c} + 0.1\,k_{t,c}$) and the calculation is re-performed. The procedure is repeated for the number of iterations requested.

In general, a set of trial rate constants is taken and each one is varied successively while the others are kept constant. The four sets of values of $\bar{\sigma}_i$ were each plotted vs the various values of k_i. In the event, each of the six rate constants is strongly coupled to two $\bar{\sigma}_i$ and very weakly coupled to the remaining two $\bar{\sigma}_i$. Thus, for example, $\bar{\sigma}_t$ and $\bar{\sigma}_c$ are sensitive, while $\bar{\sigma}_{II}$ and $\bar{\sigma}_{III}$ are insensitive, to variation in $k_{t,c}$. The values of k_i at minima in the most sensitive $\bar{\sigma}_i$ are then reinserted into the minimization procedure until each better new k_i effects less than a 1% improvement in the next iteration. At this point the minimum in $\bar{\sigma}_t$ and $\bar{\sigma}_c$, for example, appears at the same value of k. In Table 2 optimized rate constants at each temperature are reported with an uncertainty represented by the range of rate constant sufficient to increase $\bar{\sigma}_i$ to twice the value of ($\bar{\sigma}_i$) minimum. In the Ph.D. dissertation the results of all twenty-four correlations may be found.[1]

Thermal rearrangement of (+)-cis-I *and* (+)-trans-I. Rearrangements were carried out by the general procedure described above. (+)-*Cis*-I ($[\alpha]^{23}_{578}$ + 50.90°, $[\alpha]^{23}_{365}$ + 175.2° (*c* 0.8643, cyclohexane) was indicated to be 85.2% of optical purity on the basis of the indicated maximum rotation, all of which are collected in Table 7. For each point several ampoules of size B were filled with 50 μl (~700 mm final pressure) of (+)-*cis*-I and heated at 217.8° ± 0.3°. The contents of the ampoules were separated by glpc (D: 120°, He 60 ml/min) into pure components, which were rechromatographed and used for two determinations of specific rotation if enough material was available. The samples used for these determinations were checked for contamination by glpc on a second column: E at 130° and He, 35 psi. Five points at 45, 90, 135, 180, and 240 min were taken.

For the 90-min point, the starting material was 79.5% of optical purity and specific rotations for this point were corrected to 100% optical purity.

The sample of (+)-*trans*-I used as starting material for 90, 180 and 240 min had $[\alpha]^{25}_{578}$ + 167.7°, $[\alpha]^{25}_{365}$ + 529.9° (*c* 0.6805, cyclohexane) and was 91.6% optically pure. The sample of (+)-*trans*-I used for the 135 min point had $[\alpha]^{25}_{578}$ + 163.4°, $[\alpha]^{25}_{365}$ + 516.8° (*c* 0.6016, cyclohexane), 99.3% optically pure. The corrected results are summarized in Table 8. Rate constants were obtained in the same manner as for racemic material on the basis of the differential equations representing the kinetic schemes in Figs. 1 and 2. The refined rate constants with corresponding uncertainties as previously defined are collected in Table 4.

Thermal rearrangement of (−)-II. Twelve μl of (−)-II ($[\alpha]^{25}_{578}$ − 90.9°, $[\alpha]^{25}_{365}$ − 293.3° (*c* 0.9061, cyclohexane)) was heated for 12 hr at 217.8° ± 0.3°. The recovered II (D: 120°, He 60 ml/min) showed $[\alpha]^{25}_{578}$ − 88.8°, $[\alpha]^{25}_{365}$ − 286.8° (*c* 0.4180, cyclohexane). No other products were formed.

Thermal rearrangement of trans-*I and* cis-*I in lead-potash tubes.* Two-μl samples of *cis*-I and *trans*-I were heated in tubes of Corning 0120 glass (6.1 mm o.d. × 4 in) for four hours at 217.8° ±0.3°. Analysis (E: 135°, He 35 psi): *trans*-1: 81.2% *trans*-I. 5.9% *cis*-I, 6.6% II, and 6.2% III; *cis*-I: 64.6% *cis*-I, 14.9% *trans*-I, 12.9% III, 8.0% II.

Thermal rearrangement of (+)-cis-*I at* 1 mm *pressure.* Into a 12-L Pyrex flask in an air-thermostat heated to 217° 40 mg of (+)-*cis*-I ($[\alpha]^{25}_{578}$ + 41.6°, $[\alpha]^{25}_{365}$ + 143.0° (*c* 1.0505, cyclohexane), 69.5% optically pure) was transferred by vacuum within 5 min. After 240 min, the product was withdrawn quantitatively by vacuum transfer into a received cooled in liquid N_2. Analysis: (+)-*cis*-I (69.0%), $[\alpha]^{25}_{578}$ + 28.4°, $[\alpha]^{25}_{365}$ + 97.3° (*c* 0.9992, cyclohexane); (−)-*trans*-I (16.3%), $[\alpha]^{25}_{578}$ − 20.2°, $[\alpha]^{25}_{365}$ − 63.1° (*c* 0.4944, cyclohexane); (−)-II (8.3%), $[\alpha]^{25}_{578}$ − 22.6°, $[\alpha]^{25}_{365}$ − 73.1° (*c* 0.2216 cyclohexane); III (6.31%).

Thermal rearrangement of (+)-trans-I *and* (+)-cis-*I in acetonitrile.* A 50 mg sample of (+)-*cis*-I ($[\alpha]^{25}_{578}$ + 41.6°, $[\alpha]^{25}_{365}$ + 143.0° (*c* 1.0505, cyclohexane), 69.4% optically pure) in 0.5 ml CH_3CN was heated for 240 min at 217.8° ± 0.3° in a Pyrex tube. Analysis: *cis*-I (60.7%), $[\alpha]^{25}_{578}$ + 33.8°, $[\alpha]^{25}_{365}$ + 116.0° (*c* 0.9752, cyclohexane); *trans*-I (10.1%), $[\alpha]^{25}_{578}$ − 14.5°, $[\alpha]^{25}_{365}$ − 44.2° (*c* 0.1855, cyclohexane); II (12.7%), $[\alpha]^{25}_{578}$ − 12.7°, $[\alpha]^{25}_{365}$ − 40.2° (*c* 0.4646, cyclohexane); and III (16.43%).

A 200-mg sample of (+)-*trans*-I ($[\alpha]^{25}_{578}$ + 160.2°, $[\alpha]^{25}_{365}$ + 505.6° (*c* 0.6504, cyclohexane), 87.4% optically pure) in 2.0 ml CH_3CN was treated as above. Analysis: *trans*-I (78.18%), $[\alpha]^{25}_{578}$ + 153.8°, $[\alpha]^{25}_{365}$ + 485.0° (*c* 0.7905, cyclohexane); *cis*-I (5.24%), $[\alpha]^{25}_{578}$ − 5.5°, $[\alpha]^{25}_{365}$ − 19.8° (*c* 0.7186, cyclohexane); II (10.0%), $[\alpha]^{25}_{365}$ + 7.53° (*c* 0.6737, cyclohexane); and III (6.55%).

Thermal rearrangement of (+)-trans-I *in benzene.* A 200-mg sample of (+)-*trans*-I ($[\alpha]^{25}_{578}$ + 164.3°, $[\alpha]^{25}_{365}$ + 518.2° (*c* 0.7116, cyclohexane), 89.6% optically pure) in 2.0 ml benzene was heated for 4 hr at 217.8° ± 0.3° in a Pyrex tube. Analysis: *trans*-I (77.5%), $[\alpha]^{25}_{578}$ + 150.3°, $[\alpha]^{25}_{365}$ + 475.9° (*c* 0.6230, cyclohexane); *cis*-I (5.4%), $[\alpha]^{25}_{578}$ − 5.1°, $[\alpha]^{25}_{365}$ − 18.1° (*c* 0.3276, cyclohexane); II (10.9%), $[\alpha]^{25}_{578}$ + 7.66°; $[\alpha]^{25}_{365}$ + 24.6° (*c* 0.9985, cyclohexane); and III (5.12%).

Thermal rearrangement of (−)-II *in acetonitrile.* A sample of (−)-II [15 mg in 150 μl acetonitrile; $[\alpha]^{25}_{578}$ − 90.9°, $[\alpha]^{25}_{365}$ − 293.2° (*c* 0.9061, cyclohexane)] was heated in a heavy-walled Pyrex tube for 4 hr at 217.8° ± 0.3°. Analysis gave only recovered II: $[\alpha]^{25}_{578}$ − 89.8°, $[\alpha]^{25}_{365}$ − 289.4° (*c* 0.7662, cyclohexane).

Acknowledgements—We express our gratitude to the Sanger Fund, to the Petroleum Research Fund administered by the American Chemical Society and to the Norman Fund in Organic Chemistry for their support of this work. To Prof. David Dixon, University of Minnesota go our special thanks for assistance with the calculation of the rate constants.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 345 to 358, 1981
Printed in Great Britain

0040-4020/81/Suppl. 1-0345-14 $02.00/0
Pergamon Press Ltd.

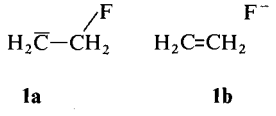
AB INITIO ELECTRON DENSITY ANALYSIS OF β-. FLUOROETHYL ANION: THE NON-IMPORTANCE OF ANIONIC FLUORINE HYPERCONJUGATION†

ANDREW STREITWIESER, JR., CARL M. BERKE, GEORGE W. SCHRIVER, DAVID GRIER and JOHN B. COLLINS
Department of Chemistry, University of California, Berkeley, CA 94720, U.S.A.

(*Received in U.S.A.* 19 *May* 1980)

Abstract—Integration of the electron density functions derived from SCF LCAO-MO calculations of β-fluoroethyl anion provide integrated spatial electron populations (ISEP) around specific regions such as the fluorine atom. Comparison of two conformations of a planar carbanion in which the C-F bond is either alligned with the carbanion lone pair or perpendicular to it shows only a very small difference in fluorine population and demonstrates that the traditional fluorine anionic hyperconjugation mechanism is essentially insignificant. The important difference is that of polarization of electrons rather than charge transfer. Similar conclusions derive from other kinds of comparisons.

Anionic hyperconjugation, particularly as concerns C–F bonds remains a controversial subject. In resonance language it may be defined as a significant contribution of a "no-bond" resonance structure with comparable charge transfer to fluorine; an example is the hyperconjugation structure 1b for β-fluoroethyl anion, **1**.



1a **1b**

In MO language the effect can be defined in terms of significant mixing of a lone-pair orbital with the σ^* orbital of a C–F bond as in Fig. 1. Such mixing should provide a stabilization of the lone pair. Moreover, by reference to the orbital diagram in Fig. 2 we see that such interaction is equivalent to the no-bond resonance in **1**; that is, mixing in additional σ^* character into the lone pair orbital has the effect of increasing π- or double-bond character between the carbons and of decreasing the C–F bonding. Moreover, charge-transfer to fluorine also results.

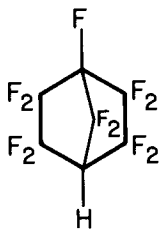
C–F no-bond resonance or hyperconjugation was first invoked as a factor important in reactivity by Roberts *et al.* in 1950.[1] The suggestion found immediate and widespread acceptance and has since been invoked frequently to explain various physical and chemical phenomena. In assessing the importance of the effect the problem has always been to dissociate hyperconjugation from purely inductive, or more properly, field effects associated with the electronegative fluorine and its attendant bond dipole. In two reviews Holtz[2,3] has presented much of the evidence in favor of fluorine anionic hyperconjugation and has compared it with results expected from inductive effects; he concluded that anionic hyperconjugation was not a significant factor in chemistry.[4]

The type of experimental argument used to support the concept is typified by acidity measurements of fluorocarbon C–H bonds. In 1964, Andreades published his kinetic acidity measurements of various fluorocarbons containing a single hydrogen.[5] Hydrogen isotope exchange rates in methanolic sodium methoxide depended strikingly on the number of β-fluorines; he found the following relative rate sequence $CF_3H:R_FCF_2H:(CF_3)_2CFH:(CF_3)_3CH$ to be $1:6:2 \times 10^5:10^9$, and considered this dependence on the number of β-F atoms to be too high to be accountable solely as an inductive effect. Shortly thereafter, Tatlow and Stephens and their research group at the University of Birmingham synthesized a number of highly fluorinated bicyclic compounds of the type **2**, and found the bridgehead hydrogens to be readily metallated.[6] The importance of these compounds is that the enforced conformational effects at the bridgehead preclude important hyperconjugation but allow for normal inductive field effects; that is, hyperconjugation as in **3** should be less important than in acyclic systems such as those studied by Andreades.

These qualitative results were quantified by kinetic and equilibrium acidity studies at Berkeley.[7] The acidities were found to be comparable to $(CF_3)_3CH$ and to be fully explicable by normal electrostatic effects between the carbanion center and C–F bond dipoles. Similarly, a study of the kinetic acidities of a series of 9-substituted fluorenes gave a normal correlation with inductive parameters with no deviation of the CF_3 substituent that would require an additional reactivity to be associated with hyperconjugation.[8]

More recent experimental studies have only reinforced these results. Ibbitson *et al.* have studied the dipole moments of a series of substituted trifluoromethylbenzenes.[9] The magnitude of the differences between the observed moments and those calculated by vector analysis are satisfactorily

† This paper is dedicated to the memory of the late Prof. Robert B. Woodward. Although Prof. Woodward did not work directly in fluorocarbon chemistry, he pioneered the applications of physical organic principles to synthetic organic chemistry.



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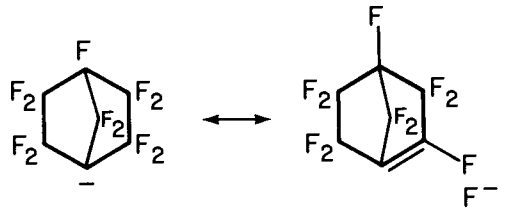

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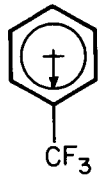

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explained in terms of a π-electron inductive effect of the trifluoromethyl group **4**.

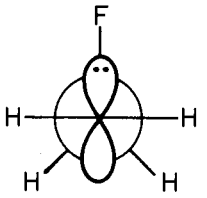
Chambers *et al.* have investigated the effects of substituted perfluoromethyl groups on the rates of nucleophilic aromatic substitution.[10] As the F atoms in the $-CF_3$ group are replaced by $-CF_3$ groups in the series, $-CF_3$, $-CF_2CF_3$, $-CF(CF_3)_2$, $C(CF_3)_3$, the extent of negative hyperconjugation should diminish and the rate constants decrease. This is demonstrably not the case, since all of the perfluoroalkylbenzenes in the series react at comparable rates with, in fact, perfluorotoluene being the least reactive. The results imply a normal inductive effect.

Theoretical considerations

Thus, the pattern of experimental results now makes the special effect of anionic fluorine hyperconjugation unnecessary. Nevertheless, theoretical results have been interpreted to require the concept. Calculated changes in C–H bond lengths adjacent to anions have been interpreted in terms of back-donation into σ^* orbitals.[11] Bingham has emphasized that the strength of C–F bonds and the large energy separation of σ and σ^* C–F orbitals may well result in small hyperconjugation effects in fluorine chemistry; however, since carbon-halogen bond strengths decrease in the order C–F > C–Cl > C–Br > C–I and σ–σ^* splitting decreases proportionately, he argues that anionic hyperconjugation should be increasingly important with the larger halogens.[12]

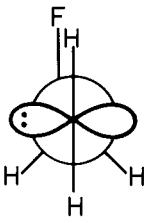
In short, the importance of anionic hyperconjugation remains controversial.[13] In part, of course, the controversy arises because of a lack of precise definition. Physical organic chemical concepts commonly deal with physical non-observables that, therefore, cannot be precisely defined. Such concepts are nevertheless useful because they frequently allow the correlation or prediction of qualitative effects of structure on reactivity. Organic compounds are so large and complex that it is essential to dissect a molecule into parts and to assess—qualitatively if not quantitatively—the contributions of different portions of the molecule to changes in reactivity behavior. Thus despite the fact that anionic fluorine hyperconjugation cannot be evaluated analytically and accurately independently of everything else that goes on in a structural change, it is, nonetheless, a significant concept that has definite implications and whose qualitative importance needs to be assessed. The problem comes in dissecting the effects of this "effect" from those of others, notably polarization. The problem arises even in theoretical calculations. In principle, it is possible to do a reasonably good quantum mechanical calculation within certain limits. Such a calculation would yield a wavefunction; the wavefunction for an MO-type calculation can generally be expressed analytically as a linear combination of basis functions. With a wavefunction we can calculate, more or less accurately, molecular properties such as the energy, dipole moment, etc, and such calculated properties can be compared, more or less satisfactorily, with experiment. But what do such calculations tell us that experiment doesn't? Inspection of page after page of computer output gives us no insight into the system unless we attempt an interpretation—again frequently with simplifying concepts that deal with physical non-observables and therefore with only qualitative significance. Such concepts clearly are useful but need to be made with care.

An example is the energy of two conformations of β-fluoroethyl anion with a planar carbanion **5a** (planar syn) and **5b** (planar perp) (X = F). In **5a** the lone pair and the C–F bond are lined up and hyperconjugation is conformationally possible; in **5b** the two units are perpendicular and hyperconjugation cannot occur. SCF-MO calculations on "standard" structures[14] with the 4-31G basis set[15] gives an energy difference of 10.8 kcal mol^{-1} (Table 1) and taken alone would suggest that hyperconjugation is a significant effect. This conclusion does not depend qualitatively on the specific structures assumed although, of course, it would be best to use energy-optimized structures. But if the effect is truly an important one it should be discernable for any reasonable structure. The use above of planar carbanions should exaggerate the effect although the true anion undoubtedly has a pyramidal structure. Some such structures based on tetrahedral carbons are **6a** (pyramidal perp), **6b**



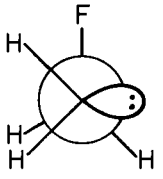
planar syn

5a



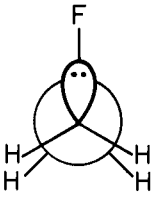
planar perp

5b



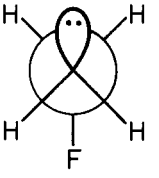
pyramidal perp

6a



pyramidal syn

6b



pyramidal anti

6c

(pyramidal syn) and **6c** (pyramidal anti). The energy difference between **6a** and **6c** is 6.8 kcal mol^{-1} (STO-3G) but this difference includes a significant torsional effect.

Pople *et al.*[16] have analyzed computed rotational barriers in terms of a Fourier series, eqn (1).

$$V = V_1 \cos\theta + V_2 \cos 2\theta + V_3 \cos 3\theta. \quad (1)$$

The V_1 term is associated with Coulombic charge interactions and the V_3 term is a torsional term. The V_2 term was considered to derive from back-donation or hyperconjugation. The rotational barrier of pyramidal β-fluoroethyl anion has recently been calculated more thoroughly by Schleyer *et al.* who find the value of V_2 (4-31G) to be 7.5 kcal mol^{-1}.[17,18] This value is an order of magnitude higher than can be accounted for on a simple Coulombic interaction of the carbanionic negative charge with a C–F bond dipole.[19,20] However, the angular dependence of the effect is also consistent with a charge-induced polarization of the appropriate σ-bond. Such polarization is expected to have many of the same consequences as hyperconjugation such as, for example, structural changes.

Nevertheless, there is one clear distinction between polarization effects and hyperconjugation. Structure **1b** clearly implies *charge-transfer to fluorine*; that is, we expect the F in an appropriately oriented β-fluoroethyl anion to be more negatively charged than that of an orthogonal analogue. We now consider the problem of charges of atoms in molecules.

Atomic charges

The concept of the charge of an atom in a molecule has been an important one in chemistry. It has heuristic value and is useful in correlating diverse facts and phenomena. Yet, such atomic charges are not physical observables and, consequently, have no precise definition. The most widespread and generally used definition based on the LCAO-MO method is the Mulliken Population Analysis.[21] Each MO is a linear combination of basis functions centered on atoms and the Mulliken Population Analysis is actually a basis function population. Unfortunately, the Mulliken scheme has important weaknesses. These were recognized by Mulliken[22] and have been further elaborated by many authors.[23,40] The problem is illustrated in Fig. 3. A diffuse function centered on one atom is used to help describe the electron distribution near a second nucleus, but part of the electrons involved are assigned to the first center because the diffuse function is centered there. Consequently, the

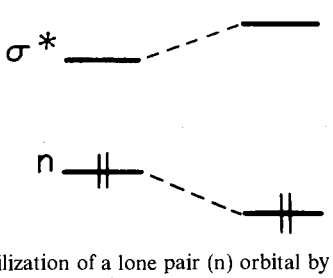


Fig. 1. Stabilization of a lone pair (n) orbital by interaction with a σ^* MO.

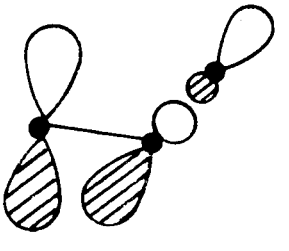


Fig. 2. Approximate orbital picture of the interaction of a lone pair p-orbital with a σ^* C–X orbital.

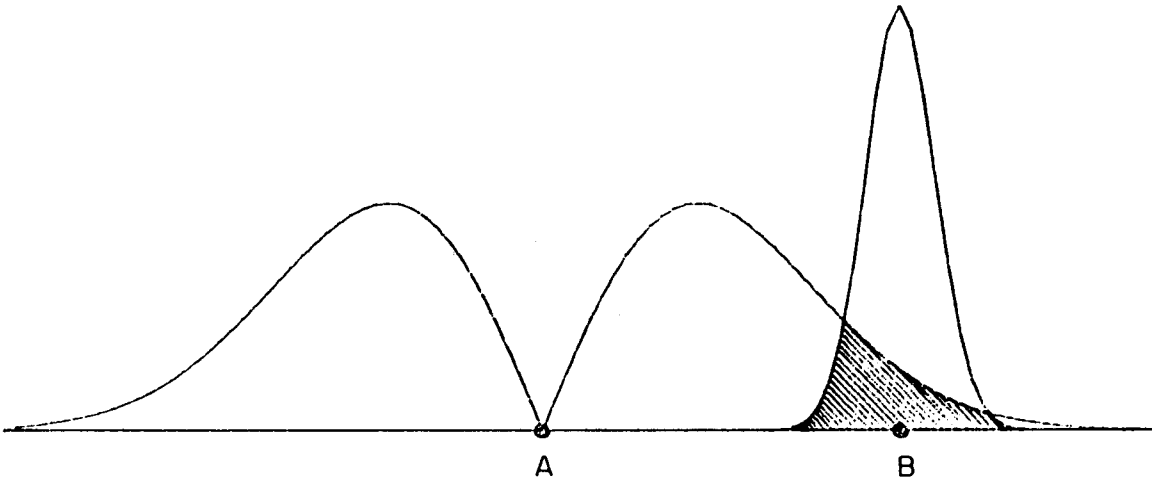


Fig. 3. Part of the electron population near atom B is assigned by the Mulliken Population method to A because a diffuse function required to describe the electron distribution at B is centered mathematically on A.

Mulliken Population is basis-set dependent. Several variations of the Mulliken scheme have been proposed but these also have similar weaknesses and are generally also basis set dependent.

An alternative is to make use of electron density functions for integrated spatial electron populations. The electron density, ρ_k, is defined for each MO, ϕ_k, by eqn (2). The total density, ρ, is a physical observable and is given for the MO method as the sum over occupied MOs, eqn 3 where $c_{i,j}$'s are coefficients of the n basis functions, $\chi_{i,j}$'s in MO ϕ_k in which N_k is the occupation number of MO ρ_k. Integration of the

$$\rho_k(x,y,z) = \phi_k^2\ (x,y,z) = \sum_{i=1}^{n} \sum_{j=1}^{n} c_i C_j \chi_i(x,y,z)\chi_j(x,y,z) \tag{2}$$

$$\rho(x,y,z) = \sum N_k \rho_k \tag{3}$$

electron density function over a region of interest gives the integrated electron population for that spatial region. The next problem is to choose boundaries for assignment of such integrated spatial electron populations (ISEP) to individual atoms. The choice of such boundaries is necessarily *ad hoc*.

Bader has made effective use of boundaries defined by limiting gradients of ρ around atoms;[41] these "virial boundaries" are uniquely defined and have some important mathematical properties. Unfortunately, these virial boundaries frequently do not correspond even closely to empirical "covalent radii" and the associated "atomic charges" differ from chemical expectations. However, when the virial boundary results from an electron density function that approaches zero in a region between atoms, the matter is far less ambiguous. This situation results, for example, when two atoms or ions are not covalently bound.[40,42] We will make use of this principle by focusing attention on difference populations rather than on individual structures.

Electron projection function

The electron density function is a four-dimensional function and as such is impossible to visualize without some restrictions. Most often, the function is displayed for a given plane of interest in a molecule either in contour or perspective plot format. Such plots work best when all or most of the atoms of a molecule lie on one plane but even for such systems this plane is often the nodal plane of π-electrons; that is, for non-linear systems one cannot compare σ and π electron density distributions with the same plane.

An alternative is to integrate the electron density function along one or more coordinates. In the planar density function of Brown and Shull,[43] the integration is along two coordinates; in effect, the electron density is projected on a line. The result provides a simple and useful display for diatomic molecules and others that are adequately represented by a straight line.[42,44,45]

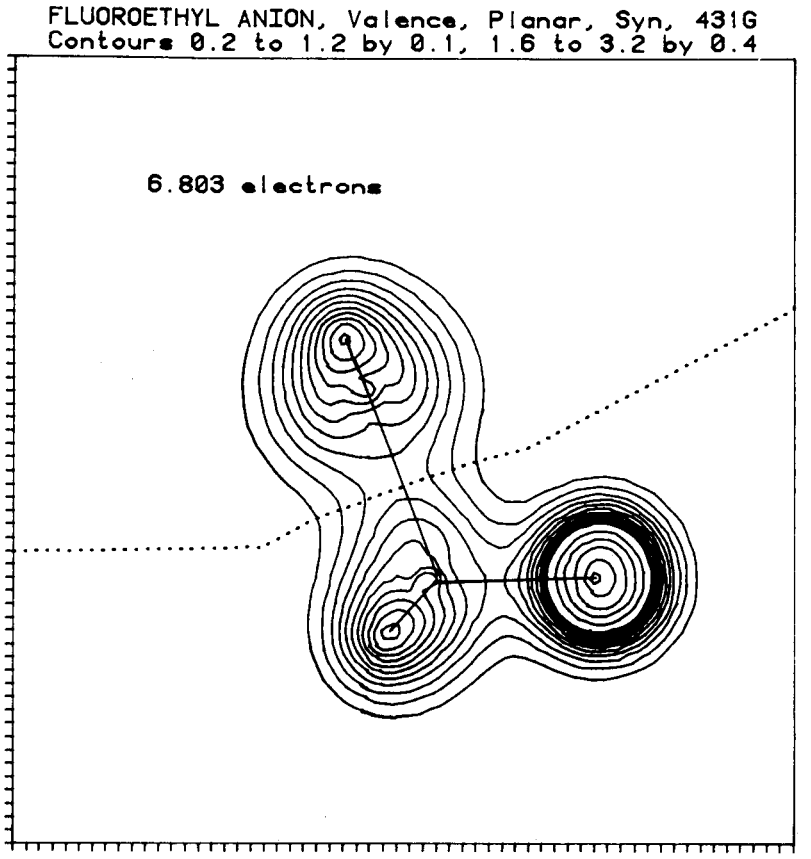
For systems adequately represented by a plane we have found it convenient to modify the linear function of Brown and Shull by integrating along a single coordinate (y) perpendicular to a plane of choice (the xz plane) (eqn 4). In this "Electron Projection Function", P_{xz},[46] all of the planes of ρ perpendicular to the y-axis may be considered to be collapsed onto the xz plane.

$$P(x,z) = \int_{-\infty}^{\infty} \rho(x,y,z)dy. \tag{4}$$

In this manner σ and π electrons can be visualized in the same coordinate frame. Of course, information is lost in going from ρ to P but perception is heightened and pattern recognition becomes more feasible. The program PROJ accomplishes these integrations for a grid superimposed on the molecule[47] and the results are plotted in contour or perspective plot format; examples of both are shown below.

Hyperconjugation in β-fluoroethyl anion

The electron projection function was calculated for different conformations of β-fluoroethyl anion. The $F-C_\beta-C_\alpha$ atoms define the xz plane and identical



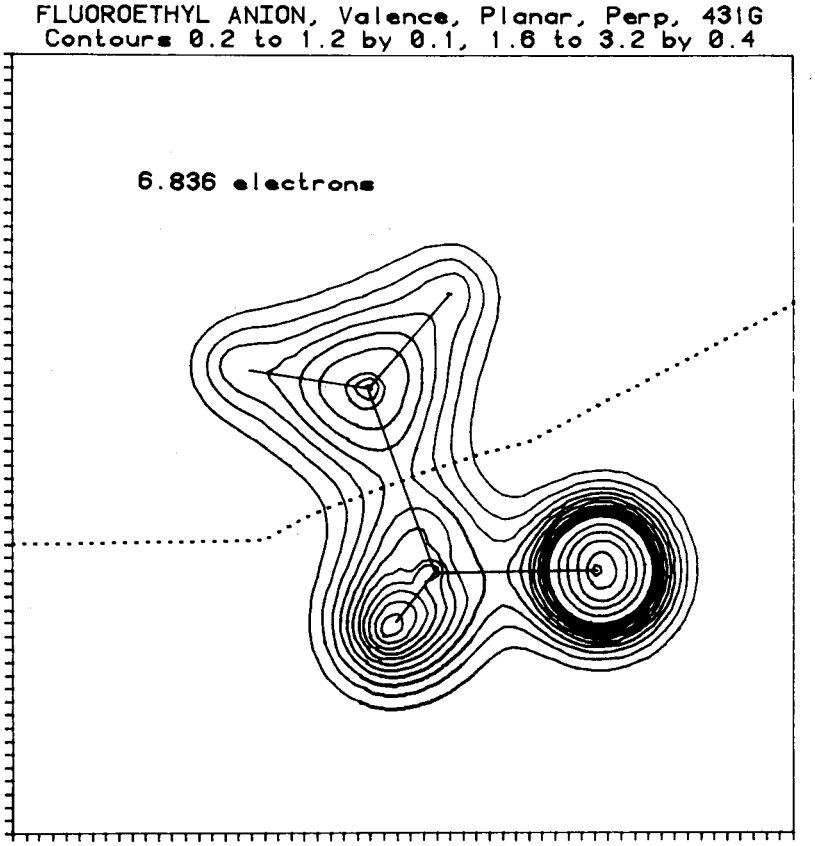


Fig. 4. Contour plots of the valence electrons of **5a** and **5b**. The dotted line is an integration boundary for the upper CH_2^- group and is identical in both figures. The $-CH_2F$ group is also identical in the two halves with the F located at the lower right.

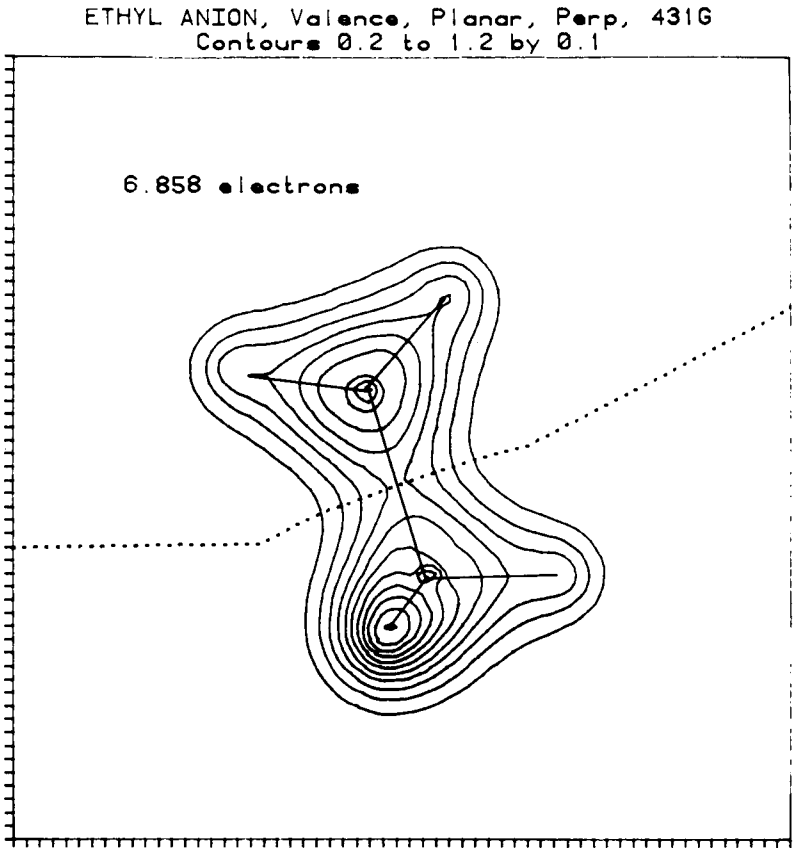


Fig. 5. Ethyl anion: Valence projection plot for planar perp conformation. The dotted line is the same integration boundary used in Fig. 4.

coordinates for these atoms were used in order to facilitate the interpretation of difference plots. For the planar carbanion the "planar syn" structure **5a** has the $C_\alpha H_2$ group perpendicular to the xz plane and the lone pair in the plane where it is best able to hyperconjugate with the C–F bond. Contour plots of the projection function, P_{xz}, for **5a** and **5b** are shown in Fig. 4. These plots pertain to valence electrons only; inclusion of core electrons makes the function more difficult to represent in this format. The dotted lines in the two parts of Fig. 4 are identical and correspond approximately to a "virial boundary".[41] Numerical integration of the upper parts, the $-CH_2^-$ portion, gives the number of valence electrons shown. The results show that the syn-CH_2^-, which is in position to hyperconjugate, has lost 0.033 electrons relative to the perp-isomer, and taken alone would suggest the operation of hyperconjugation. These results may be compared with the population of the $-CH_2^-$ group of Et anion with the same geometry and using the same integration boundary. The planar perp conformation shown in Fig. 5 has an integrated population of 6.858 electrons, 0.03–0.06 electrons more than either of the fluoroethyl conformations. As expected, the population of $-CH_2^-$ group is not sensitive to the Me orientation. A comparable treatment for the planar syn conformation gives a carbanion population of 6.862 electrons, actually slightly more than the perp conformation.

Far more revealing are the difference functions $\Delta P = P(\mathbf{5a})-P(\mathbf{5b})$ as shown in Fig. 6. Both contour and perspective representations are shown in this plot together with the superposition of the two structures. The large feature corresponds to the rotated CH_2 group in which atoms have moved. Indeed, the pattern in this region shows that the relative populations of the $-CH_2^-$ group in the two conformations will be sensitive to the precise boundary chosen—the integration boundary of Fig. 4 cuts through significant positive and negative contours.

The crucial region is that near fluorine where nuclei remain the same in both structures. We see immediately that the fluorine region is clearly defined—it is an isolated feature surrounded by regions where the ΔP function approaches zero. As such, the fluorine region shows a "difference virial boundary" in the Bader sense and differs importantly in this sense from the $-CH_2^-$ region. This region shows a depression together with a mound characteristic of *polarization*, a shift of electrons from one side of the fluorine atom to the other. This feature is especially clear in the contour plot of Fig. 7 in which negative contours are indicated as dashed lines. Integration of the region around the F (dotted circle on Fig. 7) shows an excess ISEP of 0.0272e for the hyperconjugating F. The larger integration region shows an additional diffuse 0.013 electrons. These numbers may again be compared with those for Et

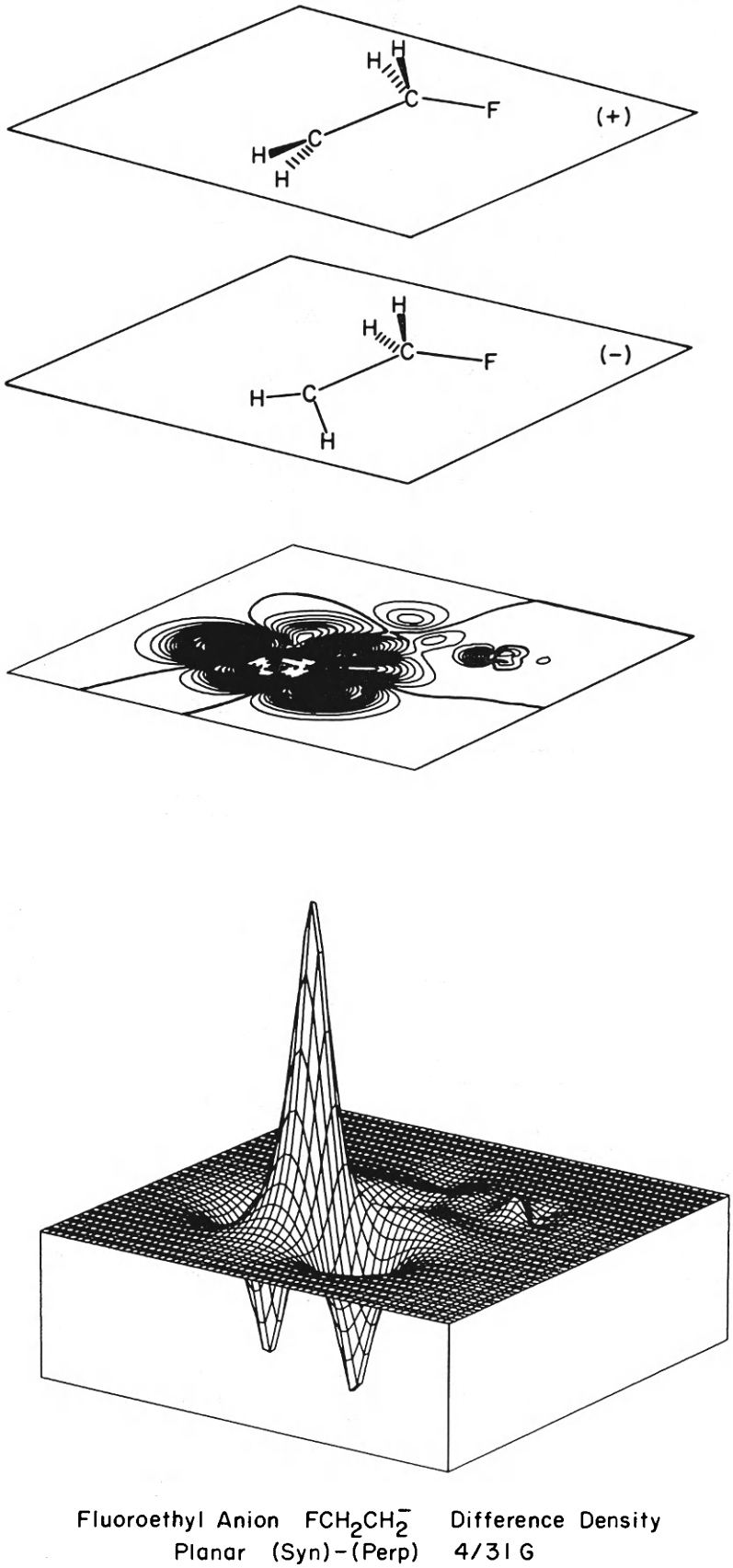


Fig. 6. Electron projection difference plots for two conformations of planar β-fluoroethyl anion, P(**5a**)–P(**5b**) (4-31G basis set).

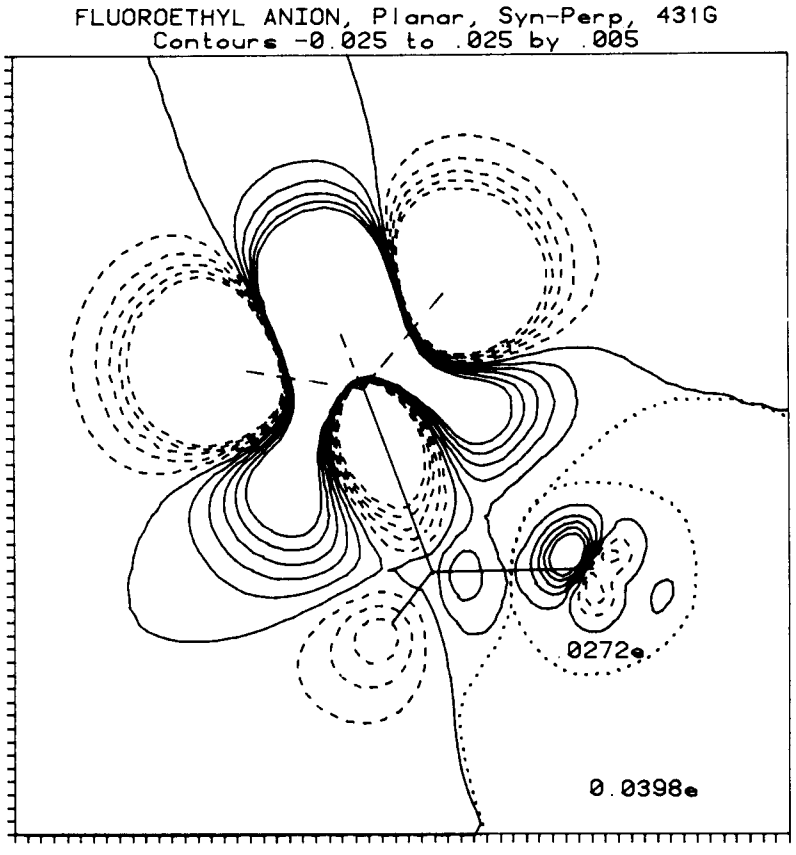


Fig. 7. Contour plot of ΔP, P(**5a**)–P(**5b**). ISEP differences are shown for two different integration regions indicated as dotted lines. The C–H bonds rotated in the two conformations are shown as straight dashed lines.

anion in a comparable treatment. Fig. 8 is arranged to compare with Fig. 6. We note the presence of a mound showing electron excess for a hyperconjugating hydrogen but no polarization. The corresponding contour plot is shown in Fig. 9. Integration boundaries comparable to those in Fig. 7 give comparable values for ISEP changes. That is, *according to the criterion of charge transfer a* C–H *bond is as effective in anionic hyperconjugation as* C–F!

Moreover, this conclusion would appear to be rather firmly established. Our integrations are reliable to about 0.001e. Our experience with a number of different systems show generally that changes in basis set would be expected to alter the specific numbers somewhat, but they are unlikely to produce such large changes as to alter the conclusion (for example, ref. 42).

The polarization phenomenon in Figs. 6a–d and 7 provides the real key to what is happening in these systems. Such polarization does not show up in typical Mulliken population calculations and is frequently ignored as a significant interaction mechanism in physical organic chemistry. Such polarization at atoms also remains unrevealed in all schemes involving complete integration of electron densities within spheres or similar definitions of net atomic charge. One of the important virtues of the ΔP plots in either contour or perspective format is that such polarization is qualitatively discernable as a characteristic pattern. Moreover, integration of the positive and negative parts is readily accomplished. In Fig. 6 we find that 0.005e have transferred from the back of the fluorine to the side towards the carbanion carbon. Moreover, we note, perhaps unexpectedly, that such polarization is in the direction that puts the additional electron population on the side *towards* the in-plane lone pair, as if the carbanion carbon nucleus is effectively less shielded by its lone pair electrons than by bonded electrons. In this connection we may note also that lone pair electrons generally have smaller optimum Slater exponents and are more diffuse than bonded electrons.

Finally, we emphasize that although the above results were calculated for planar anions with no structural optimization they are not expected to change significantly with reasonable structural modifications. An effect significant at one geometry is not expected to change dramatically with a small geometrical change; most effects behave in a continuous manner. Furthermore, hyperconjugation should be enhanced for a planar carbanion compared to a pyramidal one. Nevertheless, we shall show below that equivalent results obtain also for pyramidal systems.

Roles of inner and outer orbitals

The 4-31G basis set uses two orbitals to describe each traditional valence orbital, a linear combination of three gaussian functions with relatively high exponents for the inner (e.g. $p_z(i)$) part and a single more diffuse gaussian function for the outer (e.g. $p_z(o)$)

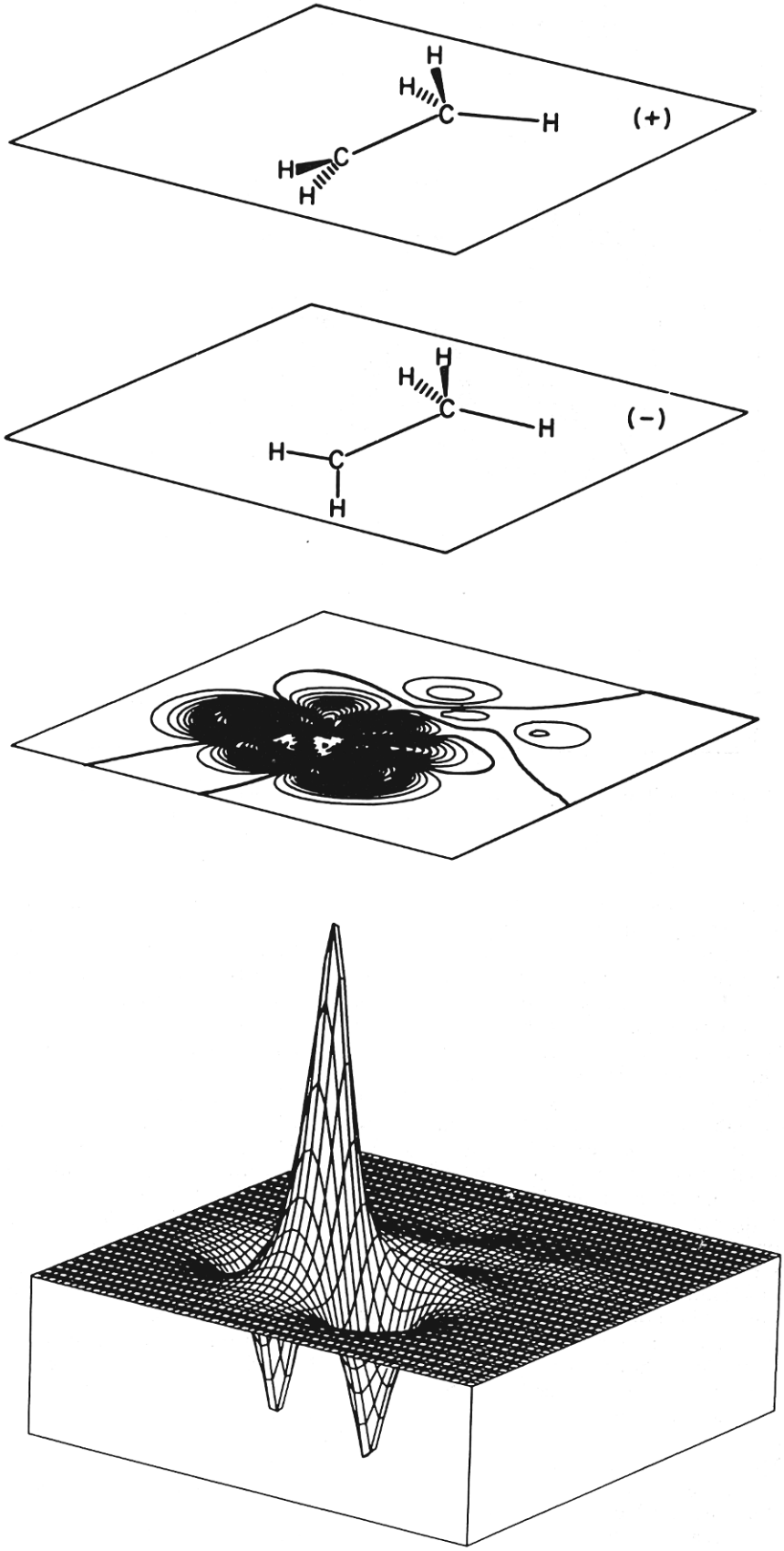


Fig. 8. The ΔP_{xy} function, P(planar syn)−P(planar perp), for ethyl anion corresponding to the function in Fig. 6 with F replaced by H.

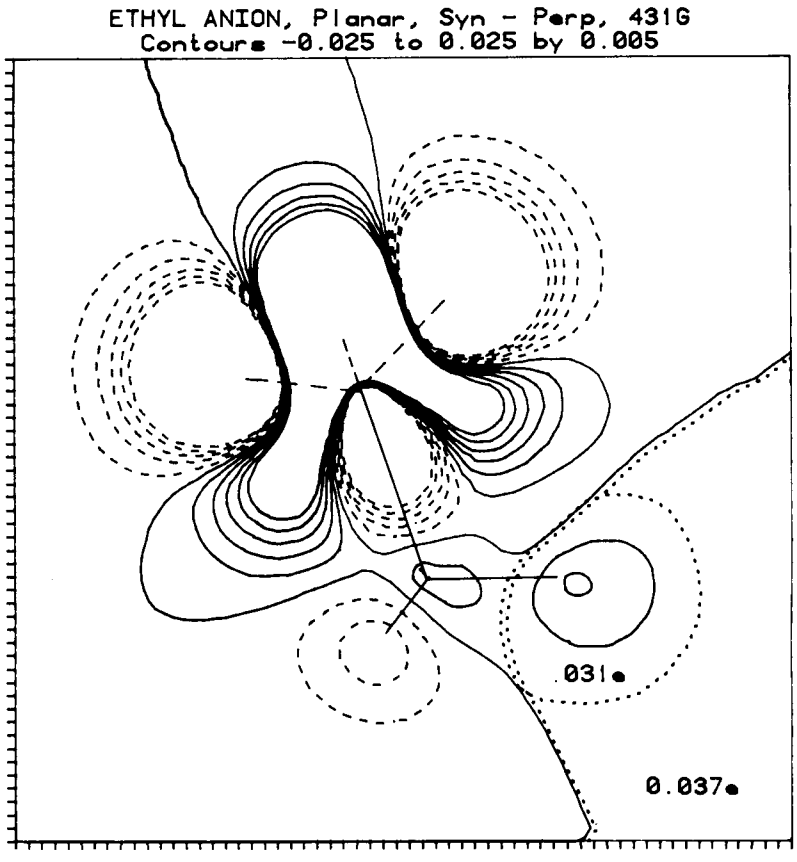


Fig. 9. Contour plot of ΔP for ethyl anion, P(syn)–P(perp) corresponding to Fig. 9. Difference ISEP values are shown for two integration regions bounded by dotted lines. The C–H bonds rotated in the two conformations are shown as straight dashed lines.

part. In individual MOs the inner and outer parts are separately optimized to give the lowest energy and, of course, it is that additional flexibility that makes the 4-31G basis set so much better than a minimum basis set such as STO-3G. The relative contributions of inner and outer parts of orbitals can be quite instructive but have generally been ignored as a source of heuristic information. For example, in bonding MOs the contribution of inner parts is generally more important than outer; that is, coefficients for a given valence orbital generally have the same sign but with $|c(i)| > |c(o)|$. On the other hand, in relatively low-lying antibonding or virtual orbitals, generally $|c(o)| > |c(i)|$ but again with the same signs. This pattern is readily understood on the basis that outer orbitals are effectively less electronegative than inner; hence, in a bonding MO the more electronegative orbitals have larger coefficients but in antibonding MOs the reverse is true in order to maintain mutual orthogonality of orbitals. An example is shown for the HOMO of planar syn ethyl anion in Table 2. This MO in the 4-31G approximation is antibonding (positive energy, $\varepsilon = 0.0604$ au) and, accordingly, $|c(o)| > |c(i)|$ for all atoms. This MO is primarily the carbanion lone pair and the ratio of inner and outer parts provides for the diffuseness of this lone pair. Note also that the signs of the orbitals are such that the Me hydrogens are antibonding with respect to the carbanion lone pair.

The corresponding HOMO of planar syn β-fluoroethyl anion shows some important contrasts (Table 3). Although for the carbanion lone pair, $c(o) > c(i)$, the ratios are not nearly so great as for Et anion. More important for the fluorine p_z orbital we find a sign reversal that provides the mathematical mechanism for polarization. The net result is not nearly as obvious as what one would have expected from a simple interaction of lone pair and σ^* as implied in Figs. 1 and 2. In fact, *a simple HOMO–LUMO argument does not suffice in this case.* Even in a first approximation we must include the effects of the corresponding σ orbital. That is, we can consider the interaction of the lone pair first with σ; this is the effect most important in normal carbonium ion hyperconjugation where only the lowest orbital considered is occupied. Next we can allow interaction with σ^* as in Fig. 10. The resulting pattern is substantially more complex than that of Fig. 2 but even so, the effects of other orbitals cannot be neglected.

We note in this connection that in their study of methyl substituent effects in conjugated systems Libit and Hoffman[48] used a second order perturbation analysis; such an analysis does involve all of the molecular orbitals.

Deprotonation of ethane and fluoroethane

Finally, we examine the electronic changes that accompany deprotonation of ethane and fluoroethane. Ethane and ethyl anion are isoelectronic. In Fig. 11 we display the ΔP function for P(ethyl anion)–P(ethane) in contour format. The C–H bond

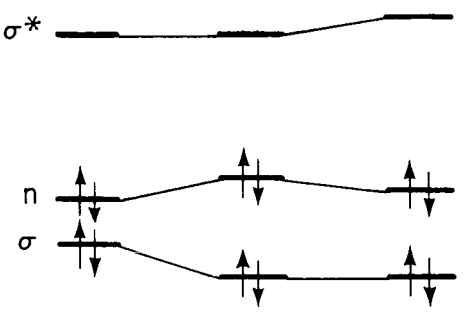


Fig. 10. Showing the approximate effects of allowing a lone pair orbital (n) the interact first with σ, then with the corresponding σ^* MO.

being broken is shown as a dashed line. The bunched negative contours at the proton being lost at the upper left show the movement of electrons towards the carbon on ionization. This region within the zero contour integrates to 0.47 e. Removal of the proton is accompanied by successive increases and decreases in electron population as shown by alternating regions of positive and negative contours. The positive contours show regions that have greater electron population in the carbanion than in the hydrocarbon. Such a region is that of the trans periplanar Me hydrogen; this region is about 0.1 e richer in ethyl anion than in ethane. The *pattern* of Fig. 11 shows that this result stems more from alternations of polarization than from direct charge transfer.

Fig. 12 displays a comparable difference plot for ethyl fluoride and the fluoroethyl anion, **6c**, derived by removing a proton with no other structural change. Again, keeping identical geometries facilitates the interpretation of difference plots. Both systems are again isoelectronic so that the integral over the entire figure vanishes. The bunched contours at the acidic proton now integrate to 0.49 e, a difference of only 0.02 e from ethyl case. Indeed, the entire figure resembles the ethyl case closely except at fluorine where we again discern the familiar pattern of polarization. The direction of polarization is aimed at the C_α nucleus and again suggests that the lone pair electrons at the rear of C_α in the carbanion provide less shielding of the carbon nucleus than in the hydrocarbon. The total region around the fluorine has 0.08 electrons more in the carbanion than in ethyl fluoride, a number again similar to the ethyl case.

The comparison is made still more dramatic by a difference plot, $\Delta\Delta P$, $(P(FCH_2CH_2^-)-P(FCH_2CH_3)-(P(CH_3CH_2^-)-P(CH_3CH_3))$, in Fig. 13. In effect this figure is Fig. 11 subtracted from Fig. 12. The shallow contours over most of the figure demonstrate graphically that deprotonation of ethane and fluoroethane cause almost identical electronic changes except for the characteristic polarization change at fluorine.

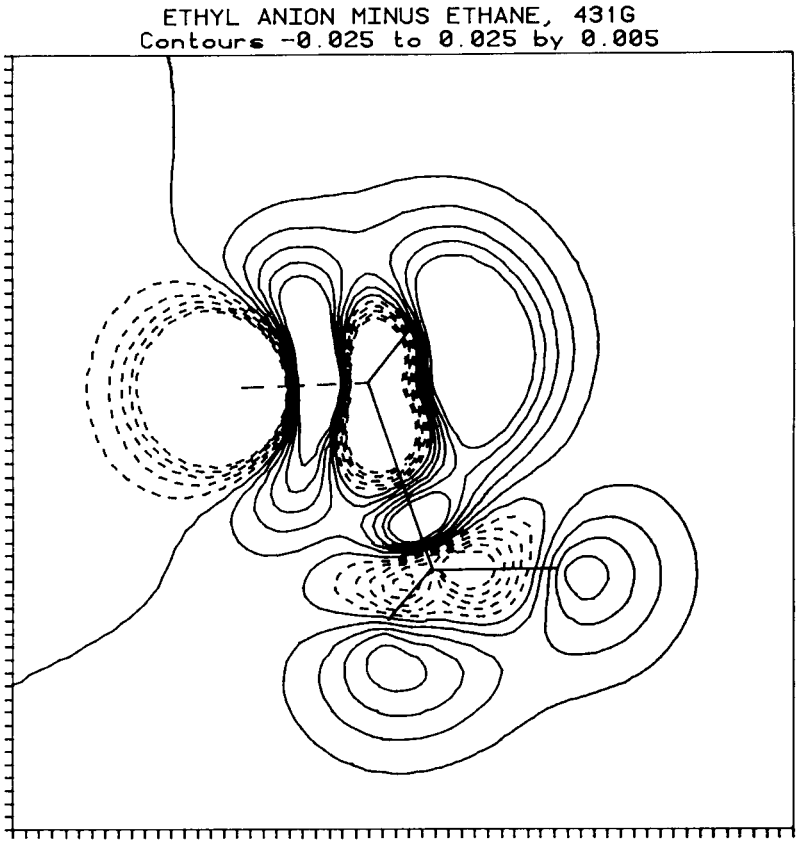


Fig. 11. The ΔP function for deprotonation of ethyl anion in a staggered conformation $(P(CH_3CH_2^-)-P(CH_3CH_3)$. The C–H bond being broken is shown as a straight dashed line. Dashed contours are negative.

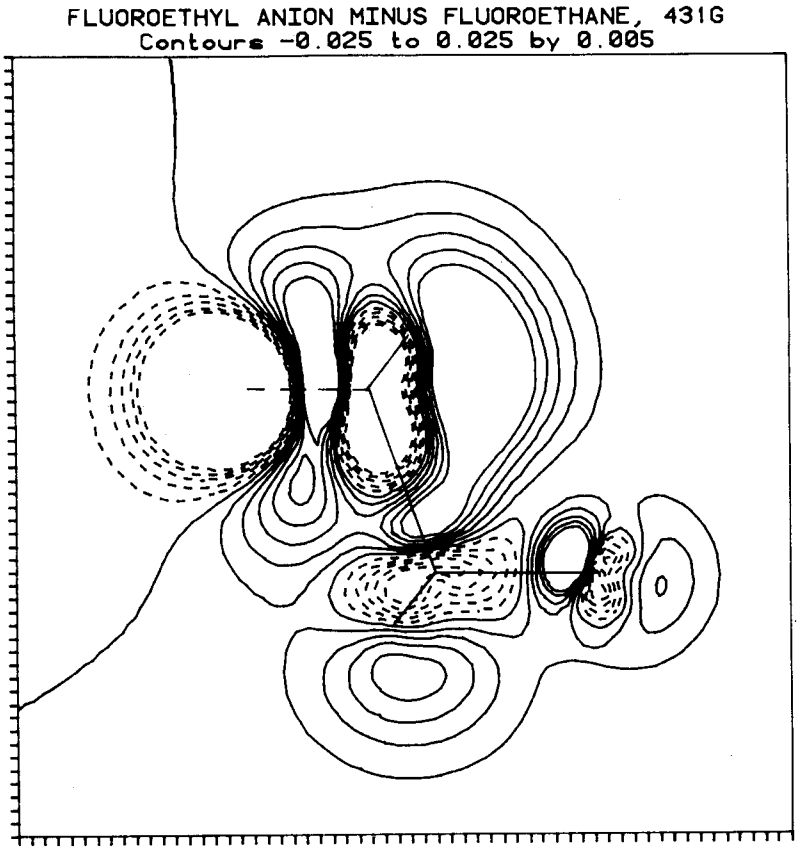


Fig. 12. ΔP function for deprotonation of fluoroethane with the same geometry as Fig. 12, the $P(FCH_2CH_2^-)-P(FCH_2CH_3)$. The fluorine is at the lower right.

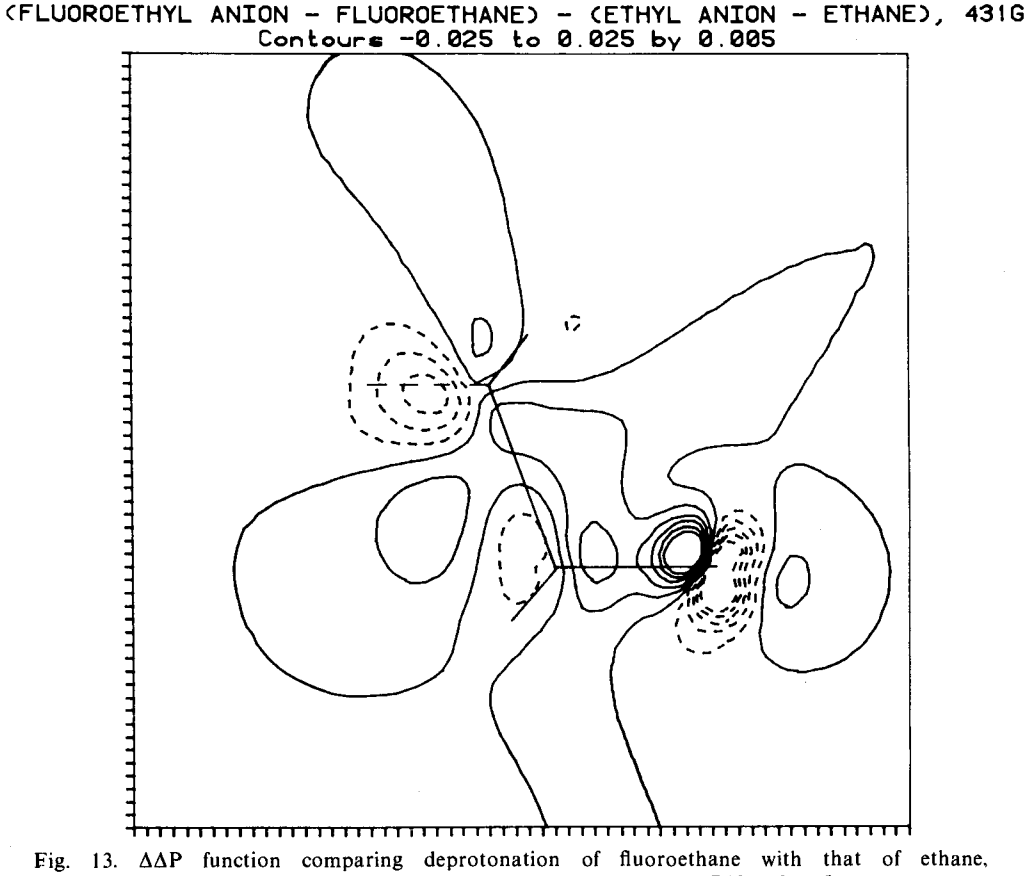


Fig. 13. ΔΔP function comparing deprotonation of fluoroethane with that of ethane, $[P(FCH_2CH_2^-)-P(FCH_2CH_3)]-[P(CH_3CH_2^-)-P(CH_3CH_3)]$.

The positive contours to the left of this fluorine integrate to 0.026 e; the negative contours to the right integrate to −0.018 e.

SUMMARY

We conclude that *charge transfer* from a carbanion lone pair to a fluorine atom in conjugating position plays no significant role; that is, the conventional concept of fluorine hyperconjugation is not significant in organic chemistry. Polarization is a much more significant phenomenon and needs to be given greater recognition as a physical organic effect. This effect does not show up in conventional Mulliken populations but is readily discernable by characteristic patterns in integrated electron density functions. Polarization may be responsible for many of the properties previously associated with hyperconjugation. However, we also emphasize that the present results apply specifically to fluorine. Anionic hyperconjugation to other halogens with weaker C–X bonds may still be significant. We are presently applying our approach to β-chloroethyl anion.

Calculations. MO calculations were run at the University of California Computer Center using the Gaussian 70 series of programs.[49] Perspective plots (Figs. 6 and 8) were done at the Computer Center using SDL graphics software.[50] The later contour plots at the Lawrence Berkeley Laboratory made use of the graphics program MOG written primarily by J. Sender. The integrations were accomplished on a Tektronix 4051 system, and most of the plotting was done on a Tektronix 4662 plotter.

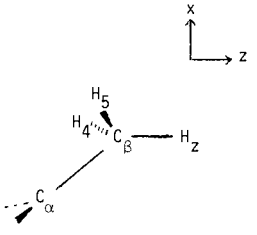
Table 1. *Ab initio* calculated energies

Compound[a]	STO-3G[b]	4/31 G[a,b]
CH_3CH_2F		
staggered	-175.752143 (0.0)	-177.841538 (0.0)
eclipsed	-175.747709 (2.8)	-177.835763 (3.6)
$^-CH_2CH_2F$		
planar syn	-174.859991 (16.0)	-177.123855 (6.7)
planar perp.	-174.846078 (24.7)	-177.106648 (17.5)
pyr. syn	-174.881251 (2.6)	-177.127077 (4.7)
pyr. perp.	-174.874610 (6.8)	-177.118855 (9.9)
pyr. anti	-174.885472 (0.0)	-177.134558 (0.0)
CH_3CH_3		
staggered	-78.305499 (0.0)	-79.114847 (0.0)
eclipsed	-78.300195 (3.3)	
$^-CH_2CH_3$		
planar syn	-77.385260 (19.1)	-78.362386 (8.4)
planar perp.	-77.385225 (19.1)	-78.362337 (8.4)
pyr. syn	-77.411177 (2.9)	
pyr. perp.	-77.413461 (1.4)	
pyr. anti	-77.415753 (0.0)	-78.375698 (0.0)

(a) Planar and pyramidal (pyr.) refer to the geometry of the CH_2^- group; syn, perpendicular (perp.), and anti refer to the angle between the carbonion lone pair and the C-F bond (0°, 90°, and 180°, resp.).

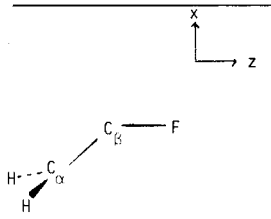
(b) Energies are in atomic units (1 a.u. = 627.49 Kcal/mole); entries in parentheses are relative energies in Kcal/mole^{-1}.

Table 2. HOMO coefficients for planar syn ethyl anion



Atom	Orbital	4-31G (i)	Coefficient (o)
H_2	1s	-0.12	-0.25
H_4,H_5	1s		.13
Cα	$2p_x$	.15	.21
	$2p_z$	.44	.62

Table 3. HOMO coefficients for planar syn β-fluoroethyl anion, **5a**



Atom	Orbital	4-31G (i)	Coefficient (o)
F	$2p_z$	0.12	-0.18
	2s		.16
C_β	$2p_z$		.16
C_α	$2p_x$	.15	.18
	$2p_z$	.44	.58

Acknowledgements—This research was supported in part by National Science Foundation grants No. CHE76-10997 and CHE79-10814 and National Institutes of Health grant No. GM-12855.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 359 to 370, 1981
Printed in Great Britain

0040–4020/81/Suppl. 1–0359–12 $02.00/0
Pergamon Press Ltd.

A LOGIC FOR SYNTHESIS DESIGN[1]

JAMES B. HENDRICKSON, ELAINE BRAUN-KELLER and GLENN A. TOCZKO
Edison-Lecks Chemistry Laboratories, Brandeis University, Waltham, MA 02254, U.S.A.

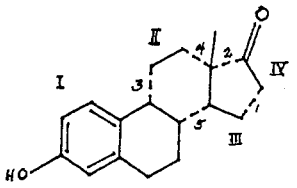
(*Received in U.S.A.* 17 *June* 1980)

Abstract—The background for synthesis design logic is presented, followed by the development of a procedure aimed at assessing all and locating the best synthetic routes. The procedure has two stages, first a dissection of skeleton, then a generation of necessary functionality on it to afford successive construction reactions. The implementation of this plan with computer programs is described, with some results. Reduction to computer has in turn served to clarify the overall logic, which is accordingly somewhat different from previous descriptions.

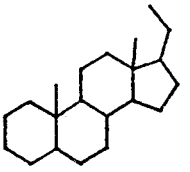
Synthesis of organic molecules has a long history but the conceptual act of design, of selecting a synthetic route or sequence of reactions, remains undefined, an art in the midst of a science. Before 1967 it was not even addressed in the literature.[2] Our minds, our knowledge, our literature, even our starting material catalogs are not organized for it. We speak of a synthesis as "elegant" but no one can define this elegance or say whether another route might have been shorter or simpler.

Size of the problem

Synthesis design is difficult because there are a vast number of synthetic routes possible to any given target from tens of thousands of available starting materials. This results from a combinatorial monster of what pieces to use, what order to take them in, and what reactions to link them with, and because the scope of possibilities is so vast it is probably not generally appreciated. In order to see this, we may consider just the possibilities of putting the target skeleton together from starting material pieces, ignoring the choice of reactions necessary to do it. This skeleton is a graph and there are a number of ways to dissect it.[4] If it has b bonds or links and we decide to make λ of them in the synthesis there are $\binom{b}{\lambda}$ combinations possible of bonds to make, or sets of starting material pieces to use. The simplest steroid synthesis is that of estrone (**1**) in which 5 out of 21 skeletal bonds are made (dotted in **1**).[5]



(**1**)



(**2**)

There are 20,349 combinations of five bonds possible, of which this is only one. Since the average starting material piece used in synthesis has three skeletal carbons,[6] a dissection of the C_{21} cortical steroid skeleton (**2**) should yield seven pieces and so $\lambda = 10$; 10 of 24 bonds to make offers almost two million possible combinations of skeletal dissection alone. Then the order in which any one of these combinations of pieces is put together is still unspecified, and there are $\lambda!$ possible orders for any starting material set. The five dotted bonds in **1** were made in the numbered order shown.[5] The combinations of pieces and orders must be multiplied, giving 2.5×10^6 routes for assembling estrone by making five skeletal bonds, or 7×10^{12} routes to the C_{21} steroid,[7] still irrespective of the chemistry, i.e. the functional groups and the reactions involved. The number of routes to create the C_{21} steroid skeleton from one-carbon units, i.e. total synthesis, is 6.2×10^{23}, more than Avogadro's number! If we made each molecule of **2** a different way we would make a mole of steroid.

The idea of routes to the target is often expressed graphically as a synthesis tree (Fig. 1) with lines indicating the reactions and points the intermediates;[8] the circled points are starting materials and two synthetic routes are marked as heavy lines from starting material to target (T). The tree shown is very deceptive in being so very small a part of the whole. The problem then is to find a systematic way to assess all the routes and locate the best ones through this enormous tree, within clearly defined constraints.

Traditional approach

The original computer procedure, used first by Corey and Wipke[8a] and since by others,[9,10] was to follow systematically the presumptive reasoning of chemists, back from the target functionality stepwise, using a built-in library to find all last reactions and their substrates and then repeating this for each intermediate so derived. This procedure immediately generates a large number of intermediates at the first level and, as each intermediate becomes target in turn, an almost exponential increase in numbers thereafter. The need to prune the tree here is met by prediction of reaction yields at each step and, in the interactive programs, by allowing the chemist to select favorites. There are several intrinsic weaknesses in this approach.

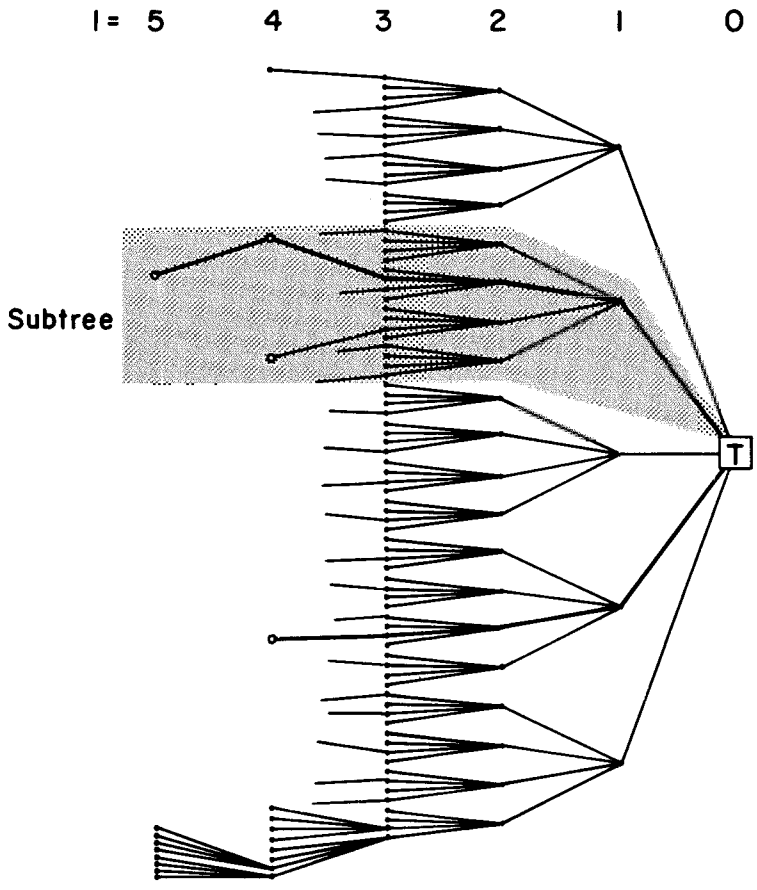


Fig. 1. The synthesis tree.

(a) The prediction of yields is notoriously imprecise and so a poor basis for comparison among thousands of routes assessed.

(b) The procedure has no direction: it ignores the available starting materials until found at the end instead of actively forcing the search to converge on them. Similarly the process is not actively directed to seek economy.

(c) Directed by functionality and reactions dictated by it, the procedure cannot synthesize unfunctionalized targets without incorporating dummy functional groups and there is no heuristic to indicate where to locate these.[8b] Furthermore, such dummy functional groups, removed before the target is reached and so leaving no trace in its structure, are not uncommon in real syntheses of functionalized targets as well.

(d) At the mercy of a library of known reactions there is no opportunity to generate new synthetic reactions.

Finally, however, while synthetic chemists rarely describe the conceptual basis for a route chosen, it seems unlikely that they have employed such a mechanical procedure. A broader grasp of the whole structure is implicit in their work and some relation to a special starting material or key assembly reaction is often apparent.

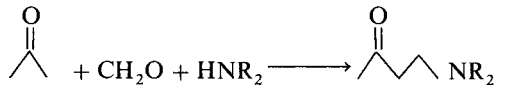
Tree searches

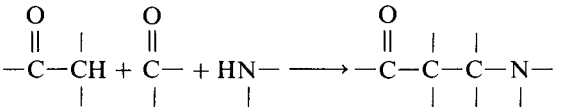
We can approach the synthesis design problem as a huge tree search, comparable to such searches in other fields. The size of the tree demands a reduction and four ways of doing this are common.

(a) *Systematize.* It is common in tree searches in other fields to define the units in the search space numerically since digital expression allows all possibilities to be simply mathematical combinations. This provides both rigorous definition and also the confidence that all combinations can be found mathematically. Also there is the advantage in digital description that it affords easy and rapid computer manipulation.

(b) *Simplify.* Here we define the material in the tree more broadly, in effect coalescing trivial distinctions so as to manipulate fewer items. Then after selection of a few optimal choices, roughly defined, these may then be refined back to normal detail. Simplification is analogous to map-making: the larger the area mapped, the fewer the distinctions made, the greater the level of abstraction in representation. Our common representation of molecules used in synthesis is a pictorial one, a graph of connected atoms, and at a level of abstraction that omits much information (interatomic distances and angles, congestion, charge distribution, etc.). Even this level of abstraction is too

(1) $CH_3COCH_3 + CH_2O + HN(CH_3)_2 \xrightarrow[25°]{H_2O} CH_3COCH_2CH_2N(CH_3)_2$

(2) 

(3) 

(4) **20 + 2 ⟶ 20·1**

detailed to map all possible involved molecules in a synthesis tree. A next level of abstraction, with more severe generalization, would reduce molecular description to a simple, linear digital one, capable of encompassing a much larger search space practically. Such a description is offered below and may be illustrated here with four levels of increasing abstraction for the Mannich reaction, each with more severe generalization than the last, each increasingly omitting more detail that is left implicit for the chemist to fill in from his general knowledge.

(c) *Subdivide.* If the tree is still too large to handle, it is reasonable to subdivide it into subtrees and so to operate on them one at a time sequentially. In order to do this the subtrees must be independent of each other, with no crossovers between them. Such a subtree is shown shaded in Fig. 1.

(d) *Select.* The crucial operation, of course, is to select a few optimal routes from so many in the tree. This requires criteria to direct the search, to reject some solutions and to assign priorities to the rest. Furthermore, the criteria must be very stringent ones if only a few routes are to be selected as optimal. The basic criterion is one of economy of time and materials. If yield prediction is to be abandoned, then the basic criterion becomes that of shortest routes, with fewest steps. This means the search will be speeded by actively directing it toward the nearest available starting materials, thus converging onto the shortest possible sequences.

Overview

Synthesis is a skeletal concept. The aim is to create a large target molecule from small starting material pieces. To put together these pieces is fundamentally to assemble the skeleton. In the combination of *pieces* × *order* × *reactions* the traditional focus has been on the *reactions*, but it is the *pieces* × *order*, i.e. the skeleton and its dissection, which is more important in taking a broader view of the problem. We can discern a dichotomy in molecular structure between the skeleton and the functionality on it. There is a parallel distinction in reactions, i.e. those that build skeleton—*constructions*—and those that alter functionality (*refunctionalizations*) with no change in skeleton.[11] Hence our first major simplification of the problem will be to consider only the skeleton. This simplification is enormous: the thousands of acyclic starting materials with six linked carbons or less are represented by only 13 skeletons. The main consequence of this focus on the skeleton is that only construction reactions are obligatory in any synthesis. It follows from this that the shortest, most economical synthetic route is a sequence of constructions only with no intervening refunctionalizations. Thus an ideal synthesis may be defined as one in which the starting materials come correctly functionalized to initiate their constructions and that the functional groups remaining after one construction are exactly those required to initiate the next. Also, at the end when the target skeleton has been fully assembled the functional groups remaining from the last construction are exactly those of the target.

Such an ideal synthetic route is a sequence of constructions only, with no refunctionalizations, and is very rare in practice;[12] the average synthesis contains twice as many refunctionalization steps as construction steps.[6] However, such a synthesis must be the shortest and constitutes a goal to aim for in seeking economy. It is also a very stringent criterion for selection since it lays such heavy demands on the overlapping functionality directing successive constructions.

This concept then dictates a procedure. We should dissect the target skeleton first in the best ways to sets of starting material skeletons and check a catalog for their availability. Only then, for the best sets found, will we generate the functionality necessary for self-consistent sequences,[12] working sequentially back from target functionality until the required functional groups on the starting materials are revealed. These are then again sought in a full starting material catalog for their availability. Hence there are two stages, the first a major simplification of the target to skeleton only and dissections of that skeleton into optimal pieces and orders. Second then comes the generation of the reactions to link them, a sequence only of constructions with the necessary functionality to drive them. In this way we must find the shortest routes from real starting materials to the target.

Skeletal dissection

The simplest gross description of any synthesis is the *bondset.* This is just the set of skeletal bonds (λ in number) which are constructed in the synthesis. The bondset may be further defined by the order in which

they are constructed (*ordered* bondset). The set of dotted bonds in **1** is the bondset for that synthesis,[5] and it is numbered in the order they were made. (Common practice is to make one in four of all skeletal bonds.[6]) The bondset directly shows the starting material skeletons and the carbon sites on each one at which construction occurs, usually 2–3 sites each. The four pieces used to make **1** are labeled with Roman numerals. The bondset defines a single independent subtree of the whole synthesis tree, containing all the reactions used to create the target from one set of starting material skeletons in all possible ways. The subtree for the bondset may therefore be fully explored without interference from other parts of the tree. In view of the many possible bondsets noted above, we shall need very stringent criteria for dissecting the target skeleton into a few best possible ones. We shall also need a basis to put these bondsets into priority order.

Synthesis plans

A basis for ranking synthetic routes can be made from the *synthesis plan*, a graph of the sequence of operations in the synthesis.[13] The synthesis plan is a small section from the whole synthesis tree, representing a single synthesis, as in the plan in Fig. 2

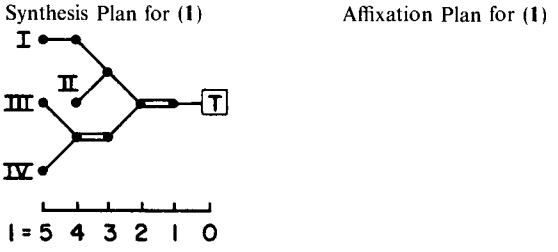


Fig. 2. Synthesis Plans.

for synthesis of estrone (**1**). The lines represent reactions, as vectors to the right. The points are compounds, those at left with one line out being starting materials, the one at far right with one line the target, and those between with 2–3 lines joining being intermediates. The horizontal lines are refunctionalizations and construction *cyclizations* (double lines). The other constructions, which join two pieces, are called *affixations* and represented by a pair of angled lines meeting at the affixation product. The starting materials are Roman numbered as in **1**. Figure 2 shows piece I being refunctionalized once, then affixed to piece II, while III and IV are separately joined and cyclized, then finally affixed to I–II, cyclized and refunctionalized to the target (T). The path-length (l) for each piece can be easily seen, none more than five. The five constructions are numbered in sequential order matching the order of the dotted bonds in structure **1**. Most syntheses are more extended, having more refunctionalization reactions. Removal of the horizontal refunctionalization lines coalesces the whole synthesis plan to a construction plan, showing construction reactions only, and a further coalescence of the cyclizations, just to circles around the intermediates which cyclize, affords the *affixation plan*, also shown in Fig. 2 for the estrone synthesis (**1**).

Overall yields can be calculated directly from the synthesis plan if all the individual step yields are known. These cannot be known in advance at the planning stage, however, but it is reasonable to assume that any mechanistically sound reaction can be optimized to a similar good yield. Hence in calculating overall yields of sequences we simply assume ~80% for each reaction. However, the more convergent a synthesis is the less meaningful is the overall yield. A more accurate measure of overall yield is the total weight of starting materials required. This is simply $W_{sm} = \Sigma_i M_i x^{l_i}$, where M_i is the molecular weight of starting material i and l_i is its path-length, the number of steps piece i passes through to the target. The term x is the inverse of the average yield (for 80% yield, x = 1.25). Values of W_{sm} can be used to compare the relative efficiency of different routes. However, at the planning stage the detailed molecular weight (M_i) will not be known and so we can substitute for it just the number of skeletal carbons (n_i) in the starting material piece. Hence we define $W = \Sigma_i n_i x^{l_i}$ as a measure of total starting material weight for purposes of comparing planned routes. It turns out that even if all reactions have the same yield the value of W is lower and hence better for some routes than others, even with the same number of steps. This is a function of the form of the synthesis plan. Therefore, we can rank various plans in a priority order, first by the number of steps and then for those with the same number of steps by total starting material weight (W).

Examination of various synthesis plans for different routes allows us to draw up some rules about the efficiency of plans, seeking minimal values of W.

(a) Obviously economy demands minimizing the number of refunctionalizations. It may be noted especially that protecting groups require two refunctionalizations; hence protecting groups may be seen as good chemistry but bad synthesis. Only if the protecting group is present in the starting material and comes off automatically in another reaction (no separate removal operation) does it represent a good plan. Most of the refunctionalizations in published syntheses are protecting group manipulations.

(b) Refunctionalizations are least damaging to efficiency and W if done early, preferably on a starting material prior to its incorporation in constructions.

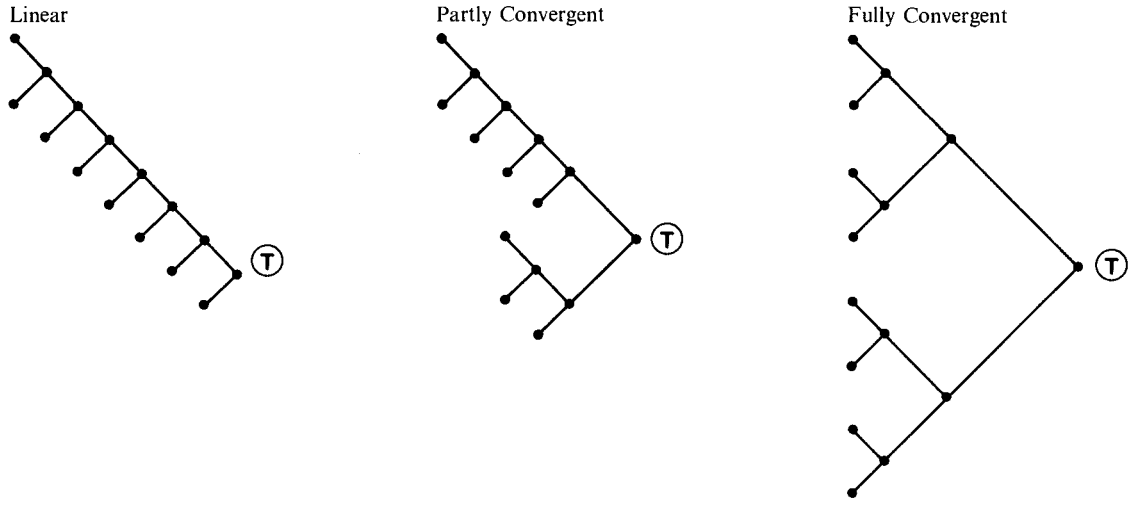
(c) Resolution to chiral intermediates is especially severe since it must be less than 50% yield. Hence a resolution is equivalent to about four refunctionalization steps since four steps at 80% is 41% overall. It is important, therefore, to resolve as early as possible on the smallest possible intermediate, if it must be done at all.

(d) The calculations of W dictate that cyclizations should occur as early in the plan as possible, before other pieces are added to the cyclizing unit.

(e) Large starting materials should be added as late in the sequence as possible to minimize W.

Convergency

The main variable affecting economy in synthesis plans is convergency, a concept first expressed by Velluz *et al.*[14] In a convergent plan the pieces are assembled separately and independently, then linked together afterwards near the end of the synthesis. This may be seen by comparing the affixation plans for three cases of affixing eight pieces (Fig. 3). There is a continuum of partially convergent sequences between a strictly linear one, at left, and a fully convergent one, at right (there are 23 possible affixation plans of



$\Sigma l_i = 35$	27	24
$\Sigma x^{l_j} = 24$	18	16

Fig. 3. Affixation plans for eight pieces.

varying convergency for eight pieces). The most convergent possible has the lowest Σl_i and also the lowest Σx^{l_i} as illustrated in Fig. 3. The extent of possible convergency is related to the bondset, as many bondsets do not allow a fully convergent sequence. Also convergency defines the order of bond making in a bondset.

The best bondsets are dictated by full convergency. These result from truncating the affixation plans for fully convergent total syntheses (i.e. from one-carbon pieces) to those with starting material pieces of 2–4 carbons already linked.[13] Thus the affixation plans for fully convergent bondsets can always be mapped onto the plans for fully convergent total syntheses.

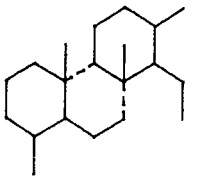
In practice the convergent bondsets are found by dividing the target skeleton first into two roughly equal parts, cutting the fewest rings. Then each part is cut again the same way until pieces of 2–4 carbons are found. The resulting ordered bondsets may then be ranked by calculating W, which will be essentially the same for all and minimal. Convergency not only defines both starting material pieces and order of assembly but is also a stringent selector of bondsets. The C_{21} steroid (**2**) cut into eight acyclic pieces affords two million bondsets but only 45 of these can have fully convergent plans from pieces of 2–4 carbons.[13] The convergent routes are only about 50% better in W than linear ones on the affixation plans but when refunctionalizations are added to string out the whole synthesis plan the preference rises sharply and can favor the convergent plans by a factor of 5–10 times.

Other dissection modes

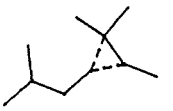
There are other heuristic bases for dissecting the target skeleton for economy, i.e. for fewest steps. All the following ideas can be sought during the search for convergency.

(a) Minimizing steps includes minimizing λ and this implies seeking the largest possible starting material pieces. Many of these can be discovered by comparing the two parts found at each cut with a catalog of starting material skeletons.

(b) Two equivalent halves or nearly equivalent halves generated by any cut can allow one half to be made from the other and so delete the steps necessary for its separate construction. The skeletons of the quassinoid family of natural products (**3**) and that of chrysanthemic acid (**4**) illustrate this idea.[15] If one part dissected by a cut is not identical to the other but contains its skeleton, one may also be made from the other more quickly than by separate construction. Again these identities can be discovered while making cuts toward convergency if the skeletons of cut parts are compared with each other.



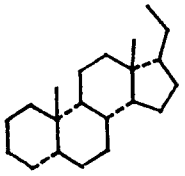
(**3**)



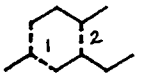
(**4**)

(c) Multiple constructions are more economical since they construct several bonds in one operation. For two constructions these can be double affixations, annelations (i.e. affixation + cyclization), or double cyclizations. Multiple cyclization is the basis for economy in the Johnson steroid syntheses,[17] one of which is shown (**5**) with the partial bondset of its multiple cyclization dotted. Such multiple cyclizations will occur last in the sequence. Annelations, including the Diels–Alder and Robinson methods, are all located when a skeleton is cut in two through a ring. The double affixation requires three pieces, two of them identical and joined to the third in a single reaction. The idea may be illustrated by the C_{10} skeleton (**6**) which has 720 possible ordered bondsets of $\lambda = 3$ but

only ten which meet this condition (with the identical pieces $\geq C_2$). One of these is shown in (**6**), with the bondset order numbered to show the double affixation as the first step.



(**5**)



(**6**)

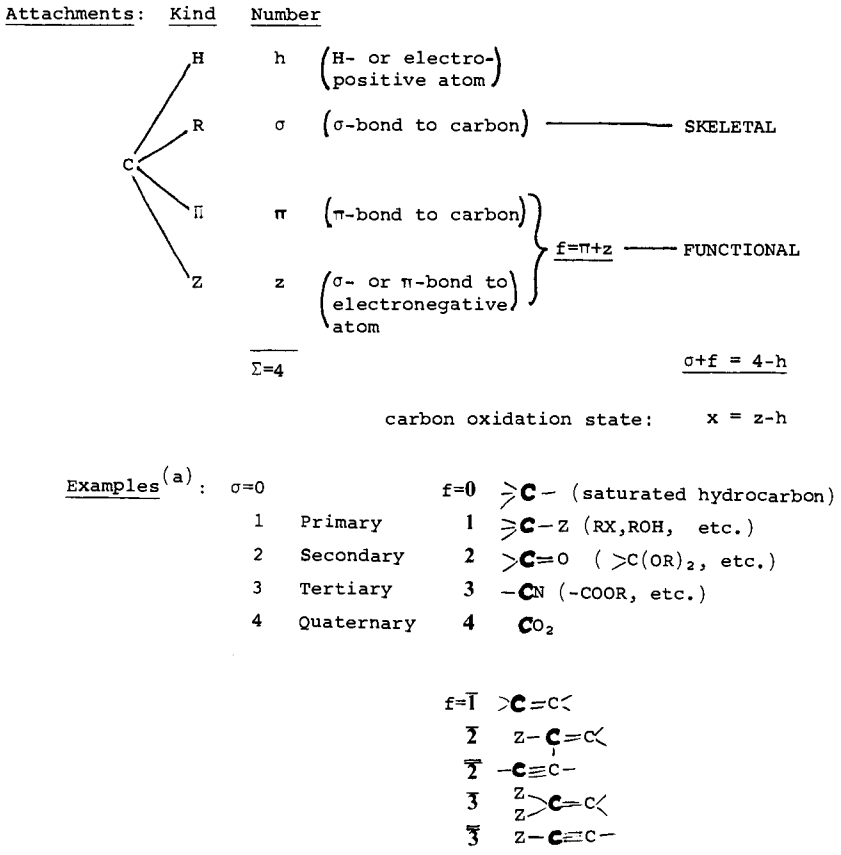
With these heuristics optimal bondsets may be found, and ranked by number of steps and weight of starting materials, via stepwise cuts of the target skeleton toward full convergency, while seeking the other conditions at each cut. The entire dissecting operation is capable of a simple and systematic treatment by the computer. It is in fact the very kind of operation that computers handle much better than people.

Reactions

Having examined the pieces and their order of assembly, we move on in the second stage to the actual reactions. Here we need to generate the functional groups necessary to direct selfconsistent sequences[12] for each bondset selected above. At this point we require a simple, rigorous definition of functionality for the computer to manipulate numerically. The point of digital description here is to coalesce trivial distinctions of functionality, to enable rapid computer handling, and especially to convert all possible variants into simple mathematical combinations so that all can be systematically treated and found. Furthermore, a really basic description will encompass all possible functionalities and reactions, including those not currently chemically feasible.

The numerical characterization of structures[18,19] starts from a definition of four kinds of attachment any carbon may have, and then assigns to each carbon the number of each kind of attachment it has, as summarized in Fig. 4. Thus any structural carbon is definable by two numbers, σ and f, denoting its skeletal level and its functional level,[20] and examples are shown. The value of x accurately gives the oxidation state of any carbon, and so $\Sigma\Delta x$ for any conversion shows the overall change in carbon oxidation state (see bottom of Fig. 5).

Any reaction is now simply defined by the *net structural change* from substrate to product, or equally in the reverse direction. A single reaction step is rigorously defined as a unit exchange of attachments,



(a) In the functionality examples the f-value refers to the boldface carbon and unspecified bonds are nonfunctional (R or H). The overbar specifies the π-value.[20]

Fig. 4. Numerical characterization of Structure.

	Oxidative	Reductive	Isohypsic	
Construction	RH	RZ	RΠ	RR
Fragmentation	ZR	HR	ΠR	
Addition	ZΠ	HΠ	RΠ	ΠΠ
Elimination	ΠH	ΠZ	ΠR	
Substitution	ZH	HZ	ZZ	HH

Relations in Reaction Changes:

$$\Delta f + \Delta\sigma + \Delta h = 0$$

$$\Sigma\Delta x = 2\,\Sigma\Delta f - \Sigma\Delta\pi + \Sigma\Delta\sigma$$

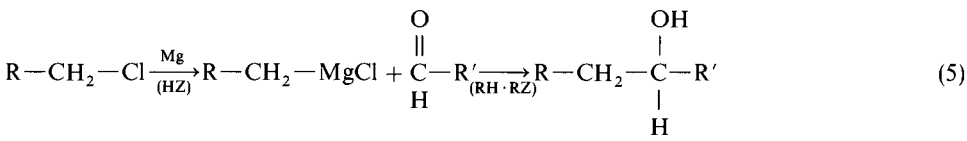
Fig. 5. Reaction labels. The label is the change at one carbon in one reaction step. Unit exchange of attachments = bond made; bond broken.

and so a reaction as commonly understood may sometimes (though seldom) consist of more than one successive reaction steps. This unit exchange is labeled by two letters, first the kind of attachment made, then the one lost; the 16 possible exchanges at one carbon are listed and described in Fig. 5. Thus reductions of ketone to alcohol or halide to hydrocarbon are equally HZ reaction steps, and $\Delta x = -2$ since all the changes in numerical values (f, σ, x, etc.) for a carbon are exactly implicit in the reaction label. A single reaction step will involve more than one carbon if R or Π exchanges occur since these demand the same change on an adjacent carbon. This system allows a simple but rigorous organization of all possible organic reactions just as the Beilstein system organizes all possible structures.[19]

Two examples of the notation are presented in eqns (5) and (6). The values of f, x and σ are shown for each specified carbon as are the letter symbols on the arrows for each reaction step.

Reaction generation

Once the ordered bondset is defined, the skeleton at each point in the sequence is specified. Hence for functionality generation we need only manipulate f-values for each carbon since the σ-values are determined. Any structure is represented by an ordered list of f-values for the list of numbered carbons

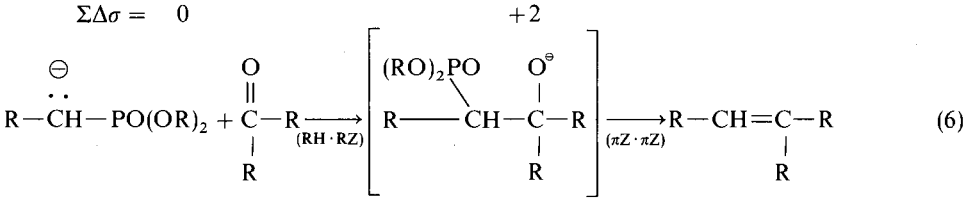


(5)

f = 1	0	2	0	1
x = −1	−3	+1	−2	0
σ = 1	1	1	2	2

$\Sigma\Delta x = -2$ 0

$\Sigma\Delta\sigma = 0$ +2



(6)

f = 1	2	1	1	$\bar{1}$	$\bar{1}$
x = −1	+2	0	+1	−1	0
σ = 1	2	2	3	2	3

$\Sigma\Delta x = 0$ −2

$\Sigma\Delta\sigma = +2$ 0

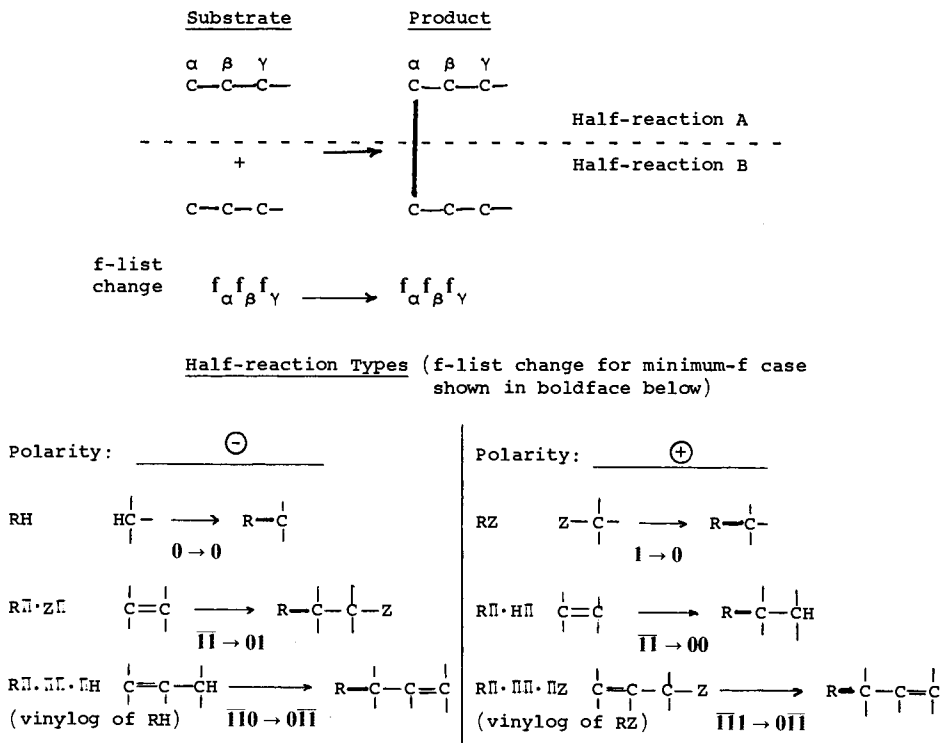


Fig. 6. Construction reactions.

in the skeleton. This *f-list* for any substrate changes in a defined way into the f-list of the product for any given reaction, and so in reverse the f-list for any substrate may be generated for a particular reaction from the f-list of the product.

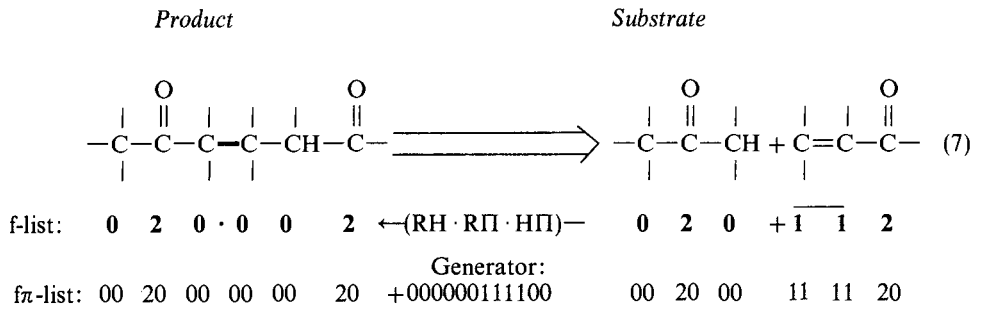
Construction reactions may be generalized with part structures as shown at the top of Fig. 6, labeling the carbons α, β, γ on each piece out from the carbon (α-carbon) forming the new bond. Each piece then displays a half-reaction which may be described by the change in the f-list ($\mathbf{f_\alpha f_\beta f_\gamma}$) from substrate to product (or vice-versa). The changes at the α-carbon must be RH, RZ or RΠ (RR is ignored as also involving a C–C bond fragmentation). With the first two the functionality at carbons β and γ does not change, but RΠ requires a loss of Π at the β-carbon also, i.e. HΠ, ZΠ or ΠΠ. Of these the first two require attachment changes at both α and β, the third a change at γ as well. Vinylogous reactions require three carbons since they exhibit a ΠΠ change at the β-carbon and so demand ΠH or ΠZ at the γ-carbon. Therefore, the six formal possibilities for construction half-reactions on up to three carbons are shown at the bottom of Fig. 6, and necessarily include all possible half-reaction steps.[21]

In these generalized structures in Fig. 6 the unspecified attachments may be made to H, R or Z. The case of minimum necessary functionality implies these attachments only to R or H and these are the f-lists shown. If one or more of these unspecified attachments is to Z it is a parallel example at higher functional level but the net change is the same,[22] as in the simple RZ half-reaction, which can be alkylation (**1 → 0**), the minimum-f case shown, or carbonyl addition (**2 → 1**), or acylation (**3 → 2**), or carbonylation (**4 → 3**).

Finally, the f-list change in a half-reaction is either oxidative ($\Delta x = +1$) or reductive ($\Delta x = -1$). The former are designated as ⊖-polarity since they are nucleophile half-reactions, and the reductive ones as ⊕-polarity since they are electrophiles. A full construction combines two half-reactions, and if one is ⊖-polarity and the other ⊕-polarity this is a common isohypsic ($-+$ or $+-$) construction, i.e. one with no overall oxidation state change ($\Sigma\Delta x = 0$). These are the only full constructions used here.[23]

The 18 possible full construction combinations (9 $+-$ and 9 $-+$ from Fig. 6) may be generated along any strand of six carbons surrounding a designated construction bond of the bondset. This is done by adding an f-list generator corresponding to the net change in f-list, to the product f-list of that strand in order to create the substrate f-list.[24] In the computer the Π-overbars must be separated from the f-values as separate digits so that an fπ-list is used. For each of the 18 full constructions this is a 12-digit number for the six carbons across the bond formed. The generator for each of the 18 reactions is simply derived by subtracting the minimal fπ-lists of product from substrate for each combination in Fig. 6, and stored in core for use. Their use is illustrated with the Michael addition in eqn (7).

By way of expansion of this procedure to approximate real chemistry more closely, we may briefly note some options. First many practical constructions are in reality a construction together with a refunctionalization. This is true in many reductions of halides to Grignard reagents and other high-energy carbanions, also in elimination following construction (Wittig, aldol, etc.). The examples of eqns (5) and (6) show two such common synthetic



operations, each of which is two reaction steps (construction and refunctionalization) in the definition here, but accepted for our self-consistent sequences as equivalent to single steps in the synthesis. These automatic refunctionalization steps may then be added to the construction generators to create new generators for these two-reaction-step operations. With the present added refunctionalizations we have expanded the list of full constructions from 9 to 32. Secondly, restrictions may be included on the use of the construction generators, i.e. restriction on inadequate activation, incorrect regiospecificity, or preference for another reaction over construction. These restrictions may be applied as tests of the values of f, π, σ, etc. at the carbons proximal to the bond constructed and may be used to invalidate reactions which, though formally correct from Fig. 6, cannot occur. This eliminates much chemically unreasonable output, such as RH constructions at unactivated sites, etc. Finally, numerical tests can be devised to delete reactions with incompatible functional groups elsewhere in the molecule.

Program

The overall logic resolves itself into a procedure for the computer.

(a) The target molecule is entered graphically as a skeleton with f-values at functionalized sites as shown at the top of Fig. 7. This is resolved by the computer into a simple carbon connectivity table or adjacency matrix of the carbon skeleton, i.e. a symmetrical n × n matrix of 1's and 0's, with the n carbons numbered. Then the f-values of the carbons are carried in the diagonal of this connectivity matrix.[29]

(b) The skeleton is cut in two all possible ways and the parts searched in a catalog of starting material skeletons. Then the procedure is repeated for those pieces not found in the catalog. The program seeks matches not only with the catalog but also with all other cut parts, to locate identical pieces for common synthesis or double affixations. It can also find all ring cuts in the whole target skeleton for multiple cyclization. When all cut parts are identified in the catalog, ordered bondsets are put in a priority order according to minimum number of steps and minimum W, and these may be displayed. The C_{10} molecule in Fig. 7 is skeletally dissected in the top row and one of the ten bondsets for double affixation (**6**) is illustrated.

(c) For each bondset the functionality generators are all applied to each cut bond successively in reverse order. The six carbons around the last bond constructed in the target are taken first and the generators added successively to the target f-list for those six carbons to generate the f-lists of last-reaction substrates; most will not give viable substrates[24] and restrictions applied before generating will eliminate more. The same procedure is then applied to the next bond back in the bondset order, using the new intermediate functionalities generated in the first pass, and so on until all bonds are cut and the resultant required functionality on the starting material skeletons is revealed. These are then searched in the full starting material catalog and the routes from available starting materials are recorded.[25]

(d) In principle the output can be displayed several ways. The starting material skeletons, oriented as they appear in the target, can be graphically displayed with f-values entered on functionalized carbons, as shown in Figs. 7 and 8. Further, each intermediate in a synthesis could be similarly laid out in sequence. For many syntheses this is too much output. More compactly, for each bondset we can list on one line the f-lists of the

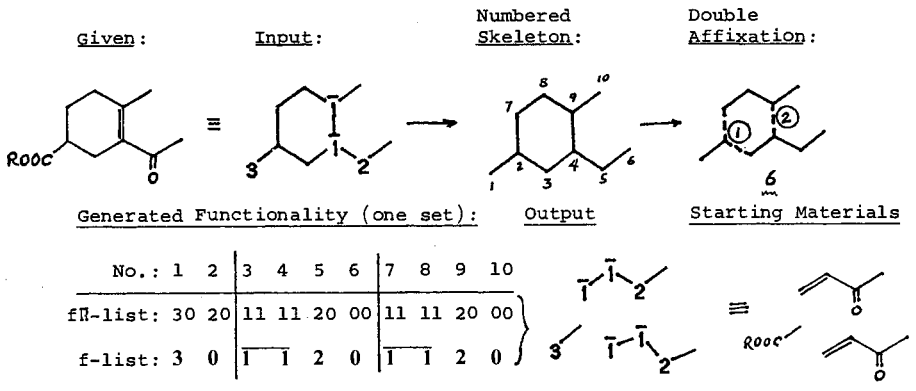


Fig. 7. Dissection of a C_{10} molecule.

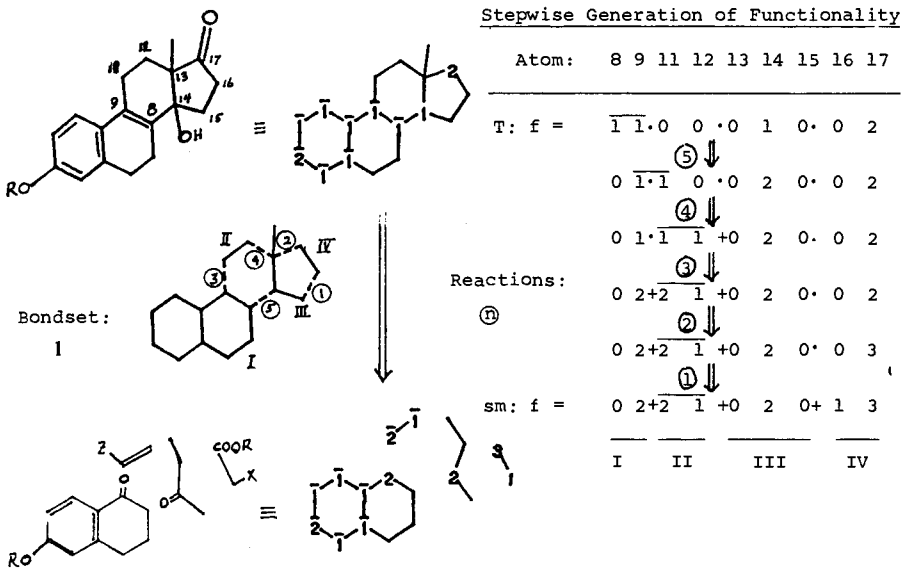


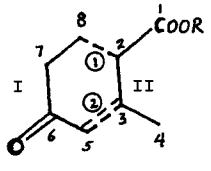
Fig. 8. Generation of estrone synthesis

starting materials followed by simple symbols denoting the nature of the two half-reactions in each successive construction. This allows the chemist to perceive immediately the net structural change and implied chemistry. Such output is shown directly as received from the computer in Fig. 9. Definition of the detailed construction labels has been omitted as trivial in this discussion,[26] but will generally be apparent in all three figures if the f-lists are all refined to normal structures and their successive conversions examined.

One double affixation route to **6** is recorded in the lower half of Fig. 7. In Fig. 8 is an illustration of the stepwise generation of one self-consistent sequence to the intermediate in the estrone (**1**) synthesis;[5] the last three reactions are those in the published synthesis, the first two are reasonable variants. The five constructions are circled in the ordered bondset and in the generated self-consistent sequence.

While the logic is basically simple, the programming details are extensive.[26] At the present time parts of the overall program have been written as separate modules for separate testing, and are not all yet complete nor tied together to make a single overall executive program. The graphics input has been created to accept a drawn structure on an ordinary CRT screen and then to normalize automatically a poorly drawn one, equalizing bond lengths and angles (Figs. 6 and 7). The present starting material catalog is about 8500 compounds.[27] The adjacency matrices of these compounds are ordered for quick search by row-column inversions such that the binary list obtained by stringing out the matrix entries is a maximum number. Then the skeleton catalog is simply a listing of these numbers in numerical order for easy searching. When a skeleton found by the program is to be looked up its matrix binary list is similarly maximized and that number sought in the catalog.[26]

Another program is being created to locate starting materials in the catalog which are one or two steps away from a structure generated by the main



STARTING MATERIALS 1	2	3	4	5	6	7	8	CONSTRUCTIONS 2- 8	3- 5
30	10	20	00	00	20	00	10	11.R1	*21.E1
30	10	20	00	00	20	11	11	11.R2	
30	00	20	00	00	20	00	10	*A1.11	
30	00	20	00	00	20	11	11	*A1.12	
30	10	20	00	00	20	00	10	R1.11	
30	10	20	00	00	20	11	11	R1.12	
31	11	20	00	00	20	00	10	B2.11	
31	11	20	00	00	20	11	11	B2.12	
32	22	20	00	00	20	00	10	C2.11	
32	22	20	00	00	20	11	11	C2.12	
30	11	21	00	00	20	00	10	B2.11	
30	11	21	00	00	20	11	11	B2.12	
30	22	22	00	00	20	00	10	C2.11	
30	22	22	00	00	20	11	11	C2.12	
30	10	10	00	20	20	00	10	11.R1	*F1.21
30	10	10	00	20	20	11	11	11.R2	
32	22	10	00	20	20	00	10	C2.11	
32	22	10	00	20	20	11	11	C2.12	
30	11	21	00	20	20	00	10	12:R1	
30	11	21	00	20	20	11	11	12.R2	
I				II					

Fig. 9. Self-consistent sequences generated.

procedure. This allows locating not only exact matches in the starting material catalog but also starting materials which might be converted to a desired compound by refunctionalization, rearrangement or fragmentation. This is possible because the numerical change in f-values between any two structures can be used to calculate the number of reaction steps separating them.[28]

The convergency dissection module is currently being built, but a separate program has been written to find all double affixation opportunities (see Fig. 7), i.e. all skeletal dissections into three pieces with two identical and each of these connected to the third from the same site.[26] Another program has been created to derive all multiple cyclizations with alternating bonds in the bondset as in **5**. The bondset in **5** is only one of 34 possible bondsets of $\lambda = 4$ with alternating bonds.

The functionality generator module is now operative and produced the functionality results in Figs. 7–9. At present its output is in the form shown in Fig. 9, generating starting materials as fπ-lists and listing the successive construction reactions used.[26] There are reproduced in Fig. 9 only 20 sequences of the 32 which were generated, but a close examination shows how closely related many of these sequences are.

CONCLUSION

The overall aim of the project is to find all the shortest routes of successive constructions to a given target from given starting materials. The basis is a major simplification first to skeleton only, in order to encompass the whole synthesis tree and find optimal bondsets. Then, second, for each bondset there is a simplification of functionality to numerical f-values to encompass the whole subtree for that bondset. Selection is based on fewest steps and highest yields (expressed as minimum W), selfconsistent sequences and available starting materials. The system is intended to be rigorous and clearly defined so that the chemist may know that it produces all possible syntheses within these constraints, including some with presently unfeasible chemistry which may challenge the chemist to invent new reactions. In this way we hope to produce a set of optimal syntheses of any target which may serve as a standard for comparison with synthetic plans invented by practicing chemists. R. B. Woodward saw himself as an artist in synthesis design and indeed his best syntheses pointed to elements incorporated in the logic here. The intent of this project is not to replace art in organic synthesis but to show where real art lies.

Acknowledgement—We are grateful to the National Science Foundation for support of this work through a grant, CHE–7712267.

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[6]Taken from a survey of syntheses. In *Art in Organic Synthesis* (Edited by N. Anand, J. S. Bindra and S. Ranganathan), Holden-Day, New York (1970). The word "pieces" here is roughly the same as "synthons"[2] but that term has been confused by several different usages and so is avoided here.

[7]For a target of n skeletal atoms and r rings the number of skeletal bonds is $b = n + r - 1$. If it is cut into k pieces, the number of bonds cut is $\lambda = k + \Delta r - 1$, or if all pieces are acyclic, $\lambda = k + r - 1$. If the average piece is three carbons, $k = n/3$ and $\lambda = n/3 + r - 1$. The combinations of pieces × orders equal $\lambda! \times \binom{b}{\lambda} = \frac{b!}{(b-\lambda)!}$.

[8a]E. J. Corey and W. T. Wipke, *Science* **166**, 78 (1969). For more recent descriptions of their programs see *Computer-Assisted Organic Synthesis* (Edited by W. T. Wipke and W. J. Howe). ACS Symposium Series 61 (1977); [b]In their first paper Corey and Wipke drove a search for Diels–Alder reactions just from a six-ring in the skeleton; the idea was further developed by: E. J. Corey, W. J. Howe and D. A. Pensak, *J. Am. Chem. Soc.* **96**, 7724 (1974).

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[10]M. Bersohn, A. Esack and J. Luchini, *Ibid.* **2**, 105 (1978); see also *Chem. Rev.* **76**, 269 (1976).

[11]The term skeleton here is used strictly to mean the carbon skeleton. It will be possible, however, at a later date to incorporate heteroatoms in rings into the definition of skeleton. Construction reactions are defined as those which create C–C σ-bonds.

[12]A sequence of constructions with no refunctionalizations is defined as a *self-consistent sequence* since the functional groups remaining after each construction are consistent with the functional requirements for the next.

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[15]A synthesis of the C_{20} quassinoids from two identical C_{10} molecules via the partial bondset of **3** is currently underway in our laboratories and the synthesis of chrysanthemic acid has been economically achieved[16] by the bondset in **4**.

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[19]J. B. Hendrickson, *J. Chem. Inf. Comput. Sci.* **3**, 129 (1979).

[20]In order to distinguish the separate functionalities of Π and Z, the value of f is used with one or two overbars to separately indicate $\pi = 1$ or 2, respectively.

[21]Half-reactions of larger span can be comparably derived, as with vinylogous addition ($R\Pi \cdot \Pi\Pi \cdot \Pi\Pi \cdot \Pi H$) by inserting four more Π symbols into the string. However, we limit ourselves to half-reactions involving up to only three carbons, as the longer spans are so uncommon.

[22]There may also be unchanging functionality on adjacent carbons, usually activators like the carbonyl at β for the RH reaction α- to ketones. Although they do not themselves change and are not part of the active f-list, these adjacent functional groups often have a strong effect on reaction course and must be recognized.

[23]Oxidative (− −) and reductive (+ +) full constructions can of course be used for affixation only if the two halves are identical and so have little synthetic value, although they can be used in cyclizations.

[24]The substrate(s) generated are then tested mathematically for structural reality: $0 \leq f \leq 4$ and $(4 - \sigma) \geq f \geq \pi$ and $\pi \geq 2$, with all values positive.

[25]The program described here first finds all skeletal dissections followed by all functionality generations. While this logically follows from the prior discussion, from the

standpoint of computing efficiency it is not yet clear whether a hybrid algorithm may not be faster. We are considering alternatives in which one skeletal cut is in some cases followed directly by functionality generation before further skeletal cuts. Some exploration of these hybrid alternatives will be required to clarify their relative efficiency.

[26]Two papers describing the details of the computer operations have been submitted for publication.

[27]The starting material catalog consists of those compounds in the Aldrich catalog which are also stored in connectivity table form in the data base of the National Institutes of Health/Environmental Protection Agency. We thank Dr. G. W. A. Milne of the NIH for providing these and Dr. A. E. Fein of Fein–Marquart Associates for providing the data base search.

[28]J. B. Hendrickson and E. Braun-Keller, *J. Comp. Chem.* in press.

[29]L. Spialter, *J. Am. Chem. Soc.* **85**, 2012 (1963); *J. Chem. Doc.* **4**, 261 (1964).

Tetrahedron, Vol. 37, Supplement No. 1, pp. 371 to 378, 1981
Printed in Great Britain

0040-4020/81/Suppl. 1-0371-08 $02.00/0
Pergamon Press Ltd.

TOTAL SYNTHESIS OF PSEUDOGUAIANOLIDES—II

(±)-AROMATICIN†

PETER T. LANSBURY* and D. G. HANGAUER, JR.
Department of Chemistry, State University of New York at Buffalo, Buffalo, NY 14214, U.S.A.

Abstract—(±)-Aromaticin (**5**), a helenanolide with five chiral centers, has been assembled from 2-methyl-1,3-cyclopentanedione in a linear synthesis characterized by high regio- and stereochemistry at all stages.

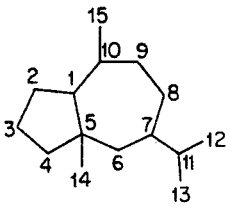
We have recently embarked upon an extended research program which focuses on the total synthesis of hydroazulenic sesquiterpene lactones characterized by the pseudoguaiane skeletal framework. Two major varieties of pseudoguaianolides[1] exist: *ambrosanolides*, which are characterized by a β-oriented C-10 methyl group and exemplified by damsin (I); and *helananolides*, which have the opposite C-10 configuration and are usually more heavily functionalized (and hence more biologically active), as shown in fastigilin C (II). In order to synthesize the structurally challenging helenanolides,[3] we feel it essential to have rapid access to an appropriate bicyclo[5.3.0]decane template, upon which stereo-controlled introduction of functionality could proceed in a rational sequence of operations. Otherwise, such a *linear* strategy would become intolerably long and impractical.

Scheme 1 summarizes the status of our investigations[3] when the present helenanolide synthesis began: solid arrows (→) designate previously completed steps[3] (→**4**) while double arrows (⇒) denote retrosynthetically the chosen route to be followed enroute to aromaticin (**5**).

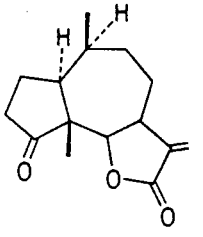
The requirement for an abundant and versatile pseudoguaiane template had been met in selectively-protected diketone **1** (Scheme 1), preparable in only three steps from 2-methyl-1,3-cyclopentanedione.[3] Subsequent functional group manipulations of **1** afforded **2**, whose configuration at carbons 1, 5 and 10 correspond to the natural product damsinic acid (**3**), thus providing the impetus for total synthesis of the latter.

After the necessary correlation of **2** with **3** had been successfully carried out,[3a] epimerization of the unactivated chiral center at C-10 was required. That task was accomplished by temporarily introducing into **2** a "bridging" vinyl group at C-8,9.[3b] This specific perturbation activated the C-10 hydrogen for reversible dienolate formation and eventually afforded the less-strained ketone **4**, without the Me–Me interactions present in **2**, (once the activating α-(phenylthio) vinyl group had been removed by hydrogenation). We were now poised to undertake the present total synthesis of (±)-aromaticin[2d] (**5**), our initial target among the helenanolides.

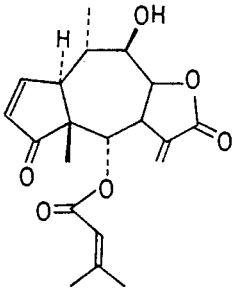
Aromaticin was first isolated by Romo *et al.*[4] from the Chilean plant *Helenium aromaticum* (Hook) Bailey. Structure **5** was correctly deduced from spectroscopic data and correlation with dihydroisotenulin, which permitted rigorous assignment of configuration at all chiral centers except C-7 (tentatively assigned on biogenetic grounds). Subsequently, aromaticin was found to be active *in vitro* against cells derived from human carcinoma of the nasopharnyx (KB) in cell culture (ED_{50} 0.34 mg/ml),[5] a consequence of the



Pseudoguaiane skeleton

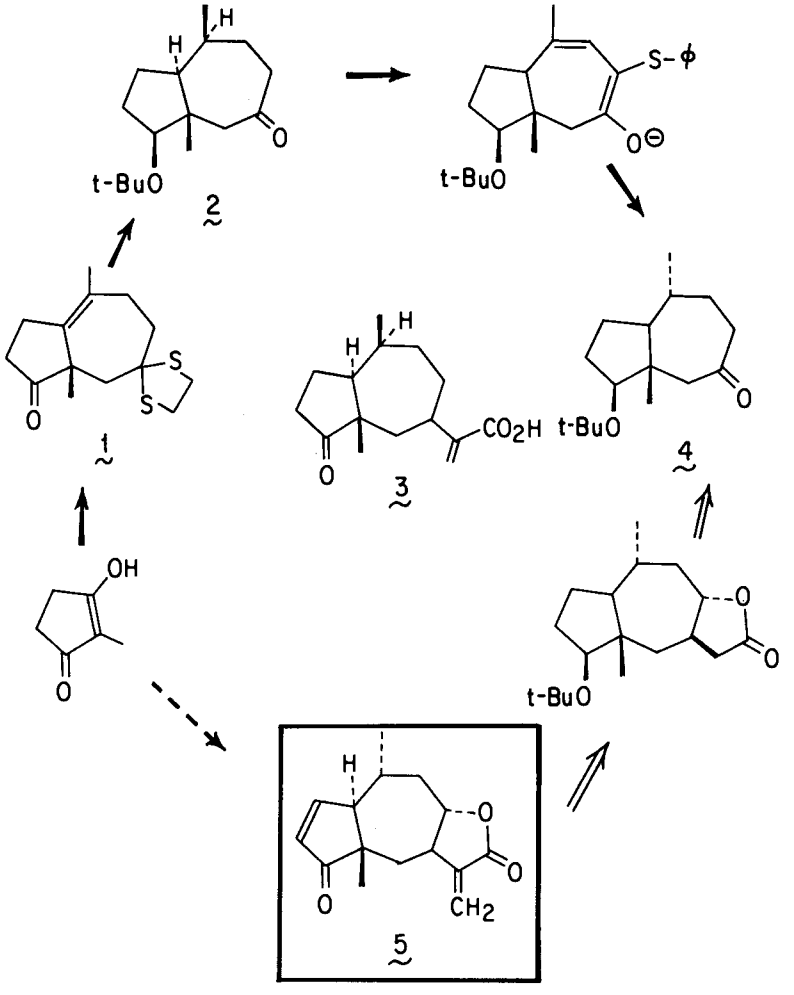


Damsin (I)



Fastiglin C (II)

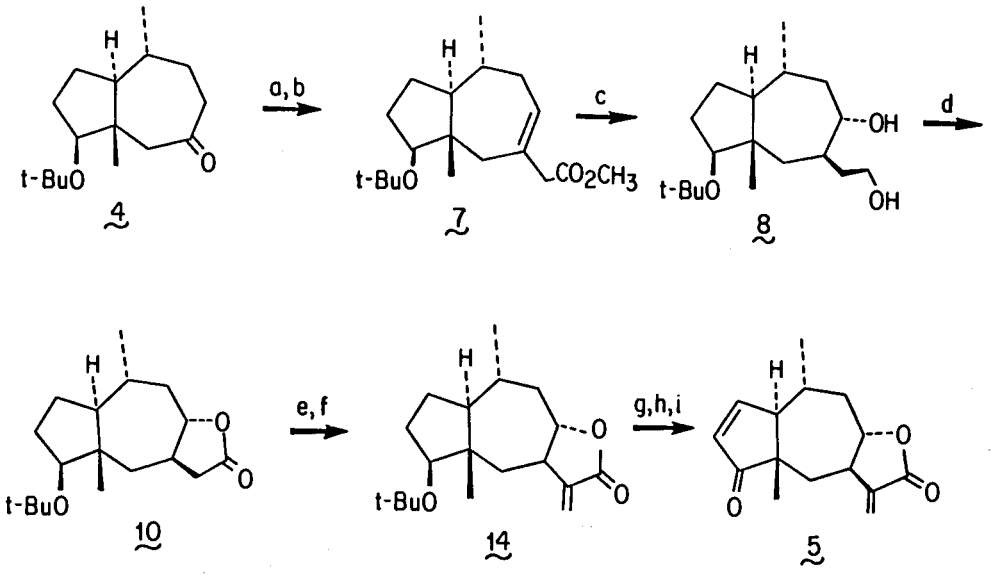
†Dedicated to the memory of Prof. R. B. Woodward, whose artistic creativity and painstaking utilization of strategic planning has inspired and guided our endeavors in the organosynthetic domain.



Scheme I.

presence of two electrophilic α,β-unsaturated carbonyl functions that irreversibly deactivate sulfhydryl enzymes by Michael addition of the latter. The sensitivity of aromaticin and other pseudoguaianolides to *multiple nucleophilic addition* (three sites in fastigilin C) *must be kept foremost in mind when developing a synthetic strategy*. Accordingly, our retrosynthetic analysis of the aromaticin problem (Scheme 1, ⇒) called for unveiling the A-ring cyclopentenone functionality in the final step. Such a structure tends to deconjugate and/or epimerize at C-1, under both acidic and basic conditions,[1a] as well as to undergo nucleophilic addition. The appearance of even the saturated cyclopentanone ring ($pK_a \sim 18$) was to be delayed until α-methylenation of the less acidic γ-lactone ($pK_a \sim 25$) had been completed.[6] The remaining links in the synthetic plan, using **4** as our starting point, were structurally obvious (see below) but their ultimate success hinged on solving the crucial stereochemical questions at C-7 and C-8 as they arose. Numerous rapidly-exchangable conformations are possible for 7-membered rings,[7] assuring that this task would by no means be a trivial one. The successful experiments that culminated in a regio- and stereocontrolled aromaticin synthesis[2d] are outlined in Scheme 2.

The reagent of choice for lactone annelation onto **4** was methyl α-(trimethylsilyl)acetate,[8] which afforded the acrylate **6**, m.p. 69–71°, in quantitative yield. Deconjugation[9] of **6** with LDA–HMPA was expected to occur by regiospecific proton abstraction at the less-hindered γ-site, i.e. C-8, followed by quenching into dilute acetic acid. The β,γ- unsaturated ester **7** isolable from **4** in 80% overall yield after chromatography, showed the anticipated vinyl proton *triplet* at δ 5.56, with J = 5.6 Hz. At this stage, *cis*-hydroboration followed by peroxide oxidation was planned for the introduction of the needed C-8 OH function, and also for establishing the remaining two chiral centers of aromaticin. This desirable outcome would result only if electrophilic attack by a borane occurred from the α-face of the molecule, which seemed to require a chair conformation (based on models). Several reports in the literature[7] supported our expectation that the chair conformation would be the more stable one. Should **7** react via the alternative twist-boat conformer, in which β-face is more accessible, both C-7 and C-8 would have the wrong configuration.

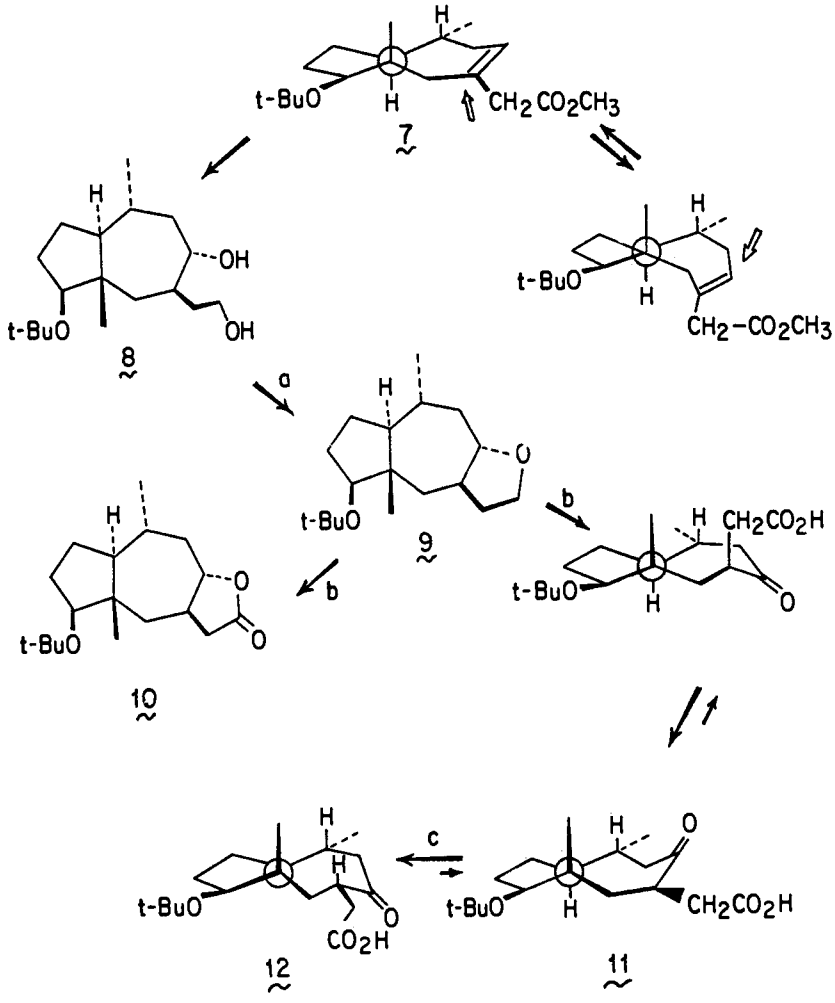


a) LDA, $(CH_3)_3SiCH_2CO_2CH_3$, THF, -78° → 25°; b) LDA-HMPA, THF, -78°, then CH_3CO_2H;
c) BH_3-THF, -78° → 25°, H_2O_2, OH^-; d) Pt, O_2, H_2O-acetone;
e) LDA-HMPA, $BrCH_2OCH_3$, -78° → -5°; f) 3 eq. KOt-Bu, 1 eq. H_2O, THF;
g) TFA, 0°/3 h, then NaOH/i-PrOH-H_2O, 25° 2h; h) PCC, CH_2Cl_2;
i) C_6H_5SeCl, EtAc, HCl, then $NaIO_4$, THF-H_2O, 25°/7 h.

Scheme II.

Before addressing this intriguing stereochemical question, we note that 9-borabicyclononane and related dialkylboranes, which exhibit high regioselectivities in many hydroborations of unsymmetrical alkenes[10] and have no "excess" hydrides for intramolecular ester reduction, were virtually useless for the task at hand. Essentially no hydroboration of the hindered π-bond occurred. After much experimentation, we reverted to borane (BH_3.THF) to achieve efficient, low temperature hydroboration ($-78° \rightarrow 0°$); this in turn, meant that unavoidable ester reduction[11] to the diol (after peroxide oxidation) would also take place and a "back oxidation" would subsequently be needed. Once the conversion of **7** to **8** was achieved in virtually quantitative yield, the first concern was to establish its steric course (Scheme 3). A portion of crude diol **8**, provisionally formulated as the desired stereoisomer, was cyclized via the primary monotosylate to the tetrahydrofuran derivative **9**, in order to facilitate analysis, as well as further transformations (see below). Gas chromatography of the cyclic ethers revealed a ~4:1 mixture of isomers but the identity of the major isomer was still unresolved. We had also planned to utilize ruthenium tetroxide oxidation[12] of **9** to generate the lactone ring in **10**. However, a fortuitous observation,† namely strong infrared carbonyl absorption at *ca* 1715 cm^{-1} in the IR spectrum of the crude product (in addition to the γ-lactone CO stretch at 1780 cm^{-1}) proved to be ultimately much more significant and led to unambiguous proof of the relative configuration of **8**! According to literature precedent,[12] ruthenium tetroxide oxidation of tetrahydrofurans such as **9** should occur mainly at the less-substituted carbon, producing the expected lactone **10**, but we obtained a ~1:1 mixture of **10** and keto-acid **11**. Since **10** is itself oxidized to **11** under our conditions (catalytic RuO_4 in acqueous acetone), it is not clear to what extent **9** is the source of **11**, but that question does not affect the role of this keto-acid in elucidating stereochemistry, as we shall now see. It is known that when RuO_4 oxidations generate ketonic groups adjacent to a chiral center, epimerization does *not* occur.[13] Ketoacid **11**, while not of apparent value as an intermediate for aromaticin, contains two sterically compressed alkyl groups (at C-5 and C-7) *if the* C-7 *acetic acid side chain is β-oriented* and should therefore, be prone to epimerization *via* reversible formation of the C-7 enolate. Apparently such "1,3-diaxial" strain is somewhat alleviated in **11** by a conformational adjustment (Scheme 3) in which the C-5 methyl group (δ 0.53) is placed in the C-8 carbonyl shielding cone. Nevertheless, intentional equilibration of **11** was readily achieved (DBN/CH_2Cl_2/25°) and produced an isomeric ketoacid (**12**), m.p. 85–87°, in *ca* 80% yield. In **12** the resultant α-oriented side chain allows a conformational change in the 7-membered ring (compared

†In his philosophical discussion of the paramount importance of careful and rigorous planning in multi-step synthesis, Woodward did not disregard the importance of serendipity, stating "The routine (IR) examination of virtually every reaction mixture, however crude, or lacking in tangible prospect of yielding a desired product, often provides a clue to important developments which could not otherwise be made". R. B. Woodward, *Perspectives in Organic Chemistry* (Edited by A. Todd), pp. 155–184. Interscience, New York (1956).



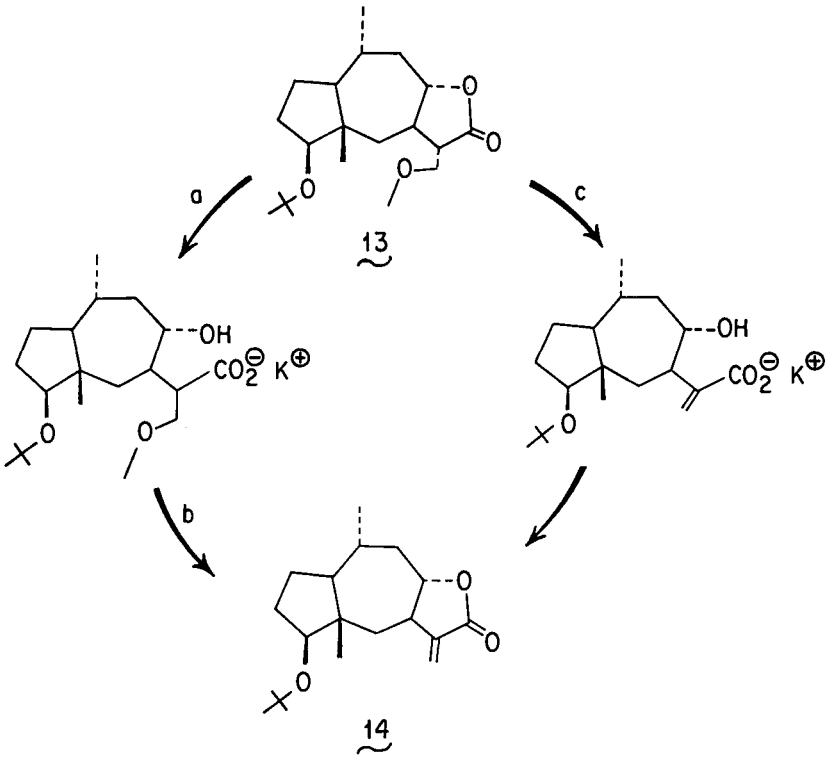
a) TosCl, C_5H_5N, 0° → 60°/56 h; b) RuO_4, acetone-H_2O, 25°/8 h;

Scheme III.

with **11**) which removes the C-5 Me group (now observed at δ 0.80) from the C-8 CO shielding cone (Scheme 3). These results fully establish the β-orientation of C-7 substituents in compounds **8**–**11**, and the C-8 oxygen substituent in **8**–**11**, originating from *cis*-hydroboration of **7**, must accordingly be alpha. For synthetic purposes, pure **10**, m.p. 88.5–89°, which possesses all the chirality in aromaticin, was prepared by catalytic oxidation[14] (Pt/O_2) of the major isomer of **8**. In this reaction **11** was not an observed by-product. It was found that improved yields can be achieved when the heterogeneous reaction is conducted in an ultrasonic bath.

We were now ready to introduce the α-methylene group into the γ-lactone ring of **10** and certainly aware of the plethora of methods available.[15] However, much of this methodology has been developed only with simple model compounds, notable exceptions being the work of Danishefsky,[16] Grieco[2a,15] and Johnson.[17,2b] It was soon apparent that enolate alkylations of **10** with alkyl halides containing potential leaving groups (e.g. $C_6H_5S-CH_2I$) proceeded in only modest yields as did the Parker–Johnson procedure;[17] moreover the known tendency of α-methylene-γ-lactones to undergo destruction by nucleophiles, if generated in their presence concerned us from the beginning. These two problems were solved concurrently by alkylating with methoxymethyl bromide, an excellent S_N2 substrate, which gave **13** (along with some dialkylation product), whose side chain resembles that encountered, via base-catalyzed methanol addition, in earlier structural investigations of sesquiterpene lactones.[1] Such a side chain is, in fact, a sturdily-protected, latent α-methylene group, capable of withstanding a variety of neutral or acidic transformations elsewhere in the molecule, but presumably susceptible to deblocking by appropriate basic reagents when desired. It was originally intended to remove the poor leaving group (–OMe) in **13** by employing excess "unsolvated" KOt–Bu/KOH in tetrahydrofuran,[18] under which conditions the more protected acrylate *anion* (from concomitant saponification) would be formed in one operation (Scheme 4). Quenching the above mixture *into* dilute acid led to isolation of **14** in satisfactory yield (*ca* 30% from **10**), as judged by IR and NMR.

Alternatively, the two steps could be experimentally separated. Methanolic potassium hydroxide effected



a) KOH/CH_3OH b) KOt-Bu/THF, then H_3O^+ c) Scheme II, steps e, f, then H_3O^+.

Scheme IV.

only saponification to give the potassium γ-hydroxycarboxylate (IR) from which solvent was removed *in vacuo*; subsequently, KOt–Bu in anhydrous THF transformed the above salt into the acrylate, followed by acid quench and work-up. This slightly longer procedure raised the yield for the **10** → **14** conversion to *ca* 60%. The crude non-crystalline α-methylene-γ-lactone **14** was directly subjected to dealkylation and oxidation at C-4, using Marshall's sequence,[19] and there was subsequently isolated pure, crystalline 2,3-dihydroaromaticin (**15**), m.p. 123–124°. At the time we were completing this research, Bohlmann[20] reported the isolation of (+)-**15**, m.p. 151°, as a constituent of *Telekia speciosa* and provided detailed 270 MHz NMR and MS Data for this natural product. Our synthetic (±)-**15** had identical spectral properties with those reported for the natural product and its successful conversion to (±)-aromaticin (see below) further confirmed its structure and relative configuration.

In order to complete the total synthesis of aromaticin from **15**, we needed only to insert a 2,3-double bond under essentially neutral conditions. Following Grieco's procedure, **15** was treated with phenylselenenyl chloride in ethyl acetate containing some hydrogen chloride (to initiate enolization). The crude selenylated **15** was oxidized with sodium metaperiodate in THF-water, heating briefly to complete selenoxide elimination. (±)-Aromaticin (**5**), prepared in ~75% crude yield from **14**, was recrystallized several times to give pure product, m.p. 178–181°, which was identical in all respects, except for optical rotation, with authentic (+)-**5** by tlc, ^1H NMR, IR and MS.

With the completion of this total synthesis, in twenty-two steps from 2-methyl-1,3-cyclopentandine, the remaining uncertainty in the configurational assignment of aromaticin, namely C-7 chirality, had been resolved. Moreover, concurrent investigations in our group have established the feasibility of inverting *trans*-fused lactones[2d] such as **10** at the carbinol position. This methodology has provided an entry to aromatin,[2d] a cogener and C-8 epimer of **5**, and should have useful ramifications in our continuing efforts to prepared *cis*-fused lactones such as fastigilin C.

EXPERIMENTAL[22]

General considerations. All of the reactions described herein were run under a blanket of dry argon. The phase "was concentrated" or "concentration gave" refers to removal of the solvent on a rotary evaporator under reduced pressure. M.ps were determined with a "Mel-Temp" capillary tube apparatus and are uncorrected. B.ps refer to the oven temps during Kügelrohr distillations and to the vapor temps during fractional distillations.

Glc was performed on either a F and M Scientific 720 dual-column gas chromatograph or a Hewlett–Packard 573A instrument. The packings used were; 10% Apiezon L, 10% and 5% Carbowax 20 M, and 3% OV-1 on Chromosorb W (mesh size 30/60). All of the columns were 0.125 in. inner diam and 6 ft long, except for the 3% OV-1 column which was 4 ft long. The carrier gas (He) flow rate was 60 cm^3/min. Peak areas were used to estimate the relative proportions of compounds in mixtures.

Adsorption chromatography was performed with silica gel GF-254 (type 60) for tlc, silica gel 60 PF254 (containing gypsum) for preparative layer chromatography, and silica gel 60 (particle size 0.063–0.200 mm) or 100–200 mesh Florisil for column chromatography. The tlc slides and preparative layer plates were generally visualized with UV light. Iodine staining, and charring (30% sulfuric acid, then heat on a hot plate), were also used on occasion.

All solvents were dried and distilled prior to use. IR spectra were run on a Perkin–Elmer 467 grating spectrophotometer and calibrated with the 1602 cm^{-1} band of polystyrene.

NMR spectra were run on a Jeol JNH-MH-100 spectrometer at 100 megahertz (MHz). With samples less than 5 mg, spectra were taken on a Varian Associates XL-100 (100 MHz) spectrometer using the Fourier Transform (FT) mode. Unless noted otherwise, the spectra were taken into $CDCl_3$ soln utilizing TMS as the internal standard. The spectra are reported in ppm as δ values. The coupling constants (J) are reported in hertz (Hz). Multiplicities of the peaks are abbreviated as s, singlet; d, doublet; t, triplet; q quartet; m, multiplet; and br, broad.

UV spectra were run on a Perkin–Elmer 202 UV-visible spectrometer and the absorptions are reported in nanometers (nm).

Mass spectra were run on a Perkin–Elmer RMU-6E instrument operating at an ionization potential of 70 eV. A reservoir inlet technique was used unless the direct probe technique is specified. Relative peak intensities were obtained using a Gerber variable scale.

Microanalysis were performed by: Atlantic Microlab, Inc., P.O. Box 80569, Atlanta, GA, 30366, U.S.A.

Methyl 2-[c-2,t-7-*dimethyl*-t-8-(t-*butyloxy*)-*r*-1*H*-*bicyclo*[5.3.0] *dec*-4,5-*en*-5-*yl*] *acetate* (**86**). In a flame dried 10 ml flask, fitted with a side arm and rubber septum, was placed 0.261 ml (1.86 mmol) dry diisopropylamine and 2.9 ml dry THF. The agitating soln was cooled to −78°, then 0.692 ml (1.49 mmol) of n-BuLi in pentane (2.15 M) was added dropwise. After 30 m, a soln of 0.2903 g (1.984 mmol) methyl trimethylsilylacetate in 0.93 ml dry THF was added dropwise. After 30 m, a soln of 0.2500 g (0.9921 mmol) of **4** in 3.50 ml dry THF was added dropwise. The reaction was kept at −78° for 1 hr, then allowed to warm to 25°. After 2 hr at 25°, the reaction was poured into 40 ml 10% HCl. The resulting mixture was extracted with ether (3 × 40 ml). The combined extracts were washed with water (2 × 100 ml), sat $NaHCO_3$aq (1 × 100 ml), brine (1 × 100 ml), dried over $MgSO_4$ and concentrated to give 0.3361 g (>100%) of a light yellow solid. A glc analysis (3% OV-1 column, 230° oven temp) indicated that **6** had been obtained as two isomers in a ratio of ~19:1. An analytical sample, m.p. 69–71°, was obtained by recrystallization from MeOH. Generally, the crude product was carried on further without purification. ^1H NMR: w 5.57 (1 H, broad s), 3.63 (3 H, s), 3.50–1.20 (complex), 1.14 (9 H, s), 0.85 (3 H, d, J = 6 Hz), 0.66 (3 H, s). IR (neat) ν_{max}: 1715, 1620 cm^{-1}. UV $\lambda_{max}^{95\%}$ C_2H_5OH (ε): 232 (13,800) nm. (Found: C, 74.02; H, 10.44. Calc. for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46%).

The crude **6** was deconjugated as described below.[9] In a flame dried 50 ml flask, fitted with a side arm and rubber septum, was placed 0.135 ml (0.965 mmol) dry diisopropyl amine and 1.3 ml dry THF. The agitating soln was cooled to −78°, then 0.365 ml (0.804 mmol) n-Buti in pentane (2.20 M) was added dropwise. After 30 m, the soln was warmed to −40° and 0.032 ml (1.85 mmol) dry hexamethylphosphoramide (HMPA) was added. The reaction was held at −40° for 20 min then −78° for 15 mins. A soln of **6** (0.1650 g, 0.5357 mmol) in 1.8 ml dry THF was added gradually (over a 10 min period) at −78°. After 1 hr at −78°, the reaction was inversely quenched into vigorously stirring 20% AcOH (20 ml) at 25°. The aqueous mixture was extracted with ether (3 × 20 ml) and the combined extracts were washed with water (1 × 60 ml), sat $CuSO_4$aq (2 × 50 ml), sat $NaHCO_3$aq (2 × 50 ml), brine (1 × 50 ml) and dried over $MgSO_4$. Concentration gave 0.1491 g (98%) of a light yellow oil. The crude product was suitable for subsequent steps without purification. If desired, the ester **7** can be purified by chromatography on silica gel (4% ethyl acetate/methylene chloride, R_f ~ 0.7) resulting in an 80% overall isolated yield from **4**. ^1H NMR: δ 5.56 (1 H, br t, J = 5.6 Hz), 3.56 (3 H, s), 3.28 (1 H, t, J = 6 Hz), 2.90 (2 H, s), 2.3–1.2 (complex), 1.10 (9 H, s), 0.77 (3 H, d, J = 6 Hz), 0.61 (3 H, s). IR (neat) ν_{max}: 1740, 1200 cm^{-1}. (Found: C, 74.02; H, 10.46. Calc. for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46%).

2-[c-2,t-7-*Dimethyl*-c-4-*hydroxy*-t-8-(*t-butyloxy*)-r-1H-*bicyclo*[5.3.0] *dec-t-5-yl*] *ethanol* (**8**). In a flame dried 10 ml flask was placed 0.1880 g (0.6104 mmol) of crude **7** and 1.0 ml dry THF. The stirring soln was cooled to −78°, then 1.83 ml (1.83 mmol) of $BH_3 \cdot THF$ complex (1 M) was added dropwise. The resulting mixture was held at −78° for 4 hr, then allowed to slowly warm to −50° over a 2 hr period. The reaction was further warmed gradually to 0° over a 2 hr period and finally held at 0° to +5° for 4 hr. A small amount of MeOH was added (until H_2 evolution ceased) to quench excess $BH_3 \cdot THF$. A 3 N NaOH was added (1.22 ml, 3.66 mmol) followed by 0.81 ml (7.29 mmol) of a 30% H_2O_2 soln. The resulting mixture was stirred at 45° for 2 hr then cooled. The reaction was diluted with 40 ml ether and washed with 5% HCl (1 × 40 ml), water (2 × 40 ml), brine (1 × 40 ml) and dried over $MgSO_4$. Concentration gave 0.1823 g (>100%) of a white solid, mp 74–96°. Recrystallization from hexane–CH_2Cl_2 gave 0.118 g (65%) pure **8**, m.p. 114–115°, as the first crop. Further crops raised the isolated yield to the 70–75% range overall from **4**. ^1H NMR δ 4.0–3.3 (~5 H, m), 3.23 (1 H, t, J = 8 Hz), 1.90–1.2 (complex), 1.12 (9 H, s), 0.90 (3 H, d, J = 5 Hz), 0.82 (3 H, s). IR (neat) ν_{max}: 3325, 1200 cm^{-1}. (Found: c, 72.59; H, 11.22. Calc. for $C_{18}H_{33}O_3$: C, 72.68; H, 11.18%).

2-[c-2,t-7-*Dimethyl*-c-4-*hydroxy*-t-8-(*t-butyloxy*)-r-1*H*-*bicyclo* [5.3.0]-*dec-t-5-yl*] *ethanol tetrahydrofuran* (**9**). In a flame-dried 10 ml flask was placed 0.0741 g (0.2487 mmol) of the crude **8** and 1.3 ml dry pyridine. The stirring soln was cooled to 0°, then a mixture of 0.0522 g (0.2735 mmol) *p*-toluene–sulfonyl chloride in 0.9 ml dry pyridine was added. The reaction was stirred at 0° for 8 hr, then allowed to warm to 25° over a 14 hr period. The temp was held at 25° for 25 hr, then raised to 60° for 5 hr. After cooling, the reaction was diluted with 40 ml ether and washed with sat $CuSO_4$aq (3 × 40 ml), water (1 × 40 ml), sat $NaHCO_3$aq (1 × 40 ml), brine (1 × 40 ml) and dried over $MgSO_4$. After concentration, 0.0569 g (82%) of a light yellow oil was obtained. A glc analysis of the crude **9** (10% Apieazon L column, 250° oven temp) indicated that this material consisted of an 8:2 ratio of two isomeric tetrahydrofurans. These isomers reflect an 8:2 preference for hydroboration of **7** from the α-face versus the β-face. ^1H NMR δ 3.9–3.1 (4 H, complex), 2.5–0.75 (complex), 1.13 (9 H, s), 0.87 (3 H, d, J = 7 Hz), 0.81 (3 H, s). IR (neat) ν_{max}: 1200, 1100, 1090, 1050 cm^{-1}, no OH band. (Found: C, 76.87; H, 11.49. Calc. for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50%).

Ruthenium tetroxide oxidation of 2-[c-2,t-7-*dimethyl*-c-4-*hydroxy*-t-8-(*t-butyloxy*)-r-1*H*-*bicyclo*[5.3.0]*dec-t-5-yl*] *ethanol tetrahydrofuran* (**9**). In a 25 ml flask was placed 0.0126 g (0.0516 mmol) RuO_2 (54.5%, Engelhard Ind. Inc.) and 3.2 ml acetone. A soln of 0.1739 g (0.8128 mmol) sodium periodate in 1.8 ml water was added to the stirring RuO_2 dispersion at 25°. After about 10 min the reaction had changed from a black dispersion to a bright yellow color, indicating RuO_4 was present. A soln of **9** in 3.6 ml acetone was added to the reaction. After 8 hr, 1.0 ml i-PrOH was added to the grey dispersion. After 15 min, the reaction was filtered through Celite which was subsequently rinsed with 100 ml hot acetone. The filtrate was concentrated then diluted with 40 ml pentane-CH_2Cl_2 (2:1). This soln was washed with water (3 × 40 ml), brine (1 × 40 ml) and dried over Na_2SO_4. Concentration gave 0.0501 g (84%) dark brown oil (contaminated with RuO_2?). The ^1H NMR and IR of the crude product indicated that it consisted largely of a 1:1 mixture of **10** and **11** with a small amount of keto-lactone also being present. The mixture was separated by preparative layer chromatography (silica gel, 4% EtOAc/95% CH_2Cl_2). The lactone **10** (R_f ~ 0.6, 10 mg) was isolated and

recrystallized from hexane (25° to −20°) to give an analytical sample with m.p. 88.5–89.0°. A small amount of keto-lactone ($R_f \sim 0.2$, 5 mg) was also isolated. The keto-acid **11** ($R_f \sim 0.1$, 20 mg) was recrystallized from hexane (25° to −20°) to give white cubes, m.p. 119–120°.

Lactone **10**. ^{1}H NMR δ 4.4–4.1 (1 H, m), 3.45 (1 H, t, J = 7 Hz), 2.7–0.7 (complex, 1.12 (9 H, s), 0.89 (3 H, d, J = 6 Hz), 0.84 (3 H, s). Ir (neat) ν_{max}: 1780, 1200 cm^{-1}. (Found: C, 73.38; H, 10.26. Calc. for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27%).

Keto-acid **11**. ^{1}H NMR δ 9.7–9.1 (1 H, br, s), 3.4–0.7 (complex), 1.12 (9 H, s), 0.94 (3 H, d, J = 6 Hz), 0.53 (3 H, s). IR (neat) ν_{max}: 2900 (broad), 1715, 1690, 1190 cm^{-1}.

Equilibration of 2-[c-2,t-7-*Dimethyl*-t-8-(*t-butyloxy*)-r-1*H-bicyclo*[5.3.0] *decan*-4-*one*-*t*-5-*yl*] *acetic acid* (**11**). In a 10 ml flask was placed 12.4 mg (0.0400 mmol) of crystalline **11** and 1.0 ml CH_2Cl_2. To this stirring soln was added 9.9 μl (0.0800 mmol) 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). After stirring for 1 week at 25°, the reaction was diluted with 40 ml pentane CH_2Cl_2 mixture (2/1). This soln was washed with 25% AcOH (2 × 40 ml), water (3 × 40 ml), dried over Na_2SO_4 and concentrated to give 0.0112 g (90%) of a clear colorless oil. The ^{1}H NMR of the crude product indicated that **11** had now epimerized so that **12** is the major constituent. The ratio of **11** to **12** was 1:4, respectively, as determined by comparing the intensities of the C-5 Me groups. A sample of purified epimerized **12** was obtained by fractional crystallization from hexane (25° to −20°), whereupon 4.5 mg white crystals with m.p. 85–87° were collected: ^{1}H NMR: δ 8.4–7.9 (1 H, br, s), 3.4–0.7 (complex), 1.12 (9 H, s), 0.93 (3 H, d, J = 6 Hz), 0.80 (3 H, s). IR (neat) ν_{max}: 3000 (broad), 1740–1700 (broad C=O stretch, 1200 cm^{-1}. Mass spectrum (direct probe): *m/e* 310 (1), 292 (10), 254 (18), 236 (33), 218 (25), 168 (30), 124 (85), 57 (100).

Platinum oxidation route to [c-2,t-7-*dimethyl*-c-4-*hydroxy*-t-8-(*t-butyloxy*)-r-1H-*bicyclo*[5.3.0] *dec*-*t*-5-*yl*] *acetic acid γ-lactone* (**10**). In a 250 ml 3-necked flask fitted with two fritted disc gas bubblers, a dry ice reflux condenser (with a bubbler attached to monitor the O_2 flow rate), and an ultrasonic bath (filled with water, in which the flask was immersed) was placed 0.497 g PtO_2 (Adams' catalyst, Aldrich Chemical Co.) and 13 ml water. The PtO_2 was reduced to Pt metal by bubbling H_2 through the dispersion while agitating with the ultrasonic bath for 1 hr. N_2 was then flushed through the reaction vessel to remove the H_2. Acetone (*reagent grade*, 30 ml) was added to the reaction, followed by a soln of 0.250 g (0.839 mmol) of **8** in 35 ml acetone. O_2 was then bubbled vigorously through the agitating dispersion which had been heated to 50°. After 10 hr, the reaction was filtered through Celite which was subsequently rinsed with copious amounts of hot acetone. The combined filtrates were concentrated, then diluted with 50 ml ether. The organic layer was washed with 50 ml water, then dried with $MgSO_4$ and concentrated to give 0.266 g of a viscous oil. A ^{1}H NMR, IR and tlc analysis of this oil indicated that it consisted of the desired **10** (IR; 1780 cm^{-1}, $R_f^* \sim 0.7$), a lactol (IR; 3375 cm^{-1}, $R_f^* \sim 0.3$) and starting material 8 (IR; 3375 cm^{-1}, $R_f^* \sim 0.1$). The oil was dissolved in hexane and cooled to −20° whereupon 0.093 g of starting **8** crystallized out cleanly, and the mother liquor (0.173 g) was free of **8**. The mother liquor was concentrated then placed in a 10 ml flask fitted with a magnetic stirrer. CH_2Cl_2 (3 ml) was added followed by 0.258 g (excess) pyridinium chlorochromate. After stirring for 2 hr, the reaction was filtered through Florisil. After rinsing the Florisil with copious amounts of CH_2Cl_2, the combined filtrates were concentrated to give 0.147 g (95% yield, 63% conversion) of pure **10**. The lactone was recrystallized from hexane (25° to −20°) to give crystals with m.p. 88.5–89.0°. The spectral properties were identical with those obtained from **10** in the ruthenium tetroxide oxidation of **9** described earlier.

The overall yield of **10** from **4** (five steps) is about 45–50% when purification is postponed until diol **8**.

2-[c-2,t-7-*Dimethyl*-c-4-*hydroxy*-t-8-(*t-butyloxy*)-r-1H-*bicyclo*[5.3.0]*dec*-*t*-5-*yl*]-3-*methoxypropionic acid γ-lactone* (**13**). In a flame dried 5 ml flask fitted with a side arm, and rubber septum, was placed 0.062 ml (0.442 mmol) dry diisopropylamine and 0.61 ml dry THF. The starting soln was cooled to −78°, then 0.210 ml (0.408 mmol) on n-BuLi (1.94 M) was added dropwise. After stirring for 40 min, a soln of 0.1000 g (0.340 mmol) of **7** in 0.74 ml of dry THF was added dropwise. After 2.2 hr, 0.128 ml dry HMPA was added and the reaction was allowed to warm to −40° gradually over 50 min, then cooled back to −78°. After 30 min, a soln of bromomethyl methyl ether (0.037 ml, 0.4421 mmol) in 0.62 ml dry THF was added. The temp was slowly allowed to rise to −20° during 2.5 hr, then to −5° in 2 hr more. The reaction was then poured into 40 ml 10% HCl and 40 ml ether. After mixing and separation, the organic layer was washed with water (1 × 4 ml), $CuSO_4$aq (2 × 40 ml), water (1 × 40 ml), brine (1 × 40 ml) and dried over $MgSO_4$. Concentration gave 0.1123 g (98%) light yellow oil. A spectral analysis of the crude indicated that it was essentially pure alkylated lactone (one epimer?) **13**. The material was suitable for subsequent reactions without purification. ^{1}H NMR δ 4.5–4.0 (1 H, m), 3.9–3.4 (3 H, m), 3.32 (3 H, s), 2.8–0.7 (complex), 1.16 (9 H, s), 0.93 (3 H, d, J = 6 Hz), 0.84 (3 H, s). IR (neat) ν_{max}: 1780, 1200 cm^{-1}.

(±)-2,3-*Dihydroaromaticin* (**15**). In a flame dried 10 ml flask was placed 0.0872 g (0.713 mmol) of BuOK, 1.50 ml dry THF and 5.4 μl (0.300 mmol) water. To this agitating mixture was added a soln of 0.0998 g of **13** (contaminated with about 15% *non*-alkylated lactone **10**) in 0.97 ml dry THF. After 19 hr at 25°, the reaction was poured into 40 ml 10% HCl and 40 ml ether. After mixing, the layers were separated and the organic layer was washed with 10% HCl (3 × 40 ml), brine (1 × 40 ml), and dried over $MgSO_4$. Concentration gave 0.0854 g (93%) light yellow solid. This material was estimated to contain about 30% of **6** based upon the ^{1}H NMR integration of the vinyl protons [δ 6.00 (1 H, d, J = 3 Hz), 5.26 (1 H, d, J = 3 Hz)] versus the C-8 lactone proton [δ 4.3–3.9 (1 H, m)]. The reaction was judged complete by the total disappearance of the OMe adsorption at δ 3.32. The IR (neat) shows an absorption at 1760 cm^{-1} for the α-methylene lactone. This material was carried on to **19** as described below without purification.

In a flame dried 10 ml flask was placed 0.0718 g of the crude **14** above and 1.3 ml dry trifluoroacetic acid (distilled from P_2O_5). The resulting soln was immediately cooled to 0°. After 3 hr, the trifluoroacetic acid was removed at 0° under vacuum. The residue was dissolved in 5.2 ml i-PrOH and then 1.3 ml 15% NaOHaq was added. The resulting mixture was warmed to 25°. After 2 hr, the i-PrOH was removed on a rotary evaporator and the residue was diluted with 40 ml ether. This was followed by washing with 10% HCl (1 × 40 ml), water (2 × 40 ml), brine (1 × 40 ml) and drying over $MgSO_4$. Concentration gave 0.0411 g (70%) of a glassy solid. The IR (neat) showed a large OH absorption (3450 cm^{-1}) and the absence of a t-butyloxy absorption (1200 cm^{-1}). The ^{1}H NMR indicated that the vinyl protons were still present [δ 6.13 (1 H, d, J = 3 Hz), 5.46 (1 H, d, J = 3 Hz)] and that the t-butyloxy peak [δ 1.14 (9 H, s)] had disappeared. A strong, broad, CO absorption in the IR (1780–1760 cm^{-1}) indicated that the lactone(s) was still present. The crude product containing hydroxylactone was carried on as described below without purification.

In a 5 ml flask was placed 0.0371 g of the crude hydroxylactone above and 1.2 ml CH_2Cl_2. To this stirring soln was added 0.0633 g (excess) of pyridinium chlorochromate. After 3 hr at 25°, the reaction was filtered through a 17 × 23 mm Florisil plug, which was subsequently rinsed with 250 ml of CH_2Cl_2. Concentration of the filtrate gave 0.0079 g of crystalline **15**. The Florisil was then rinsed with 75 ml EtOAC and this filtrate was concentrated to give 0.0237 g of a yellow glassy solid. A spectral analysis of this solid revealed the presence of a small amount of **15**, but the majority of the material was unidentifiable. Chromatography of this fraction (silica gel, 8% EtOAc/CH_2Cl_2) on a preparative layer plate yielded 0.0022 g more **15** [$R_f \sim 0.4$]. The overall yield of (±) **15** from **10** was 17%. Recrystallization from hexane/CH_2Cl_2

at 25° gave white needles with *m.p.* 123–124°. ^{1}H NMR: Found, δ 2.50 ($H_{6\alpha}$, dd, J = 15, 6), 1.52 ($H_{6\beta}$, dd, J = 15, 11 Hz), 4.28 ($H_{8\beta}$, ddd, J = 10, 9, 3), 6.19 (H_{12}, d, J = 3.5), 5.51 (H_{13}, d, J = 3), 1.10 (C-10 methyl, d, J = 6), 1.03 (C-5 methyl, s). Reported data, which agrees with that above, is in Ref. 20. Mass spectrum (direct probe): *m/e* 248 (100), 233 (16), 204 (45). Reported data, which agreed with that above, is in ref. 20.

(±)-*Aromaticin* (**5**). In a flame dried 5 ml flask was placed 5.4 mg (0.0218 mmol) of (±)-**15** and 0.18 ml dry EtOAc, "spiked" with HCl gas. To this stirring soln was added 4.6 mg phenylselenenyl chloride. After 8 hr at 25°, the reaction was poured into 20 ml of an ether–pentane mixture (1/1) and 20 ml $NaHCO_3$aq. The organic layer was washed with more $NaHCO_3$aq (1 × 20 ml), water (1 × 20 ml), brine (1 × 20 ml) and dried over $MgSO_4$. Concentration gave 8.9 mg (91 %) of a yellow oil. This material was carried on to the next step crude. ^{1}H NMR (crude): δ 7.8–7.5 (5 H, complex), 6.18 (1 H, d, J = 3 Hz), 5.47 (1 H, d, J = 3 Hz), 4.4–3.8 (~2 H, m), 3.0–1.1 (complex), 0.98 (C-5 methyl group and the downfield peak of the C-10 methyl doublet), 0.94 (upfield peak of the C-10 methyl doublet).

In a 5 ml flask was placed the crude selenylated ketone above and 0.40 ml of a tetrahydrofuran–water mixture (6/1). To this stirring soln was added 5.0 mg (0.0597 mmol) $NaHCO_3$ then 12.8 mg (0.0597 mmol) sodium periodate. After 15 min a large amount of ppt appeared. After 2 hr, the reaction was poured into 20 ml of an ether–pentane mixture (1/1) and washed with $NaHCO_3$aq (2 × 20 ml), water (1 × 20 ml), brine (1 × 20 ml) and dried over $MgSO_4$. Concentration gave 6.1 mg (>100 %) of a yellow oil. An IR analysis of the crude product indicated that it consisted of about a 1:1 mixture of starting material (1730 cm^{-1}) and (±)-**5** (1710 cm^{-1}). Consequently, the crude product was resubjected to the oxidation conditions above except that the $NaHCO_3$ was reduced to 3.3 mg (0.0398 mmol) and the reaction was run for 5 hr. Workup, as above, gave 4.0 mg (75 % overall crude) of a yellow oil. The IR now indicated that the reaction had proceeded essentially to completion.

The crude product was chromatographed (silica gel 4 % EtOAc/–CH_2Cl_2) on two tlc slides using natural (±)-aromaticin as a control. The spot with an identical R_f (0.21) to the natural material was isolated as 0.5 mg of a light yellow oil. The synthetic (±)-**5** was crystallized from acetone to give needles with m.p. 178–181° (taken on a Fisher-Johns apparatus). A ^{1}H NMR comparison (100 MHz, FT) of the synthetic and natural aromaticin showed the samples to be identical. A FT-IR of the natural aromaticin, as a KBr pellet, gave a shift in the cyclopentenone CO band from the reported[3] 1710 cm^{-1} ($CHCl_3$ soln) to 1701 cm^{-1}. The α-methylene lactone CO absorbed at 1762 cm^{-1} as a KBr pellet. The remaining spectral data were in good agreement with that reported and found for our sample of natural (+)-aromaticin. ^{1}H NMR (Found, 100 MHz, FT); δ 7.64 (1 H, dd, J = 6.0, 1.8 Hz), 6.14 (1 H, dd, J = 6.1, 3.0 Hz), 6.20 (1 H, d, J = 3.4 Hz), 5.53 (1 H, d, J = 3.2 Hz), 4.51 (1 H, ddd, J = 11.3, 9.4, 3.2 Hz), 1.26 (3 H, d, J = 6.4 Hz), 1.10 (3 H, s), 3.0–1.3 (complex). ^{1}H NMR (reported,[4] 60 MHZ): δ 7.70 (1 H), 6.20 (1 H), 6.15 (1 H), 5.55 (1 H), 4.53 (1 H), 1.25 (3 H), 1.19 (3 H). IR ($CHCl_3$ soln, FT) ν_{max}: 1763, 1710 (Reported[4] 1760, 1710 cm^{-1}). Mass spectrum (direct probe): for (±)-**5**, *m/e* 246 (100), 231 (23), 218 (19), 204 (21), 175 (23), 159 (26), 136 (40). For (+)-**5**, *m/e* 246 (100), 231 (24), 218 (19), 204 (19), 175 (20), 159 (24), 136 (35).

Acknowledgements—We are grateful to the National Science Foundation (Grant CHE-7720815) for financial support and to the Allied Chemical Corporation for a 1979–80 fellowship to D. G. H., Jr. Kevan Thompson and Thomas Nickson rendered valuable assistance in model studies and preparation of intermediates, respectively. We are most grateful to Professor P. Joseph-Nathan for providing an authentic sample of (+)-aromaticin and also thank Dr. George Lee for aid in securing mass spectra and Dr. Stanley Sojka for FT infrared and NMR spectra.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 379 to 385, 1981
Printed in Great Britain

0040-4020/81/Suppl. 1-0379-07 $02.00/0
Pergamon Press Ltd.

THE STERPURIC ACIDS

A NEW TYPE OF SESQUITERPENOID†

WILLIAM A. AYER* and M. HOSSEIN SAEEDI-GHOMI
Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

and

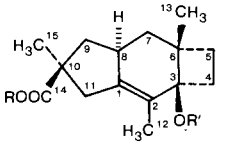
DONNA VAN ENGEN, BRUCE TAGLE and JON CLARDY*
Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, NY 14853, U.S.A.

Abstract—The fungus *Stereum purpureum*, the cause of the so-called silver leaf disease, produces a new type of sesquiterpenoid when grown in liquid culture. The structures and reactions of sterpuric acid (**1**), methyl hydroxysterpurate (**17**), and methyl hydroxysterpurate ethylidene acetal (**22**) are reported. An X-ray crystallographic structure determination of sterpuric acid (**1**) is presented.

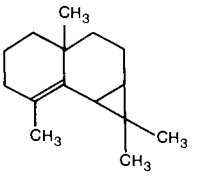
The fungus *Stereum purpureum* (Pers. ex Fr.) Fr. (≡ *Chondrostereum purpureum* (Pers. ex Fr.) Pouz.) causes the so-called silver leaf disease common on plum, apple, and other fruit trees.[1,2] In Alberta it is also found on mountain ash, cotoneaster, and aspen.[3] The fungus enters through wounds, grows first in the heartwood, then kills the sapwood and bark. Infected trees develop foliage with a dull leaden or metallic lustre, thus the name silver leaf disease.[1] In this paper we report the structures of three sesquiterpenoid metabolites produced when *S. purpureum* is grown in liquid culture. These metabolites represent a new structural type among the sesquiterpenoids.

S. purpureum was grown in malt extract-dextrose-peptone liquid culture. Extraction of the culture broth with ethyl acetate provided crude metabolites which caused "silvering" in mountain ash seedlings.[3] The crude metabolites were separated into neutral and acidic fractions and the latter fraction was further separated by chromatography over silica gel to give a nicely crystalline acid $C_{15}H_{22}O_3$, m.p. 203–207°, for which we propose the name *sterpuric acid*. Esterification (diazomethane) of the remaining fractions followed by further chromatographic purification led to the isolation of two other metabolites, *hydroxysterpuric acid* ($C_{15}H_{22}O_4$) and *hydroxysterpuric acid ethylidene acetal* ($C_{17}H_{24}O_4$), in the form of their methyl esters.

In order to facilitate the discussion, the chemistry of sterpuric acid, which led to the derivation of the



1 R = R′ = H
2 R = CH_3, R′ = H
3 R = CH_3, R′ = $COCH_3$



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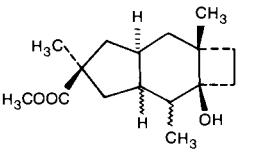

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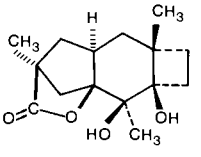

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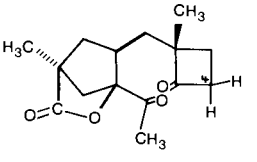

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†Dedicated to the memory of Professor R. B. Woodward.
Presented in part at the 63rd Canadian Chemical Conference, Ottawa, June 1980. Abstracts, p. 120.

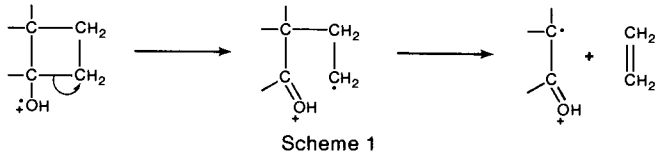
complete structure, is presented in terms of the final structure **1**.‡ This structure has been confirmed by an X-ray crystallographic study which is presented subsequently. Sterpuric acid readily forms a methyl ester (**2**) when treated with diazomethane. The tertiary (and hindered) nature of the OH group is reflected by the fact that formation of methyl O-acetylsterpurate (**3**) requires treatment of **2** with acetic anhydride pyridine at room temperature for 16 days (3 days in the presence of 4-N,N-dimethylaminopyridine). The remaining functionality of sterpuric acid (2 quaternary Me's, vinylic Me, fully substituted double bond), and thus its tricyclic nature, was apparent from examination of the ^{1}H and ^{13}C NMR spectra of **1**, **2** and **3**. The mass spectra of sterpuric acid and its derivatives all display a striking peak at $M^+ - 28$, shown by high resolution measurements to be due to the loss of ethylene, at first suggestive of a retro-Diels–Alder fragmentation in a β-maaliene-type (**4**) tricyclic sesquiterpene.[4] However, methyl dihydrosterpurate (**5**), prepared by catalytic hydrogenation of **2**, also shows a strong $M^+ - 28$ peak. At this point it was apparent that sterpuric acid possesses a carbon skeleton different from that of any of the known sesquiterpenes.

The carbon skeleton was first deduced in the following way. The 400 MHz ^{1}H NMR spectrum of sterpuric acid, analyzed in detail in the Experimental, shows the presence of an isolated allylic methylene group (C-11), an allylic methine proton (C-8) coupled to two otherwise isolated methylene groups (C-7 and C-9), along with an isolated 4-spin system corresponding to two methylene groups (C-4 and C-5). Assuming that the loss of ethylene in the mass spectra could be explained by cleavage of a cyclobutanol as shown in Scheme 1, and that sterpuric acid is derived without rearrangement from farnesyl pyrophosphate (**6** in Scheme 2) we arrived at the carbon skeleton **7** (Scheme 2) for sterpuric acid. At this stage it was not possible to say which of the starred Me groups is the carboxyl group of sterpuric acid.

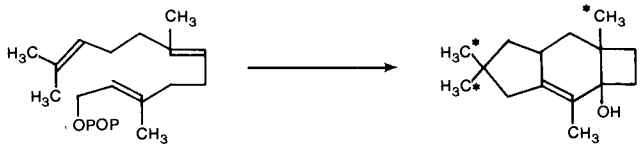
Treatment of methyl sterpurate (**2**) with osmium tetroxide in warm pyridine followed by sodium bisulfite led directly to the γ-lactone diol **8** (IR 3600, 1775 cm^{-1}), presumably formed by spontaneous lactonization of the intermediate triol. The Me group at C-2 appears as a singlet at δ 1.48 in **8**. Periodate cleavage of diol **8** gave the cyclobutanone **9**, absorbing at 1790 cm^{-1} (cyclobutanone), 1775 (γ-lactone), and 1715 (methyl ketone) in the IR. The Me group at C-2, now part of a methyl ketone, appears at δ 2.35 in the ^{1}H NMR spectrum. The methylene group at C-4 appears as a triplet at δ 3.00, characteristic of a cyclobutanone α-methylene.[5] The formation of **9** provided the first direct evidence for the presence of a 4-membered ring in sterpuric acid. These experiments also serve to locate the carboxyl group at C-10 rather than at C-6.

Ozonolysis of methyl sterpurate (**2**) proceeded with the uptake of two atoms of O. The product, however, displays only one CO absorption (1745 cm^{-1}) in the IR. The ^{1}H NMR spectrum reveals that the olefinic Me group is no longer present as such, but there is no signal for a methyl ketone. Instead, a Me signal appears at δ 1.39. The ozonolysis product is believed to possess structure **10**, arising from the expected diketone **11** by double hemiacetal formation as indicated by the arrows in **11**. In order to prevent this side reaction the ozonolysis was carried out on methyl O-acetylsterpurate (**3**) and the diketone **11** (as its O-acetyl derivative) was obtained. The cleavage product shows CO absorption at 1736 and 1710 cm^{-1} in the IR and a methyl ketone signal (δ 2.12) in the ^{1}H NMR spectrum.

The assignment of the stereochemistry in sterpuric acid was based on the results of the following experiments. Treatment of methyl sterpurate with *m*-chloroperbenzoic acid in CH_2Cl_2 provided the epoxide **12**, the *cis*-relationship of the epoxide and the tertiary OH group being assigned on the basis of the known preference for allylic alcohols to undergo *cis*-epoxidation.[6] Treatment of the epoxide **12** with *p*-toluenesulfonic acid in benzene brought about smooth rearrangement of the 1-hydroxybicyclo[4.2.0]octane derivative to the bicyclo[3.2.1]octan-8-one **13** *with concurrent γ-lactone formation.* The facile lactone formation indicates that the epoxide in **12**, and thus the OH in **2**, is *syn* to the carbomethoxy group. Saponification of the ester **12** gave the corresponding acid **14** without lactone formation, again in agreement with the *syn*-relationship of the carboxyl and epoxide functions. Treatment of the acid **14** with *p*-



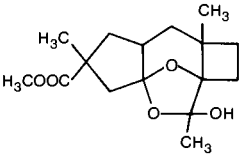
Scheme 1



6 **7**

Scheme 2

‡The numbering reflects the fact that sterpuric acid is a derivative of tricyclo[6,3,0,0^{3,6}]undec-1-ene.



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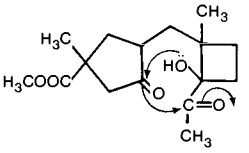

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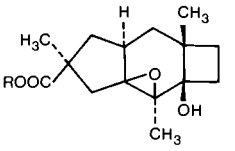
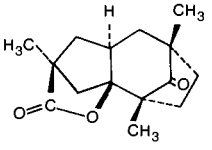


12 R = CH_3
14 R = H



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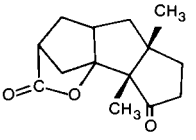

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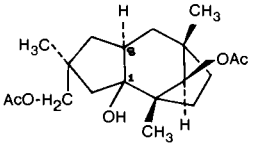

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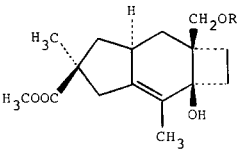
toluenesulfonic acid in chloroform provided the rearrangement product **13**. Evidence that the rearrangement of **12** proceeds with migration of the C-4 to C-3 bond rather than the C-6 to C-3 bond (to give the bicyclo[3.3.0]octanane **15**) was provided by LAH reduction of **13** to the corresponding triol followed by acetylation to give **16**. The proton geminal to the secondary acetoxyl group gives rise to a *sharp singlet* in the ^{1}H NMR spectrum, thus ruling out structure **15** for the rearrangement product.

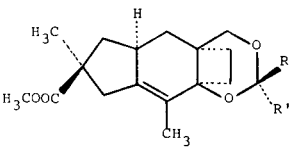
The *cis*-relationship of the C-3 OH to the C-6 Me was first suggested by the large pyridine shift[7] ($\delta_{CDCl_3} - \delta_{Py} = -0.15$ ppm) observed for this Me group in the ^{1}H NMR spectra of methyl sterpurate. It is interesting to note that the vinylic Me, which is also proximate to the OH group, likewise undergoes a substantial (-0.18 ppm) pyridine shift. The *cis*-relationship of the C-3 and C-6 substituents is further confirmed by the chemistry of hydroxysterpuric acid (see below). The configuration at C-8 was assigned on the basis of a pyridine shift study on the hydroxydiacetate **16**. The proton at C-8 shows the same chemical shift (δ 1.90) in pyridine as in $CDCl_3$, indicating that it is *trans* to the C-1 OH group, and thus *anti* to the carboxyl group in sterpuric acid. The results of the X-ray crystallographic study described below place these chemical deductions on a firm basis.

Methyl hydroxysterpurate, the ester of the second metabolite isolated, is assigned structure **17** on the basis of the following observations. The ^{1}H NMR spectrum is very similar to that of methyl sterpurate (**2**), except that the signal for the Me group at C-6 is replaced by a signal for a two proton AB quartet at δ 3.80. Brief treatment of **17** with acetic anhydride-pyridine at room temperature affords the monoacetyl derivative **18**, the C-13 methylene group now appearing as a singlet at δ 4.30. Methyl hydroxysterpurate (**17**) rapidly forms an acetonide (**19**) when treated with 2,2-dimethoxypropane under acid catalysis, confirming the 1,3-relationship of the two hydroxyl groups and the *cis*-nature of the ring fusion.

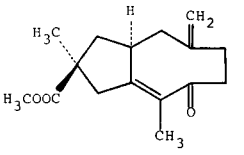
Attempts to transform the hydroxymethyl group of **17** to a Me group were unsuccessful, mainly because of the tendency of the hydroxymethylcyclobutanol system to undergo ring cleavage. Tosylation (sodium hydride, ether, *p*-toluenesulfonyl chloride)[8] of methyl hydroxysterpurate at $-10°$ followed by room temperature work-up and chromatography provided the tosylate **20**, along with small amounts of the fragmentation product **21**. Reactions designed to bring about replacement of the tosyloxy group with hydrogen invariably led to fragmentation. Thus, treatment of **20** with sodium iodide and Zn dust in HMPA[9] gave **21** as the only isolable product. Similarly, attempts to transform the tosylate to the bromide[10] gave only **21**, and LAH reduction provided the allylic alcohol from reduction of **21**. Due to the paucity of starting material, the direct



17 R = H
18 R = Ac
20 R = Ts



19 R = R' = CH_3
22 R = CH_3, R' = H
23 R = H, R' = CH_3



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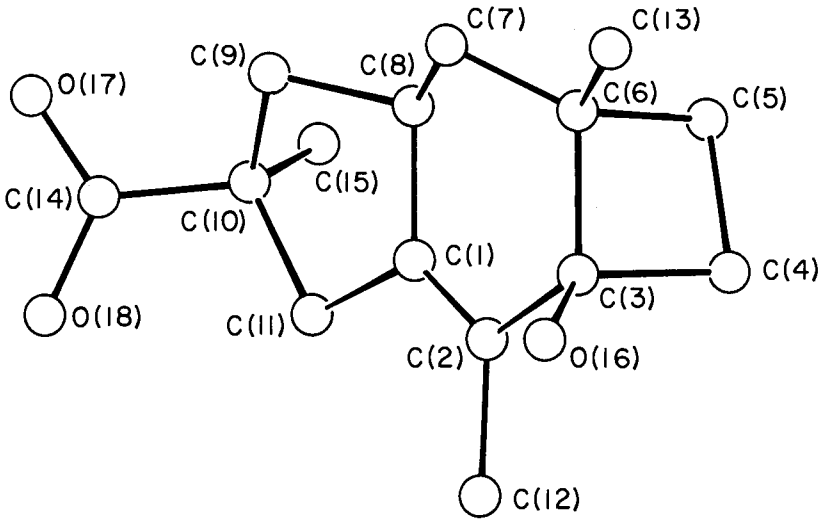

Fig. 1. A computer generated perspective drawing of sterpuric acid. Hydrogens have been omitted for clarity and no absolute configuration is implied.

correlation of methyl hydroxysterpurate (**17**) with methyl sterpurate (**2**) was not further pursued.

The third metabolite isolated is the ethylidene acetal of methyl hydroxysterpurate (**22**). The compound shows very similar spectral properties to those of the isopropylidene derivative **19**, except that the two Me singlets of the *gem*-dimethyl group of **19** are replaced by a Me doublet at δ 1.30 and a one proton quartet at δ 5.05. Acid hydrolysis of the acetal grouping in **22** gave methyl hydroxysterpurate **17**. Treatment of **17** with acetaldehyde in the presence of *p*-toluenesulfonic acid gave a *ca* 1:1 mixture of the two epimeric ethylidene acetals **22** and **23**. The two acetals were separable by repeated chromatography. Since the unnatural acetal shows both the Me signal (δ 1.25) and the methine signal (δ 4.57) at higher field than those of the natural epimer, the two are tentatively assigned the stereochemistry shown (Me group axial in **22**, equatorial in **23**).[11] The fact that only one of the epimers is isolated from the natural source, and both are formed during the laboratory preparation, suggests that **22** is not an artefact produced during the isolation process.

Sterpuric acid (**2**) and its congeners represents a new structural type among the sesquiterpenes. Interestingly, an intermediate of this carbon skeleton was proposed[12] as a possible biogenetic precursor to the isolactarane skeleton, but the biogenetic route was not seriously considered since the carbon skeleton was not among those known at the time. In order to put the structural hypothesis on a firm basis, an X-ray crystallographic study of sterpuric acid has been carried out. Figure 1 is a computer generated perspective drawing of the final X-ray model of sterpuric acid. Both of the independent molecules in the asymmetric unit have the same structure and conformation and only one molecule is shown. The X-ray experiment defined only the relative stereostructure and the enantiomer shown represents an arbitrary choice. The relative stereochemistry can be designated as 3(R*), 6(S*), 8(R*) and 10(S*). The carboxyl, OH and Me group at C-6 are all on the same face and the bridgehead hydrogen at C-8 and the Me at C-15 are on the opposite face. The cyclopentane ring has the envelope (Cs) conformation with C-9 serving as the flap; the cyclohexene ring has the 1,2-diplanar conformation with 0° torsional angles about C(1)–C(2) and C(2)–C(3) and the cyclobutane ring is puckered. In general bond distances and angles agree with commonly accepted values. The two independent molecules do not form a H-bonded carboxylic acid dimer; the closest intermolecular contacts are H-bonds between 0(16)–0(18′), 2.63 Å and 0(16′)–0(18), 2.66 Å.

Biosynthetic studies designed to test whether the sterpuric acid skeleton is derived directly from farnesyl pyrophosphate (as outlined in Scheme 2), or *via* the protoilludane pathway,[12] are in progress.

EXPERIMENTAL

General. Mass spectra were recorded on an AEI model MS-50 mass spectrometer. The formulas of all peaks reported were determined by high resolution measurements. IR spectra were recorded on a Nicolet 7199 F.T. interferometer. Optical rotations were measured on a Perkin–Elmer model 141 automatic polarimeter. ^{1}H NMR spectra were determined on a Varian HA-100, or Bruker WH 200, or Bruker WH 400 spectrometer with TMS as internal standard. Complete spectra are reported for compounds **1**, **2**, **17** and **22**, otherwise only diagnostically significant peaks are given. Melting points were recorded on a Fisher–Johns m.p. apparatus and are uncorrected. Skellysolve B refers to Skelly Oil Company light petroleum, b.p. 62–70°. Column chromatography was carried out using Machery Nagel Kieselgel 60 (100 g/g substrate). Preparative layer chromatography (plc) was carried out on silica gel G (E. Merck, 0.75 mm layers) containing 1% electronic phosphor (General Electric, Cleveland). All solvents were distilled prior to use. All compounds for which spectral data are reported showed single spots on tlc using at least two different solvent systems.

Growth of Stereum purpureum *and extraction of metabolites.* Slant tubes of *S. purpureum* (strain C-663) were obtained from Dr. Y. Hiratsuka, Northern Forest Research Centre, Edmonton, and were maintained at 4° on potato dextrose agar. The fungus was grown in still culture at room temp on an aq. liquid medium containing malt extract (2.5%), dextrose (1.3%) and peptone (0.07%) in ten 2.81 Fernbach

flasks containing 1 l medium per flask. After 30 days growth the mycelium was removed by filtration and the broth was concentrated at red. pres. to 1.5 l. The concentrate was extracted with ether (3 × 1.5 l) and then with EtOAc (2 × 1.5 l). The ether extract was washed with water, then brine, dried (Na_2SO_4) and evaporated to give a viscous light brown oil (1.29 g). The EtOAc extract was worked up similarly to give a dark brown oil (0.4 g).

Isolation of sterpuric acid (**1**). The ether extract from above (1.25 g) was dissolved in EtOAc (100 mL) and extracted with 10% $NaHCO_3$. The organic phase was washed with water, then brine, dried and concentrated to provide neutral material (0.83 g)† as a yellow oil. The bicarbonate extract was washed twice with $CHCl_3$ (25 mL), then cooled with ice and acidified to pH 3 with 6M HCl, and extracted with $CHCl_3$ (3 × 50 mL). The $CHCl_3$ extract was washed with water, dried and evaporated to provide a viscous oil (0.34 g). The crude acids were chromatographed over silica gel. Elution with 7.5–12.5% acetone in benzene gave crude sterpuric acid (28 mg). Repeated crystallization from EtOAc provided *sterpuric acid* (**1**) as colorless crystals, m.p. 203–207°, $[\alpha]_D^{25°}$ + 72° (MeOH; *c* 0.03). IR spectrum (film): 3020–3600, 1700 cm^{-1}. MS (probe, 150°) 70 eV *m/e* (rel. int.): $C_{15}H_{22}O_3$ [M^+, calcd: 250.1569; found 250.1573] (30), $C_{13}H_{18}O_3$ (100), $C_{12}H_{15}O$ (49), $C_{11}H_{13}O$ (49), $C_9H_{12}O$ (53), C_7H_7 (25). ^1H NMR (CD_3OD) (400 MHz): δ 2.86 (1 H on C-11, d, J_{gem} 17 Hz), 2.61 (1 H, C-8, br. mult., coupled to C-7 and C-9 methylenes (see below)), 2.25 (1 H on C-11, d, J_{gem} 17 Hz), 2.20 (1 H on C-4, complex mult.), 1.92 (1 H on C-4, complex mult.), 1.86 (1 H on C-9, dd, J_{gem} 12 Hz, $J_{8,9}$ 7 Hz), 1.64 (1 H on C-9, J_{gem} 12 Hz, $J_{8,9}$ 11 Hz), 1.62 (3 H, C-12, s), 1.58 (1 H on C-7, dd, J_{gem} 13 Hz, $J_{7,8}$ 6 Hz), 1.56 (1 H on C-5, complex mult.), 1.32 (3 H, C-15, s), 1.23 (1 H on C-5, complex mult.), 1.20 (3 H, C-13, s), 0.88 (1 H on C-7, dd, J_{gem} 13 Hz, $J_{7,8}$ 11 Hz). The assignments of coupling partners were confirmed by double irradiation experiments.

Methyl sterpurate (**2**). Diazomethane in ether (3 ml, 0.3 M) was added to a soln of sterpuric acid (25 mg) in ether–MeOH (3 ml, 1:1). After 15 min the solvents were removed to give methyl sterpurate (26 mg) as an oil which was purified by plc. IR spectrum (film): 3600, 1730 cm^{-1}. MS (probe, 200°) 70 eV *m/e* (rel. int.): $C_{16}H_{24}O_3$ [M^+, Calc.: 264.1726; Found: 264.1720] (43), $C_{14}H_{20}O_3$ (100), $C_{14}H_{21}O$ (47), $C_{12}H_{15}O$ (64), $C_{11}H_{13}O$ (47), $C_9H_{12}O$ (48), C_7H_7 (35). ^1H NMR ($CDCl_3$): δ 1.22 (3 H, s), 1.35 (3 H, s), 1.67 (3 H, s), 3.70 (3 H, s). ^1H NMR (Py-d_5): δ 1.35 (3 H, s), 1.37 (3 H, s), 1.85 (3 H, s), 3.60 (3 H, s). ^{13}C NMR ($CDCl_3$): δ 176.6 (s), 138.3 (s), 127.8 (s), 73.4 (s), 51.9 (q), 47.1 (s), 44.3 (t), 43.9 (s), 41.3 (dd), 36.8 (d), 34.9 (dd), 34.4 (t), 25.4 (q), 23.4 (q), 22.1 (t), 12.8 (q).

Methyl O-acetyl sterpurate (**3**). To a soln of methyl **2** (11 mg) in ether (4 ml) was added Ac_2O (0.15 ml), Et_3N (0.2 ml) and 4-N,N-dimethylaminopyridine (5 mg). The soln was heated under reflux for 3 days, then diluted with ether (50 ml) and washed successively with dil. HCl, water, and brine. Evaporation of the solvent and chromatography (eluent benzene–acetone (1:19)) gave **3** (11 mg) as a colorless oil. IR spectrum (film): 1737 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.20 (3 H, s), 1.36 (3 H, s), 1.50 (3 H, s), 2.00 (3 H, s), 3.68 (3 H, s). *Exact mass* Calc. for $C_{18}H_{26}O_4$: 306.1831. Found: 306.1827.

Methyl dihydrosterpurate (**5**). Methyl sterpurate (13 mg) in MeOH (5 mL) was shaken under H_2 (4 kg/cm^2) for 7 days in the presence of 5% Pd-C (80 mg). Filtration, evaporation, and plc provided methyl dihydrosterpurate (5 mg) as a colorless oil. IR spectrum (film): 3600, 1730 cm^{-1}. *Exact mass* calcd for $C_{16}H_{26}O_3$: 266.1882; found, 266.1888. The base peak in the mass spectrum appeared at *m/e* 238 and corresponded to $C_{14}H_{22}O_3$.

Osmium tetroxide oxidation of methyl sterpurate (**2**). A soln of methyl sterpurate (20 mg) and OsO_4 (30 mg) in dry pyridine (2 ml) was kept at 50° for 12 hr, then cooled and a soln of $NaHSO_3$aq (0.18 g) in water (3 mL) and pyridine (2 ml) added. This was stirred at room temp for 3 hr, then diluted with water and extracted with ether (3 × 30 ml). Evaporation followed by chromatography (eluent benzene-ether (7:3)) gave **8** (7 mg) as a colorless solid, m.p. 145–150°. IR spectrum (film): 3600, 1775; ^1H NMR ($CDCl_3$): δ 1.23 (3 H, s), 1.26 (3 H, s), 1.48 (3 H, s). *Exact mass* Calc. for $C_{15}H_{22}O_4$: 266.1518. Found: 266.1509.

Periodate cleavage of diol **8**. Paraperiodic acid (H_5IO_6, 20 mg) was added to a soln of **8** (7 mg) in dry THF (0.5 ml) and the soln was stirred at room temp for 10 min. Addition of ether (40 ml) and work-up in the usual manner followed by chromatography (eluent benzene-ether (9:1)) gave **9** as an oil (6 mg). IR spectrum (film): 1790, 1775, 1718 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.17 (3 H, s), 1.34 (3 H, s), 2.35 (3 H, s), 3.00 (2 H, t, J 8.8 Hz, cyclobutanone α-methylene). *Exact mass* Calc. for $C_{15}H_{20}O_4$: 264.1361. Found: 264.1372.

Ozonolysis of metal sterpurate (**2**). A soln of methyl sterpurate (6 mg) in MeOH (1 ml) was cooled to −60° and O_3 was bubbled in until the soln remained blue. After flushing with N_2 at −60°, Me_2S (0.2 mL) was added and the mixture was allowed to come to room temp. Evaporation of the solvent left an oil which was purified by chromatography (eluent benzene-acetone (19:1)) to give **10** (6 mg) as an oil. IR spectrum (film): 3485, 1745 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.88 (3 H, s), 1.16 (3 H, s), 1.39 (3 H, s), 3.74 (3 H, s). *Exact mass* Calc. for $C_{16}H_{24}O_5$: 296.1623; Found: 296.1626.

Ozonolysis of methyl O-acetylsterpurate (**3**). Methyl O-acetylsterpurate (11 mg) was subjected to ozonolysis as described above for methyl sterpurate to give after chromatography **11** as a colorless solid (3 mg). IR spectrum (film): 1736, 1710 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.27 (3 H, s), 1.40 (3 H, s), 2.06 (3 H, s), 2.12 (3 H, s), 3.71 (3 H, s). The strongest peak in the mass spectrum corresponded to $M^+ - C_2H_2O$. *Exact mass* Calcd for $C_{16}H_{24}O_5$ ($M^+ - C_2H_2O$): 296.1624. Found: 296.1626.

Epoxidation of methyl sterpurate (**2**). *m*-Chloroperbenzoic acid (25 mg of 85%) was added to a soln of **2** (17 mg) in CH_2Cl_2 (0.75 mL). The mixture was kept at room temp for 1 hr, then diluted with ether (50 ml) and washed successively with sat $NaHCO_3$aq, water, and brine. Evaporation left an oil (17 mg) which was purified by chromatography (eluent benzene–ether (9:1)) to give **12** (15 mg) as a colorless oil. IR spectrum (film): 3460, 1735 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.07 (3 H, s), 1.33 (3 H, s), 1.38 (3 H, s), 3.68 (3 H, s). *Exact mass* Calc. for $C_{16}H_{24}O_4$: 280.1675. Found: 280.1672.

Rearrangement of epoxide **12**. *p*-Toluenesulfonic acid (5 mg) was added to a stirred soln of **12** (8 mg) in benzene (0.5 ml) at room temp. After 4 hr CH_2Cl_2 (30 ml was added and the resultant soln was washed successively with sat $NaHCO_3$aq, water (3 ×), and brine. Evaporation of the solvents and chromatography (eluent benzene-ether (9:1)) gave **13** (5 mg) as a colorless solid, m.p. 145–148°. IR spectrum (film): 1767, 1748 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.06 (3 H, s), 1.12 (3 H, s), 1.33 (3 H, s). *Exact mass* Calc. for $C_{15}H_{20}O_3$: 248.1412. Found: 248.1409.

Hydrolysis of epoxide **12** *and rearrangement of acid* **14**. The epoxide **12** (32 mg) was heated under reflux with 10% NaOH in MeOH–H_2O (4:1, 5 ml) for 3 hr. Most of the MeOH was removed at the pump and water (10 ml) added. The soln was washed with ether, then acidified (ice bath) with dil HCl, and extracted with $CHCl_3$ (4 × 25 ml) to give crude **14** (25 mg). A small portion of the acid was esterified (CH_2N_2) to give **12**. The remainder (24 mg) was dissolved in $CHCl_3$ and *p*-toluenesulfonic acid (5 mg) added. After 2 days at room temp the mixture was worked up as described above to give the rearrangement product **13**, identical (tlc, IR, ^1H NMR) with that prepared directly from **12**.

Preparation of hydroxydiacetate **16**. The product **13** (4.5 mg) was dissolved in THF (1 ml) and LAH (15 mg) added. After 20 min excess hydride was destroyed by the addition of wet ether. The usual work-up provided an oil (3.5 mg) which was dissolved in pyridine (0.5 ml) and Ac_2O (0.25 ml) added. After 48 hr at room temp ether (40 mL) was added and the soln worked up as usual. Chromatography (eluent benzene–ether (4:1)) provided **16** as a colorless oil (3 mg). IR spectrum (film): 3510, 1739 cm^{-1}. ^1H NMR

†A study of the neutral metabolites is presently underway.

($CDCl_3$): δ 0.92 (3 H, s), 1.05 (3 H, s), 1.07 (3 H, s), 1.9 (1 H, m, proton on C-8). 2.04 (3 H, s), 2.14 (3 H, s), 4.00 (2 H, AB quartet, J 10.5 Hz, $C\underline{H}_2OAc$), 4.72 (1 H, s, $C\underline{H}OAc$). *Exact mass* Calc. for $C_{17}H_{26}O_3$ [M^+ –HOAc]: 278.1881. Found: 278.1881. The electron impact MS did not show the molecular ion, but the chemical ionization MS indicated MW 338 ($C_{19}H_{30}O_5$).

Isolation of methyl hydroxysterpurate (**17**). The crude acidic metabolites remaining after removal of sterpuric acid (0.7 g) were dissolved in ether–MeOH (2:1, 30 ml) and treated with excess ethereal CH_2N_2. Evaporation of the solvents and chromatography (eluent benzene–ether (7:3)) gave crude methyl hydroxysterpurate (0.125 g) which was further purified by plc (triple elution with ether) and further column chromatography (eluent $CHCl_3$–MeOH (99:1)) to give *methyl hydroxysterpurate* (46 mg) as a colorless oil. IR spectrum (film): 3300, 1731 cm^{-1}. MS (probe 150°) 70 eV *m/e* (rel. int.): $C_{16}H_{24}O_4$ [M^+, Calc.: 280.1675. Found: 280.1673] (21), $C_{14}H_{20}O_4$ (52), $C_{15}H_{22}O_3$ (52), $C_{15}H_{22}O_3$ (27), $C_{12}H_{15}O$ (47), $C_{12}H_{14}O$ (100), $C_{11}H_{13}O$ (28), C_7H_7 (21). ^1H NMR ($CDCl_3$): δ 3.80 (2 H, C-13, ABq, J_{gem} 12 Hz), 3.70 (3 H, s, ester Me), 2.86 (1 H on C-11, d, J_{gem} 17 Hz), 2.63 (1 H, C-8, br m), 2.28 (1 H on C-11, d, J_{gem} 17 Hz), 2.23 (1 H on C-4, complex mult.), 2.02 (1 H on C-4, complex mult.), 1.90 (1 H on C-9, dd, J_{gem} 13 Hz, $J_{8,9}$ 7 Hz), 1.72 (1 H on C-9, dd, J_{gem} 13 Hz, $J_{8,9}$ 12 Hz), 1.65 (3 H, C-12, s), 1.51 (1 H on C-7, dd, J_{gem} 13 Hz, $J_{7,8}$ 7 Hz), 1.48 (2 H, C-5, complex mult.), 1.36 (3 H, C-15, s), 1.20 (1 H on C-7, dd, J_{gem} 13 Hz, $J_{7,8}$ 11 Hz). The assignments of coupling partners were verified by double irradiation experiments.

Acetylation of methyl hydroxysterpurate (**17**). Ac_2O (0.25 ml) was added to a soln of **17** (15 mg) in pyridine (0.5 ml) and the soln kept at room temp for 1.5 hr. After removal of the solvents the crude product was chromatographed (eluent benzene–ether: (9:1)) to give **18** (13 mg) as a colorless oil (13 mg). IR spectrum (film): 3340, 1735 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.34 (3 H, s), 1.65 (3 H, s), 2.08 (3 H, s), 3.68 (3 H, s), 4.31 (2 H, s). *Exact mass* Calc. for $C_{18}H_{26}O_5$: 322.1780. Found: 322.1791.

Methyl hydroxysterpurate acetonide (**19**). Compound **19** (15 mg) was dissolved in 2,2-dimethoxypropane (2 ml) and a catalytic amount of *p*-toluenesulfonic acid added. After 1 hr at room temp ether (40 ml) was added and the soln was washed with sat $NaHCO_3$aq. Evaporation of the solvent and purification by chromatography gave the **19** as an oil (15 mg). IR spectrum (film): 1731 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.26 (3 H, s), 1.36 (3 H, s), 1.39 (3 H, s), 1.59 (3 H, s), 3.00 (2 H, AB q, J 12 Hz), 3.70 (3 H, s). *Exact mass* Calc. for $C_{19}H_{28}O_4$: 320.1988. Found: 320.1994.

Methyl hydroxysterpurate p-*toluenesulfonate* (**20**). NaH (12 mg) was added to a soln of methyl hydroxysterpurate (30 mg) in ether (2 ml) and the mixture stirred at room temp for 12 hr. The soln was then cooled to −10° and *p*-toluenesulfonyl chloride (22 mg) in ether (1 ml) added. Stirring was continued 1 hr at −10°, then 1 hr at room temp. Brine (5 ml) was added and the mixture extracted with ether (3 × 20 ml). Evaporation of solvent and chromatography (eluent benzene–ether (19:1)) gave **20** as an oil (20 mg). ^1H NMR ($CDCl_3$): δ 1.33 (3 H, s), 1.60 (3 H, s), 2.45 (3 H, s), 3.70 (3 H, s), 4.21 (2 H, AB q, J 9 Hz), 7.33 (2 H, d, J 8 Hz), 7.79 (2 H, d, J 8 Hz). The highest peak in the MS corresponded to M^+ –H_2O. *Exact mass* Calc. for $C_{23}H_{29}O_5{}^{32}S$: 416.1657. Found: 416.1659. Earlier fractions from the chromatography gave the cleavage product **21** (3 mg) described below.

Attempted transformation of **20** *to methyl sterpurate* (**2**). The *p*-toluenesulfonate **20** (7 mg) was dissolved in HMPA (2 ml) and NaI (19 mg) and Zn dust (17 mg) were added. The mixture was heated at 105° for 3 hr, cooled, and diluted with ether (40 ml). Work-up in the usual manner and purification by plc gave the fragmentation product **21** (3 mg) as a colorless oil. IR spectrum (film): 1730, 1650 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.28 (3 H, s), 1.82 (3 H, s), 3.72 (3 H, s), 4.63 (2 H, br, exocyclic methylene). *Exact mass* Calc. for $C_{16}H_{22}O_3$: 262.1569. Found: 262.1572.

Isolation of methyl hydroxysterpurate ethylidene acetal (**22**). Fractions from chromatography of the crude acidic metabolites (total of 1.5 g crude acids, see isolation of sterpuric acid) eluted with 2.5% to 5% acetone in benzene gave solid material (43 mg) which was shown by tlc to be impure. Esterification of this material (CH_2N_2) and purification by plc (eluent, benzene–ether (3:1)) gave an oil (15 mg) which was further purified by column chromatography (eluent Skellysolve B-ether (9:1)) to give *methyl hydroxysterpurate ethylidene acetal* (**22**) as a colorless oil (12 mg). IR spectrum (film): 1731 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.05 (1 H (acetal proton), q, J 5 Hz), 4.00 (2 H, C-13, AB q, J 12 Hz), 3.70 (3 H, s, ester methyl), 2.92 (1 H on C-11, d, J_{gem} 17 Hz), 2.75 (1 H, dd, J's 9.5 and 10.5 Hz), 2.58 (1 H, C-8, br), 2.24 (1 H on C-11, d, J_{gem} 17 Hz), 1.98–1.70 (3 H, complex), 1.60 (3 H, C-12, s), 1.52–1.42 (3 H, complex), 1.34 (3 H, C-15, s), 1.30 (3 H (acetal Me), d, J 5 Hz), 1.20 (1 H, dd, J's 9 and 10 Hz). MS (probe, 150°), 70 eV *m/e* (rel. int.): $C_{18}H_{26}O_4$ [M^+ Calc.: 306.1831. Found: 306.1830] (16), $C_{16}H_{22}O_4$ (18), $C_{12}H_{15}O$ (31), $C_{12}H_{14}O$ (100), C_8H_9O (27).

Methyl hydroxysterpurate (**17**) *from acetal* **22**. The acetal **22** (7 mg) was dissolved in THF (0.5 ml) and 3 M HCl (0.5 ml) added. After 3 hr at room temp ether (30 ml) was added and the soln worked up in the usual manner to give an oil (6 mg) which was purified by chromatography (eluent benzene–ether (4:1)) to give **17** (4 mg) identical (tlc, IR, ^1H NMR) with an authentic sample.

Preparation of ethylidene acetals **22** *and* **23**. A soln of metal hydroxysterpurate (30 mg), acetaldehyde (1.7 ml), and *p*-toluenesulfonic acid (1 mg) was stirred at room temp for 1 hr, then the soln was evaporated and the residue taken up in ether (50 ml). Work-up in the usual manner followed by chromatography (eluent Skellysolve B-ether (97:3)) gave a mixture of **22**, **23** and acetaldehyde trimer. This mixture was separated by repeated plc (eluent Skellysolve B-ether (4:1), triple elution) to give the unnatural epimer **23** (3.5 mg), and the natural epimer **22** (4.3 mg), both as colorless oils. The natural epimer **22** was identical (IR, ^1H NMR) with authentic material. The unnatural epimer **23** shows the following properties: IR spectrum (film): 1731 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.25 (3 H (acetal Me), d, J 5 Hz), 1.33 (3 H, s), 1.65 (3 H, s), 3.70 (3 H, s), 3.80 (2 H, AB q, J 10.5 Hz), 4.57 (1 H (acetal proton), q, J 5 Hz). *Exact mass* Calc. for $C_{18}H_{26}O_4$: 306.1831. Found: 306.1824.

Single crystal X-ray diffraction analysis of sterpuric acid (**1**). An irregularly shaped crystal of sterpuric acid crystallized from EtOAc was chosen for X-ray analysis. Preliminary x-ray photographs showed only triclinic symmetry. Precise lattice constants of $\mathbf{a} = 6.672$ (1), $\mathbf{b} = 10.446$ (2), $\mathbf{c} = 11.113$ (2) Å, $\alpha = 96.36$ (1), $\beta = 109.00$ (2) and $\gamma = 72.52$ (1)° were obtained by a least-squares fit of fifteen moderate 2θ-values measured on a diffractometer. The limited sample precluded a density measurement but a plausible density of 1.52 g/cm^3 was calculated assuming two molecules of $C_{15}H_{22}O_3$ per unit cell. Since sterpuric acid is known to be chiral, these observations are uniquely accommodated by space group P1 with two molecules in the asymmetric unit.

All unique diffraction maxima with $2\theta \leq 114°$ were surveyed using a variable speed, 1° ω-scan with graphite monochromated CuKα radiation (1.54178 Å). A total of 1820 reflections were surveyed in this fashion and after correction for Lorentz, polarization and background effects, 1809 (99%) were judged observed ($|F_o| \geq 3\sigma(F_o)$). No corrections were deemed necessary for absorption or decomposition.

The intensity data were converted to normalized structure factors and attempts were made to achieve a phasing model using direct methods.[13] These initial attempts ended in completely centrosymmetric solutions which contained no plausible molecular fragments. Explicit assumption of an inversion center did not alter this result. In these attempts 150 E's with $|E| \geq 1.61$ were employed. Careful examination of these revealed that planes with h = 0 and 1 had abnormally large numbers of E's with large E values. To reduce this dominance all of the E's were rescaled; the 0kl and 1kl reflections were reduced to 85% of their initial value and all others were increased to 115% of their initial value. Phase determination was repeated with these rescaled E's and a

weighted E-synthesis of the most probable solution showed two plausible, identical 11 atom fragments. The remaining H atoms were located in a subsequent F-synthesis.[14] All 44 H atoms were located on a ΔF-synthesis following isotropic block diagonal refinement of the non H atoms. Full matrix least-squares refinements with anisotropic non H atoms and isotropic H's have converged to the current crystallographic residual of 0.061 for the observed reflections. Tables of fractional coordinates, bond distances, bond angles and observed and calculated structure factors have been deposited with the Cambridge Crystallographic Data File.[15]

At least part of the difficulty in solving this structure can be attributed to the strongly centrosymmetric distribution of atoms in two dimensions. The two molecules in the asymmetric unit are related by $y' = 1.46-y$ and $z' = 1.14-z$.

Acknowledgements—The work at the University of Alberta was financially supported by the Natural Sciences and Engineering Research Council (grant NSERC-A1473) and that at Cornell University by the National Institutes of Health (grant NIH-CA-24487). To both of these agencies we extend our thanks. We also wish to thank Dr. Y. Hiratsuka, Northern Forest Research Centre, Edmonton, for bringing the silver-leaf disease problem to our attention, and for providing cultures of *S. purpureum*.

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[14]The following library of major crystallographic programs was employed: MULTAN, G. Germain, P. Main and M. M. Woolfson; ORFLS (locally modified), W. R. Busing, K. O. Martin and H. A. Levy, Oak Ridge National Laboratory Report ORNL-TM-305; ORFFE, W. R. Busing and H. A. Levy, Oak Ridge National Laboratory publication ORNL-59-12-3; ORTEP, C. K. Johnson, Oak Ridge National Laboratory Report ORNL-TM-3794.

[15]Tables of crystallographic data for sterpuric acid are available from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW and from J.C.

Tetrahedron, Vol. 37, Supplement No. 1, pp. 387 to 391, 1981
Printed in Great Britain

0040-4020/81/Suppl. 1-0387-05 $02.00/0
Pergamon Press Ltd.

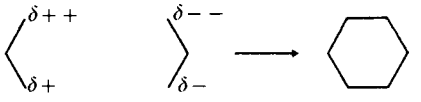
REGIO-CONTROLLED SYNTHESIS OF SUBSTITUTED PHENOLS[1]

T. H. CHAN* and P. BROWNBRIDGE,
Department of Chemistry, McGill University, Montreal, Quebec, Canada H3A 2K6

(*Received in USA* 16 *July* 1980)

Abstract—2,4-Bis(trimethylsiloxy)-penta-1,3-diene (**2**) condenses with various equivalents of β-dicarbonyl compounds and titanium tetrachloride to give substituted *o*-acetylphenols in a regio-controlled manner. Replacing **2** with 2,4-bis (trimethylsiloxy)-1-methoxypenta-1,3-diene (**10**) in the condensation reaction gives substituted methyl salicylates. The salicylates can be converted to phenols by decarboxylation. Condensation of 1,3-bis(trimethylsiloxy)-1-methoxy-2-methylpenta-1,3-diene (**19**) with β-carbonyl equivalents gives cyclisation products which can be aromatised by decarboxylation.

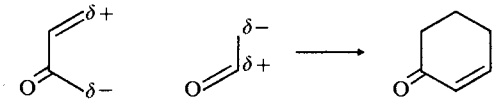
There are no well-established methods for the synthesis of benzeneoid compounds from acyclic precursors. Recently, we described[2] a novel cycloaromatisation reaction involving the condensation of two 3-carbon units, one with two nucleophilic sites and the other containing two electrophilic sites, as in eqn (1). The regiochemistry of



(1)

the reaction is controlled by the differential reactivities of these sites. 1,3-Bis-(trimethylsiloxy)-1-methoxybuta-1,3-diene (**1**) constitutes the 3-carbon fragments with two nucleophilic sites. Condensation of **1** with various equivalents of β-dicarbonyl compounds and titanium tetrachloride gave substituted methyl salicylates. The regiochemistry is controlled by the order of reactivity of the electrophilic sites, which is conjugate position of enone > ketone > monothioacetal, acetal.

This method of construction of 6-membered rings is different conceptually from the classical methods such as Diels–Alder reaction or Robinson annelation which consist of the union of two fragments, one with two C atoms and the other with four carbons. Furthermore, regiochemistry in these reactions is essentially controlled by the direction of polarization within each fragment as represented schematically in eqn (2) for the Robinson annelation.



(2)

In this paper, we wish to extend the generality of eqn (1) to other 3-carbon nucleophilic fragments. We have established as well the reaction as a general synthesis of substituted phenols.

2,4-*Bis(trimethylsiloxy)-penta*-1,3-*diene* (**2**). We are interested to see if eqn (1) can be used for the synthesis of substituted *o*-acetylphenols. For this purpose, compound **2**, the dianion equivalent of acetylacetone, is required. Compound **2** was prepared[3] from 4-trimethylsiloxypent-3-en-2-one (**3**)[2] by Danishefsky's method[4] in 96% yield, as a 1:1 mixture of geometric isomers. It was pure by ^{1}H NMR and gc, and was used without distillation.

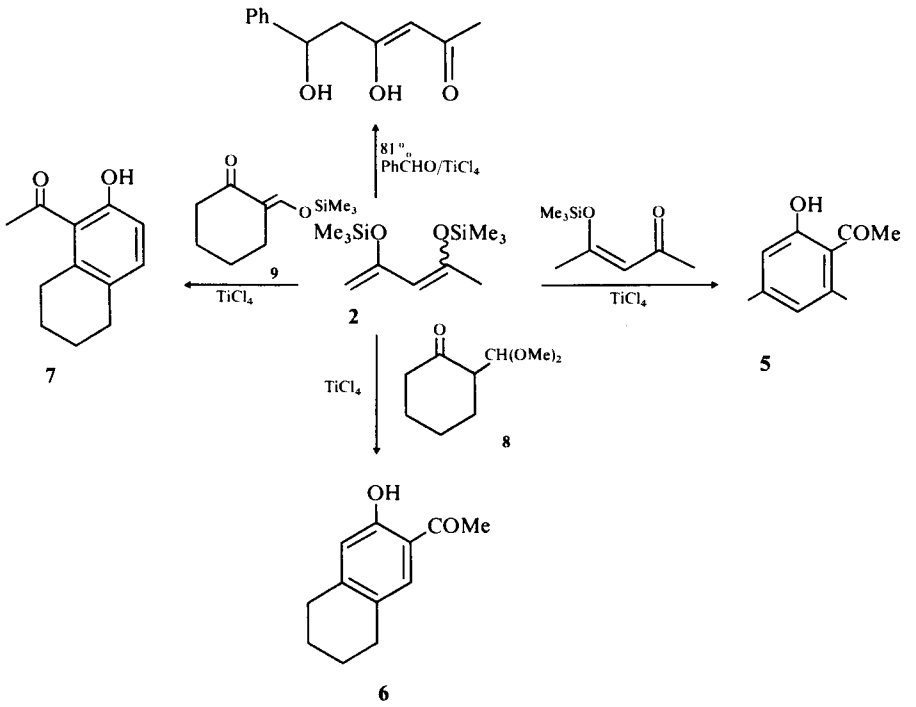
Compound **2** reacts with benzaldehyde in the presence of titanium tetrachloride to give 6-hydroxy-6-phenylhexane-2,4-dione (**4** in enol form) in good yield (Scheme 1). This reaction establishes that, of the two nucleophilic sites in **2**, carbon-1 is the more reactive. Condensation of **2** and **3** with titanium tetrachloride gave compound **5** as product.

It is clear that by using **2** as the nucleophilic component, synthesis of *o*-acetylphenol according to eqn (1) is indeed viable. The control of regiochemistry of the reaction can be demonstrated by the preparation of the regio-isomers **6** and **7**. Using β-oxo acetal **8** as the electrophile[2] in condensation with **2**, compound **6** was obtained exclusively. The regiochemistry of **6** is in accordance with the reactivity order of ketone > acetal. On the other hand, with β-siloxyenone **9** as the electrophile, the isomeric compound **7** was produced without a trace of presence of **6**, again, in agreement with prediction from the reactivity order of the electrophilic sites (Scheme 1).

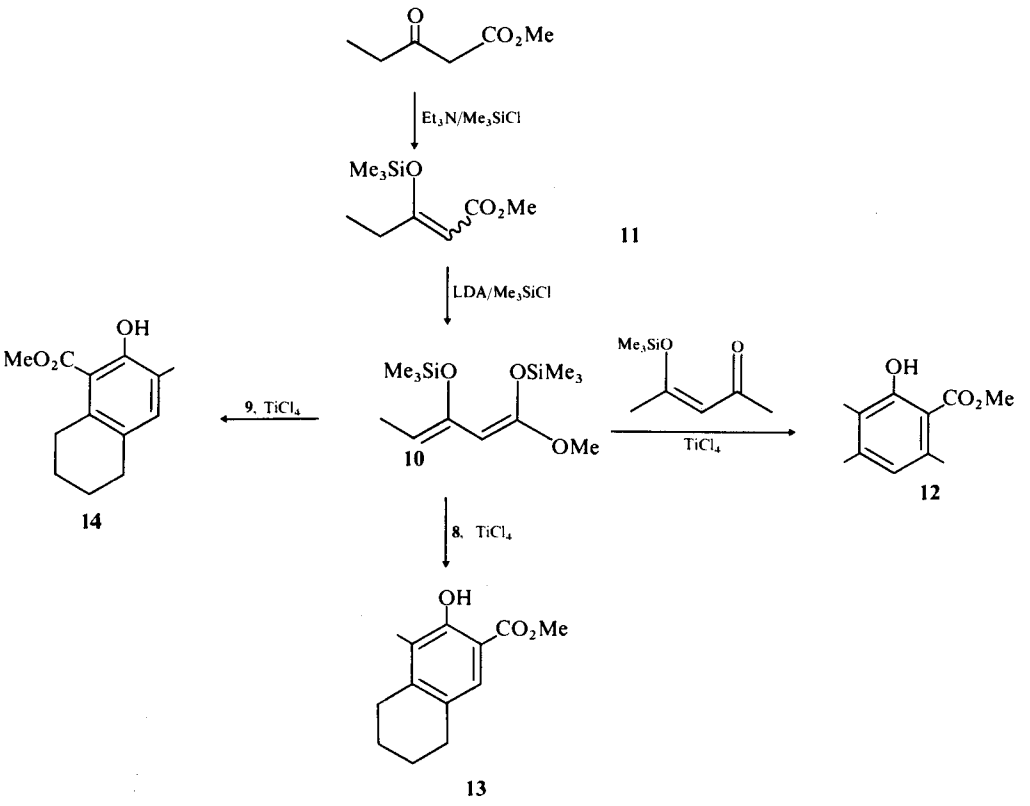
1,3-*Bis(trimethylsiloxy)*-1-*methoxypenta*-1,3-*diene* (**10**). So far, of all the salicylates[2] and *o*-acetylphenols prepared according to eqn (1), they are unsubstituted at the *o'*-position. This is a consequence of the structure of the nucleophilic components used. Both **1** and **2** are unsubstituted at the more reactive site. We are interested in examining the effect of substitution on the order of nucleophilic reactivity.

Methyl 3-trimethylsiloxypent-2-enoate (**11**) was prepared from methyl 3-oxovalerate in 95% yield as a 7:2 mixture of *E* and *Z* isomers. Reaction of **11** with lithium di-isopropylamide followed by quenching with trimethylchlorosilane gave compound **10**, a yellowish oil, in 95% yield. Judging from ^{1}H NMR, we tentatively assigned it to be a 5:1 mixture of 1*E*, 3*Z* and 1*E*, 3*E* isomers.

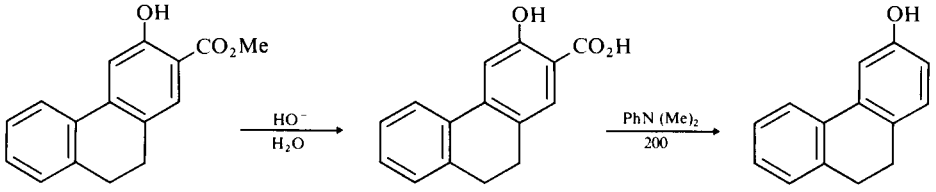
Condensation of **10** with 3-trimethylsiloxybut-3-en-2-one (**3**) and titanium tetrachloride gave methyl 3,4,6-trimethylsalicylate (**12**). The regiospecific nature of the reaction is again demonstrated by the condensation of **10** with either **8** or **9** to give the regioisomeric tetralin derivatives **13** and **14** respectively. The structures of the products establish that the nucleophilic reactivity



Scheme 1.



Scheme 2.



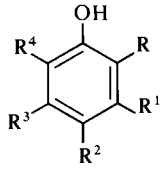
15 **17** **16**

order in **10** is not changed with respect to **1** because of the presence of the extra Me group.

Conversion of salicylates into phenols. It is obvious that by using **1** or **10** as the nucleophilic components in eqn (1), the products derived must have the substituted salicylate structure. The reaction represents nevertheless a general synthesis of substituted phenol because of the ease of removal of the carboxyl group.

This is demonstrated by the conversion of methyl 2-hydroxy-9,10-dihydrophenanthrene-3-carboxylate[2] (**15**) into 9,10-dihydrophenanthen-2-ol (**16**). Alkaline hydrolysis of **15** gave the carboxylic acid **17** in essentially quantitative yield. Decarboxylation of **17** in a solution of N,N-dimethylaniline at 200° gave the phenol **16** in 92% yield.

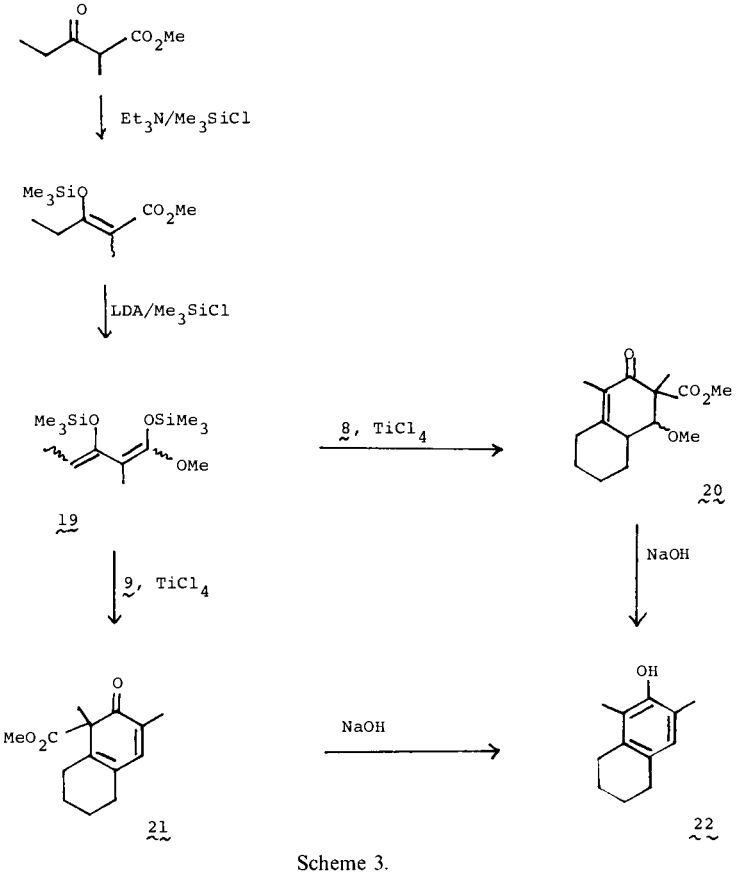
The cycloaromatisation reaction can thus be used for the regiocontrolled synthesis of substituted phenols of general structure **18** where R can be $-CO_2Me$, CO_2H, COMe or H. It remains to be seen whether the reaction can be used for the synthesis of *o,o'*-disubstituted phenols (i.e. R and R^4 both alkyl).



18

1,3-*Bis(trimethylsiloxy)*-1-*methoxy*-2-*methylpenta*-1,3-*diene* (**19**). To answer this point, we prepared compound **19** and examined its suitability as the nucleophilic component in eqn (1). Methyl 2-methyl-3-oxopentanoate was converted first to methyl 2-methyl-3-trimethylsiloxypent-2-enoate and thence to compound **19** according to standard procedures (Scheme 3).

Reaction of **19** with compound **8** and titanium tetrachloride gave as product compound **20**. It is clear that cyclisation according to eqn (1) has taken place,



Scheme 3.

but because of the gem-disubstitution at one of the ring carbon, aromatisation could not occur.

The structure of **20** is evident from its spectroscopic data, particularly from its mass spectra (EI-MS, $M^+ = 266$, CI-MS, $MH^+ = 267$). On the other hand, reaction of **19** with compound **9** and titanium tetrachloride gave the cyclohexadienone **21** as product (Scheme 3). The cyclohexadienone structure is consistent with its UV spectrum (λ_{max} (CH_3-OH) = 326 nm).

Hydrolysis of either of the foregoing β-ketoesters (**20** or **21**) with hot aqueous sodium hydroxide caused decarboxylation and aromatisation to give 1,3-dimethyl-5,6,7,8-tetrahydronaphthalen-2-ol in 89% yield.

The above sequence of reactions indicates that the cycloaromatisation reaction can be used for a general synthesis of substituted phenols with diverse substitution patterns and functionalities. Since many natural occurring compounds have the phenolic structure, we are confident that the method described here will find application in the synthesis of some of these compounds.

EXPERIMENTAL

General. M. and b.ps are uncorrected. IR spectra were obtained from films on NaCl plates for liquids and from solns in 0.1-mm NaCl cell for solids, using a Perkin–Elmer 297 spectrophotometer. ^{1}H NMR spectra were recorded on Varian T-60 and T-60A instruments, with Me_4Si as internal standard. Mass spectra were obtained on a Hewlett–Packard 5984A or an LKB 9000 machine operating at 70 eV. Column chromatography was performed on silica gel 60 (Merck). Et_3N, i-Pr_2NH, and TMEDA were dried by distillation from CaH_2; hexane, CCl_4, and benzene from P_2O_5; CH_2Cl_2 from P_2O_5 and then from CaH_2. THF was distilled under N_2 from sodium-benzophenone directly into the reaction vessel. Microanalyses were performed by Guelph Chemical Laboratories Ltd.

2,4-*Bis(trimethylsiloxy)-penta*-1,3-*diene* (**2**)[3] was prepared from **3**[2] by Danishefsky's method[4] in 96% yield as a 1:1 mixture of geometrical isomers. It was pure by ^{1}H NMR and gc and was used without distillation. ^{1}H NMR ($CDCl_3$): δ 0.19 and 0.20 (each s, 4.5 H, Me_3Si), 0.22 (s, 9 H, Me_3Si), 1.83 and 1.99 (each s, 1.5 H, MeC=), 4.04, 4.09, 4.27 br, 4.67, 4.70 br and 5.15 (each s, 0.5 H, HC=); IR (film): 1653, 846 cm^{-1}.

Reaction of **2** *with benzaldehyde.* $TiCl_4$ (0.55 ml, 5 mmol) was added to a mixture of **2** (1.09 g, 4.5 mmol) and benzaldehyde (0.53 g, 5 mmol) in dry CH_2Cl_2 (5 ml) under N_2 at $-78°$. The dark red soln was stirred at $-78°$ for 3 hr, then allowed to warm to 0°, added to $NaHCO_3$aq and extracted with ether. The extracts were dried ($MgSO_4$) and evaporated to give a yellowish oil (0.88 g) which was substantially pure 6-hydroxy-6-phenylhexane-2,4-dione. Column chromatography caused partial dehydration of this alcohol to *E*-6-phenylhex-5-ene-2,4-dione. The *benzylic alcohol* (0.62 g, 68%) was a colourless oil, R_f 0.47 (CH_2Cl_2), ^{1}H NMR ($CDCl_3$): δ 2.01 (s, 3 H, MeC=), 2.55 and 2.65 (ABX system, 2 H, J_{AB} 16.5, J_{AX} 5.5, J_{BX} 11.5 Hz, $C\underline{H}^*_2CH$), 5.23 (dd, 1 H, *J* 5.5, 11.5 Hz, $PhC\underline{H}CH^*_2$), 5.28 (s, 1 H, HOC=C$\underline{H}$CO), 7.20 (s, 5 H, Ph); IR (film 3420 br, 1666, 1609 cm^{-1} (entirely in the enol form). The *styrene derivative* (0.11 g, 13%) was colourless needles m.p. 83–4° (from cyclohexane), R_f 0.63 (CH_2Cl_2), ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3 H, MeC=), 5.46 (s, 1 H, HOC=C$\underline{H}$CO), 6.23 and 7.36 (each d, 1 H, $\underline{J}$ 15 Hz, *trans*-HC=CH), 7.0–7.4 (m, 5 H, Ph); IR ($CHCl_3$) 3500 br, 1638, 1583 cm^{-1} (entirely in the end form); MS *m/e* 188 (M^+, 89%), 145 (100), 131 (91) 103 (64).

1-(4,6-*Dimethyl*-2-*hydroxyphenyl)ethanone* (5) was prepared as above from **2**, **3** and $TiCl_4$ in 44% yield after column chromatography eluted with CH_2Cl_2. It was colourless needles m.p. 57.5–58° (from water) (lit.[5] 58°), R_f 0.62, ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 3 H, 4-Me), 2.51 (s, 3 H, 6-Me), 5.28 (s, 3 H, MeCO), 6.42 and 6.51 (each brs, 1 H, Ar), 12.52 (s, 1 H, OH).

1-(2-*Hydroxy*-5,6,7,8-*tetrahydronaphth*-1-*yl)ethanone* (**7**) was prepared similarly [using 2-(trimethylsiloxymethylene) cyclohexanone],[2] in 40% yield. It was colourless needles, m.p. 110–112° (lit.[6] 112–3°), R_f 0.54, ^{1}H NMR ($CDCl_3$) δ 1.6–1.9 (m, 4 H, β-CH_2), 2.56 (s, 3 H, MeCO), 2.6–3.0 (m, 4 H, α-CH_2), 6.60 (d, 1 H, *J* 8 Hz, H-3), 6.95 (d, 1 H, *J* 8 Hz, H-4), 10.2 (brs, 1 H, OH). No isomeric products were observed.

1-(3-*Hydroxy*-5,6,7,8-*tetrahydronaphth*-2-*yl)ethanone* (**6**). Cyclohexanone silyl enol ether (0.85 g, 5 mmol) was added to a well-stirred mixture of trimethyl orthoformate (0.53 g, 5 mmol) and $TiCl_4$ (0.55 ml, 5 mmol) in dry CH_2Cl_2 (5 ml) under N_2 at $-78°$. After 1 hr, **2** (1.09 g, 4.5 mmol) in dry CH_2Cl_2 (5 ml), and $TiCl_4$ (0.55 ml) were added. The dark red soln was stirred at $-78°$ for a further 3 hr, then allowed to warm to 0°, poured into $NaHCO_3$aq and extracted with ether. The extracts were dried ($MgSO_4$), evaporated and the residual oil (0.86 g) purified by column chromatography (eluant CH_2Cl_2) to give the acetyl tetralin derivative **6** as cream needles, (0.39 g, 45%), m.p. 71–2° (from EtOH) (lit.[6] m.p. 72–3°), R_f 0.61, ^{1}H NMR ($CDCl_3$): δ 1.6–1.9 (m, 4 H, β-CH_2), 2.48 (s, 3 H, MeCO), 2.5–2.8 (m, 4 H, α-CH_2), 6.45 (s, 1 H, H-4), 7.17 (s, 1 H, H-1), 11.08 (s, 1 H, OH). No isomerise products were observed.

Methyl 3-*trimethylsiloxypent*-2-*enoate* (**11**) was prepared from methyl 3-oxovalerate by Danishefsky's method[4] in 95% yield. It had b.p. 65–69° (1.4 mm), ^{1}H NMR ($CDCl_3$); (a 7:2 mixture *E* and *Z* of isomers) δ 0.27 (s, 9 H, Me_3Si), 1.07 (t, 3 H, *J* 7.5 Hz, $\underline{M}eCH_2$), 2.12 ^{Z} and 2.69 ^{E} (2 H, each q, *J* 7.5 Hz, $Me\underline{CH_2}$), 3.61 (s, 3 H, CO_2Me), and 5.02 ^{E} and 5.09 ^{Z} (1 H, each s, HC=); IR (film) 1720, 1622 cm^{-1}; MS *m/e* 202 (M^+, 4%), 187 (100), 89 (92) and 73 (92).

1,3-*Bis(trimethylsiloxy)*-1-*methoxypenta*-1,3-*diene* (**10**) was prepared from **3**, **10** and $TiCl_4$ as described for **5**. After preparation of **1**.[2] It was a yellowish oil (91–98% yield). Its ^{1}H NMR shows a single isomer about C1–2, and a *ca* 5:1 mixture isomers about C3–4: δ ($CDCl_3$) 0.18 and 0.22 (each s, 9 H, Me_3Si), 1.51 ^{E} and 1.58 ^{Z} (3 H, each d, *J* 7 Hz, MeCH=), 3.49 (s, 3 H, MeO), 3.88 (s, 1 H, HC=), 4.21 ^{E} and 4.87 ^{Z} (1 H, each q, *J* 7 Hz, MeCH=); IR (film): 1657, 1622 cm^{-1}; MS: *m/e* 274 (M^+, 4%), 259 (2), 245 (4), 170 (19), 73 (100).

Methyl 2-*hydroxy*-3,4,6-*trimethylbenzoate* (**12**) was prepared from **3**, **10** and $TiCl_4$ as described for **5**. After purification and recrystallization from hexane, **12** was obtained as colourless plates (70% yield), m.p. 68–68.5°; ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3 H, 4-Me), 2.21 (s, 3 H, 3-Me), 2.43 (s, 3 H, 6-Me), 3.87 (s, 3 H, CO_2Me), 6.42 (s, 1 H, Ar), 11.62 (s, 1 H, OH); IR ($CHCl_3$) 3100 br, 1660, 1616 cm^{-1}; MS *m/e* 194 (M^+, 61%), 162 (100), 134 (85).

Methyl 2-*hydroxy*-3-*methyl*-5,6,7,8-*tetrahydronaphthalene*-1-*carboxylate* (**14**) [from 2- (trimethylsilylmethylene)cyclohexanone, **10** and $TiCl_4$] was purified by elution with CCl_4 through a bed of Fluorisil and recrystallization from MeOH: colourless needles (58% yield), m.p. 59–60°; ^{1}H NMR ($CDCl_3$) δ 1.5–1.9 (m, 4 H, β-CH_2), 2.19 (s, 3 H, 3-Me), 2.5–3.1 (m, 4 H, α-CH_2), 3.93 (s, 3 H, CO_2Me), 6.98 (s, 1 H, Ar), 11.11 (s, 1 H, OH); IR ($CHCl_3$) 3100 br, 1662, 1618, 1590 cm^{-1}; MS *m/e* 220 (M^+, 51%), 188 (100), 160 (53). No isomeric products were observed. (Found: C, 70.73; H, 7.18. Calc. for $C_{13}H_{16}O_3$: C, 70.89, H, 7.32%).

Methyl 3-*hydroxy*-4-*methyl*-5,6,7,8-*tetrahydronaphthalene*-2-*carboxylate* (**13**) was prepared from trimethyl orthoformate, cyclohexanone trimethylsilyl enol ether, $TiCl_4$ and **10** as described previously for **6**. It was purified by column chromatography eluted with CH_2Cl_2 (41% yield), and had m.p. 59.5–60° (from methanol); R_f 0.63; ^{1}H NMR ($CDCl_3$): δ 1.6–2.0 (m, 4 H, β-CH_2), 2.09 (s, 3 H, 4-Me), 2.4–2.8 (m, 4 H, α-CH_2), 3.86 (s, 3 H, CO_2Me), 7.33 (s, 1 H, Ar), 10.77 (s, 1 H, OH); IR ($CHCl_3$) 3200 br, 1670, 1619 cm^{-1}; MS *m/e* 220 (M^+, 100%), 188 (94), 160 (74). No isomeric products were observed. (Found: C, 70.60; H, 7.33. Calc. for $C_{13}H_{16}O_3$: C,

70.89; H, 7.32%). The identify of this compound was confirmed by hydrolysis to the known acid: 3-hydroxy-3-methyl-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (98%), m.p. 238–238.5° (from MeOH) [lit.[7] 237–8°] ^{1}H NMR (1:1 $CDCl_3$–CD_3OD) δ 1.6–1.9 (m, 4 H, β-CH_2), 2.14 (s, 3 H, Me), 2.5–2.9 (m, 4 H, α-CH_2), 4.3 (brs, 2 H, OH), 7.43 (s, 1 H, Ar).

9,10-*Dihydrophenanthren-2-ol* (**16**). Compound **17**[2] (0.12 g, 0.5 mmol) was heated at 200° in N,N-dimethylaniline (5 ml)[8] under N_2 for 3 hr. Colourless crystals were deposited. The mixture was cooled, acidified with 5 M HCl and extracted with ether. The extracts were dried ($MgSO_4$) and evaporated to give colourless needles of 9,10-dihydrophenanthren-2-ol (0.09 g, 92%), m.p. 110–111° after one recrystallization from CCl_4 (lit.[9] 111.5–113°), ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 4 H, CH_2), 5.5 (brs, 1 H, OH), 6.66 (brs, 1 H, H-1), 6.72 (brd, 1 H, *J* 7 Hz, H-3), 7.0–7.3 (m, 3 H, H-6, 7, 8), 7.4–7.7 (m, 2 H, H-4, 5).

Methyl 2-methyl-3-trimethylsiloxypent-2-enoate. Methyl 2-methyl-3-oxopentanoate was prepared by the method of McElvain.[10] It was silylated directly by Danishefsky's method[4] to give methyl 2-methyl-3-trimethylsiloxypent-2-enoate (51.8 g, 48% overall), a colourless oil, b.p. 71–3° (0.7 mm); ^{1}H NMR ($CDCl_3$) (a 5:1 mixture of *E* and *Z* isomers) δ 0.25 (s, 9 H, Me_3Si), 1.10 (t, J 7.5 Hz, $\underline{Me}CH_2$), 1.77 ^{E} and 1.82 ^{Z} (3 H, each s, MeC=), 2.22 ^{Z} and 2.64 ^{E} (2 H, each q, *J* 7.5 Hz, $Me\underline{CH_2}$), 3.68 (s, 3 H, CO_2Me); IR (film) 1714, 1620 cm^{-1}; MS *m/e* 216 (M^+, 7%), 201 (21), 198 (26), 160 (17), 94 (81), 73 (100), 66 (89).

1,3-*Bis(trimethylsiloxy)-1-methoxy-2-methylpenta-1,3-diene* (**19**) was prepared from methyl 2-methyl-3-trimethylsiloxypent-2-enoate as described previously for compound **1**.[2] It was an orangish oil (84% yield), whose NMR showed a single isomer: δ ($CDCl_3$) 0.15 and 0.20 (each s, 9 H, Me_3Si), 1.57 (d, 3 H, $\underline{J}$ 7 Hz, MeCH=), 1.65 (s, 3 H MeC=), 3.53 (s, 3 H, MeO), 4.73 (q, 1 H, $\underline{J}$ 7 Hz, MeCH=); IR (film) 1667 cm^{-1}, MS *m/e* 288 (M^+, 9%), 273 (6), 259 (23), 184 (20), 73 (100).

Methyl 2,4-dimethyl-1-methoxy-3-oxo-1,2,3,5,6,7,8,8a-octohydronaphthalene-2-carboxylate (**20**) was prepared from trimethyl orthoformate, cyclohexanone trimethylsilyl enol ether, $TiCl_4$ and **19** as described previously for **6**. Purification by column chromatography eluted with CH_2Cl_2 gave **20** as a colourless oil (40%), R_f 0.54, ^{1}H NMR ($CDCl_3$) δ 1.0–2.6 (m, 8 H, CH_2), 1.19 (s, 3 H, Me), 1.73 (s, 3 H, MeC=), 2.7–3.0 (m, 1 H, H-8a), 3.32 (s, 3 H, MeO), 3.6–3.9 (m, 1 H, H-1), 3.70 (s, 3 H, CO_2Me); IR (film) 1745, 1664, 1618 cm^{-1}, UV (CH_3OH) 252.5 nm; MS *m/e* 266 (M^+, 1%), 234 (2), 175 (19), 136 (100); CI-MS (isobutane) 267 (MH^+, 100%), 235 (52), 136 (23).

Methyl 1,3-dimethyl-2-oxo-1,2,5,6,7,8-hexahydronaphthalene-1-carboxylate (**21**) was prepared from **19**, 2-(trimethylsiloxymethylene)cyclohexanone[2] and $TiCl_4$ as described previously for **7**. It was purified by column chromatography eluted with CH_2Cl_2, giving a colourless oil (40%), R_f 0.58, ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 3 H, Me), 1.5–1.8 (m, 4 H, β-CH_2), 1.90 (s, 3 H, MeC=), 2.0–2.4 (m, 4 H, α-CH_2), 3.68 (s, 3 H, CO_2Me), 6.66 (s, 1 H, HC=); IR (film) 1748, 1669, 1648, 1595 cm^{-1}; UV (CH_3OH) 326 nm; MS *m/e* 234 (M^+, 8%), 175 (100); CI-MS (isobutane) 235 (MH^+, 100), 203 (4), 175 (14).

1,3-*Dimethyl-5,6,7,8-tetrahydronaphthalen-2-ol* (**22**). Hydrolysis of either of the foregoing β-ketoesters (**20** or **21**) with hot NaOHaq causes decarboxylation and aromatization to give 1,3-dimethyl-5,6,7,8-tetrahydronaphthalen-2-ol (89% in each case), colourless needles from methanol, m.p. 97–8° (lit.[11] 97.5–98°), ^{1}H NMR ($CDCl_3$) δ 1.6–2.0 (m, 4 H, β-CH_2), 2.10 and 2.19 (each s, 3 H, Me), 2.4–2.8 (m, 4 H, α-CH_2), 4.4 (brs, 1 H, OH), 6.66 (s, 1 H, Ar).

Acknowledgement—We thank the NSERC of Canada and the Ministry of Education, Government of Quebec, for financial support of this research.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 393 to 397, 1981
Printed in Great Britain.

0040-4020/81/Suppl. 1-0393-05 $02.00/0
Pergamon Press Ltd.

SUBSTITUTION NUCLÉOPHILE AROMATIQUE RADICALAIRE.[1] NOUVELLE SYNTHÈSE DU SQUELETTE INDOLE

RENÉ BEUGELMANS* et GEORGES ROUSSI
Institut de Chimie des Substances Naturelles du C.N.R.S., 91190-Gif-sur-Yvette, France

(*Received in France* 17 *July* 1980)

Abstract—A new method is described, based on the $S_{RN}1$ reaction, which takes advantage of the regiospecific formation of an *ortho*-NH_2-functionalized aryl radical. In the presence of three different series of nucleophiles, (aliphatic ketone enolates, aldehyde enolates, cyclic and heterocyclic ketone enolates), some used for the first time in an $S_{RN}1$ reaction, the indole skeleton is obtained in one step in yields ranging from 20 to 85%. Ketone enolates give 2-substituted indoles while aldehyde enolates give 3-substituted indoles; cyclic enolates tricyclic indoles (**29** and **30**). This versatile indolization method (using non-acidic conditions) is thus of synthetic utility and considerably enlarges the scope of the $S_{RN}1$ reaction.

Bien qu'il existe de nombreuses méthodes de synthèse du squelette indole, certaines classiques,[2,3] d'autres plus particulières,[3] la recherche de nouvelles méthodes permettant en particulier d'opérer en milieu non acide demeure d'un intérêt permanent.[4a–c]

Nous rapportons ici une nouvelle méthode répondant à cette exigence, reposant sur la réaction de substitution nucléophile aromatique radicalaire $S_{RN}1$.[5a,b] Cette réaction, découverte par Bunnett et coll,[6a,b] résumée sur le schéma 1, est une réaction en chaîne initiée par transfert monoélectronique qui implique successivement un radical anion aryle (I), un radical aryle (II) qui est attaqué par le nucléophile Nu^- et enfin un second radical anion (III). Le principe de la méthode de synthèse rapportée ici repose sur la formation et l'utilisation d'intermédiaires (I') (II') et (III') portant une fonction amine primaire en *ortho* du groupe partant (Schéma 2). Ainsi, en une étape, et sans isolement des intermédiaires, le squelette indole est obtenu, et selon la nature de l'énolate (de cétone aliphatique, d'aldéhyde, de cétone cyclique ou hétérocyclique) utilisé comme nucléophile, les indoles ramifiés en 2, en 3 ou tricycliques sont obtenus.

RÉSULTATS

Synthèse d'indoles ramifiés en position 2

Les énolates de cétones aliphatiques sont les nucléophiles les plus fréquemment utilisés et la $S_{RN}1$ est, à ce titre, une méthode réputée d'arylation[7] ou d'hétéroarylation des cétones. Nous avons donc, dans un premier stade, employé les énolates **2** (R=CH_3), **3** (R = *i* Prop), **4** (R = *t* But) qui, opposés à l'o-iodo aniline **1**, permettent d'accéder au méthyl-2 indole **6**, à l'isopropyl-2 indole **7** et au *t*-Butyl-2 indole **8** en une seule étape, sans isoler l'arylamino cétone intermédiaire. Une cétone dissymétrique, telle que la méthyl éthyl cétone livre un mélange de deux énolates **5**″ et **5**′. Le mélange des deux indoles **9** et **10** qui en résulte reflète l'équilibre existant dans les conditions de la réaction, et la réactivité propre de chacune des entités vis-à-vis du substrat aromatique **1**. Il est possible de former de manière régiosélective les énolates, à basse température, dans les solvants aprotiques et en utilisant le diisopropylamidure de lithium, l'énolate cinétique **5** prédomine nettement sur **5**′ (énolate thermodynamique).[8] Or, il ne nous a pas été possible de contrôler la régiosélectivité de la réaction en opérant au sein de l'ammoniac liquide au moyen de l'amidure ou du *t*-butylate de lithium. Dans ces conditions, en effet, le rapport **9**/**10** reste du même ordre de grandeur qu'avec l'amidure ou le tertiobutylate de potassium, mais le rendement global ne dépasse pas 5%.

Cette réaction permet donc la construction du squelette indole à partir des énolates de cétone, et, compte tenu d'une part du contrôle de l'énolisation (non résolu actuellement dans les conditions expérimentales de la $S_{RN}1$) et des restrictions inhérentes à la $S_{RN}1$ elle-même[6b,c] elle est générale. Cette méthode présente, par rapport à la réaction de

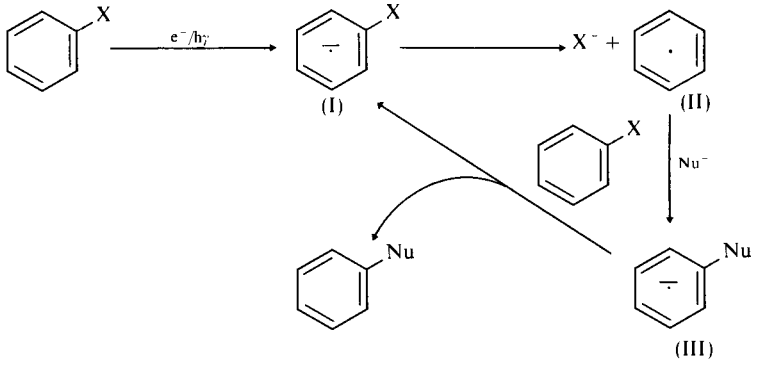
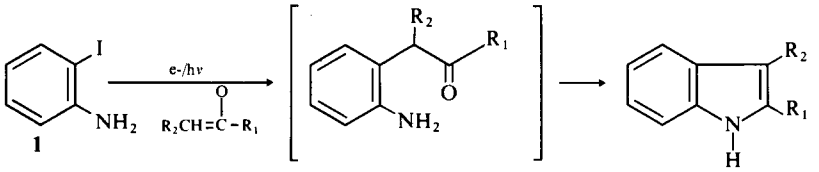
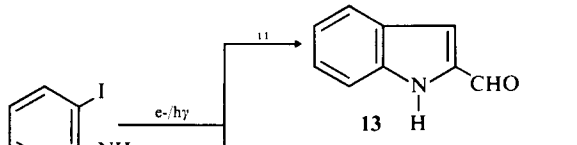


Schéma 1.



2 $R_1 = CH_3$; $R_2 = H$
3 R_1 = iProp; $R_2 = H$
4 R_1 = tBut; $R_2 = H$
5 $R_1 = CH_3-CH_2$; $R_2 = H$
5 $= CH_3-CH = C(O-)-CH_3$

6 $R_1 = CH_3$; $R_2 = H$
7 R_1 = iProp; $R_2 = H$
8 R_1 = tBut; $R_2 = H$
9 $R_1 = CH_2-CH_3$; $R_2 = H$
10 $R_1 = R_2 = CH_3$



11 = $CH_2=C(O^-)-CH(OCH_3)_2$

12 = $CH_2=C(O^-)-C(OCH_3)_2-CH_3$

Fischer qui est la plus classique réaction d'indolisation, l'avantage d'être effectuée en milieu non acide.

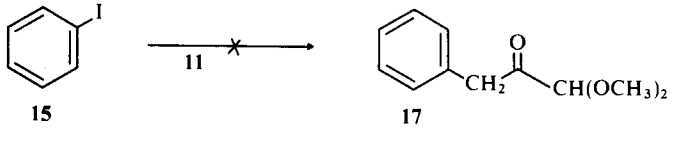
Ceci rend possible l'utilisation d'énolates *bifonctionnels* tels ceux issus de l'aldéhyde pyruvique et du biacétyl, dont la seconde fonction carbonyle est protégée sous forme de diméthyl acétal, stables dans les conditions basiques de la réaction. Ces énolates, traités dans les conditions standard par l'-iodo aniline **1** livrent les indoles correspondants **13** et **14** *fonctionnalisés en position* 2.

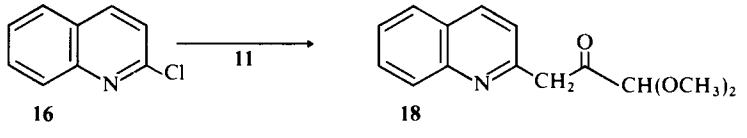
Ces énolates n'avaient jamais encore été employés dans la réaction $S_{RN}1$ et leur utilisation ne semble pas pouvoir être généralisée à tous les substrats aromatiques simples classiquement utilisés. En effet, après avoir obtenu les indoles **13** et **14**, il nous a semblé judicieux de traiter l'énolate **11** par des substrats aromatiques réputés pour leur réactivité dans la réaction $S_{RN}1$ telsque **15** et **16**.[6a,b]

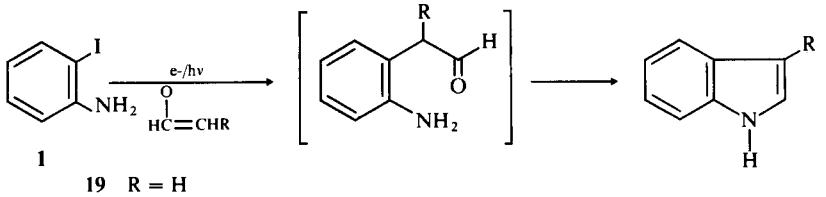
Or, si à partir de **16**, on obtient le produit de substitution **18** avec un excellent rendement, aucune réaction ne prend place avec **15**.[9]

Synthèse d'indoles ramifiés en 3

Les énolates de cétone **2**, **3**, **4**, **5**, **11** et **12** permettent d'obtenir sélectivement les indoles ramifiés en position

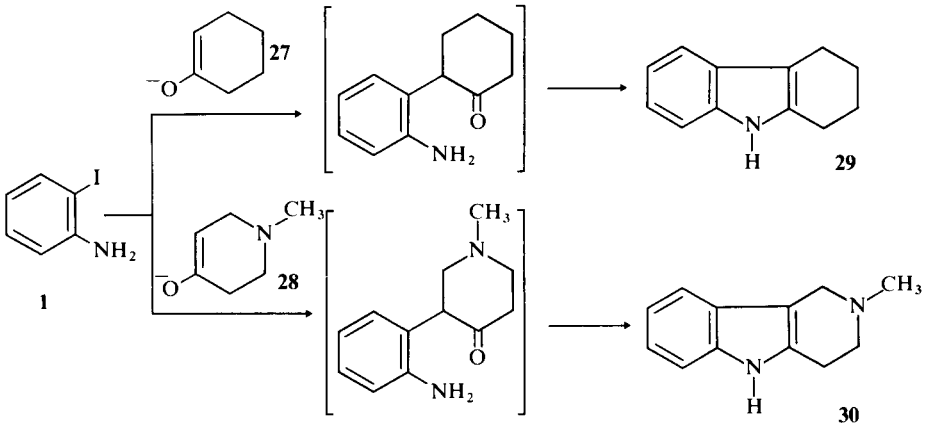






19 R = H
20 R = CH_3
21 R = CH_2-CH_3
22 R = $CH_2-CH-(CH_3)_2$

23 R = H
24 R = CH_3
25 R = CH_2-CH_3
26 R = $CH_2-CH(CH_3)_2$



2 (**6**, **7**, **8**, **9**, **13** et **14**). Nous avons découvert que les énolates d'aldéhyde permettent d'obtenir régiosélectivement les indoles substitués sur la position 3.

Les rendements en indoles ramifiés **23**, **24**, **25** et **26** sont, en règle générale, inférieurs à ceux des indoles ramifiés en position 2 obtenus grâce aux énolates de cétone. Des quantités relativement plus importantes d'aniline ($\simeq 60\,\%$) résultant de la réduction du radical aryle (II′) sont obtenues. Les énolates d'aldéhyde (ou l'aldéhyde non énolisé présent dans le milieu) s'avèrent être réducteurs vis-à-vis du radical aryle (II′) alors que les énolates de cétone ne le sont que très peu.

La même remarque que celle faite ci-dessus au sujet de l'emploi des énolates **11** et **12** peut être formulée au sujet des énolates d'aldéhyde lesquels sont signalés dans la littérature récente[10] comme n'étant pas utilisables en tant que nucléophiles dans la $S_{RN}1$. Bien que les détails de ce travail ne nous soient pas actuellement accessibles,[11] il y a tout lieu de penser que les observations de Rossi *et al.* concernent la réactivité de substrats aromatiques ne comportant pas de substituants en ortho.

Synthèse d'indoles tricycliques

Le groupe des indoles tricycliques est obtenu à l'aide de notre méthode en utilisant comme nucléophiles des énolates de cétones cycliques. Parmi ceux-ci, l'énolate de cyclohexanone **27**, classique dans la $S_{RN}1$, permet d'obtenir le tetrahydrocarbazole **29**, accompagné d'aniline résultant de la réduction du radical (II′).

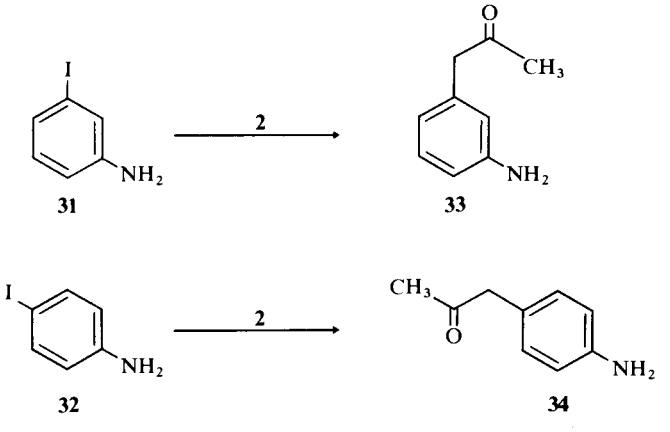
L'énolate hétérocyclique **28** permet d'accéder en une étape à la tétrahydrocarboline **30**.

DISCUSSION

La réaction de substitution nucléophile subie par le substrat aromatique fonctionnalisé **1** traité par les énolates de cétones et d'aldéhydes répond aux critères communément requis pour une $S_{RN}1$. La vitesse de la réaction entre **1** et l'énolate **2** (prise comme réaction-type) est ralentie par l'oxygène agissant comme piège à radicaux. En l'absence de photostimulation par la lumière ultra-violette, aucune réaction n'intervient, toutes choses étant égales par ailleurs. Une réaction passant par un intermédiaire arynique, également envisageable[6b] ne répondrait pas aux deux critères précédents, et de plus, ne serait pas régiospécifique. Or, nous avons confirmé la régiospécificité de la réaction en effectuant des expériences avec le même énolate **2** opposé cette fois à la meta iodo aniline **31** et à la p-iodo aniline **32**.

Dans chaque cas, un produit unique **33** et **34** respectivement est obtenu résultant de l'attaque régiospécifique du nucléophile sur le site réactionnel occupé par le groupe partant alors qu'une réaction impliquant un intermédiaire arynique aurait livré, à partir de **33**, le mélange (**6** + **33** et/ou **34**) et à partir de **32** la mélange (**33** + **34**).

La réaction subie par **1** se déroule bien selon un processus de transfert monoélectronique et implique les intermédiaires (I′), (II′) et (III′). La formation de quantités notables d'aniline peut se comprendre si l'on admet que les énolates d'aldéhyde sont moins bons nucléophiles, mais par contre meilleurs réducteurs que les énolates de cétones. Ils peuvent, compétitivement,



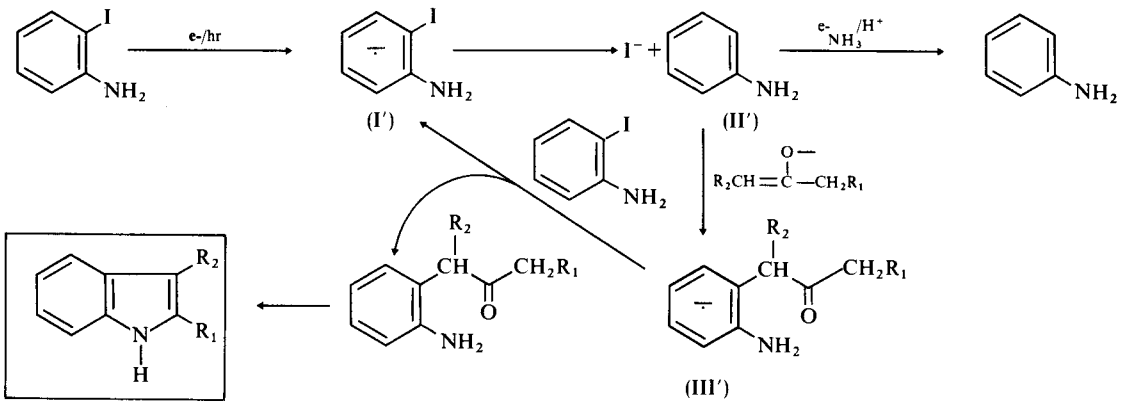


Schéma 2.

réduire le radical aryle (II′), et mener à l'aniline, ou subir l'attaque electrophile menant à (III′). Ceci peut expliquer *à la fois* les rendements moindres observés avec les énolates **19**, **20**, **21**, **22**, **28** et les importantes quantités d'aniline retrouvées.

D'autre part, nous avons constaté, au cours d'une expérience de contrôle effectuée avec la para iodo aniline **32** et l'énolate d'aldéhyde **19** que la réduction en aniline est la réaction prenant très majoritairement place, à l'exclusion de toute substitution en position para, ce qui contraste avec le comportement de **32** vis-à-vis de l'énolate de cétone **2**. Il est donc évident qu'un radical aryle ortho fonctionnalisé tel que II′ (Schéma 2) possède par rapport au radical aryle II (Schéma 1) une réactivité particulière vis-à-vis de certains nucléophiles. Pour l'instant, nous avons tiré parti de cette propriété pour des buts de synthèse, mais il est certain que la nature de ce phénomène doit être mieux comprise.

CONCLUSION

L'utilisation des radicaux aryles ortho fonctionnalisés par une fonction amine primaire, l'emploi en tant que nucléophiles d'un certain nombre d'énolates de cétones non encore utilisés, en particulier les énolates bi-fonctionnels **7** et **8**, la démonstration que les énolates d'aldéhyde sont utilisables ont permis de proposer une voie de synthèse nouvelle et d'un caractère général pour le squelette indole. De plus, le domaine d'utilisation de la $S_{RN}1$ se trouve notablement élargi; des travaux complémentaires sont en cours.

PARTIE EXPÉRIMENTALE

Les spectres de résonance magnétique nucléaire (RMN) ont été enregistrés en solution dans $CDCl_3$ (TMS: $\delta = 0$) sur un appareil Perkin–Elmer R 12 à 60 MHz. Les spectres infrarouge (IR) ont été enregistrés, en solution dans $CHCl_3$, sur un appareil Perkin–Elmer 297. Les spectres de masse ont

Tableau. Réaction photostimulée de l'ortho-iodo-aniline avec les énolates de potassium des dérivés carbonylés dans l'ammoniac liquide

Énolate	durée d'irradiation (mn)	Rendements (%) Aniline[a]	Indoles[b]		Point de Fusion Indoles	litt
2	16	0	**6**	83	59°	58–60°
3	10	traces	7	78	74°	74°[12]
4	20	0	**8**	53	73°	73°[13]
5[c]	25	10	**9**	20		Ref. 14
5′			**10**	40		Ref. 15
11	20	traces	**13**[d]	45	139°	140–142°[16]
12	25	traces	**14**[d]	55	149°	149°[17]
19	13	25	**23**	50		
20	20	40	**24**	49		
21	23	9	**25**	33	120°[e]	120°[18]
22	40	12	**26**	26	102°[e]	102–103°[18]
28	30	60	**29**	33		
28	10	22	**30**	22	166–168°	171°[19]

[a]Rendements déterminés par CPG, exprimés par rapport à l'o.iodo aniline.
[b]Rendements en produits isolés purs par chromatographie sur colonne de silice, exprimés par rapport à l'o.iodo-aniline.
[c]L'énolate de lithium préparé à partir de l'amidure de lithium ou du *t*-butylate de lithium n'a donné que des traces de **9** et **10** dans les mêmes proportions.
[d]**13** et **14** sont obtenus purs par hydrolyse, sur colonne de silice, des dimethylacétals correspondants.
[e]Point de fusion du picrate.

été obtenus au moyen d'un spectromètre AEI MS 50. L'analyse des produits par chromatographie en phase gazeuse (CPG) a été réalisée sur un appareil Girdel type 75, en utilisant une colonne OV1 (3 m, 8 %). Les points de fusion ont été mesurés sur un banc Kofler et ne sont pas corrigés. Les irradiations sont effectuées à l'aide d'une lampe à vapeur de mercure moyenne pression 100 W Hanau NK 6/20.

Mode opératoire général

L'énolate de potassium est préparé sous argon dans un tricol équipé d'un réfrigérant à CO_2 et d'un septum en caoutchouc, par action de 672 mg (6 mmols) de *t*-butylate de potassium fraîchement sublimé, sur 6 mmols de dérivé carbonylé, dans 50 ml d'ammoniac liquide séché par passage dans une colonne de potasse. Lo-iodo aniline commerciale, purifiée par chromatographie sur colonne, est ajoutée (220 mg, 1 mmol). Le mélange réactionnel fortement agité est irradié par une lampe de 100 W. L'avancement de la réaction est suivi par analyse chromatographique des prélèvements effectués à l'aide d'un siphon passé à travers le septum. Lorsque l'-iodo aniline a complètement réagi, le réfrigérant est retiré et $ClNH_4$ est ajouté au mélange. L'extraction au $CHCl_3$ et les traitements habituels se font après évaporation totale de l'ammoniac. La détermination du rendement en aniline se fait par CPG sur le mélange brut, avant séparation de l'indole sur colonne de silice (elution pentane:chloroforme 5–10 %).

Identification des produits

Les produits **6**, **14**, **23**, **24**, **29** ont été caractérisés par comparaison (CPG, RMN) à des échantillons authentiques. Les composés **7**, **8**, **13**, **14**, **26**, **30** ont été identifiés par leurs spectres (masse, IR, RMN) et par leur point de fusion identique à ceux décrits dans la littérature. Les indoles **9** et **10** ont été obtenus en mélange. Leur structure, ainsi que celle des composés **18**, **33** et **34**, a été déterminée par l'étude de leurs spectres (masse, IR, RMN).

Pyruvaldéhyde diméthyl acétal-2 quinoléine **18**

La 2-chloro quinoléine (0,163 g, 0,1 mmol) traitée par l'énolate **11** fournit après irradiation pendant 60 minutes et par les traitements habituels le produit **18** (0,199 g, 0.08 mmol) F: 82. R_f: 80 %. Spectre de masse *m/e* 245 (M^+, 68 %); 187 (50 %); 170 (100 %). IR (cm^{-1}): 3400, 1620 (énol); 1040 (éther). R.M.N. δ ppm 2,6 (s) 6 H; 4,8 (s) 1 H; 6,3 à 7,2 (m) 6 H. $C_{14}H_{15}O_2N$ Calc: C, 68,58; H, 6,12; O, 19,57; N 5,71. Tr: C, 68,43; H, 6,20; O, 19,32; N, 5,76 %.

Propanone-2 (aminophényl-3)-1 **33**

La m-iodo aniline (110 mg, 0,5 mmol) traitée par l'énolate de potassium de l'acétone dans les conditions habituelles, fournit, après 4 min d'irradiation et les traitements habituels 50 mg (0,3 mmol, 66 %) de **33**. Masse *m/e*: 149 (M^+), 106, IR ν_{NH_2} 3350–3500 cm^{-1}, $\nu_{C=O}$ 1650 cm^{-1}. RMN δ ppm 2,15 (s, 3 H), 3,4–4 (4 H), 6,5–7,6 (m, 4 H),

Propanone-2 (aminophényl-4)-1 **34**

La p-iodo aniline (220 mg, 1 mmol) conduit avec l'énolate de l'acétone, à 45 mg (0,3 mmol, 33 %) de **34**, se dégradant rapidement à l'air. Masse *m/e*: 149,083 (M^+ $C_9H_{11}NO$), 106,065 (C_7H_8N, 100 %). IR ν_{NH_2} 3350–3450 cm^{-1}, $\nu_{C=O}$ 1650 cm^{-1}. RMN δ ppm 2,10 (s, 3 H), 3,5 (s, 2 H), 3,5–3,8 (s, 2 H), 6,5–7,5 (m, 4 H).

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 399 to 403, 1981
Printed in Great Britain.

0040-4020/81/Suppl. 1-0399-05 $02.00/0
Pergamon Press Ltd.

PARTIAL SYNTHESIS OF CHLOROPHYLL-A FROM RHODOCHLORIN

KEVIN M. SMITH* and W. MICHAEL LEWIS
Department of Chemistry, University of California, Davis, CA 95616, U.S.A., and
The Robert Robinson Laboratories, University of Liverpool, Liverpool, England

(*Received in UK* 14 *July* 1980)

Abstract—A synthesis of chlorophyll-a from a relay degradation product, rhodochlorin dimethyl ester, is described. Key steps involve formation of methyl pheophorbide-a by thallium(III) promoted photocyclization of the corresponding chlorin-6-β-keto-ester, and magnesium(II) insertion using Eschenmoser's BHT method.

Twenty years ago, Woodward *et al.* described their remarkable approach[1] to the synthesis of chlorin-e_6 trimethyl ester and chlorophyll-a. This achievement contributed in no small way to the total body of inspired work for which the 1965 Nobel Prize for "*meritorious contributions in the art of organic synthesis*" was awarded.[2]

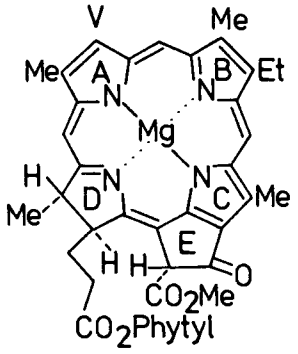
A key structural feature in the chlorophyll-a (**1**) molecule is the 5-membered carbocyclic ring ("E") which is formed biosynthetically from the 6-propionic side chain in protoporphyrin-IX (**2**). During the course of a study to investigate the possibility that a porphyrin-6-β-keto-ester magnesium(II) complex is a metabolic intermediate between **2** and **1**, we have achieved efficient syntheses of porphyrin-6-β-keto-esters[3] and have successfully cyclized these to pheoporphyrins using a novel thallium(III) promoted photo-reaction.[4] In the present paper we describe an application of this fundamental chemistry to the chlorin series, thereby establishing an efficient route from rhodochlorin dimethyl ester (**3**) to methyl pheophorbide-a (**4**). Furthermore, we also describe a method for transformation of methyl pheophorbide-a (**4**) into chlorophyll-a(**1**). Woodward's chlorophyll-a synthesis depended upon "well trodden paths"[1] for conversion of chlorin-e_6 ester (**5**) into chlorophyll-a, but though both the phytyl ester formation and magnesiation reactions are feasible,[5] no experimental details were available for the magnesiation of pheophytin. In our hands, magnesium insertion using Grignard reagents decomposed with alcohols leads to products which have suffered transesterification;[6] no doubt the Grignard reagent decomposed with phytol would have been effective in the synthesis of chlorophyll-a from pheophytin, but the recent introduction of Eschenmoser's "butylated hydroxy-toluene" method[7] has elegantly solved any real problems which might have existed.

For elaboration of the carbocyclic ring in the chlorin series we chose the chlorophyll-a degradation product, rhodochlorin dimethyl ester (**3**). This compound is readily available from natural pheophytin-a,[8] and is related to 2-vinylrhodoporphyrin-XV dimethyl ester (**6**) which lacks only the *trans*-hydrogens present in ring D of **3**. Since we have already achieved a total synthesis of 2-vinylrhodoporphyrin-XV dimethyl ester (**6**)[9] it was hoped that we might eventually achieve our own synthesis of chlorophyll-a if we could transform 2-vinylrhodoporphyrin-XV dimethyl ester into rhodochlorin dimethyl ester. So far, this "simple" addition of two hydrogens has eluded us, but this has not deterred us from completing the synthesis by transforming rhodochlorin into chlorophyll-a.

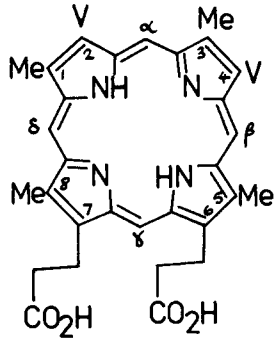
Treatment of rhodochlorin dimethyl ester (**3**) with methanolic potassium hydroxide effected hydrolysis of both esters, and gave rhodochlorin (**7**) which was partially esterified at the propionic side chain using 5% sulfuric acid in methanol, to give **8**. With N,N'-carbonyldi-imidazole, (**8**) gave the imidazolide (**9**) in 82% yield. This was treated with the magnesium salt (**10**) of methyl hydrogen malonate[10] and gave a 73% yield of the chlorin-β-keto-ester (**11**). Cyclization of the β-keto-ester to give methyl pheophorbide-a (**4**) was achieved in 46% yield by photolysis of the keto-ester after addition of about 2 mol equiv of thallium(III) trifluoroacetate[4] and the product, obtained as a thallium(III) chelate, was demetalated using sulfur dioxide and hydrochloric acid.[11] NMR spectroscopy showed that the cyclization had occurred to give the expected mixture of methyl pheophorbide-a and methyl pheophorbide-a' (the 10-epimer).[12]

The phytyl ester was introduced using a modification of a method developed by Willstätter and Stoll.[13] Synthetic methyl pheophorbide-a (**4**) was hydrolyzed to the free acid (**12**) by treatment with cold conc hydrochloric acid, and upon treatment with purified commercial phytol and phosgene, gave pheophytin-a (**13**) in an overall yield of 80%.

Magnesiation of pheophytin-a was accomplished using iodomagnesium(II) 2,6-di-t-butyl-4-methyl-phenoxide,[7] which avoids all problems such as transesterification and degradation of the carbocyclic ring which could be brought about by treatment of pheophytin-a with strong nucleophiles. In a trial reaction, natural methyl pheophorbide-a was treated with a freshly prepared solution of Eschenmoser's reagent[7] in dry methylene chloride/ether under an atmosphere of dry argon for 10 min at ambient temperature. This resulted in complete magnesiation (spectrophotometry) and methyl chlorophyllide-a (**14**)

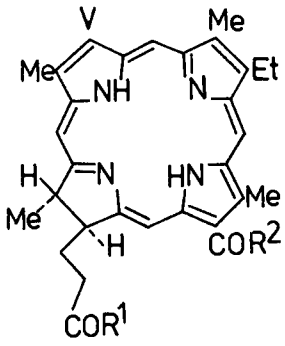


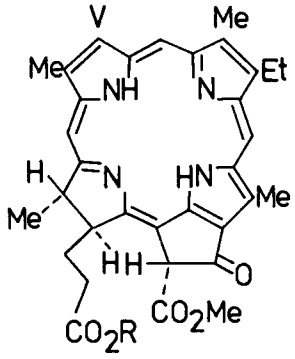
(1)



(2)

V = CH=CH2





(3) $R^1 = R^2 = OMe$

(7) $R^1 = R^2 = OH$

(8) $R^1 = OMe$; $R^2 = OH$

(9) $R^1 = OMe$; $R^2 =$

(4) R = Me

(12) R = H

(13) R = Phytyl

was obtained in 87% yield after purification. A similar reaction with synthetic pheophytin-a (**13**) gave synthetic chlorophyll-a (**1**) in 54% yield.

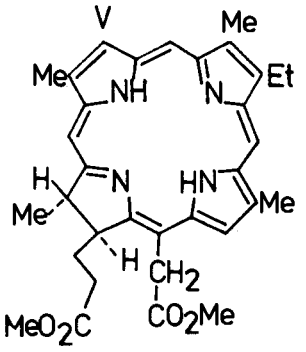
Attempts to reduce 2-vinylrhodoporphyrin dimethyl ester (**6**) to give rhodochlorin dimethyl ester (**3**) have so far been unsuccessful. Completion of a synthesis of chlorophyll-a would also require resolution and attachment of a sample of chiral phytol.

EXPERIMENTAL

M.ps were measured on a hot-stage apparatus, and are uncorrected. Neutral alumina (Fluka) was used for column chromatography, and reactions were monitored using glass microscope slides coated with Merck GF 254 silica gel. Electronic absorption spectra were measured on Unicam SP800 and SP8000 spectrophotometers with samples dissolved in CH_2Cl_2, and NMR spectra were recorded at 100 or 220 MHz using Varian XL100 or Perkin–Elmer R34 spectrometers; samples were dissolved in $CDCl_3$ with TMS as an internal standard. Mass spectra were determined using AEI MS 12 or MS 902 instruments (direct insertion probe, 70 eV, 50 μA, source temperature approx. 200°).

Rhodochlorin dimethyl ester (**3**)

Methyl pheophorbide-a (540 mg)[8] in freshly distilled pyridine (3 ml) was added to a 25% soln of KOH in dry MeOH (70 ml) and cooled to 0° in an ice-bath. The soln was saturated for 15 min with a stream of O_2 and the intense green soln was kept at 0° with stirring for 30 min. N_2 was then passed through the soln for 25 min, after which it was heated under reflux for another 10 min. The mixture was cooled rapidly, diluted with water (270 ml) and the green alkaline soln was acidified with 18% HCl aq in the presence of CH_2Cl_2 (400 ml) until pH 3. The organic phase was separated and the aqueous layer was further extracted with CH_2Cl_2 (3 × 100 ml) before evaporation of all the organic fractions to dryness (some residual water was azeotroped with toluene). The residue was dissolved in MeOH (50 ml) and treated with excess ethereal diazomethane for 15 min before evaporation to dryness. The residual black solid was chromatographed on alumina (Brockmann Grade III, elution with CH_2Cl_2) and the appropriate eluates were evaporated to dryness. Crystallization from CH_2Cl_2/MeOH gave the required diester as shiny blue crystals (340 mg; 69%), m.p. 206–208° (lit.[14] 207°). NMR, δ ppm, 9.80, 9.72, 9.58, 8.74 (each 1 H, s, 4 meso H); 8.12–7.97, 6.37–3.12 (1 H, m and 2 H, m, CH=CH_2); 4.50 (1 H, m, 8-H); 4.40–4.30 (1 H, m, 7-H); 4.36, 3.80, 3.64, 3.46, 3.28 (each 3 H, s, 5 × Me); 3.84–3.67, 1.72 (2 H, m, 3 H, t, CH_2CH_3); 2.82–2.30 (4 H, m, $C\underline{H}_2C\underline{H}_2CO_2Me$); 1.90 (3 H, d,



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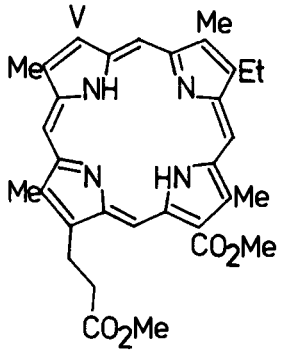

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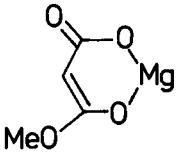

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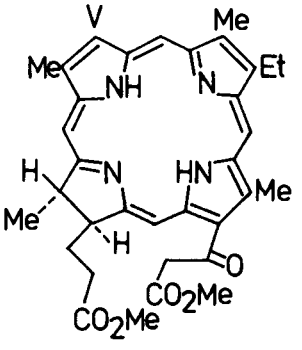

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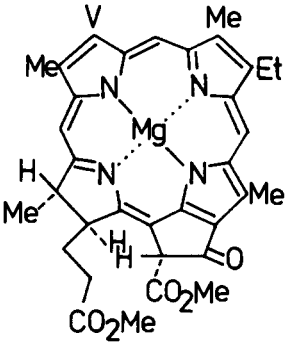

(14)

8-Me). MS, *m/e* (%), 566 (100), 551 (26), 535 (7), 503 (7), 479 (76), 449 (10), 420 (7), 405 (12). λ_{max} 399 (ε 86, 300), 496 (6700), 526 (2500), 558 (1200) and 664 nm (28,000).

6-*Imidazoylrhodochlorin methyl ester* (**8**)

Compound **3** (400 mg) in freshly distilled THF (20 ml) was treated with a 10% soln of KOH in dry MeOH (20 ml) and stirred at room temp for about 20 hr. Glacial AcOH (3 ml) was added dropwise until the soln was slightly acidic and the resulting black ppt was washed with water and dried *in vacuo*. The rhodochlorin (386 mg) was suspended in a 5% soln of conc HSO_4 in MeOH (150 ml) overnight with stirring before being poured into a stirred mixture of $CHCl_3$ (200 ml) and a 5% aqueous soln of 0.880 ammonia (300 ml). The organic phase was washed with water (2 × 200 ml), dried over Na_2SO_4, and evaporated. The residue was crystallized from THF/hexane to give black crystals (378 mg) which were dissolved in freshly distilled THF (100 ml) containing N,N'-carbonyldi-imidazole (410 mg) and then heated under reflux for 30 min. The soln was evaporated to about 50 ml and then applied to an alumina column (Brockmann Grade V; elution with CH_2Cl_2). The appropriate eluates were evaporated and the residue was crystallized from CH_2Cl_2/hexane to give **8** as blue-black needles (368 mg; 82%), m.p. 208–209°. (Found: C, 71.91; H, 6.35; N, 14.09. $C_{36}H_{38}N_6O_3$ requires: C, 71.74; H, 6.36; N, 13.95%). NMR, δ ppm, 9.63, 9.59, 9.57, 9.53 (each 1 H, s, 4 meso H); 8.20, 7.73, 7.22 (each 1 H, s, m, m, 3 imidazole H); 8.16–7.92, 6.32–5.97 (1 H, m, 2 H, m, $CH{=}CH_2$); 4.55–4.18 (2 H, m, 7- and 8-H); 3.70–3.60, 1.65 (2 H, m, 3 H, t, CH_2CH_3); 3.54, 3.49, 3.36, 3.19 (each 3 H, s, 4 × Me); 2.70–2.45 (4 H, m, $C\underline{H}_2C\underline{H}_2CO_2Me$), 1.80 (3 H, d, 8-Me). MS, *m/e* (%), 602 (100), 587 (5), 566 (9), 535 (47), 503 (9), 515 (14), 449 (20). λ_{max} 399 (ε 102,500), 496 (8800), 525 (3200), 554 (1500), 607 (4100) and 662 nm (37,800).

6-(*Methoxycarbonylacetyl*)-*rhodochlorin methyl ester* (**11**)

A soln of i-PrMgBr was prepared by refluxing under dry N_2 a mixture of Mg turnings (300 mg) and i-PrBr (1 g) in freshly distilled THF (30 ml). When the metal had dissolved the soln was cooled to 0° and redistilled methyl hydrogen malonate (750 mg) in dry THF (6 ml) was added. The mixture was warmed to 65° and stirred for 10 min before introduction of a soln of **8** (100 mg) in dry CH_2Cl_2 (30 ml). Stirring was maintained for 2.5 hr while heating under reflux, and glacial AcOH (3 ml) was added. Heating and stirring were continued for a further 15 min after which the mixture was diluted with $CHCl_3$ (300 ml), washed with 0.1 M HCl (300 ml) and water (2 × 300 ml), and then dried over $NaSO_2$ and evaporated to dryness. The residue was chromatographed on alumina (Brockmann Grade V; elution with 5% acetone in CH_2Cl_2) and after evaporation of the appropriate eluates the product was recrystallized from CH_2Cl_2/hexane to give the required chlorin-β-keto-ester as dark blue needles (74 mg; 73%), m.p. 149–151°. (Found: C, 70.92; H, 6.59; N, 9.27. $C_{36}H_{40}N_4O_5$

requires: C, 71.03; H, 6.62; N, 9.21%). NMR, δ ppm, 13.16 (1 H, s, enol-OH); 9.70 (2 H, m) 9.62 (1 H, s) 9.52 (2 H, m), 9.28 (1 H, s), 8.80 (1 H, s), 8.66 (1 H, s) (8 × meso H, i.e. 4 for keto and 4 for enol forms); 8.06–7.86, 6.21–5.94 (2 H, m, 5 H, m, 2 × CH=CH_2 and C$\underline{H}$=C(OH) in enol); 4.80–4.20 (4 H, m, 2 × 7 H and 2 × 8 H); 4.60, 3.96, 3.86, 3.66, 3.58, 3.44, 3.38, 3.27, 3.22, 3.20 (each 3 H, s, 10 × Me); 3.72–3.64, 1.78, 1.76 (4 H, m, 3 H, t, 3 H, t, 2 × CH_2CH_3); 2.94–2.26 (10 H, m, 2 × C$\underline{H}_2$C$\underline{H}_2$$CO_2$Me and COC$\underline{H}_2$$CO_2$Me); 1.88, 1.82 (each 3 H, d, 2 × 8-Me). MS, *m/e* (%), 608 (42), 591 (11), 530 (66), 488 (100), 473 (22), 443 (25), 401 (78). λ_{max} 399 (ε 164,400), 496 (12,800), 527 (3700), 558 (1200), 611 (4900), and 666 nm (59,600).

Methyl pheophorbide-a (**4**)

The foregoing **11** (100 mg) in dry CH_2Cl_2 (100 ml) was treated with a soln of freshly prepared thallium(III) trifluoroacetate[15] (240 mg; 2.05 mol equiv) in dry THF (25 ml). Using a quartz-iodine lamp, the soln was photolyzed for 2 hr before SO_2 was bubbled through the soln for 1 min and conc HCl (0.5 ml) was added. The mixture was then washed with water (100 ml), sat $NaHCO_3$ aq (100 ml), water again (2 × 100 ml) and then dried over $NaSO_4$. The soln was evaporated to dryness and the residue was chromatographed on alumina (Brockmann Grade III, elution with 2% acetone in CH_2Cl_2). The appropriate eluates were collected, evaporated to dryness, and the residue was crystallized from CH_2Cl_2/MeOH to give methyl pheophorbide-a as black shiny plates (58 mg; 59%), m.p. 220–225° (lit.[16] 229°, lit.[8] 224–226°). Mixed mp with authentic methyl pheophorbide-a, 220–225°. (Found: C, 71.11; H, 6.38; N, 9.10. $C_{36}H_{38}N_4O_5$ requires: C, 71.26; H, 6.31; N, 9.24%). NMR, δ ppm, 9.49, 9.35, 8.57 (each 1 H, s, 3 meso H, each peak having a small resonance to higher field for the a′ compound); 8.05–7.91, 6.34–6.16 (1 H, m, 2 H, m, CH=CH_2); 6.28, 4.51, 4.25 (1 H, s, 1 H, m, 1 H, m, 10-H, 8-H and 7-H); 3.91, 3.71, 3.61, 3.41, 3.22 (each 3 H, s, 5 × Me); 3.75–3.60, 1.69 (2 H, m, 3 H, t, CH_2CH_3); 2.40–2.20 (4 H, m, C$\underline{H}_2$C$\underline{H}_2$$CO_2$Me); 1.83 (3 H, d, 8-Me). MS, *m/e* (%), 606 (100), 574 (34), 548 (96), 487 (8), 459 (26). λ_{max} 411 (ε 116,500), 506 (9300), 535 (8400), 558 (3700), 606 (7500), 666 nm (39,600).

Pheophytin-a (**13**). Methyl pheophorbide-a (100 mg) in cold conc HCl (20 ml) was stirred for 30 min before addition of ether (100 ml) and dilution with water until no more color remained in the aqueous layer. The etheral soln was washed with water (5 × 100 ml), dried over Na_2SO_4, and then evaporated to give pheophorbide-a (80 mg) which was dissolved in freshly distilled pyridine (3 ml). Distilled phytol (125 mg) was added and the soln was cooled to 0° before bubbling in a gentle stream of dry phosgene gas for about 10 min with stirring, until the soln became a solid greenish-white mass. The mixture was left in a closed vessel for 3 hr with cooling in ice, and was then cooled to −10° in an ice/salt bath. To this now completely solid mass was added, with care, a 0.5% HCl aq soln, until the violent reaction subsided. The temp was kept at 0° throughout, and as excess HCl was added the phytyl ester precipitated as greasy lumps which were filtered, washed thoroughly with water, and dried in a desiccator. The crude pheophytin-a was dissolved in CH_2Cl_2 (40 ml), washed with a 1% HCl aq soln (3 × 40 ml), and then dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on alumina (Brockmann Grade V, elution with CH_2Cl_2), the appropriate eluates being collected, evaporated to dryness, and the residue being crystallized from CH_2Cl_2/hexane to give pheophytin-a (116 mg; 80%), m.p. 178–181° (lit.[17] 178–180°). A mixed mp with authentic pheophytin had mp 175–180°. (Found: C, 76.14; H, 8.64; N, 6.67. $C_{55}H_{74}N_4O_5$ requires: C, 75.86; H, 8.51; 6.44%). NMR, δ ppm, 9.45, 9.31, 8.56 (each 1 H, s, 3 meso-H); 8.10–7.80, 6.24–6.10 (1 H, m, 2 H, m, CH=CH_2); 6.30 (2 H, m, 19 CH of phytyl and 10-H); 5.25–5.10 (1 H, m, 8-H); 4.55–4.40 (2 H, m, 2-OCH_2 of phytyl); 4.30–4.18 (1 H, m, 7-H); 3.88, 3.67, 3.37, 3.16 (each 3 H, s, 4 × Me); 3.74–3.54, 1.66 (2 H, m, 3 H, t, CH_2CH_3); 2.60–2.10 (4 H, m, C$\underline{H}_2$C$\underline{H}_2$$CO_2$Phy); 1.80 (3 H, d, 8-Me); 1.57 (3 H, s, 18-Me of phytyl); 1.40–0.90 (18 H, m, phytyl CH_2's). MS, *m/e* (%), 870 (11), 856 (9), 855 (7), 854 (10), 575 (10), 278 (100). λ_{max} 410 (ε 121,000), 471 (5800), 504 (12,300), 533 (8800), 555 (3900), 603 (7300), and 659 nm (48,300).

Chlorophyll-a (1)

(a) 0.87 *M Ethyl magnesium iodide*. Washed dry Mg turnings (250 mg) in a 50 ml 2-necked flask containing dry ether (7 ml) and a crystal of I_2 was flushed with dry N_2 and a soln of freshly distilled EtI (1.6 g) in dry ether (7 ml) was added slowly until the reaction was initiated, and then steadily to keep the mixture at reflux temp. When all of the EtI was added the mixture was heated under reflux for 30 min.

(b) 0.2 *M Iodomagnesium(II) 2,6-t-butyl-4-methylphenoxide*.[7] 2,6-t-Butyl-4-methylphenol (2.34 g) in dry CH_2Cl_2 (40 ml) in a 3-necked flask protected from light (Al foil) was treated, through a rubber septum, with freshly prepared 0.87 M EtMgI (12 ml) carefully over a period of about 15 sec. The clear and colorless soln was stirred for 10 min and then used immediately.

(c) *Magnesium insertion*. A soln of pheophytin-a (73 mg) in dry CH_2Cl_2/ether (86:14, 5 ml) was added to 10 ml of the soln prepared in (b), and the mixture was stirred at room temp under an atmosphere of argon for 10 min. The mixture was poured into pH 4.5 phosphate buffer M/15 aqueous soln of NaH_2PO_4 (200 ml) and ether (200 ml); the ether layer was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was dissolved in the minimum volume of CH_2Cl_2 and chromatographed on alumina (Brockmann Grade V, elution with CH_2Cl_2). The first greyish-blue band collected was unreacted pheophytin-a, but the second, slower-running, bright-green band was chlorophyll-a. Evaporation of the eluates gave a dark green shiny solid (35 mg; 54%) which proved very difficult to crystallize from CH_2Cl_2/hexane, only 2.5 mg of dark green microcrystals being isolated, m.p. 118–120° (lit.[18] 117–120°). A mixed m.p. with authentic chlorophyll-a had m.p. 117–120°. NMR, δ ppm, 9.56, 9.33, 8.35 (each 1 H, s, 3 meso-H); 8.10–7.80 (1 H, m, C$\underline{H}$=CH_2); 6.32–5.89 (4 H, m, 19-CH of phytyl, 10-H, and CH=C$\underline{H}_2$), 3.10–3.50 (1 H, m, 8-H); 4.65–4.60 (2 H, m, 20-CH_2 of phytyl); 4.40–4.30 (1 H, m, 7-H); 3.66, 3.47, 3.27, 3.15 (each 3 H, s, 4 × Me); 3.80–3.50, 1.59 (2 H, m, 3 H, t, CH_2CH_3); 2.41–2.15 (4 H, m, C$\underline{H}_2$C$\underline{H}_2$$CO_2$Phy); 1.70 (3 H, d, 8-Me); 1.56 (3 H, s, 18-Me of phytyl); 1.40–0.90 (18 H, m, CH_2's of phytyl). λ_{max} 406 (ε 120,500), 426 (86,200), 497 (4600), 526 (4400), 569 (6300), 608 (14,800) and 656 nm (88,000).

Acknowledgements—We thank the National Science Foundation (CHE-78-25557) for partial support of this research. Helpful discussions with the late Professor G. W. Kenner, F.R.S., are also gratefully acknowledged.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 405 to 409, 1981
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0040-4020/81/Suppl. 1-0405-05 $02.00/0
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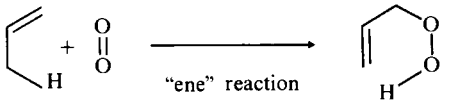
CHARACTERIZATION OF THE HYDROPEROXIDES DERIVED FROM SINGLET OXYGEN OXIDATION OF (+)-LIMONENE

B. C. CLARK, JR., B. B. JONES and G. A. IACOBUCCI*
Corporate Research and Development Department, The Coca-Cola Company, Atlanta, GA 30301, U.S.A.

(*Received in USA* 31 *July* 1980)

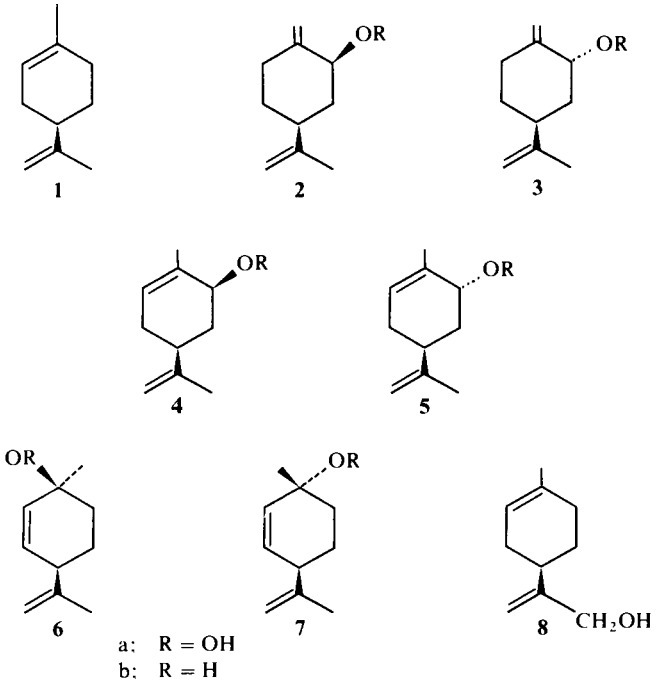
Abstract—Six hydroperoxides (**2a**–**7a**) have been identified as the primary reaction products of the singlet oxygen oxidation of (+)-limonene. The products were isolated by semi-preparative hplc and characterized by NMR, IR, glc pyrolysis, and reduction to known alcohols.

(+)-Limonene (**1**) has been employed in several of the pioneering studies concerning the reaction of singlet oxygen ($^1O_2$) with olefins.[1–3] It has also been used to test for the presence of $^1O_2$.[4] The postulated primary reaction products of limonene $^1O_2$ oxidation, hydroperoxides **2a**–**7a**, are formed by the well known "ene" reaction,[5] the 1,3-addition of $^1O_2$ at the endocyclic, most highly substituted double bond. They have never been separated and characterized; rather, their structures have been inferred from the reduction products (**2b**–**7b**).



A previous report of a partial resolution of limonene hydroperoxides performed by tlc[6] appeared to hold little promise for their complete separation and subsequent characterization. Recent studies have demonstrated the power of high performance liquid chromatography (hplc) in the separation of lipid[7,8] and cholesterol[9] hydroperoxides. By modifying the hplc procedures developed for the separation of terpene alcohols,[10] we have resolved the limonene $^1O_2$ hydroperoxides on a semipreparative scale and have characterized them fully.

Limonene hydroperoxides were prepared in methanol by $^1O_2$ oxidation, using a modification of published procedures.[1,11] The composition of the reaction mixture was determined by glc after reduction with aqueous sodium bisulfite to alcohols **2b**–**7b** and **8**. The weight percent of each alcohol and unreacted limonene, corrected for glc detector response, is given in Table I along with the area percent of each alcohol. The area percents agree very well with previously reported data[1,2,11] for alcohols **2b**–**7b**. (Absolute weight percents are reported here for the first time.) The alcohols **2b**–**7b** were identified by IR and MS comparison either to spectra of authentic samples or known spectra.



Alcohol **8**, previously unreported from the $^1O_2$ oxidation of limonene, was found present in 0.3% weight percent. It was identified by comparison of the IR to a published spectrum,[12] and the MS to a MS of authentic material.[13] Alcohol **8** is present in nature as a minor constituent in a variety of essential oils[13] and in tangerine essence.[14] The unisolated precursor hydroperoxide of compound **8** should result from attack of $^1O_2$ on the exocyclic, least substituted double bond of limonene, unlike all the previously found products.

The crude photolysate was purified on a silica gel (Activity III) column to yield the hydroperoxides. Previously reported IR absorptions of free OOH in some representative hydroperoxides occurred over the range of 3512–3555 cm^{-1}, while absorptions of the free OH in corresponding alcohols were observed at 3613–3632 cm^{-1}.[15] An IR of the above purified hydroperoxide fraction shows a strong free hydroperoxide absorption at 3550 cm^{-1}, a trace of alcohol at 3610 cm^{-1} and no carbonyl. The alcohol and hydroperoxide bands are sharp and well resolved.

The six individual hydroperoxides (**2a–7a**) were isolated by semipreparative hplc, and they were best separated using both a 10 μm and a 5 μm silica gel column in tandem. They were first separated with ethyl acetate: toluene (0.5:99.5, v/v) into five fractions, with peak identifications as shown in Fig. 1a. The unisolated hydroperoxide precursor to alcohol **8**, which would be present in *ca* 0.5%, co-eluted with compound **6a**. The fraction containing **3a** and **5a** was then resolved by rechromatography employing 100% methylene chloride. (A chromatogram of the six hydroperoxides using 100% methylene chloride is shown in Fig. 1b.) Each compound could be prepared in greater than 95% purity. In order to calculate the area percents for the individual hydroperoxides shown in Table 1, a third run using ethyl acetate:hexane (4:96, v/v) was also necessary. The hplc area percents of the hydroperoxides correspond very well with the glc area percents of the reduction products, alcohols **2b–7b**, This supports the previously postulated, direct qualitative and quantitative correspondence of a particular alcohol to its hydroperoxide precursor.

The structures of the purified hydroperoxides were confirmed mainly by IR and 60 MHz NMR analysis. In addition, some stereochemical assignments were secured by reduction of selected hplc fractions and glc pyrolysis. The IR spectrum of each individual hydroperoxide in carbon tetrachloride exhibits a strong free OOH band at 3550 cm^{-1}. Additionally, two terminal double bonds are confirmed for both **2a** and **3a**, by adsorptions at 3085, 1648, and a doublet at *ca* 890 and 905 cm^{-1}. Both a terminal double bond at *ca* 3080, 1645 and 890 and an endocyclic double bond at *ca* 3030 and 1680 cm^{-1} are observed for **4a–7a**.

The NMR spectrum of hydroperoxide **2a** shows a narrow 3-proton multiplet at

$$\delta\ 1.73 (C{=}C(CH_3)),$$

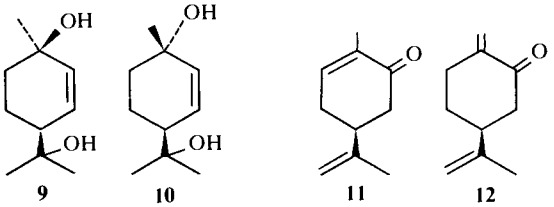
a broad 1-proton triplet with additional splitting at 4.46 (J = 10 Hz, H–C–OO–), a narrow 2-proton multiplet at 4.73 (isopropenyl $C = C\begin{smallmatrix}/H\\ \backslash H\end{smallmatrix}$), two one-proton multiplets at 4.78 and 4.90 (exocyclic $C = C\begin{smallmatrix}/H\\ \backslash H\end{smallmatrix}$), and a narrow 1-proton multiplet at 7.90 (OOH). As would be expected, the NMR of *trans*-isomer **3a** exhibits very similar resonances with two exceptions: (1) the 1-proton triplet at 4.46 (H–C–OO–) has a J = 3 Hz, and (2) the 2-proton exocyclic vinylic resonance at 4.98 shows a narrow multiplet indicating almost equivalent protons. These results confirm the stereochemical assignments for **2a** and **3a**, since inspection of models shows that for *cis*-isomer **2a**, the proton α to OOH is axial and split by an axial vicinal proton (180° dihedral angle), giving a large coupling (J = 10 Hz); for *trans*-isomer **3a**, the equatorial proton α to OOH has a gauche butane type interaction with both vicinal protons yielding a much smaller coupling (J = 3 Hz). The models further indicate a severe interaction between one of the exocyclic vinylic protons and the OOH function in *cis*-**2a**, thus, the 1-proton multiplets at 4.78 and 4.90. No such interaction is present in *trans*-**3a**.

The NMR spectrum of *trans*-hydroperoxide **5a** shows a narrow 6-proton multiplet at

$$\delta\ 1.76 (2 \times C{=}C(CH_3)),$$

a broad 1-proton multiplet at 4.23 (H–C–OO–), a narrow 2-proton multiplet at 4.71 ($C{=}C\begin{smallmatrix}/H\\ \backslash H\end{smallmatrix}$), a broad 1-proton multiplet at 5.68 ($\begin{smallmatrix}H\\ >\end{smallmatrix}C{=}C\begin{smallmatrix}/\\ \backslash\end{smallmatrix}$), and a broad 1-proton multiplet at 7.66 (OOH). The *cis*-isomer (**4a**) exhibits a very similar pattern; therefore, the stereochemistry for this pair (**4a**, **5a**) was determined by reduction and glc pyrolysis.

The *trans*-hydroperoxide (**6a**) exhibited a 3-proton singlet at δ 1.26 (CH_3–C–OO–), a narrow 3-proton multiplet at 1.70 (CH_3–C=C–), a broad 1-proton multiplet at 2.56 (H), a narrow 2-proton multiplet at 4.72 ($C{=}C\begin{smallmatrix}/H\\ \backslash H\end{smallmatrix}$), a 2-proton AB quartet at 5.46 and 5.75 (J = 11 Hz) with additional splitting ($\begin{smallmatrix}H\\ >\end{smallmatrix}C{=}C\begin{smallmatrix}<\\ H\end{smallmatrix}$), and a narrow 1-proton multiplet at 6.98 which exchanges with D_2O (OOH). The NMR of *cis*-isomer **7a** shows similar features except for the vinylic protons. The endocyclic vinylic protons ($\begin{smallmatrix}H\\ >\end{smallmatrix}C{=}C\begin{smallmatrix}<\\ H\end{smallmatrix}$) exhibit a broad 2-proton singlet at 5.70. This is consistent with the stereochemistry assigned to **6a** and **7a**, since the NMR of diols **9** and **10** shows a quartet for the vinylic protons of *trans*-isomer **9** and a singlet for those of *cis*-isomer **10**.[16]



9 **10** **11** **12**

Table 1. Composition of selected reaction mixtures

Compound number	REDUCTION PRODUCTS Weight %† - alcohols and unreacted limonene	Area %* alcohols	HYDROPEROXIDES Area %* HPLC	Area %* GLC pyrolysis
1	21			
2	14	21.1	19.8	9.9
3	12	18.1	20.0	10.9
4	3	4.5	5.7	1.2
5	6	9.1	10.7	4.1
6	25	37.7	34.9	31.5
7	6	9.1	8.9	9.0
8	0.3	0.5		
11				13.6
12				19.8

† Employing Tetradecane as internal standard and correcting for response.

* (Area of peak of interest/Total area of peaks of interest) x 100.

Lier[17] and Teng[18] observed that the attempted separation of cholesterol hydroperoxides by glc led to a complex but reproducible mixture of alcohols and carbonyls. An analytical glc determination on our limonene hydroperoxide mixture also yielded, by pyrolysis, alcohols **2b**–**7b** and ketones **11** and **12** in addition to several unidentified products, with no remaining hydroperoxides. Table 1 shows the expected correspondence between the area percents of the alcohols and their hydroperoxide precursors. The glc results for the major pyrolysis products of the individually purified hydroperoxides are given in Table 2. Each of the secondary hydroperoxides (**2a**–**5a**) yields a ketone and the specific alcohol in high yield (Table 2), confirming the assigned stereochemistry. The pyrolysis[19] of **2a** can be pictured as involving homolytic cleavage to yield ·OH followed by both a β-scission of the resulting alkoxy radical to yield ketone **12**, and a transformation of the alkoxy radical by a multistep chain mechanism to alcohol **2b**. For each tertiary hydroperoxide (**6a**–**7a**), the related alcohol predominates in the complex mixture of pyrolysis products.

Table 2. GLC pyrolysis of individual limonene hydroperoxides

Starting compound	Product (Area %)†
2a	2b (15) + 12 (69)
3a	3b (20) + 12 (56)
4a	4b (8) + 11 (68)
5a	5b (17) + 11 (73)
6a	6b (55)
7a	7b (54)

† (Area of peak of interest/Total area of all peaks) x 100.

The proposed structure of ketone **12** is compatible with its MS which exhibits a molecular ion at m/z 150, and also a peak at 108 which is similar in intensity to that in the MS of carvone for loss of ketene. The structure was confirmed by LAH reduction of **12** to alcohol **2b**. Ketone **12** was prepared by glc pyrolysis of a mixture of **2a** and **3a**; the yield was dependent upon concentration, sample size, and instrument conditions. If samples of greater than *ca* 1 μl in size and 5000 ppm in concentration were used, the yield of ketone was drastically lowered relative to alcohols **2b** and **3b**. In spite of these difficulties a few μg of **12** were collected.

To further confirm the stereochemistry of hydroperoxides **4a** and **5a**, the individual peaks from the methylene chloride hplc separation (Fig. 1b) were reduced with aqueous sodium bisulfite. The first peak, which contained hydroperoxides **2a**, **3a** and **4a**, yielded only alcohols **2b**, **3b** and **4b**. The second one, which contained only hydroperoxide **5a**, gave alcohol **5b** exclusively. The third and fourth peaks yielded alcohols **6b** and **7b**, respectively, as expected.

EXPERIMENTAL

Analyses by glc were performed on a PE-900 or Varian-3700 equipped with an on-column injector, an FID detector, and a 12 ft, $\frac{1}{8}$ in. i.d. glass column packed with 5% Triton X-305 on Chromosorb W.H.P. 80–100 mesh. The oven temp was generally programmed from 70° to 170° at 5°/min with 5 min initial hold. The injector and detector were maintained at 150° and 250°, respectively. A flow rate of 35 ml/min of helium was employed. Compounds isolated by glc were collected in glass capillaries from an F & M 810 equipped with a TC detector and a $\frac{1}{4}$ in. glass column packed and used as above.

The hplc system was a Waters Model ALC/GPC 201 which included a M-6000 pumping system, a M-U6K universal injector, and a M-R 401 differential refractometer. The columns were Whatman Partisil-PXS consisting of 25 cm × 4.5 mm I.D. stainless steel tubing packed with 10 or 5 μm microparticulate silica. The columns were used in tandem. A description of the hplc conditions adopted in this work is being reported elsewhere in greater detail. IR spectra were determined using a PE-281; NMR, a Varian T-60; and GC–MS, a HP-5993 or Hitachi-RMU-6L.

Singlet oxygen oxidation of limonene. The photolysis apparatus consisted of a cylindrical, one-necked flask equipped with a very efficient magnetic stirrer and a water cooled condenser. O_2 was introduced into the bottom of the vessel with a $\frac{1}{16}$ in. teflon tube at a rate of 6.7 ml/min. A 200 W clear tungsten light was employed with the bulb positioned about 5 in. from the flask and slightly above it so that it could be aimed into the mixture at a 45° angle. The lamp was shaded with Al foil and foil was placed under the vessel. The apparatus was placed in a hood and a combination of air and condenser cooling maintained the reaction at about 25°.

(+)-Limonene (98.5% from distilled, cold pressed orange oil) was further purified by percolation through a column of basic alumina (Activity I) to yield material of 99.8% purity by glc. Rose bengal (0.26 g, 2.5×10^{-4} mole) was dissolved in MeOH (200 ml; dried over molecular sieves), and limonene (13.6 g, 0.1 mole) was added with the aid of MeOH (60 ml). The mixture was periodically sampled, extracted, and analyzed by glc using a tetradecane internal standard. When only 20% of the original limonene remained (48 hr), the mixture was concentrated to 50 ml. The concentrate was taken up in ether (175 ml), washed with water (1 × 50, 1 × 30 ml) and sat NaCl aq (1 × 30 ml), and concentrated to yield crude hydroperoxide (17.1 g) containing a small amount of solvent. Chromatography on SiO_2 (Activity III) consisted of elution, first, of limonene with hexane, followed by elution of the pure hydroperoxide mixture with CH_2Cl_2.

Reduction of hydroperoxide mixture. In a separate reaction, the above described hydroperoxide:methanol mixture was concentrated to 50 ml. Na_2SO_3 (25 g, 0.2 mole) in water (150 ml) was added dropwise to the above mixture, with ice cooling and stirring. After one-half of the Na_2SO_3 had been added, a thick ppt formed and stirring was then facilitated by removal of the ice bath. The mixture was stirred overnight at r.t., heated 2.5 hr at 70°, cooled, water (50 ml) added to dissolve the ppt, and extracted with ether (3 × 100 ml). The combined ethereal soln was washed with water (40 ml) and sat $NaHCO_3$ aq (40 ml), dried over Na_2SO_4, and concentrated to yield 12.2 g (65.5% absolute yield of alcohols from limonene by glc, using an internal standard and correcting for unreacted limonene). The weight % of each component is given in Table 1.

Preparative hplc separation of hydroperoxides. The hydroperoxides were separated into 5 fractions using EtOAc:toluene (0.5:99.5, v/v) with *ca* 10 μl injections. Toluene was removed by rotary evaporation at 28°, full aspirator vacuum, to a volume of 0.5 ml in order to avoid decomposition of the hydroperoxides. Rechromatography (twice) of the sample of interest with CH_2Cl_2 resulted in removal of interfering toluene.

Reduction of hydroperoxide fractions. Fractions (2–4 mg) were collected for each peak using the CH_2Cl_2, hplc separation (Fig. 1b). The fractions were concentrated at 25°, aspirator vacuum, to 0.25 ml with no change by glc. MeOH (0.5 ml) was added to each fraction and most of the remaining CH_2Cl_2 removed as above. Each fraction was transferred, with the aid of MeOH (1 ml), to a flask and Na_2SO_3 (1.5 ml of 1.19 × 10^{-3} M) soln added. The mixture was periodically shaken 4 hr at r.t., heated 25 hr at 75°, cooled, extracted with CH_2Cl_2 (2 × 3 ml), washed with water (2 ml) and concentrated.

cis-2-*Methylene*-5-(1-*methylethenyl*)-*cyclohexyl hydroperoxide* (**2a**). IR (CCl_4), ν_{max} 3550 (free OOH), 3085 and 1648 ($C{=}C\begin{smallmatrix}H\\H\end{smallmatrix}$), 1440 and 1455 (d), 1320 and 1340 (d), 1010, 892 and 905 ($C{=}C\begin{smallmatrix}H\\H\end{smallmatrix}$) cm^{-1}. NMR (CCl_4), δ 1.73 (3 H, n, m), 4.46 (1 H, br, t with additional splitting, J = 10 Hz), 4.73 (2 H, n, m), 4.78 (1 H, br, m), 4.90 (1 H, br, m) 7.90 (1 H, m, m).

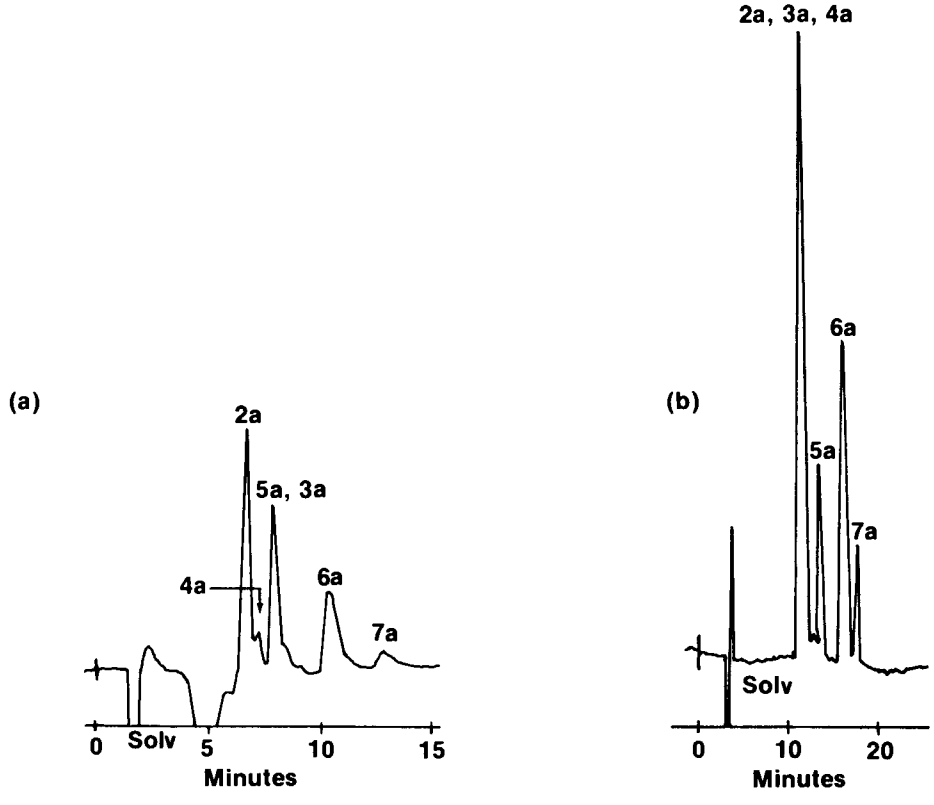


Fig. 1. Hydroperoxide separations on Partisil 10 + 5. (a) 0.5% ethyl acetate: 99.5% toluene (10 μl), (b) 100% methylene chloride (5 μl).

trans-2-*Methylene*-5-(1-*methylethenyl*)-*cyclohexyl hydroperoxide* (**3a**). IR (CCl_4), ν_{max} 3450 (free –OOH), 3440 (H bonded OOH), 3088 and 1648 ($C{=}C\langle^{H}_{H}$), 1440 and 1452 (d), 1300 and 1360 (d), 1075, 965, 885 and 905 ($C{=}C\langle^{H}_{H}$). NMR (CCl_4), δ 1.73 (3 H, n, m), 4.46 (1 H, t with additional splitting, J = 3 Hz), 4.73 (2 H, n, m), 4.98 (2 H, n, m), 7.45 (1 H, br, m).

cis-2-*Methyl*-5-(1-*methylethenyl*)-2-*cyclohexen*-1-*yl hydroperoxide* (**4a**). IR (CCl_4), ν_{max} 3550 (free –OOH), 3080 ($C{=}C\langle^{H}_{H}$), 3040 and 1672 ($^{H}\rangle C{=}C\langle$), 1645 ($C{=}C\langle^{H}_{H}$), 1435 and 1450 (d), 1375, 1320, 1015, 890 ($C{=}C\langle^{H}_{H}$). NMR (CCl_4), δ 1.76 (6 H, n, m), 4.73 (2 H, n, m), 5.56 (1 H, br, m).

trans-2-*Methyl*-5-(1-*methylethenyl*)-2-*cyclohexen*-1-*yl hydroperoxide* (**5a**). IR (CCl_4), ν_{max} 3550 (free –OOH), 3080 ($C{=}C\langle^{H}_{H}$), 3030 and 1680 ($^{H}\rangle C{=}C\langle$), 1645 ($C{=}C\langle^{H}_{H}$), 1445 and 1455 (d), 1300 and 1320 (d), 890 ($C{=}C\langle^{H}_{H}$). NMR (CCl_4), δ 1.76 (6 H, n, m), 4.23 (1 H, br, m), 4.71 (2 H, n, m), 5.68 (1 H, br, m), 7.66 (1 H, br, m).

trans-1-*Methyl*-4-(1-*methylethenyl*)-2-*cyclohexen*-1-*yl hydroperoxide* (**6a**). IR (CCl_4), ν_{max} 3555 (free –OOH), 3440 (H bonded OOH), 3080 ($C{=}C\langle^{H}_{H}$), 3030 and 1680 ($^{H}\rangle C{=}C\langle^{H}$), 1645 ($C{=}C\langle^{H}_{H}$), 1445, 1370, 1320, 1145, 1105, 890 ($C{=}C\langle^{H}_{H}$). NMR (CCl_4), δ 1.26 (3 H, s), 1.70 (3 H, n, m), 2.56 (1 H, br, m), 4.72 (2 H, n, m), 5.46 and 5.75 (2 H, quartet with additional splitting, J = 11 Hz), 6.98 (1 H, n, m) exchanges D_2O.

cis-1-*Methyl*-4-(1-*methylethenyl*)-2-*cyclohexen*-1-*yl hydroperoxide* (**7a**). IR (CCl_4), ν_{max} 3550 (free –OOH), 3420 (H bonded, OOH), 3075 ($C{=}C\langle^{H}_{H}$), 3022 ($^{H}\rangle C{=}C\langle^{H}$), 1642 ($C{=}C\langle^{H}_{H}$), 1450, 1365, 1320, 1205, 1135 (d), 1100 (d), 895 ($C{=}C\langle^{H}_{H}$), 840. NMR (CCl_4), δ 1.26 (3 H, s), 1.73 (3 H, n, m), 2.71 (1 H, br, m), 4.68 (1 H, n, m), 4.75 (1 H, n, m), 5.70 (2 H, br. s), 7.05 (1 H, m).

4-*Methyl*-*β*-*methylene*-3-*cyclohexene*-1-*ethanol* (**8**). The minor product from reduction of the hydroperoxide mixture was isolated by preparative glc and shown to be **8**: IR (CCl_4), ν_{max} 3610 (free –OH), 3070 ($C{=}C\langle^{H}_{H}$), 1660 ($_{H}\rangle C{=}C\langle$), 1640 ($C{=}C\langle^{H}_{H}$), 1430 and 1445 (d), 1370, 1100, 1065, 1035, 1010, 890 ($C{=}C\langle^{H}_{H}$). MS: *m/z* (relative abundance) 152 (7.3), 134 (33), 119 (66), 106 (85), 93 (55), 91 (71), 79 (85), 77 (48), 68 (84), 67 (100), 55 (69), 53 (57), 41 (76), 39 (80).

2-*Methylene*-5-(1-*methylethenyl*)-*cyclohexanone* (**12**). MS: *m/z* (relative abundance) 150 (62), 135 (40), 122 (26), 108 (85), 107 (81), 93 (50), 81 (61), 79 (100), 67 (49), 53 (62), 41 (50).

Acknowledgements—We thank Dr. W. Raymond and Mr. J. Barabas of our Foods Division Citrus R & D Laboratory, Plymouth, Fla. and Mr. R. Welch of this department, for MS determinations.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 411 to 420, 1981
Printed in Great Britain.

0040-4020/81/Suppl. 1-0411-10 $02.00/0
Pergamon Press Ltd.

SYNTHESES OF $PGF_{2\alpha}$ AND CLOPROSTENOL

N. R. A. BEELEY, R. PEEL and J. K. SUTHERLAND*

Chemistry Department, University of Manchester, Manchester M13 9PL, England

and

J. J. HOLOHAN, K. B. MALLION* and G. J. SEPENDA

Process Development Department, Pharmaceuticals Division, I.C.I. Ltd., Hurdsfield Industrial Estate, Macclesfield, Cheshire SK10 2NA, England

(*Received in U.K.* 17 *July* 1980)

Abstract—Prins reaction of norbornadiene leads to an efficient synthesis of the ketoacid (**5**) which is cleaved regio- and stereo-specifically with acids to 5-*exo*-substituted norbornan-2-one-7-carboxylic acids. Baeyer–Villiger oxidation of these ketones leads to bridged lactones, e.g. **18**, which can be converted into derivatives of the Corey aldehyde (**1**). In particular, the chlorolactone **19** is converted efficiently into the aldehyde **32** which, by four different routes, can be converted into known precursors of prostanoids.

In connection with a synthetic problem we observed[1] that a variant of the Prins reaction could be used to homologate conjugated dienes. Norbornadiene, though not formally a conjugated diene, reacts in a conjugate manner with most electrophiles, giving nortricyclane derivatives as the major or sole products.[2] Stereochemically the attack of electrophile is predominantly *exo* while the neutralisation of the nortricyclyl carbonium ion is not stereoselective. Should the hydroxymethylation of norbornadiene take such a course then it was apparent that such a product could be a potential precursor for the Corey aldehyde (**1**), widely used in the synthesis of prostaglandins.[3] To achieve this, cleavage of the C-1 and C-2 and C-3 and C-4 bonds of structure **2** was necessary, together with the introduction of oxygen functions at C-1 and C-4 with retention of configuration.

In the event, reaction of norbornadiene with $H.CO_2H$–H_2CO† gave a mixture which could be separated by distillation into three crude fractions. The most volatile (*ca* 10%) was nortricyclylformate, the major fraction (*ca* 60%) was the mixture of formates (**2**), while the residue contained **2**, the dimer **4**,‡ and other unidentified components. The diformates were readily hydrolysed to the mixture of fiols **3** which on oxidation with Jones' reagent gave the crystalline ketoacid **5**. The constitution of **5** was established by Wolff–Kishner reduction to the known[4] tricyclo-[2.2.1.$0^{2,6}$]heptan-3-carboxylic acid. From the crystallisation mother liquors an isomeric ketoacid could be isolated; the epimeric relationship of the two acids was established by equilibration of the ester **6** with NaOMe–MeOH yielding a mixture of the two esters. It was also possible to obtain the ketoacid **5** in 61% yield by oxidation[5] of the Prins adduct with Jones' reagent. The isomeric acid **16** was formed in *ca* 10% yield but remained in the crystallisation mother liquors. This must arise from a Prins adduct formally derived by *endo* attack on norbornadiene; this proportion of *endo* attack is unexpected and it could be formed by hydride migration in the *exo* intermediate **7**.

With plentiful supplies of the acid **5** available attention was now turned to the opening of the cyclopropyl ring,[6] which was accomplished using 45% HBr in CH_3CO_2H, 10NHCl 40% HI in H_2O, and $HClO_4$ in CH_3CO_2H to give **8**, **9**, **10** and **11** in good yield. In the latter reaction the acetate **11** was formed together with the γ-lactone **17**; both could be hydrolysed to the same hydroxyacid **12** which on heating regenerated the γ-lactone. These informative reactions confirmed the stereochemistry of the ketoacid **5**, and established the regio- and stereochemistry of the ring opening. The ketoester **6** also ring-opened with $HClO_4$–CH_3CO_2H and HBr–AcOH. In one experiment when the HBr–AcOH inadvertently contained some Br_2 a dibromide was obtained; the first order NMR spectrum of this compound (Fig. 1) confirmed the regio- and stereochemistry proposed. On reaction with Zn in AcOH at 20° the dibromide was transformed into the monobromide **8**. On treatment with base the haloacids **8**, **9**, and **10** were converted into **5**. The reasons for the remarkably regiospecific cleavage of **5** are not obvious; similar regiospecific cleavage is observed with the isomer **16**. In both cases the field effect of the carboxyl could destabilise positive charge developing β to it to a greater extent than a γ charge.

The oxygen required at C-4 was introduced by Baeyer–Villiger oxidation of the bromo- and chloroacids. Use of peracetic acid buffered by sodium acetate gave 71% of **18** and 74% of **19**. The crystallisation mother liquors were composed mainly of the isomeric oxidation products in which CH_2 migration had occurred. Baeyer–Villiger oxidation of the iodo-acid **10** took an unexpected course, yielding, after methylation (CH_2N_2) and chromatography, the lactones **20** and **21** in poor yield. Since it was likely that

†The preparation of compounds **2**, **3**, **5**, **9**, **19**, and **17** has been done independently by Bindra, Grodski, Schaaf and Corey,[11] and these have been used in prostaglandin syntheses in a manner different from that described herein. The acid **5** has been resolved by these workers. We thank Professor Corey for informing us of his work before publication.

‡Oxidation of the residue with Jones' reagent gave the acid **5** and a neutral fraction containing the dione corresponding to **4** which reacted with HBr–AcOH to give a readily purified dibromide. Elimination of HBr then gave a pure sample of the dione.

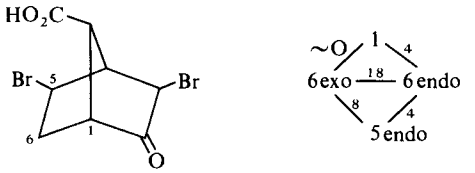


Figure 1. H-H Couplings in Hz.

20 was being formed by acid catalysed rearrangement[7] of **21**, the methyl ester **14** was oxidized (*m*-chloroperbenzoic acid) and the reaction isomerised [*p*-toluenesulphonic acid–benzene) to give **20** in 81% yield.† The oxidative elimination of iodine is not without precedent: Ogata[8] has shown that oxidation of cyclohexyl iodide yields products derivable from the interaction of cyclohexene, iodonium ion, and solvent. In our case it appeared that oxidative elimination occurred to form the norbornene, the double bond of which was too hindered to react with any electrophile present, but which underwent a rapid Baeyer–Villiger oxidation. Oxidation of an authentic sample of **23**‡ to **20** and **21** provided some support for this view.

Since Baeyer–Villiger oxidation of the ketoacid gave the lactone **24** in acceptable yield we investigated its reaction with HBr–AcOH. It proved to be much less reactive than the ketoacid but under forcing conditions the lactone **25** could be isolated in *ca* 50% yield.

The conversion of **18** and **19** into a cyclopentanoid of the required functionality formally requires opening of the lactone ring and displacement of halogen by carboxylate with inversion of configuration. Treatment of **18** and **19** with aqueous base effected 1,3-elimination to form the parent lactone **24**; none of the required lactone was formed. This very facile elimination is probably due to a most favourable geometrical relationship between proton and halogen similar to that established in the norbornane series by Nickon.[9] Two general solutions to the problem are possible, *viz* (a) use of a strong nucleophile for sp^2 carbon which is weakly basic, e.g. NH_2OH, NH_2NH_2, $O^{\ominus}OH$, and (b) alteration of the molecule to produce a less favourable geometry for elimination. In the event, reaction of **18** with NH_2OH in collidine gave the γ-lactone **26** in 52% yield but a substantial amount of elimination was also occurring. Preliminary experiments on the chlorolactone **19** showed the mixture of γ-lactone and elimination product (4:1) was formed in high yield using NH_2OH in isopropanol/H_2O. This procedure was not developed further since a satisfactory solution had been found using the second strategy. Treatment of **18** with HBr–AcOH gave the bromoester **31** which, on treatment with 8% NaOH gave the acid **26** (79%) while on reaction with 8% $NaHCO_3$ the acetate **27** (82%) was obtained.§

A formal total synthesis[3] of various prostaglandins was completed by reduction of the acid **27** to the alcohol **29** both by the mixed-anhydride procedure and, in better yield, by desulphurisation of the thiophenyl ester. However, for practical reasons it was best that the Corey aldehyde be protected as the *p*-phenylbenzoate; direct acylation of the hydroxy acid **26** was not possible since elimination to **25** occurred, presumably from the mixed anhydride. It was possible to prepare the Corey alcohol **30** by the sequence phenacyl ester formation, acylation, removal of phenacyl ester,[10] diborane reduction, but this was clearly not an attractive, practical route.¶ Our failure to develop a practical one-pot conversion of acid to aldehyde led to our abandonment of this route.

To overcome the acylation problem it was necessary to change the carboxyl functionality while the OH was still protected; the lactone **19** was a suitable stage at which to do this. The aldehyde **32** can be prepared *via* the primary alcohol[11] but the overall yields are not high and the most satisfactory route to this rather unstable compound is by Rosenmund reduction[12] of the acid chloride. In the first route (Scheme 1) the aldehyde was condensed with the anion of dimethyl 2-oxoheptylphosphonate to give mainly the crystalline enone **34** contaminated with the elimination product **33** which could be prepared by stirring **34** with aqueous sodium hydroxide. Reduction of **34** with $NaBH_4$ or $ZnBH_4$ gave the mixture of epimeric alcohols **35** which was converted to the γ-lactones **36** using Corey's procedure[13] ($NaOH/H_2O_2$); this method was superior to both the hydroxylamine route and the acidolysis procedure. The mixture of alcohols and the derived acetates was identical to that obtained by a different route.[14]

Three routes have been developed for the synthesis of cloprostenol; they are attractive in that they allow the synthesis of the intermediate **41** from the acid **19** by 'one-pot', ambient temperature reactions. The starting point was the acid chloride of **19**, purified and free of catalyst poisons, which undergoes Rosenmund reduction to the aldehyde **32** (*ca* 90%). The aldehyde could be isolated, but was rather unstable and thus in all the routes to be described, the Rosenmund reaction mixture was used directly.

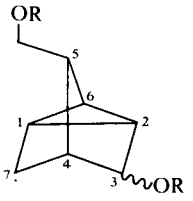
In Scheme 2 to enone **41** the Rosenmund reaction mixture was treated with *p*-toluenesulphonic acid in dry methanol at ambient temperature when **32** underwent smooth cleavage of the lactone ring and acetalisation of the formyl group to afford the soluble monocyclic hydroxyester **37**. Addition of an excess of aqueous alkali then brought about a sequence of three rapid, efficient (tlc) reactions. Ester hydrolysis gave the acid **38** which cyclised spontaneously to the lactone **39** this finally suffering hydrolysis to the hydroxyacid **40** (sodium salt). The reaction mixture, still at ambient temperature, was then brought to *ca* 0.5–1.0N HCl to promote two further very clean (tlc) stages, *viz* rapid relactonisation to **39** followed by slower (*ca* 3 hr) deprotection to the very water-soluble hydroxy-aldehyde (**1**). This compound has been prepared

†Oxidation of the trichloroethyl **15** ester with *m*-chloroperbenzoic acid gave the bridged lactone **22** uncontaminated with γ-lactone, but the conditions required to remove the protective group brought about partial isomerisation to the γ-lactone.

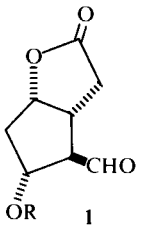
‡The ester **23** was prepared from the dimethyl acetal of norborn-5-en-2-on-7-carboxaldehyde by hydrolysis, CrO_3 oxidation, and methylation (CH_2N_2).

§Since AcOH is the common solvent for the sequence **5** → **8** → **31** and the conversions **31** → **26** or **27** only require treatment of the residue with aqueous base, these conversions could be carried out as 'one-pot' processes with addition of the appropriate reagents. The overall yield **5** → **26** was 46%.

¶**26** could also be prepared from the benzyl ester of **19** by the sequence $NaOH/H_2O_2$, p-$PhC_6H_4CO.Cl$/pyridine, H_2/Pd.



2 R = CHO
3 R = H



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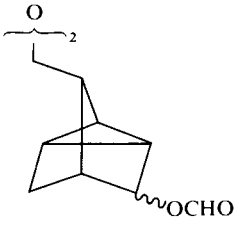

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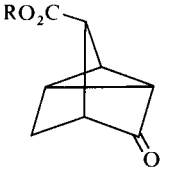
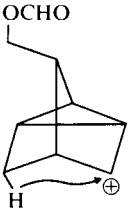


5 R = H
6 R = Me



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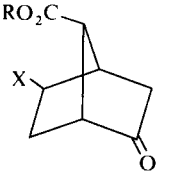
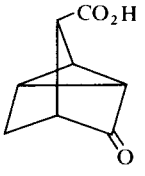


8 R = H X = Br
9 R = H X = Cl
10 R = H X = I
11 R = H X = OAc
12 R = H X = OH
13 R = Me X = OAc
14 R = Me X = I
15 R = CH_2CCl_3 X = I



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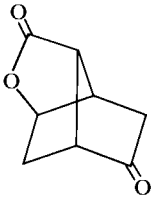

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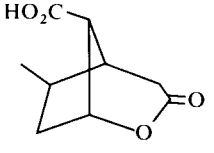
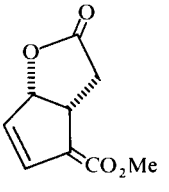


18 X = Br
19 X = Cl



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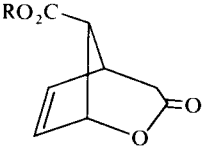
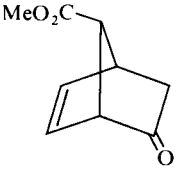


21 R = Me
22 R = CH_2CCl_3



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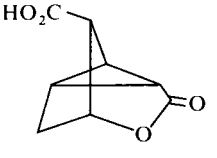

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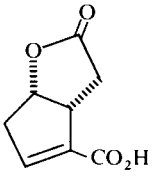

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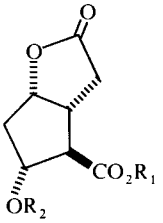
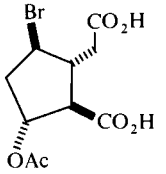


26 $R_1 = H, R_2 = H$
27 $R_1 = H, R_2 = Ac$
28 $R_1 = H, R_2 = COC_6H_4Ph\text{-}p$



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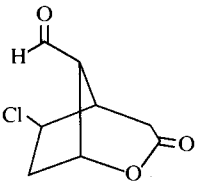

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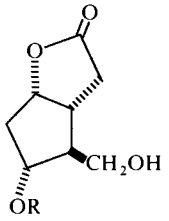
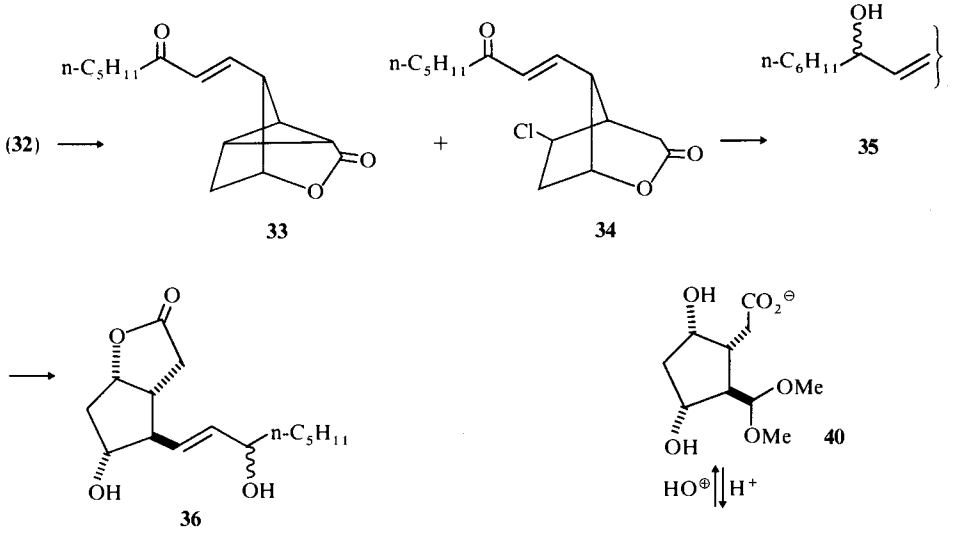
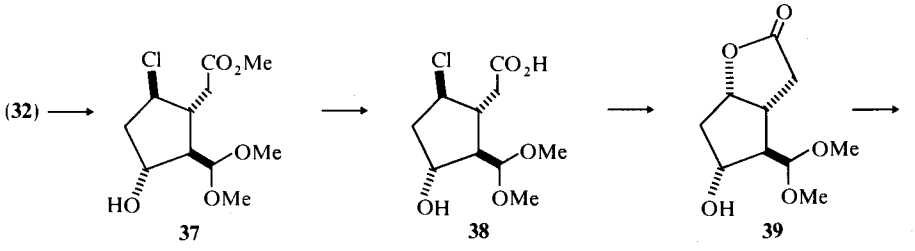


29 R = Ac
30 R = $CO.C_6H_4Ph\text{-}p$

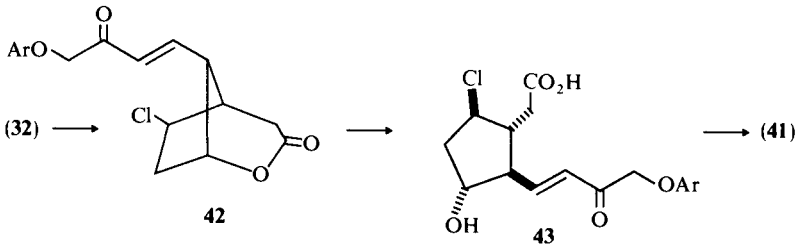


Scheme 1



41 R = H
45 R = $CO.C_6H_4Ph\text{-}p$

Scheme 2.

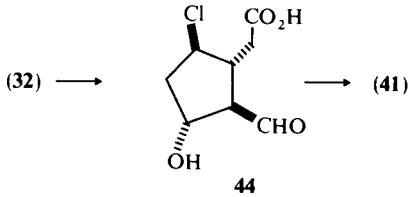


Scheme 3.

previously (but also not isolated) in low yield *via* a different route and was reported as insufficiently stable to survive chromatographic separation.[13] However, in the 0.5–1.0N HCl solution in which it was produced in this investigation it was stable with only traces of elimination over 36 hr. On treatment of the aqueous solution with excess potassium carbonate and then the phosphonate *m*-$ClC_6H_4OCH_2COCH_2PO(OMe)_2$,[15] **1** rapidly gave crystalline **41** isolated in 36% yield from **19**. (A similar condensation but under different conditions has been reported by E. J. Corey *et al.* in the $F_{2\alpha}$ series).[13]

In Scheme 3 to the enone **41**, the Rosenmund reaction mixture was treated directly with potassium carbonate and the phosphonate to afford the crystalline enone **42** [29% from **19**] which could be, but was not normally, isolated, the reaction mixture being treated with dilute acid to produce the hydroxyacid **43** and then with excess potassium carbonate which promoted efficient cyclisation to the required **41** [13.5% from **19**]. [If isolated *crude* **42** was separately taken to **41** the overall yield from **19** was 25.5%].

In Scheme 4, the mixture from the Rosenmund reduction was acidified with dilute acid to effect hydrolysis of **32** to give mainly the monocyclic aldehyde **44** which, without isolation was treated with excess potassium carbonate and the phosphonate. Rapid reactions led to the enone **41** [33% from **19**]. The enone **41** was *p*-phenylbenzoylated to give an intermediate **45** on an established route to the prostanoid chloprostenol. These routes constitute a relatively short and efficient synthesis of prostaglandins and related compounds.



Scheme 4.

EXPERIMENTAL

M.ps were determined on a Kofler block and are uncorrected. IR spectra were recorded on a Perkin–Elmer 257 instrument in $CHCl_3$ soln. NMR spectra were recorded at 60 MHz on a Perkin–Elmer R12B, at 90 MHz on a Perkin–Elmer R32, and at 100 MHz on a Varian HA100 using $CDCl_3$ as solvent unless otherwise specified. High resolution mass spectra were measured on A.E.I.MS9 and MS30 instruments. Tlc was carried out on Merck silica gel F_{254} plates. The statement "worked up in the usual way" implies that the organic extract was washed with saturated brine, dried over Na_2SO_4 or $MgSO_4$, and the solvent evaporated under reduced pressure.

Anti-5-oxo-tricyclo[2.2.1.0^{2,6}]*heptan-3-carboxylic acid* (**5**)

Norbornadiene (368 g) was added dropwise to a soln of paraformaldehyde (124 g) in 98% formic acid (2 l) containing H_2SO_4 (10 ml); the stirred soln initially warmed up to 50°. After addition of norbornadiene was complete the soln was stirred for a further 12 hr. Most of the formic acid was removed *in vacuo* and the residue dissolved in diethyl ether and filtered through a pad of Celite. After washing with $NaHCO_3$ aq the organic extract was worked up in the usual way to give a mixture which was distilled under vacuum to give nortricyclyl formate (40 g) b.p. 35–40°/0.05 mm and **2** (620 g; 79%) b.p. 92–102°/0.05 mm, ν_{max} 1720 cm^{-1}, τ 1.97 (2 H, s), 5.18 (0.5 H), 5.26 (0.5 H), 5.90 (1 H, d), 6.03 (1 H, d).

(a) A solution of CrO_3 (214 g) in conc H_2SO_4 (184 ml) and water (800 ml) was added dropwise to a stirred soln of the diformate (123 g) in acetone (2 l) while maintaining the temp of the mixture at 5°. Celite (300 g) was suspended in the acetone soln prior to addition of the oxidant. After stirring for a further 12 hr at 25° the liquid was decanted, most of the acetone removed *in vacuo*, and the residue filtered through Celite. The filtrate was extracted with EtOAc (×4) and the extracts worked up in the usual way to give **5** m.p. 143–146° (62 g; 65%) after trituration with ether. Recrystallisation from Me_2CO–petroleum ether b.p. 60–80° gave a sample m.p. 145–147°; (Found: C, 63.3; H, 5.1. $C_8H_8O_3$ Requires: C, 63.2; H, 5.3%), τ [$(CD_3)_2CO$] 7.02 (1 H, s), 8.6 (1 H, t).

Fractional crystallisation (Me_2CO–petroleum ether b.p. 60–80°) of the mother liquors gave the *syn*-acid **16**, m.p. 119–121°, (Found: C, 63.2; H, 5.3%), τ [$(CD_3)_2CO$] 7.10 (1 H, s), 8.66 (1 H, t).

The methyl esters of **5**, b.p. 94°/0.55 m, (Found: C, 65.4; H, 6.1. $C_9H_{10}O_3$ Requires: C, 65.1; H, 6.1%), τ 6.95 (1 H, s), 8.53 (1 H, t) and of **16**, b.p. 100°/0.12 mm. (Found: C, 64.8: H, 5.9%), were prepared by treatment with ethereal diazomethane. Methyl ester **6** (420 mg) on reflux with NaOMe in MeOH for 3 hr gave starting ester (209 mg) and the ester of **16** (147 mg).

(b) The diformate (40 g) in EtOH (200 ml) and water (100 ml) was cooled to 0° and 8° NaOH aq (220 ml) added dropwise with stirring. After addition was complete most of the EtOH was removed *in vacuo* and the residue extracted with EtOAc (6 × 80 ml). Work-up in the usual way gave the viscous diol (27.6 g), b.p. 160°/0.02 mm, τ [$(CD_3)_2CO$] 6.19 ($\frac{1}{2}$H), 6.27 ($\frac{1}{2}$H), 6.54 ($\frac{2}{2}$H), (Mass measurement: found 140.0842. $C_8H_{12}O_2$ Requires: 140.0837). A soln of CrO_3 (70 g), conc H_2SO_4 (61 ml), and water (500 ml) was added dropwise with stirring to a cooled soln of the diol (27.6 g) in AnalaR acetone (500 ml). After addition was complete the soln was stirred at ambient temp for 16 hr. Excess oxidant was destroyed by addition of sodium metabisulphite soln and most of the acetone removed under reduced pressure. The residue was extracted with EtOAc (5 × 200 ml) and worked up in the usual way to give **5** (15.79 g after recrystallisation).

Tricyclo[2.2.1.0^{2,6}]*heptan-3-carboxylic acid*

The acid **5** (573 mg), powdered KOH, and hydrazine hydrate (2 ml) in triethyleneglycol (25 ml) were heated at

140–150° for 1.5 hr. Solvent was distilled off until the reflux temp reached 220°, at which stage the soln was refluxed for a further 3 hr. The cooled soln was poured into water, acidified and extracted with ether (4 × 50 ml). Work-up in the usual way gave the acid, m.p. 49–50° (petroleum ether b.p. 60–80°) (Lit.[4] m.p. 49–50.6°).

Reaction of ketoacid (5) *with hydrogen bromide*

The acid **5** (21.5 g) in glacial AcOH (150 ml) and 45% HBr in AcOH (40 ml) was heated at 60° for 1 hr. The cooled soln was poured in water and extracted with EtOAc (×4). Work-up in the usual way gave **8** (29.1 g), m.p. 183.5–185.5° (acetone-petroleum ether b.p. 60–80°), (Found: C, 41.2; H, 3.9; Br, 34.3. $C_8H_9O_3Br$ Requires: C, 41.4; H, 3.9; Br, 34.3%), τ [$(CD_3)_2CO$] 5.66 (1 H, m). Esterification with diazomethane gave the *methyl ester*, m.p. 90–91° (petroleum ether b.p. 60–80°), (Found: C, 43.9; H, 4.5; Br, 32.4. $C_9H_{11}O_3Br$ Requires: C, 43.7; H, 4.5; Br, 32.3%).

If the ring-opening reaction was carried out in the presence of bromine the ketoacid (4 g) gave the *dibromide* (Fig. 1) (7.06 g), m.p. 188–193°, (Found: C, 31.0; H, 2.5; Br, 50.8. $C_8H_8O_3Br_2$ Requires: C, 30.8; H, 2.6; Br, 51.2%). Reduction of the dibromide with Zn dust and AcOH for 1 hr at ambient temp gave **8** (69%).

Reduction of **8** (2.1 g) with Zn dust (4.66 g) and AcOH (30 ml) (12 hr reflux) gave *norbornan-2-one-7-anti-carboxylic acid* (0.96 g) m.p. 104–106° (benzene–petroleum ether b.p. 60–80°), (Found: C, 62.2; H, 6.7. $C_8H_{10}O_3$ Requires: C, 62.3; H, 6.5%).

When **8** (411 mg) was dissolved in 1N NaOH (20 ml) and left for 10 min acidification gave **5** (201 mg).

Reaction of the ketoacid (**5**) *with hydrochloric acid*

The ketoacid **5** (12.9 g) and conc HCl (75 ml) was refluxed for 1.25 hr. On cooling a solid (15.8 g) precipitated. Recrystallisation gave **9** m.p. 157–160° (benzene–petroleum ether b.p. 60–80°), (Found: C, 51.1; H, 4.8; Cl, 18.4. $C_8H_9O_3Cl$ Requires: C, 50.9; H, 4.8; Cl, 18.8%), τ [$(CD_3)_2CO$] 5.67 (1 Hm).

Reaction of the ketoacid (**5**) *with hydriodic acid*

The ketoacid **5** (20 g) was refluxed in 57% HI (60 ml) for 1 hr. After addition of sodium metabisulphite soln the mixture was extracted with EtOAc (×6). Work-up in the usual way gave **10** (33.5 g) m.p. 227–228° (Me_2CO–EtOAc). (Found: C, 34.6; H, 3.2; I, 45.0. $C_8H_9O_3I$ Requires: C, 34.3; H, 3.2; I, 45.3%), τ [$(CD_3)_2CO$] 5.75 (1 H, q).

Reaction of the ketoacid with perchloric acid

The ketoacid **5** (4.1 g), glacial AcOH (50 ml), and 70% aqueous perchloric acid were refluxed for 6.25 hr. The black soln was poured into water (250 ml) and extracted with EtOAc (1 × 130, 3 × 80 ml). Work-up in the usual way gave a residue which was dissolved in $NaHCO_3$ aq and extracted with EtOAc (×3). Work-up in the usual way gave **17** (1.36 g), m.p. sublimes (acetone–petroleum ether b.p. 60–80°), (Found: C, 63.2; H, 5.2. $C_8H_8O_3$ Requires: C, 63.2; H, 5.3%), ν_{max} 1790, 1760 cm^{-1}, τ 5.15 (1 H, bs), 6.76 (1 H, bs), 7.01 (1 H, bs).

Acidification of the bicarbonate soln and extraction with EtOAc (×5) gave, after work-up in the usual way, a brown solid (2.53 g). Recrystallisation from acetone–petroleum ether b.p. 60–80° gave **11** (1.35 g), m.p. 186–187°, (Found: C, 56.9; H, 5.9. $C_{10}H_{12}O_5$ Requires: C, 56.6; H, 5.7%), τ (D_5–pyridine) 4.98 (1 H, m), 8.08 (3 H, s). Esterification with diazomethane gave **13** m.p. 101.5–103° (petroleum ether b.p. 60–80°), (Found: C, 58.4; H, 6.3. $C_{11}H_{14}O_5$ Requires: C, 58.4; H, 6.2%), τ 5.12 (1 H, m), 6.28 (3 H, s), 8.00 (3 H, s).

Dissolution of **17** (1.03 g) in 0.5N NaOH (50 ml), followed by acidification 30 min later, gave after EtOAc extraction (×8) **12** (0.81 g) m.p. 165–167°, (Found: C, 56.5; H, 6.0. $C_8H_{10}O_4$ Requires: C, 56.5; H, 5.9%), τ(D_5-pyridine) 5.71 (1 H, m). On sublimation the acid was converted to **17**. Hydrolysis of **11** under the same conditions for 1.5 hr also gave **12**.

The acid **12** with toluene-*p*-sulphonyl chloride and pyridine gave a *tosylate*, m.p. 125–126° (CCl_4), (Found: C, 56.9; H, 5.4; S, 9.2. $C_{16}H_{18}O_6S$ Requires: C, 56.8; H, 5.4; S, 9.5%), τ 5.30 (1 H, m).

The acid **12** on oxidation with Jones's reagent gave *norbornan-2,5-dione-7-carboxylic acid* (70%) m.p. 150–151°, (Found: C, 57.4; H, 4.7. $C_8H_8O_4$ Requires: C, 57.1; H, 4.8%).

Baeyer–Villiger oxidation of bromo-acid **8**

A mixture of **8** (18.6 g), anhyd NaOAc (2.82 g), 40% peracetic acid (20 ml), and glacial AcOH (175 ml) was stirred at ambient temp for 12 hr. Excess oxidant was destroyed by addition of sodium metabisulphite, the soln diluted with water, and then sat with NaCl. Extraction with EtOAc and work-up in the usual way gave a crystalline residue which was triturated with ether to give **18** (14.1 g) m.p. 178–182° (dec) (acetone–petroleum ether b.p. 60–80°), (Found: C, 38.6; H, 3.7; Br, 32.3. $C_8H_9O_4Br$ Requires: C, 38.6; H, 3.6; Br, 32.1%), τ [$(CD_3)_2CO$] 4.98 (1 H, bs), 5.40 (1 H, m).

The methyl ester of **8** was oxidized with *m*-chloroperbenzoic acid in CH_2Cl_2 to the *methyl ester of* **18** (70%), m.p. 113–114 (CCl_4), (Found: C, 41.2; H, 4.3; Br, 30.4. $C_9H_{11}O_4Br$ Requires: C, 41.1; H, 4.2; Br, 30.4%), τ 5.90 (1 H, m), 6.26 (3 H, s), 6.70 (1 H, bs).

Baeyer–Villiger oxidation of chloroacid **9**

The chloroacid **9** (4.8 g) was oxidized as for **8** to give **19** (3.30 g), m.p. 175–178° (acetone–petroleum ether b.p. 60–80°), (Found: C, 46.8; H, 4.3; Cl, 17.5. $C_8H_9O_4Cl$ Requires: C, 47.0; H, 4.4; Cl, 17.3%), τ [$(CD_3)_2CO$], 4.96 (H, bs), 5.41 (1 H, m).

Baeyer-Villiger oxidation of the iodoacid esters **14** *and* **15**

(a) The ester **14** (1.294 g) in EtOAc (20 ml) containing 40% peracetic acid (5 ml) and NaOAc (4 g) was stirred at ambient temp for 35 hr. After addition of water the aqueous layer was extracted with EtOAc (×4). The organic extracts were washed with sodium metabisulphite soln and $NaHCO_3$ aq and then worked up in the usual way to give a mixture of **21** with some **20** (NMR). The mixture was dissolved in benzene (20 ml) containing toluene-*p*-sulphonic acid (500 mg) and set aside for 24 hr. Work-up in the usual way (ether extraction) gave **20** (629 mg), τ, 3.94 (2 H, m), 4.41 (1 H, m) 6.30 (3 H, s), ν_{max} 1780, 1740 cm^{-1}.

(b) The iodoacid **10** (10 g), pyridine (2.86 g), dicyclohexylcarbodiimide (7.37 g), and trichlorethanol (5.34 g) were stirred at ambient temp in CH_2Cl_2 (60 ml) for 24 hr. The dicyclohexylurea was filtered off and washed with CH_2Cl_2. The combined filtrate was washed with $NaHCO_3$ aq and worked up in the usual way **15** (14.5 g), m.p. 117–118° (EtOAc), (Found: C, 29.1; H, 2.4; Cl, 26.0; I, 30.4. $C_{10}H_{10}O_3Cl_3I$ Requires: C, 29.2; H, 2.5; Cl, 25.9; I, 30.8%). A mixture of 40% peracetic acid (120 ml) containing NaOAc (20 g) was added slowly to **15** (39.1 g) in EtOAc (200 ml). After 5 min an exothermic reaction began and the soln refluxed. The rate of addition was controlled to avoid over-vigorous reaction and after completion of addition the mixture, now containing a white solid, was stirred overnight. 2N HCl was added and the mixture extracted with $CHCl_3$ (×5). Work-up in the usual way gave **22** (25.7 g), m.p. 108–109° (CCl_4), (Found: C, 40.1; H, 3.1; Cl, 34.3. $C_{10}H_{10}O_4Cl_3I$ Requires: C, 40.1; H, 30.0; Cl, 35.5%), τ 3.50 (1 H, q), 3.70 (1 H, q), 4.62 (1 H, bs), 5.29 (2 H, s), ν_{max} 1765 cm^{-1}.

The δ-lactone **22** (73 mg) in benzene (15 ml) containing toluene-*p*-sulphonic acid (200 mg) was set aside for 24 hr. After addition of EtOAc, work-up in the usual way gave the *γ-lactone* of **20** as a viscous oil (70 mg), ν_{max} 1795, 1765 cm^{-1}, τ 3.88 (2 H, m), 4.38 (1 H, m), 5.25 (2 H, s).

Refluxing **22** (319 mg) in 90% AcOH (4 ml) and benzene (8 ml) with Zn dust (1.2 g) gave, after filtration, addition of 2N HCl and work-up in the usual way, the *γ-lactone* acid of **20**

(162 mg) m.p. 117–119° (acetone–petroleum ether b.p. 60–80°), (Found: C, 56.8; H, 5.3. $C_8H_8O_3$ Requires: C, 57.1; H, 4.8%) ν_{max} 1785, 1720 cm^{-1}, τ [$(CD_3)_2CO$] 3.85 (1 H, m), 4.05 (1 H, m), 4.45 (1 H, m).

Baeyer–Villiger oxidation of ketoacid **5** *and ketoester* **6**

The acid **5** (3.06 g) was stirred with 40% peracetic acid (10 ml) in glacial AcOH (30 ml) for 12 hr. Sodium metabisulphite was added, the soln diluted with water and extracted with EtOAc (×5) and then worked up in the usual way to give **24** (1.8 g) m.p. 178.5–181° (acetone–petroleum ether b.p. 60–80°), (Found: 57.2; H, 4.9. $C_8H_8O_4$ Requires: C, 57.1; H, 4.8%), τ 5.30 (1 H, bs).

Oxidation of **6** (740 mg) with *m*-chloroperbenzoic acid (1.128 g) in CH_2Cl_2 (11 ml) gave after work-up an oil (780 mg). Two crystallisations from benzene-petroleum ether b.p. 60–80° gave the *methyl ester* of **24**, m.p. 60–61°, (Found: C, 59.3; H, 5.6. $C_9H_{10}O_4$ Requires: C, 59.3; H, 5.5%), τ 5.26 (1 H, bs). Chromatography on silica gel with ether as eluant gave the *isomeric lactone* (28 mg). m.p. 96.5–97.5° (CCl_4) (Found: C, 59.6; H, 5.6%), τ 5.78 (1 H, t).

Reaction of the lactone **24** *with hydrogen bromide*

The lactone **24** (1.02 g) in 45% HBr in AcOH (20 ml) was refluxed for 19 hr. The soln was evaporated to dryness and a further portion of 45% HBr in AcOH (45 ml) was added. After 60 hr reflux the soln was again evaporated to dryness. The black residue was dissolved in EtOH and treated with charcoal. After filtration through a pad of Celite evaporation gave a light brown crystalline residue. Recrystallisation from $CHCl_3$ gave **25** (507 mg) m.p. 152–157°, (Found: C, 57.3; H, 5.0. $C_8H_8O_4$ Requires: C, 57.1; H, 4.8%), τ [$(CD_3)_2CO$] 3.20 (1 H, m), 4.83 (1 H, t), ν_{max} 1785, 1710 cm^{-1}.

Reaction of the bromolactone **18** *with sodium hydroxide*

The bromoacid **18** (68 mg) dissolved in water (5 ml) containing NaOH (30 mg) was set aside for 10 min. Acidification, extraction with EtOAc (×4), and work-up in the usual way gave **24** (41 mg) identical with the compound previously prepared.

Preparation of the lactone acid **26**

(a) The lactone **18** (6.11 g), hydroxylamine hydrochloride (6.82 g), and collidine (200 ml) were heated at 120° for 2 hr. The cooled soln was acidified to pH 1 with HI and continuously extracted with ether for 56 hr. Evaporation of the ether extract gave a residue which on trituration with $CHCl_3$ gave **26** (1.58 g), m.p. 150–152°, (acetone–petroleum ether b.p. 60–80°), (Found: C, 51.6; H, 5.3. $C_8H_{10}O_5$ Requires: C, 51.6; H, 5.4%), τ (CF_3CO_2H) 4.5 (1 H, m), 5.06 (1 H, m). The mother liquors were esterified with diazomethane and chromatographed on silica gel. Elution with ether–acetone (9:1) first gave the methyl ester of **24** (1.087 g) and then the *methyl ester of* **26** (636 mg), m.p. 71–73° (benzene–petroleum ether b.p. 60–80°), (Found: C, 54.4; H, 6.1. $C_9H_{12}O_5$ Requires: C, 54.0; H, 6.0%), τ 4.98 (1 H, dt), 5.52 (1 H, q), ν_{max} 1770, 1730 cm^{-1}.

The methyl ester of **26** was acetylated (Ac_2O–pyridine) to give the *acetate*, m.p. 89–90.5° (CCl_4), (Found: C, 54.8; H, 5.8. $C_{11}H_{14}O_6$ Requires: C, 54.5; H, 5.8%), τ 4.64 (1 H, q), 4.92 (1 H, m), 7.99 (3 H, s), ν_{max} 1775, 1740, 1735 cm^{-1}. The methyl ester of **26** was also *p*-phenylbenzoylated to give an *ester* identical to that obtained from Jones's oxidation of the Corey aldehyde **1** R = *p*-phenylbenzoyl) followed by treatment with diazomethane, m.p. 145–146° (MeOH), (Found: C, 69.7; H, 5.3. $C_{22}H_{20}O_6$ Requires: C, 69.5; H, 5.3%).

(b) Reflux of **19** (303 mg) with NaOAc (618 mg), hydroxylamine hydrochloride (522 mg), water (3.5 ml) and isopropanol (7.5 ml) for 12 hr gave a 4:1 mixture of **26**:**24** (272 mg). Similar reaction of **18** gave a 4:5 ratio.

(c) The bromolactone (5.98 g) in 48% HBr–AcOH (23 ml) and AcOH (7 ml) was heated at 100° for 1 hr. The cooled soln was poured into water, extracted with EtOAc (×4), and worked up in the usual way to give **31** (6.24 g), τ [$(CD_3)_2CO$] 4.64 (1 H, q), 5.68 (1 H, m), 8.00 (3 H, s). Recrystallisation from ether–petroleum ether b.p. 60–80° gave a solid, m.p. 110–113° but satisfactory analyses could not be obtained due to ready loss of HBr.

The acetate **31** (4.7 g) was dissolved in excess 8% NaOH aq and set aside from 30 min. After acidification to pH 1 with HCl the soln was continuously extracted with ether for 39 hr. After evaporation of the extract the product was triturated with ether to give **26** (2.69 g).

The acetate **31** (3.51 g) was stirred in water (25 ml) containing $NaHCO_3$ (1.92 g) for 1 hr. The soln was acidified to pH 1 with 2N HCl and extracted with EtOAc (×5). Work-up in the usual way gave **27**, m.p. 177–184°, (acetone–petroleum ether b.p. 60–80°), (Found: C, 52.5; H, 5.3. $C_{10}H_{12}O_6$ Requires: C, 52.6; H, 5.3%), τ (CF_3CO_2H), 4.32 (1 H, q). 4.63 (1 H, m), 7.81 (3 H, s).

(d) The ketoacid **5** (24.12 g) was dissolved in 45% HBr in AcOH (90 ml) and heated at 60° for 1 hr. The excess reagent was distilled off and the crystalline residue dissolved in glacial AcOH (200 ml). NaOAc (2.42 g) and 40% peracetic acid (32 ml) were added and the soln stirred at room temp for 12 hr. Conc H_2SO_4 (24 ml) was added and the soln stirred for a further 12 hr. Sodium metabisulphite was then added and the soln diluted with water, saturated with NaCl, and extracted with EtOAc (×5). Work-up in the usual way gave an oil which was dissolved in water (100 ml) and a soln of NaOH (40.5 g) in water (50 ml) added dropwise with stirring and cooling. After 1 hr at ambient temp the soln was acidified to pH 1 with 10N HCl and the volume reduced to *ca* 50% by warming *in vacuo*. Continuous extraction with ether for 3.5 hr gave an oil (11 g) and **26** (1.36 g). Extraction for a further 37 hr gave the acid (12.1 g). The yield based on **5** is 46%.

Preparation of the acetoxy alcohol **29**

(a) The acid **27** (1.135 g) in THF (40 ml) at 0° was treated sequentially with Et_3N (0.505 g) and ethyl chloroformate (0.543 g) and the mixture stirred for 15 min. The solid was filtered off and $NaBH_4$ (0.7 g) added to the filtrate. After 3 hr at 0° 2N HCl was added and the mixture extracted with EtOAc (×5). Work-up in the usual way gave **29** as an oil (0.443 g), τ 5.00 (2 H,)m, 6.42 (2 H, d), 7.96 (3 H, s), ν_{max} 3500, 1780, 1740 cm^{-1}, (Mass measurement Found: 214.0835. $C_{10}H_{14}O_5$ Requires: 214.0841).

(b) The γ-lactone **27** (1.135 g) was added to dicyclohexylcarbodiimide (1.032 g), pyridine (0.396 g), and thiophenol (0.55 g) in CH_2Cl_2 (50 ml) and the mixture stirred overnight. The urea was filtered off and washed with EtOAc. The soln was washed with 2N HCl, $NaHCO_3$ aq and worked up in the usual way to give the *thiolo ester* (1.544 g), ν_{max} 1780, 1740, 1695 cm^{-1}, m^+ 320. A portion of the thiolo ester (995 mg) in EtOH (15 ml) was stirred with W2 Raney Ni for 1.5 hr. After filtration through a pad of Celite and washing the pad with EtOAc, evaporation of the solvent gave **29** (593 mg).

Preparation of the Corey alcohol **30**

The acid **26** (739 mg) in water (10 ml) was neutralised with 5% NaOH aq (phenolphthalein) then a solution of *p*-bromophenacyl bromide (1.22 g) in MeOH was added and the mixture refluxed for 1.25 hr. On cooling **28** (736 mg) separated, m.p. 158–160° (acetone–petroleum ether b.p. 60–80°) (Found: C, 50.5; H, 4.4; Br, 21.0. $C_{16}H_{15}BrO_4$ Requires: C, 50.2; H, 4.0; Br, 20.9%). The phenacyl ester (344 mg), *p*-phenylbenzoyl chloride (365 mg) and pyridine (6 ml) were stored at ambient temp for 2.5 hr. The soln was poured into water, extracted with $CHCl_3$ (×3) and worked up in the usual way to give the *phenylbenzoate* (423 mg), m.p. 161–163° (acetone–petroleum ether b.p. 60–80°) (Found: C, 62.0; H, 4.3; Br, 14.1. $C_{29}H_{23}O_7Br$ Requires: C, 61.8; H, 4.1; Br, 14.2%). This ester (104 mg) in glacial AcOH (10 ml) was stirred with Zn dust (960 mg) for 1.25 hr. The mixture was diluted with ether, filtered, and the filtrate concentrated. Excess $NaHCO_3$ aq was added and the soln extracted with ether. The aqueous phase was then acidified with 2N H_2SO_4 and extracted with CH_2Cl_2 (×4). Work-up in the usual way gave **28** (52 mg), m.p. 174.5–175.5° (EtOAc–petroleum ether

b.p. 60–80°), (Found: C, 68.9; H, 5.1. $C_{21}H_{18}O_6$ Requires: C, 68.8; H, 5.0%), which was identical to a sample prepared by Jones's oxidation of the Corey aldehyde **1** R = *p*–PhC_6H_4CO).

Diborane was passed into a soln of **28** (366 mg) in THF (5 ml) at 0°. After 45 min water was added and the soln extracted with EtOAc (×5) and worked up in the usual way to give **30** (171 mg), m.p. 150–152°, identical with an authentic sample.

Scheme 1. *Preparation of the γ-lactone diol* **36**

The chloroacid **19** (5.193 g) in THF (50 ml) containing one drop of DMF was cooled to 0° and oxalyl chloride (2.33 ml) added dropwise. After the vigorous effervescence had subsided the flask was aspirated for a few min and then a soln of lithium tri-t-butoxyaluminium hydride (*ex* 2.114 g LAH) in THF (50 ml) was added and the mixture stirred for 30 min. at 0°. 1N HCl was added carefully, followed by EtOAc. The aqueous layer was further extracted with EtOAc (×3) and the combined organic extracts were shaken with $NaHCO_3$ aq and then worked up in the usual way to give a dark oil which was chromatographed on silica gel. Elution with ether–acetone (9:1) gave the crystalline alcohol (2.529 g), m.p. 96–99° (acetone–petroleum ether b.p. 60–80°) τ 5.10 (1 H, m), 5.74 (1 H, q), 6.07 (2 H, d, J ≡ 8 Hz).

The alcohol (1.135 g) in CH_2Cl_2 (5 ml) was added to a soln of CrO_3 (3.575 g) and pyridine (5.74 ml) in CH_2Cl_2 (100 ml) and stirred at ambient temp for 15 min. After addition of EtOAc the organic soln was decanted, washed with 1 N HCl and worked up in the usual way to give **32** (645 mg), τ 0.24 (1 H, s), 4.78 (1 H, m), 5.60 (1 H, m), which solidified on trituration with ether. This compound could not be purified readily and was used as soon as possible after preparation.

Dimethyl 2-oxoheptylphosphonate (2.763 g) was dissolved in dry dimethoxy ethane (175 ml) and sodium hydride (486 mg of 50% dispersion in paraffin) added in portions with vigorous stirring. The soln was cooled to −30° and a soln of **32** (1.57 g) in dimethoxyethane (10 ml) added. The mixture was kept at −15° to −20° for 40 min then diluted with a mixture of ether and EtOAc, water added, and worked up in the usual way. The product was chromatographed on silica gel. After removal of paraffin elution with ether gave three fractions (i) mainly **34** (298 mg), (ii) pure **34** (826 mg), and (iii) the *tricyclic enone* **33** (50 mg). The *enone* **34** was recrystallised from benzene-petroleum ether b.p. 60–80°, m.p. 65–67°, τ 3.08 (1 H, dd, J = 15 and 7 Hz), 3.76 (1 H, d, J = 15 Hz), 5.18 (1 H, d, J = 4 Hz), 5.68 (1 H, q, J = 4 Hz). The tricyclic enone **33** was an oil, τ 3.44 (1 H, dd, J = 15 and 5 Hz), 3.76 (1 H, d, J = 15 Hz), 5.60 (1 H, bs).

Zinc borohydride soln (20 ml of a soln prepared from 4.24 g $NaBH_4$ and 290 ml ether) was added to **34** (419 mg) in dimethoxyethane (20 ml). After stirring at ambient temp for 2 hr the soln was diluted with EtOAc, shaken with 10N HCl and worked up in the usual way to give **35** (415 mg), τ 4.22 (2 H, m), 5.27 (1 H, m), 5.72 (1 H, m), 5.92 (1 H, m).

The epimers **35** (421 mg) in THF (10 ml) were treated with 9.5% NaOH aq (6.2 ml) and 30% H_2O_2 (3 ml). After 20 min a few drops of 2N HCl were added and the soln extracted with EtOAc (×3). After washing the extracts with sodium metabisulphite work-up in the usual way gave **36** (330 mg) as an oil. Comparison of this sample with an authentic 1:1 mixture of the C-15 epimers of **36** by tlc, and NMR established their identity. Similar comparison of the diacetates confirmed the assignment of structure.

6-exo-*Chloro*-3-*oxo*-2-*oxabicyclo*-[3.2.1]*octane*-8-*anti-carbonyl chloride* [*acid chloride of acid* **19**]

The acid **19** (6.0 g) was suspended in dry toluene (24 ml) containing a catalytic quantity of dry DMF (0.15 ml) under an argon atmosphere. $SOCl_2$ (3.174 ml) was then added and the suspension stirred and heated at 50° until a clear soln was obtained (usually in about 4 hr). (The evolved gases were led through a $CaCl_2$ tower to a water scrubber). Heating was continued for a further 30 min and then most of the excess $SOCl_2$ and residual HCl and SO_2 dioxide removed, by holding the soln, still at 50°, under a slight vacuum (*ca* 20″ water) for 30 min. Addition of hexane (22 ml) over 10 min then precipitated most of the product as a dense white crystalline solid. With the heating bath removed, precipitation was completed by the addition of more hexane (26 ml). The mixture was stirred for 1 hr, periodically evacuating and refilling the reaction vessel with argon. The supernatant liquors were then removed *in situ* by suction through a sinter-tipped glass tube pushed through the suspension to the bottom of the flask at the same time keeping the contents under positive argon pressure from a balloon. The residual solid was stirred overnight with dry toluene (14.6 ml) and then the suspension was treated with hexane (29 ml) and stirred a further 1 hr before removing the supernatant liquors as previously described. The residue was finally stirred for 2 hr with fresh hexane (29 ml) which was again removed by suction *in situ*. The hexane-damp, white, moisture-sensitive, crystalline acid chloride now free from catalyst poisons, was used directly in the next stage but could be vacuum dried (6.02 g) (92%), ν_{max} (mull) 1762, 1722 cm^{-1}. τ [$(CD_3)_2CO$] 4.85 (1 H, m), 5.3 (1 H, m), 6.0 (1 H, bs).

6-exo-*Chloro*-3-*oxo*-2-*oxabicyclo*-[3.2.1]*octane*-8-*anti-carboxyaldehyde* **32**

A soln of the acid chloride (6.02 g) in AR acetone (48 ml) was added from a syringe *via* a septum cap to a soln of dimethylaniline (4.36 ml) in AR acetone (27 ml) containing 3% Pd/C (2.18 g) all under argon. The argon was exchanged for H_2 and with the reaction vessel connected to a gas-burette supplying H_2 at NTP, the mixture was vigorously stirred. Theoretical H_2 uptake was observed after 40–60 min. After exchange of H for argon, the mixture containing **32** (*ca* 90%) was used directly. Crude **32** could be obtained as a gum containing EtOAc (*ca* 10%) as follows. The soln was filtered through Hyflo and evaporated to a residue which was partitioned between EtOAc (120 ml) and 2N HCl (1 × 30 ml, 1 × 20 ml). The combined aqueous layers were extracted with EtOAc (30 ml) and the combined organic layers washed with brine (3 × 20 ml), dried and evaporated to give crude **32** as a gum (5.087 g), τ 0.24 (1 H, s), 4.78 (1 H, m), 5.60 (1 H, m). Tlc R_f *ca* 0.5 (10% v/v $MeOH/CHCl_3$) visualised by UV and ceric sulphate. Attempts to purify **32** by column chromatography led to decomposition. The compound was fairly stable in soln but darkened at room temp when isolated.

Scheme 2. 4*β*-[4-(3-*Chloro-phenoxy*-3-*oxobut*-1-trans-*enyl*]-2.3.3a*β*6 a*β*-*tetrahydro*-5*α*-*hydroxy*-2-*oxocyclopenteno* [*b*] *furan* **41**

The complete Rosenmund mixture containing **32** (*ca* 5.09 g) was treated under argon with toluene-*p*-sulphonic acid (monohydrate) (4.53 g) in dry MeOH (22 ml) and stirred overnight at ambient temp. Tlc showed clean conversion to **37** R_f *ca* 0.8 (10% v/v $MeOH/CHCl_3$) visualised by ceric sulphate (non-UV-active). [Hydroxyester **37** could be isolated as follows: a soln of crude **32** (*ca* 5.09 g) isolated as described, in MeOH (20 ml) containing toluene-*p*-sulphonic acid (0.20 g) was allowed to stand overnight. Saturated $NaHCO_3$ aq (6–8 ml) was added and most of the MeOH was evaporated. The residue was partitioned between EtOAc (80 ml) and water (30 ml) followed by brine (30 ml). The EtOAc was evaporated to a gum (5.4 g) which was chromatographed on a Kieselgel 60 column eluted with 5% $Pr^iOH/Ph.CH_3$ to afford **37** as a gum (3.98 g), τ 5.85 (3 H, m), 6.33 (3 H, s), 6.60 (3 H, s), 6.64 (3 H, s)].

Continuing the telescoped sequence, the mixture was then treated rapidly at ambient temp with a soln of NaOH (7.63 g) in water (53 ml) and allowed to stand for 1 hr. Tlc now showed the Na salt (40) at R_f 0–0.1 (20% v/v $(Me_2)CO/CH_2Cl_2$) visualised with ceric sulphate (non-UV-active). 6N HCl (44 ml) was then added and the mixture set aside for 3 hr. Tlc now showed **2** as a rather diffuse spot, R_f *ca* 0.3–0.4 (40% v/v Me_2CO/CH_2Cl_2) visualised by ceric sulphate. The soln was

filtered through Hyflo to remove the catalyst washing with acetone (7 ml)–water (13 ml). The filtrate was neutralised with K_2CO_3 (*ca* 14.8 g)and then the phosphonate (8.54 g) was added, followed by acetone (22 ml) to assist its dissolution. The stirred mixture was treated with K_2CO_3 (10 g) in water (52 ml) over 45 min. After stirring for 30 min after the addition, the reaction was treated with glyoxylic acid (4.36 g) to convert the excess of the neutral phosphonate to the alkali soluble acid (A)† allowing 30 min for this reaction. The mixture was extracted with toluene (110 ml) and the aqueous layer further extracted with a toluene (65 ml)–EtOAc (44 ml) mixture. The combined organic layers were washed with sat $NaHCO_3$ aq (65 ml) [to remove (A) and excess glyoxylic acid], then 2N HCl (1 × 130 ml, 1 × 45 ml) to remove $PhNMe_2$, then brine (85 ml) and finally dried, decolourised with charcoal (1.0 g) and evaporated at *ca* 50° to *ca* 30 ml. On cooling **41** crystallised out. It was filtered off and washed with a toluene (30 ml)–hexane (22 ml) mixture, then with hexane (10 ml) and dried *in vacuo* to give **41** (3.55 g) [36% from **19**], m.p. 101–102°, ν_{max} 3360, 1755, 1695 cm^{-1}. τ [$(CD_3)_2CO$] 2.50–3.3 (5 H, m), 3.54 (1 H, d, J = 16.5 Hz), 5.04 (2 H, s), 5.00 (1 H, m), 5.85 (2 H, m), (Found: C, 60.3; H, 5.2; Cl, 10.6. $C_{17}H_{17}OCl$ Requires: C, 60.6; H, 5.1; Cl, 10.5%).

Scheme 3

A Rosenmund reduction was carried out on 0.249 × the scale described earlier. Under argon, the soln containing **32** (*ca* 1.27 g) was diluted with water (3 ml) and then the phosphonate (2.74 g) was added followed dropwise by a soln of K_2CO_3 (1.3 g) in water (10 ml) over 15 min. After 10 min tlc showed complete conversion to **42** R_f 0.7–0.8 (20% v/v Me_2CO/CH_2Cl_2) visualised by UV and ceric sulphate. [Enone **42** could be isolated as follows: The mixture was treated with glyoxylic acid (1.3 g) and K_2CO_3 (4.0 g) (as in Scheme 2) and stirred for 10 min. It was then acidified (2N HCl) to pH 6 and filtered through Hyflo washing with acetone (5 ml) and water (2 ml). The acetone was evaporated *in vacuo* at ambient temp and the residue partitioned between EtOAc (50 ml) and 2N HCl (20 ml). The aqueous layer was re-extracted with EtOAc (15 ml) and the combined organic layers were washed in turn with 2N HCl (5 ml), sat $NaHCO_3$ aq (2 × 10 ml) and NaCl aq (10 ml) then dried and evaporated to give a gum (1.543 g) which crystallised on stirring in MeOH (4 ml)–ether (10 ml). Crystalline **42** was filtered off and washed with ether (10 ml) [0.696 g (29.6%) from **1**], m.p. 111–114°, ν_{max} 1722, 1710 cm^{-1}. τ 2.5–3.3 (5 H, m), 3.45 (1 H, d, J = 16.5 Hz), 5.15 (1 H, m), 5.3 (2 H, s), 5.75 (1 H, m), (Found: C, 57.7; H, 4.5; Cl, 19.7. $C_{17}H_{16}O_4Cl_2$ Requires: C, 57.5; H, 4.5; Cl, 20.0%)].

Continuing with the telescoped process, the mixture was brought to pH 4 with 50% HCl then filtered through Hyflo. Toluene-*p*-sulphonic acid (1.13 g) was added and the soln set aside for 13 days at ambient temp. Tlc now showed **43**, R_f 0.3 (20% v/v Me_2CO/CH_2Cl_2) visualised with ceric sulphate. The pH was adjusted to 8–9 with K_2CO_3 to effect cyclisation to **41** and then glyoxylic acid (1.3 g) and K_2CO_3 (4.0 g) were added as in Scheme 2. After $1\frac{1}{2}$ hr the mixture was neutralised with 2N HCl (*ca* 5 ml). The acetone was evaporated and the residue partitioned with EtOAc (2 × 90 ml) and water (30 ml). The combined organic extracts were washed successively with 2N HCl (1 × 50 ml, 1 × 30 ml), Na_2CO_3 aq (2 × 20 ml) and then brine (20 ml) and were dried and decolourised with charcoal. Evaporation of the solvent left a gum which crystallised on trituration with EtOAc (1.4 ml)–ether (14 ml) to give **41** isolated as in Scheme 2 [0.331 g, 13.5% from **19**] identical to the sample from Scheme 2.

†The formation of acid (A), m-$ClC_6H_4OCH_2$-$COCH{=}CHCO_2H$, was used as a device for the removal of excess phosphonate.

Scheme 3. *Non-telescoped*

Crude **42** (1.543 g) prepared as described above was dissolved in THF (18 ml) and water (6 ml) containing toluene-*p*-sulphonic acid (0.6 g) and the soln allowed to stand for 6 days at room temp. Sat K_2CO_3 aq was added to pH 8–9 and after $1\frac{1}{2}$ hr the mixture was neutralised with 2N HCl. The THF was removed *in vacuo* and water (30 ml) was added. The mixture was extracted with EtOAc (2 × 90 ml) which in turn was washed with $NaHCO_3$ aq (40 ml) and brine (30 ml) and then dried and decolourised with charcoal. Evaporation of the solvent left a gum which crystallised on stirring under ether (20 ml)–EtOAc (5 ml) to afford **41** isolated as in Scheme 2 [0.567 g, 25.5% from (**19**)], identical to the sample from Scheme 2.

Scheme 4

A Rosenmund mixture prepared on 0.224 × scale of Scheme 2 containing **32** (1.138 g) was filtered free from the catalyst and then treated with toluene-*p*-sulphonic acid (1.275 g) in water (5 ml) and allowed to stand 7 days at room temp. Tlc then showed **44** as the main spot at R_f *ca* 0.2 (20% v/v Me_2CO/CH_2Cl_2) visualised by ceric sukphate. The stirred soln was treated with the phosphonate (1.96 g) followed dropwise by K_2CO_3 (3.69 g) in water (16 ml) over 1 hr. After 40 min glyoxylic acid (1.0 g) was added as in Scheme 2. After 30 min the mixture was extracted with toluene (30 ml) and then toluene–EtOAc (2:1, 2 × 30 ml). The combined organic layers were washed with 2N HCl (20 ml), sat $NaHCO_2$ (20 ml) and finally brine (20 ml). The organic phase was dried and then evaporated to a gum which crystallised on trituration with toluene to give **41**, (0.754 g) [30.6% from **19**] isolated as in Scheme 2, and identical to the sample from the latter.

4*β*-[4-(3-*Chloro-phenoxy*-3-*oxobut*-1-*trans-enyl*]-2.3.3 a*β*,6 a*β*-*tetrahydro*-5-(4-*phenylbenzoyloxy*)-2-*oxocyclopenteno* [*b*] *furan* **45**

The hydroxyenone **41** (3.36 g) was dissolved under argon in a mixture of dry toluene (20 ml), THF (10 ml) and pyridine (4 ml). The soln was treated with *p*-phenylbenzoylchloride (3.80 g) and stirred overnight. EtOAc (20 ml) was added and the mixture extracted with water (15 ml) then sat $NaHCO_3$ aq (20 ml), and finally brine. The dried extracts were evaporated to leave a solid which crystallised from acetone (25 ml)–ether (100 ml) to afford **45** (3.6 g) (70%) m.p. 139–142°, 1760, 1710, 1695 cm^{-1}. τ 1.9–3.95 (14 H, m) 3.54 (1 H, d, J = 16 Hz), 4.45–5.05 (2 H, m), 5.34 (2 H, s). (Found: C, 69.6; H, 4.9; Cl, 6.9. $C_{30}H_{25}O_6Cl$ Requires: C, 69.7; H, 4.9; Cl, 6.9%).

Acknowledgements—We wish to thank the Science Research Council for C.A.S.E. Awards to R.P. and N.R.A.B., I.C.I. Limited (Pharmaceuticals Division) for financial support for some of the work carried out at Manchester and permission to publish the work, and Drs. E. D. Brown, R. Clarkson and N. Crossley, I.C.I. Limited, Alderley Park, for their interest and constructive suggestions.

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Tetrahedron, Vol. 37, Supplement No. 1, pp. 421 to 427, 1981
Printed in Great Britain

0040-4020/81/Suppl. 1-0421-07 $02.00/0
Pergamon Press Ltd.

MOLECULAR STRUCTURE AND TAUTOMERISM OF THE 1,3,2-BENZODIOXAARSOLE ETHER OF TROPOLONE

V. I. MINKIN,* L. P. OLEKHNOVICH and V. P. METLUSHENKO
Institute of Physical and Organic Chemistry, Rostov-on-Don University, 344006 Rostov-on-Don, U.S.S.R.

N. G. FURMANOVA
Institute of Crystallography, U.S.S.R.—Academy, Moscow, U.S.S.R.

IOANA BALLY
Institute for Nuclear and Engineering Physics, Bucharest, Roumania

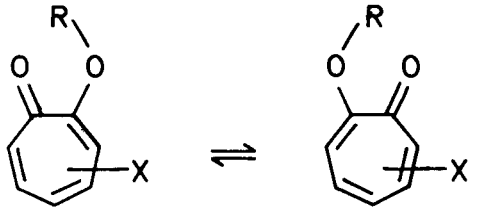
and

ALEXANDRU T. BALABAN*
Organic Chemistry Department, The Polytechnic, Bucharest, Roumania

(*Received in U.K.* 20 *October* 1980)

Abstract—The molecular structure of 2′-tropolonyl-1,3,2-benzodioxaarsole (A) was determined by X-ray analysis substantiating the previous structure assignment as II, and refining it. The molecular structure evidences three short O–As bonds and a longer fourth O–As bond, which however is much shorter than the sum of Van der Waals radii. The incipient intramolecular coordination between the CO oxygen and the As atom requires an unusual configuration (distorted trigonal bipyramid) around the As atom, leading to a conformation which is similar to the structure of the transition state for Berry pseudorotations. This explains the ^{13}C NMR spectra of II which indicates a rapid reversible migration of the 1,3,2-benzodioxaarsole moiety from one tropolone oxygen to another. Since the ^{13}C NMR spectra show no broadening at −70°, the upper limit for the free energy of activation is $\Delta G^{\ddagger}_{-70} < 6.5$ kcal/mole.

Several examples of rapid reversible O,O′-migration were found involving acyl,[1–4] polynitrophenyl[4] and trialkylsilyl groups[5] bonded to tropolone, Ia ⇌ Ib.



Ia ⇌ Ib

R = COR′; p-$C_6H_4NO_2$; $C_6H_3(NO_2)_2$; SiR'_3
X = H; 3,5,7-Me_3; 3,7-$(PhCH_2)_2$

In the present paper we bring evidence that the previously obtained[6,7] analogous derivative (A) of tropolone involving a benzodioxaarsole moiety with trivalent arsenic I,R = As⟨O⟩C_6H_4, X = H, also undergoes an extremely rapid degenerate rearrangement of type Ia ⇌ Ib and we discuss the mechanism of this rearrangement on the basis of spectral and molecular structure data. On the basis of IR and ^{1}H NMR spectra, as well as of electronic absorption spectra in various solvents, a non-chelated structure II had been proposed[6] for this compound A. On the contrary, the analogous derivative with boron instead of arsenic was shown to be fully chelated with pairwise equivalent O atoms.[7]

RESULTS AND DISCUSSION

The proton noise-decoupled ^{13}C NMR spectrum of 2′-tropolonyl-1,3,2-benzodioxaarsole, A, in the

Table 1. ^{13}C NMR spectra of compounds, I, II, V (ppm relative to TMS, in CH_2Cl_2). Only the tropolone carbon resonances are shown

Compound	$C^{(1)}$	$C^{(2)}$	$C^{(3)}$	$C^{(4)}$	$C^{(5)}$	$C^{(6)}$	$C^{(7)}$	Ref.
Ha ⇌ IIb[a]	172.3	172.3	126.4	138.2	130.0	138.2	126.4	[b]
V	175.1	175.1	126.9	146.8	135.4	146.8	126.9	[b]
I,R = OCH_3	180.1	165.0	112.2	132.4	127.6	136.3	136.3	25
I,R = $COCH_3$[a]	178.3	157.5	128.1	132.3	134.1	137.5	139.5	2, 25
I,R = COOMe[a]	177.5	155.2	126.4	130.5	133.1	136.2	136.3	[b]

[a] At −70 °C.
[b] Present work.

temperature range from +100° (in N-methylpyrrolidone) to −70° (in CH_2Cl_2) consists of only seven lines (Fig. 1), indicating that this compound contains a real, or an effective (on the ^{13}C NMR time scale), symmetry plane of the molecule. This deceptively simple ^{13}C NMR spectrum can be explained by one of the following four structural possibilities.

(1) Compound A has a chelate structure with tetracoordinated arsenic and with pairwise equivalent As–O bonds. There are again two possibilities, depicted by structures III and IV for the coordinating centre, namely (i) tetragonal pyramid (III) or (ii) tetrahedral arrangement of oxygen (IV) as found[7,8] for the corresponding 1,3,2-benzodioxaborole derivative of tropolone (V) whose ^{13}C NMR spectrum (Fig. 1 and Table 1) also is temperature independent and consists of seven peaks. However, neither of these two possibilities agrees with the theoretical requirements of

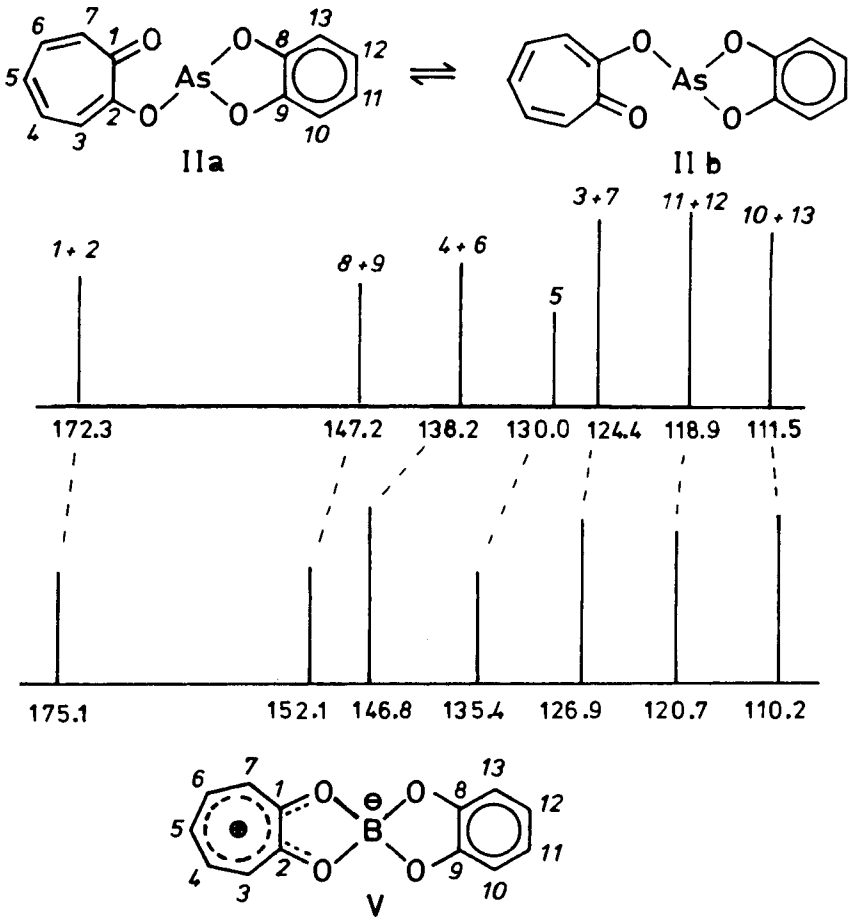
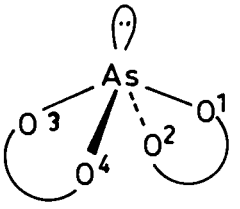
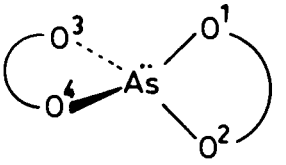


Fig. 1. Proton noise-decoupled ^{13}C NMR spectra of compounds A (II) and V in CH_2Cl_2 at −70°. Chemical shifts are in ppm, referenced to internal TMS.

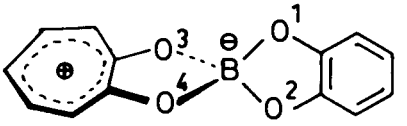
the Valence Shell Electron Pair Repulsion (VSEPR) theory.



III



IV



V

(2) Compound **A** has a tetracoordinated chelate trigonal–bipyramidal structure VI in agreement with the VSEPR theory. Such a structure is only possible when in each of the two chelate 5-membered rings one As–O bond is axial and the other one equatorial, owing to steric reasons (valence angle O–As–O close to 90°, leading to negligible ring strain). In such a structure there is no symmetry plane.

The two As–O bonds in the benzodioxaarsole moiety may differ slightly because one is equatorial and the other is axial; the other two As–O bonds may also be of slightly different lengths since again one of them is axial, the other is equatorial. However, owing to rapid intramolecular rearrangements VIa $\rightleftharpoons$ VIb all bonds become equalized; as indicated by theoretical calculations[9,10] and by analysis of NMR spectra of conformationally non-rigid trigonal bipyramidal structures,[11,12] such polytopal rearrangements occur preferentially through a Berry pseudorotation mechanism[13] involving tetragonal–pyramidal transition states similar to structure III.

(3) Compound A has a tricoordinated As atom in a non-chelate structure II. The observed time averaging of the ^{13}C NMR spectra is explained by rapid direct O,O′-migration of the benzodioxaarsole moiety Ha $\rightleftharpoons$ IIb through a bond breaking (ion pair) mechanism, resulting in intermolecular processes.

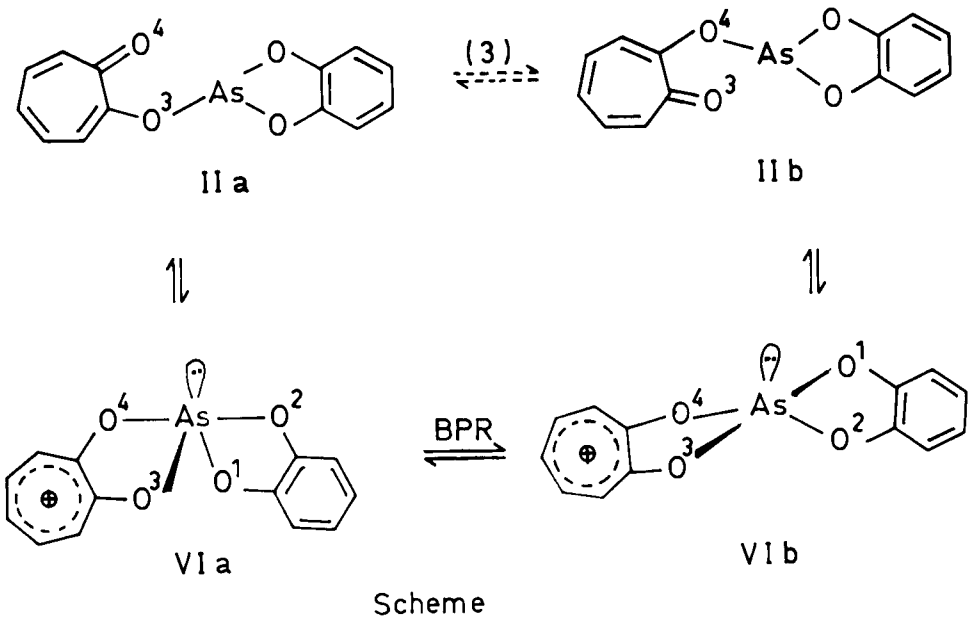
(4) Compound **A** has a tricoordinated arsenic in a practically non-chelate structure II. The O,O′-migration takes place intramolecularly through an associative internal nucleophilic displacement at the tricoordinated arsenic, involving as intermediate or transition state trigonal-bipyramidal structure VI.

The formation and rapid polytopal rearrangement of such intermediate structures are necessary conditions for the axial attack and axial bond breaking of the entering and leaving groups in the AdE mechanism of nucleophilic substitutions involving elements of the fifth and sixth groups in the periodic system.[14,15] Quantum-chemical calculations of the reaction path for this mechanism in nucleophilic substitutions involving P atoms were reported.[16]

Scheme 1 illustrates the last two possibilities, with dotted arrows for (3) and full arrows for (4).

In order to discriminate between these possibilities for compound **A**, its IR spectrum and the X-ray analysis of molecular structure were investigated for ascertaining whether the As–O bonds have pairwise equal lengths as requested by (1) or (2) on the basis of structures III, IV or VI, or whether on the contrary they have a non-chelated structure (II) proposed earlier,[6,7] as required by (3) or (4). The IR spectrum of **A**, either as a solid or in solution (with $CHCl_3$ or $CH\ Cl_2$ as solvents), differs from the spectrum of the corresponding tetrahedral boron chelate V, since **A** evidences a tropone CO stretching band at 1580 cm^{-1}. Such a band exists in all IR spectra of non-chelated compounds I.[4]

X-ray crystallographic analysis of **A** brings decisive data concerning its molecular structure. Figure 2 presents the bond lengths, while Figs. 3 and 4 depict the bond angles. Three As–O bonds are normal covalent bonds which are only slightly longer (1.819–1.879 Å) than ordinary As–O bonds in known tricoordinated arsenic compounds (1.79–1.83 Å)[17] or in spiroarsoranes with pentacoordinated arsenic (1.741–1.817 Å).[18] The fourth As–$O^{(4)}$ bond, however, is appreciably longer, 2.161 Å, indicating that this compound A possesses structure II with a strong intramolecular coordination. The high degree of this intramolecular As–$O^{(4)}$ coordination results from the fact that the indicated bond length is shorter by 1.2 Å relative to the sum of Van der Waals radii for As and O atoms. A consideration of bond angles (Fig. 3) supports this view: the three short As–O bonds are part of a distorted trigonal bipyramid with the arsenic at the centre (two bonds being equatorial, and the third axial with the longest As–$O^{(1)}$ distance, 1.879 Å, from these



Scheme

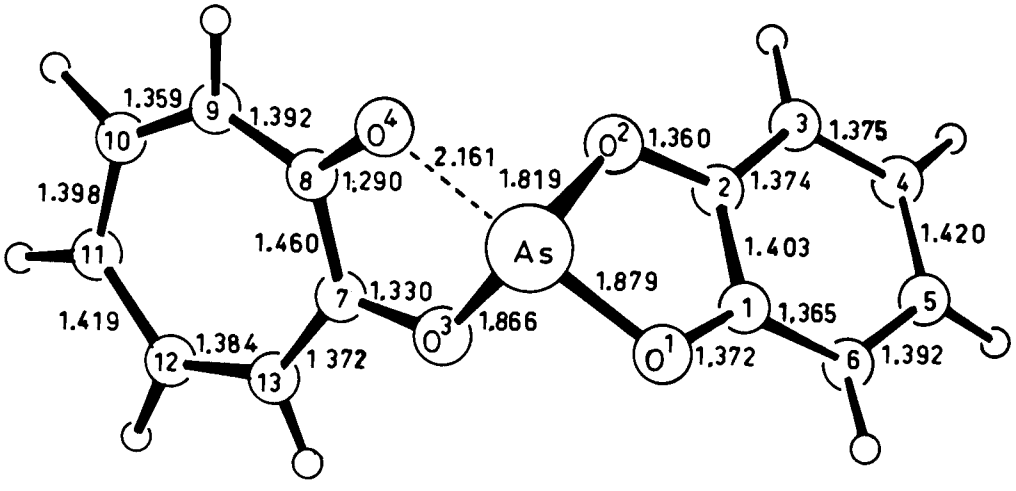


Fig. 2. Projection of the molecule II on the *ab* plane of the unit cell and bond lengths (in Å). Standard deviations of bond lengths: As–O, 0.004; C–O and C–C, 0.008–0.013 Å. Bond lengths for C–H bonds: 0.88–1.22 Å with σ(C–H) = 0.07–0.08 Å.

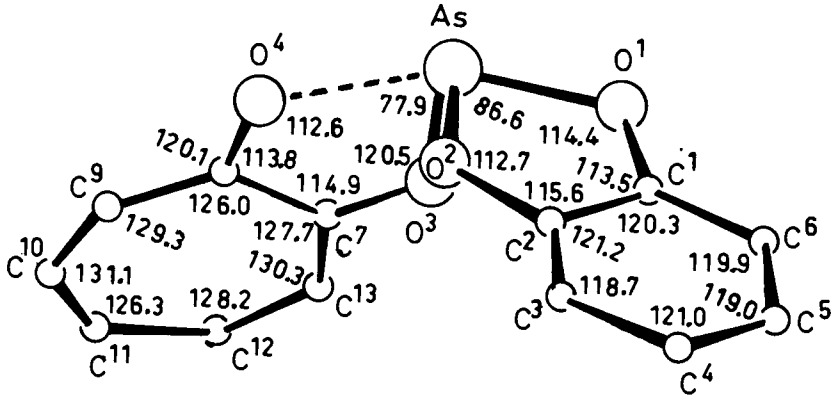


Fig. 3. Projection of the molecule II on the plane $O^{(1)}$–As–$O^{(4)}$ and valence angles (only two O–As–O angles are shown here, the other ones are presented in Fig. 4). Standard deviations of angles: O–As–O, 0.2°; As–O–C, 0.4°; O–C–C and C–C–C, 0.6–0.8°.

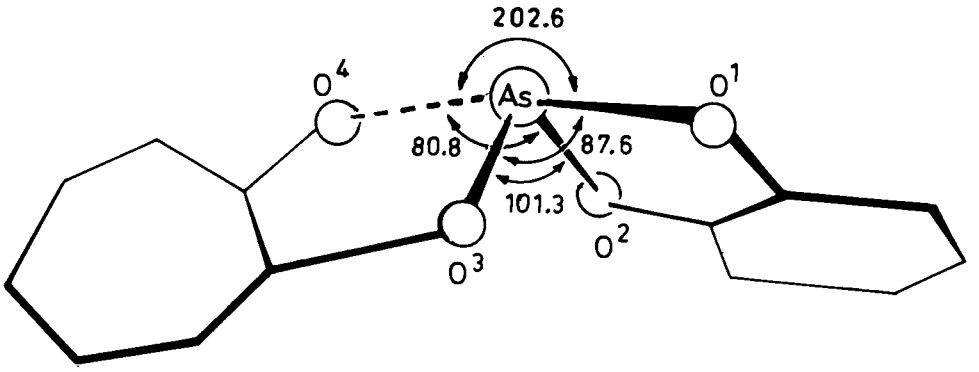


Fig. 4. Another view of molecule II along the plane of the benzenoid ring showing the remaining four angles around the arsenic atom. The chirality of the frozen molecule is clearly apparent.

three bonds). The long As–$O^{(4)}$ bond constitutes the second axial bond. The whole assembly around the arsenic atom is a trigonal bipyramid VI (where one equatorial ligand, invisible on Figs. 2–4, is the unshared electron pair) distorted towards a tetragonal pyramid III.

In the tropolone moiety the C–O vonds are also non-equivalent, in that the carbonyl bond $C^{(8)}{=}O^{(4)}$ has a length of 1.290 Å (it coordinates intramolecularly by nucleophilic attack, to a certain extent, the tri-coordinated As atom), while the $C^{(7)}$–$O^{(3)}$ bond length is 1.330 Å. As a whole, the molecular structure of this tropolone fragment is close to that of tropolone derivatives with intramolecular H-bonds, in which there is a substantial contribution of a tropolonic structure with localized double bonds and delocalized 10 π-electron system.[19] There is a remarkably close similarity between structure II and the tautomeric tropolone ethers I, e.g. the 2,6-dinitrophenyl ether of 3,5,7-trimethyltropolone,[20] although in the latter compound the delocalized structure has a smaller contribution.

The above particular aspects of the molecular structure reveal a very close similarity to the structure of the transition state in the rearrangement VIa $\rightleftharpoons$ VIb, explaining the extremely rapid migration of the benzodioxaarsole fragment between the two O atoms of the tropolone moiety. These aspects also suggest a preferential AdE-mechanism of the rearrangement which includes a supplementary polytopal rearrangement of the intermediate, i.e. IIa $\rightleftharpoons$ VIa $\rightleftharpoons$ VIb $\rightleftharpoons$ IIb. Indeed, as shown by several analyses,[21,22] molecular deformations in crystalline phase mirror exactly the lowest energy pathways for intramolecular rearrangements; thus the unusually large difference found between the sum of Van der Waals radii for As and O atoms (3.4 Å with Pauling's values) and the length of the As–$O^{(4)}$ bond in IIa indicates that in the stable conformation presented in Figs. 2–4, the intramolecular reaction is already strongly displaced along the reaction coordinate towards the end product IIb.

Analogously, it may be remarked that the 2,6-dinitrophenyl ether of 3,5,7-trimethyltropolone (which rearranges between structures Ia $\rightleftharpoons$ Ib with R = 2.6-$(O_2N)_2C_6H_3$ and X = Me_3) has a strong attractive interaction between the CO oxygen and the *ipso*-C atom, manifested in a shortening of this C...O distance with 0.55 Å relative to the sum of Van der Waals radii; the O,O′-migration of the dinitrophenyl group in this compound also proceeds with such a high frequency that the reaction rate can no longer be determined by dynamic NMR spectroscopy.[4]

Thus the data we obtained for the 2′-tropolonyl-1,3,2-benzodioxaarsole (A) agree with mechanism (4) for the migration of the arsinyl group. Though mechanism (3) cannot be completely ruled out, this is an unlikely pathway since, on adding to a solution of II a solution of the 2,4-dinitrophenyl ether of 3,5,7-trimethyltropolone (for this compound, dynamic NMR spectroscopy allows[4] the determination of $\Delta G^{\neq}_{25}$ = 11.7 kcal/mol), NMR spectroscopy indicates the presence of two independent processes; intermolecular or dissociative pathways would have resulted in interactions between the two reactions. On the other hand, an intermolecular mechanism was advocated[24] for the O,C-transfer of AsR_2 groups in elementotropic ketoenolic equilibration of O- and C-arsenylated ketones, since the rate of these equilibrations increases on adding R_2AsCl.

One may estimate the upper limit of the energy barrier and the frequency of the arsinyl migration of II by comparing its time—averaged ^{13}C NMR spectrum (Fig. 1) with NMR spectra of compounds I whose tautomerization is either absent (R = CH_3), or can be "frozen" at low temperatures (R = COOMe, $COCH_3$), as presented in Table 1.

In the absence of a degenerate rearrangement IIa $\rightleftharpoons$ IIb, the difference between the chemical shifts of $C^{(1)}$ and $C^{(2)}$, by analogy with compounds I, ought to be at least 20–25 ppm (500–600 Hz at the working frequency, 25.2 MHz, of the NMR spectrometer). Since even at −70° in the ^{13}C NMR spectra of II one cannot observe any line broadening of the peaks corresponding to isochronous nuclei (Fig. 1), the frequency of arsinyl migration at this temperature must be higher than 10^5–10^6 sec^{-1}, and therefore $\Delta G^{\neq}_{-70}$ < 6.5 kcal/mole. This value is lower than the energy barrier of trialkylsilyl O,O′-migration in tropolone derivatives (I, R = $SiAlk_3$), which was estimated by line broadening of the averaged $C^{(1)}$ and $C^{(2)}$ peaks at low temepratures to be approximately 8 kcal/mole.[5] The frequency for II is

Table 2. Atomic coordinates ($\times 10^4$ for non-hydrogen atoms, and $\times 10^3$ for hydrogens).

Atom	x	y	z	Atom	x	y	z
As	4343 (0)	3723 (1)	4559 (1)	$C^{(10)}$	6243 (3)	2762 (6)	1325 (10)
$O^{(1)}$	3723 (2)	4711 (4)	4258 (6)	$C^{(11)}$	6364 (3)	3838 (7)	657 (9)
$O^{(2)}$	3970 (2)	2692 (4)	3319 (6)	$C^{(12)}$	6023 (3)	4844 (6)	754 (9)
$O^{(3)}$	4726 (2)	4596 (4)	3045 (6)	$C^{(13)}$	5511 (3)	4981 (6)	1517 (8)
$O^{(4)}$	5040 (2)	2603 (4)	3950 (6)	$H^{(3)*}$	329 (3)	167 (7)	144 (9)
$C^{(1)}$	3340 (3)	4245 (6)	3222 (8)	$H^{(4)}$	233 (3)	253 (8)	60 (9)
$C^{(2)}$	3478 (3)	3121 (5)	2734 (7)	$H^{(5)}$	208 (3)	462 (7)	114 (10)
$C^{(3)}$	3130 (3)	2511 (7)	1738 (8)	$H^{(6)}$	280 (3)	567 (7)	300 (9)
$C^{(4)}$	2642 (4)	3026 (8)	1210 (10)	$H^{(9)}$	581 (3)	152 (7)	272 (10)
$C^{(5)}$	2501 (3)	4171 (8)	1667 (10)	$H^{(10)}$	658 (3)	222 (7)	111 (9)
$C^{(6)}$	2859 (3)	4763 (6)	2689 (10)	$H^{(11)}$	681 (3)	396 (7)	23 (10)
$C^{(7)}$	5213 (3)	4227 (6)	2449 (8)	$H^{(12)}$	621 (3)	551 (7)	33 (9)
$C^{(8)}$	5373 (3)	3058 (5)	2916 (8)	$H^{(13)}$	529 (3)	558 (6)	136 (9)
$C^{(9)}$	5819 (3)	2418 (6)	2299 (9)				

* The numbering of hydrogens is identical to the numbering of the carbons bonded to them.

similar to that calculated on the basis of ESR spectroscopy for the interligand exchange of the odd electron in a stable radical derived from 2′-(*o*-phenoxyloxy)-1,3,2-benzodioxaarsole,[26] in which the arsinyl migration involves an intramolecular homolytic substitution at the tricoordinated As atom.

Thus II, the 1,3,2-benzodioxaarsole ether of tropolone, more than other tropolone derivatives of type I,[1–5,20] illustrates the possibility of modelling extremely rapid rearrangements based on the idea of matching the structure of starting materials with the structure of the transition state in the rearrangement.

EXPERIMENTAL

The ^{13}C NMR spectra were recorded with a Varian XL-100 spectrometer using TMS as internal standard. IR spectra were recorded on a Specord IR-71 instrument. Compounds II[6] and V[7] were prepared as described previously, and were purified by repeated recrystallizations from benzene and n-hexane. O-Carboxymethyltropolone (I, R = COOMe), m.p. 78° from n-hexane, was obtained in 60% yield from the sodium salt of tropolone and methyl chloroformate in benzene.

X-Ray crystallography. Single crystals of II were grown from the analytically pure compound using n-hexane as solvent. The crystals of $C_{13}H_9AsO_4$ are rhombic with a = 23.693(5), b = 11.577(12), c = 8.456(2) Å, calculated density 1.75 g/cm^3, z = 8. Space group P_{bca}. The parameters of the unit cell were determined on an automatic diffractometer CAD-4F, using Mo-K_α X-rays and a graphite monochromator. The intensities of 1359 reflexions were measured with $I > 2\sigma$ (I) ($\theta/2\theta$ scanning, $1° < \theta < 25°$).

The molecular structure was determined by the heavy atom method and was refined by the full matrix least square method in the anisotropic approximation till R = 0.069. All calculations were effected using a computer program.[27] At this stage of the difference synthesis the H atoms appeared. Further structure refinement, including the coordinates and the isotropic temperature factors for the H atoms, led to the final value R = 0.063. The atomic coordinates are presented in Table 2. The bond lengths and bond angles may be seen on Figs 2–4. The table of the temperature factors is available on request.

Acknowledgement—The authors express their gratitude to Z. N. Budarina for a sample of O-carboxymethyltropolone and for assistance in the purification of compound H.

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A CONVENIENT SYNTHESIS OF α-AMINO-β-LACTAMS[1,a]

AJAY K. BOSE*, M. S. MANHAS, J. M. VAN DER VEEN, S. G. AMIN, I. F. FERNANDEZ, K. GALA, R. GRUSKA, J. C. KAPUR, M. S. KHAJAVI, J. KREDER, L. MUKKAVILLI, B. RAM, M. SUGIURA and J. E. VINCENT

Department of Chemistry and Chemical Engineering, Stevens Institute of Technology, Hoboken, NJ 07030, U.S.A.

(*Received U.S.A.* 5 *August* 1980)

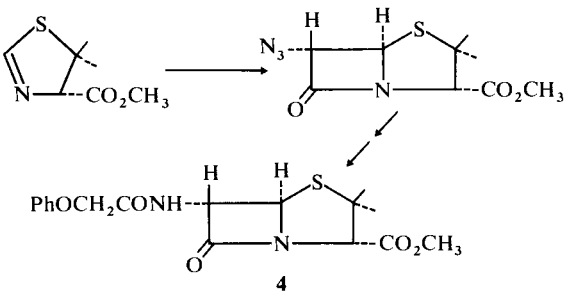
Abstract—A safe and convenient method is described for the synthesis of α-amido-β-lactams starting with glycine and an azomethine. The amino group of glycine is protected by reaction with a β-dicarbonyl compound following the method of Dane *et al.* and the carboxyl group is activated through the formation of a mixed anhydride or an active ester. Condensation between these glycine derivatives and acyclic or cyclic imino compounds (including thioimidates) in presence of triethylamine leads to stereospecific synthesis of 3-(β-carbonyl-vinylamino)-2-azetidinones in 40–60% yield. The vinylamino side chain can be hydrolyzed under mild acid conditions to form 3-amino-2-azetidinones which can be acylated to α-amido-β-lactams. Alternatively, the vinylamino side chain can be converted to an amido side chain by ozonolysis. The molecular parameters of a 3-(β-carbonyl-vinylamino)-2-azetidinone were determined by X-ray crystallography. Usefulness of this α-amido-β-lactam synthesis is illustrated by the preparation of isotope-labeled β-lactams and intermediates for some β-lactam antibiotics.

Penicillins, cephalosporins and other major β-lactam antibiotics in clinical use are characterized by the presence of a 3-amido-2-azetidinone unit. Therefore, synthetic approaches to them and their analogs require an easy access to α-amido-β-lactams under conditions that will not cleave or rearrange the β-lactam ring. To be of practical value such synthetic methods should be safe and economical when attempted on a large scale.

α-Azido-β-lactam approach

In 1967 we[2] reported a method for the synthesis of α-amido-β-lactams that utilizes an azido group as a cryptoamino function. The first step in this synthesis is the reaction between azidoacetyl chloride (**1**) (or mixed anhydride or an active ester) and an azomethine (**2**) in presence of a tertiary amine to produce an α-azido-β-lactam (**3**). Reduction of the azido group and subsequent acylation can be conducted under mild conditions that do not affect the β-lactam ring.

This method was used in our laboratory for a stereospecific, total synthesis of a 6-epi-penicillin ester[3] (**4**).



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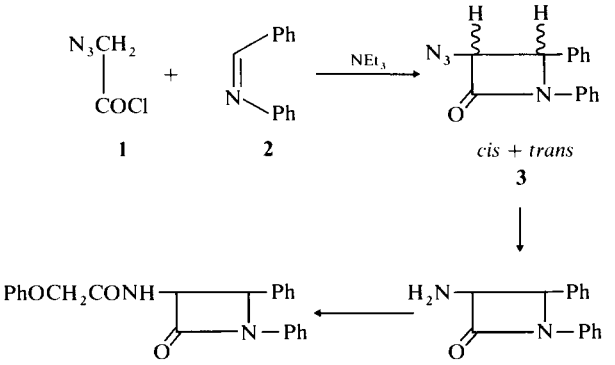
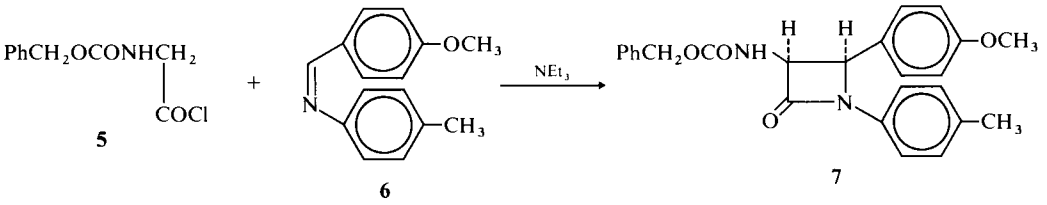
Many other laboratories[4] have adopted the α-azido β-lactam approach for the total synthesis of diverse types of β-lactam antibiotics including penicillins, cephalosporins and nocardicins.

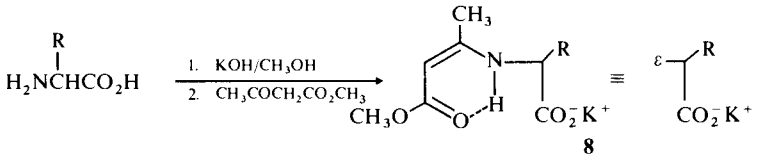
The α-azido-β-lactam approach suffers from a disadvantage in that it is unsuitable for use on a large scale because of the potential of azidoacetic acid and its derivatives for explosive decomposition. To avoid the use of hazardous chemicals, we have attempted to



1 **2** *cis + trans* **3**

[a] Dedicated to the memory of Robert Burns Woodward, this paper will be included in the Book version of the special Woodward Memorial Supplement.





devise alternative methods for the synthesis of 3-amino-2-azetidinones.

One step α-carbamato-β-lactam synthesis

We[5] have found that N-carbobenzyloxyglycyl chloride (**5**) reacts with a Schiff base (**6**) and a tertiary amine to produce a *cis*-β-lactam (**7**) with a carbamate side chain. Alternatively, t-BOC-glycine can be used in the form of a mixed anhydride in place of N-carbobenzyloxyglycine. The carbamate group can be converted to an amino group under mild conditions. This method has received very limited attention so far.[6] The starting glycine derivatives are not very economical for large scale use.

α-Vinylamino-β-lactam approach

Continuing our search for a safe and economical synthesis of α-amido β-lactams we have investigated the possibility of using a protective group developed by Dane *et al.*[7] for peptide synthesis. The key to this approach is the easy formation of a "Dane salt" (**8**) by allowing methanol solution of the potassium salt of an α-amino acid to react with a β-dicarbonyl compound, for example, methyl acetoacetate. The protective group can be removed efficiently under very mild acid treatment.

Synthesis of 3-(β-carbonyl-vinylamino)-2-azetidinones. We[8] have discovered that Dane salts from glycine can be allowed to react with a chloroformate ester first and then with a Schiff base and triethylamine to produce 3-(β-carbonyl-vinylamino)-2-azetidinones in 40–60% yield. The annelation reaction is stereospecific—only *cis*-β-lactams (**9**) were formed with the Schiff bases studied.

The protective group could be removed by treatment with a weak acid such as, p-toluenesulfonic acid monohydrate to afford *cis*-3-amino-2-azetidinones (**10**) which could be acylated to the desired α-amido-β-lactams (**11**).

We have studied several aspects of this new synthesis of α-amido-β-lactams. Some of our findings are presented here.

Scope of the reaction. There are four essential components of this β-lactam forming reaction each of which is considered below.

(a) *α-Amino acid.* Dane salts from alanine and phenylalanine have been used before for the preparation of esters and peptides. We were unsuccessful in obtaining any β-lactam from the reaction of these two N-protected amino acid salts, ethyl chloroformate, triethylamine and benzalaniline. Under identical conditions the Dane salts from glycine afforded α-vinylamino-β-lactams but the yield did not exceed 60%. The other reaction products have not been identified but it is known that vinylamino ketones are multifunctional, reactive molecules capable of undergoing various types of reaction.

Auricchio *et al.*[9] have reported the formation of substituted aniline as well as pyridine derivatives from 4-ethylamino-3-penten-2-one.

Gupta[10] has found that vinylamino acid salts and alkyl chloroformates react together to produce 1,3-oxazolidin-5-ones in high yield.

In another communication Gupta[11] has reported

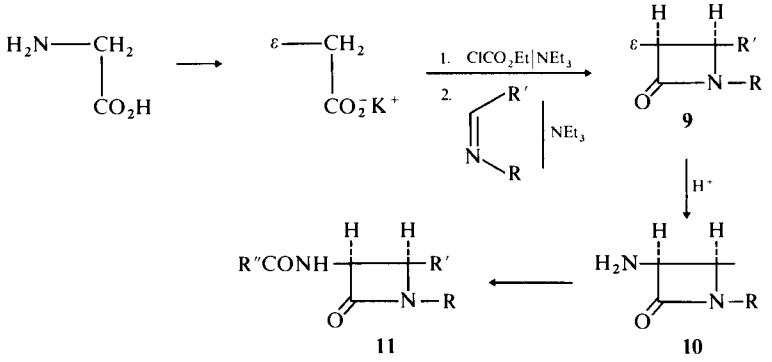
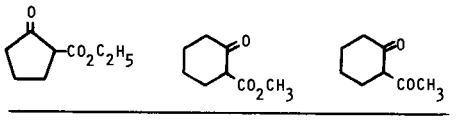


Table 1. β-Dicarbonyl compounds used for β-lactam synthesis R–CO–CH_2–CO–R′

	R	R′
(a)	CH_3	OCH_3
(b)	CH_3	OC_2H_5
(c)	CH_3	$OC(CH_3)_3$
(d)	CH_3	CH_3
(e)	C_6H_5	CH_3



that vinyl-amino acid salts react with trifluoroacetic anhydride to produce pyrrole derivatives.

(b) *β-Dicarbonyl compounds.* Probably the most economical β-dicarbonyl compounds to use for preparing Dane salts from glycine are ethyl and methyl acetoacetates. The size of the ester group does not appear to affect the ring closure reaction: the t-butyl ester of acetoacetic acid produces about the same yield of β-lactam as the methyl ester. Table 1 shows the various β-dicarbonyl compounds used as the protective group for the synthesis of 3-(β-carbonyl-vinylamino)-2-azetidinones.

Cyclic β-keto esters also can be used, as can substituted acetoacetate esters, for example, methyl phenylacetoacetate.

β-Diketones, such as acetylacetone and benzoylacetone can be employed but β-lactam formation is slower and the yield is smaller.

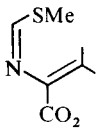
(c) *Reagents for activating the carboxyl group of N-protected glycine.* Haloformate esters, such as, methyl, ethyl, isobutyl or t-butyl chloroformate, in presence of triethylamine were found to be suitable for activating the carboxyl group of the β-carbonyl-vinylamino acetic acid salts. Chloroacetonitrile which has been employed for peptide bond formation reaction of Dane salts was found to be ineffective for β-lactam synthesis.

Table 2 shows the yield of β-lactam obtained from one imino compound using a number of activating agents for the carboxyl group.

Sharma and coworkers[12] have shown that phosphorus oxychloride and triethylamine are suitable for producing β-lactams from "Dane salt" and imino compounds.

An activating agent that is economical as well as very effective is cyanuric chloride. The work-up procedure is easy and the β-lactam product is usually quite pure.[13]

(d) *Azomethines.* We have tested a number of imino compounds (Tables 3a and 3b) and found that the rate of β-lactam formation can vary considerably, but, in every case we have obtained only a single isomer of the β-lactam. Thioimidates (**12**) can also serve as the imino component for the stereoselective β-lactam forming reaction. With Schiff bases the stereochemistry of the β-lactam was *cis*, while with thioimidates only the *trans* isomer (**13**) was formed.



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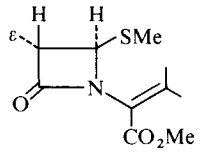

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Bicyclic and tricyclic β-lactams were prepared from cyclic imino compounds (Table 3a, b). The β-lactam formation was again stereospecific but it was not possible in most cases to deduce the stereochemistry of the β-lactam from ^{1}H NMR spectra.

Table 2. Some reagents for activating carboxyl groups

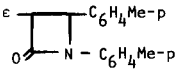
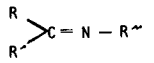
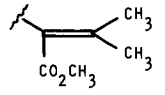
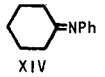
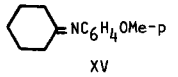
Condensing Agents	Yield of β-lactam
	
$C\ell CO_2Me$ + NEt_3 $C\ell CO_2Et$ + NEt_3 $C\ell CO_2CH_2CHMe_2$ + NEt_3 $C\ell CO_2CMe_3$ + NEt_3	40 - 60%
$C\ell - \overset{O}{\overset{\uparrow}{P}}(OEt)_2$	30%
$C\ell - \overset{O}{\overset{\uparrow}{P}}(OPh)_2$	20%
$(CF_3CO)_2O$	5%

Table 3(a). Some acyclic imines used for β-lactam synthesis



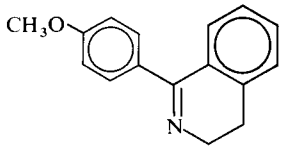
	R	R′	R″
I	Ph	H	Ph
II	$C_6H_4N(CH_3)_2$ – p	H	Ph
III	$C_6H_4N(CH_3)_2$ – p	H	$C_6H_4SCH_3$ – p
IV		H	$C_6H_4OCH_3$ – p
V	$C_6H_4OCH_3$p	H	$C_6H_4CH_3$ – p
VI	SCH_3	H	
VII	SCH_3	Ph	Ph
VIII		H	$CH_2C_6H_3(OCH_3)_2$ – 3,4
IX		H	$CH_2C_6H_3(OCH_3)_2$ – 2,4
X	CH=CHPh	H	$C_6H_4OCH_3$ – p
XI	——— $(CH_2)_5$ ———		Ph
XII	Ph	H	$CH_2C_6H_3(OCH_3)_2$ – 3,4
XIII	Ph	H	$CH_2C_6H_3(OCH_3)_2$ – 2,4
	 XIV		 XV

X-ray crystallography of a vinylamino-β-lactam. In the case of the vinylamino-β-lactam (**15**) prepared from the bicyclic imine (**14**), we carried out single crystal X-ray diffraction study to determine the stereochemistry as well as exact molecular parameters. This compound crystallizes as clear, colorless prisms. A crystal having the dimensions 0.30 × 0.30 × 0.30 mm was used for data collection.

Crystal data: $C_{24}H_{26}N_2O_4$, M = 406.5. Monoclinic, $a = 8.913\,(2)$, $b = 9.608\,(2)$, $c = 25.517\,(5)$ Å, $\beta = 96.16\ (2)^0$, Dc = 1.24 g/cm^3, Z = 4. Space Group $P2_1/c$ (hO1:1 = 2n + 1 absent). Ni—filtered CuK_α radiation, $\lambda = 1.5418$ Å, $\mu\,(CuK_\alpha) = 6.98\,cm^{-1}$.

The structure was solved using the direct phasing program *Multan*.[14] The resulting E-map revealed 28 of the 30 non-hydrogen atoms. A difference–electron density map obtained from this phasing model showed the remaining two atoms, as well as the fact that one of these was clearly disordered. Since the two peaks labelled C (17) and C (117) corresponding to this disordered methyl were of equal size, each was assigned an occupation factor of 0.5. Subsequent refinement of these occupation factors gave unreliable results, (probably due to additional disorder in their positions, as evidenced by their high and unsymmetrical thermal parameters) and so the occupation factors were fixed at 0.5.

Full matrix least-squares refinement using isotropic and then anisotropic thermal parameters resulted in an R-factor of 11.3%. The hydrogen atom



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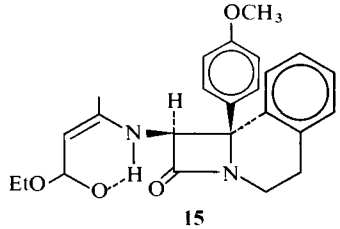
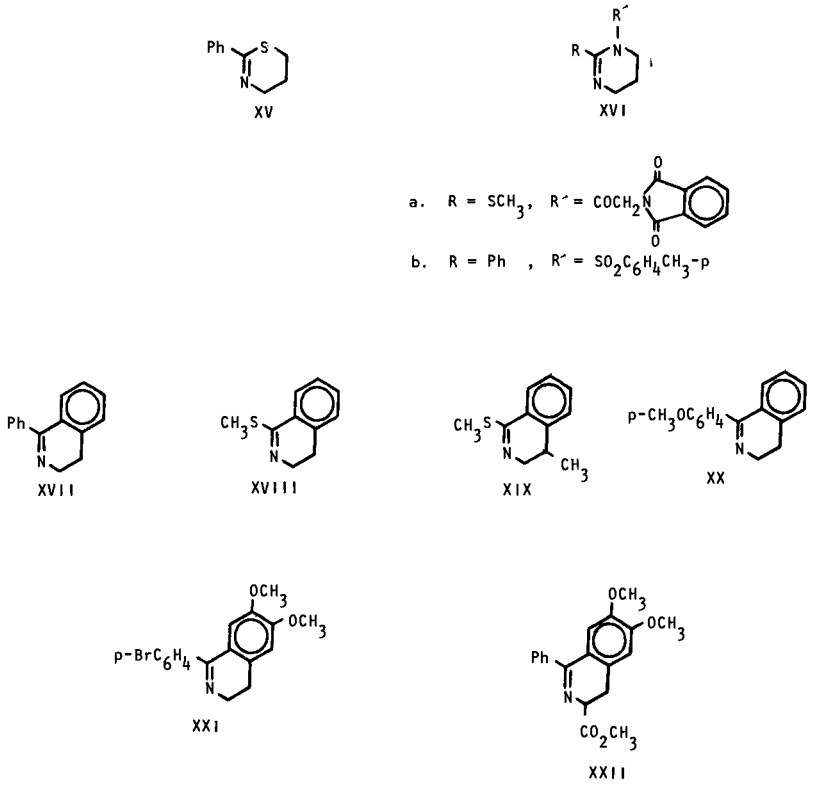


15

Table 3(b). Some cyclic imines used for β-lactam synthesis



positions were then calculated, when possible, from known atom positions, or else were located on difference electron density map, the hydrogen atoms labelled H (116A) and H (116B) were calculated using the coordinates of C (117). Their positional and thermal parameters were held constant during subsequent refinement, which gave a final R-factor of 9.4 % and a weighted R (using unitary weights) of 10.8 %. Adopting the weighting scheme:

$$W = [\sigma_F^2 + (0.009F)^2]^{-1}$$

further refinement resulted in an R-factor of 8.8 % and a weighted R of 12.9 %. H atom positions were not refined as they drifted too much from their original positions.

An ORTEP drawing of the molecule is shown in Fig. 1. Final positional parameters are shown in Table 4a, b. There is a H-bond between atoms N (2) and O (2) with the following parameters.

N (2) – O (2) 2.712 (2) Å

H (N2) – O (2) 1.923 Å

∠ N (2) – H (N2) – O (2) 117.2°

The 6-member ring defined by O (2), C (15), C (14), C (13), N (2), H (N2), is planar with the average deviation from planarity of 0.023 Å.

The β-lactam ring defined by N (1), C (2), C (3), C (4) is planar with an average distance from the plane of 0.023 Å. The N (1) atom however lies 0.17 Å above the plane defined by its three substituents. In biologically active penicillins and cephalosporins this nitrogen is 0.40 Å above the equivalent plane and this has been proposed as an essential condition for antibiotic activity.[15]

The X-ray structure established the vinyl amino structure of **15** rather than that of the imine tautomer. This was confirmed by subsequent oxidation of the double bond to yield an amide. The amino groups and anisyl groups are in *cis* configuration as shown in Fig. 1.

Some applications of the α-vinylamino-β-lactam synthesis. (a) *Synthesis of intermediates for β-lactam antibiotics.* In a previous publication we have reported the synthesis of N-unsubstituted *cis*-3-amido-2-azetidinones (**16a**) by using the α-vinyl amino approach[8b] (Scheme 1).

We have also prepared **17** which we have converted to a key intermediate (**16b**) for the synthesis of isocephalosporins by our method.[16] (Scheme 2.)

The α-vinylamino-β-lactam approach has also been used for the synthesis of an intermediate (**18**) for nocardicins.

The thioimidate ester (**12**)[17] which is readily obtained from penicillin was used as the imino component for condensation with the Dane salt. A single isomer of the α-vinylamino-β-lactam (**13**) was

Table 4(a). Fractional atomic coordinates for hydrogen atoms with estimated standard deviations in parentheses

ATOM	X	Y	Z
H N2	.2621	.6878	.0521
H 3	.1334	.7753	.1478
H 5A	.4840	.3979	.2077
H 5B	.4036	.5015	.2544
H 6A	.2617	.2682	.1872
H 6B	.2647	.2928	.2558
H 8	.0079	.3049	.2741
H 9	-.2448	.4084	.2563
H 10	-.3019	.5748	.1846
H 11	-.1003	.6405	.1278
H 14	.1913	1.0393	.0014
H 16A	.3733	.7547	-.1123
H 16B	.1775	.7271	-.1262
H 17A	.1557	.9404	-.1755
H 17B	.3516	.9680	-.1615
H 17C	.2845	.8234	-.1999
H 18A	.2380	.9930	.1390
H 18B	.1580	1.1020	.0880
H 18C	.0450	.9660	.1120
H 20	-.0273	.4261	.0730
H 21	-.0035	.3008	-.0109
H 23	.4757	.3449	.0131
H 24	.4528	.4694	.0981
H 25A	.4411	.3193	-.0722
H 25B	.4469	.1571	-.0397
H 25C	.3814	.1685	-.1066
H 116A	.2811	.6987	-.1073
H 116B	.1715	.8101	-.1510
H 117A	.3866	.9649	-.1530
H 117B	.4962	.8536	-.1092
H 117C	.4231	.7920	-.1724

Table 4(b). Fractional atomic coordinates for non-hydrogen atoms with estimated standard deviations in parentheses

ATOM	X	Y	Z
O 1	0.4570(2)	0.7670(2)	0.19236(8)
O 2	0.2726(2)	0.7109(2)	-0.02231(6)
O 3	0.2379(3)	0.8953(2)	-0.07616(7)
O 4	0.2378(2)	0.2498(2)	-0.05076(6)
N 1	0.3356(2)	0.5532(2)	0.17551(7)
N 2	0.2300(2)	0.7602(2)	0.07973(7)
C 2	0.3605(3)	0.6909(3)	0.17104(8)
C 3	0.2173(2)	0.7098(2)	0.13190(8)
C 4	0.1955(2)	0.5483(2)	0.13891(8)
C 5	0.3811(3)	0.4497(3)	0.2158(1)
C 6	0.2533(3)	0.3458(3)	0.2176(1)
C 7	0.0982(3)	0.4114(3)	0.2099(1)
C 8	-0.0154(4)	0.3771(4)	0.2414(1)
C 9	-0.1573(4)	0.4365(4)	0.2320(1)
C 10	-0.1881(3)	0.5290(3)	0.1921(1)
C 11	-0.0762(2)	0.5669(2)	0.16021(9)
C 12	0.0662(2)	0.5085(2)	0.16968(8)
C 13	0.2027(3)	0.8926(2)	0.06270(9)
C 14	0.2126(3)	0.9308(2)	0.0120(1)
C 15	0.2438(3)	0.8347(3)	-0.02854(9)
C 16	0.2668(6)	0.8086(4)	-0.1196(1)
C 17	0.274(2)	0.893(1)	-0.1664(3)
C 18	0.1646(5)	0.9972(3)	0.1026(1)
C 19	0.2097(2)	0.4601(2)	0.09050(8)
C 20	0.837(2)	0.4096(2)	0.05958(8)
C 21	0.0973(2)	0.3388(2)	0.01350(8)
C 22	0.2386(2)	0.3170(2)	-0.00357(8)
C 23	0.3657(2)	0.3645(2)	0.0269(1)
C 24	0.3510(2)	0.4337(2)	0.07359(9)
C 25	0.3802(4)	0.2233(4)	-0.0695(1)
C 117	0.393(2)	0.860(1)	-0.1419(6)

obtained. Hydrolysis of the side chain with *p*-toluenesulfonic acid monohydrate in acetone–water followed by acylation with phenyl–acetyl chloride provided the amido-β-lactam (**19**). Proton NMR studies established the *trans* stereochemistry of this β-lactam ($J_{3,4}$ = 1.5 Hz).

Raney nickel hydrogenation led to the desulfurized product (**20**). To obtain the corresponding N-unsubstituted β-lactam, Stoodley's method was used. Treatment of **20** with N-bromosuccinimide under acidic conditions led to the bromohydrin in excellent yield. Subsequent treatment with triethylamine provided the desired lactam **18** in 87% yield. Intermediates such as **18** may be N-alkylated by known methods to nocardicin analogs.[19]

(b) *Synthesis of stable isotope labeled β-lactams.* Concern over radiation hazard from radio isotope labeled compounds for studies in the human—especially, children and women of child-bearing age is reflected in the growing interest in stable isotope labels

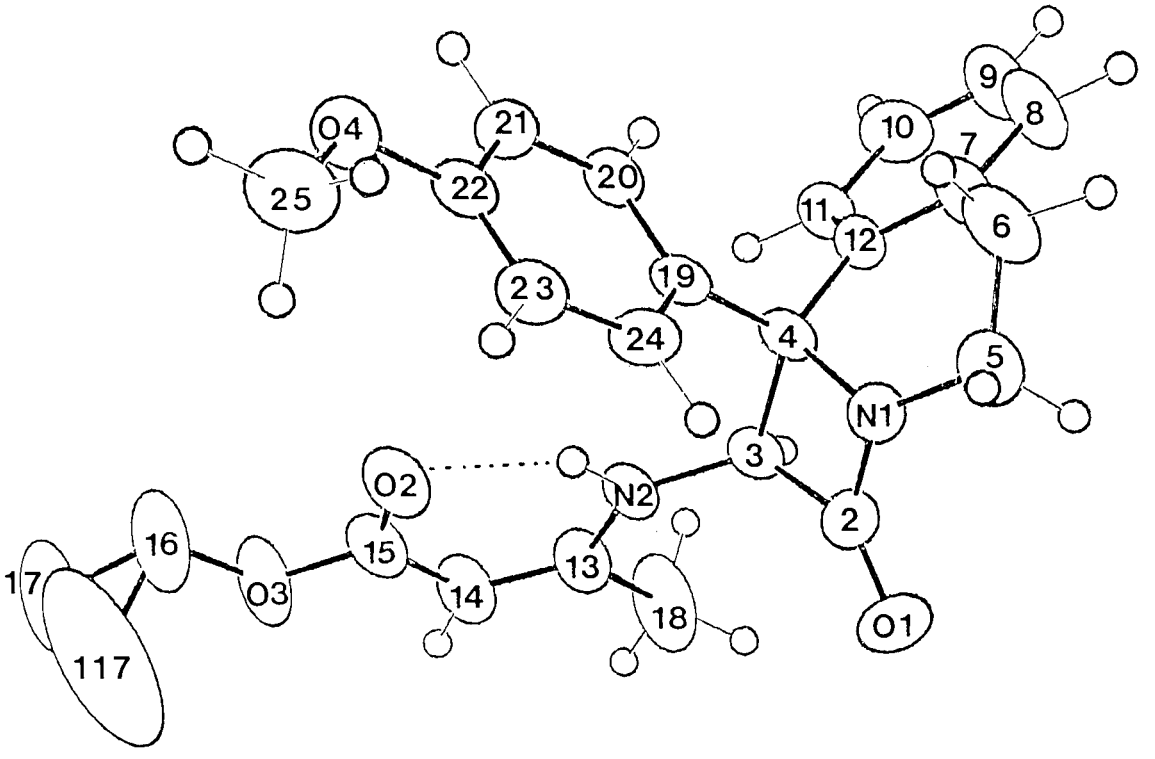
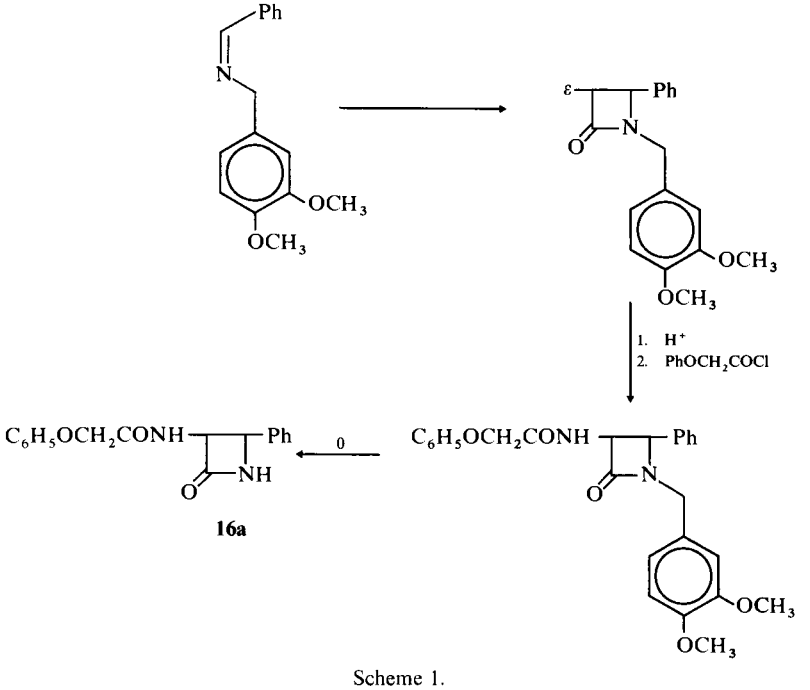
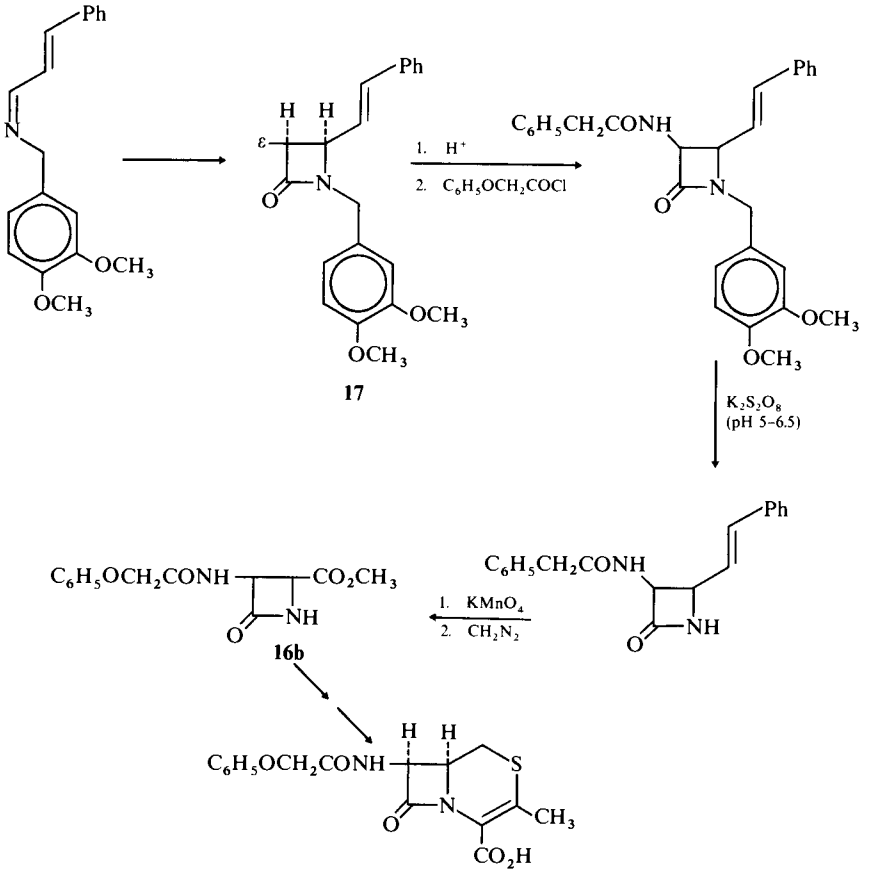


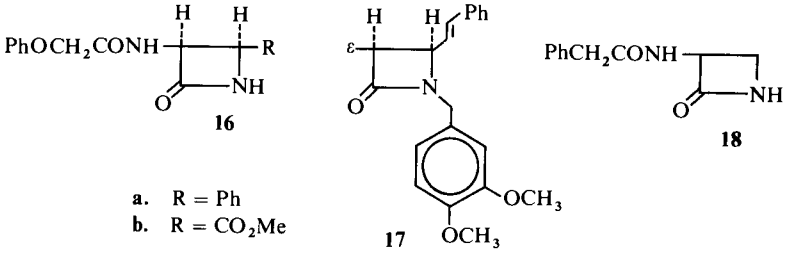
Figure 1.

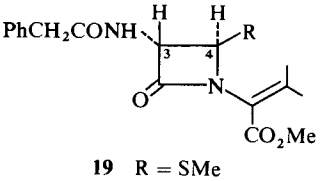


Scheme 1.

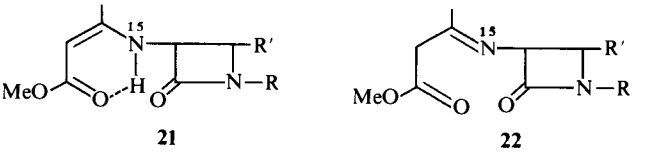


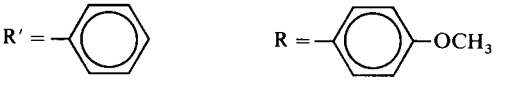
Scheme 2.

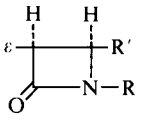




19 R = SMe
20 R = H







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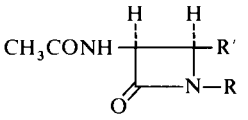

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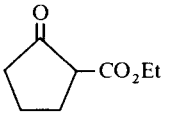

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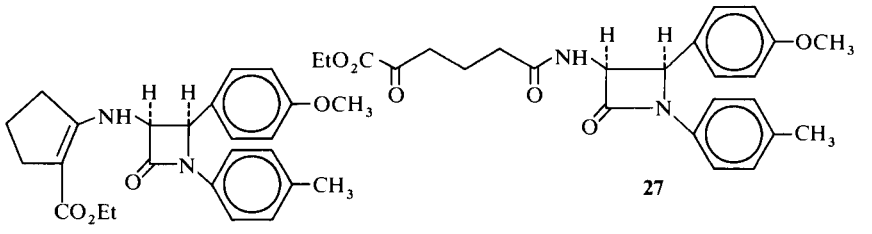


26 27

for metabolic and diagnostic studies. The α-vinylamino-β-lactam synthesis provides a convenient and economical route to α-amino-β-lactams bearing one or more stable isotope labels (^{13}C, ^{2}H, ^{15}N, ^{18}O).

Glycine is commercially available with high levels of stable isotopes. When we condensed the "Dane Salt" from [^{15}N]-glycine with benzylidene-p-anisidine, a labeled β-lactam (**21**) was obtained in about 60% yield. Study of the ^{1}H and ^{13}C NMR spectra of this ^{15}N-labeled β-lactam allowed us to determine that in solution the β-lactam (**21**) exists in a β-oxovinylamine structure rather than the alternative β-oxoimino structure **22**. As mentioned in an earlier section, X-ray diffraction studies have shown that the oxovinylamine structure is favored in the solid state also. A practical use of this structural feature is described in the next section.

(c) *Shortened route to α-amido-β-lactams.* The α-vinylamino-β-lactam structure can be converted to an α-amido-β-lactam in two steps as described earlier. It is possible, however, to obtain an α-amido-β-lactam (**24**) in one step from **23** by ozonation[20] since **23** exists in the β-carbonyl-vinylamino form.[21]

When a cyclic β-keto ester, such as **25**, was employed as the dicarbonyl component, β-lactams of the type **26** were obtained.[20] Ozonation of such vinylamino-β-lactams led to **27** containing an amide side chain with an α-keto ester as an additional functional group. Such α-keto acids can be converted to α-amino acids by known methods. Thus, access to cephalosporin C type of side chain becomes available.

CONCLUSIONS

The synthesis of α-amido β-lactams described here has several advantages over the α-azido-β-lactam approach.

The synthesis of α-amido-β-lactams via 3-(β-carbonyl-vinylamino)-2-azetidinones is a convenient and economical process that can be conducted on a large scale without hazard. The stereospecificity of the annelation reaction is a further advantage in planning synthesis of monocyclic and polycyclic β-lactams. The commercial availability of glycine labeled with one or more stable or radio-isotopes simplifies the preparation of β-lactams with multiple labels of high isotope content. The versatility of this new β-lactam synthesis is under active investigation in our laboratory.

EXPERIMENTAL

All m.ps are uncorrected and were determined in open capillary tubes using a "Mel-Temp" apparatus. IR spectra were obtained with a Perkin–Elmer Infracord. PMR spectra were recorded on a Varian EM 390 NMR spectrometer using TMS as an internal standard in $CDCl_3$. Mass spectra were obtained with a Perkin–Elmer RMU-7 mass spectrometer or CIMS-Biospect mass spectrometer.

General method for the synthesis of "Dane salt"

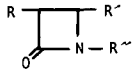
Potassium salt of α-methyl-β-carbomethoxyvinylamino acetic acid. To a soln of KOH (0.25 mol) in anyd MeOH (500 ml) was added 0.25 mol glycine and the mixture stirred till the soln became clear. Methyl aceto–acetate (0.2 mol) was then added to this soln. After 30 min, the solid that separated out was filtered and dried. The title compound was obtained in 75% yield, m.p. 235–237° and was used as such without further purification.

Using the same general conditions, "Dane salts" from other β-keto compounds (see Table 1) were also prepared.

General method for the synthesis of β-lactams

1-(3′,4′-Dimethoxybenzyl)-3-(1′-methyl-2′-carbomethoxy vinylamino)-4-phenyl azetidin-2-one. A soln of St_3N (0.015 mol) in anhyd. ether (10 ml) was added to a stirred suspension of K-salt of α-methyl-β-carbomethyoxyvinylamino acetic acid (0.01 mol) in anhyd. ether (5 ml) at −25° under N_2. To this suspension was added dropwise a soln of ethyl chloroformate (0.015 mol) in ether (10 ml). The mixture was allowed to stir at this temp. for 15 min, followed by a dropwise addition of a soln containing 0.01 mol Schiff base (derived from benzaldehyde and 3,4-dimethoxybenzylamine) and 0.015 mol Et_3N in 100 ml CH_2Cl_2 over a period of 1 hr. The mixture was stirred for 2 hr at 0° and then for 10–12 hr at room temp. The mixture was filtered, and the residue washed

Table 5. Analytical and spectral data on monocyclic β-lactams



No.	R	R′	R″	mp °C	Yield	Molecular Formula	Analysis C	H	N	Spectral Data
1	ε	Ph	$CH_2C_6H_3(OCH_3)_2$-3,4	155-156	65	$C_{23}H_{26}N_2O_5$	67.25 (67.30)	6.48 (6.38)	6.73 (6.82)	IR: 1740, 1655 cm^{-1}; NMR: 1.7 (s,3H), 3.4 (s,3H), 3.7 (s,3H), 3.8 (s,3H), 4.25 (s,1H), 4.6-5.2 (m,4H) 6.7-7.4 (m,8H), 8.5 (d,1H);mass spec.:M^+ at m/e 410.
2	ε	Ph	$C_6H_3(OCH_3)_2$-2,4	135-136	60	$C_{22}H_{24}N_2O_5$	66.49 (66.65)	6.18 (6.10)	7.04 (7.07)	IR: 1740, 1660 cm^{-1}; NMR: 1.9 (s,3H), 3.5 (s,3H), 3.65 (s,3H), 5.2 (q,1H), 5.65 (d,1H), 6.4-7.8 (m,8H), 8.5 (d,1H); mass spec.: M^+ at m/e 396.
3	ε		$CH_2C_6H_3(OCH_3)_2$-3,4	116	50	$C_{21}H_{24}N_2O_6$	62.89 (62.99)	6.08 (6.04)		IR: 1740, 1640 cm^{-1}; NMR: 1.8 (s,3H), 3.55 (s,3H), 3.83 (s,3H), 3.86 (s,3H), 4.45 (s,1H), 4.6 (d,1H), 4.7 (q,2H), 5.1 (d,1H), 6.4-7.7 (m,6H), 8.7 (d,1H), mass spec.: M^+ at m/e 400.
4	ε		$CH_2C_6H_3(OCH_3)_2$-2,4	100-101	50	$C_{21}H_{24}N_2O_6$	62.98 (62.99)	6.06 (6.04)		IR: 1740, 1650 cm^{-1}; NMR: 1.9 (s,3H), 3.6 (s,3H), 3.75 (s,3H), 3.85 (s,3H), 4.3 (q,2H), 4.7 (s,1H), 4.85 (d,1H), 5.0 (q,1H), 6.3-7.6 (m,6H), 8.8 (d,1H).
5	ε	$-C_5H_{10}-$	Ph	164	60	$C_{19}H_{24}N_2O_3$	68.24 (69.49)	7.19 (7.37)		IR: 1740, 1660 cm^{-1}; NMR: 2.15 (s,3H), 1.2-2.1 (m,10H), 3.7 (s,3H), 4.55 (d,1H, J=8 Hz), 4.7 (s,1H), 7.1-7.7 (m,5H), 9.3 (d,1H), J=8 Hz); mass spec.: M^+ at m/e 328.
6	ε		$C_6H_4OCH_3$-p	174-175	50	$C_{19}H_{20}N_2O_5$	63.85 (64.04)	5.63 (5.66)	7.74 (7.86)	IR: 1740, 1650, 1600 cm^{-1}; NMR: 2.0 (s,3H), 3.7 (s,3H), 3.85 (s,3H), 4.6 (s,1H), 5.2 (d,1H), 5.4 (m,1H), 6.3-7.6 (m,7H), 8.9 (d,1H); mass spec.: M^+ at m/e 356.
7	$NHCOCH_2OPh$	Ph	$CH_2C_6H_3(OCH_3)_2$-3,4	130	50	$C_{26}H_{26}N_2O_5$	69.79 (69.94)	5.92 (5.87)		IR: 3200, 1750, 1660 cm^{-1}; NMR: 3.8 (s,3H), 3.9 (s,3H), 4.3 (q,2H), 4.9 (s,2H), 5.05 (d,1H), 5.7 (q,1H), 6.7-7.6 (m,14H).
8	$NHCOCH_2OPh$		$CH_2C_6H_3(OCH_3)_2$-3,4	128	50	$C_{24}H_{24}N_2O_6$	66.07 (66.05)	5.52 (5.54)		IR: 3200, 1745, 1660 cm^{-1}
9	$NHCOCH_2Ph$		$CH_2C_6H_3(OCH_3)_2$-3,4	138	60	$C_{24}H_{24}N_2O_5$	68.38 (68.56)	5.80 (5.75)		IR: 3150, 1745, 1640 cm^{-1}; NMR: 3.5 (s,2H), 3.75 (s,3H), 3.85 (s,3H), 4.2 (q,2H), 4.7 (d,1H), 5.6 (q,1H), 6.0-7.5 (m,12H), mass spec.: M^+ at m/e 420.
10	$NHCOCH_2OPh$	$-C_5H_{10}-$	Ph	140	65	$C_{22}H_{24}N_2O_3$	72.49 (72.51)	6.63 (6.64)		IR: 3500, 1765, 1660 cm^{-1}; NMR: 1.3-2.0 (m,10H), 4.55 (s,2H), 5.1 (d,1H), J=8 Hz), 6.9-7.6 (m,11H).

with CH_2Cl_2. The combined organic phase was washed with water and dried ($MgSO_4$). Removal of the solvent provided the title compound in 65% yield, m.p. 155–156° (CH_2Cl_2 + n-hexane).

IR (Nujol): 1740, 1655 cm^{-1}; NMR ($CDCl_3$) δ: 1.7 (s, 3H), 3.4 (s, 3H), 3.7 (s, 3H), 3.8 (s, 3H), 4.25 (s, 1H), 4.6–5.2 (m, 4H), 6.7–7.4 (m, 8H), 8.5 (d, 1H); mass spectrum: M^+ at *m/e* 410. (Found: C, 67.25., H, 6.48, N, 6.73. Calc. for $C_{23}H_{26}N_2O_5$: C, 67.30, H, 6.38, N, 6.82%.)

Cleavage of vinylaminocarbonyl side chain

1-(3′,4′-*Dimethoxy benzyl*)-3-*amino*-4-*phenylazetidin*-2-*one*. A soln of **1g** described above in acetone (15 ml) was treated with 2N HCl (10 ml) and stirred for 15 min at room temp. and filtered. The filtrate was diluted with water, neutralized with Na HCO_3 aq and extracted with CH_2Cl_2. The CH_2Cl_2 soln was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to obtain the title compound (520 mg, 65% yield), IR (Nujol), 1730 cm^{-1}. This compound was used as such for the next step.

Acylation of α-amino-β-lactam

1-(3′,4′-*Dimethoxy benzyl*)-3-*phenoxyacetamido*-4-*phenylazetidin*-2-*one*. A soln of 0.01 mol of the above α-amino-β-lactam in 20 ml CH_2Cl_2 was stirred with 0.01 mol Et_3N and 0.01 mol phenoxyacetyl chloride at 0°. The mixture was stirred for about 3 hr and filtered through celite. The filtrate was washed with water, dried ($MgSO_4$), concentrated under reduced pressure, and passed through a short Florisil column using CH_2Cl_2 as the eluant. The product crystallized as white needles (CH_2Cl_2-n-hexane) m.p. 130° (50% yield).

IR (Nujol): 3200, 1750, 1660 cm^{-1}; NMR ($CDCl_3$) δ: 3.8 (s, 3H), 3.9 (s, 3H), 4.3 (q, 2H), 4.9 (s, 2H), 5.05 (d, 1H), 5.7 (q, 1H), 6.7–7.6 (m, 14H). (Found: C, 69.79, H, 5.92. Calc. for $C_{26}H_{26}N_2O_5$: C, 69.94, H, 5.87.)

3-*Phenoxyacetamido*-4-*phenylazetidin*-2-*one*. To a refluxing soln of 1-(3′,4′-dimethoxy benzyl) β-lactam (0.004 mol) in acetonitrile (100 ml) was added a soln of Na_2HPO_4. $7H_2O$ (0.008 mol) and $K_2S_2O_8$ (0.016 mol) in water (50 ml).[22] The progress of the oxidative cleavage was monitored through tlc. The starting N-substituted β-lactam disappeared after approximately 1.5 hr. The acetonitrile was then evaporated under reduced pressure and the aqueous phase extracted with CH_2Cl_2 (2 × 50 ml). The combined organic extract was evaporated to afford the title compound, m.p. 134–136°[23] (yield, 35%).

Using a similar sequence of reactions 3-phenylacetamido-4-phenylazetidin-2-one was also prepared, m.p. 187–188°.[23]

Following essentially the same conditions, **15** was obtained in 80% yield from the Dane salt derived from glycine and ethylacetoacetate and 1-*p*-methoxyphenyl-3, 4-dihydroisoquinoline, m.p. 165°. IR (Nujol): 1750, 1640 cm^{-1}; NMR ($CDCl_3$) δ: 1.15 (t, 3H), 2.0 (s, 3H), 7.5–2.9 (m, 2H), 3.4–3.65 (m, 2H), 3.75 (s, 3H), 3.95 (g, 2H), 4.4 (s, 1H), 5.05 (d, 1H), 6.7–7.5 (m, 8H), 8.6 (d, 1H).

β-Lactam **17** was prepared from the Schiff base derived from cinnamaldehyde and 3,4-dimethoxybenzylamine in 46% yield as a viscous oil. IR (Nujol): 2900, 1720, 1250 cm^{-1}; NMR ($CDCl_3$) δ: 1.9 (s, 3H), 3.7 (s, 3H), 3.9 (s, 6H), 4.35 (dd, 1H, J = 4.5 Hz and 9 Hz), 4.6 (d, 2H, J = 5H), 4.9 (dd, 1H, J = 4.5 Hz and 9 Hz), 6.05 (dd, 1H, J = 9 Hz and 16 Hz), 6.7 (s, 1H), 6.85 (d, 1H, J = 16 Hz), 6.9 (s, 3H), 7.35 (s, 5H), 9,1 (d, 1H, J = 9 Hz).

Using similar reaction conditions, the Dane salt derived from ^{15}N-glycine (Bio–RAD) was used to synthesize **21** in 50% yield, m.p. 165°.

IR (Nujol): 1730, 1655 cm^{-1}; NMR ($CDCl_3$) δ: 1.89 (s, 3H), 3.47 (s, 3H), 3.79 (s, 3H), 4.40 (d, 1H, J = 6 Hz), 6.78–7.50 (m. 9H), 8.52 (dd, 1H, J_{15N-H} = 93 Hz, J_{NH,C_3H} = 9 Hz).

Synthesis of 3-*phenylacetamidoazetidin*-2-*one* (**18**)

(a) 1-(2′-*Methyl*-1′-*carbomethoxy*) *propenyl*-3-(α-*methyl*-β-*carbomethoxy*-*vinylamino*)-4-*methylthioazetidin*-2-*one* (**13**). This compound was prepared as a viscous oil from **12**[15] and the Dane salt as described above.

IR (Nujol): 1770, 1725, 1660 cm^{-1}; NMR ($CDCl_3$) δ: 2.0 (s, 3H), 2.05 (s, 3H), 2.15 (s, 3H), 2.26 (s, 3H), 3.63 (s, 3H), 3.82 (s, 3H), 4.66 (s, 1H), 4.5–4.9 (m, 2H), 9.1 (d, 1H, J = 9 Hz); Mass spectrum: M^+ at *m/e* 342.

(b) The β-lactam (**13**) was hydrolyzed to the 3-amino-β-lactam by the method described earlier, IR. 1760 cm^{-1}, EI–MS: *m/e* 244. The structure of this compound which was obtained as an oily liquid was further confirmed through its alternative synthesis. The Schiff base (**12**) on treatment with azidoacetyl chloride in the presence of Et_3N afforded the α-azido β-lactam which on catalytic reduction (H_2/Pd–C) gave an amino compound which was identical to the one obtained through the vinylamino sequence.

(c) *The α-amino-β-lactam* (200 mg) described above was acylated with phenylacetyl chloride (127 mg) in the presence of triethylamine (83 mg) at 0° in CH_2Cl_2 to obtain 200 mg of **19** (67% yield), m.p. 87–91° (ether).

IR (Nujol): 1765, 1720, 1660 cm^{-1}; NMR ($CDCl_3$) δ: 1.93 (s, 3H), 2.12 (s, 3H), 2.23 (s, 3H), 3.6 (s, 2H), 3.73 (s, 3H), 4.77 (q, 1H), 4.95 (d, 1H, J = 2 Hz), 7.35 (s, 6H); Mass spectrum: M^+ at *m/e* 362.

(d) 1-(1′-*Methoxycarbonyl*-2′-*methylprop*-1-*enyl*) - 3 - *phenylacetamidoazetidin*-2-*one* (**20**). To a soln of 67 mg of **19** in 20 ml acetone was added prewashed activated Raney Ni (1 g). The mixture was refluxed with stirring for 20 min, cooled and filtered. The filtrate was evaporated under reduced pressure. The residual oil was redissolved in $CHCl_3$ (20 ml) and this soln was washed with brine (3 × 10 ml), dried (Na_2SO_4) and evaporated to yield 35 mg of **20** as an oil sufficiently pure for further use.

IR (neat): 3300–3200, 2900, 1760, 1720, 1660, 1540 cm^{-1}; NMR ($CDCl_3$) δ: 1.95 (s, 3H), 2.20 (s, 3H), 3.50 (s, 2H), 3.60 (m, 2H), 3.65 (s, 3H), 5.00 (m, 1H), 6.90 (m, 1H), 7.30 (s, 5H); mass spectrum: CIMS (NH_3), peaks at *m/e* 316 (M^+), 334 ($M^+ + NH_4^+$).

(e) To a cooled (0°) soln of (20, 35 mg) in water (0.9 ml) and acetone (5 ml) was added IN H_2SO_4 (0.032 ml) followed by a dropwise addition of a soln of N-bromosuccinimide (23 mg) in acetone (0.5 ml). The mixture was stirred at room temp. for 1 hr. Acetone was evaporated under reduced pressure. The remaining aqueous soln was extracted with $CHCl_3$ (2 × 5 ml). The combined organic layers were washed with 10% Na_2SO_3 (5 ml), dried (Na_2SO_4) and evaporated to yield the bromohydrin (40 mg, 87% yield) as an oil.

IR (neat): 3300–3100, 2900, 1755, 1720, 1660, 1520 cm^{-1}; CIMS (CF_2Cl_2): *m/e* 447, 449 (1:1) [M^+ + 35].

This bromohydrin (40 mg) was dissolved in anhyd CH_2Cl_2 (5 ml) containing Et_3N (25 mg). The soln was stirred overnight at room temp. The mixture was then washed with brine (20 ml), dried (Na_2SO_4) and evaporated to yield 15 mg (76% yield) of **18**.

IR (neat): 3250, 2900, 1745, 1660, 1540 cm^{-1}; NMR ($CDCl_3$) δ: 3.50 (s, 2H), 3.60 (m, 2H), 5.00 (m, 1H), 6.90 (m, 1H), 7.30 (s, 6H); CIMS (NH_3): *m/e* at 220 ($M^+ + NH_4^+$); (High resolution): 204.2272. Calc. for $C_{11}H_{12}N_2O_2$: 204.2280.

cis-1-p-*Tolyl*-4-p-*anisyl*-3-*acetamidoazetidin*-2-*one* (**24**). Ozo was bubbled through a precooled soln (−78°) of the corresponding O_3 **23**, (300 mg); derived from the Dane salt and *p*-anisylidin-*p*-toluidine) in dry CH_2Cl_2 for approximately 20 min until the soln was saturated with O_3 (tested with KI soln). The blue soln obtained was transferred to a round bottom flask and the solvent evaporated carefully under reduced pressure. The resulting slurry was dissolved in acetone (25 ml), cooled to 0° and treated with Jones reagent to cleave this ozonide. The mixture was stirred for another 15 min. This soln was diluted with water and extracted with $CHCl_3$ (3 × 100 ml). The $CHCl_3$ extract was dried ($MgSO_4$) and evaporated. The resulting solid was chromatographed over Florisil using CH_2Cl_2 as an eluant. The title compound was obtained as brownish crystals (125 mg) m.p. 171°.

IR (Nujol): 3200, 1720, 1640 cm^{-1}; NMR ($CDCl_3$) δ: 1.70 (s, 3H), 2.30 (s, 3H), 3.75 (s, 3H), 5.3 (d, 1H), 5.6 (q, 1H), 6.1 (d, 1H), 6.7–7.3 (m, 8H).

Using similar ozonolysis conditions, **27** was prepared from

the β-lactam derived from the Dane salt of **25** and *p*-anisidin-*p*-toluidine in 50% yield, m.p. 129–131°.

IR (Nujol): 3200, 1760, 1640 cm^{-1}; NMR ($CDCl_3$) δ: 1,3 (s, 2H), 1.8 (t, 3H), 1.95 (s, 2H), 2.3 (s, 3H), 2.7 (s, 2H), 2.9 (q, 2H), 3.7 (s, 3H), 5.3 (d, 1H), 5.6 (m, 1H), 6.0 (d, 1H), 6.8–7.4 (m, 8H); mass spectrum: M^+ at *m/e* 452.

1-*Thia-6-phenyl-7-(1′-methyl-2′-carbomethoxyvinylamino) octam* was prepared from 5,6-dihydro-2-phenyl-4H-1,3-thiazine and Dane salt, m.p. 162–163°, (55% yield); IR: 1760, 1660 cm^{-1}.

1-*Thia-6-phenyl-7-phenoxyacetamidooctam*, m.p. 151–152°[24] and 1-*thia-6-phenyl-7-phenylacetamidooctam*, m.p. 175–176° were prepared by acylation of the corresponding 7-aminooctam.

1,1-*Dimethyl-2-thia-6-phenyl-7-phenoxyacetamidooctam*, m.p. 173–174°[25] was similarly prepared by the reaction of 5,6-dihydro-2,2-dimethyl-3-phenyl-1,4-thiazine with Dane salt followed by cleavage of the amino protective group and acylation of the resulting amino compound with phenoxyacetyl chloride.

1-*Phthalimidoacetyl-1-aza-6-methylthio - 7 - phenoxyacetamido octam*, m.p. 241–243° was obtained by the reaction of Dane salt with 2-methylthio-3-phthalimidoacetyl-3,4,5,6-tetra hydropyrimidine followed by acid hydrolysis of the vinyl amino product and acylation to the resulting amino compound with phthalimidoacetyl chloride.

1-p-*Toluenesulfonyl-1-aza-6-methylthio - 7 - (1′ - methyl - 2′ - carbomethoxyvinylamino) octam* was prepared by the condensation of the Dane salt with 2-methyl-mercapto-1-(*p*-toluenesulfonyl)-Δ^2-tetrahydropyrinidine, m.p. 161–162°; IR ($CHCl_3$): 1770, 1650 cm^{-1}.

1,2-*Benzo-6-phenyl-7-(1′-methyl-2′-carbomethoxyvinylamino)-octam*; m.p. 148–150° was prepared in 45% yield by treating 1-phenyl-3,4-dihydroisoquinoline with Dane salt, IR: 1760, 1660 cm^{-1}; NMR: 2.0 (s, 3H), 2.75 (m, 2H), 3.45 (s, 3H), 3.75 (m, 2H), 4.45 (s, 1H), 5.0 (d, 1H), 7.1–7.6 (b, 9H), 8.45 (d, 1H).

1,2-*Benzo-6-phenyl-7-(1′-methyl-2′-carbo - t - butoxylvinylamino) octam* was prepared in 33% yield from 1-phenyl-3,4-dihydroisoquinaline and the Dane salt derived from t-butyl acetoacetate and glycine, m.p. 149–150°; NMR: 1.3 (s, 9H), 1.9 (s, 3H), 2.7 (m, 2H), 3.6 (b, 2H), 4.3 (s, 1H), 5.1 (b, 1H), 7.3–7.5 (b, 9H), 8.6 (b, 1H); mass spectrum: M^+ at *m/e* 405 (CIMS).

1,2-*Benzo-6-methylthio-7-(1′ - methyl -2′ - carbomethoxyvinylamino) octam*, m.p. 117°, was prepared from 1-methylthio-3,4-dihydroiso-quinoline and Dane salt in 40% yield, IR: 1760, 1660 cm^{-1}; NMR: 2.0 (s, 3H), 2.1 (s, 3H), 3.0 (m, 2H), 3.65 (s, 3H), 3.3 (m, 2H), 4.7 (b, 1H), 4.9 (s, 1H), 7.1–7.3 (b, 4H), 9.3 (b, 1H).

1,2-*Benzo-3-methyl-6-thiomethyl-7-(1′ - methyl - 2′ - carbomethoxyvinylamino) octam* was prepared by the method described earlier from Dane salt (8, R = H) and 1-thiomethyl-4-methyl-3,4-dihydroisoquinoline in 60% yield, m.p. 102–104°; IR: 1760, 1660 cm^{-1}; NMR: 1.4 (d, 3H), 2.05 (s, 3H), 2.2 (s, 3H), 3.7 (s, 3H), 3.0–4.0 (m, 3H), 4.7 (s, 1H), 4.9 (d, 1H), 7.4 (s, 4H).

1,2-*Benzo-6-p-methoxyphenyl-7-(1′ - methyl - 2′ - carbethoxyvinylamino) octam* was prepared from the Dane salt derived from glycine and ethyl acetoacetate and 1-*p*-methoxyphenyl-3,4-dihydroisoquinoline, m.p. 165° (80% yield); IR: 1750, 1640 cm^{-1}; NMR: 1.15 (t, 3H), 2.0 (s, 3H), 7.5–2.9 (m, 2H), 3.4–3.65 (m, 2H), 3.75 (s, 3H); 3.95 (q, 2H), 4.4 (s, 1H), 5.05 (d, 1H), 6.7–7.5 (m 8H), 8.6 (d, 1H).

1,2-*Benzo-6-p-methoxyphenyl-7-(1′ - methyl - 2′ - carbomethoxyvinylamino) otcam* was prepared in 80% yield from the Dane salt (8, R = H) and the appropriate dihydroisoquinoline, m.p. 149–150°; IR: 1760, 1660 cm^{-1}; NMR: 2.0 (s, 3H), 2.7 (m, 2H), 3.45 (s, 3H), 3.6 (m, 2H), 3.75 (s, 3H), 4.4 (s, 1H), 5.0 (d, 1H, J = 10 Hz), 6.75–7.45 (m, 8H), 8.45 (d, 1H), J = 10 Hz).

1,2-(4″,5″-*dimethoxybenzo)-4-carbomethoxy - 6 - phenyl - 7 - (1′ - methyl - 2′ - carbomethoxyvinylamino) octam* was prepared in 80% yield from the appropriate dihydroisoquinoline and Dane salt **8** (R = H); IR: 1760, 1750, 1660 cm^{-1}; NMR: 2.0 (s, 3H), 2.7 (m, 2H), 3.45 (s, 3H), 3.85 (s, 3H), 3.9 (s, 3H), 4.05 (s, 3H), 4.2 (m, 1H), 5.1 (d, 1H, J = 10 Hz), 6.66–7.50 (m, 7H).

1,2-(4″,5″-*Dimethoxybenzo)-4-carbomethoxy - 6 - phenyl - 7 - phenylacetamidooctam* was obtained by the acid cleavage of the amino protective group of the above compound followed by acylation with phenylacetyl chloride as described earlier, m.p. 188–190.[26]

1,2-(4″,5″-*Dimethoxybenzo)-6-p-bromophenyl - 7 - (1′ - methyl - 2′ - carbomethoxyvinylamino) octam* was obtained in 55% yield, m.p. 188–190° from Dane salt (s, R = H) and 1-*p*-bromophenyl-3,4-dihydro-6,7-dimethoxyisoquinoline, IR: 1760, 1660 cm^{-1}; NMR: 2.0 (s, 3H), 2.7 (m, 2H), 3.5 (s, 3H), 3.5 (m, 2H), 3.85 (s, 3H), 3.95 (s, 3H), 4.5 (s, 1H), 5.1 (d, 1H, J = 10 Hz), 6.7–7.6 (m, 6H), 8.5 (d, 1H, J = 10 Hz).

Hydrolysis of this octam with dil HCl followed by acylation with phenylacetyl chloride afforded the corresponding 7-phenylacetamido octam in 60% yield, m.p. 170°.

1,2-*Benzo-6-phenyl-7-(1′-methyl-2′-acetylvinylamino) octam* was prepared by treating 1-phenyl-3,4-dihydroisoquinoline and Dane salt derived from glycine and acetylacetone in 40% yield, m.p. 167–169°.

1,2-*Benzo-6-phenyl-7(2′-acetylcyclohexenylamino) octam* was similarly prepared from the potassium salt of 2′-acetylcyclohexenylamino acetic acid and 1-phenyl-3,4-dihydroisoquinoline in 54% yield, m.p. 166° (CH_2Cl_2 + n-hexane); NMR: 1.4–2.8 (b, 11H), 3.5–3.88 (b, 4H), 5.15 (d, 1H), 7.1–7.6 (b, 9H), 8.2 (b, 1H).

Spectral and other properties of some representative monocyclic β-lactams and their derivatives synthesized by the Dane salt method are presented in Table 5.

Acknowledgements—The authors express their sincere thanks to Gist–Brocades N.V., The Netherlands, and Stevens Institute of Technology for generous support of this research. They are grateful to Provost L. Z. Pollara and Prof. J. Biesenberger of Stevens Institute of Technology and Dr. J. De Flines and Dr. P. L. Hoogland of Gist Brocades for their interest and encouragement.

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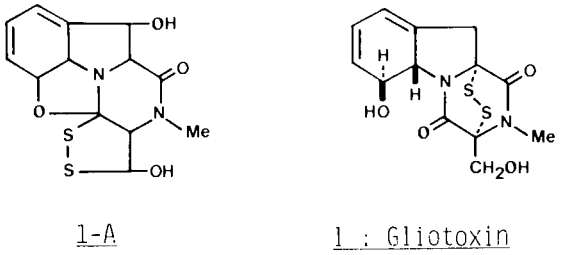
TOTAL SYNTHESIS OF GLIOTOXIN, DEHYDROGLIOTOXIN AND HYALODENDRIN†

TOHRU FUKUYAMA, SHIN-ICHI NAKATSUKA (in part) and YOSHITO KISHI*
Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge, MA 02138, U.S.A.

(*Received in U.S.A.* 31 *December* 1980)

Abstract—Two general methods, Method A and Method B in Scheme 19, to synthesize epidithiapiperazinediones, are described. A total synthesis of racemic and optically active gliotoxin (**1**) and of racemic dehydrogliotoxin (**53**) was achieved by using Method A, whereas a total synthesis of racemic hyalodendrin (**52**) was completed by using Method B.

Gliotoxin was first isolated from cultures of the wood fungus *Gliocladium fimbriatum* by Weindling and Emerson in 1936.[1] This substance was since isolated as the metabolite of a variety of microorganisms, including *Aspergillus fumigatus* and *Penicillium terlikowskii*.[2,3] Gliotoxin was found to be a powerful bacteriostatic agent and to exhibit remarkable antifungal and antiviral activity.[4–6] However, the toxicity of gliotoxin observed with test animals precluded its therapeutic use.[7] The structure determination of gliotoxin was undertaken by Johnson *et al.* in the early 1940s. In 1953 they proposed structure **1–A** for gliotoxin on the basis of extensive degradation studies.[8] Since this formula could not account for all of the experimental observations, Bell, Johnson, Wildi and Woodward proposed structure **1** for gliotoxin in 1958.[9] Later, an X-ray crystallographic analysis of gliotoxin confirmed the proposed structure and established at the same time the stereochemistry including its absolute configuration.[10]



Scheme 1.

Since the discovery of gliotoxin, a number of antibiotics containing the epidithiapiperazinedione system, including sporidesmins,[11] aranotins,[12] dehydrogliotoxin,[13] chaetocins[14] (verticillins[15]), chetomin,[16] hyalodendrin,[17] melacidins[18] and sirodesmins,[19] have been isolated as metabolites of various microorganisms. These natural products, like gliotoxin, exhibit remarkable antiviral, antifungal and bacteriostatic activity.[20] Apparently the biological activity is associated with the epidithiapiperazinedione moiety, since removal of the disulfide group results in loss of activity. For example, desulfurized products of gliotoxin and sporidesmin A show no antibacterial activity.[21] With this fact in mind, Trown first synthesized the simple epidithiapiperazinedione **5**, which did indeed exhibit strong antiviral activity.[22]

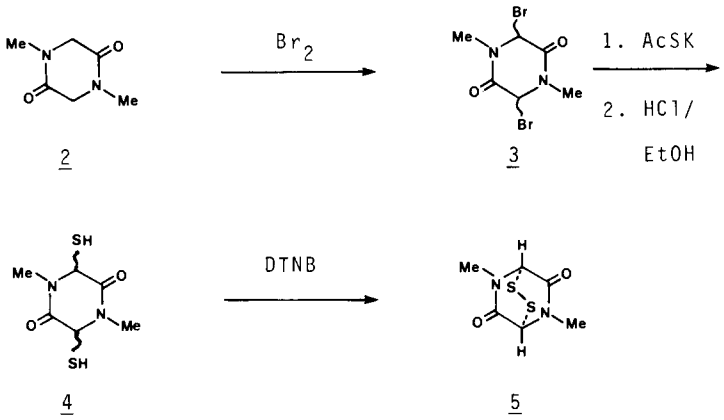
†Dedicated to the memory of Robert Burns Woodward, this paper will be included in the final book version of the Woodward revised supplement.

EPIDITHIAPIPERAZINEDIONE SYNTHESES: METHOD A (BICYCLIC ROUTE)

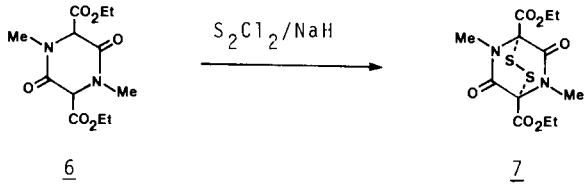
The unique structural features of this class of natural products have attracted considerable interest of many synthetic organic chemists. Apparently, the central problem in synthesizing these natural products was construction of the epidithiapiperazinedione system. In the fall of 1972 when we undertook this synthesis, there were only three epidithiapiperazinediones synthesized. Perhaps the most historical synthesis is the one achieved by Trown in 1968.[22] Hino *et al.* introduced the disulfide bridge into **6** by using carbanion chemistry.[23] Schmidt *et al.* succeeded in the synthesis of epidithiaproline anhydride **11** by a method somewhat similar to Hino's.[24,25]

We started this project with a brief examination of the chemical properties of the epidithiapiperazinediones and realized that they are extremely labile under oxidative (N-bromosuccinimide, bromine, *m*-chloroperbenzoic acid), reductive (lithium aluminum hydride, sodium borohydride),[26] and basic (sodium hydroxide, sodium methoxide, triethylamine) conditions,[27] but are acceptably stable under acidic (acetic acid, trifluoroacetic acid, boron trichloride) conditions. Accordingly, it seemed wise to introduce this system to a synthetic intermediate at as late a stage as possible. With this reasoning in mind, two extreme strategies were considered for the construction of the disulfide bridge on a synthetic intermediate; one to introduce the disulfide bridge at a late stage in the synthesis, and the other to introduce the protected disulfide bridge at an early stage, with the hope that the chemical properties of the protected disulfide group would be improved and consequently cause no technical problems in carrying out the synthesis, and to regenerate the disulfide bridge at a later stage. Recognizing the vigorous conditions required for introduction of the disulfide or thiol groups to a piperazinedione by any of the three known methods, we felt that the chances for suc-

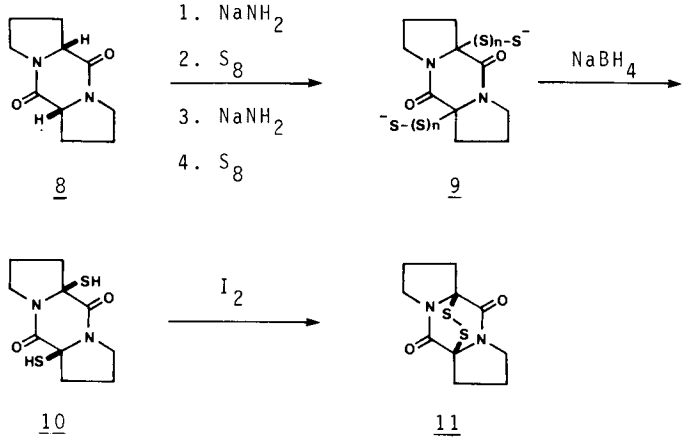
Trown Synthesis[22]



Hino Synthesis[23]



Schmidt Synthesis[24]

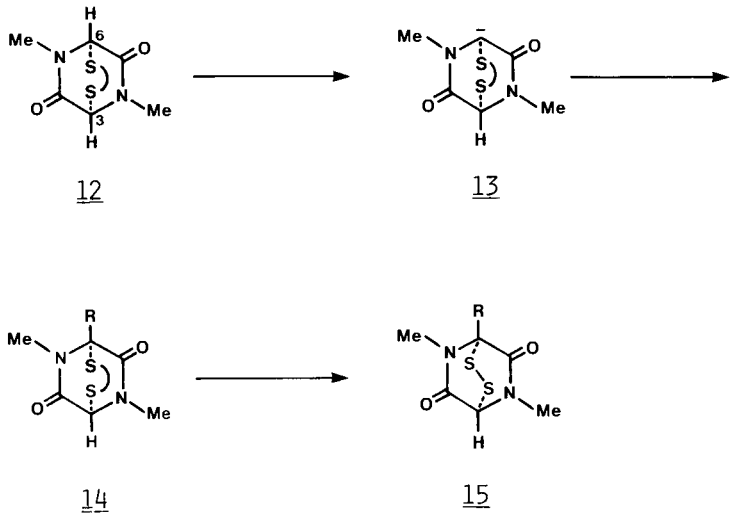


Scheme 2.

cess in the former approach would be extremely small, unless a new method were to be developed which allowed introduction of the disulfide bridge to a piperazinedione under conditions mild enough not to disturb other delicate functionalities existing in the target molecule such as a hydrated benzene ring. Based on this analysis, our decision was to pursue the latter approach.

The basic plan is depicted in Scheme 3, involving three major aspects, i.e. protection of the disulfide bridge as a bicyclic system such as **12**, functionalization of the C-6 (and C-3) position by using carbanion chemistry and regeneration of the disulfide bridge. A bycyclic system **12** was considered for controlling the stereochemistry of the C-3 and C-6 positions on the functionalization steps. The proposed carbanion formation at the bridgehead position might be difficult, but would not be necessarily unreasonable to propose, knowing of a facile deuterium–hydrogen exchange at the bridgehead position of a sulfur-containing bicyclic system as observed by Oae *et al.*[28]

Attempted preparation of the formaldehyde thioacetal **16**, with paraformaldehyde and *cis*-



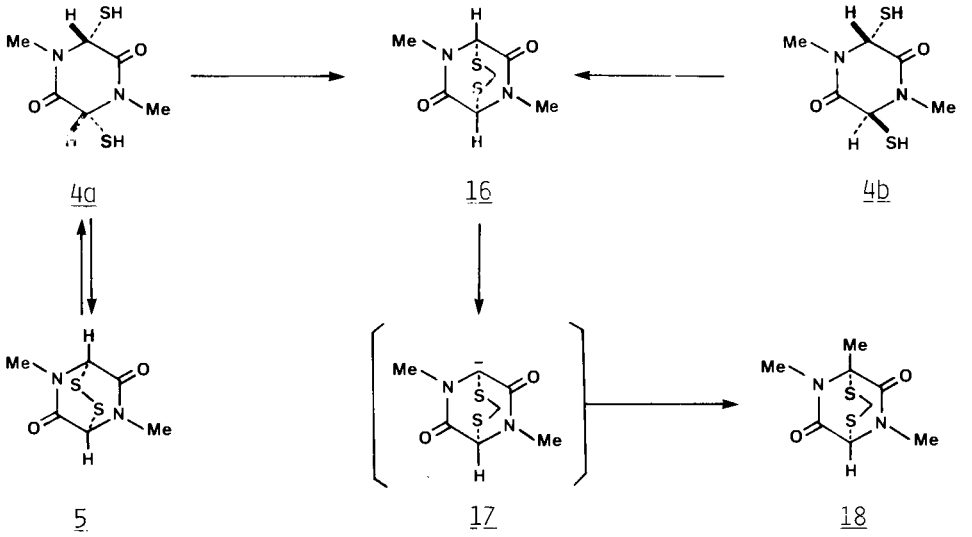
Scheme 3.

dithiopiperazinedione **4a**[22] under acidic conditions was fruitless. However, treatment of **4a** with diiodomethane and pyridine at room temperature yielded the thioacetal **16** in 51% yield. The thioacetal **16** was obtained also from *trans*-dithiopiperazinedione **4b**[22] under the same conditions in comparable yield, which allowed the utilization of the *cis*- and the *trans*-dithiopiperazinediones **4a** and **4b** for the following synthesis. Although at least three different mechanistic explanations for epimerization at the C-6 position in this thioacetalization could be postulated,[29] no experimental support is available to differentiate them at this time.

The crucial carbanion formation at the bridgehead position of **16** was realized by using a strong base such as *n*-butyllithium or lithium diisopropylamide (LDA) in tetrahydrofuran at −78°. This carbanion **17** was subsequently alkylated at −78° with methyl iodide to give the monomethylthioacetal **18** in 54% yield. There was no indication of carbanion formation at the methylene carbon of the thioacetal moiety, structurally somewhat similar to dithianes.

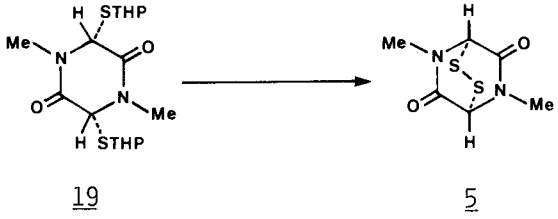
The next stage of the investigation was to establish a method to generate the disulfide bridge from the bicyclic thioacetal. Thioacetals and thioketals are often used for protection of aldehydes and ketones and a number of methods for their deprotection have been known.[30] However, most of them have focused on the regeneration of aldehydes or ketones rather than on the recovery of the sulfur-containing counterpart. Attempts to deprotect the thioacetal **16** under a variety of conditions including concentrated hydrochloric acid, sulfuric acid, hydrobromic acid, mercuric chloride, mercuric acetate-formic acid, silver nitrate and silver chloride–hydrochloric acid, were fruitless; in each case the starting material was recovered.

Since the deprotection of the thioacetal **16** to the *cis*-dithiol **4a** proved difficult, we turned our attention to the direct conversion of the thioacetal **16** into the epidithiapiperazinedione **5**. Related to this, we observed a clean formation of the epidithiapiperazinedione **5** from the *cis*-ditetrahydropyranyl derivative **19**, readily prepared from the *cis*-dithiol **4a**, upon treatment with iodine in



Scheme 4.

methylene chloride at room temperature. However, the thioacetal **16** was recovered unchanged under the same conditions.[31]

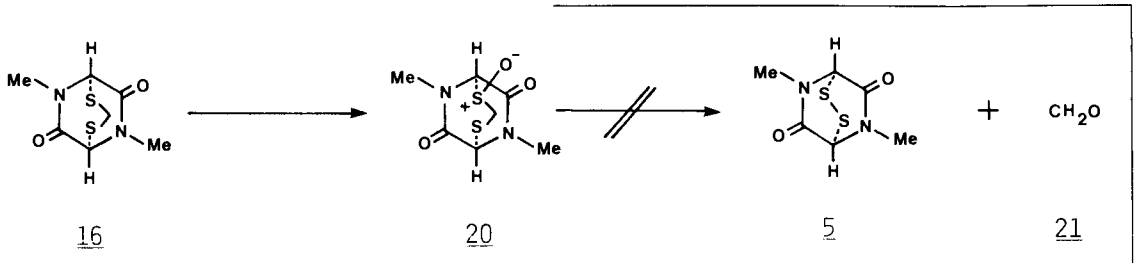


Scheme 5.

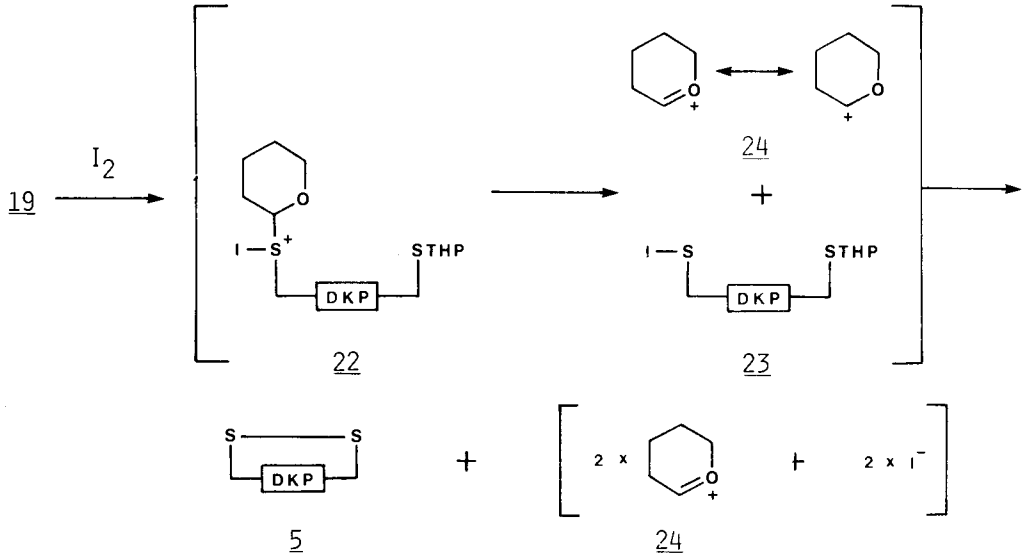
Under these circumstances, an alternative possibility depicted in Scheme 6 was investigated. Some literature precedents for this type of reaction are known in the carbohydrate field.[32] Treatment of the thioacetal **16** with 1 equivalent of *m*-chloroperbenzoic acid (MCPBA) at 0° in methylene chloride yielded the monosulfoxide **20** in quantitative yield. Attempts to convert the monosulfoxide into the epidithiapiperazinedione **5** under a variety of acidic conditions including perchloric acid, hydrobromic acid, boron trifluoride etherate and boron trichloride, were fruitless; in each case the starting material was recovered.[31] One of the reasons for the failure of these experiments could be attributed to the carbon-sulfur bond strength; namely, the formation of the disulfide bridge on the iodine oxidation of **19** might be facilitated by the two weak carbon-sulfur bonds due to the resonance stabilization for the fragment **24**, but there was no such assist in the case of the protonated form of **20**.

With this reasoning in mind, similar experiments using the thioacetals **25a–c** were investigated. Upon treatment with an aldehyde (acetaldehyde, benzaldehyde or *p*-anisaldehyde) and boron trifluoride etherate, the thioacetals **25a–c** were obtained from a mixture of the *cis*- and *trans*-dithiopiperazinediones **4a,b**, in yields of 73, 92 and 81%, respectively (see above). Since these thioacetals **25a–c** were again found to be inert against iodine,[31] they were subsequently converted to the monosulfoxides **26a–c** with *m*-chloroperbenzoic acid in quantitative yield. NMR and tlc analyses showed that the monosulfoxides **26a–c** were stereochemically homogeneous but their stereochemistry still remained unknown. Under a variety of acidic conditions such as perchloric acid, boron trichloride, boron trifluoride etherate and sulfuric acid, the monosulfides **26a** and **b**, derived from acetaldehyde and benzaldehyde, did not undergo the acid–cleavage reaction. However, under the same conditions, the sulfoxide **26c**, derived from *p*-anisaldehyde, clearly yielded the desired epidithiapiperazinedione **5** along with *p*-anisaldehyde!

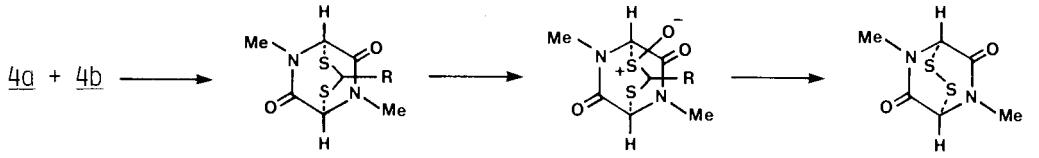
The reaction conditions used for generation of



Scheme 6.



Scheme 7.



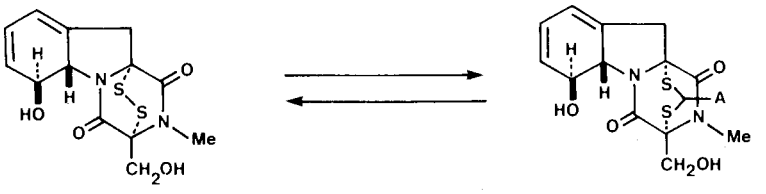
a = CH_3

b = C_6H_5

c = $C_6H_4OCH_3$(p)

Scheme 8.

the epidithiapiperazinedione **5** from the thioacetal **25c** were confirmed mild enough to apply this method to the gliotoxin synthesis. Namely, treatment of natural gliotoxin (**1**)[33] with sodium borohydride and then with *p*-anisaldehyde and boron trifluoride etherate yielded a diastereomeric mixture of the thioacetals **27a,b**, which were separated by preparative thin layer chromatography. From either of these diastereomers **27a** and **b**, gliotoxin (**1**) was successfully generated in 65% yield upon treatment with 1.2 equivalents of *m*-chloroperbenzoic acid and then with a trace amount of perchloric acid at room temperature.



A = C_6H_4OMe(p)

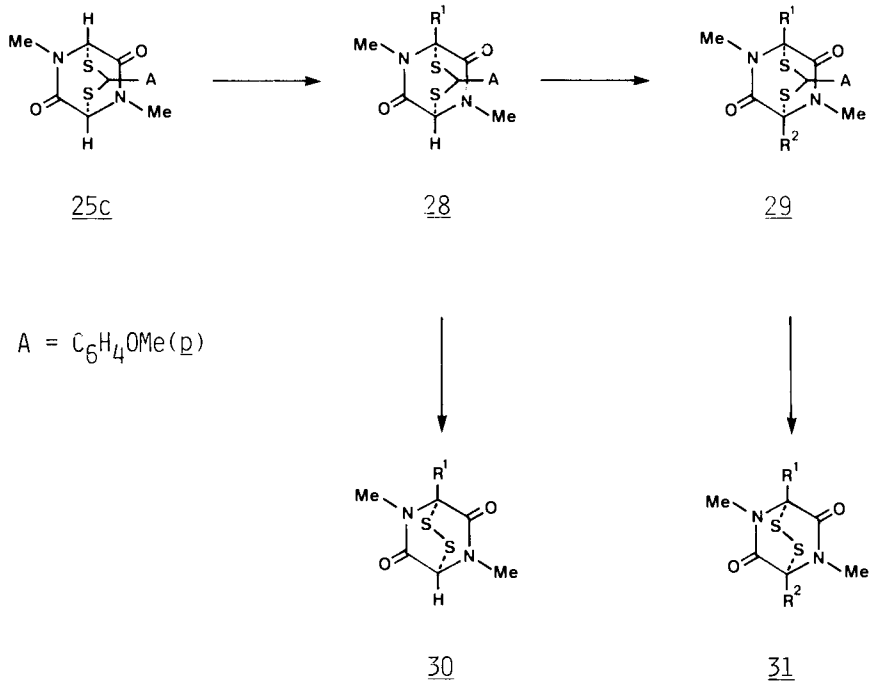
Scheme 9.

The remarkable stability of the thioacetal **25c** under a variety of conditions such as strongly acidic (concentrated hydrochloric acid at 100°), strongly basic (6 N sodium hydroxide at 50°), reductive (sodium borohydride, lithium borohydride), and certain oxidative (Collins reagent) conditions made this method even more attractive. However, one conceivable disadvantage of this system was that, because of introduction of a chiral center in the protecting group, a diastereomeric mixture might result upon alkylation at the bridgehead position, which fortunately turned out *not* to be the case (*vide infra*). Related to this, it should be mentioned that attempts to prepare the thioketal of the *cis*-dithiopiperazinedione **4a** with acetone or benzophenone were unsuccessful.

Monoalkylation or monoacylation of **25c** was successfully achieved by forming the carbanion with *n*-butyllithium or lithium diisopropylamide (LDA) in tetrahydrofuran, followed by treatment with alkyl halides, aldehydes, or acyl halides. The mono-substituted thioacetals **28** were further alkylated or acylated to yield the di-substituted acetals **29** in the same manner. Since the half-life of the bridgehead carbanions was about 10 min at −78°, better yield was often realized by addition of the base to the mixture of the thioacetal and alkylating reagent. However, this procedure was limited to preparation of the symmetrically disubstituted thioacetals. Conversion of the substituted thioacetals into the corresponding epidithiapiperazinediones was realized in a manner similar to that described for the thioacetal **25c**.

By this method, it was possible to synthesize a variety of epidithiapiperazinediones **30** and **31**, formerly derived from various amino-acids, from sarcosine anhydride (**2**).[33]

In the course of the alkylation or acylation studies of the thioacetal **25c**, an extremely interesting phenomenon was observed. Assuming that the acidity of the two bridgehead protons H_A and H_B is of the same order, a diastereomeric mixture should result; however, a *single* product was produced in each alkylation or acylation reaction. The following experiments clearly demonstrated this: the benzyl methyl thioacetals **29a** and **29b**, prepared from **25c** by methylation followed by benzylation or benzylation followed by methylation, were found to be distinctly different, judging

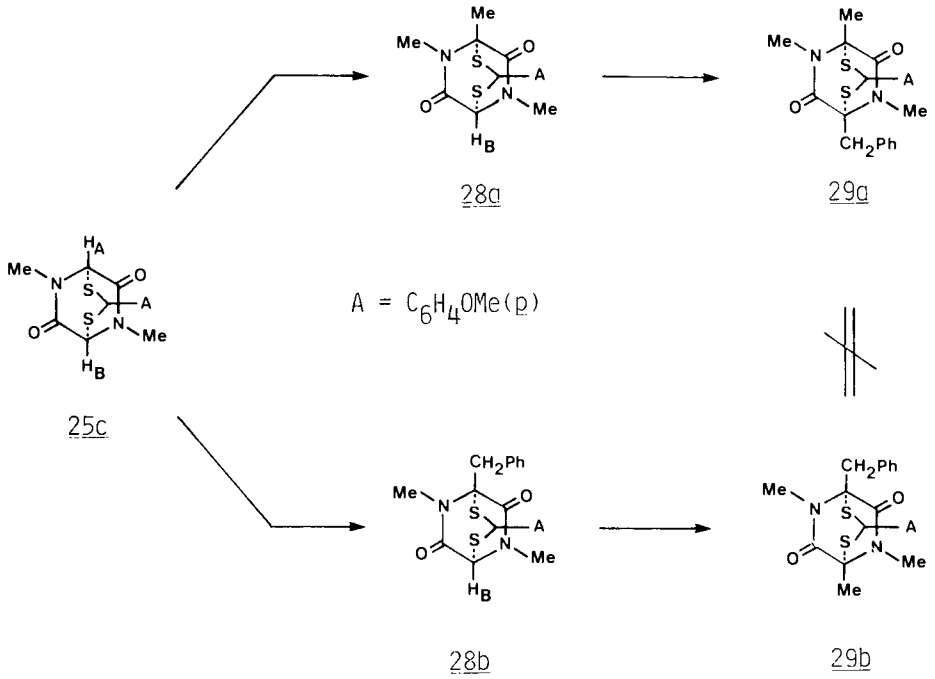


Scheme 10.

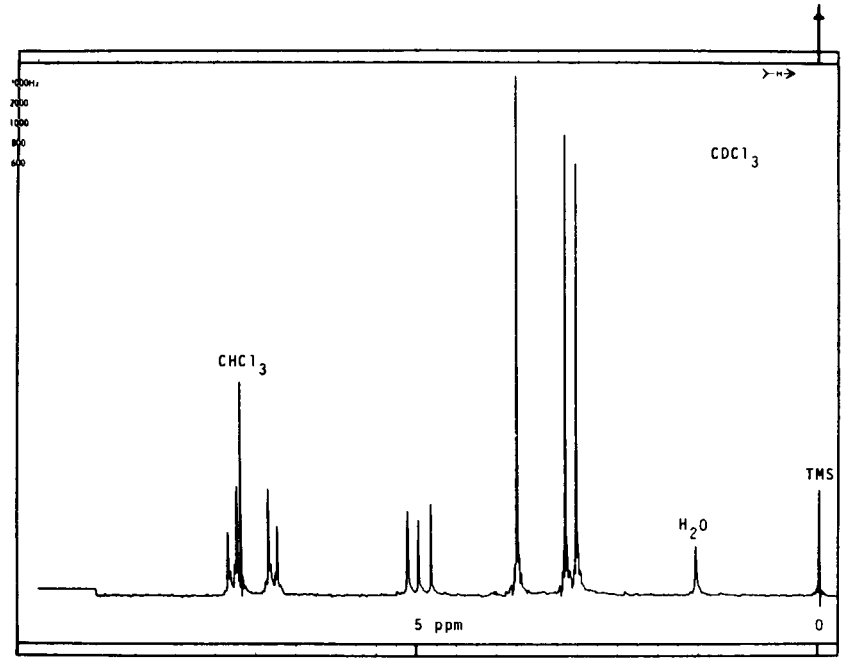
from NMR and IR spectra and also from the mixed m.p. determination. The only explanation for this observation was that the formation of the carbanion on **25c** took place in a *regiospecific* manner.

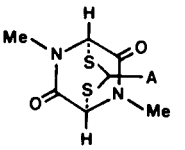
A deuterium exchange experiment also produced the same conclusion. Mono-deuterated thioacetal **25c** was obtained upon treatment with 1 equivalent of *n*-butyllithium at −78° in tetrahydrofuran, followed by addition of deuterium chloride in deuterium oxide. As shown in Fig. 1, only a singlet at δ 4.84 ppm was exchanged with deuterium (80% deuterium incorporation estimated from mass and NMR spectra).

Further evidence for the regiospecific carbanion formation was obtained in the course of the total synthesis of dehydrogliotoxin. The stereochemistry of the chlorides **32** and **35** was assigned as shown, based on the NMR spectrum (*vide infra*). Treatment of **32** with 1.2 equivalents of phenyl-

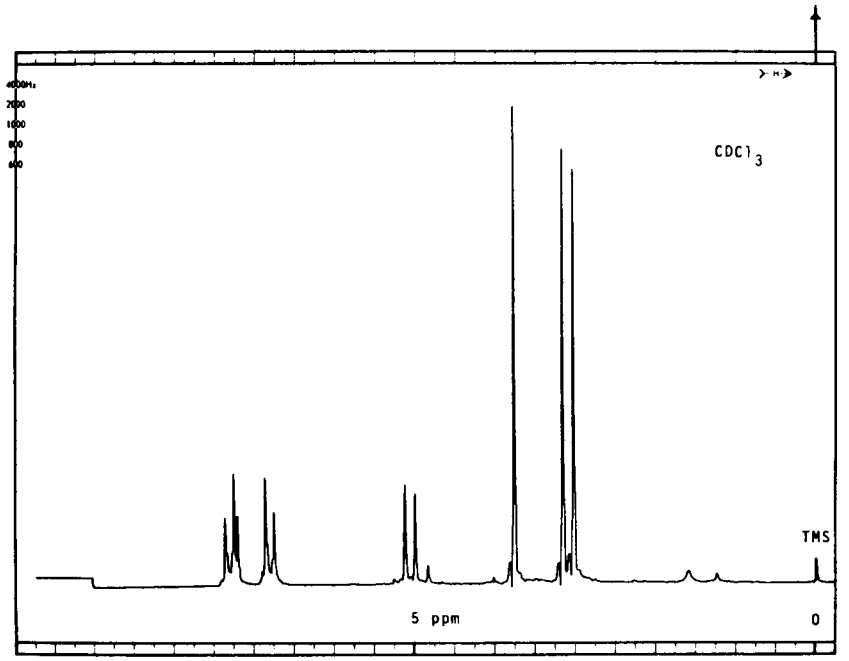


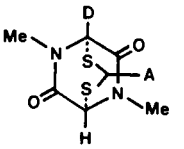
Scheme 11.





25c : A = C_6H_4OMe(p)

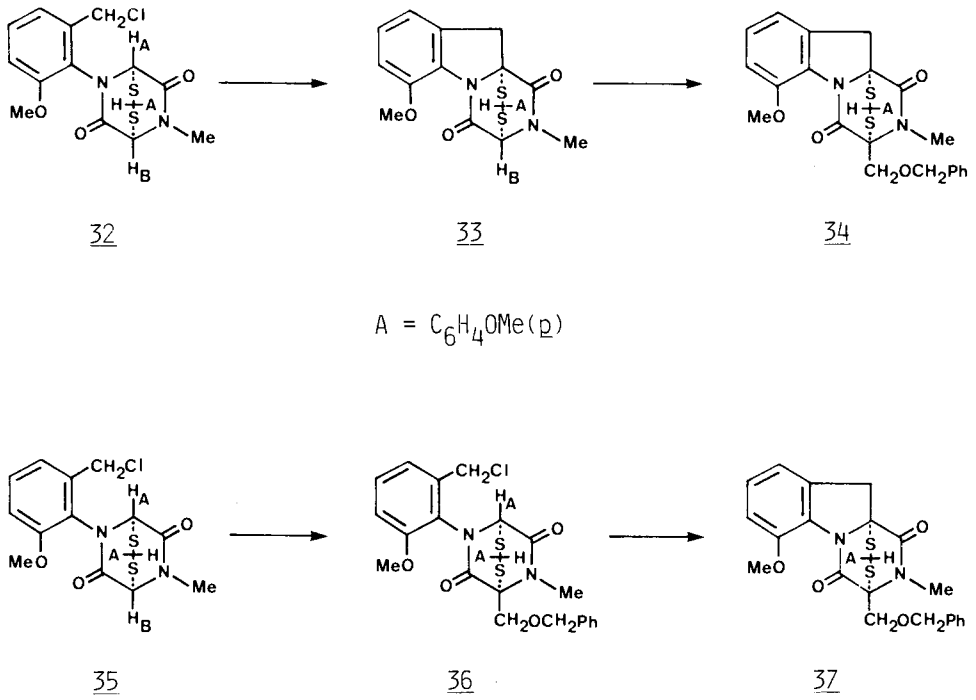




25c (monodeuterated)

Fig. 1.

lithium at −78° in tetrahydrofuran effected the cyclization to give **33** in 79% yield. Subsequent alkylation of **33** with phenyllithium and benzyl chloromethyl ether yielded the protected dehydrogliotoxin thioacetal **34** in 71% yield. On the other hand, the chloride **35**, a stereoisomer of **32** with respect to the anisaldehyde residue, did not undergo cyclization on treatment with 1.2 equivalents of phenyllithium at −78° in tetrahydrofuran, but instead on addition of benzyl chloromethyl ether gave the alkylated product **36** in 72% yield. The alkylated product **36** was successfully cyclized upon treatment with 1.2 equivalents of phenyllithium to give the protected dehydrogliotoxin thioacetal **37** in 93% yield. These experiments clearly demonstrated that: (a) H_A is more acidic than H_B in the thioacetal **32**, whereas H_B is more acidic than H_A in **35**. (b) A difference in acidity of the bridgehead protons is associated with the stereochemistry of the anisaldehyde residue. (c) The carbanion at the bridgehead is kinetically formed and no appreciable scrambling of the carbanion takes place.



Scheme 12.

In order to bring to light the reason(s) for this regiospecific carbanion formation, more conclusive structural information on the alkylated or acylated thioacetals was desired. Accordingly, an X-ray crystallographic analysis of the ethyl thioacetal **28c** (racemic), prepared from **25c** in the usual manner, was carried out.[35] The structure was consistent with that anticipated from results obtained in the dehydrogliotoxin synthesis. X-ray analysis showed that the dihedral angle of C(8)–S(9)–C(6)–H(154°) was close to that for C(8)–S(7)–C(3)–Et(155.7°), making it difficult to attribute the regiospecificity to the difference in the efficiency in overlap of the 3d orbitals of sulfur and the orbital of the bridgehead carbanion.[39] One possible explanation might be that the regiospecificity could arise as a result of the interaction between the lone pair of the sulfur atom and the carbonyl group. Examination of Dreiding molecular models revealed that one of the lone pairs on S(7) is sterically close to C(2), whereas no such interaction is expected for the lone pair on S(9) with C(5). Assuming such an interaction as represented by the canonical structure **25c–B**, the proton at C(3) could be more acidic than that at C(6).

EPIDITHIAPIPERAZINEDIONE SYNTHESES: METHOD B (MONOCYCLIC ROUTE)

Although the synthetic method of epidithiapiperazinediones using a bicyclic thioacetal proved to be useful for a variety of compounds, there still remained two problems which caused technical trouble in some cases; one was the short half-life (about 10 min at −78° in tetrahydrofuran) of the bridgehead carbanion, and the other was the subtle reaction conditions required for acid cleavage of the thioacetal monosulfoxide. To overcome these potential problems, a different route was investigated. The key question in this approach was the stereochemical outcome of an alkylation reaction on a protected dithiopiperazinedione like **19**. This was first studied by using the *cis*-dimethylthio compound **38**.[24] Upon treatment with 2.2 equivalents of *n*-butyllithium and excess methyl iodine, the dimethylation of **38** yielded a *single* product in 84% yield. This product was found to be identical (NMR, IR, MS, tlc) with dimethyl dimethylthiopiperazinedione **40**, prepared from the dimethyl epidithiapiperazinedione **31c** by

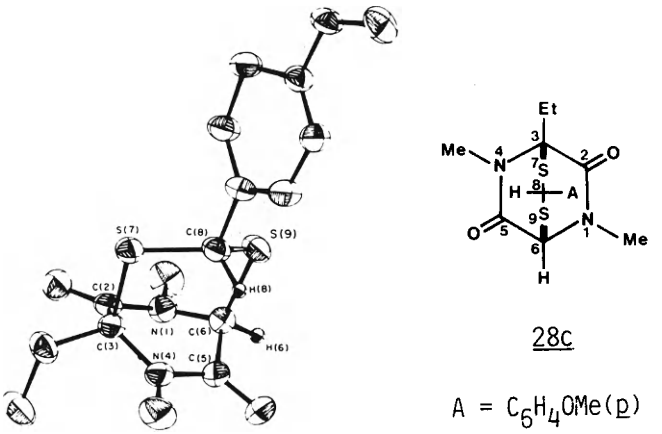


Fig. 2.

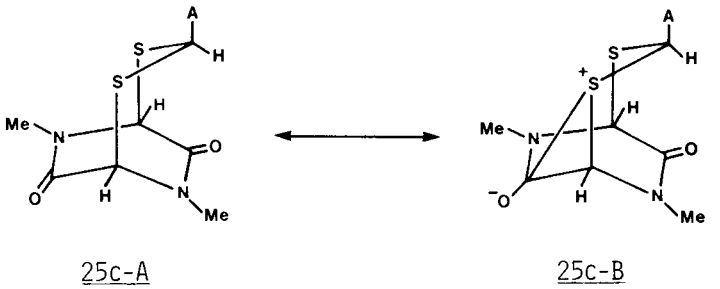
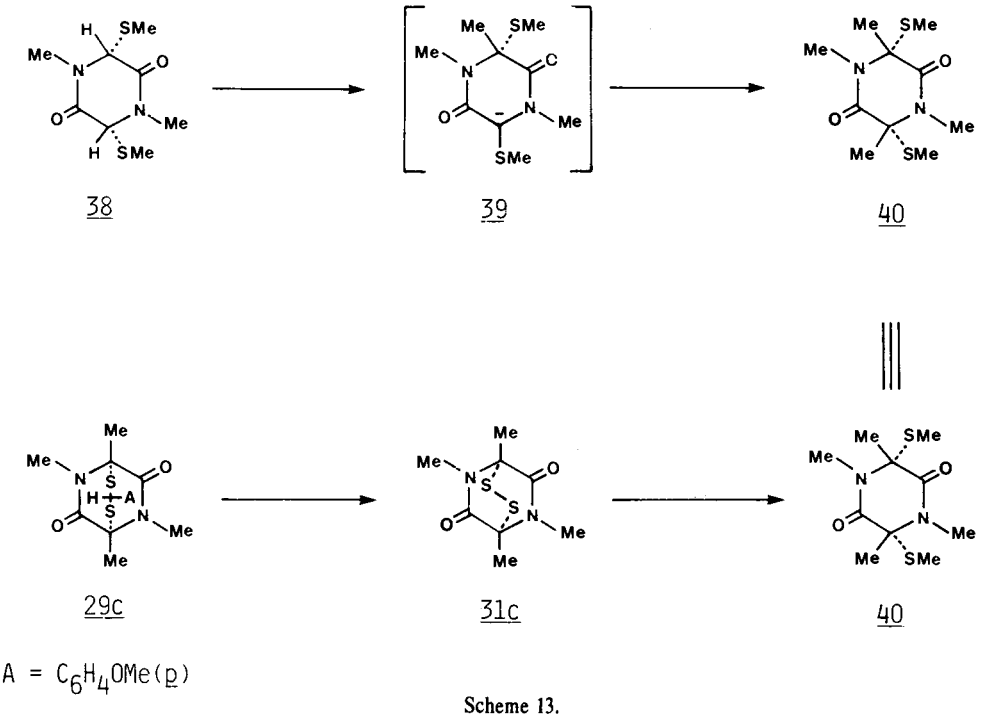


Fig. 3.

sodium borohydride reduction, followed by methyl iodide and pyridine treatment. Taking into account the easy epimerization observed before in a similar system (see above), this experiment did not necessarily establish but strongly suggested that the relative stereochemistry at the C-3 and C-6 positions of the alkylation product was *cis*.[36]

The carbanion in these experiments was shown to be generated under thermodynamic conditions. Namely, when the carbanion generated from **38**



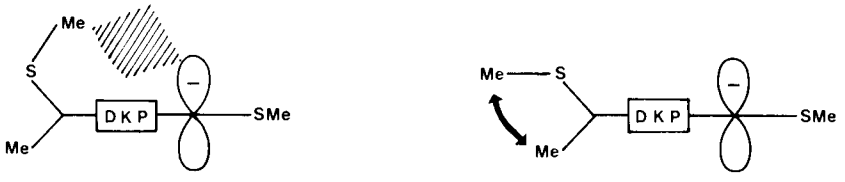
Scheme 13.

with 1.0 equivalents of *n*-butyllithium in tetrahydrofuran at −78° was quenched with deuterium chloride, net 41% deuterium incorporation, due to 10% of the di-, 60% of the mono- and 30% of the non-deuterated **38**, was observed. Almost identical deuterium distribution, i.e. 9% of the di-, 60% of the mono- and 31% of the non-deuterated **38**, was found when the dicarbanion generated from **38** with 2.0 equivalents of *n*-butyllithium was mixed with 1.0 equivalent of **38** at −78° and immediately quenched with deuterium chloride. Thus, it was evident that rapid scrambling of the carbanions took place under the conditions employed for the alkylation reaction.

The stereochemical course of this reaction could be analyzed as follows. Two extreme conformations **39-A** and **39-B** would be considered for the carbanion of the monoalkylated product **39**. Conformation **39-A** might be preferred to conformation **39-B** which is destabilized due to steric compression between the two methyl groups (see the double arrow in **39-B**). The β-face of conformation **39-A** would be more sterically crowded (see the shadow in **39-A**), allowing the alkylating agent access from the α-face.

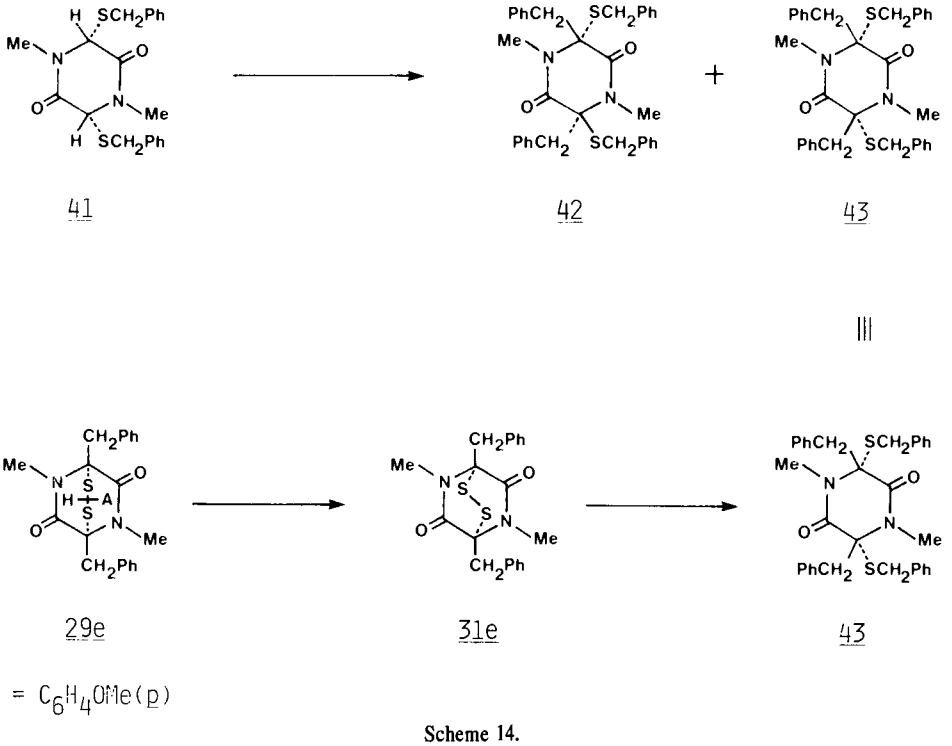
To demonstrate that the primary factor controlling the *cis*-alkylation was steric, dibenzylation of the *cis*-dibenzylthiopiperazinedione **41** was studied. Upon treatment with 2.1 equivalents of *n*-butyllithium and excess benzyl bromide, **41** yielded a 5:4 mixture of two stereoisomers **43** and **42** in 64% yield. The *cis*-configuration was assigned to the major product **43** by comparison with the authentic sample, prepared from the dibenzyl epidithiapiperazinedione **31e**. Four extreme conformations, *A*, *B*, *C* and *D*, would be considered for this case. Among them, conformations *C* and *D* would be less important for the analysis of the stereochemical course of the alkylation reaction. The benzylthio group would cover the β-face of conformation *A*, whereas the benzyl group would cover the α-face of conformation *B*, resulting in *cis* and *trans* isomers in almost equal amounts.

In order to apply this stereospecific alkylation reaction to a general synthesis of epidithiapiperazinediones, a suitable protecting group for the thiol moieties was needed. As described before, the ditetrahydropyranyl derivative **19** was cleanly oxidized to **5** with iodine; unfortunately, attempted alkylation of **19** with 2 equivalents of *n*-butyl-



39-A 39-B

Fig. 4.



Scheme 14.

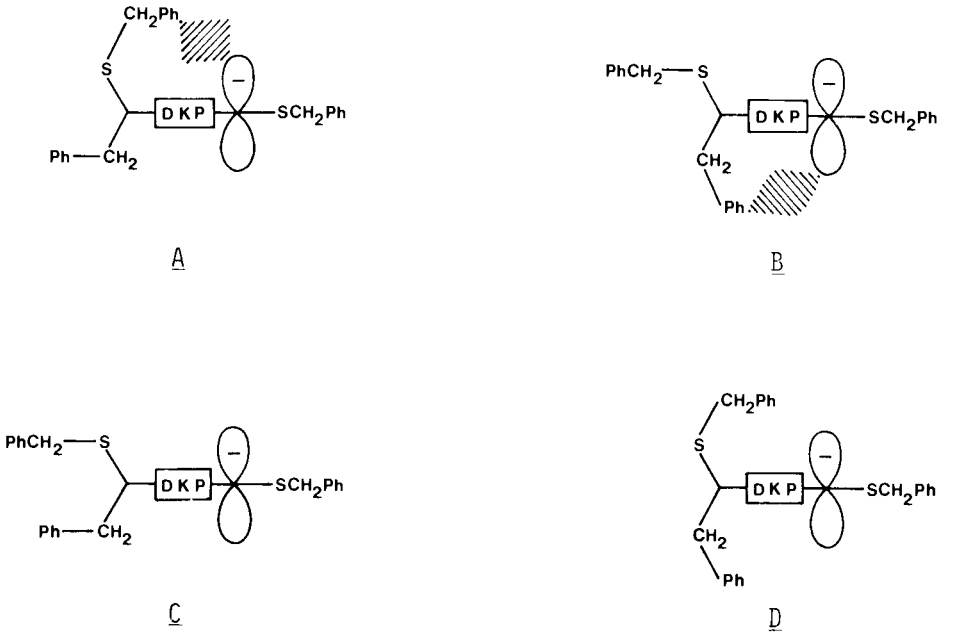
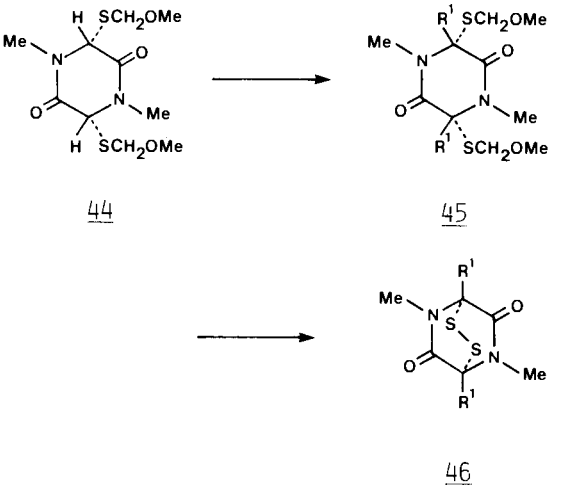


Fig. 5.

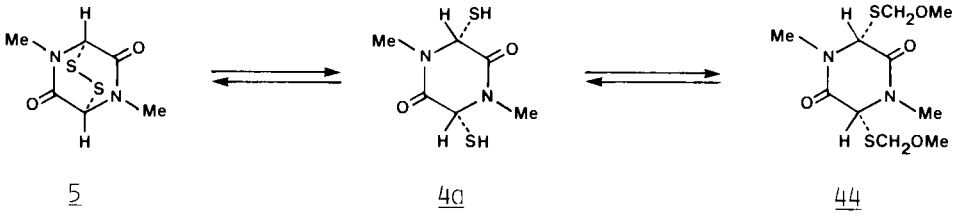
lithium and excess methyl iodide resulted in a complex mixture of products. This complexity was, at least partially, attributable to the two chiral centers in the protecting groups. For this reason, the dimethoxymethylthio compound **44** was prepared from **4** by treatment with 2.1 equivalents of potassium *t*-butoxide and chloromethyl methyl ether in 80% yield. The *cis*-configuration was tentatively assigned to **44**, based on the data of thermodynamic stability of the corresponding dimethylthio compound **38**.[24] Based on the previous observations (see above), it was not surprising to find that **44** was stable against iodine in methylene chloride at room temperature. Oxidation of **44** with *m*-chloroperbenzoic acid did not give encouraging results. Attempted hydrolysis to the *cis*-dithiol **4a** with protic acids such as sulfuric, hydrochloric, hydrobromic, perchloric, or trifluoroacetic acid under a variety of conditions were also uniformly fruitless. However, boron trichloride cleanly attacked the methoxymethyl group of **44** at 0° in methylene chloride, to give the *cis*-dithiol **4a**, after methanol workup. This facile deprotection could be attributed to the complex formation of boron trichloride and the carbonyl group. The *cis*-dithiol **4a** was then oxidized with iodine to yield the epidithiapiperazinedione **5**.

The dianion, generated from **44** using 2.3 equivalents of lithium diisopropylamide (LDA) in tetrahydrofuran at −78°, reacted with a variety of alkylating agents to yield *exclusively* one product **45**. The *cis*-configuration of the product was supported by the fact that **45** yielded cleanly the corresponding epidithiapiperazinedione **46** upon treatment with boron trichloride, followed by iodine oxidation.



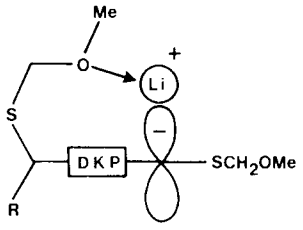
Scheme 16.

The remarkable stereospecificity observed for various alkylation reagents, even for benzyl bromide (compare the results discussed previously), could be explained in the following manner: coordination of the oxygen lone pairs towards



Scheme 15.

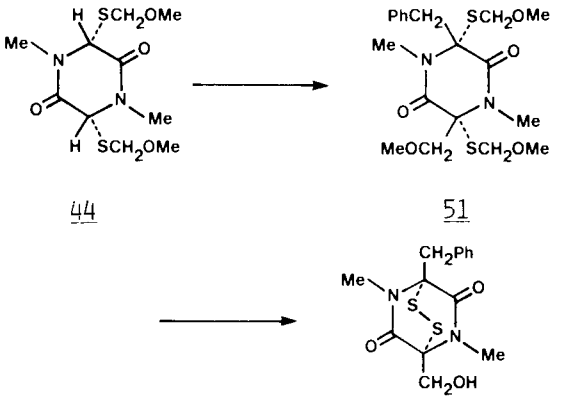
the lithium cation might stabilize the conformation of the monoalkylated carbanion shown in *E*, making the β-face sterically more crowded for the incoming alkylating reagent than the α-face.



E

Fig. 6.

During the alkylation studies, a remarkable difference in reactivity between the dicarbanion and the carbanion of the monoalkylated derivative was recognized. When the dicarbanion of **44** was treated with excess alkyl halide and then worked up with acetic acid *at* −78°, the *cis*-mono-alkylated piperazinedione **47** was obtained in high yield. The mono-alkylated piperazinedione was subsequently converted to the corresponding epidithiapiperazinedione **48** in the same manner as described for the dialkylated compounds. Furthermore, the unsymmetrically di-substituted epidithiapiperazinedione **50** was readily available by alkylation of the mono-substituted derivative **47**, followed by the usual deprotection–oxidation procedure.



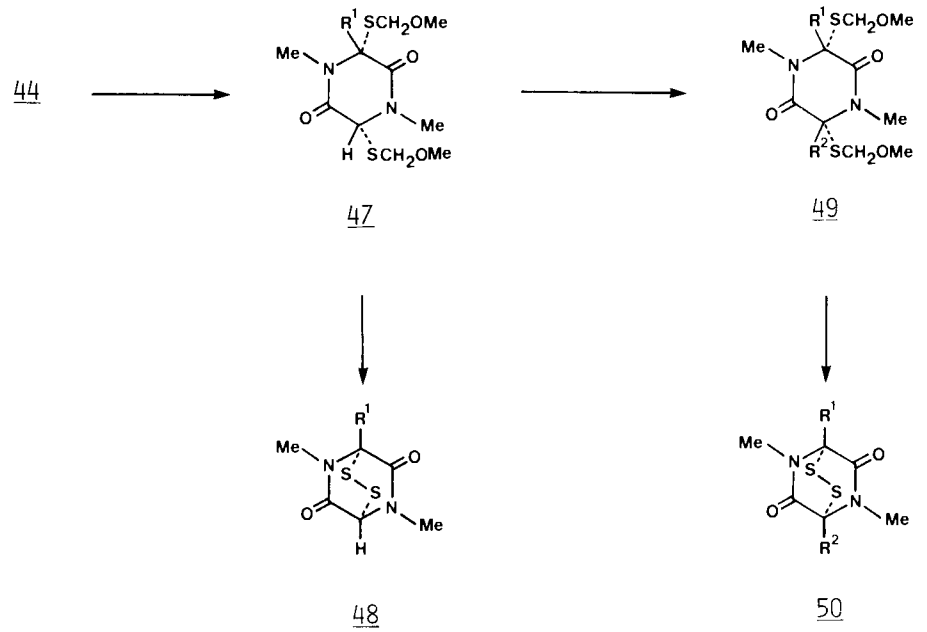
44 51

52 : Hyalodendrin

Scheme 18.

benzyl bromide for 20 min at −78° and then with 4 equivalents of bromoethyl methyl ether for 10 min at −78°, giving the benzyl methoxymethyl derivative **51** in 63% yield, which was converted to *dl*-hyalodendrin (**52**) in the usual manner in 28% overall yield.[34] The synthetic compound was found to be identical with natural hyalodendrin on comparison of spectroscopic (NMR, MS) and tlc data.[38] The NMR spectra of synthetic and natural hyalodendrin are illustrated in Fig. 7.

We have now established two general methods for the synthesis of epidithiapiperazinediones.



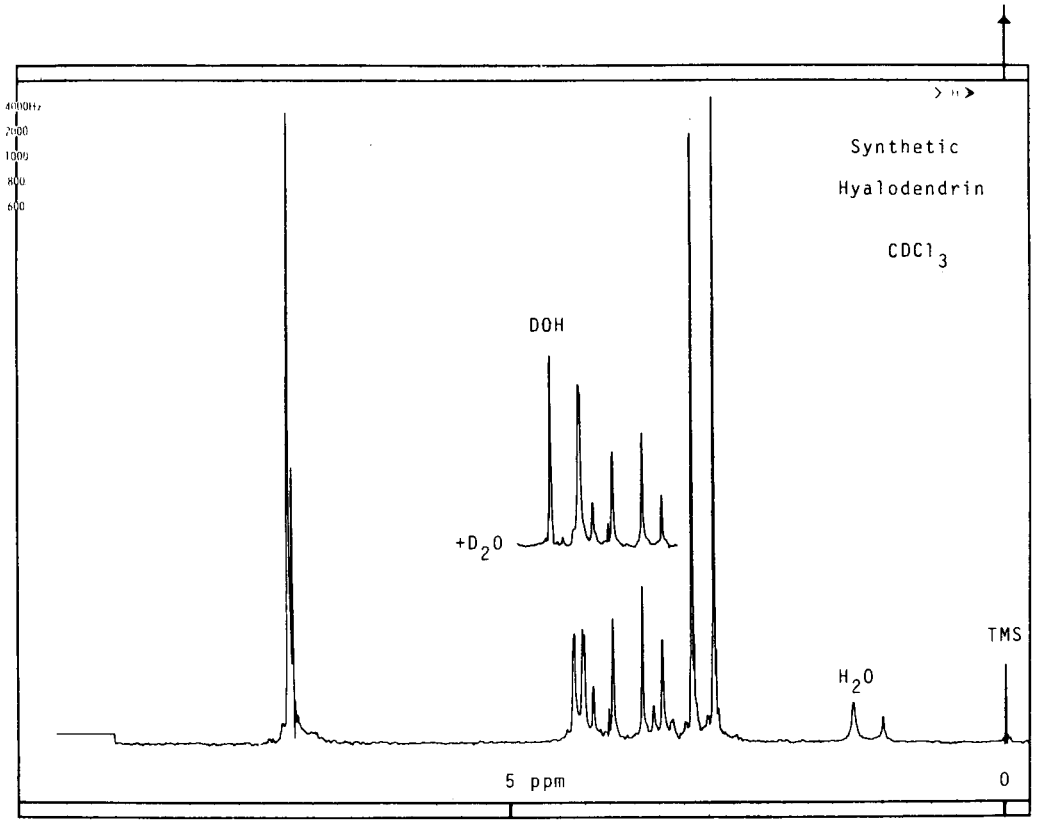
47 49

48 50

Scheme 17.

By utilizing the reactivity difference of alkylating agents, one-pot synthesis of the unsymmetrically di-substituted compounds was also possible. This procedure was demonstrated in a total synthesis of hyalodendrin **52**.[17] The dicarbanion generated from **44** with 2.3 equivalents of lithium diisopropylamide was treated with 5 equivalents of

Comparison between these methods reveals that the first (Route A)[39] is more suitable for multistage synthesis of complex molecules because of the stability of the thioacetals under various conditions as demonstrated in the total syntheses of dehydrogliotoxin,[40] sporidesmin A,[41] sporidesmin B,[42] hyalodendrin[43] and gliotoxin.[44] On the other


Synthetic
Hyalodendrin
CDCl3
DOH
+D2O
H2O
TMS
5 ppm
0

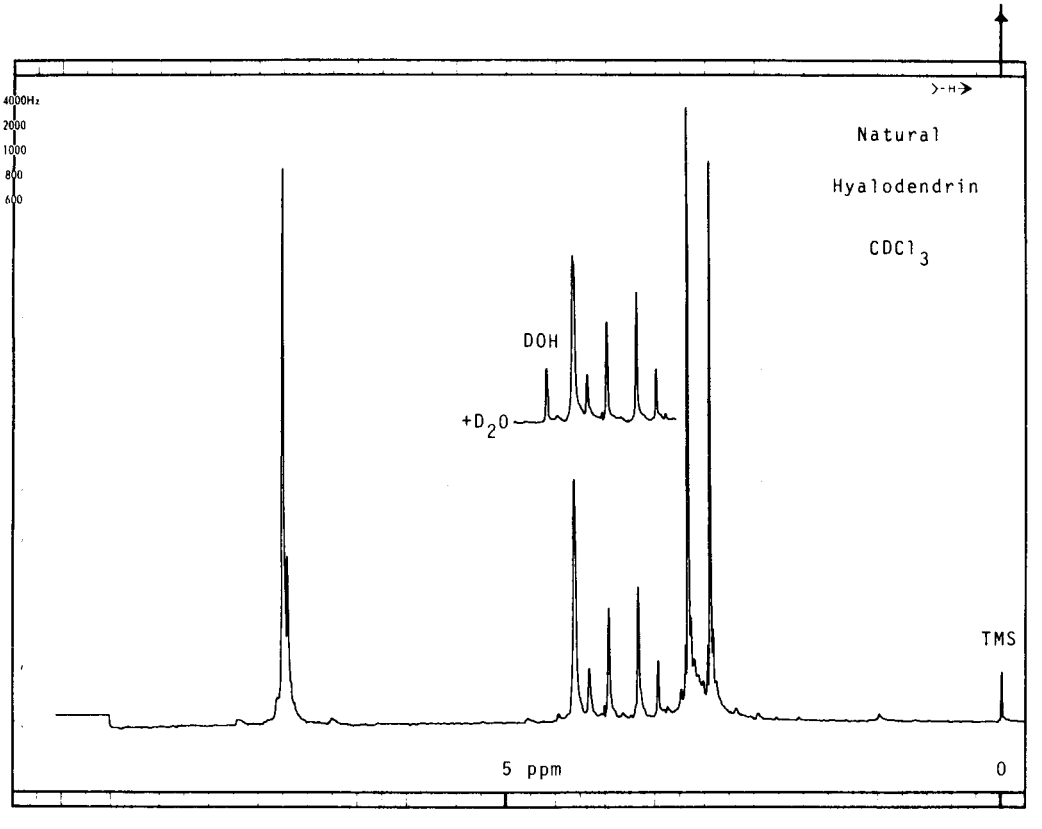
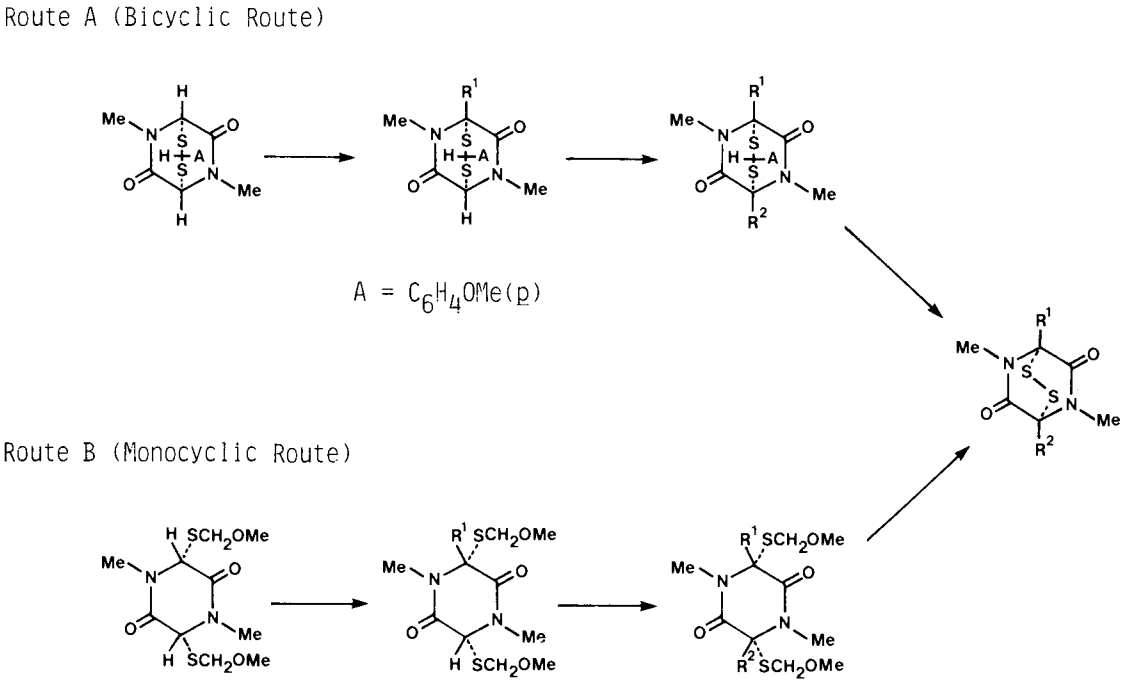

4000Hz
2000
1000
800
600
Natural
Hyalodendrin
CDCl3
DOH
+D2O
TMS
5 ppm
0

Fig. 7.



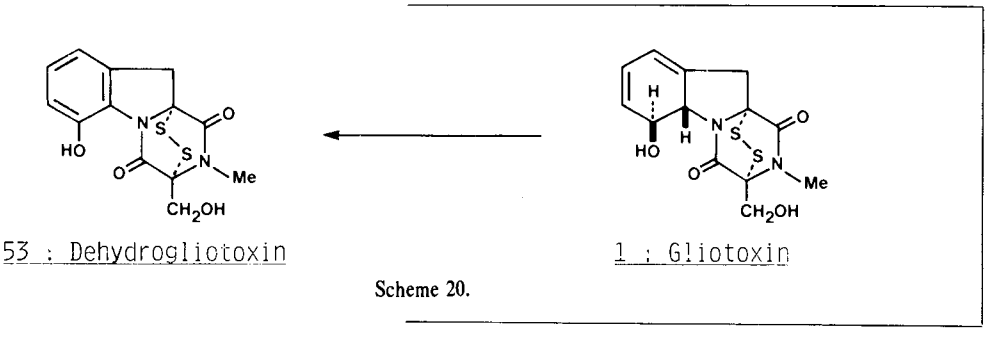
Scheme 19.

hand, the second method (Route B)[45] is more suitable for large-scale synthesis of simple epidithiapiperazinediones because of the simplicity of procedures and high yields.

TOTAL SYNTHESIS OF DEHYDROGLIOTOXIN

Dehydrogliotoxin was isolated by Taylor *et al.* from surface cultures of *Penicillium terlikowskii.*[13] The structure determination of dehydrogliotoxin (**53**) was carried out primarily by degradation and NMR studies. The most conclusive evidence for the proposed structure was that dehydration of gliotoxin (**1**) with *o*-chloranil yielded a product which was found to be identical with dehydrogliotoxin (**1**).

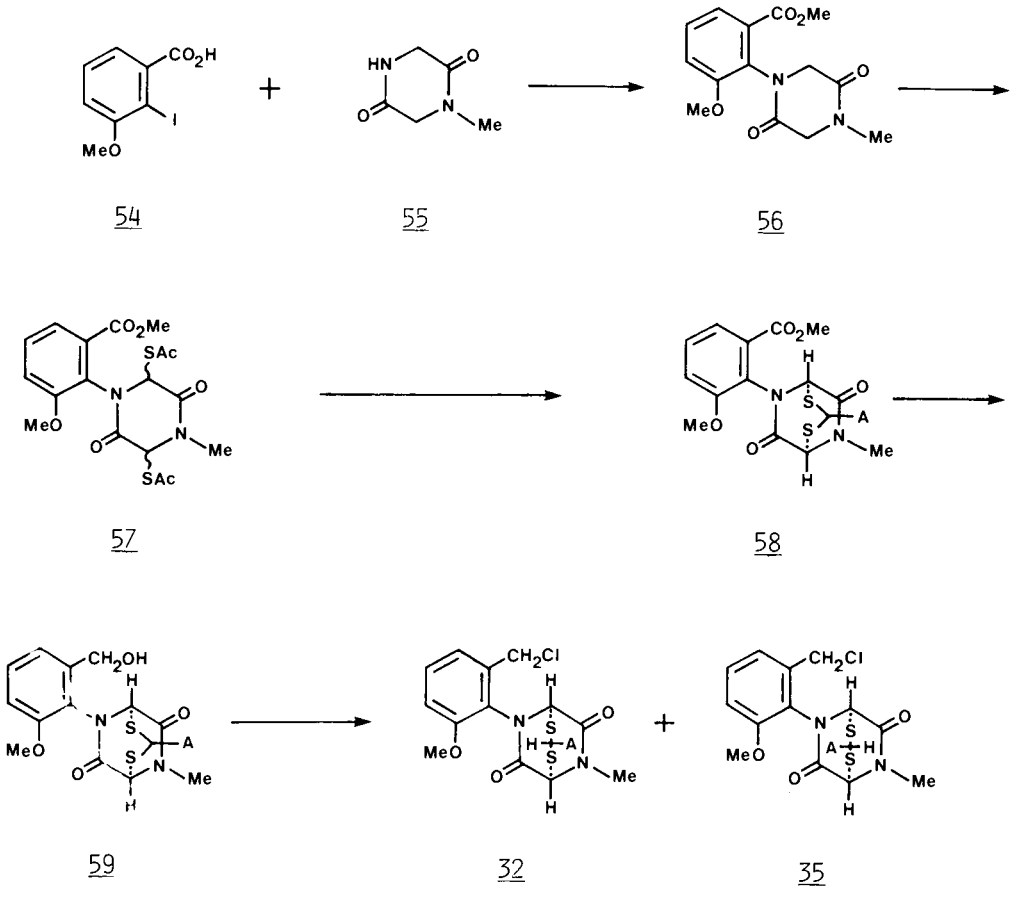
Ullmann-type reaction of 2-iodo-3methoxybenzoic acid (**54**)[46] and glysine–sarcosine anhydride (**55**)[47] in the presence of cuprous iodide and potassium carbonate in nitrobenzene at 170° for 40 min gave, after esterification with diazomethane, the sterically crowded piperazinedione **56** in 35% yield (based on **54**). A 1:1 mixture of *cis*- and *trans*-dithioacetates **57** was obtained from **56** in 65% overall yield by refluxing 2.8 equivalents of N-bromosuccinimide in the presence of a catalytic amount of benzoyl peroxide in carbon tetrachloride for 90 min, followed by treatment with potassium thioacetate in methylene chloride at room temperature. Methanolysis of the thioacetates **57** with methanolic hydrogen chloride



Scheme 20.

Dehydrogliotoxin seemed to be a good target molecule to test the applicability of the synthetic methods developed in the previous section. For the reasons summarized above, the synthesis of dehydrogliotoxin was planned via the thioacetals **32** and **35**; namely, formation of the two carbon–carbon bonds was envisioned by using the carbanion chemistry discussed before.

The hitherto unknown piperazinedione **56** was chosen as starting material for this synthesis. The at 50° for 40 min, followed by treatment with *p*-anisaldehyde and boron trifluoride etherate in methylene chloride at room temperature overnight, gave an approximately 1:1 diastereomeric mixture of the thioacetals **58** in 72% overall yield. Conversion of the ester **58** to the alcohol **59** was realized via the mixed anhydride; reduction of the mixed anhydride, prepared from **58** by a routine method, was most conveniently achieved by direct addition of a chilled methanolic solution of excess



Scheme 21.

sodium borohydride to an ice-cooled solution of the mixed anhydride in methylene chloride. Overall yield of **59** from **58** was 69%. Subsequent treatment of the alcohol with methanesulfonyl chloride and triethylamine at room temperature gave the mesylate, which was converted into an about 1:1 diastereomeric mixture of the chlorides **32** and **35** with lithium chloride in dimethylformamide at room temperature in 89% overall yield.

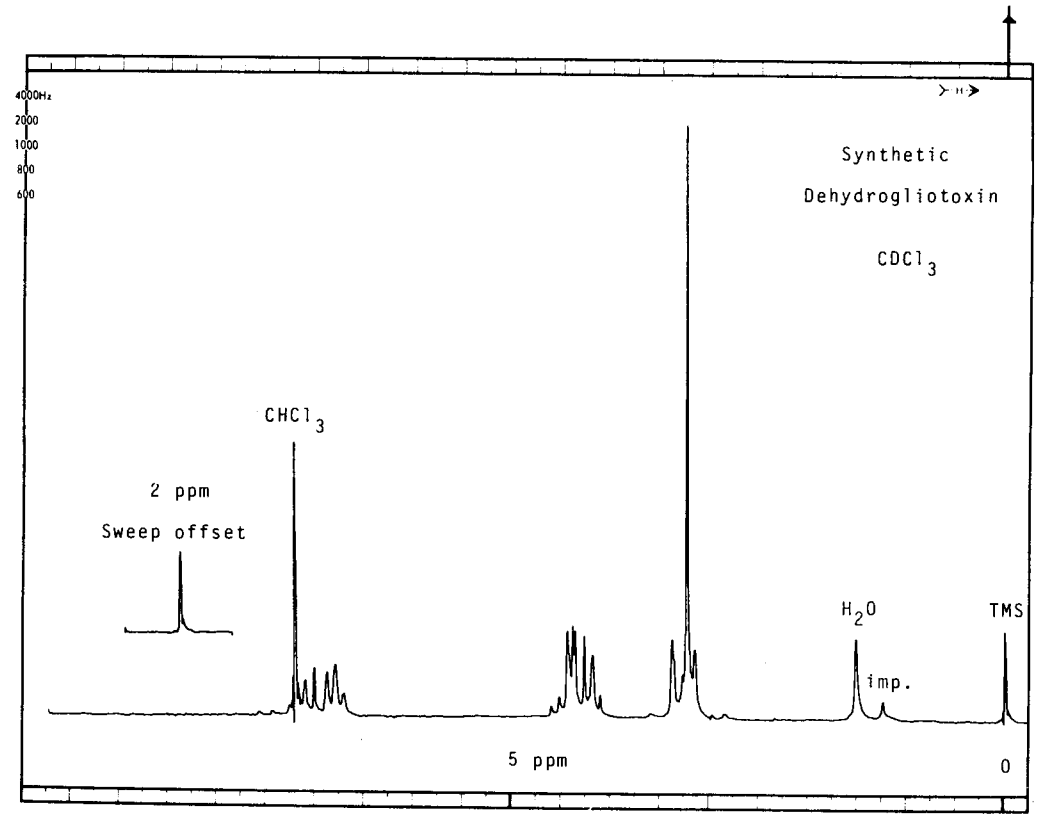
The diastereomeric chlorides **32** and **35** could not be separated chromatographically, but one of the isomers was highly crystalline, allowing their separation by fractional crystallization from ethyl acetate. The stereochemistry of the diastereomers **32** and **35** was assigned, based on the NMR spectra. The signal of the proton on the thioacetal bridge of **32** appeared at δ 6.32 ppm, whereas that of **35** was at δ 5.37 ppm, which is close to the chemical shift, δ 5.13 ppm, of the bridgehead proton of the simple thioacetal **25c**. The unusual downfield shift observed for one of the diastereomers could be attributed to the deshielding effect of the aromatic ring, establishing the stereochemistry of the diastereomeric chlorides **32** and **35**.

The regiospecific metallation at the bridgehead positions of **32** and **35** was cleanly realized as discussed previously. Thus, the acetals **34** and **37** were obtained from **32** and **35**, respectively, in good yield (see above). A more convenient one-pot synthesis of **34** from **32** was also realized by careful addition of 2.5 equivalents of phenyllithium to a solution of **32** and benzyl chloromethyl ether in tetrahydrofuran at −78°, affording **34** in 69% yield. Following exactly the same procedure, **35** gave **37** in 61% yield.

Cleavage of both the benzyl and methyl ethers of **34** and **37** with boron trichloride in methylene chloride at 0° smoothly yielded the dehydrogliotoxin thioacetals **60** and **61** in 67 and 66% yield, respectively. Finally, *dl*-dehydrogliotoxin **53** (m.p. 177–178°) was obtained from **60** and **61** in 72% yield, using the conditions established for the conversion of the natural gliotoxin thioacetals into gliotoxin (see earlier). The synthetic substance was found to be identical with natural dehydrogliotoxin[13,33] on comparison of spectroscopic (NMR, IR, UV, MS) and tlc data. The NMR spectra of synthetic and natural dehydrogliotoxin are illustrated in Fig. 8.

TOTAL SYNTHESIS OF GLIOTOXIN

At this stage in the study, the most difficult problem remaining unsolved for the synthesis of gliotoxin was apparently the method to incorporate the dihydrobenzene ring system to a synthetic intermediate, since construction of the rest of the molecule was expected to be achieved by using the method tested in the synthesis of dehydrogliotoxin. Berchtold *et al.* reported a synthesis of 4-carbo-*t*-butoxyoxepin, which exists primarily as the tautomer **62-A** but reacts with a nucleophile


4000Hz
2000
1000
800
600
Synthetic
Dehydrogliotoxin
CDCl3
CHCl3
2 ppm
Sweep offset
H2O
TMS
imp.
5 ppm
0

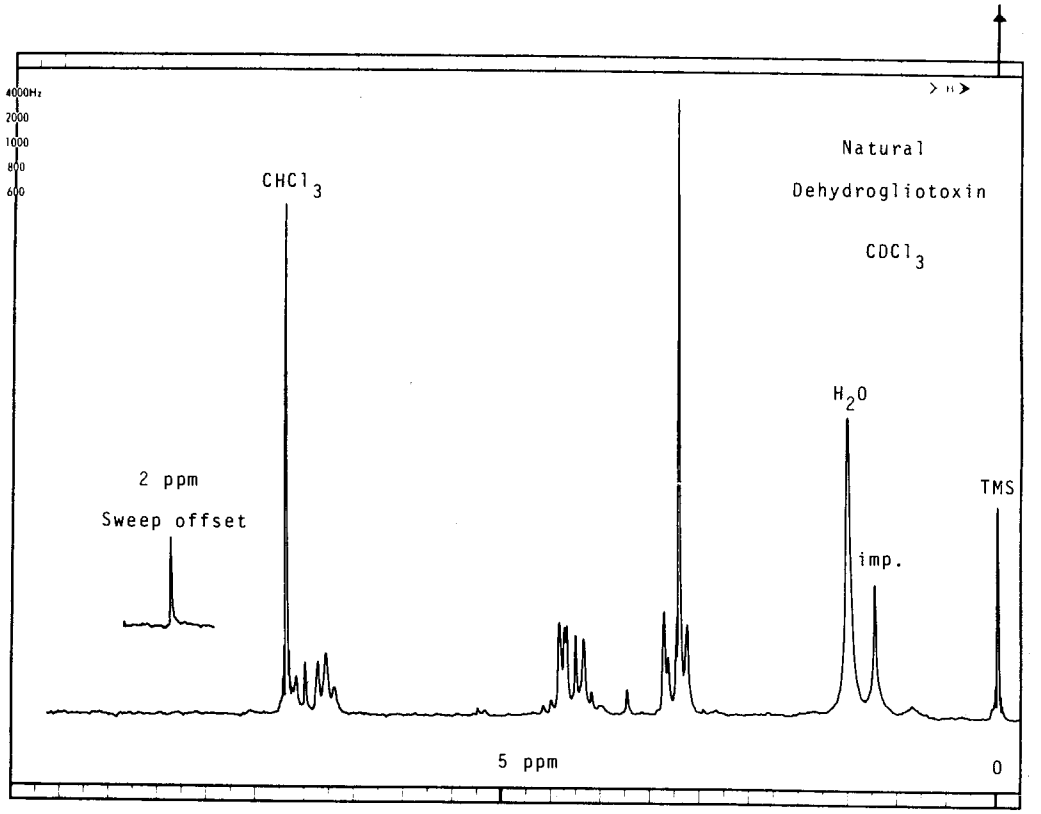
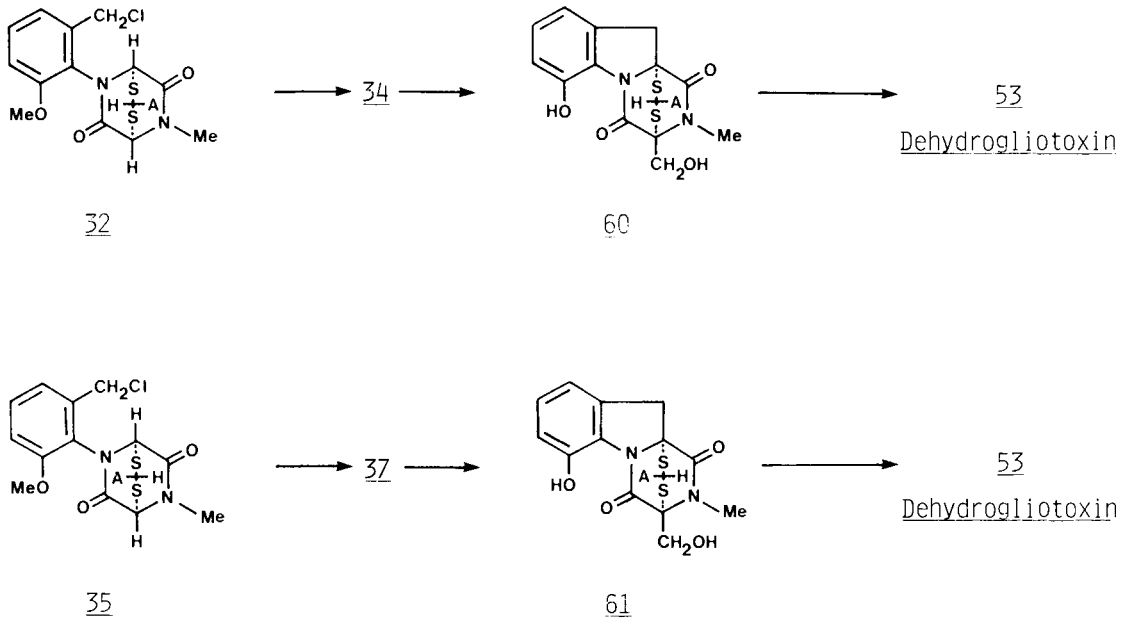
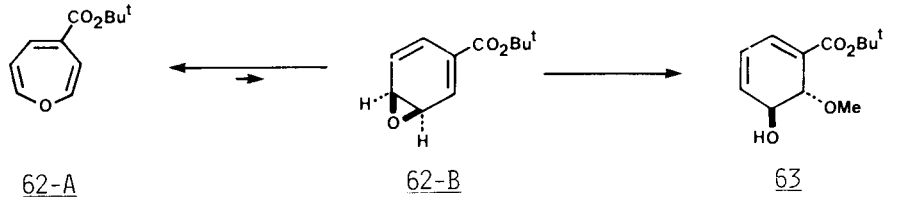

4000Hz
2000
1000
800
600
Natural
Dehydrogliotoxin
CDCl3
CHCl3
H2O
2 ppm
Sweep offset
TMS
imp.
5 ppm
0

Fig. 8.



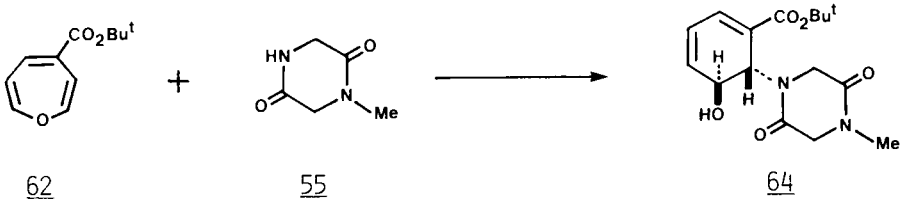
Scheme 22.

via the tautomer **62-B**; thus **62** yields exclusively the *trans*-adduct **63** upon treatment with lithium hydroxide in refluxing methanol.[48] This reaction seemed to suggest an interesting possibility for solving the present problem, which was first verified by using glycine–sarcosine anhydride (**55**). In fact, **55** was found to react smoothly with **62** in methylene chloride containing benzyltrimethylammonium methoxide (Triton B) at room temperature, to yield the expected product **64** in 36% yield. Encouraged by these results, we began the synthesis of the thioacetal **68**.



Scheme 23.

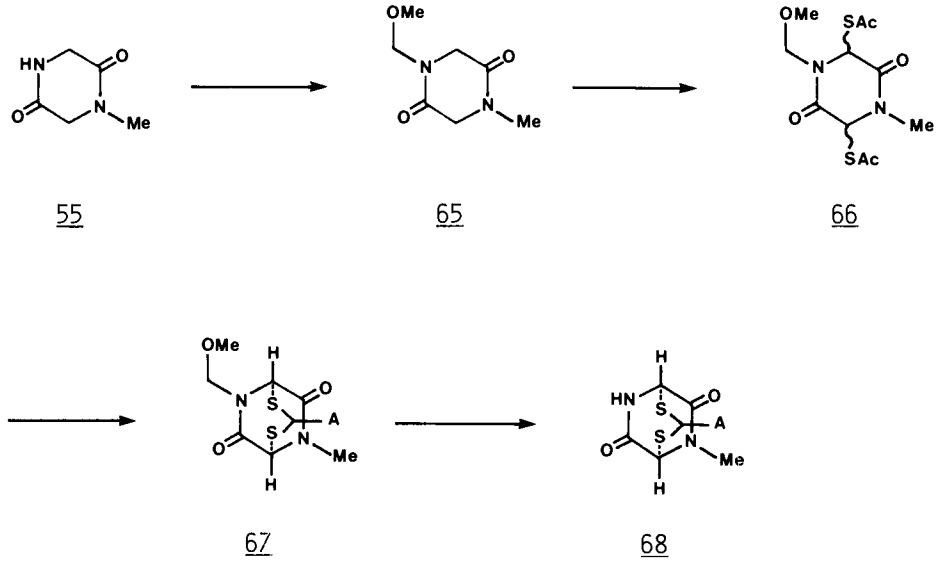
The N–H group of glycine–sarcosine anhydride (**55**) was protected as a methoxymethyl group, using potassium *t*-butoxide and chloromethyl methyl ether at 0° in 75% yield. The methoxymethyl derivative **65** was converted to a *cis* and *trans* mixture of the dithioacetates **66** upon treatment with 2.5 equivalents of N-bromosuccinimide and catalytic amounts of benzoyl peroxide in refluxing carbon tetrachloride, followed by potassium thioacetate in methylene chloride at room temperature. The resultant mixture of *cis*- and *trans*-dithioacetates **66** was subjected to methanolysis with methanolic hydrogen chloride at 50° to give the dithiols, which were then treated with *p*-anisaldehyde and boron trifluoride etherate in methylene chloride at room temperature to yield the methoxymethyl thioacetal **67**. Removal of the methoxymethyl group of **67** was most efficiently



Scheme 24.

achieved in a refluxing solution of concentrated hydrochloric acid–ethanol (1:1). Since a diastereomeric mixture of the thioacetal **68** crystallized out from the crude reaction mixture, no chromatographic separation of the intermediates was necessary from **65** to **68**. The overall yield from **65** to **68** by this procedure was 30%.

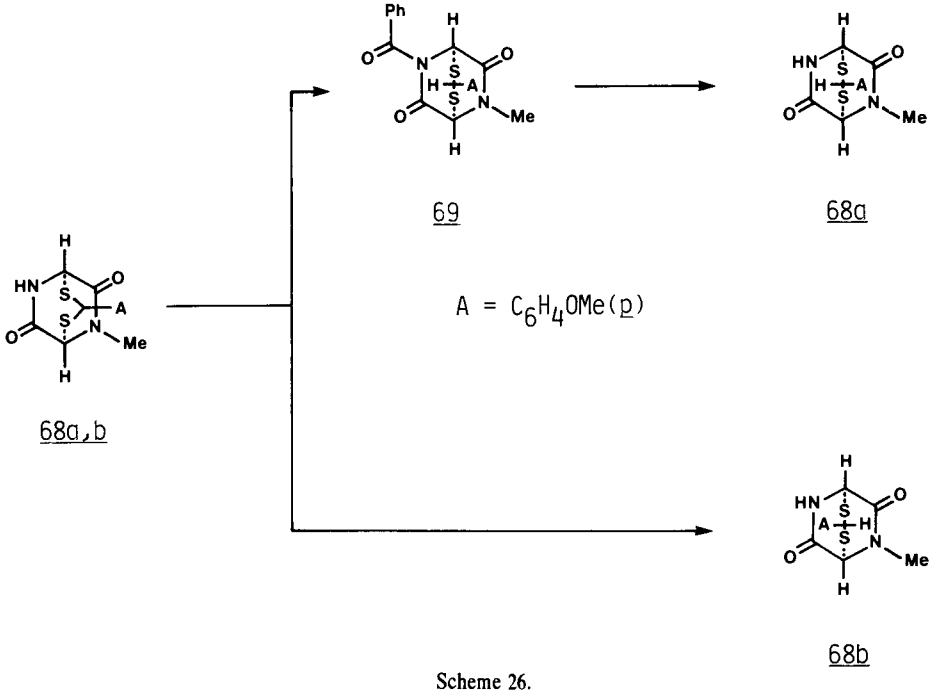
diastereomeric mixture of the thioacetals **68a,b** in methylene chloride was treated with benzoyl chloride and triethylamine at room temperature, and the reaction was intercepted when about half of the starting material had been consumed. The mixture was then separated on silica gel column chromatography. Analysis of the NMR spectra



Scheme 25.

Attempted separation of the diastereomeric mixture of the thioacetals **68** by chromatography or fractional crystallization was fruitless, but it was realized by using the remarkable reactivity difference between these two diastereomers for N-benzoylation. A solution of a 1:1

showed that the N-benzoyl thioacetal **69** was an about 10:1 mixture favoring the one diastereomer, whereas the recovered thioacetal **68** was an about 10:1 mixture favoring the other diastereomer. The thioacetal **68a** was readily recovered by passing ammonia through a methylene chloride solution of



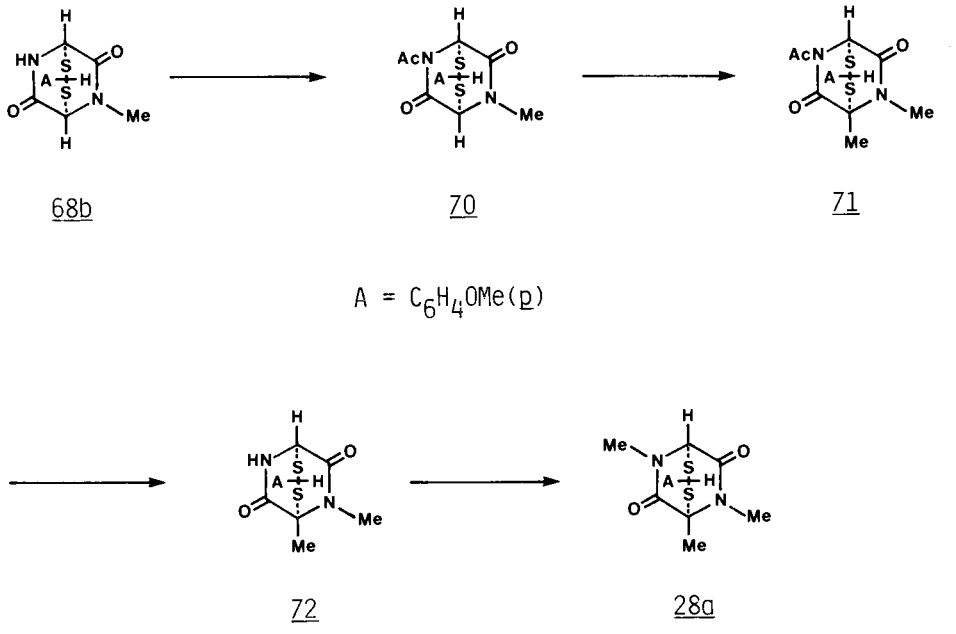
Scheme 26.

the N-benzoyl thioacetal **69**. Recrystallization of the thioacetals **68a** and **68b**, thus obtained, from hot ethanol, allowed isolation of the pure diastereomers, **68a** and **68b**, respectively.

The stereochemistry of the thioacetals **68a** and **68b** was established by chemical transformation. After N-acetylation with acetic anhydride at 130°, **68b** was alkylated on treatment with methyl iodide and *n*-butyllithium in tetrahydrofuran at −78°, to give the N-acetyl-C-methyl thioacetal **71**. Ammonolysis of **71** yielded exclusively the monomethyl thioacetal **72**. The structure of **72**, except the stereochemistry of the anisaldehyde residue, was evidenced by the NMR spectrum; the signal of the bridgehead proton appeared as a doublet at δ 5.37 ppm (J = 6 Hz), which became a singlet on addition of deuterium oxide. Upon treatment with potassium *t*-butoxide and methyl iodide in tetrahydrofuran, **72** yielded the N-methyl thioacetal **28a**. The substance was found to be identical with the authentic thioacetal **28a**, derived from **25c** by treatment with *n*-butyllithium and methyl iodide (see earlier), on comparison of spectroscopic data (NMR, IR, MS) and mixed m.p. determination.

yield. The ratio of the Michael adducts in this reaction was found to be dependent on the solvent and the reaction time. Thus, a 3:1 ratio favoring the adduct **74**, the minor product in Triton B-methylene chloride, was realized when the reaction was conducted in dimethyl sulfoxide at room temperature for 30 min. A slow elimination reaction, regenerating the thioacetal **68b** from the adducts **73** and **74**, was observed at room temperature either in methylene chloride or dimethyl sulfoxide in the presence of Triton B. Thus, an approximately 1:1 mixture of the adducts **73** and **74** resulted from either **68b**, **73** or **74** on Triton B treatment in methylene chloride or dimethyl sulfoxide in the presence of excess **62** at room temperature overnight.

Since the overall *trans* ring opening was expected for **62**, the adducts **73** and **74** should be the epimers with respect to the relative configuration of the thioacetal bridge and the alcoholic group. Two probable orientations *F* and *G* were considered for the transition state of the Michael reaction when **62** and **68b** approached each other in such a way as to cause the least steric hindrance. It was anticipated that the favorable dipole



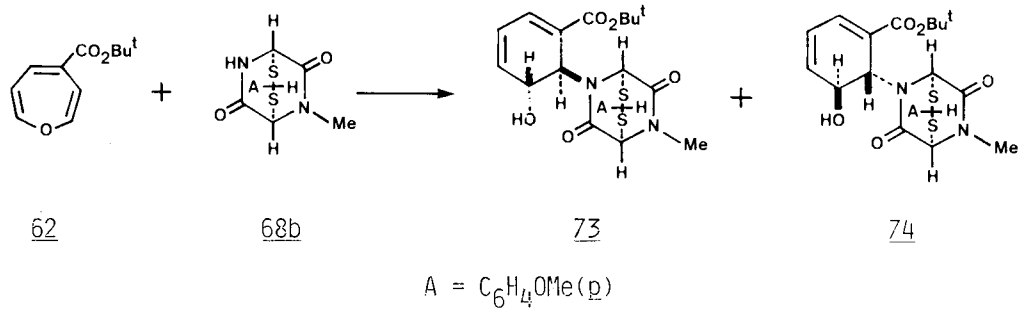
Scheme 27.

The pronounced reactivity difference in the N-benzoylation of the two diastereomers **68a** and **68b** allowed the establishment of a practical method for their separation, however the reason for the origin of the reactivity difference remained obscure. From analysis of the molecular models, the steric effect did not seem to provide a reasonable explanation for the observed phenomena. Some electronic effect like that discussed earlier might be important to consider.

Treatment of a methylene chloride solution of **68b** and 4-carbo-*t*-butoxyoxepin (**62**) with Triton B at room temperature for 30 min yielded a 3:1 mixture of the Michael adducts **73** and **74** in 60%

interaction involved in *F* might be favored over *G* in a non-polar solvent such as methylene chloride. Thus, the undesired stereochemistry was tentatively assigned to the adduct **73** and the desired stereochemistry to **74**. This assignment was later confirmed by the fact that the adduct **74** yielded gliotoxin, whereas the adduct **73** gave the epimer of gliotoxin at the sulfur bridge.

The adduct **74** was treated with acetic anhydride and pyridine at room temperature to yield the acetate **75** in 97% yield. The carboxylic acid **76** was obtained upon treatment of **75** with trifluoroacetic acid at room temperature for 8 min. The acid **76** was then converted to the mixed



Scheme 28.

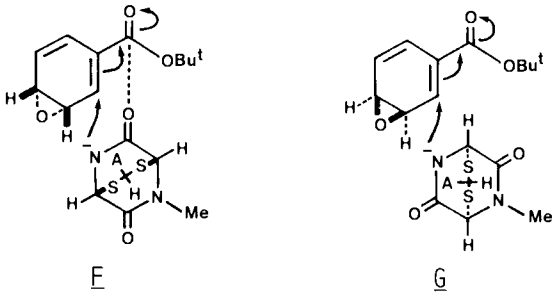
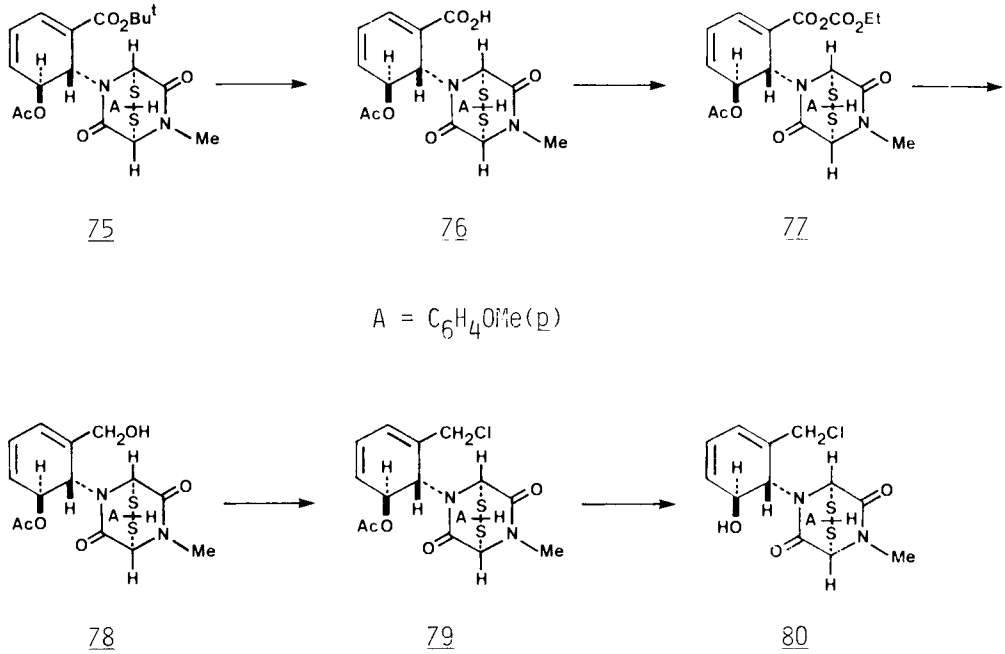


Fig. 9.

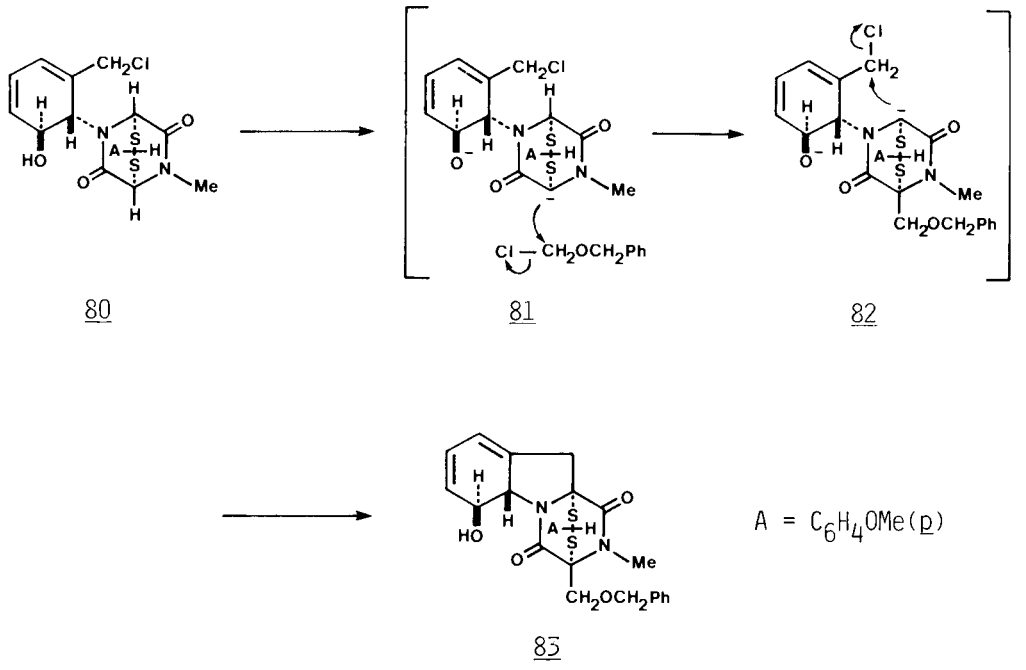
anhydride **77** by adding triethylamine to a solution of **76** and ethyl chloroformate in methylene chloride at room temperature. The reduction of the mixed anhydride **77** to the alcohol **78** was most efficiently achieved by the direct addition of a chilled solution of excess sodium borohydride in methanol to an ice-cooled solution of **77** in methylene chloride. The overall yield of **78** from **75** was 79%. The alcohol **78** was treated with methanesulfonyl chloride and triethylamine in methylene chloride and then with lithium chloride in dimethylformamide at room temperature to afford the chloride acetate **79** in 96% overall yield. Methanolysis of **79** with 0.5 equivalent of sodium methoxide in 10% methanol in methylene chloride at room temperature gave the chloride alcohol **80** in 94% yield.

The crucial cyclization–alkylation reaction was accomplished by careful addition of 3.2 equivalents of phenyllithium to a solution of **80** and benzyl chloromethyl ether in tetrahydrofuran at −78°, to yield the desired cyclized compound **83** in 52% yield. Apparently the presence of the free alcoholic group of **80** was essential to prevent aromatization under these conditions.[49]

Cleavage of the benzyl ether of **83** was achieved upon treatment with boron trichloride in methylene chloride at 0° to give the gliotoxin thioacetal **27b** in 60% yield. The unusual stability of the cyclohexadienol system under such strongly acidic conditions could be explained in terms of the complex formation with boron trichloride, which might hold the alcohol group equatorial, hence preventing the elimination of water. The *dl*-gliotoxin thioacetal **27b** was identical with an authen-

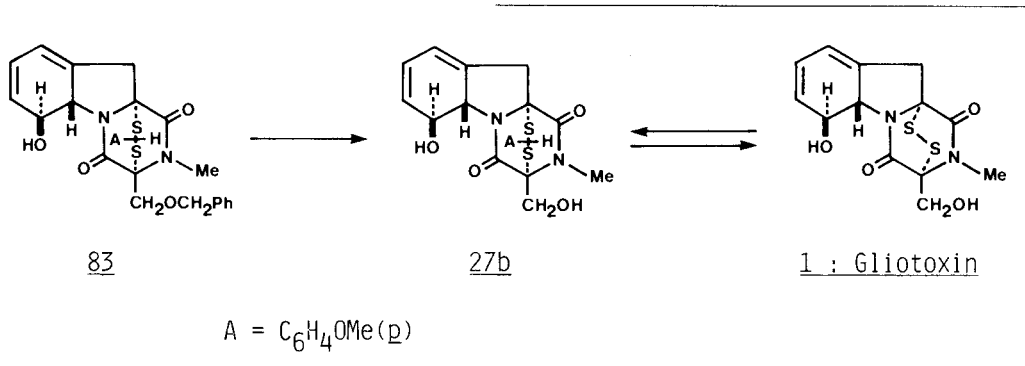


Scheme 29.



Scheme 30.

tic sample, prepared by treating natural gliotoxin[33] with sodium borohydride and then with *p*-anisaldehyde and boron trifluoride etherate, by comparison of spectroscopic (NMR, IR, UV, MS) and tlc data.



Scheme 31.

Finally the *dl*-gliotoxin thioacetal was treated with 1.2 equivalents of *m*-chloroperbenzoic acid in methylene chloride at 0° and then with a catalytic amount of perchloric acid at room temperature to afford *dl*-gliotoxin (**1**) (m.p. 165–166°, capillary) in 58% yield. The synthetic substance was found to be identical with natural gliotoxin[33] on comparison of spectroscopic (NMR, IR, UV, MS) and tlc data.

Exactly parallel results were obtained for the thioacetal **68a**, yielding totally synthetic *dl*-gliotoxin.

The NMR spectra of synthetic and natural gliotoxin are shown in Fig. 10.

SYNTHESIS OF OPTICALLY ACTIVE GLIOTOXIN

Having completed the synthesis of racemic gliotoxin, optical resolution of the thioacetal **68a** was studied, resulting in the efficient method shown in Scheme 32. Treatment of **68a** with (−)-α-methylbenzyl isocyanate[50] and triethylamine in methylene chloride at room temperature yielded a diastereomeric mixture of the ureas **84** and **85** in 71% yield. The diastereomers **84** and **85** could be readily separated by silica gel chromatography. Removal of the resolving agent was effected by pyrolysis of 230° under an argon atmosphere. Thus, optically active thioacetals **86** and **87** were obtained from the racemic thioacetal **68a** in 64% and 66% yields (based on each enantiomer in racemic **68a**), respectively.[51]

The absolute configurations of the thioacetals **86** and **87** were tentatively assigned by comparison of the circular dichroism (CD) spectra with that of the gliotoxin thioacetal **27a**, whose absolute configuration was known from an X-ray analysis of gliotoxin.[10] Since the CD band at the 230 nm region of gliotoxin was assigned as peptide n-π^* transitions,[52] the close resemblance of the CD band of **86** and **27a** would suggest that the

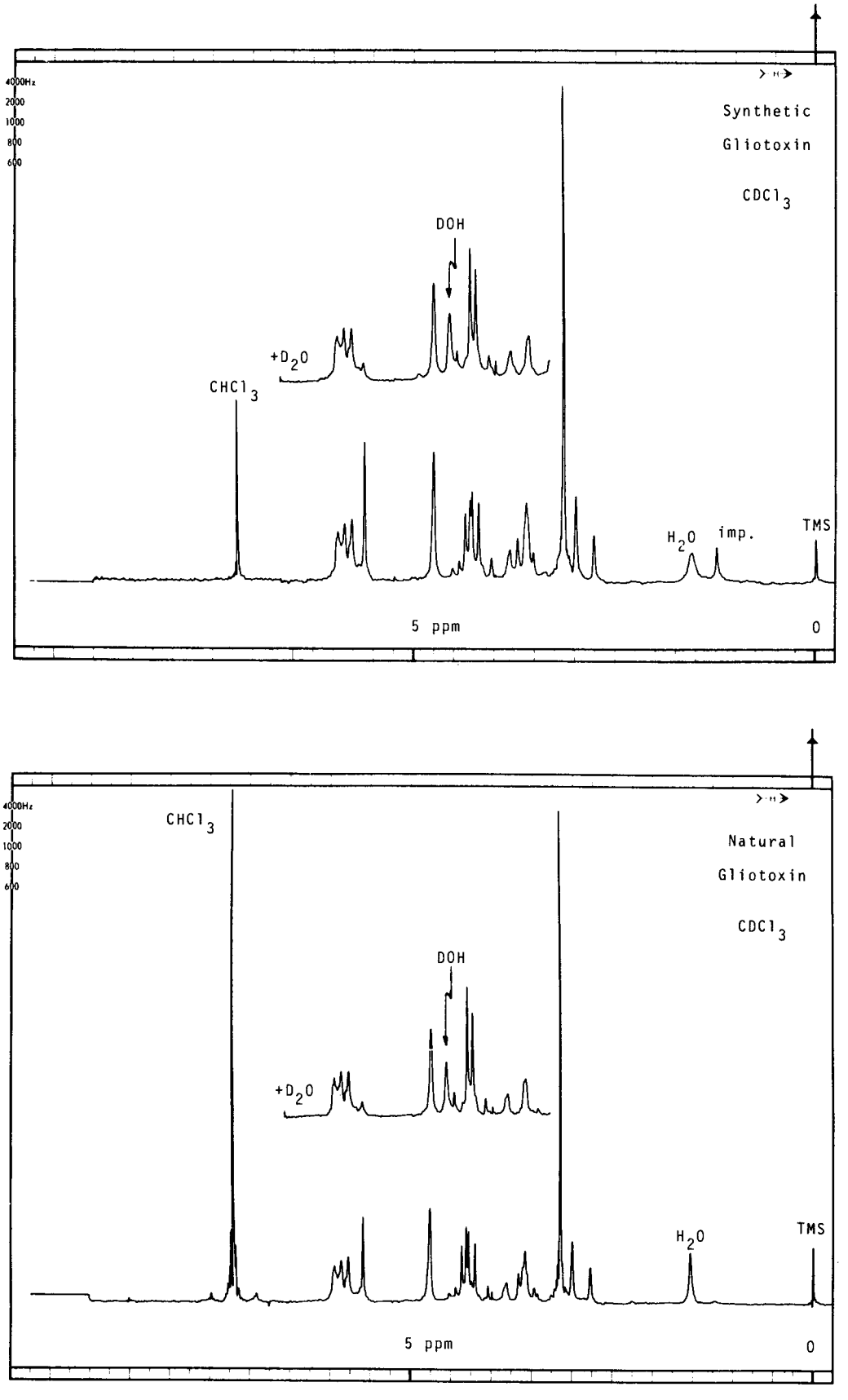
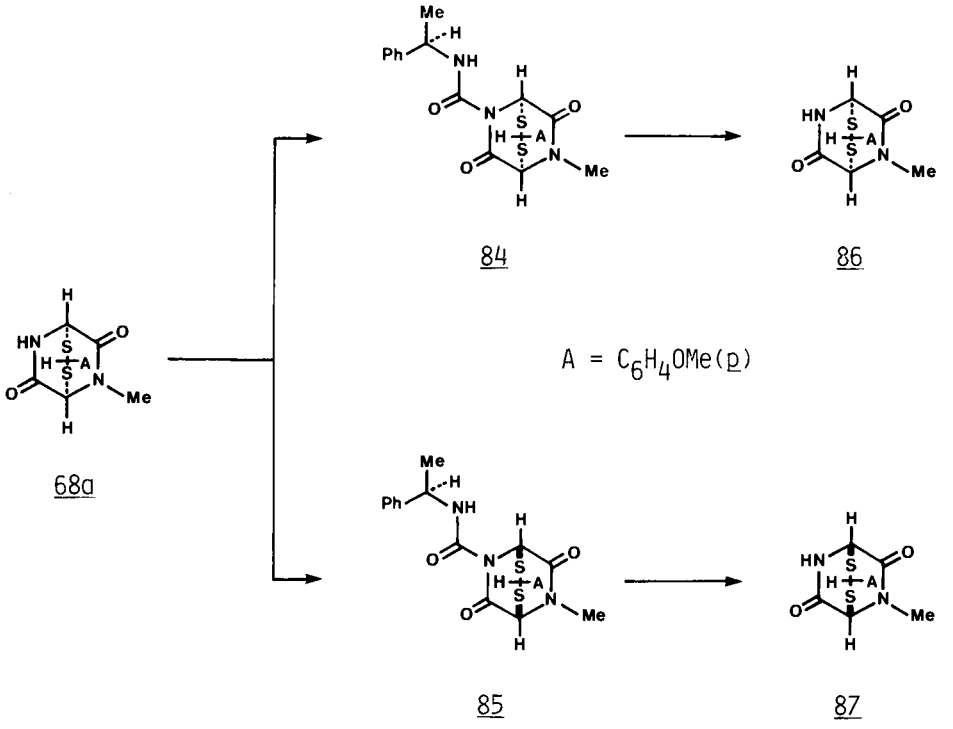

4000Hz
2000
1000
800
600
Synthetic
Gliotoxin
CDCl3
DOH
+D2O
CHCl3
H2O
imp.
TMS
5 ppm
0
4000Hz
2000
1000
800
600
CHCl3
Natural
Gliotoxin
CDCl3
DOH
+D2O
H2O
TMS
5 ppm
0

Fig. 10.



Scheme 32.

thioacetal **86** had the absolute configuration desired for the gliotoxin synthesis.

Using the optically active thioacetal **86** as starting material, the optically active gliotoxin thioacetal **27a** was prepared by following exactly the same procedure established for the total synthesis of *dl*-gliotoxin. The assignment of the absolute configuration for **86** was confirmed by the fact that both synthetic and natural gliotoxin thioacetal showed the same optical rotation. Conversion of the gliotoxin thioacetal **27a** into gliotoxin **1** was performed in the same manner as before. The

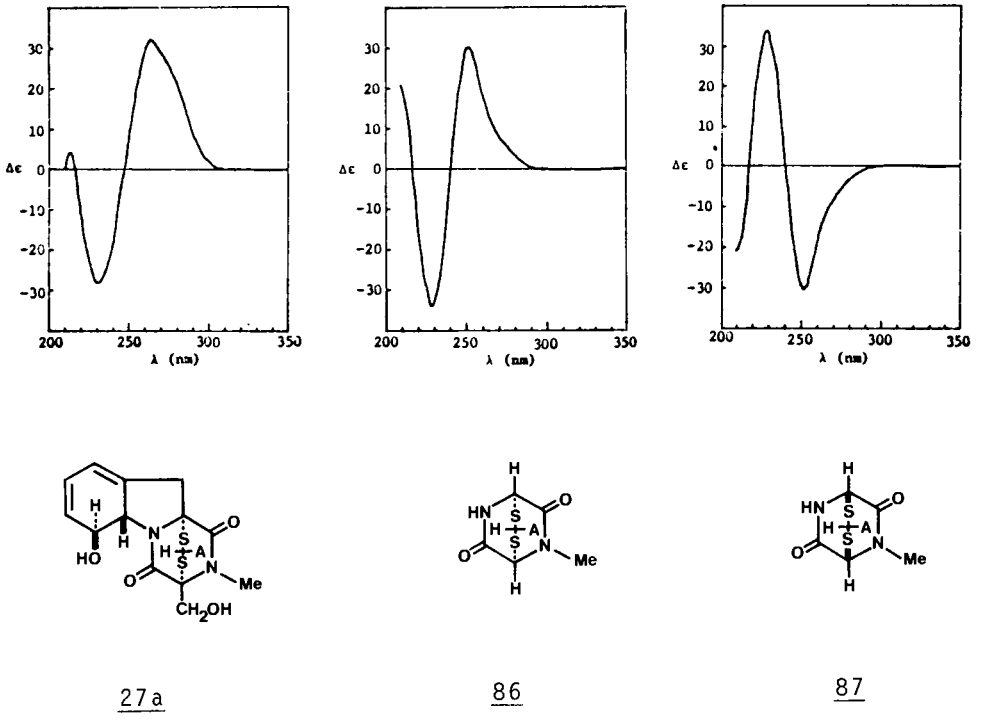
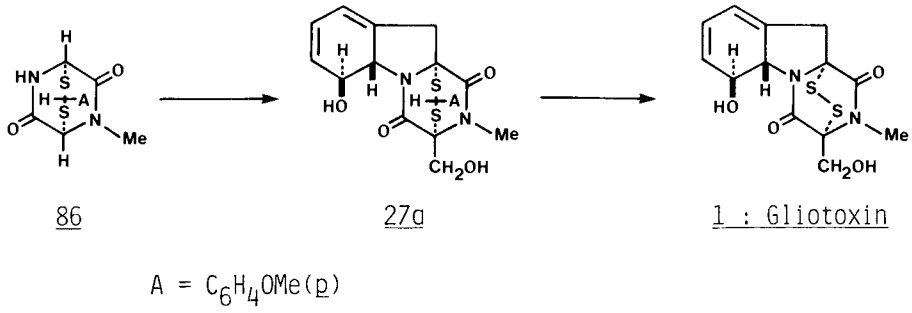


Fig. 11.



Scheme 33.

totally synthetic substance was found to be identical with natural gliotoxin[33] on comparison of spectra (NMR, IR, UV, MS, α_D) and tlc data.

Acknowledgements—Financial support from the National Institutes of Health (NS 12108), National Science Foundation (CHE 78-06296) and the Hoffmann-La Roche Company is gratefully acknowledged.

EXPERIMENTAL

Melting points (m.p.), determined on a Kofler hot stage and boiling points (b.p.) are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 727 spectrophotometer and are reported in wave numbers (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were determined on a Varian HFT-80 instrument in the Fourier Transform mode. Chemical shifts are reported in parts per million downfield from tetramethylsilane (δ) as internal standard. Following abbreviations are used for spin multiplicity; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra (MS) and high resolution mass spectra (Exact Mass) were determined on an AEI MS-9 double-focusing instrument at 70 eV using direct probe insertion at a temperature of 150–200°. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter at ambient temperature. Circular dichroism (CD) spectra were determined on a Cary Model 60 spectropolarimeter. Elemental analyses were performed by Analytical Laboratories, Meijo University, Nagoya, Japan. Analytical thin layer chromatography (tlc) was performed on either 0.25 mm pre-coated silica gel or aluminum oxide Type T plates supplied by E. Merck. Preparative TLC separations were made on plates (20 × 20 cm) prepared with a 2-mm layer of silica gel PF_{254} or aluminum oxide PF_{254} Type T both obtained from E. Merck. Column chromatography was performed on silica gel obtained from Kanto Chemical Co., Japan. Reagents and solvents were commercial grades and were used as supplied with the following exceptions: Methylene chloride: distilled. Ether (dry): distilled from sodium benzophenone ketyl. Tetrahydrofuran (dry): distilled from sodium benzophenone ketyl. *t*-Butanol (dry): distilled from sodium. Pyridine: dried over potassium hydroxide. Diisopropyl amine: distilled from sodium hydride. Dihydropyran: distilled. All alkylating or acylating agents were passed through a short aluminum oxide column prior to use. Lithium diisopropylamide (LDA) was prepared by dropwise addition of *n*-butyllithium in hexane to a stirred solution of diisopropylamine in tetrahydrofuran at 0° and was used after stirring for 5 min. All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.

Epidithiapiperazinedione syntheses (Method A)

Formaldehyde thioacetal **16**. A mixture of 200 mg (0.971 mmol) of dithiopiperazinedione **4**[22] (*cis* and *trans* mixture) and 1 ml of diiodomethane in 4 ml of pyridine was stirred at room temperature for 15 hr. The mixture was evaporated to a small volume under reduced pressure, diluted with methylene chloride and poured into a mixture of ice and concentrated hydrochloric acid. The aqueous layer was thoroughly extracted with methylene chloride. The combined extracts were washed with 10% hydrochloric acid, dried over anhydrous sodium sulfate, filtered, evaporated and chromatographed on a silica gel column (eluted with 1% methanol in methylene chloride) to give 109 mg (51.5%) of **16** as white crystals, m.p. 236–237° (methanol–ethyl acetate). IR (KBr): 1681, 1664. NMR ($CDCl_3$): 3.08 (6H, s), 3.90 (2H, s), 4.82 (2H, s). MS: 218 (43, M), 140 (100), 112 (38). Exact Mass: Found: 218.0184. Calc. for $C_7H_{10}N_2O_2S_2$: 218.0184. Analysis (recrystallized from methanol–ethyl acetate): Found: C, 38.45; H, 4.58; N, 12.86. Calc. for $C_7H_{10}N_2O_2S_2$: C, 38.52; H, 4.62; N, 12.83%.

By using the same procedure, the formaldehyde thioacetal **16** was obtained from pure *cis*-dithiopiperazinedione **4a**[22] or *trans*-dithiopiperazinedione **4b**[22] in comparable yield.

Monomethyl thioacetal **18**. A solution of 57.0 mg (0.261 mmol) of the thioacetal **16** in 10 ml of dry tetrahydrofuran was cooled in a dry ice–acetone bath. To the stirred solution was added dropwise 0.150 ml (1.2 eq) of 2.10 N *n*-butyllithium in hexane over a period of 1 min. After 30 sec, 85 μl (5 eq) of methyl iodide was added and stirring was continued for an additional 30 min. The solution was allowed to warm to room temperature and poured into a saturated sodium chloride solution. The aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel tlc [eluted with ethyl acetate–hexane (7:3)] to give 33.1 mg (54.5%) of **18** as white crystals, m.p. 175–176° (ethyl acetate). IR (KBr): 1690, 1660. NMR ($CDCl_3$): 1.85 (3H, s), 3.09 (6H, s), 3.86 (2H, s), 4.91 (1H, s). MS: 232 (1, M), 186 (5), 154 (100), 126 (56). Exact Mass: Found: 232.0342. Calc. for $C_8H_{12}N_2O_2S_2$: 232.0340.

Ditetrahydropyranyl derivative **19**. A mixture of 200 mg (0.971 mmol) of *cis*-dithiopiperazinedione **4a**,[22] 3 ml of dihydropyran and 50 mg of *dl*-camphorsulfonic acid in 50 ml of benzene was heated under reflux for 2 h. After cooling, the mixture was washed with a saturated sodium bicarbonate solution. The aqueous layer was thoroughly extracted with methylene chloride. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, evaporated and chromatographed on a silica gel column (eluted with 0.5% methanol in methylene chloride) to afford 188 mg (51.7%) of **19** as white crystals, m.p. 163–165° (ethyl acetate). IR (KBr): 1680. MS: 374 (<1, M), 290 (10), 174 (86), 141 (90), 140 (58), 85 (100). Exact Mass: Found: 374.1343. Calc. for $C_{16}H_{26}N_2O_4S_2$: 374.1334.

Iodine oxidation of **19**. To a stirred solution of 100 mg (0.267 mmol) of ditetrahydropyranyl derivative **19** in 10 ml of methylene chloride was added dropwise a methylene chloride solution of iodine (1 g in 20 ml) at

room temperature until **19** completely disappeared (monitored by silica gel tlc by using 5% methanol in methylene chloride as the eluent). The reaction mixture was evaporated to dryness under reduced pressure. The crystalline residue was crystallized from methanol to afford 39.2 mg (72%) of **5**, m.p. 180–183° (lit.[22] 185° dec.), as pale yellow crystals.

p-*Anisaldehyde thioacetal* **25c**. To a stirred solution of 100 mg (0.486 mmol) of dithiopiperazinedione **4**[22] (*cis* and *trans* mixture) and 0.3 ml of *p*-anisaldehyde in 10 ml of methylene chloride was added 50 μl of boron trifluoride etherate. After stirring at room temperature for 12 hr, the solution was poured into a saturated sodium bicarbonate solution. The aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered and evaporated to give crystals which were collected with ether to yield 130 mg (82.6%) of **25c**, m.p. 267–268° (ethyl acetate).
IR (KBr): 1680, 1608, 1510. NMR ($CDCl_3$): 3.05 (3H, s), 3.18 (3H, s), 3.79 (3H, s), 4.84 (1H, s), 5.00 (1H, s), 5.13 (1H, s), 6.82 (2H, d, J = 9 Hz), 7.31 (2H, d, J = 9 Hz). MS: 324 (2, M), 260 (3), 140 (100), 112 (13). Exact Mass: Found: 324.0593. Calc. for $C_{14}H_{16}N_2O_3S_2$: 324.0602. Analysis (recrystallized from methylene chloride–ether): Found: C, 51.64; H, 4.86; N, 8.53. Calc. for $C_{14}H_{16}N_2O_3S_2$: C, 51.83; H, 4.97; N, 8.64%.

By using the same procedure, the *p*-anisaldehyde thioacetal **25c** was obtained from pure *cis*-dithiopiperazinedione **4a**[22] or *trans*-dithiopiperazinedione **4b**[22] in comparable yield.

By using the same procedure, the thioacetals **25a** and **25b** were synthesized.

Acetaldehyde thioacetal **25a**. Yield: 73.2%. M.P. 186–188° (capillary, methanol). IR (KBr): 1670. NMR ($CDCl_3$): 1.55 (3H, d, J = 7.5 Hz), 3.01 (3H, s), 3.11 (3H, s), 4.26 (1H, q, J = 7.5 Hz), 4.77 (1H, s), 4.94 (1H, s). MS: 232 (15, M), 140 (100), 112 (22). Exact Mass: Found: 232.0338. Calc. for $C_8H_{12}N_2O_2S_2$: 232.0340. Analysis (recrystallized from methanol): Found: C, 41.22; H, 5.14; N, 12.08. Calc. for $C_8H_{12}N_2O_2S_2$: C, 41.36; H, 5.21; N, 12.06%.

Benzaldehyde thioacetal **25b**. Yield: 92.4%. M.P. 272–273° (capillary, ethyl acetate). IR (KBr): 1680. NMR ($CDCl_3$): 3.05 (3H, s), 3.19 (3H, s), 4.85 (1H, s), 5.01 (1H, s), 5.16 (1H, s), 7.35 (5H, m). MS: 294 (1, M), 230 (17), 140 (100), 112 (14). Exact Mass: Found: 294.0492. Calc. for $C_{13}H_{14}N_2O_2S_2$: 294.0497. Analysis (recrystallized from methylene chloride–ether): Found: C, 52.79; H, 4.66; N, 9.39. Calc. for $C_{13}H_{14}N_2O_2S_2$: C, 53.04; H, 4.79; N, 9.52%.

Monomethyl thioacetal **28a**. A solution of 300 mg (0.926 mmol) of the thioacetal **25c** in 36 ml of dry tetrahydrofuran was cooled in a dry ice–acetone bath. To the stirred solution was added dropwise 0.463 ml (1.1 eq) of 2.20 N *n*-butyllithium in hexane over a period of 1 min. After 30 sec, 0.276 ml (5 eq) of methyl iodide was added and stirring was continued for an additional 5 min. The cooling bath was removed and the solution was allowed to warm to room temperature. The mixture was poured into a saturated sodium chloride solution and the aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel tlc [eluted with ethyl acetate–hexane (1:1)] to give 196 mg (62.6%) of **28a** as white crystals, m.p. 205–206° (ethyl acetate). IR (KBr): 1690, 1679, 1603, 1509. NMR ($CDCl_3$): 1.87 (3H, s), 3.07 (3H, s), 3.18 (3H, s), 3.79 (3H, s), 5.07 (1H, s), 5.10 (1H, s), 6.81 (2H, d, J = 9 Hz), 7.28 (2H, d, J = 9 Hz). MS: 338 (5, M), 154 (100), 126 (26). Exact Mass: Found: 338.0753. Calc. for $C_{15}H_{18}N_2O_2S_2$: 338.0759. Analysis (recrystallized from methanol): Found: C, 53.17; H, 5.32; N, 8.22. Calc. for $C_{15}H_{18}N_2O_3S_2$: C, 53.23; H, 5.36; N, 8.28%.

The mono-substituted thioacetals **28** were synthesized by using the same procedure as the one given for **28a**.[39]

Monobenzyl thioacetal **28b**. Reagent: $C_6H_5CH_2Br$ (3 eq). Yield: 65.5%. M.P.: 268–270° (chloroform–methanol). IR (KBr): 1680, 1603, 1510. NMR ($CDCl_3$): 3.10 (3H, s), 3.13 (3H, s), 3.22 (1H, AB, J = 17 Hz), 3.80 (3H, s), 4.10 (1H, AB, J = 17 Hz), 5.08 (1H, s), 5.15 (1H, s), 6.83 (2H, d, J = 9 Hz), 7.15 (5H, m), 7.30 (2H, d, J = 9 Hz). MS: 414 (4, M), 230 (100), 202 (9), 91 (26). Exact Mass: Found: 414.1070. Calc. for $C_{21}H_{22}N_2O_3S_2$: 414.1072. Analysis (recrystallized from chloroform–methanol): Found: C, 58.27; H, 5.14; N, 6.37. Calc. for $C_{21}H_{22}N_2O_3S_2 \cdot H_2O$: C, 58.31; H, 5.59; N, 6.48%.

Monoethyl thioacetal **28c**. Reagent: C_2H_5I (5 eq). Yield: 60.2% M.P.: 202–203° (ethyl acetate). IR (KBr): 1680, 1602, 1503. NMR ($CDCl_3$): 1.00 (3H, t, J = 7 Hz), 1.90 (1H, m), 2.50 (1H, m), 3.07 (3H, s), 3.19 (3H, s), 3.79 (3H, s), 5.01 (1H, s), 5.08 (1H, s), 6.81 (2H, d, J = 9 Hz), 7.27 (2H, d, J = 9 Hz). MS: 352 (5, M), 168 (100), 140 (8). Exact Mass: Found: 352.0909. Calc. for $C_{16}H_{20}N_2O_3S_2$: 352.0915. Analysis (recrystallized from methanol): Found: C, 54.29; H, 5.80; N, 7.83. Calc. for $C_{16}H_{20}N_2O_3S_2$: C, 54.52; H, 5.72; N, 7.95%.

Benzyl methyl thioacetal **29a** *from* **28a**. A solution of 108 mg (0.319 mmol) of the monomethyl thioacetal **28a** and 0.114 ml (3 eq) of benzyl bromide in 11 ml of dry tetrahydrofuran was cooled in a dry ice–acetone bath. To the stirred solution was added dropwise 0.198 ml (1.3 e) of 2.10 N *n*-butyllithium in hexane over a period of 15 min. Stirring was continued for an additional 5 min and the solution was allowed to warm to room temperature. The mixture was poured into a saturated sodium chloride solution and thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel tlc [eluted with ethyl acetate–hexane (2:3)] to give 107 mg (78.3%) of **29a** as white crystals, m.p. 219–110° (methanol–ethyl acetate). IR (KBr): 1679, 1604, 1511. NMR ($CDCl_3$): 1.94 (3H, s), 2.94 (3H, s), 3.10 (1H, AB, J = 14 Hz), 3.31 (3H, s), 3.80 (3H, s), 4.36 (1H, AB, J = 14 Hz), 5.10 (1H, s), 6.81 (2H, d, J = 9 Hz), 6.95–7.35 (7H, m). MS: 428 (<1, M), 244 (100), 216 (14), 91 (23). Exact Mass: Found: 428.1223. Calc. for $C_{22}H_{24}N_2O_3S_2$: 428.1228. Analysis (recrystallized from methanol–ethyl acetate): Found: C, 61.73; H, 5.54; N, 6.51. Calc. for $C_{22}H_{24}N_2O_3S_2$: C, 61.66; H, 5.64; N, 6.54%.

The di-substituted thioacetals **29** were synthesized by using the same procedure as the one given for **29a**.[39]

Benzyl methyl thioacetal **29b** from **28b**. Reagent: CH_3I (5 eq). Yield: 76.0%. M.P.: 231–232° (methylene chloride–ether). IR (KBr): 1681, 1670, 1602, 1510. NMR ($CDCl_3$): 1.97 (3H, s), 3.15 (6H, s), 3.24 (1H, AB, J = 14 Hz), 3.78 (3H, s), 4.16 (1H, AB, J = 14 Hz), 5.04 (1H, s), 6.81 (2H, d, J = 9 Hz), 6.95–7.35 (7H, m). MS: 428 (<1, M), 244 (100), 216 (13), 91 (21). Exact Mass: Found: 428.1223. Calc. for $C_{22}H_{24}N_2O_3S_2$: 428.1228. Analysis (recrystallized from methylene chloride–ether): Found: C, 61.53; H, 5.52; N, 6.43. Calc. for $C_{22}H_{24}N_2O_3S_2$: C, 61.66; H, 5.64; N, 6.54%.

Dimethyl thioacetal **29c** (*one-pot procedure*). A solution of 100 mg (0.309 mmol) of the thioacetal **25c** and 0.184 ml (10 eq) of methyl iodide in 12 ml of dry tetrahydrofuran was cooled in a dry ice–acetone bath. To the stirred solution was added dropwise 0.338 ml (2.3 eq) of 2.10 N *n*-butyllithium in hexane over a period of 10 min. The progress of the reaction was carefully monitored by tlc. After stirring for an additional 5 min, the cooling bath was removed and the solution was allowed to warm to room temperature. The mixture was then poured into a saturated sodium chloride solution and the aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel tlc [eluted with ethyl acetate–hexane (1:1)] to give 88.0 mg (81.0%) of **29c** as white crystals, m.p. 190–191° (methanol). IR (KBr): 1679, 1606, 1510. NMR ($CDCl_3$):

1.89 (3H, s), 1.91 (3H, s), 3.09 (3H, s), 3.11 (3H, s), 3.76 (3H, s), 5.01 (1H, s), 6.78 (2H, d, J = 9 Hz), 7.24 (2H, d, J = 9 Hz). MS: 352 (4, M), 168 (100), 140 (17). Exact Mass: Found: 352.0906. Calc. for $C_{16}H_{20}N_2O_3S_2$: 352.0915. Analysis (recrystallized from methanol): Found: C, 54.34; H, 5.73; N, 7.83. Calc. for $C_{16}H_{20}N_2O_3S_2$: C, 54.52; H, 5.72; N, 7.95%.

Monomethyl epidithiapiperazinedione **30a**. To an ice-cooled stirred solution of 50 mg (0.148 mmol) of the monomethyl thioacetal **28a** in 5 ml of methylene chloride was added 36 mg (85%, 1.2 eq) of *m*-chloroperbenzoic acid in one portion. After stirring for 10 min, the solution was poured into a saturated sodium bicarbonate solution containing sodium thiosulfate and thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered and evaporated.

The resulting monosulfoxide was dissolved in 10 ml of methylene chloride and treated with a solution of 12.5 μl (1 eq) of 70% perchloric acid in 0.5 ml of tetrahydrofuran. The solution was stirred at room temperature for 4 hr and then poured into a saturated sodium bicarbonate solution. The aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and chromatographed on a silica gel column (eluted with 1% methanol in methylene chloride) to give 18.0 mg (55.8%) of **30a** as pale yellow crystals, m.p. 127–128° (methanol). IR (KBr): 1688, 1671. NMR ($CDCl_3$): 1.98 (3H, s), 3.03 (3H, s), 3.13 (3H, s), 5.26 (1H, s). MS: 218 (9, M), 154 (100), 126 (47). Exact Mass: Found: 218.0189. Calc. for $C_7H_{10}N_2O_2S_2$: 218.0184. Analysis (recrystallized from methanol): Found: C, 38.47; H, 4.67; N, 12.85. Calc. for $C_7H_{10}N_2O_2S_2$: C, 38.52; H, 4.62; N, 12.83%.

The mono-substituted and di-substituted epidithiapiperazinediones **30** and **31** were synthesized by using the same procedure as the one given for **30a**.[39] For the m.ps of some of the compounds (see Table 1).

Epidithiapiperazinedions syntheses (Method B)

cis-*Dimethyl dimethylthiopiperazinedione* **40**. A solution of 292 mg (1.25 mmol) of dimethylthiopiperazinedione **38**[24] in 20 ml of dry tetrahydrofuran was cooled in a dry ice–acetone bath. To the stirred solution was added dropwise 1.307 ml (2.2 eq) of 2.10 N *n*-butyllithium in hexane over a period of 1 min. After 1 min, 0.777 ml (10 eq) of methyl iodide was added. The solution was stirred for an additional 5 min and allowed to warm to room temperature. The mixture was poured into a saturated sodium chloride solution and the aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel tlc [eluted with ethyl acetate–hexane (1:1)] to give 275 mg (84.1%) of **40** as a colorless oil. IR (CH_2Cl_2): 1658, 1375. NMR ($CDCl_3$): 1.85 (6H, s), 2.21 (6H, s), 3.12 (6H, s). MS: 262 (1, M), 215 (86), 168 (100), 140 (86). Exact Mass: Found: 215.0853. Calc. for $C_9H_{15}N_2O_2S$ (M–SCH_3): 215.0854.

Dimethoxymethylthiopiperazinedione **44**. To an ice-cold stirred solution of 500 mg (2.43 mmol) of *cis*-dithiopiperazinedione **4a**[22] in 100 ml of dry tetrahydrofuran was added 4.64 ml (2.1 eq) of 1.10 N potassium *t*-butoxide in *t*-butanol over a 1 min period. After 1 min, 2.3 ml of chloromethyl methyl ether was added and stirring was continued for an additional 40 min. The mixture was poured into water and the aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered and evaporated to give white crystals which were collected with chilled ether to yield 574 mg (80.4%) of **44**, m.p. 141–142° (ethyl acetate). IR (KBr): 1678, 1075. NMR ($CDCl_3$): 3.04 (6H, s), 3.44 (6H, s), 4.50 (2H, AB, J = 12 Hz), 4.83 (2H, s), 5.22 (2H, AB, J = 12 Hz). MS: 294 (1, M), 218 (46), 217 (54), 171 (100). Exact Mass: Found: 294.0705. Calc. for $C_{10}H_{18}N_2O_4S_2$: 294.0708. Analysis (recrystallized from methanol): Found: C, 40.76; H, 6.37; N, 9.45. Calc. for $C_{10}H_{18}N_2O_4S_2$: C, 40.80; H, 6.16; N, 9.52%.

Dibenzylthiopiperazinedione **41**. This substance was prepared from **4a** by using the same procedure as the one given for **44**. Reagent: $C_6H_5CH_2Br$. Yield: 63.6%. M.P.: 134–135° (methanol). IR (KBr): 1679. NMR ($CDCl_3$): 2.65 (6H, s), 3.90 (2H, AB, J = 14 Hz), 3.98 (2H, AB, J = 14 Hz), 4.33 (2H, s), 7.15–7.5 (10H, m). MS: 386 (<1, M), 264 (11), 141 (53), 91 (100). Exact Mass: Found: 386.1123. Calc. for $C_{20}H_{22}N_2O_2S_2$: 386.1123. Analysis (recrystallized from methanol): Found: C, 62.02; H, 5.79; N, 7.26. Calc. for $C_{20}H_{22}N_2O_2O_2$: C, 62.15; H, 5.74; N, 7.25%.

Dibenzyl dibenzylthiopiperazinediones **42** *and* **43**. A solution of 33.7 mg (0.087 mmol) of dibenzylthiopiperazinedione **41** in 3.4 ml of dry tetrahydrofuran was cooled in dry ice–acetone bath. To the stirred solution was added dropwise 0.109 ml (2.1 eq) of 1.68 N *n*-butyllithium in hexane over a period of 1 min. After 1 min, 55 μl of benzyl bromide was added and stirring was continued for 5 min. The solution was allowed to warm to room temperature and poured into water. The aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative alumina tlc [developed twice with hexane–methylene chloride (3:2)] to give 17.5 mg (35.4%) of the *cis* product **43**, m.p. 122–123° (methanol) and 14.1 mg (28.5%) of the *trans* product **42**, m.p. 165–166° (ethyl acetate–methanol).

cis-*Dibenzyl dibenzylthiopiperazinedione* **43**. IR (KBr): 1661, 1642, 1602, 1581, 1496. NMR ($CDCl_3$): 3.00 (2H, AB, J = 14.5 Hz), 3.16 (6H, s), 3.47 (2H, AB, J = 14.5 Hz), 3.98 (4H, s), 6.7–7.35 (20H, m). Analysis (recrystallized from methanol): Found: C, 71.96; H, 6.08; N, 4.86. Calc. for $C_{34}H_{34}N_2O_2S_2$: C, 72.05; H, 6.05; N, 4.94%.

trans-*Dibenzyl dibenzylthiopiperazinedione* **42**. IR (KBr): 1655, 1602, 1495. NMR ($CDCl_3$): 2.95 (2H, AB, J = 12 Hz), 3.03 (2H, AB, J = 14 Hz), 3.10 (2H, AB, J = 12 Hz), 3.27 (6H, s), 3.62 (2H, AB, J = 14 Hz), 6.75–7.30 (20H, m). Analysis (recrystallized from ethyl acetate–methanol): Found: C, 71.95; H, 6.14; N, 4.86. Calc. for $C_{34}H_{34}N_2O_2S_2$: C, 72.05; H, 6.05; N, 4.94%.

Dibenzyl dimethoxymethylthiopiperazinedione **45a**. A solution of 300 mg (1.02 mmol) of dimethoxymethylthiopiperazinedione **44** in 21 ml of dry tetrahydrofuran was cooled in a dry ice–acetone bath. A solution of 2.34 mmol (2.3 eq) of lithium diisopropylamide in 1.1 ml of tetrahydrofuran was added dropwise with stirring over a 2 min period. After 1 min, 1.21 ml (10 eq) of benzyl bromide was added and stirring was continued for 1 hr. The solution was then allowed to warm to room temperature and poured into a saturated sodium chloride solution. The aqueous layer was thoroughly extracted with chloroform. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and chromatographed on a silica gel column (eluted with 0.5% methanol in methylene chloride) to give 406 mg (83.9%) of **45a** as white crystals, m.p. 106–107° (methylene chloride–hexane). IR (KBr): 1661, 1080. NMR ($CDCl_3$): 2.97 (2H, AB, J = 14 Hz), 3.06 (6H, s), 3.12 (2H, AB, J = 14 Hz), 3.34 (6H, s), 4.45 (2H, AB, J = 12 Hz), 5.20 (2H, AB, J = 12 Hz), 6.80–7.25 (10H, m). MS: 397 (89, M–SCH_2OCH_3), 320 (68), 91 (100). Exact Mass: Found: 397.1598. Calc. for $C_{22}H_{25}N_2O_3S$ (M–SCH_2OCH_3): 397.1586. Analysis (recrystallized from methylene chloride–hexane): Found: C, 60.51; H, 6.31; N, 5.78. Calc. for $C_{24}H_{30}N_2O_4S_2$: C, 60.73; H, 6.37; N, 5.90%.

The symmetrically di-substituted piperazinediones were synthesized by using the same procedure as the one given for **45a**. Some of them are listed in Table 1.

Monomethyl dimethoxymethylthiopiperazinedione **47a**. A solution of 200 mg (0.680 mmol) of dimethoxymethylthiopiperazinedione **44** in 14 ml of dry tetrahydro-

furan was cooled in a dry ice–acetone bath. A solution of 1.56 mmol (2.3 eq) of lithium diisopropylamide in 1 ml of tetrahydrofuran was added dropwise with stirring over a period of 2 min. After 1 min, 0.6 ml (6.5 mmol) of methyl iodide was added and stirring was continued for 2 hr. The solution was treated with 0.1 ml of acetic acid and then allowed to warm to room temperature. The mixture was poured into a saturated sodium bicarbonate solution and the aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and chromatographed on a silica gel column (eluted with 2% methanol in methylene chloride) to give 200 mg (95.4%) of **47a** as white crystals, m.p. 78–79° (methylene chloride–hexane). IR (KBr): 1660, 1081. NMR ($CDCl_3$): 1.94 (3H, s), 3.05 (3H, s), 3.10 (3H, s), 3.34 (3H, s), 3.45 (3H, s), 4.48 (2H, AB, J = 12 Hz), 4.91 (1H, s), 5.06 (1H, AB, J = 12 Hz), 5.29 (1H, AB, J = 12 Hz). MS: 308 (<1, M), 231 (72), 154 (49), 153 (84), 56 (100). Exact Mass: Found: 231.0803. Calc. for $C_9H_{15}N_2O_3S$ ($M-SCH_2OCH_3$): 231.0803. Analysis (recrystallized from methylene chloride–hexane): Found: C, 42.85; H, 6.66; N, 9.20. Calc. for $C_{11}H_{20}N_2O_4S_2$: C, 42.84; H, 6.54; N, 9.08%.

The mono-substituted piperazinediones **47** were synthesized by using the same procedure as the one given for **47a**. Some of them are listed in Table 1.

Benzyl methyl dimethoxymethylthiopiperazinedione **49a**. A solution of 200 mg (0.649 mmol) of monomethyl dimethoxymethylthiopiperazinedione **47a** in 10 ml of dry tetrahydrofuran was cooled in a dry ice–acetone bath. A solution of 0.779 mmol (1.2 eq) of lithium di-isopropylamide in 0.4 ml of tetrahydrofuran was added dropwise with stirring over a 2 min period. After 1 min, 0.39 ml (5 eq) of benzyl bromide was added and stirring was continued for 2 hr. The solution was then allowed to warm to room temperature and poured into a saturated sodium chloride solution. The aqueous layer was thoroughly extracted with chloroform. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel tlc (eluted with 1.5% methanol in methylene chloride) to give 194 mg (75.0%) of **49a** as white crystals, m.p. 117–118° (methylene chloride–hexane). IR (KBr): 1660, 1648, 1080. NMR ($CDCl_3$): 0.80 (3H, s), 2.79 (3H, s), 3.14 (1H, AB, J = 13.5 Hz), 3.27 (6H, s), 3.36 (3H, s), 3.49 (1H, AB, J = 13.5 Hz), 4.33 (1 H, AB, J = 12 Hz), 4.49 (1H, AB, J = 12 Hz), 5.05 (1H, AB, J = 12 Hz), 5.23 (1H, AB, J = 12 Hz), 6.90–7.30 (5H, m). MS: 321 (34, $M-SCH_2OCH_3$), 244 (29), 91 (85), 56 (100). Exact Mass: Found: 321.1273. Calc. for $C_{16}H_{21}N_2O_3S$ ($M-SCH_2OCH_3$): 321.1273. Analysis (recrystallized from methylene chloride–hexane): Found: C, 54.20; H, 6.56; N, 6.97. Calc. for $C_{18}H_{26}N_2O_4S_2$: C, 54.25; H, 6.58; N, 7.03%.

The unsymmetrically di-substituted piperazinediones were synthesized by using the same procedure as the one given for **49a**. Some of them are listed in Table 1.

Dimethyl epidithiapiperazinedione **46b**. To an ice-cooled solution of 250 mg (0.776 mmol) of dimethyl dimethoxymethylthiopiperazinedione **45b** in 12.5 ml of methylene chloride was added 1.25 ml of boron trichloride with stirring. After 5 min, the solution was evaporated to dryness. The residue was dissolved in 25 ml of 10% methanol in methylene chloride and treated with a solution of 197 mg (1 eq) of iodine in 4 ml of chloroform. The solution was allowed to stand at room temperature for 5 min and then poured into a saturated sodium bicarbonate solution containing sodium thiosulfate. The aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and chromatographed on a silica gel column (eluted with 0.5% methanol in methylene chloride) to give 159 mg (88.2%) of **46b** as pale yellow crystals, m.p. 143–145° (methanol). IR (KBr): 1680. NMR ($CDCl_3$): 2.00 (6H, s), 3.06 (6H, s). MS: 232 (1, M), 168 (77), 56 (100). Exact Mass: Found: 232.0342. Calc. for $C_8H_{12}N_2O_2S_2$: 232.0340. Analysis (recrystallized from methanol): Found: C, 41.30; H, 5.29; N, 12.18. Calc. for $C_8H_{12}N_2O_2S_2$: C, 41.36; H, 5.21; N, 12.06%.

The synthesis of the symmetrically di-substituted, unsymmetrically di-substituted and mono-substituted dithiopiperazinediones **46, 48** and **50** were synthesized by using the same procedure as the one given for **46b**. Some of them are listed in Table 1.

Benzyl methoxymethyl dimethoxymethylthiopiperazinedione **51** (*one-pot procedure*). A solution of 300 mg (1.02 mmol) of dimethoxymethylthiopiperazinedione **44** in 21 ml of dry tetrahydrofuran was cooled in a dry ice–acetone bath. A solution of 2.34 mmol (2.3 eq) of lithium diisopropylamide in 1.1 ml of tetrahydrofuran

Table 1.

	44 →			45, 47, or 49 →		46, 48, or 50	
	compound		alkyl halide	yield	mp	yield	mp
46a.	$R^1=R^2=CH_2C_6H_5$		$C_6H_5CH_2Br$	84%	106-107°	82%	152-153°
46b:	$R^1=R^2=CH_3$		CH_3I	41%	92-93°	88%	143-145°
46c.	$R^1=R^2=CH_2CH_3$		CH_3CH_2I	31%	95-96°	75%	113-114°
46d:	$R^1=R^2=CH_2CO_2Et$		EtO_2CCH_2Br	65%	85-86°	51%	179-180°
48a:	$R^1=CH_3$	1.	CH_3I				
	$R^2=H$	2.	(AcOH)	95%	78-79°	98%	127-128°
48b	$R^1=CH_2C_6H_5$	1.	$C_6H_5CH_2Br$				
	$R^2=H$	2.	(AcOH)	59%	86-87°	89%	175-176°
50a:	$R^1=CH_3$	1.	CH_3I				
	$R^2=CH_2C_6H_5$	2.	$C_6H_5CH_2Br$	75%	117-118°	91%	129-130°
50b:	$R^1=CH_2C_6H_5$	1.	$C_6H_5CH_2Br$				
	$R^2=CH_2OH$	2.	CH_3OCH_2Br	63%	oil	28%[34]	101-102°

was added dropwise with stirring over a 2 min period. After 1 min, 0.61 ml (5 eq) of benzyl bromide was added and stirring was continued for 20 min. The solution was then treated with 0.33 ml (4 eq) of bromomethyl methyl ether and stirring was continued for an additional 10 min. The mixture was allowed to warm to room temperature and poured into a saturated sodium chloride solution. The aqueous layer was thoroughly extracted with chloroform. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel tlc [eluted with ethyl acetate–hexane (2:3)] to give 275 mg (62.9%) of **51** as an oil. IR (CH_2Cl_2): 1660, 1080. NMR ($CDCl_3$): 2.90 (3H, s), 3.04 (3H, s), 3.19 (3H, s), 3.19 (1H, AB, J = 14 Hz), 3.31 (3H, s), 3.39 (3H, s), 3.49 (1H, AB, J = 10 Hz), 3.53 (1H, AB, J = 10 Hz), 3.84 (1H, AB, J = 14 Hz), 4.40 (1H, AB, J = 14 Hz), 4.55 (1H, AB, J = 12 Hz), 5.34 (2H, AB, J = 12 Hz), 6.9–7.35 (5H, m). MS: 351 (100, M–SCH_2OCH_3), 274 (28), 273 (43), 91 (56). Exact Mass: Found: 351.1382. Calc. for $C_{17}H_{23}N_2O_4S$ (M–SCH_2OCH_3): 351.1378.

dl-*Hyalodendrin* **52**. A solution of 430 mg (1.00 mmol) of benzyl methoxymethyl dimethoxymethylthiopiperazinedione **51** in 15 ml of methylene chloride was cooled in a dry ice–acetone bath. To the stirred solution was added 0.5 ml of boron trichloride. After stirring at −78° for 20 min, the solution was allowed to warm to room temperature and evaporated to dryness. The residue was dissolved in 43 ml of 10% methanol in methylene chloride. The solution was treated with a solution of 255 mg (1 eq) of iodine in 5 ml of chloroform and allowed to stand at room temperature for 5 min. The mixture was poured into a saturated sodium bicarbonate solution containing sodium thiosulfate and thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered and evaporated.

The residue was dissolved in 15 ml of methylene chloride and cooled in an ice bath. The solution was treated with 0.1 ml of boron trichloride and allowed to stand at 0° for 15 min. The solution was evaporated and separated on preparative silica gel tlc (developed twice with 2% methanol in methylene chloride) to give 91.0 mg (27.9%) of **52** as pale yellow crystals, m.p. 101–102° (ethanol). IR (KBr): 3350, 1680, 1648. NMR ($CDCl_3$): 2.98 (3H, s), 3.20 (3H, s), 3.48 (1H, t, J = 7 Hz), 3.63 (1H, AB, J = 14 Hz), 4.05 (1H, AB, J = 14 Hz), 4.32 (2H, d, J = 7 Hz), 7.27 (5H, s). MS: 324 (2, M), 260 (100), 91 (29). Exact Mass: Found: 324.0593. Calc. for $C_{14}H_{16}N_2O_3S_2$: 324.0602. Analysis (recrystallized from ethanol): Found: C, 51.78; H, 4.81; N, 8.74. Calc. for $C_{14}H_{16}N_2O_3S_2$: C, 51.83; H, 4.97; N, 8.64%.

Synthesis of dehydrogliotoxin

Methyl ester piperazinedione **56**. A mixture of 6.275 g (22.6 mmol) of 2-iodo-3-methoxybenzoic acid (**54**),[46] 5.78 g (45.1 mmol) of glycine–sarcosine anhydride (**55**),[47] 4.30 g (22.6 mmol) of cuprous iodide and 6.23 g (45.1 mmol) of anhydrous potassium carbonate in 63 ml of nitrobenzene was heated at 170° for 40 min with vigorous stirring. After cooling, the solvent was removed by decantation. The residue was dissolved in methanol and the pH of the solution was adjusted to 3 with concentrated hydrochloric acid. The solution was filtered and evaporated to dryness. The residue was then dissolved in 300 ml of methanol. A solution of diazomethane in ether was added at room temperature until the esterification had been complete. The mixture was concentrated and chromatographed on a silica gel column (eluted with 2% methanol in methylene chloride) to give 2.34 g (35.5%, based on **54**) of **56** as white crystals, m.p. 140–141° (ethyl acetate). IR (KBr): 1718, 1679, 1662, 1581. NMR ($CDCl_3$): 3.04 (3H, s), 3.85 (6H, s), 4.06 (2H, s), 4.22 (2H, s), 7.00–7.65 (3H, m). MS: 292 (100, M), 261 (16). Exact Mass: Found: 292.1070. Calc. for $C_{14}H_{16}N_2O_5$: 292.1059.

Dithioacetate **57**

A mixture of 2.278 g (7.80 mmol) of the piperazinedione **56**, 3.88 g (2.8 eq) of N-bromosuccinimide and 116 mg of benzoyl peroxide in 230 ml of carbon tetrachloride was heated under reflux for 90 min. After cooling, succinimide was filtered and washed with carbon tetrachloride. The filtrate and the washings were combined and the solvent was removed.

The residue was dissolved in 140 ml of methylene chloride and treated with 6.8 g of potassium thioacetate. The mixture was stirred overnight at room temperature. The salts were filtered and washed with methylene chloride. The filtrate and the washings were combined, concentrated and chromatographed on a silica gel column eluted with 1% methanol in methylene chloride) to give 2.23 g (65.0%) of **57** as a 1:1 *cis* and *trans* mixture, m.p. 168–175° (benzene). IR (KBr): 1698, 1580. MS: 440 (3, M), 397 (24), 365 (100), 323 (77), 295 (79), 291 (54). Exact Mass: Found: 440.0705. Calc. for $C_{18}H_{20}N_2O_7S_2$: 440.0712.

Thioacetal ester **58**. To a solution of 2.20 g (5 mmol) of the dithioacetate **57** in 200 ml of methanol was added 20 ml of HCl in methanol (saturated at 0°). The mixture was heated at 50° for 40 min and then the solvent was removed. The residue was dissolved in 110 ml of methylene chloride and treated with 3.3 ml of *p*-anisaldehyde and 0.22 ml of boron trifluoride etherate. The mixture was allowed to stand overnight at room temperature and then poured into a saturated sodium bicarbonate solution. The aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and chromatographed on a silica gel column (eluted with 0.5% methanol in methylene chloride) to give 1.71 g (72.0%) of **58** as an about 1:1 diastereomeric mixture, m.p. 222–225° (benzene). IR (KBr): 1719, 1685, 1602, 1580, 1508. MS: 474 (<1, M), 410 (14), 290 (100), 262 (17). Exact Mass: Found: 474.0927. Calc. for $C_{22}H_{22}N_2O_6S_2$: 474.0919.

Thioacetal alcohol **59**. To a solution of 1.68 g (3.54 mmol) of the ester **58** in 84 ml of dioxane was added 35.4 ml (10 eq) of 1 N sodium hydroxide with vigorous stirring at room temperature. The mixture was stirred for 3 hr and then 3.3 ml of concentrated hydrochloric acid was added. The mixture was evaporated to a small volume and thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered and evaporated.

The residue was dissolved in 80 ml of methylene chloride. To the stirred solution was added dropwise 1.04 ml of triethylamine at room temperature, followed by 1.6 ml of ethyl chloroformate. After stirring at room temperature for 10 min, the solution was evaporated to dryness.

The residue was dissolved in 130 ml of methylene chloride and cooled in an ice bath. A chilled solution of 1.6 g of sodium borohydride in 16 ml of methanol was added in one portion with stirring. After 5 min, the mixture was poured into a saturated sodium chloride solution containing dilute hydrochloric acid and thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and chromatographed on a silica gel column (eluted with 1.5% methanol in methylene chloride) to give 1.09 g (69.2%) of **59** as an about 1:1 diastereometeric mixture m.p. 146–150° (benzene). IR (KBr): 3370, 1685, 1603, 1582, 1507. MS: 446 (1, M), 382 (7), 262 (100). Exact Mass: Found: 446.0981. Calc. for $C_{21}H_{22}N_2O_5S_2$: 446.0970.

Thioacetal chlorides **32** *and* **35**. To a stirred solution of 16.0 g (2.38 mmol) of the alcohol **59** and 1 ml of triethylamine in 50 ml of methylene chloride was added dropwise 0.6 ml of methanesulfonyl chloride at room temperature. The solution was stirred at room temperature for 10 min and evaporated to dryness.

The residue was dissolved in 30 ml of dimethylformamide and treated with 2.1 g of lithium chloride. The mixture was stirred at room temperature for 15 min and then poured into ice water. The aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and chromatographed on a silica gel column (eluted with 0.5% methanol in methylene chloride) to give a 960 mg (86.9%) of amorphous solid which was fractionally crystallized from ethyl acetate to yield 338 mg (30.6%) of **32**, m.p. 212–213° and 242 mg (21.9%) of **35**, m.p. 151–153°.

Thioacetal chloride **32**. IR (KBr): 1683, 1603, 1580, 1507. NMR ($CDCl_3$): 3.15 (3H, s), 3.81 (3H, s), 3.94 (3H, s), 4.39 (2H, s), 5.10 (1H, s), 5.15 (1H, s), 6.32 (1H, s), 6.65–7.50 (7H, m). MS: 464 (1, M), 282 (33), 280 (100). Exact Mass: Found: 464.0629. Calc. for $C_{21}H_{21}N_2O_4S_2{}^{35}Cl$: 464.0631.

Thioacetal chloride **35**. IR (KBr): 1686, 1605, 1583, 1505. NMR ($CDCl_3$): 3.29 (3H, s), 3.81 (3H, s), 3.95 (3H, s), 4.43 (2H, s), 4.99 (1H, s), 5.21 (1H, s), 5.37 (1H, s), 6.70–7.50 (7H, m). MS: 464 (1, M), 282 (31), 280 (100). Exact Mass: Found: 464.0620. Calc. for $C_{21}H_{21}N_2O_4S_2{}^{35}Cl$: 464.0631.

Cyclized thioacetal **33**. A solution of 30.0 mg (0.0646 mmol) of the chloride **32** in 6 ml of dry tetrahydrofuran was cooled in a dry ice–acetone bath. To the stirred solution was added dropwise 66 μl (1.2 eq) of 1.17 N phenyllithium in benzene–ether (7:3) over a 2 min period. After the solution had been stirred for 10 min, 50 μl of acetic acid was added. The solution was allowed to warm to room temperature and poured into a saturated sodium bicarbonate solution. The aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel tlc [eluted with ethyl acetate–hexane (1:1)] to give 22.0 mg (79.5%) of **33** as white crystals, m.p. 223–224° (benzene). IR (KBr): 1689, 1608, 1510. NMR ($CDCl_3$): 3.16 (3H, s), 3.16 (1H, AB, J = 18 Hz), 3.77 (3H, s), 3.96 (1H, AB, J = 18 Hz), 4.01 (3H, s), 5.04 (1H, s), 5.47 (1H, s), 6.65–7.40 (7H, m). MS: 428 (1, M), 224 (100). Exact Mass: Found: 428.0878. Calc. for $C_{21}H_{20}N_2O_4S_2$: 428.0864.

Protected dehydrogliotoxin thioacetal **34**. A solution of 32.0 mg (0.0747 mmol) of the thioacetal **33** in 6.4 ml of dry tetrahydrofuran was cooled in a dry ice-acetone bath. To the stirred solution was added dropwise 77 μl (1.2 eq) of 1.17 N phenyllithium in benzene–ether (7:3) over a 1 min period. After 30 sec, 32 μl of benzyl chloromethyl ether was added. The solution was stirred at −78° for 10 min and then poured into a saturated sodium chloride solution and thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel tlc [eluted with ethyl acetate–hexane (1:1)] to afford 29.0 mg (71.0%) of **34** as white crystals, m.p. 144–145° (ethyl acetate). IR (KBr): 1700, 1683, 1604, 1508. NMR ($CDCl_3$): 3.15 (1H, AB, J = 18 Hz), 3.22 (3H, s), 3.76 (3H, s), 3.85 (1H, AB, J = 11 Hz), 3.98 (1H, AB, J = 18 Hz), 4.02 (3H, s), 4.40 (1H, AB, J = 11 Hz), 4.62 (1H, AB, J = 11 Hz), 4.71 (1H, AB, J = 11 Hz), 5.40 (1H, s), 6.60–7.40 (12H, m). MS: 548 (<1, M), 364 (86), 257 (48), 91 (100). Exact Mass: Found: 548.1452. Calc. for $C_{29}H_{28}N_2O_5S_2$: 548.1440.

Protected dehydrogliotoxin thioacetal **34** (*one-pot procedure*). A solution of 50.0 mg (0.108 mmol) of the chloride **32** and 0.15 ml of benzyl chloromethyl ether in 10 ml of dry tetrahydrofuran was cooled in a dry ice–acetone bath. To the stirred solution was added dropwise 0.228 ml (2.5 eq) of 1.17 N phenyllithium in benzene–ether (7:3) over a 15 min period. The progress of the reaction was carefully monitored by tlc. After stirring at −78° for an additional 5 min, the solution was allowed to warm to room temperature. The solution was poured into a saturated sodium chloride solution and thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel tlc [eluted with ethyl acetate–hexane (1:1)] to give 41.0 mg (69.5%) of **34** as white crystals. This was identical with the compound prepared by a stepwise procedure.

Benzyloxymethyl chloride **36**. A solution of 30.0 mg (0.646 mmol) of the chloride **35** in 6 ml of dry tetrahydrofuran was cooled in a dry ice–acetone bath. To the stirred solution was added dropwise 66 μl (1.2 eq) of 1.17 N phenyllithium in benzene–ether (7:3) over a 1 min period. After 30 sec, 30 μl of benzyl chloromethyl ether was added. The solution was stirred at −78° for 10 min and then poured into a saturated sodium chloride solution and thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel tlc [eluted with ethyl acetate–hexane (1:1)] to afford 27.4 mg (72.5%) of **36** as white crystals, m.p. 153–154° (ethyl acetate). IR (KBr): 1687, 1603, 1582, 1506. NMR ($CDCl_3$): 3.34 (3H, s), 3.80 (3H, s), 3.93 (1H, AB, J = 11 Hz), 3.95 (3H, s), 4.21 (1H, AB, J = 11 Hz), 4.30 (1H, AB, J = 11 Hz), 4.39 (1H, AB, J = 11 Hz), 4.55 (1H, AB, J = 11 Hz), 4.65 (1H, AB, J = 10 Hz), 5.10 (1H, s), 5.42 (1H, s), 6.70–7.45 (12H, m). MS: 584 (1, M), 402 (18), 400 (53), 294 (16), 91 (100). Exact Mass: Found: 584.1219. Calc. for $C_{29}H_{29}N_2O_5S_2{}^{35}Cl$: 584.1206.

Protected dehydrogliotoxin thioacetal **37**. A solution of 25.0 mg (0.0427 mmol) of the chloride **36** in 5 ml of dry tetrahydrofuran was cooled in a dry ice–acetone bath. To the stirred solution was added dropwise 44 μl (1.2 eq) of 1.17 N phenyllithium in benzene–ether (7:3) over a 1 min period. After stirring for 10 min at −78°, the solution was allowed to warm to room temperature and poured into a saturated sodium chloride solution. The aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel tlc [eluted with ethyl acetate–hexane (1:1)] to give 22.0 mg (93.8%) of **37** as white crystals, m.p. 149–151° (ethyl acetate). IR (KBr): 1701, 1682, 1603, 1510. NMR ($CDCl_3$): 3.17 (1H, AB, J = 18 Hz), 3.35 (3H, s), 3.75 (3H, s), 3.88 (1H, AB, J = 11 Hz), 3.95 (3H, s), 4.08 (1H, AB, J = 18 Hz), 4.25 (1H, AB, J = 11 Hz), 4.58 (1H, AB, J = 12 Hz), 4.68 (1H, AB, J = 12 Hz), 5.25 (1H, s), 6.60–7.35 (12H, m). MS: 548 (3, M), 364 (100), 257 (58), 91 (90). Exact Mass: Found: 548.1452. Calc. for $C_{29}H_{28}N_2O_5S_2$: 548.1440.

Protected dehydrogliotoxin thioacetal **37** (*one-pot procedure*). A solution of 50.0 mg (0.108 mmol) of the chloride **35** and 0.15 ml of benzyl chloromethyl ether in 10 ml of dry tetrahydrofuran was cooled in a dry ice–acetone bath. To the stirred solution was added dropwise 0.230 ml (2.5 eq) of 1.17 N phenyllithium in benzene–ether (7:3) over a 15 min period. The progress of the reaction was carefully monitored by tlc. After stirring at −78° for an additional 5 min, the solution was allowed to warm to room temperature. The solution was poured into a saturated sodium chloride solution and thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel tlc [eluted with ethyl acetate–hexane (1:1)] to give 36.2 mg (61.3%) of **37** as white crystals. This substance was identical with the compound prepared by a stepwise procedure.

Dehydrogliotoxin thioacetal **60**. To a solution of 40.0 mg (0.0730 mmol) of the thioacetal **34** in 8 ml of methylene chloride was added 0.13 ml of boron trichloride at room temperature. The solution was allowed to stand at room temperature for 20 min and then poured into ice water. The aqueous layer was thoroughly extracted with methylene chloride. The extracts were

dried over anhydrous sodium sulfate, filtered and evaporated to give white crystals which were collected with ethyl acetate–ether to yield 21.7 mg (66.9%) of **60**, m.p. 275–276° (capillary, methylene chloride). IR (KBr): 3420, 1678, 1650, 1602, 1505. NMR ($CDCl_3$): 2.48 (1H, d of d, J = 6, 10 Hz), 3.21 (1H, AB, J = 18 Hz), 3.24 (3H, s), 3.76 (3H, s), 3.91 (1H, d of d, J = 10, 13 Hz), 3.93 (1H, AB, J = 18 Hz), 4.63 (1H, d of d, J = 6, 13 Hz), 5.31 (1H, s), 6.60–7.35 (7H, m), 10.48 (1H, s). MS: 444 (1, M), 260 (35), 243 (18), 185 (100). Exact Mass: Found: 444.0816. Calc. for $C_{21}H_{20}N_2O_5S_2$: 444.0814.

Dehydrogliotoxin thioacetal **61**. This substance [m.p. 249–250° (capillary, methylene chloride–ether)] was synthesized from **37** in 66.2% yield by using the same procedure as the one given for **60**. IR (KBr): 3420, 1679, 1643, 1603. NMR ($CDCl_3$): 2.64 (1H, d of d, J = 6, 10 Hz), 3.25 (1H, AB, J = 18 Hz), 3.39 (3H, s), 3.76 (3H, s), 4.11 (1H, AB, J = 18 Hz), 3.95–4.45 (2H, m), 5.20 (1H, s), 6.60–7.35 (7H, m), 10.67 (1H, s). MS: 444 (7), 260 (44), 185 (100). Exact Mass: Found: 444.0824. Calc. for $C_{21}H_{20}N_2O_5S_2$: 444.0814.

dl-*Dehydrogliotoxin* **53**. To a stirred solution of 10.0 mg (0.0225 mmol) of the dehydrogliotoxin thioacetal **60** in 5 ml of methylene chloride was added 5.5 mg (85%, 1.2 eq) of *m*-chloroperbenzoic acid at room temp. After 5 min of stirring at room temperature, 10 μl of dimethyl sulfide was added. The solution was then treated with 20 μl of a solution of 70% perchloric acid in methanol (1:5). The solution was allowed to stand at room temperature for 7 hr and then poured into a saturated sodium bicarbonate solution. The aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and chromatographed on a silica gel column (eluted with 0.5% methanol in methylene chloride) to afford 5.3 mg (72%) of **53** as pale yellow crystals, m.p. 177–178° (methanol). IR (KBr): 3460, 1678, 1663, 1603, 1480. NMR ($CDCl_3$): 3.25 (3H, s), 3.28 (1H, AB, J = 18 Hz), 4.28 (1H, AB, J = 18 Hz), 4.10–4.60 (2H, m), 6.65–7.30 (3H, m), 10.39 (1H, s). MS: 324 (3, M), 260 (100), 243 (33), 242 (30). Exact Mass: Found: 324.0238. Calc. for $C_{13}H_{12}N_2O_4S_2$: 324.0238.

dl-Dehydrogliotoxin (**53**), was synthesized also from **61** in 72% yield by using the same procedure as the one given for **60**.

Synthesis of Gliotoxin

Methoxymethyl piperazinedione **65**. To a stirred solution of 9.80 g (76.5 mmol) of glycine–sarcosine anhydride (**55**)[47] in 135 ml of *t*-butanol was added 110 ml (1.3 eq) of 0.904 N potassium *t*-butoxide in *t*-butanol over a period of 2 min at room temperature. After 1 min, 7.6 ml (1.3 eq) of chloromethyl methyl ether was added and stirring was continued for 10 min. The solution was treated with 2 ml of acetic acid and the solvent was removed. The residue was taken up in a dilute sodium chloride solution and thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered and evaporated to give an oil which was short-path distilled under reduced pressure to yield 9.83 g (74.6%) of **65** b.p. 142–144° (0.3 torr). IR (CH_2Cl_2): 1676. NMR ($CDCl_3$): 2.98 (3H, s), 3.33 (3H, s), 4.03 (4H, s), 4.81 (2H, s). MS: 172 (25, M), 157 (100). Exact Mass: Found: 172.0846. Calc. for $C_7H_{12}N_2O_3$: 172.0848.

Unprotected thioacetal **68**

A mixture of 9.83 g (57 mmol) of the piperazinedione **65**, 25.4 g (2.5 eq) of N-bromosuccinimide and 760 mg of benzoyl peroxide in 1180 ml of carbon tetrachloride was heated under reflux for 1 hr. The succinimide was removed by filtration and washed with carbon tetrachloride. The filtrate and the washings were combined and evaporated to dryness.

The residue was dissolved in 500 ml of methylene chloride and treated with 25 g of potassium thioacetate. The mixture was stirred overnight at room temperature. The salts were removed by filtration and washed with methylene chloride. The filtrate and the washings were combined and evaporated.

The residue was dissolved in 900 ml of methanol and treated with 100 ml of a saturated hydrogen chloride solution in methanol (saturated at 0°). The solution was heated at 50° for 40 min with stirring and the solvent was removed.

The residue was taken up in 300 ml of methylene chloride and treated with 15 ml of *p*-anisaldehyde and 1.25 ml of boron trifluoride etherate. The solution was allowed to stand overnight at room temperature and then poured into a saturated sodium bicarbonate solution. The aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered and evaporated.

The residue was dissolved in 1000 ml of concentrated hydrochloric acid–ethanol (1:1). The solution was heated under reflux for 45 min. Evaporation of the solvent gave off-white crystals which were collected with methanol–ether to yield 5.26 g (29.6% from **65**) of **68** as a 1:1 diastereomeric mixture.

Separation of the diastereomers **68a** *and* **68b**. A mixture of 500 mg (1.61 mmol) of the diastereomers **68**, 0.25 ml of benzoyl chloride and 1 ml of triethylamine in 50 ml of methylene chloride was stirred at room temperature for 1 hr. The solution was poured into a saturated sodium chloride solution containing dilute hydrochloric acid. The aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and chromatographed on a silica gel column to give 264 mg (39.5%) of the N-benzoyl thioacetal **69**, m.p. 197–198° (methylene chloride–ether) and 178 mg (35.6%) of the unreacted diastereomer **68b**, m.p. 249–251° (ethanol).

Ammonia was passed through a solution of 264 mg of the N-benzoyl thioacetal **69** in 20 ml of methylene chloride for 5 min at room temp. Removal of the solvent afforded off-white crystals which were collected with ethyl acetate yielding 192 mg (38.4%) of **68a**, m.p. 250–252° (ethanol).

N-Benzoyl thioacetal **69**. IR (KBr): 1721, 1685, 1602, 1508. NMR ($CDCl_3$): 3.13 (3H, s), 3.80 (3H, s), 5.13 (1H, s), 5.53 (1H, s), 5.81 (1H, s), 6.70–7.75 (9H, m). MS: 414 (<1, M), 350 (6), 105 (100). Exact Mass: Found: 350.1270. Calc. for $C_{20}H_{18}N_2O_4$ (M–S_2): 350.1267. Analysis (recrystallized from benzene): Found: C, 57.96; H, 4.23; N, 6.68. Calc. for $C_{20}H_{18}N_2O_4S_2$: C, 57.96; H, 4.38; N, 6.76%.

Unprotected thioacetal **68a**. IR (KBr): 3190, 1673, 1605, 1510. NMR ($CDCl_3$): 3.07 (3H, s), 3.79 (3H, s), 4.96 (1H, d, J = 2 Hz), 5.01 (1H, d, J = 6 Hz), 5.53 (1H, s), 6.46 (1H, m), 6.84 (2H, d, J = 9 Hz), 7.34 (2H, d, J = 9 Hz). MS: 310 (3, M), 185 (100), 126 (31). Exact Mass: Found: 310.0436. Calc. for $C_{13}H_{14}N_2O_3S_2$: 310.0446. Analysis (recrystallized from ethanol): Found: C, 50.20; H, 4.62; N, 8.92. Calc. for $C_{13}H_{14}N_2O_3S_2$: C, 50.31; H, 4.55; N, 9.03%.

Unprotected thioacetal **68b**. IR (KBr): 3210, 1669, 1605, 1510. NMR ($CDCl_3$): 3.20 (3H, s), 3.79 (3H, s), 4.78 (1H, d, J = 2 Hz), 5.13 (1H, s), 5.18 (1H, d, J = 6 Hz), 6.34 (1H, m), 6.84 (2H, d, J = 9 Hz), 7.33 (2H, d, J = 9 Hz). MS: 310 (2, M), 185 (100), 126 (27). Exact Mass: Found: 310.0442. Calc. for $C_{13}H_{14}N_2O_3S_2$: 310.0446. Analysis (recrystallized from ethanol): Found: C, 50.28; H, 4.54; N, 8.83. Calc. for $C_{13}H_{14}N_2O_3S_2$: C, 50.31; H, 4.55; N, 9.03%.

Michael adducts **73** *and* **74**. To a solution of 100 mg (0.322 mmol) of the thioacetal **68b** and 200 mg (1.03 mmol) of 4-carbo-*t*-butoxyoxepin **62**[48] in 4 ml of dimethyl sulfoxide was added 60 μl of a 40% methanolic solution of benzyltrimethylammonium methoxide (Triton

B) with stirring at room temperature. After 30 min, the solution was poured into a mixture of ice and a saturated sodium chloride solution. The aqueous layer was thoroughly extracted with ethyl acetate. The extracts were washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, evaporated and separated on preparative silica gel tlc [eluted with ethyl acetate–hexane (2:1)] to give 52.0 mg (32.0%) of **73**, m.p. 225–227° (dec., ethyl acetate) and 108 mg (66.4%) of **74**, m.p. 205–207° (dec., ethyl acetate).

Michael adduct **73**. IR (KBR): 3350, 1699, 1680, 1668, 1603, 1507. NMR ($CDCl_3$): 1.55 (9H, s), 3.15 (3H, s), 3.77 (3H, s), 4.15 (1H, br. s), 4.79 (1H, s), 4.92 (1H, s), 5.01 (1H, s), 5.56 (1H, br. s), 6.40 (2H, m), 6.77 (2H, d, J = 9 Hz), 7.25 (1H), 7.27 (2H, d, J = 9 Hz). Analysis (recrystallized from methanol): Found: C, 57.12; H, 5.57; N, 5.37. Calc. for $C_{24}H_{28}N_2O_6S_2$: C, 57.13; H, 5.59; N, 5.55%.

Michael adduct **74**. IR (KBr): 3370, 1680, 1602, 1508. NMR ($CDCl_3$): 1.45 (9H, s), 2.25 (1H, d, J = 6 Hz), 3.15 (3H, s), 3.78 (3H, s), 4.60 (1H, m), 4.68 (1H, s), 4.91 (1H, s), 5.02 (1H, s), 5.54 (1H, br. s), 6.10–6.55 (2H, m), 6.80 (2H, d, J = 9 Hz), 7.27 (2H, d, J = 9 Hz), 7.40 (1H). Analysis (recrystallized from methanol): Found: C, 56.11; H, 5.69; N, 5.19. Calc. for $C_{24}H_{28}N_2O_6S_2 \cdot 1/2\ H_2O$: C, 56.12; H, 5.69; N, 5.45%.

A 1:3 ratio of **73** and **74** was realized in small scale experiments (1 ~ 5 mg scale) in DMSO.

When the reaction was run in methylene chloride using the same ratio of the reactants and the base, a 3:1 mixture of **73** and **74** was obtained in comparable yield.

Thioacetal acetate **75**. A mixture of 108 mg (0.214 mmol) of the alcohol **74**, 1 ml of acetic anhydride and 1 ml of pyridine was allowed to stand at room temperature for 1 hr. The solution was evaporated under reduced pressure to give white crystals which were collected with hexane–ether to yield 114 mg (97.4%) of **75**, m.p. 211–212° (ethyl acetate). IR (KBr): 1737, 1709, 1685, 1603, 1509. NMR ($CDCl_3$): 1.46 (9H, s), 2.05 (3H, s), 3.15 (3H, s), 3.79 (3H, s), 4.68 (1H, s), 4.90 (1H, s), 5.04 (1H, s), 5.53 (1H, d, J = 6 Hz), 5.56 (1H, br. s), 6.17–6.62 (2H, m), 6.84 (2H, d, J = 9 Hz), 7.31 (2H, d, J = 9 Hz), 7.40 (1H). MS: 546 (<1, M), 490 (3), 362 (2), 306 (11), 126 (100). Exact Mass: Found: 546.1499. Calc. for $C_{26}H_{30}N_2O_7S_2$: 546.1494. Analysis (recrystallized from methanol–ethyl acetate): Found: C, 56.78; H, 5.80; N, 4.92. Calc. for $C_{26}H_{30}N_2O_7S_2$: C, 57.13; H, 5.53; N, 5.12%.

Thioacetal alcohol **78**. A solution of 100 mg (0.183 mmol) of the ester **75** in 1 ml of trifluoroacetic acid was allowed to stand at room temperature for 8 min. Trifluoroacetic acid was removed under reduced pressure. To a stirred mixture of the resulting acid and 0.1 ml of ethyl chloroformate in 10 ml of methylene chloride was added 45 μl of triethylamine. After stirring at room temperature for 10 min, the solution was evaporated to dryness. The residue was dissolved in 20 ml of methylene chloride and cooled in an ice bath. An ice-cooled solution of 100 mg of sodium borohydride in 1 ml of methanol was added in one portion with stirring. After 10 min, the mixture was poured into a saturated sodium chloride solution and thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel tlc [eluted with ethyl acetate–hexane (3:1)] to give 69.0 mg (79.1%) of **78**, m.p. 174–175° (ethyl acetate). IR (KBr): 3410, 1729, 1682, 1666, 1603, 1510. NMR ($CDCl_3$): 2.06 (3H, s), 3.18 (3H, s), 3.80 (3H, s), 4.15 (2H, s), 4.86 (1H, s), 4.90 (1H, s), 5.04 (1H, s), 5.19 (1H, br. s), 5.57 (1H, m), 6.18 (2H, m), 6.41 (1H, br. s), 6.85 (2H, d, J = 9 Hz), 7.31 (2H, d, J = 9 Hz). MS: 476 (<1, M), 292 (1), 232 (100). Exact Mass: Found: 476.1068. Calc. for $C_{22}H_{24}N_2O_6S_2$: 476.1076. Analysis (recrystallized from methanol): Found: C, 55.22; H, 5.21; N, 5.67. Calc. for $C_{22}H_{24}N_2O_6S_2$: C, 55.45; H, 5.08; N, 5.88%.

Thioacetal chloride **79**. To a solution of 130 mg (0.273 mmol) of the alcohol **78** and 0.130 ml of triethylamine in 13 ml of methylene chloride was added 65 μl of methanesulfonyl chloride with stirring at room temperature. After 10 min, the solvent was removed under reduced pressure. A solution of the resulting mesylate and 650 mg of lithium chloride in 13 ml of dimethylformamide was stirred at room temperature for 15 min. The solution was then poured into ice–water. The aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel tlc [eluted with ethyl acetate–hexane (3:2)] to afford 130 mg (96.2%) of **79** as white crystals, m.p. 159–160° (ethyl acetate). IR (KBr): 1727, 1689, 1603, 1515. NMR ($CDCl_3$): 2.05 (3H, s), 3.16 (3H, s), 3.79 (3H, s), 4.09 (2H, s), 4.80 (1H, s), 4.90 (1H, s), 5.03 (1H, s), 5.26 (1H, br. s), 5.54 (1H, m), 6.20 (2H, m), 6.51 (1H, m), 6.84 (2H, d, J = 9 Hz), 7.30 (2H, d, J = 9 Hz). MS: 494 (1, M), 432 (5), 430 (14), 312 (3), 310 (7), 252 (16), 250 (46), 126 (100). Exact Mass: Found: 494.0746. Calc. for $C_{22}H_{23}N_2O_5S_2{}^{35}Cl$: 494.0737. Analysis (recrystallized from methanol): Found: C, 53.30; H, 4.80; N, 5.48. Calc. for $C_{22}H_{23}N_2O_5S_2Cl$: C, 3.38; H, 4.68; N, 5.66%.

Thioacetal alcohol **80**. To a solution of 250 mg (0.505 mmol) of the acetate **79** in 12.5 ml of 10% methanol in methylene chloride was added 79 μl (0.5 eq) of 3.20 N sodium methoxide in methanol with stirring at room temperature. After 5 min, the solution was poured into a saturated sodium chloride solution containing dilute hydrochloric acid. The aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered and evaporated to give white crystals which were collected with ether–hexane to yield 215 mg (94.0%) of **80**, m.p. 145–146° (ethyl acetate). IR (KBr): 3410, 1681, 1605, 1509. NMR ($CDCl_3$): 3.17 (3H, s), 3.79 (3H, s), 4.08 (2H, s), 4.59 (1H, m), 4.83 (1H, s), 4.93 (1H, s), 5.04 (1H, s), 5.28 (1H, m), 6.16 (2H, m), 6.51 (1H, m), 6.83 (2H, d, J = 9 Hz), 7.29 (2H, d, J = 9 Hz). MS: 434 (2, M–H_2O), 252 (35), 250 (100). Exact Mass: Found: 434.0532. Calc. for $C_{20}H_{19}N_2O_3S_2{}^{35}Cl$ (M–H_2O): 434.0526. Analysis (recrystallized from ethyl acetate): Found: C, 52.64; H, 4.49; N, 6.01. Calc. for $C_{20}H_{21}N_2O_4S_2Cl$: C, 53.03; H, 4.67; N, 6.18%.

Benzylgliotoxin thioacetal **83**. A solution of 179 mg (0.395 mmol) of the chloride **80** and 0.54 ml of benzyl chloromethyl ether in 36 ml of dry tetrahydrofuran was cooled in a dry ice–acetone bath. To the stirred solution was added dropwise 1.08 ml (3.2 eq) of 1.17 N phenyllithium in benzene–ether (7:3) over a 15 min period. The progress of the reaction was carefully monitored by tlc. After stirring at −78° for an additional 5 min, 0.18 ml of acetic acid was added and the solution was allowed to warm to room temperature. The solution was poured into a saturated sodium bicarbonate solution and thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel tlc [eluted with ethyl acetate–hexane (1:1)] to give 111 mg (52.3%) of **83** as white crystals, m.p. 173–175° (methanol). IR (KBr): 3320, 1683, 1658, 1602, 1505. NMR ($CDCl_3$): 2.92 (1H, AB, J = 18 Hz), 3.24 (3H, S), 3.37 (1H, AB, J = 18 Hz), 3.77 (3H, s), 3.80 (1H, AB, J = 11 Hz), 4.17 (1H, AB, J = 11 Hz), 4.55 (1H, AB, J = 12 Hz), 4.68 (1H, AB, J = 12 Hz), 4.95 (1H, br. s), 5.02 (1H, br. s), 5.08 (1H, S), 5.80 (3H, m), 6.16 (1H, s), 6.80 (2H, d, J = 9 Hz), 7.24 (2H, d, J = 9 Hz), 7.30 (5H, s). MS: 536 (7, M), 352 (26), 334 (36), 91 (100). Exact Mass: Found: 536.1428. Calc. for $C_{28}H_{28}N_2O_5S_2$: 536.1440. Analysis (recrystallized from methanol): Found: C, 61.95; H, 5.28; N, 5.00. Calc. for $C_{28}H_{28}N_2O_5S_2 \cdot 1/2H_2O$: C, 61.93; H, 5.47; N, 5.07%.

Gliotoxin thioacetal **27b**. To an ice-cooled solution of 100 mg (0.186 mmol) of the benzylgliotoxin thioacetal **83**

in 20 ml of methylene chloride was added 0.2 ml of boron trichloride. The solution was allowed to stand at 0° for 10 min and then poured into ice water. The aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel tlc (developed twice with 2% methanol in methylene chloride) to give 49.8 mg (59.8%) of **27b** as white crystals, m.p. 155–157° (ethyl acetate–methanol). IR (KBr): 3400, 1662, 1651, 1603, 1515. NMR ($CDCl_3$): 2.85 (1H, m), 2.91 (1H, AB, J = 18 Hz), 3.30 (3H, s), 3.35 (1H, AB, J = 18 Hz), 3.76 (3H, s), 3.75–4.40 (2H, m), 4.90 (1H, br. s), 4.97 (1H, br. s), 5.09 (1H, s), 5.65–5.95 (4H, m), 6.79 (2H, d, J = 9 Hz), 7.24 (2H, d, J = 9 Hz). MS: 446 (21, M), 294 (24), 262 (100), 245 (11), 244 (29), 185 (78). Exact Mass: Found: 446.0973. Calc. for $C_{21}H_{22}N_2O_5S_2$: 446.0970. Analysis (recrystallized from ethyl acetate–methanol): Found: C, 56.51; H, 5.02; N, 6.11. Calc. for $C_{21}H_{22}N_2O_5S_2$: C, 56.49; H, 4.97; N, 6.27%.

dl-*Gliotoxin* (**1**). To an ice-cooled solution of 40.0 mg (0.0896 mmol) of the *dl*-gliotoxin thioacetal **27b** in 20 ml of methylene chloride was added 21.8 mg (85%, 1.2 eq) of *m*-chloroperbenzoic acid with stirring. After 10 min of stirring at 0°, 20 μl of dimethyl sulfide was added. The solution was then treated with 40 μl of a solution of 70% perchloric acid in methanol (1:5). The solution was allowed to stand at room temperature for 9 hr and then poured into a saturated sodium bicarbonate solution. The aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and chromatographed on a silica gel column (eluted with 1% methanol in methylene chloride) to afford 17.0 mg (58.1%) of **1** as pale yellow crystals, m.p. 165–166° (capillary, methanol). IR (KBr): 3350, 1683, 1663. NMR ($CDCl_3$): 2.93 (1H, AB, J = 18 Hz), 3.17 (3H, s), 3.65 (1H, m), 3.69 (1H, AB, J = 18 Hz), 4.00–4.55 (2H, m), 4.76 (2H, br. s), 5.62 (1H, s), 5.55–6.05 (3H, m). MS: 326 (3, M), 262 (100), 245 (6), 244 (31). Exact Mass: Found: 326.0399. Calc. for $C_{13}H_{14}N_2O_4S_2$: 326.0395. Analysis (recrystallized from methanol): Found: C, 47.56; H, 4.40; N, 8.37. Calc. for $C_{13}H_{14}N_2O_4S_2$: C, 47.84; H, 4.32; N, 8.58%.

Gliotoxin thioacetal **27a** *and* **27b** *from natural gliotoxin.* A solution of 100 mg (0.307 mmol) of natural gliotoxin (**1**)[33] in 30 ml of methylene chloride was cooled in an ice bath. To the stirred solution was added an ice-cooled solution of sodium borohydride in methanol. After the reduction had been complete, the mixture was treated with 1 ml of *p*-anisaldehyde and 1 ml of boron trifluoride etherate and allowed to warm to room temperature. The solution was stirred at room temperature for 4 hr and then poured into a saturated sodium bicarbonate solution. The aqueous layer was thoroughly extracted with methylene chloride. The extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel tlc (developed three times with 2% methanol in methylene chloride) to afford 30.8 mg (22.5%) of **27a**, m.p. 228–230° (ethyl acetate) and 66.1 mg (48.3%) of **27b**, m.p. 204–206° (methanol).

Gliotoxin thioacetal **27a**. IR (KBr): 3300, 1678, 1659, 1603, 1510. NMR ($CDCl_3$): 2.88 (1H, AB, J = 18 Hz), 3.17 (3H, s), 3.21 (1H, AB, J = 18 Hz), 3.76 (3H, s), 3.79 (1H, AB, J = 12 Hz), 4.56 (1H, AB, J = 12 Hz), 4.85 (2H, br. s), 5.20 (1H, s), 5.60–6.05 (4H, m), 6.81 (2H, d, J = 9 Hz), 7.27 (2H, d, J = 9 Hz). MS: 446 (3, M), 294 (3), 262 (77), 245 (13), 244 (44), 185 (100). Exact Mass: Found: 446.0960. Calc. for $C_{21}H_{22}N_2O_5S_2$: 446.0970. $[\alpha]_D^{23}$ + 15.7° (c = 0.0065, 10% methanol in chloroform) CD (ethanol): 230 ($\Delta\epsilon$ −28), 264 nm ($\Delta\epsilon$ +32).

Gliotoxin thioacetal **27b**. IR (KBr): 3350, 1680, 1655, 1603, 1509. NMR ($CDCl_3$): 2.91 (1H, AB, J = 18 Hz), 3.30 (3H, s), 3.35 (1H, AB, J = 18 Hz), 3.77 (3H, s), 3.75–4.40 (2H, m), 4.91 (1H, br. s), 4.98 (1H, br. s), 5.09 (1H, s), 5.65–5.95 (4H, m), 6.80 (2H, d, J = 9 Hz), 7.25 (2H, d, J = 9 Hz). MS: 446 (4, M), 294 (6), 262 (34), 245 (11), 244 (46), 185 (100). Exact Mass: Found: 446.0969. Calc. for $C_{21}H_{22}N_2O_5S_2$: 446.0970. $[\alpha]_D^{23}$ + 30° (c = 0.0049, 10% methanol in chloroform).

The gliotoxin thioacetals **27a** and **27b** were converted back to gliotoxin (**1**) by using the same procedure as the one given in the totally synthetic series.

Synthesis of optically active gliotoxin

Thioacetal ureas **84** *and* **85**. A solution of 500 mg (1.61 mmol) of the thioacetal **68a**, 1 ml of α-(−)-methylbenzyl isocyanate,[50] and 2 ml of triethylamine in 100 ml of methylene chloride was stirred at room temperature for 3 hr. The solution was then concentrated under reduced pressure and separated on preparative silica gel tlc (developed three times with 0.6% methanol in methylene chloride) to give 256 mg (34.7%, R_f 0.22) of **84**, m.p. 203–220° (dec., ethyl acetate) and 271 mg (36.7%, R_f 0.20) of **85**, m.p. 190–198° (dec., ethyl acetate).

Thioacetal urea **84**. IR (KBr): 3270, 1719, 1693, 1603, 1525, 1510. NMR ($CDCl_3$): 1.62 (3H, d, J = 7 Hz), 3.03 (3H, s), 3.79 (3H, s), 5.06 (1H, s), 5.12 (1H, q, J = 7 Hz), 5.35 (1H, s), 6.17 (1H, s), 7.81 (2H, d, J = 9 Hz), 7.30 (5H, s), 7.33 (2H, d, J = 9 Hz), 8.94 (1H, br. s). MS: 393 (26, M–S_2), 185 (100), 105 (98). Exact Mass: Found: 393.1679. Calc. for $C_{22}H_{23}N_3O_4$ (M–S_2): 393.1688. $[\alpha]_D^{23}$ − 18.5° (c = 0.0338, 10% methanol in chloroform).

Thioacetal urea **85**. IR (KBr): 3280, 1710, 1685, 1665, 1603, 1506. NMR ($CDCl_3$): 1.58 (3H, d, J = 7 Hz), 3.05 (3H, s), 3.76 (3H, s), 5.07 (1H, s), 5.14 (1H, q, J = 7 Hz), 5.23 (1H, s), 6.20 (1H, s), 6.79 (2H, d, J = 9 Hz), 7.25 (2H, d, J = 9 Hz), 7.33 (5H, s), 8.95 (1H, br. s). MS: 393 (26, M–S_2), 185 (91), 105 (100). Exact Mass: Found: 393.1690. Calc. for $C_{22}H_{23}N_3O_4$(M–S_2): 393.1688. $[\alpha]_D^{23}$ − 3.1° (c = 0.032, 10% methanol in chloroform).

Optically active thioacetal **86** (*optically active form of* **68a**). In a 25 ml round-bottomed flask was placed 230 mg (0.503 mmol) of the crystalline urea **84**. The crystals were heated at 230° in an oil bath under slow stream of argon for 10 min. After cooling, the resulting crystals were triturated with ether to yield 145 mg (92.9%) of **86**, m.p. 251–253° (ethyl acetate). $[\alpha]_D^{23}$ + 73° (c = 0.0056, 10% methanol in chloroform) CD (ethanol): 228 ($\Delta\epsilon$ −34), 251 nm ($\Delta\epsilon$ +30).

Following the sequence of reactions from **68b** to **1**, the totally synthetic gliotoxin (**1**) was obtained in racemic and optically active forms from the racemic thioacetal **68a** and its optically active form **86**. Since the experimental procedures for each step were identical to those described for the sequence from **68b** to **1**, only the yields and physical data for the intermediates are listed below.

Michael adduct corresponding to **73**. *Racemic form.* Yield: 34.4%. M.P.: 217–219° (dec., ethyl acetate). IR (KBr): 3440, 1691, 1679, 1657, 1604, 1509. NMR ($CDCl_3$): 1.35 (9H, s), 2.42 (1H, d, J = 6 Hz), 3.00 (3H, s), 3.77 (3H, s), 4.17 (1H, br. s), 4.58 (1H, s), 5.02 (1H, s), 5.55 (1H, s), 5.64 (1H, br. s), 6.37 (2H, m), 6.78 (2H, d, J = 9 Hz), 7.35 (2H, d, J = 9 Hz), 7.38 (1H). *Optically active form.* Yield: 28.0%. M.P.: 227–229° (dec., ethyl acetate). $[\alpha]_D^{23}$ − 463° (c = 0.0094, 10% methanol in chloroform).

Michael adduct corresponding to **74**. *Racemic form.* Yield: 62.1%. M.P.: 225–227° (dec., ethyl acetate). IR (KBr): 3390, 1702, 1690, 1604, 1510. NMR ($CDCl_3$): 1.44 (9H, s), 2.15 (1H, d, J = 8 Hz), 3.01 (3H, s), 3.77 (3H, s), 4.62 (1H, br. s), 4.66 (1H, s), 5.06 (1H, s), 5.53 (1H, s), 5.77 (1H, d of d, J = 1, 6 Hz), 6.0–6.5 (2H, m), 6.81 (2H, d, J = 9 Hz), 7.29 (2H, d, J = 9 Hz), 7.3 (1H). *Optically active form.* Yield: 59.0%. M.P.: 266–268° (dec., ether). $[\alpha]_D^{23}$ + 108° (c = 0.00846, 10% methanol in chloroform).

Thioacetal acetate corresponding to **75**. *Racemic form.* Yield: 96.8%. M.P.: 195–196° (ethyl acetate). IR (KBr): 1734, 1690, 1603, 1508. NMR ($CDCl_3$): 1.44 (9H, s), 2.12

(3H, s), 3.00 (3H, s), 3.78 (3H, s), 4.59 (1H, s), 5.05 (1H, s), 5.57 (1H, s), 5.65 (1H, m), 5.75 (1H, br. s), 6.10–6.45 (2H, m), 6.83 (2H, d, J = 9 Hz), 7.36 (2H, d, J = 9 Hz), 7.36 (1H). MS: 546 (1, M), 490 (4), 362 (2), 306 (13), 126 (100). Exact Mass: Found: 546.1499. Calc. for $C_{26}H_{30}N_2O_7S_2$: 546.1494. *Optically active form.* Yield: 92.0%. M.P.: 187–188° (ethyl acetate). $[\alpha]_D^{23}$ + 241° (c = 0.00979, 10% methanol in chloroform).

Thioacetal alcohol corresponding to **78**. *Racemic form.* Yield: 68.8%. M.P.: 181–182° (ethyl acetate). IR (KBr): 3400, 1720, 1695, 1675, 1603, 1508. NMR ($CDCl_3$): 1.85 (1H, t, J = 5 Hz), 2.14 (3H, s), 3.04 (3H, s), 3.80 (3H, s), 4.08 (2H, d, J = 5 Hz), 4.70 (1H, s), 5.04 (1H, s), 5.44 (1H, br, s), 5.71 (1H, s), 5.75–6.45 (4H, m), 6.84 (2H, d, J = 9 Hz), 7.39 (2H, d, J = 9 Hz). MS: 476 (<1, M), 292 (4), 232 (100), 126 (61). Exact Mass: Found: 476.1072. Calc. for $C_{22}H_{24}N_2O_6S_2$: 476.1076. *Optically active form.* Yield: 71.5%. M.P.: 180–181° (ethyl acetate). $[\alpha]_D^{23}$ + 258° (c = 0.0104, 10% methanol in chloroform).

Thioacetal chloride corresponding to **79**. *Racemic form.* Yield: 95.4%. M.P.: 179–180° (ethyl acetate). IR (KBr): 1730, 1682, 1673, 1608, 1515. NMR ($CDCl_3$): 2.12 (3H, s), 3.02 (3H, s), 3.79 (3H, s), 4.03 (2H, s), 4.65 (1H, s), 5.05 (1H, s), 5.52 (1H, br, s), 5.66 (1H, s), 5.70–6.55 (4H, m), 6.85 (2H, d, J = 9 Hz), 7.37 (2H, d, J = 9 Hz). MS: 494 (<1, M), 312 (2), 310 (6), 252 (7), 250 (20), 126 (100). Exact Mass: Found: 494.0737. Calc. for $C_{22}H_{23}N_2O_5S_2{}^{35}Cl$: 494.0737.

Optically active form. Yield: 92.1%. M.P.: 177–179° (ethyl acetate). $[\alpha]_D^{23}$ + 239° (c = 0.00955, 10% methanol in chloroform).

Thioacetal alcohol corresponding to **80**. *Racemic form.* Yield: 95.1%. M.P.: 200–201° (ethyl acetate). IR (KBr): 3410, 1692, 1603, 1512. NMR ($CDCl_3$): 3.04 (3H, s), 3.78 (3H, s), 4.02 (2H, s), 4.71 (1H, br. d, J = 6 Hz), 4.80 (1H, s), 5.09 (1H, s), 5.64 (1H, m), 5.65 (1H, s), 6.08 (2H, m), 6.36 (1H, m), 6.83 (2H, d, J = 9 Hz), 7.32 (2H, d, J = 9 Hz), MS: 436 (1, M–H_2O), 434 (3, M–H_2O), 252 (36), 250 (100). Exact Mass: Found: 434.0536. Calc. for $C_{20}H_{19}N_2O_3S_2{}^{35}Cl$ (M–H_2O): 434.0526. *Optically active form.* Yield: 97.4%. M.P.: 110–113° (ether). $[\alpha]_D^{23}$ + 67° (c = 0.0107, 10% methanol in chloroform).

Benzylgliotoxin thioacetal corresponding to **83**. *Racemic form.* Yield: 47.5%. M.P.: 210–212° (ethyl acetate). IR (KBr): 3350, 1676, 1668, 1603, 1513. NMR ($CDCl_3$): 2.85 (1H, AB, J = 18 Hz), 3.13 (3H, s), 3.24 (1H, AB, J = 18 Hz), 3.72 (1H, AB, J = 11 Hz), 3.78 (3H, s), 4.37 (1H, AB, J = 11 Hz), 4.57 (1H, AB, J = 12 Hz), 4.64 (1H, AB, J = 12 Hz), 4.88 (2H, m), 5.21 (1H, s), 5.86 (3H, m), 6.11 (1H, br. s), 6.79 (2H, d, J = 9 Hz), 7.26 (2H, d, J = 9 Hz), 7.31 (5H, s). MS: 536 (1, M), 352 (26), 334 (38), 91 (100). Exact Mass: Found: 536.1458. Calc. for $C_{28}H_{28}N_2O_5S_2$: 536.1440.

Gliotoxin thioacetal (**27a**). *Racemic form.* Yield: 55.0%. M.p.: 241–242° (methylene chloride). IR (KBr): 3350, 3280, 1670, 1602, 1512. NMR ($CDCl_3$): 2.65 (1H, m), 2.88 (1H, AB, J = 18 Hz), 3.17 (3H, s), 3.22 (1H, AB, J = 18 Hz), 3.77 (3H, s), 3.80 (1H, m), 4.60 (1H, m), 4.88 (2H, br. s), 5.23 (1H, s), 5.60–6.10 (4H, m), 6.81 (2H, d, J = 9 Hz), 7.28 (2H, d, J = 9 Hz). MS: 446 (4, M), 294 (5), 262 (100), 245 (11), 244 (38), 185 (84). Exact Mass: Found: 446.0981. Calc. for $C_{21}H_{22}N_2O_5S_2$: 446.0970. *Optically active form.* Yield: 52%. M.P. 228–230° (ethyl acetate). $[\alpha]_D^{23}$ + 15.5° (c = 0.00303, 10% methanol in chloroform).

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[26]Reduction of an epidithiapiperazinedione with sodium borohydride yields the corresponding dithiol, which can be oxidized back to the starting epidithiapiperazinedione. However, this is often complicated because of elimination of hydrogen sulfide from the dithiol.

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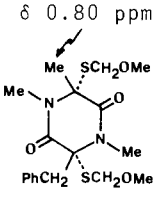
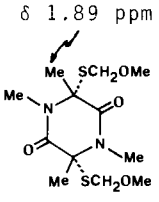


49a



45b

[37]The low yield of this reaction is probably due to a competitive demethylation and demethoxymethylation with boron trichloride.

[38]We are indebted to Dr. G. M. Strunz, Canadian Forestry Service, New Brunswick, Canada, for a sample of natural hyalodendrin.

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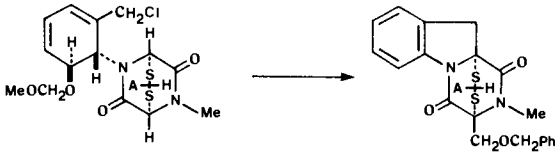

88 89

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THE CORAXENIOLIDES, CONSTITUENTS OF PINK CORAL, *CORALLIUM* SP.[1a]

ROBERT E. SCHWARTZ and PAUL J. SCHEUER*
Department of Chemistry, University of Hawaii at Manoa, Honolulu, HI 96822, U.S.A.

and

VOLKER ZABEL and WILLIAM H. WATSON
Department of Chemistry, Texas Christian University, Fort Worth, TX 76129, U.S.A.

(*Received in USA* 26 *August* 1980)

Abstract—From a deep-sea (-350 m) gorgonian, *Corallium* sp., we have isolated five diterpenes, which are structurally related to the xenicins, previously known from soft corals and brown algae. The structure of the principal constituent, coraxeniolide-A (**1**) was determined by X-ray diffraction studies. Spectral analysis and chemical correlations elucidated the structures of coraxeniolides B(**3**), C(**7**), C'(**10**), and of corabohcin (**13**).

Man's fascination with ornaments fashioned from coral dates back at least 25,000 years, as judged by archeological evidence.[2] Until very recently coral was gathered in shallow caves by skin divers or in deep water by the use of *ingegno*, a device that is dragged over the ocean floor breaking and entangling corals—as well as everything else in its path.[2] In Hawaii, most black coral is collected by skin divers, but pink and other precious (gold, bamboo) corals are harvested by manned minisubmersible at depths of −300 to −350 m. This commercial operation has spearheaded scientific study of many previously inacessible animals.

Most corals suitable for fabrication of jewelry are gorgonians (order Gorgonacea, subclass Alcyonaria, class Anthozoa, phylum Cnidaria) with brightly colored and gracefully shaped endoskeletons, which are composed of calcium carbonate spicules that are embedded in a matrix of organic polymer. Shallow water (≤ -75 m) gorgonians are virtually absent in Hawaiian waters, but more than 90 deep-sea species have been described. The Hawaiian pink coral of commerce is pale pink ("angel skin") and is the endoskeleton of a *Corallium* sp.[3], which is harvested in the Molokai channel off Makapuu, Oahu, by the submersible *Star II*.

When the submarine returns to Makai Pier, Makapuu, from its daily dive the polyps of *Corallium* sp. were scraped off the skeleton and steeped in methanol. Cold methanol extraction was repeated twice. The combined extracts were filtered and concentrated. The concentrate was partitioned between methylene chloride and water. The organic residue ($\sim 0.3\%$ of whole wet animal) was purified by column chromatography on BioSil A, followed by hplc on Partisil.

The most abundant constituent, which we have named coraxeniolide-A (**1**) in recognition of its biological origin from *Corallium* sp. and its structural relationship to xenicin (**2**),[4] was isolated in about 650 mg/kg yield from the animal as a viscous colorless oil. Its composition of $C_{20}H_{30}O_2$, obtained by high resolution mass measurement, and salient spectral data (one each isopropyl, methyl, and exocyclic methylene group) pointed to the diterpenoid nature of the molecule. Furthermore, the presence of two additional carbon-carbon double bonds (four ^{13}C signals between δ153 and 124) and of a δ-lactone ring (1748 cm^{-1}) established the bicyclic nature of the molecule. However, neither extensive decoupling experiments nor transformations of **1** to a mixture of two epimeric hexahydro derivatives and to a diol, nor attempted double bond cleavage by ozone or by osmium tetroxide/periodate, provided unequivocal evidence of the size of the carbocyclic ring of **1**. Fortunately, coraxeniolide-A after prolonged standing in dichloromethane at −10° crystallized and its structure was determined by X-ray diffraction methods (Fig. 1). Coraxeniolide-A is an unrearranged diterpenoid. Its δ-lactone ring is *trans*-fused to a cyclononene. The lactone is in a boat conformation and the carbocyclic ring is approximately perpendicular to it. The shape of the ring system explains why only two and not four hexahydro-**1** were isolated after catalytic hydrogenation: the endocyclic double bond can be hydrogenated only from the outside of the ring, which makes the two hexahydro derivatives epimeric at C-11.

Prior to the isolation by Schmitz *et al.*[4] of xenicin (**2**, numbering according to Schmitz) from the soft coral *Xenia elongata* (order Alcyonacea, subclass Alcyonaria) in 1977 only a few cyclononane terpenoids had been described. Notable among these were the sesquiterpenoid caryophyllenes, constituents of many essential oils, and the diterpenoid jatrophatrione, isolated from a member of the Euphorbiaceae.[5] Since 1977, however, numerous xenicin derivatives have been reported from marine sources—by Kashman and Groweiss[6a,b] from *X. macrospiculata*, by Tursch and his group[7] from *X. novae-brittaniae*, by Fenical and coworkers[8] from the brown alga *Dictyota crenulata*, and by Finer *et al.*[9] from *D. flabellata* and from the sea hare *Aplysia depilans*.

The second most abundant constituent of *Corallium* sp. (325 mg/kg) was coraxeniolide-B (**3**), a colorless oil of composition $C_{20}H_{28}O_2$, thus possessing one more unsaturation than **1**. One additional carbon-carbon double bond was indicated by eight rather than six ^{13}C resonances in the olefinic region. Again, an exocyclic methylene (113.5 ppm, t) was present in **3**. Other parallel features included a δ-lactone (1729 cm^{-1}), in boat conformation and *trans*-fused to the carbocyclic ring, as evidenced by similar *vic* and *gem* *J*-values of the C-1 protons. The difference in chemical shifts of the C-1 protons

[a] Dedicated to the memory of Robert Burns Woodward, this paper will be included in the Book version of the special Woodward Memorial Supplement.

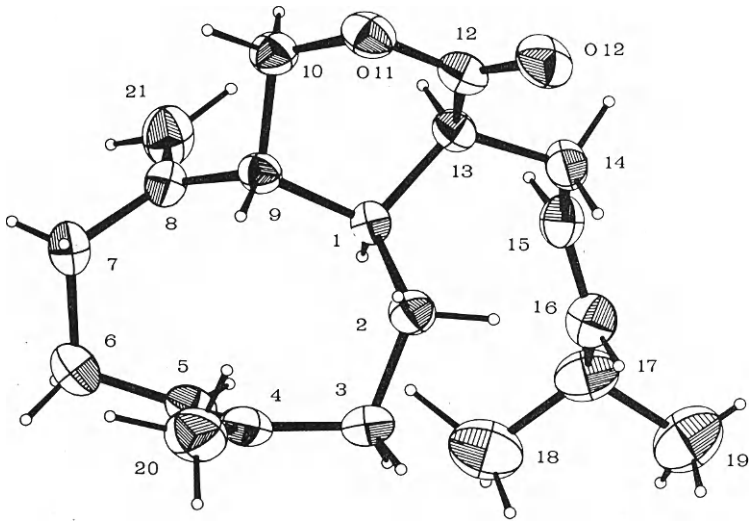


Fig. 1. Single crystal X-ray structure of coraxeniolide-A (1).

(4.05–3.54 = 0.51 ppm), however, is large when compared with the data for **1**, where $\Delta\delta = 4.19–3.93 = 0.26$ ppm. This difference is reflected in the multiplicity of the off-resonance C-1 carbon signal, which appears as a doublet of doublets in the spectrum of **3**, but as a triplet in the spectrum of **1**. This is consistent with Hagaman's[10] observation that the multiplicity of the carbon signal varies with the chemical shift difference of the geminal proton signals vs the geminal coupling constant, which is 12 Hz in our case. Whenever $\Delta\delta > 3xJ_{gem}$, the carbon signal will change from a triplet to a doublet of doublets.

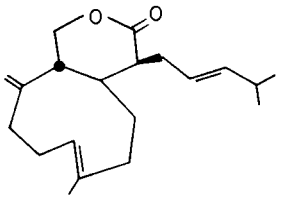
The ^{13}C spectrum of **3** also revealed *E*-geometry of the C-7 (8) double bond. The quartet signal for the C-18 methyl resonates at 16.73 ppm and not in the 22–25 ppm region anticipated for *Z*-configuration.[11] Entirely consistent with this assignment is the corresponding 16.73 ppm signal in **1**, where *E*-geometry is known from X-ray data.

The UV spectrum of **3**, λ_{max}^{MeOH} 270 nm (log ϵ 4.08), when compared with that of **1** (end absorption), proved that the additional carbon–carbon double bond of **3** is conjugated. Since NMR data had shown that size and shape of the rings in **1** and **3** were similar, the additional olefinic linkage had to be in the side chain, exocyclic and *alpha* to the lactone (ν_{max} 1729 cm^{-1}).

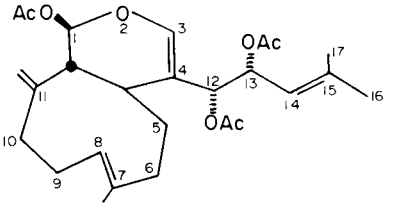
The remaining structural ambiguity, the configuration of the C-4 (12) double bond was resolved by comparison with appropriate models. In coraxeniolide-B (**3**) H-12 appears as a doublet ($J = 12$ Hz) at δ7.16, coupled to H-13, which resonates as a broad doublet of doublets ($J = 15$, 12 Hz) at δ6.38. H-13 in turn is *trans*-coupled to a doublet of doublets ($J = 15$, 8 Hz) at δ5.84, a signal assigned to H-14. In 13-*trans*-retinal (**4a**) H-12 (comparable to H-13 in **3**) resonates at δ6.27, while in 13-*cis*-retinal (**4b**) the signal appears downfield at δ7.28.[12] In both cases (**3** and **4a**) the upfield signal represents a γ-proton *trans* to the carbonyl. This is also the case in the synthetic intermediate **5**, where the comparable H-3 resonates at δ6.21.[13] Finally, the data for xeniolide-A (**6a**)[6b] and for isoxeniolide-A (**6b**)[7] (Table 1) agree with our assignment. The γ-proton (H-13) of **6a** resonates at δ6.53 vs δ6.85 in **6b**. In the UV spectra of **6a** and **6b** λ_{max}

Table 1. ^1H NMR spectral data of coraxeniolide-B (**3**), xeniolide-A (**6a**), and isoxeniolide-A (**6b**)

	3 (100 MHz, C_6D_6)	**3**, (100 MHz, $CDCl_3$)	**6a** (270 MHz, $CDCl_3$)	**6b** (100 MHz, $CDCl_3$)
HC-12	7.16 1H d (J=12 Hz)	6.86 1H d (J=12 Hz)	6.92 1H d (J=11 Hz)	6.39 1H d (J=10 Hz)
HC-13	6.38 1H bdd (J=15,12 Hz)	6.40-6.04	6.53 1H dd (J=15,11 Hz)	6.85 1H dd (J=15,10 Hz)
HC-14	5.84 1H dd (J=15,8 Hz)	2H m	6.26 1H d (J=15 Hz)	6.06 1H d (J=15 Hz)
H_3C-16,17	0.91 6H d (J= 6 Hz)	1.04 6H d (J=7 Hz)	1.38 6H s	1.33 6H s
HC-1β	3.88 1H dd (J=12,6 Hz)	4.05 1H dd (J=12,6 Hz)	4.08 1H dd (J=11,6 Hz)	4.07 1H dd (J=12,6 Hz)
HC-1α	3.46 1H dd (J=12,12 Hz)	3.54 1H dd (J=12,12 Hz)	3.61 1H dd (J=11,11 Hz)	3.61 1H dd (J=12,12 Hz)
H_2C-19	4.71 2H s	4.94 1H s 4.82 1H s	5.09 1H s 4.91 1H s	5.09 1H s 4.95 1H s
HC-8	5.37 1H m	5.38 1H m	5.32 1H d (J=8 Hz)	5.24 1H d (J=8 Hz)
H_3C-18	1.46 3H d (J=1.5 Hz)	1.69 3H d (J=1 Hz)	1.70 3H s	1.67 3H s



1(A)



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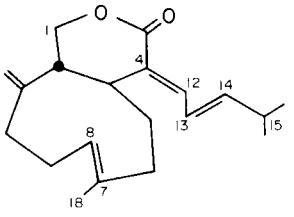

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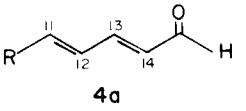
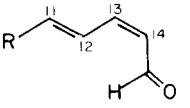


4a



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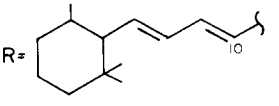
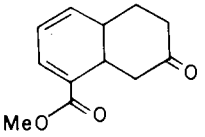
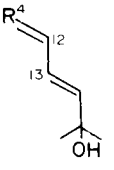
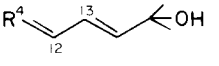




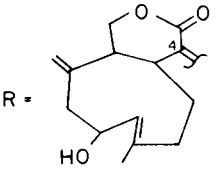
5



6a



6b



for **6a** [*E*-C-4(12)] is observed at 268 nm and at 263 nm in **6b** [*Z*-C-4(12)], consistent with the 270 nm maximum of coraxeniolide-B (**3**).

Coraxeniolide-C (**7**), $C_{20}H_{28}O_2$, which is isomeric with **3**, was isolated from pink coral (65 mg/kg) as a crystalline white solid, m.p. 68–69°. The spectral data (*see* Experimental Section) showed that the principal structural features of coraxeniolide-B (**3**) were also present in **7**. UV data (λ_{max}^{MeOH} 215 nm, log ϵ3.89) suggested an α,β-unsaturated-δ-lactone (1737 cm^{-1}) and hence C-14 (15) as the site of the unassigned olefinic linkage. This point should be subject to proof by conversion of coraxeniolide-C (**7**) into coraxeniolide-B (**3**) *via* DBU-induced double bond migration: the C-14 (15) olefin was expected to move into conjugation with the C4 (12) olefin. The reaction, however, yielded two white solids, coraxeniolides-D (**8**) and -D′ (**9**), neither of them identical with coraxeniolide-B (**3**). Apparently, proton abstraction from doubly allylic C-13 by DBU preferentially generated an enolate anion, followed by ketonization and proton delivery to C-4. If this rationalization was correct, coraxeniolides-D (**8**) and D′ (**9**) should be epimeric at C-4.

The major crystalline product (26%), m.p. 127–129°, was designated coraxeniolide-D (**8**), and the minor amorphous compound (20%), m.p. 115–118°, coraxeniolide-D′ (**9**). In coraxeniolide-D (**8**) the UV maximum had shifted to 239 nm (log ϵ 4.11), thereby indicating formation of a conjugated dienic side chain in **8**. Loss of the side chain in the mass spectrum of **8** (*m/z* 219, 13%) from the molecular ion supports this assignment.

Although NMR data suggested persuasively that coraxeniolides-A (**1**), -B (**3**), and -C (**7**) shared *trans*-configuration of the ring juncture, independent proof appeared desirable. Attempts to hydrogenate coraxeniolide-C (**7**) to presumably the same epimeric pair of hexahydro derivatives that were obtained by hydrogenation of **1**, were unsuccessful and led only to an inseparable mixture of hexa- and octahydro compounds, presumably because of the difficultly reducible C-4 (12) double bond. However, hydrogenation of D (**8**) obtained from C (**7**) by double bond migration should be more amenable to hydrogenation and provide equally rigorous proof of ring fusion geometry. Indeed, hydrogenation of coraxeniolide-D (**8**) over palladium on carbon in methanol furnished a mixture of epimeric products identical with that obtained previously by hydrogenation of coraxeniolide-A (**1**). This reaction not only secured the *trans*-geometry of the ring juncture, but also proved that the side chain

configuration of coraxeniolide-D (**8**) is identical with that of A (**1**), namely *beta*.

Coraxeniolide-D′ (**9**), the C-4 epimer of D (**8**), exhibits the ^{1}H NMR signals expected for the assigned structure (Table 2), except for the surprising difference of the signals for the C-1 hydrogens. At 360 MHz the C-1 protons absorb at δ4.15 and 4.01, both doublets of doublets, with J_{gem} = 12 Hz, and J_{vic} = 4.5, 3.5 Hz. The comparable signals in coraxeniolide-D (**8**) are doublets of doublets at δ4.21 and 3.96, with J_{gem} = 12 Hz, and J_{vic} = 8, 12 Hz. This radical change in vicinal coupling must be caused by a change in conformation of the lactone ring. The C-1 proton coupling constants of D (**8**) parallel those of coraxeniolide-A (**1**), which was determined by X-ray diffraction. In these two compounds the lactone ring is in boat conformation with C-1 and C-4 pointing downward. In coraxeniolide-D′ (**9**), on the other hand, the δ-lactone boat is reversed, with C-1 and C-4 pointing up. In that conformation the dihedral angle between H-11a and both C-1 protons is approximately 45°, resulting in J_{vic} values of 3.5 and 4.5 Hz. The dihedral angle between H-4 and H-4a is approximately 170°, leading J_{vic} of 8 Hz.

Another constituent of pink coral, a colorless oil (200 mg/kg) of composition $C_{20}H_{28}O_2$ behaves chromatographically much like coraxeniolide-B (**3**), and could therefore not be rigorously purified. It was designated coraxeniolide-C′ (**10**) since all spectral data, including decoupling experiments, pointed to a close relationship with coraxeniolide-C (**7**), most likely one of C-12 epimers (Table 2).

Reaction of coraxeniolide-C′ (**10**) with DBU furnished a 29% yield of coraxeniolide-D (**8**) and 38% of D′ (**9**), as evidenced by full spectral comparison.

†*Cora* denotes the origin of the compound from *Corallium* sp., and *Boh* expresses our appreciation to Boh Bartko, the skipper of *Star II*.

The only significant differences between the two compounds are the ^{1}H NMR data for protons at C-12 and C-13. In C′ (**10**) H 12 is a triplet (J = 8 Hz) resonating at δ6.57, coupled to a broad 2H doublet of doublets (J = 8, 8 Hz) at δ2.72 (H_2-13). In turn, these protons are coupled to H-14, a triplet (J = 8 Hz) with additional fine coupling, absorbing at δ5.08. Conversely, in coraxeniolide-C (**7**) H-12 is a triplet (J = 8 Hz) observed at δ5.61. This proton is coupled (J = 8,8 Hz) to H_2-13, seen as a broad doublet of doublets at δ3.25. H-14 of coraxeniolide-C (**7**) was part of a 2H multiplet at δ5.28, which could not be resolved.

The large difference in chemical shifts of H-12 in C (**7**) and in C′ (**10**) is undoubtedly caused by anisotropy originating in the lactone carbonyl. But it is not immediately obvious whether the carbonyl causes an upfield or a downfield shift for the spatially proximate (E geometry) proton. Among the numerous α-methylene-δ-lactones for which ^{1}H NMR data are available the observed chemical shift differences were equally substantial, but we could find none, where the shift values had been assigned to specific protons. In compound **11** e.g. the pertinent protons resonate at δ6.47 and 5.78,[14] but the values are not assigned.

In many cases the situation-large shift differences, but no or contradictory assignments—was analogous for α-methylene-γ-lactones. However, for the isomeric cyclobuxines (**12a, b**) the proton or methyl that is closest to the carbonyl experiences the downfield shift.[15] On this basis, coraxeniolide-C (**7**) possesses Z, and C′ (**10**) E-geometry for the C-4 (12) olefin.

A trace constituent of pink coral (32 mg/kg) was isolated as a colorless oil of composition $C_{22}H_{34}O_2$. Spectral data indicated a normal diterpene biogenetically related to the coraxeniolides, for which we suggest the trivial name corabohcin (**13**).† Unlike the coraxeniolides, corabohcin (**13**) is a monocyclic acetate (ν_{max} 1732 cm^{-1},

Table 2. 100 MHz ^{1}H NMR spectral data of coraxeniolide-C (**7**), D (**8**), D′ (**9**), and C′ (**10**)

	7 (C_6D_6)	**8** ($CDCl_3$)[a]	**9** ($CDCl_3$)[a]	**10** (C_6D_6)	**8** ($CDCl_3$)[b]	**9** ($CDCl_3$)[b]
H-1	3.81 1H dd (J=12,7 Hz) 3.48 1H dd (J=12,12 Hz)	4.21 1H dd (J=12,8 Hz) 3.96 1H dd (J=12,12 Hz)	4.19 1H dd (J=12,4 Hz) 4.03 1H dd (J=12,4 Hz)	3.84 1H dd (J=12,6 Hz) 3.38 1H dd (J=12,12 Hz)	4.20 1H dd (J=12,8 Hz) 3.95 1H dd (J=12,12, Hz)	4.19 1H dd (J= 12,4 Hz) 4.03 1H dd (J=12,4 Hz)
H-4		3.58 1H bdd (J=7,7 Hz)	2.89 1H dd (J=8,8 Hz)		3.59 1H dd (J=7,7 Hz)	2.90 1H dd (J=8,8 Hz)
H-8	5.28 2H m	5.34 1H bt (J=7 Hz)	5.34 1H m	5.34 1H m	5.33 1H bt (J=7 Hz)	5.35 1H m
H-14		5.89 1H bd (J=10 Hz)	5.88 1H d (J=10 Hz)	5.08 1H mt (J=8 Hz)	5.89 1H bd (J=10 Hz)	5.89 1H bd (J=10 Hz)
H-13 H_2-13	3.25 2H bdd (J=8,8 Hz)	6.39 1H dd (J=15,10 Hz)	6.29 1H dd (J=15,10 Hz)	2.72 2H bdd (J=8,8 Hz)	6.39 1H dd (J=15,10 Hz)	6.30 1H dd (J=15,10 Hz)
H-12	5.61 1H t (J=8 Hz)	5.90 1H dd (J=15,7 Hz)	5.55 1H dd (J=15,8 Hz))	6.57 1H t (J=8 Hz)	5.90 1H dd (J=15,7 Hz)	5.56 1H dd (J=15,8 Hz)
H_3-16	1.66 3H bs	1.78 6H bs	1.79 3H bs	1.62 3H bs	1.77 6H bs	1.80 3H bs
H_3-17	1.62 3H bs	1.68 3H d (J=2 Hz)	1.76 3H bs	1.50 3H bs	1.67 3H d (J=2 Hz)	1.77 3H bs
H_3-18	1.40 3H d (J=1 Hz)		1.70 3H d (J=2 Hz)	1.42 3H d (J=1 Hz)		1.71 3H d (J=2 Hz)
H_2-19	4.73 1H s 4.69 1H s	5.04 1H s 5.01 1H s	4.92 1H s 4.82 1H s	4.72 1H s 4.67 1H s	5.04 1H s 5.00 1H s	4.90 1H s 4.81 1H s

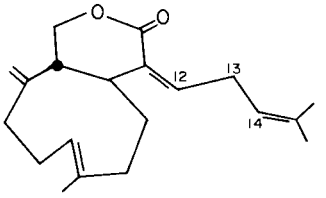
[a] prepared from coraxeniolide-C (**7**)
[b] prepared from coraxeniolide-C′ (**10**)

M^+-60 mass peak) with four isolated double bonds, two of them terminal methylenes. The ^1H NMR spectrum of corabohcin (**13**) is characterized by four methyl singlets, resonating at δ1.94 (acetate) and at δ1.69, 1.63, and 1.57 (three vinylic methyls), and by two one-proton olefin signals at δ5.28 and 5.21. Irradiation of the signal at δ5.28 enhances the methyl singlet at δ1.57, while irradiation at δ5.21 enhances the remaining methyl signals at δ1.69 and 1.63. These experiments rule out a plausible alternate structure, which has the sidechain olefins placed at C-10 (17) and at C-14 (15). A quartet signal at δ26.33 in the ^{13}C off-resonance spectrum of **13** is compatible only with a methyl at C-15. Methyls attached to trisubstituted olefins do not absorb below 23 ppm.[11] The C-18 protons of corabohcin (**13**) are seen as doublets (J = 12, 6 Hz) of doublets (J = 12, 12 Hz) at δ4.01 and 3.81, indicating the rather hindered position of the methylene group.

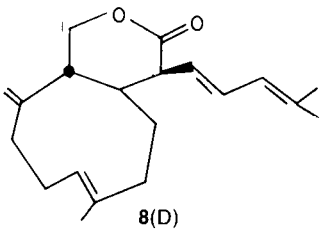
The mass spectrum of corabohcin (**13**) is in full accord with the proposed structure. The C-11 (12) bond is doubly allylic and should break readily. Indeed a peak at m/z 201 (M^+-60-69) displays 59% relative intensity. Another intense (77%) peak at m/z 227 represents a fragment of composition $C_{17}H_{23}$, corresponding to losses of acetic acid and of C_3H_7. Loss of isopropyl from **13** appears at first puzzling, but may be explained by analogy with the mass spectrum of $\Delta^{4(8)}$-menthene (**14**). Here, Weinberg and Djerassi[16] showed by deuterium labelling studies that the base peak corresponds to a loss of C_3H_7 and results from sidechain scission following double bond migration.

We have no firm evidence for the orientation of the side chains at C-2 and C-3. Because of the close structural relationship of corabohcin (**13**) to the coraxeniolides we would expect the C-2 (18) bond to have *alpha* and the C-3(10) bond to have *beta* orientation.

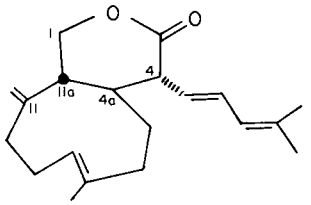
It is worth nothing that the gorgonian from which these metabolities have been isolated because of its deep-sea habitat must be devoid of symbiotic photosynthetic algae. These compounds, therefore, must be biosynthetic products of the animal or ingested with its diet.



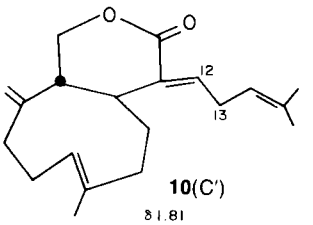
7(C)



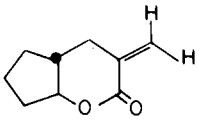
8(D)



9(D')

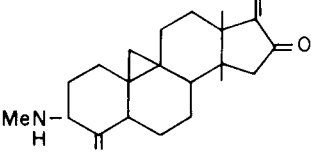


10(C')



11

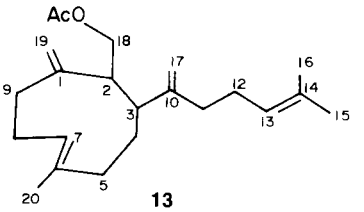
δ 1.81
Me H δ 6.47



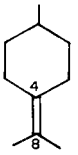
12a

δ 5.65 H Me δ 2.08

12b



13



14

EXPERIMENTAL

Apparatus, methods and materials. Natural abundance ^{13}C NMR spectra were recorded on a Varian XL-100 Fourier transform spectrometer at 25.2 MHz. The deuterium signal of $CDCl_3$ provided field/frequency locking. Proton NMR spectra were recorded on a Varian XL-100 NMR spectrometer at 100 MHz; field/frequency locking was provided by the deuterium signals of $CDCl_3$ and C_6D_6. Two hundred twenty MHz ^1H NMR spectra were obtained on a Varian HR220 NMR spectrometer; TMS was used as an internal reference. Three hundred sixty MHz ^1H NMR spectra were recorded on a Nicolet NTC 360 NMR spectrometer; field/frequency locking was provided by the deuterium signals of $CDCl_3$ and C_6D_6. The ^1H NMR spectra of many compounds contain signals which appear to be triplets but are due to coupling with two nonequivalent protons and, therefore, are referred to as doublets of doublets (dd).

Mass spectra were determined on a Varian MAT 311 high resolution mass spectrometer at an ionizing voltage of 70 eV. Field desorption mass spectra were obtained using a Varian MAT 731 high resolution mass spectrometer equipped with a field desorption ion source.

Infrared spectra were recorded on a Perkin–Elmer 467 grating infrared spectrophotometer. A Beckman ACTA III spectrophotometer was used for the UV spectra. Optical rotations were obtained on an ETL-NPL type 143A automatic polarimeter.

M.p. were taken on a Fisher–Johns apparatus. New England Nuclear silica gel of 250 μ plates were used for all tlc's.

Many separations were performed on a Waters Associates HLPC system consisting of an M-6000 solvent delivery system, a U6K injector, an R401 differential refractometer, a 440 absorbance detector, and a Varian 9176 recorder. A Whatman Partisil PXS 10 μ, 25 cm column or a Whatman Partisil M9 10 μ, 25 cm column was used for all separations requiring hplc. Waters Associates silica gel Sep-Paks were often used for preliminary clean-up of mixtures to be separated by hplc.

Isolation. Seven hundred and sixty grams of freshly collected pink coral (*Corallium* sp.) was steeped in MeOH 3X. This extract was filtered, concentrated, and partitioned between CH_2Cl_2 and water; the aqueous extract was discarded.

The CH_2Cl_2 layer (*ca* 2.2 g) was chromatographed on Bio-Sil A using CH_2Cl_2 as the eluent. Final purification of most compounds was accomplished by hplc with 10 μ Partisil as the absorbent and the eluents as indicated for each particular compound.

Coraxeniolide-A (**1**). Coraxeniolide-A (**1**) was purified by hplc with CH_2Cl_2 as the eluent; approximately 500 mg of **1** was present in the CH_2Cl_2 extract. Compound **1** forms white, plate-like crystals upon concentration, m.p. 88–91°C, R_f 0.38, CH_2Cl_2, and chars red with H_2SO_4/vanillin; $C_{20}H_{30}O_2$ (Calc. 302.224 586; Found 302.224 28), $C_{14}H_{20}O_2$ (Calc. 220.146 334; Found 220.142 98) *m/z* 302 (57%, M^+), 259 (13, M^+-C_3H_7), 220 (72, M^+-C_6H_{10}), 219 (57, M^+-C_6H_{11}). ^{13}C NMR: ($CDCl_3$) 175.16 (s), 153.06 (s), 140.73 (d), 139.97 (s), 124.00 (d), 123.47 (d), 112.20 (t), 70.80 (t), 49.93 (d), 44.39 (d), 42.98 (d), 39.89 (t), 35.84 (t), 31.35 (d), 30.03 (t), 25.28 (t), 22.90 (q), 22.90 (q), 16.73 (q) ppm. ^1H NMR: (220 MHz, $CDCl_3$) 5.50 1H dd (J = 15 Hz), 5.36 2H m, 4.98 2H s, 4.19 1H dd (J = 12 Hz, J = 7 Hz), 3.93 1H dd (J = 12 Hz, J = 12 Hz), 2.80 1H m, 1.70 3H bs, 1.00 6H d (J = 7 Hz) ppm; (100 MHz, C_6D_6) 5.58–5.12 3H m, 4.66 1H s, 3.82 1H dd (J = 12 Hz, J = 7 Hz), 3.48 1H dd (J = 12 Hz, J = 12 Hz), 1.41 (3H d (J = 1.5 Hz), 0.97 6H d (J = 7 Hz) ppm. Decoupling: (220 MHz, $CDCl_3$) irr 4.19 1H dd, 3.93 1H dd-d; irr 3.93 1H dd, 4.19 1H dd-d. UV: (MeOH) end absorption. IR: (CH_2Cl_2) 1748 (lactone C=O), 1640 (C=C), 1391 (CMe_2), 898 (C=CH_2) cm^{-1}. $[\alpha]_D^{25}$ +82° (*c*0.95, $CHCl_3$).

Hexahydro derivatives of coraxeniolide-A (**1**). Twenty-three milligram of **1** were dissolved in MeOH and stirred overnight with 10% Pd/C in an H_2 atmosphere. The reaction mixture was filtered, concentrated, and chromatographed by hplc (CH_2Cl_2) to give 19 mg of an inseparable mixture, as a colorless oil, R_f 0.42 (single spot), CH_2Cl_2, and chars red with H_2SO_4/vanillin; $C_{20}H_{36}O_2$ (Calc. 308.271 537; Found 308.270 16) *m/z* 308 (9%, M^+), 224 (100, M^+-C_6H_{12}). ^{13}C NMR: ($CDCl_3$) 176.22, 175.78, 69.57, 68.87 ppm and a large number of overlapping aliphatic carbons. ^1H NMR: (360 MHz, $CDCl_3$) 4.20–4.05 m, 2.50–2.37 m, 2.13–2.04 m, 0.95–0.82 8 3H d (J = 8 Hz) ppm. UV: (MeOH) end absorption. IR (CH_2Cl_2) 1741 cm^{-1} (lactone C=O), no C=C stretch in the region 1550–1650 cm^{-1}.

Diol derived from coraxeniolide-A (**1**). Eighteen milligram of **1** was reduced with $LiAlH_4$ in anhydrous Et_2O in an argon atmosphere. The reaction mixture was filtered, concentrated, and chromatographed by hplc with EtOAc/CH_2Cl_2 (7:3) as the eluent to give 4.5 mg of diol as a colorless oil, R_f 0.39, EtOAc, and chars red with H_2SO_4/vanillin; $C_{20}H_{34}O_2$, $C_{20}H_{32}O$ (Calcd. 288.245 321; Found 288.248 66) m/z 306 (1%, M^+), 288 (7, M^+-H_2O), 257 (33, M^+-H_2O, CH_2OH). ^1H NMR: (360 MHz, C_6D_6) 5.40 1H dd (J = 15 Hz, J = 6 Hz), 5.32–5.27 2H m, 4.73 1H ms, 4.72 1H ms, 3.65 1H dd (J = 11 Hz, J = 6 Hz), 3.50 1H dd (J = 11 Hz, J = 6 Hz), 3.29 1H dd (J = 11 Hz, J = 7 Hz), 3.24 (J = 11 Hz, J = 7 Hz), 1.51 3H s, 0.96 3H d (J = 7 Hz) ppm. UV: (MeOH) end absorption.

Coraxeniolide-B (**3**). Approximately 250 mg of **3** was isolated from the crude extract by hplc with CH_2Cl_2 as the eluent. Although coraxeniolide-B (**3**) is chromatographically similar to coraxeniolide-C′ (**10**), **3** was obtained with purity greater than 99%. Coraxeniolide-B (**3**) is a colorless oil, R_f 0.28, CH_2Cl_2, and chars blue with H_2SO_4/vanillin; $C_{20}H_{28}O_2$ (Calcd 300.208 936; Found 300.210 33) *m/z* 300 (20%, M^+), 257 (40, M^+-$C_{37}H_7$). ^{13}C NMR: ($CDCl_3$) 171.38 (s), 151.74 (s), 151.38 (d), 138.26 (d), 137.03 (s), 131.31 (s), 124.70 (d), 121.09 (d), 113.52 (t), 71.07 (dd), 49.76 (d), 43.59 (d), 40.69 (t), 38.31 (t), 34.70 (t), 32.14 (d), 25.28 (q), 22.28 (q), 16.73 (q) ppm. ^1H NMR data see Table 1.

Decoupling: (100 MHz, C_6D_6) irr 7.16 1H d, 6.38 1H dd-d; irr 6.38 1H bdd, 7.16 1H d-s, 5.84 1H dd-m; irr 5.84 1H dd, 6.38 1H dd-m; irr 3.88 1H dd, 3.46 1H dd-m; irr 3.46 1H dd, 3.88 1H dd-m; irr 0.91 6H d, 6.38 1H bdd-ddd (J = 15 Hz, J = 12 Hz, J = 1 Hz). UV λ_{max} (log ϵ): (MeOH) 270 nm (4.08). IR: (CH_2Cl_2) 1729 (lactone, C=O), 1640 (C=C), 890 (C-CH_2) cm^{-1}. $[\alpha]_D^{27}$ + 35° (*c* 1.38, CH_2Cl_2).

Coraxeniolide-C (**7**). Approximately 50 mg of **7** was isolated and purified from the CH_2Cl_2 extract by HPLC with CH_2Cl_2 as the eluent. Coraxeniolide-C (**7**) is a white, crystalline solid, m.p. 68–69°, R_f 0.44, CH_2Cl_2, and chars blue with H_2SO_4/ vanillin; $C_{20}H_{28}O_2$ (Calcd. 300.208 936; Found 300.207 40) *m/z* 300 (100%, M^+), 257 (14, M^+-C_3H_7). ^{13}C NMR: ($CDCl_3$) 169.44 (s), 152.44 (s), 137.12 (d), 135.62 (s), 133.77 (s), 133.07 (s), 124.26 (d), 121.00 (d), 112.81 (t), 71.16 (dd) (Fig. 37), 51.77 (d), 50.02 (d), 40.16 (t), 38.04 (t), 35.23 (t), 28.27 (t), 25.89 (q), 25.01 (t), 18.05 (q), 16.56 (q), ppm. ^1H NMR: see Table 2. Decoupling: irr 5.79 1H t, 3.02 1H bdd-d; irr 5.22 1H bt, 3.02 1H bdd-d; irr 4.05 1H dd, 3.56 1H dd-d, 3.56 1H dd, 4.05 1H dd-d; irr 3.02 2H bdd, 5.79 1H t-s, 5.22 1H bt-d (J = 1.5 Hz); irr 1.68 6H bs, 5.22 1H bt-t, 3.02 2H bdd-dd. UV λ_{max} (log ϵ): (MeOH) 215 nm (3.89). IR: (CH_2Cl_2) 1737 (lactone C=O), 1643 (C=C), 1388 (CH_3), 900 (C=CH_2)$^{cm^{-1}}$. $[\alpha]_D^{25}$ + 113: (*c* 1.24, $CDCl_3$).

Twenty-eight milligram of coraxeniolide-C (**7**) was dissolved in toluene and stirred overnight with 24 μL of DBU. The reaction mixture was passed through a silica gel Sep-Pak, concentrated, and chromatographed by hplc (CH_2Cl_2) to give 7.2 mg of coraxeniolide-D (**8**) and 5.6 mg of coraxeniolide-D′ (**9**).

Coraxeniolide-D (**8**). Coraxeniolide-D (**8**) forms white, plate-like crystals upon purification and concentration, m.p. 127–129°, R_f 0.41, CH_2Cl_2, and chars red with H_2SO_4/vanillin; $C_{20}H_{28}O_2$ (Calc. 300.208 936; Found 300.207 40) *m/z* 300 (28%, M^+), 219 (13, M^+-C_6H_9). ^1HNMR data see Table 2. Decoupling: (100 MHz, $CDCl_3$) irr 6.39 1H dd, 5.90 1H dd-d, 5.89 1H d-s; irr 3.58 1H dd, 5.90 1H dd-d; irr 1.78 6H bs, 5.89 1H bd-d. UV λ_{max} (log ϵ): (MeOH) 239 nm (4.11). IR: (CH_2Cl_2) 1754 (lactone C=O), 1637 (C=C), 890 (C=CH_2)$^{cm^{-1}}$. $[\alpha]_D^{28}$ +31° (*c* 0.65, CH_2Cl_2).

Hexahydro derivatives of **1** *from coraxeniolide-D* (**8**). Four milligram of coraxeniolide-D (**8**) was hydrogenated by stirring overnight with 10% Pd/C in MeOH in a H_2 atmosphere. The reaction mixture was filtered and concentrated to give 2.9 mg of a mixture of two products identical to hexahydro compounds from **1**. The mixture is a colorless oil, R_f 0.44, CH_2Cl_2, and chars red with H_2SO_4/vanillin: $C_{20}H_{36}O_2$ (Calc. 308.271 537; Found 308.270 16) *m/z* 308 (12%, M^+), 224 (100, M^+-C_6H_{12}). ^1H NMR: (100 MHz, $CDCl_3$) 4.20–4.05 m 2.60–2.25 m, 0.85–0.92 (envelope of CH_3 doublets). UV: (MeOH) end absorption. IR: CH_2Cl_2) 1739 cm^{-1} (lactone C=O), no C=C stretch in the region 1550–1650 cm^{-1}.

Coraxeniolide-D′ (**9**). Compound **9** forms a white, amorphous solid upon isolation and concentration, m.p. 115–118°, R_f 0.35, CH_2Cl_2, and chars red with H_2SO_4/vanillin; $C_{20}H_{28}O_2$ (Calc. 300.208 936; Found 300.207 06) *m/z* 300 (100%, M^+), 219 (12, M^+-C_6H_9). ^1H NMR: (360 MHz, $CDcl_3$) 6.35 1H dd (J = 15 Hz, J = 10 Hz), 5.86 1H bd (J = 10 Hz), 5.51 1H dd (J = 15 Hz, J = 8 Hz), 5.32 1H bt (J = 8 Hz), 4.89 1H s, 4.78 1H s, 4.15 1H dd (J = 12 Hz, J = 4.5 Hz), 4.05 1H dd (J = 12 Hz, J = 3.5 Hz), 2.89 1H dd (J = 8 Hz, J = 8 Hz), 1.76 3H bs, 1.73 3H s, 1.67 3H bs ppm; 100 MHz data see Table 2. Decoupling: (100 MHz, $CDCl_3$) irr 6.26 1H dd, 5.85 1H bd-bs, 5.52 1H dd-m; irr 5.85 1H bd, 6.26 1H dd-m; irr 5.52 1H dd, 6.30 1H dd-m, 2.89 1H dd-d; irr 5.31 1H m, 1.67 3H d-s; irr 2.89 1H dd, 5.52 1H dd-bd. UV λ_{max} (log ϵ): (MeOH) 237 nm (4.00). IR: (CH_2Cl_2) 1735 (lactone C=O), 890 (C=CH_2). $[\alpha]_D^{27}$ −96° (*c* 0.56, CH_2Cl_2).

Coraxeniolide-C′ (**10**). Final purification of coraxeniolide-C′ (**10**) was accomplished by HPLC (CH_2Cl_2); the crude extract from pink coral contains approximately 150 mg of **10**. Due to its chromatographic similarity to coraxeniolide-B (**3**), coraxeniolide-C′ (**10**) was obtained in small quantities and its purity was somewhat greater than 90%. It is a colorless oil, R_f 0.36, CH_2Cl_2 and chars red with H_2SO_4/vanillin; $C_{20}H_{28}O_2$ (Calc. 300.208 936; Found 300.210 33) *m/z* 300 (11%, M^+), 257 (10, M^+-C_2H_7). ^{13}C NMR: ($CDCl_3$) 171.29, 152.44, 137.82, 135.53, 134.30, 133.77, 124.52, 119.86, 113.08, 71.07, 49.67, 43.68, 40.51, 38.04, 34.87, 27.04, 25.89, 25.10, 18.14, 16.64 ppm. ^1H data see Table 2. Decoupling: (100 MHz, C_6D_6) irr 6.57 1H t, 2.72 2H bdd-d; irr 5.34 1H m, 1.42 3H d-s; irr 5.08 1H mt, 2.72 2H bdd-d; irr 2.72 2H bdd, 6.57 1H t-s, 5.08 1H mt-bs; irr 1.62 bs, 5.08 1H mt-bt; irr 1.50 bs, 5.08 1H mt-bt. UV λ_{max} (log ϵ): (MeOH) 213 nm (3.81). IR (CH_2Cl_2) 1730 (lactone C=O), 1640 (C=C), 892 (C=CH_2)$^{cm^{-1}}$. α_D^{26} +85° (*c* 1.08, $CHCl_3$).

Thirteen milligram of coraxeniolide-C′ (**10**) was dissolved in toluene and stirred overnight with 30 μL of DBU. The reaction mixture was then passed through a silica gel Sep-Pak, concentrated, and chromatographed by hplc ($CHCl_2$) to give 3.7 mg of coraxeniolide-D (**8**) and 5.0 mg of coraxeniolide D′ (**9**).

Coraxeniolide-D (**8**). Coraxeniolide-D (**8**), from the reaction of coraxeniolide-C′ (**10**) with base, forms white, plate-like crystals upon concentration, m.p. 128-131°C, R_f 0.41, CH_2Cl_2, and chars red with H_2SO_4/vanillin; $C_{20}H_{28}O_2$ (Calcd. 300.208 936; Found 300.208 40) *m/z* 300 (45%, 219 (21, M^+-C_6H_9). All spectral data were identical with those of natural coraxeniolide-D (**8**).

Coraxeniolide-D′ (**9**). Coraxeniolide-D′ (**9**) is a white, amorphous solid, m.p. 116–118°, R_f 0.35, CH_2Cl_2, and chars red with H_2SO_4/vanillin; $C_{20}H_{28}O_2$ (calcd 300.208 936; found 300.210 33) *m/z* 300 (100%, M^+), 219 (17, M^+-C_6H_9). Spectral data were identical with those for **9** isolated from the DBU reaction on **7**.

Corabohcin (**13**). Approximately 25 mg of corabohcin (**13**) was isolated by HPLC with CH_2Cl_2/hexane (1:1) as the eluent. Corbohcin (**13**) is a colorless oil, R_f 0.55, CH_2Cl_2), and chars red with H_2SO_4/vanillin; $C_{22}H_{34}O_2$ (field desorption, Calcd. 330.255 67; Found 330.255 68), $C_{20}H_{30}$ (field desorption, calcd 270.234 59; found 270.234 65), $C_{17}H_{23}$ (70 eV, Calc. 227.179 980; found

Table 3. Anisotropic thermal parameters are of the form exp $[-2\pi^2\Sigma\Sigma U_{ij}h_ih_ia_i^*a_j^*]$ (x10^3) while thermal parameters for hydrogen atoms are given as isotropic U values (×10^2)

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	46(1)	48(1)	49(1)	2(1)	-0(1)	-1(1)
C(2)	72(1)	66(1)	51(1)	11(1)	2(1)	2(1)
C(3)	79(2)	78(1)	62(1)	6(1)	26(1)	-0(1)
C(4)	73(1)	68(1)	74(1)	5(1)	26(1)	-16(1)
C(5)	67(1)	68(1)	84(1)	16(1)	16(1)	-5(1)
C(6)	99(2)	65(1)	107(2)	26(1)	21(2)	6(1)
C(7)	91(2)	47(1)	95(2)	2(1)	15(2)	7(1)
C(8)	67(1)	51(1)	62(1)	-3(1)	9(1)	4(1)
C(9)	50(1)	48(1)	50(1)	-2(1)	1(1)	-9(1)
C(10)	51(1)	59(1)	70(1)	-6(1)	12(1)	-7(1)
O(11)	43(1)	73(1)	84(1)	5(1)	1(1)	-13(1)
C(12)	52(1)	62(1)	62(1)	11(1)	0(1)	-9(1)
O(12)	65(1)	84(1)	86(1)	27(1)	-9(1)	3(1)
C(13)	50(1)	51(1)	51(1)	6(1)	-3(1)	-3(1)
C(14)	67(1)	49(1)	73(1)	3(1)	-0(1)	3(1)
C(15)	65(1)	54(1)	69(1)	-9(1)	-5(1)	3(1)
C(16)	72(1)	71(1)	71(1)	-7(1)	-7(1)	0(1)
C(17)	67(1)	113(2)	75(1)	-10(2)	3(1)	-7(2)
C(18)	77(2)	136(2)	124(3)	18(2)	0(2)	-5(2)
C(19)	87(2)	136(4)	131(4)	-35(3)	14(2)	7(3)
C(20)	111(3)	92(2)	88(2)	-14(2)	12(2)	-32(2)
C(21)	101(2)	78(1)	68(1)	3(1)	-17(1)	10(1)
H(1)	5.1(5)					
H(2a)	5.4(6)					
H(2b)	7.0(7)					
H(3a)	9.8(10)					
H(3b)	7.2(7)					
H(5)	9.7(9)					
H(6a)	11.9(13)					
H(6b)	9.0(9)					
H(7a)	9.6(9)					
H(7b)	9.3(10)					
H(9)	6.8(7)					
H(10a)	8.9(9)					
H(10b)	5.5(5)					
H(13)	5.7(6)					
H(14a)	10.0(10)					
H(14b)	7.6(8)					
H(15)	8.4(8)					
H(16)	7.0(7)					
H(17)	10.4(10)					
H(18a)	11.8(12)					
H(18b)	14.6(18)					
H(18c)	15.6(11)					
H(19a)	10.2(10)					
H(19b)	8.0(11)					
H(19c)	15.3(15)					
H(20a)	13.4(15)					
H(20b)	14.2(17)					
H(20c)	10.7(12)					
H(21a)	7.6(7)					
H(21b)	8.6(8)					

227.182 27) *m/z* (70 eV) 330 (4%, M^+), 270 (43, M^+-CH_3CO_2H), 227 (77, M^+-CH_3CO_2H, C_3H_7), 201 (59, M^+-CH_3CO_2H, C_5H_9) (Fig. 56). ^{13}C NMR: ($CDCl_3$) 170.85 (s), 152.71 (s), 147.33 (s), 136.15 (s), 131.83 (s), 124.60 (d), 124.50 (d), 117.58 (t), 109.03 (t), 65.62 (t), 52.31 (d), 47.73 (d), 40.25 (t), 33.91 (t), 32.23 (t), 31.26 (t), 28.71 (t), 26.68 (t), 26.33 (q), 21.22 (q), 18.14 (q), 17.97 (q) ppm. ^1H NMR: (220 MHz, $CDCl_3$) 5.28 1H bd (J = 8 Hz), 5.15 1H m, 4.91 2H s, 4.82 1H s, 4.71 1H s, 4.01 1H dd (J = 12 Hz, J = 6 Hz), 3.81 1H dd (J = 12 Hz, J = 12 Hz), 1.94 3H s, 1.69 3H s, 1.63 3H s, 1.57 3H s ppm. Decoupling: (220 MHz, $CDCl_3$) irr 5.28 1H bd, 1.57 3H s enhanced; irr 5.15 1H m, 1.63 3H s enhanced, 1.69 3H s enhanced. UV: (MeOH) end absorption. IR: (CH_2Cl_2) 1732 (lactone C=O), 1640 (C=C), 1386 (CH_3), 890 ($C=CH_2$)$^{cm^{-1}}$. $[\alpha]_D^{27}$ −169° (*c* 0.71, $CHCl_3$).

X-ray Crystallography. Good crystals were obtained by the slow evaporation in a refrigerator of a CH_2Cl_2 solution of coraxeniolide-A (1). A crystal of dimensions 0.45 × 0.4 × 0.5 mm was cut from a larger crystal and was used in the collection of all data. Room-temperature (20°) lattice parameters were refined by a least-squares procedure utilizing 15 reflexions whose angles were measured by a centering routine associated with the Syntex $P2_1$ diffractometer.

Crystal data. $C_{20}H_{30}O_2$, M = 302.45, a = 11.037(2), b = 18.899(3), c = 0.050(1) Å, V = 1887.9(4) Å^3, Z = 4, d_c = 1.065 Mg m^{-3}. Systematic absences were consistent with space group $P2_12_12_1$.

All intensity data were collected by the θ: 2θ scanning technique ($2\theta < 140°$) using a variable scan speed and a graphite monochromator (CuK_α, λ = 1.54178 Å). A periodically monitored reference reflexion showed no significant change in intensity during data collection. Of the 1947 independent reflexions measured, 148 had intensities less than $2\sigma(I)$. These intensities were not used in least-squares refinements. Lorentz and polarization corrections were applied, but no absorption corrections were made.

The direct methods program MULTAN[17] was used to calculate phases for the 269 |E| values greater than 1.4. After manual intervention in the phasing procedure, a subsequent E map revealed the positions of all nonhydrogen atoms. Isotropic and subsequent anisotropic full-matrix least-squares refinement yielded an R value of 0.089. Hydrogen atom positions were obtained from a difference Fourier map, and refinement with hydrogen thermal parameters isotropic led to a final R of 0.046 for 1795 reflexions (3 reflexions were given zero weight because of secondary extinction). $R = \Sigma||F_0| - |F_c||/\Sigma|F_0|$ and the function minimized was $\Sigma\omega\ (|F_0| - F_c|)^2$ where $\omega = 1/\sigma(I)$ was determined from counting statistics.

All parameter shifts of nonhydrogen atoms during the final cycle were less than 0.3σ and a final difference map showed no peak larger than 0.2e/Å^3. Atomic scattering factors and anomalous dispersion corrections for carbon and oxygen atoms were taken from the International Tables for X-ray Crystallo-

Table 4. Atomic positional coordinates x 10^4 for carbon and oxygen atoms and x 10^3 for hydrogen atoms

atom	x/a	y/b	z/c
C(1)	6242(2)	5984(1)	4180(2)
C(2)	6252(2)	5966(1)	5883(2)
C(3)	5272(3)	6421(1)	6626(3)
C(4)	5355(2)	7182(1)	6146(3)
C(5)	4759(2)	7388(1)	4967(3)
C(6)	5025(3)	8031(1)	4039(4)
C(7)	6172(3)	7894(1)	3114(4)
C(8)	6274(2)	7138(1)	2578(2)
C(9)	6969(2)	6624(1)	3546(2)
C(10)	8061(2)	6359(1)	2665(3)
O(11)	8722(1)	5813(1)	3458(2)
C(12)	8063(2)	5251(1)	3896(2)
O(12)	8562(2)	4786(1)	4577(2)
C(13)	6744(2)	5287(1)	3526(2)
C(14)	6087(2)	4611(1)	3992(3)
C(15)	4779(2)	4622(1)	3618(3)
C(16)	3888(2)	4593(1)	4552(3)
C(17)	2578(3)	4607(2)	4164(3)
C(18)	2054(3)	5343(3)	4417(5)
C(19)	1869(4)	4063(4)	5024(6)
C(20)	6266(4)	7628(2)	6951(4)
C(21)	5784(3)	6934(2)	1305(3)
H(1)	542(2)	603(1)	390(2)
H(2a)	697(3)	611(1)	627(3)
H(2b)	612(3)	548(2)	628(3)
H(3a)	433(3)	628(2)	642(4)
H(3b)	549(2)	637(1)	767(4)
H(5)	426(3)	701(2)	431(4)
H(6a)	424(4)	810(3)	340(5)
H(6b)	499(3)	847(2)	457(4)
H(7a)	700(4)	801(2)	387(4)
H(7b)	621(3)	816(2)	242(4)
H(9)	730(2)	689(1)	448(3)
H(10a)	861(3)	675(2)	256(4)
H(10b)	774(2)	615(1)	167(3)
H(13)	664(2)	535(1)	251(3)
H(14a)	627(3)	455(2)	515(4)
H(14b)	644(3)	424(2)	339(3)
H(15)	464(3)	471(2)	261(4)
H(16)	393(3)	456(2)	548(4)
H(17)	240(4)	447(2)	305(5)
H(18a)	119(4)	527(2)	410(5)
H(18b)	251(5)	571(3)	368(6)
H(18c)	219(6)	538(3)	576(7)
H(19a)	208(4)	413(2)	620(5)
H(19b)	208(3)	367(3)	490(4)
H(19c)	083(5)	430(3)	473(6)
H(20a)	650(5)	808(3)	642(6)
H(20b)	604(5)	774(3)	808(7)
H(20c)	707(5)	746(2)	690(5)
H(21a)	520(3)	723(2)	062(3)
H(21b)	606(3)	645(2)	092(4)

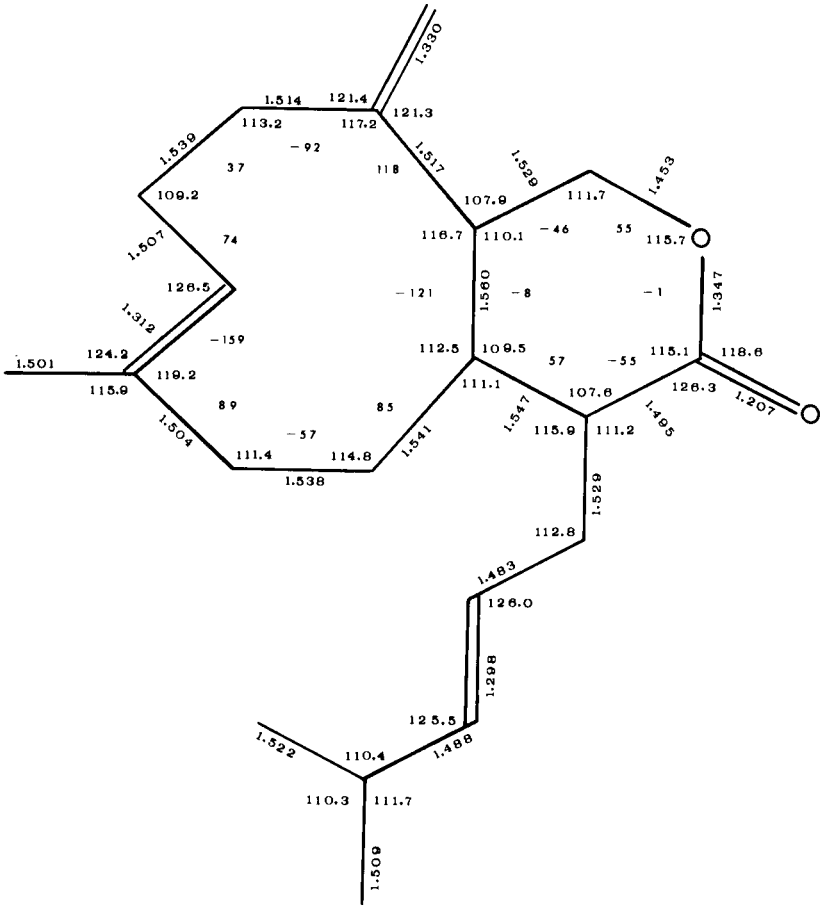


Fig. 2. Diagram of bond lengths, bond angles, and torsion angles.

graphy, Vol. IV[18] while those for hydrogen atoms were taken from Stewart *et al.*[19]

Tables 3 and 4 give the final atomic and thermal parameters. Figure 1 is an ORTEP drawing [20] of **1** with anisotropic thermal parameters drawn at the 35% probability level. The bond lengths 0.002 – .005 with an average of .003 Å, bond angles 0.1 – 0.3 with an average of 0.2°, and torsion angles 0.2–0.4 with an average of 0.3° are shown in Fig. 2.

The bond parameters lie within the expected ranges. The conformation of the nine-membered ring is similar to that found in xenicin by Vanderah *et al.*[4] The six-membered ring exhibits a boat conformation. The torsion angles associated with the ring jucture, 10-9-1-13 = – 8° and 8-9-1-2 = – 121°, may be compared with the –31° and –134° found in xenicin. Although the –8° value might normally be associated with a *cis* ring juncture, the function of the two rings is *trans*. This may be attributed to the high degree of flexibility of the cyclononene ring system.

Acknowledgments—We should like to thank Boh Bartko and Maui Divers, Inc. for procurement of the animals; Richard Grigg and Katherine Muzik for identification; and the National Science Foundation and the Robert A. Welch Foundation (P-074) for generous financial support.

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STERIC MODE OF ENZYMIC HYDROXYLATION AT PRIMARY CARBON ATOMS[a]

HYDROXYLATION OF (1*R*)- AND (1*S*)-[1-^{3}H, ^{2}H, ^{1}H][1-^{14}C]-OCTANES BY *PSEUDOMONAS OLEOVORANS*†

ELIAHU CASPI*, STUART SHAPIRO and JAMES U. PIPER‡
The Worcester Foundation for Experimental Biology, Shrewsbury, MA 01545, U.S.A.

(*Received in the U.S.A.* 3 *November* 1980)

Abstract—(1*R*)- and (1*S*) [1-^{3}H, ^{2}H, ^{1}H]-octanes and mixed with [1-^{14}C]-octane, were synthesized. The mixed samples were incubated with homogenats of *P. oleovorans* strain TF4-1L and the biosynthesized mixtures of octanols isolated. It was shown that mainly the achiral termini [-C^{1}H$_3$] were hydroxylated and that chiral methyls were oxygenated to the extent of 20–30%. In all instances the products derived from hydroxylation at the chiral methyls [-C-^{3}H, ^{2}H, ^{1}H] were mixtures of (1*R*)- and (1*S*)-octanols, the major component of which was the alcohol obtained by displacement of ^{1}H. The results indicate that hydroxylation proceeded with a normal isotope effect $k_H > k_D > k_T$. The amount of (1*R*)-octanol in the mixtures of octanols derived from (1*R*)- and (1*S*)-octane was determined. It was found that the C-1 hydroxylation of octane proceeded with *retention*, i.e. the incoming hydroxyl assumed the orientation of the displaced hydrogen (or isotopic hydrogen) atom.

The pioneering concepts of Ogston[1] have greatly advanced out understanding of enzyme catalyzed reactions of *pro*-chiral molecules. For the current discussion we will assume that for a reaction to occur, a three-point attachment of substrate to the enzyme surface is required (Fig. 1). The particular group or *atom* of the substrate to undergo reaction must be bound at the *catalytic site* of the enzyme while two other groups are attached at their respective *binding sites*. The active site region of an enzyme constitutes a dissymmetric environment. Differences in the *size* and *shape* of substrate binding sites provide for the observed discrimination between enantiotopic groups of *pro*-chiral substrates. When binding a *pro*-chiral substrate [C–$R_1R_2X_aX_b$][$R_1 \neq R_2$; $X_a = X_b$] an enzyme sterically distinguishes between R_1 and R_2 through its ability to accommodate them in the available binding sites. This imposes a particular steric orientation on the enzyme-substrate complex in which only one of the enantiotopic groups (in this case, X_a) is bound at the catalytic site (Fig. 1). Additionally, the reaction at the *catalytic site* may also be sterically controlled. The events at a pro-chiral center can be illustrated by the transformation of citrate to isocitrate by *cis*-aconitase which involves the *pro-R* hydrogen atom of the *pro-R* carboxymethyl branch of citrate.[2]

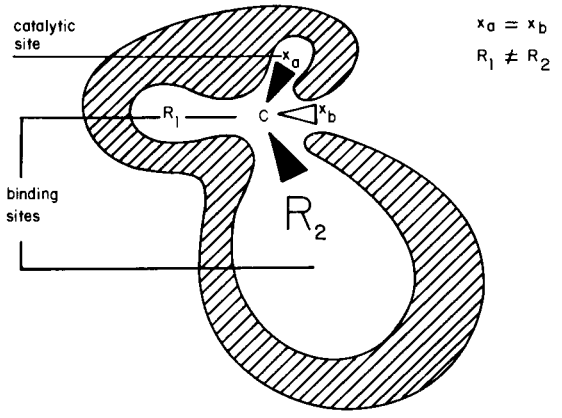


Fig. 1.

The above rationalization is not *sensu stricto* applicable to enzymic reactions at primary carbons of the type shown in Fig. 2 (H=D=T). A molecule possessing a freely-rotating methyl group has a statistically equal probability of binding to the enzyme with any of three hydrogen atoms in the catalytic site of the enzyme.

Because the steric differences between the isotopic hydrogen atoms of a chiral methyl group (Fig. 2) (D=^{2}H; T=^{3}H) are small, they will also have a statistically equal probability of binding at the catalytic site of the enzyme. Determination of the steric course of the enzymic reaction will be possible, however, if the transformation of the chiral methyl group involves a substantial kinetic isotope effect.

Our approach to the study of th esteric course of hydroxylation at primary carbon atoms was based

†An account of this work was reported at the 12th IUPAC Symposium on the Chemistry of Natural Products, 21–27 September, 1980, Tenerife, Spain and in a preliminary communication (*Chem. Comm.*, 76 (1981)). This work is abstracted from the Ph.D. Thesis of Stuart Shapiro, submitted to the joint (Clark University, University of Massachusetts Medical School, Worcester Poly-Technic Institute) Doctoral Program in Biomedical Sciences.

‡On sabbatical leave from the Department of Chemistry, Simmons College, Boston, Massachusetts.

[a]Dedicated to the memory of Robert Burns Woodward this paper will be included in the book version of the special Woodword Memorial Supplement.

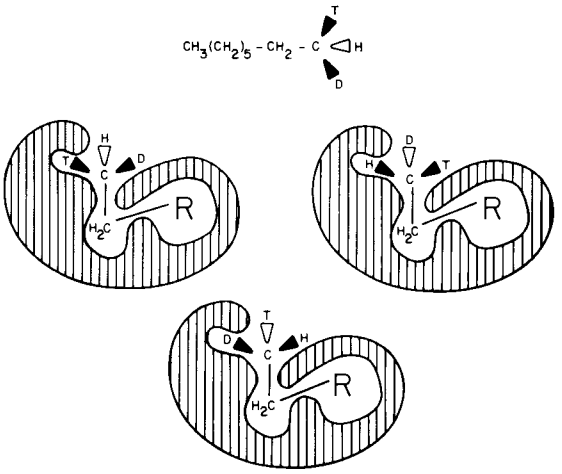


Fig. 2.

on the presumed operation of a normal kinetic hydrogen isotope effect $k_H > k_D > k_T$. We anticipated that enzymic hydroxylation at a chiral methyl group would proceed with such an isotope effect to yield alcohols of the type R–C–^{3}H, ^{2}H(OH) > R–C–^{3}H, ^{1}H(OH) > R–C–^{2}H, ^{1}H(OH). If the chirality of the methyl moiety of the substrate is known, then by determining the chirality of the predominant (tritated) alcohol, the steric course of the hydroxylation reaction could be deduced.

Since octane has been demonstrated to be efficiently metabolized to n-octanol by *Pseudomonas oleovorans* we selected (1*R*)- and (1*S*)-octanes as model substrates for the study of the stereochemistry of enzymic hydroxylation at a primary carbon atom.

Enzymic hydroxylation may proceed either with *retention*, *inverse*, or *racemization*. The terms "retention" and "inversion" are meant to indicate that the incoming hydroxyl assumes the same or the opposite orientation to the displaced hydrogen (or isotopic hydrogen) atom, respectively. The outcome of the hydroxylation of the (1*R*)- and (1*S*)-methyls of octane with retention and inversion, based on the operation of a normal kinetic hydrogen isotope effect, is summarized in Scheme 1. As the isotope effect involved in C–^{3}H bond breakage is usually large, little R–C–^{2}H, ^{1}H(OH) will be formed and can be disregarded. Besides, our analysis of the products of the reaction is based on the determination of the amount of (1*R*)[1–^{3}H]-alcohol present in the mixture (see below), and this precludes the detection of any species not tritiated at C–1.

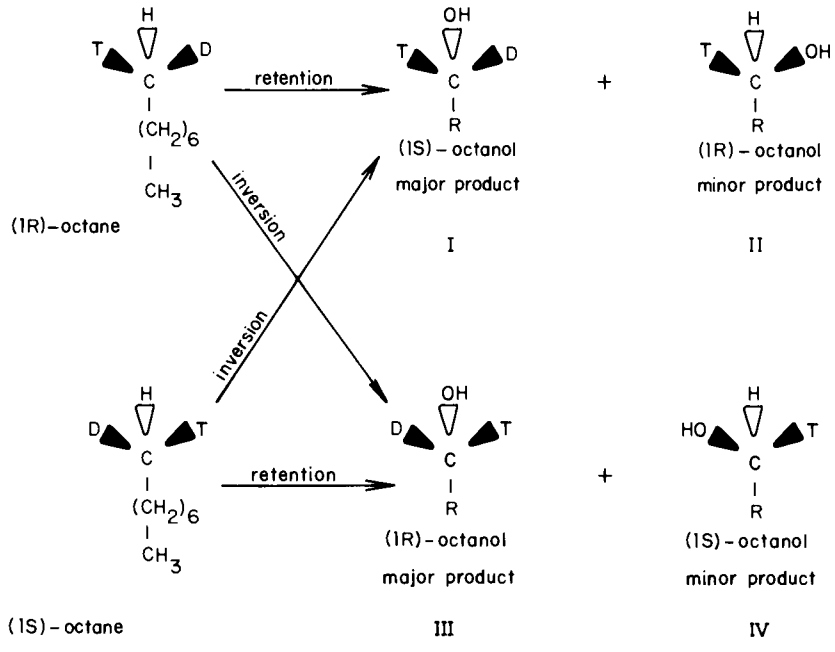
If hydroxylation proceeds with *retention* and $k_H > k_D$, then the major product derived from (1*R*)-octane will be (1*S*)-octanol (**I**), with a lesser amount of (1*R*)-octanol (**II**). Were the reaction to proceed with *inversion*, however, the major product would be (1*R*)-octanol (**III**) and the minor product (1*S*)-octanol (**IV**) (Scheme 1).

By the same reasoning, hydroxylation of (1*S*)-octane with *retention* would yield (1*R*)-octanol (**III**) as the major product and (1*S*)-octanol (**IV**) as the minor product, while for *inversion* the major and minor products would be (1*S*)-octanol (**I**) and (1*R*)-octanol (**II**), respectively.

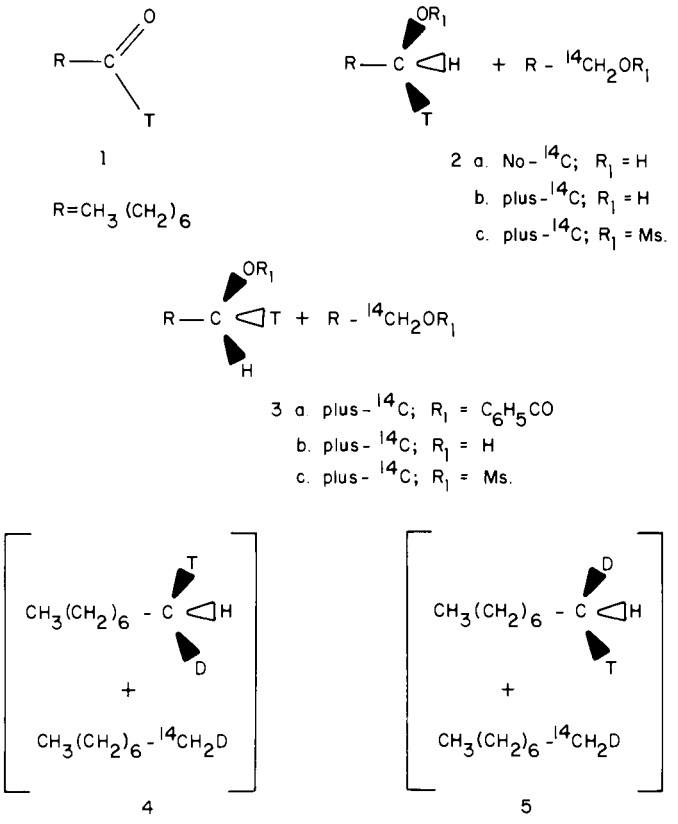
Should hydroxylation proceed with racemization, or stereospecifically in the absence of an isotope effect, then equal amounts of (1*R*)- and (1*S*)-octanols would be formed, *regardless of the chirality of the substrate octane.*

A solution to the problem of the stereochemistry of octane hydroxylation required: (i) (1*R*)- and (1*S*)-octanes; (ii) a method for enzymic production of 1-octanols from chiral octanes; (iii) a procedure for analyzing the chiral composition of octanols derived from oxygenation at the *chiral* methyls.

We first addressed the problem of synthesis of (1*R*)- and (1*S*)-octanes. Our approach was to syn-



Scheme 1.



Flow Sheet 1.

thesize (1*S*)- and (1*R*) [1–^{3}H, ^{1}H]-octanols,[3] convert them to the corresponding mesyl esters, and finally hydrogenolyze the (1*S*)- and (1*R*)-mesyl esters with lithium triethylborodeuteride ($LiBEt_3D$) to (1*R*)- and (1*S*) [1–^{3}H, ^{2}H, ^{1}H]-octanes, respectively. The methodology for the syntheses of the key intermediates, (1*S*)- and (1*R*)-octanols, was developed with deuterated compounds and was reported in an earlier paper.[3] For the current study two modifications were introduced.

To avoid the troublesome hydrolysis of a [1–^{3}H]-octanal thioacetal,[3] the aldehyde (**1**) (Flow Sheet 1) was prepared by oxidation of (1*RS*) (1-^{3}H]-octanol. The second modification involved the use of sodium dithionite to recycle NAD to NADH in the horse liver alcohol dehydrogenase (HLAD) reduction[4] of [1–^{3}H]-octanal (**1**). The aldehyde was reduced in batches of *ca.* 1 g to give (1*S*) [1–^{3}H]-octanol containing no more than 10% of [1–^{3}H]-octanal.

The alcohol was freed of aldehyde (**1**) by column chromatography to yield (1*S*) [1–^{3}H]-octanol (**2a**) (*ca.* 50% yield from (1*RS*)-octanol). To the homogeneous (1*S*)-octanol (**2a**), [1–^{14}C]-octanol was added and the [^{3}H: ^{14}C]-ratio of the mixed sample (**2b**) was determined (as the 3,5-dinitrobenzoate ester). Jones' oxidation of (1*S*) [1–^{3}H][1–^{14}C]-alcohol to octanoic acid proceeded with the loss of more than 99% of tritium, indicating that octanol, and hence the derived octanes, contain less than 1% of tritium at sites other than C–1.

Treatment of (1*S*) [1–^{3}H][1–^{14}C]-octanol (**2b**) with a mixture of diethyl azodicarboxylate, benzoic acid and triphenylphosphine in THF gave (1*R*) [1–^{3}H][1–^{14}C]-octyl benzoate[3] (**3a**) (90% yield). The (1*R*)-ester (**3a**) was reduced with $LiAlH_4$ to give, after column chromatography, (1*R*)-octanol (**3b**) (50% yield from **2b**).

The enantiomeric purity of the (1*R*) [1–^{3}H][1–^{14}C]-octanol (**3b**) was assayed by oxidation with HLAD–NAD to octanal. Oxidation to octanal proceeded with the loss of 95–96% of tritium, indicating that the alcohol (**3b**) contained at least 95–96% of (1*R*) [1–^{3}H]-octanol. By implication, the parent (1*S*) [1–^{3}H][1–^{14}C]-octanol (**2b**) must have contained at least 95–96% of the (1*S*)-alcohol. These results are in full accord with the results of our model studies with (1*R*)- and (1*S*) [1–^{2}H]-octanols, the chiral purities of which were also determined by (^{1}H)-NMR.[3]

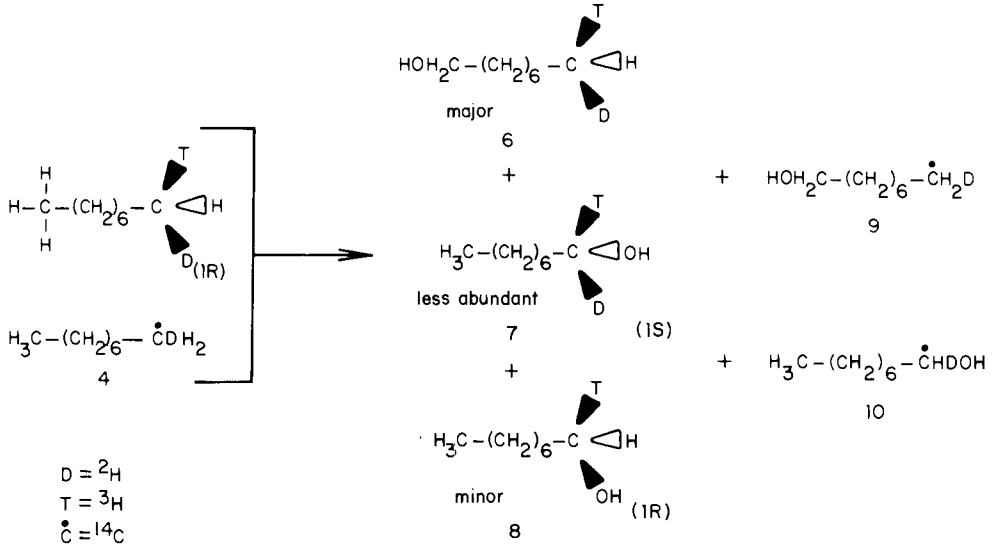
At this point we noticed that the alcohol dehydrogenase-NAD oxidation procedure could not be used for the determination of the enantiomeric purity of (1*S*) [1–^{3}H][1–^{14}C]-octanol (**2b**). We observed that, irrespective of whether horse liver, yeast, or *P. oleovorans* alcohol dehydrogenase was used, the [^{3}H: ^{14}C]-ratios of the resulting aldehydes were higher (up to 40%) than the [^{3}H: ^{14}C]-ratio of the (1*S*) [1–^{3}H][1–^{14}C]-octanol (**2b**) substrate. It is likely that the observed increase in [^{3}H: ^{14}C]-ratio is caused by further oxidation of the obtained octanals to octanoic acid.[5] Possibly the produced [1–^{3}H]-octanal (R–$\underline{C^3H}$O) is oxidized to octanoic acid at a considerably *slower rate* than [1–^{14}C]-octanal (R–$^{14}\underline{C^1H}$O); hence, at any point in time (ranging from 7 min to 24 h), the

mixture is depleted of [^{14}C]-aldehyde, and the isolated octanal shows a higher [^{3}H: ^{14}C]-ratio than the starting alcohol (**2b**).

The samples of (1*S*) [1-^{3}H][1-^{14}C]-octanol (**2b**) and (1*R*) [1-^{3}H][1-^{14}C]-octanol (**3b**) were converted to the corresponding mesyl esters [(**2c**) and (**3c**)], treatment of which with $LiBEt_3D$ in diglyme gave (1*R*) [1-^{3}H, ^{2}H, ^{1}H][1-^{14}C]-octane (**4**) and (1*S*) [1-^{3}H, ^{2}H, ^{1}H][1-^{14}C]-octane (**5**), respectively.[6]

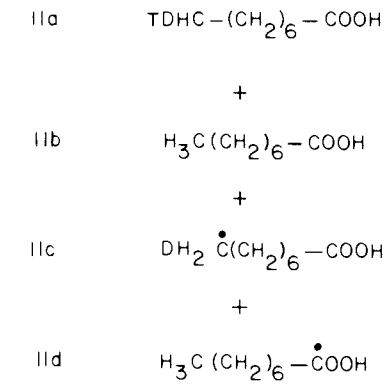
Having secured the required chiral substrates, we focused our attention on enzymic hydroxylation. Let us consider the composition of the radioactive alcohols obtained if the enzymic hydroxylation of (1*R*)[1-^{3}H, ^{2}H, ^{1}H][1 - ^{14}C]-octane (**4**) proceeds with retention (Flow Sheet 2). If $k_H > k_D > k_T$, then the major product will be (**6**) resulting from oxygenation at the achiral methyl terminus (-C^{1}H$_3$). The main product of attack at the *chiral* methyl will be alcohol (**7**) arising from displacement of the C-1 hydrogen atom. In addition, a smaller amount of alcohol (**8**), obtained by displacement of a deuterium atom, will be formed. The [^{14}C]-octanols (**9**) and (**10**) are internal standards against which the loss of tritium is measured. As explained above, we will disregard the small amount of product obtained by C-^{3}H bond breakage.

The stereochemistry of the hydroxylation can only be related to tritiated products of hydroxylation at the chiral methyl, namely octanols (**7**) and (**8**). For determination of the extent of oxygenation at the chiral terminus, the mixture of biosynthesized alcohols (**6–10**) was oxidized with Jones' reagent to give a mixture of acids (**11a–d**). Since only C-1 chiral octanols (**7**) and (**8**) lost tritium in this oxidation, differences between the [^{3}H: ^{14}C]-ratio of the mixture of alcohols (**6–10**) and the mixture of acids (**11a–d**) gave the extent of oxidation at the chiral terminus of octane. This also defined the maximal amount of C-1 tritium potentially available for enzymic exchange in the chirality determination.



Flow Sheet 2.

As indicated above, alcohol dehydrogenase-NAD could not be used for assaying the chirality of a mixture of biosynthesized octanols. We therefore examined the equilibration procedure of primary alcohols catalyzed by HLAD-NAD and porcine heart diaphorase.[7] This method is based on the premise of exclusive exchange of the 1-*pro*-R hydrogen atom of alcohol with water.[8] In our hands, both (1*R*)- and (1*S*)-tritium atoms of [1-^{3}H]-octanols were exchanged, although the (1*S*)-tritium atom was exchanged at a considerably slower rate. Under the experimental conditions employed by us, (1*R*) [1-^{3}H, ^{1}H][1-^{14}C]-octanol lost essentially all its tritium in 12 h. To assure the *complete* exchange of the (1*R*) tritium the reaction was allowed to proceed for 24 h, during which time (1*S*) [1-^{3}H, ^{1}H][1-^{14}C]-octanol (**2b**) lost 30–40% of its tritium and (1*RS*) [1-^{3}H, ^{1}H][1-^{14}C]-octanol lost 65–70% of tritium. Since (1*RS*)-octanol contains only 50% of (1*S*) [1-^{3}H, ^{1}H]-octanol, it follows that 30–40% of the tritium of the (1*S*)-enantiomer was lost after 24 h. In parallel control experiments with octanols derived from (1*R*)- and (1*S*)-octanes and synthetic (1*RS*)-octanol, the loss of C-1 tritium was reproducible within a narrow range (Table 1). Hence, by sub-



Flow Sheet 3.

Table 1. Determination of [^{3}H: ^{14}C] ratios of octanols of different origin following incubation with HLAD, NAD, NADH and diaphorase for 24 hr (see text)

	SOURCE OF OCTANOL		
	HYDROXYLATION OF OCTANE		SYNTHETIC
SAMPLE	(1R)	(1S)	(1RS)
	^{3}H:^{14}C	^{3}H:^{14}C	^{3}H:^{14}C
1	7.33	6.65	1.84
2	7.51	6.55	2.09
3	7.47	6.49	2.01
Av.	7.44	6.56	1.98

tracting the amount of tritium lost from (1*S*)-octanol from the total amount of tritium lost during equilibration, the fraction of (1*R*)-octanol in the biosynthetic mixture can be computed.

We indicated above that the exchange procedure was purposely allowed to proceed for 24 h to *assure the complete* exchange of the tritium of (1*R*)-octanol. Since tritium has the *largest* kinetic hydrogen isotope effect, then by allowing the exchange of tritium from (1*R*)-octanol to proceed to completion secondary isotope effects of C-1 deuterium atoms are overridden. To test this hypothesis, we equilibrated in parallel under identical conditions (1*RS*) [1–^{3}H, ^{1}H][1–^{14}C]-octanol and (1*RS*) [1–^{3}H, ^{2}H][1–^{14}C]-octanol (99% 1–^{2}H$_1$). In both instances, identical amounts of tritium (64% and 65%, respectively) were lost in 24 h. This validates the outlined method of determining the amount of (1*R*)-octanols in the biosynthesized mixtures containing R–C–^{3}H, ^{2}H(OH) and R–C–^{3}H, ^{1}H(OH)-octanols of opposite configuration. It should be stressed, however, that conclusions on the course of the reaction could only be drawn from parallel hydroxylation experiments of (1*R*)- and (1*S*)-octanes. To be valid, the results of the two sets of experiments must be complementary.

For determination of the chirality of products of enzymic hydroxylation, the mixture of the octanols obtained from (1*R*) [1–^{3}H, ^{2}H, ^{1}H][1–^{14}C]-octane (**4**) and (1*S*) [1–^{3}H, ^{2}H, ^{1}H][1–^{14}C]-octane (**5**), and (1*RS*) [1–^{3}H] [1–^{14}C]-octanol were equilibrated in parallel under identical conditions. The equilibrated alcohols were recovered and converted to 3,5-dinitrobenzoate esters, which were extensively purified by tlc and multiple crystallizations for the [^{3}H: ^{14}C]-ratio determinations. The correction for the fraction of tritium lost from biosynthetic (1*S*)-alcohols was calculated on the basis of tritium lost from (1*RS*) [1-^{3}H, ^{1}H][1–^{14}C]-octanol. The results are summarized in Table 2.

Oxidation of the biosynthesized octanols derived from (1*R*)- (**4**) and (1*S*)-octane (**5**) with Jones' reagent gave octanoic acids and involved the loss of 20–30% of the tritium (Column 2, Table 2). This revealed that oxygenation of the octanes occurred mainly at the achiral methyl (–C^{1}H$_3$) to give, e.g. (**6**). The results are in accord with the anticipated operation of a normal kinetic hydrogen isotope effect.

The average deviation in the [^{3}H: ^{14}C] ratios from successive crystallization of the octanol and octanoic acid derivatives [see Table 4, Experimental] is ±0.05. The resulting *relative* error[9] in the calculated percent of (1*R*)-octanol (Column 4, Table 2) is ±7%.

Equilibration of the mixture of octanols derived from (1*R*)-octane (**4**) proceeded with the net (corrected) loss of 37%±3% and 38%±3% of the tritium available at C-1 (Table 2). This establishes that the main product of oxygenation of the (1*R*)-methyl of octane (**4**) is (1*S*)-octanol (**7**) and the minor product is (1*R*)-octanol (**8**). These results are in full agreement with the hypothesis that the reaction proceeds with retention and $k_H > k_D$.

The equilibration of products of oxygenation of (1*S*)-octane (**5**) occurred with the net (corrected) loss of 74%±5% and 82%±6% of the tritium available at C-1. It follows that the main product of oxygenation at the (1*S*)-methyl of octane (**5**) is (1*R*)-octanol (Scheme 1; III), with (1*S*)-octanol (Scheme 1; IV) the minor product. Again, the results are in agreement with the view that hydroxylation proceeds with retention and $k_H > k_D$.

The above results show that attack by hydroxy-

Table 2. Hydroxylation of (1*R*) and (1*S*) [1–^{3}H, ^{2}H, ^{1}H][1–^{14}C]-octanes by homogenates of *Pseudomonas oleovorans* strain TF4-1L

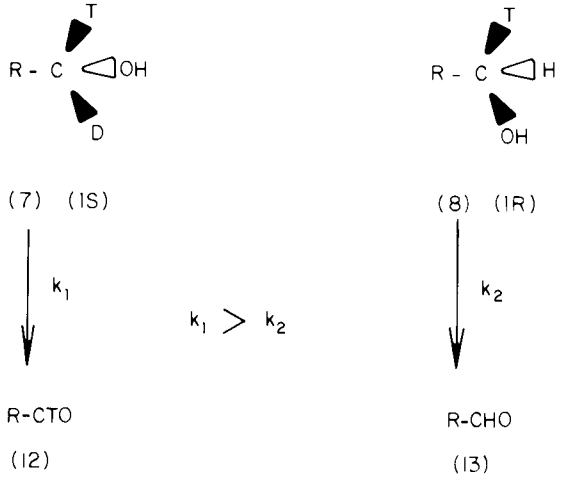
EXPERIMENT	CHIRALITY OF OCTANE	% OF –^{3}H AT C-1 OF OCTANOLS	% of (1R)-OCTANOL*	C-1 CHIRALITY OF THE MAJOR OCTANOL	STEREOCHEMISTRY OF HYDROXYLATION
1	1R	26	38 ± 3	1S	Retention
	1S	22	82 ± 6	1R	Retention
2	1R	29	37 ± 3	1S	Retention
	1S	29	74 ± 5	1R	Retention

* The (±) limits indicate the estimated error calculated on the basis of the variations of [^{3}H: ^{14}C]-ratios during several crystallizations of the derivatives listed in Table 4.

lase proceeded predominantly at the achiral methyls of (**4**) and (**5**). The oxygenation of an (*R*)- or (*S*)-methyl invariably produced (complementary) chiral mixtures of C-1 alcohols, the major component of which was obtained by *removal of* ^{1}H. These results are consistent with the operation of a kinetic isotope effect $k_H > k_D > k_T$ and, indicate that the hydroxylation proceeds with retention.

We considered the possibility that the endogenous alcohol dehydrogenase in the *P. oleovorans* cell-free extract could selectively utilize one of the biosynthesized octanol isomers. This might distort the isomeric composition of the recovered octanols and so lead to erroneous conclusions. Although we expected the dehydrogenase to utilize primarily the large amount of C-1 protiated alcohols derived from the oxidation of [1–^{14}C]-octane and from the archiral methyl of chiral octane, a selective attack on the C-1 chiral alcohols could still not be excluded *a priori*.

To clarify this point we will again consider the pool of products (**6–10**) obtained by oxygenation of (1*R*) [1–^{3}H, ^{2}H, ^{1}H][1–^{14}C]-octane. Octanols (**6**), (**9**), and (**10**) can be disregarded since their oxidation by the dehydrogenase has no bearing on the overall C-1 chirality of the pool of octanols. The oxidation of (1*S*) [1–^{3}H, ^{2}H][1–^{14}C]-octanol (**7**) by *P. oleovarans* alcohol dehydrogenase to octanal (**12**) will involve abstraction of the (1*R*)-deuterium atom while oxidation of the (1*R*) [1–^{3}H, ^{1}H][1–^{14}C]-octanol (**8**) to (**13**) will proceed with the loss of a tritium atom (Scheme 2). It is likely, therefore, that the rate of oxidation (k_1) of (**7**) will be greater than the rate of oxidation (k_2) of (**8**) ($k_1 > k_2$). It follows that at any point in time a faster depletion of the (1*S*)-octanol (**7**) could occur. However, our results distinctly and unambiguously show that the (1*S*)-octanol (**7**) is the main product of oxidation of (1*R*)-octane and that (1*R*)-octanol (**8**) is the minor product. This is in full agreement with the view that the oxygenation of (1*R*)-octane proceeds with retention. It also proves that (1*S*)-octanol was not removed from the pool of biosynthesized octanol in sufficient amounts to obscure the results. The same rationalization is equally applicable to the pool of octanols obtained from (1*S*)-octane.



Scheme 2.

EXPERIMENTAL

Materials. Hores liver alcohol dehydrogenase (EC 1.1.1.1, lot #128C-8050, 1.9 U/mg protein), ovalbumin (grade V), NAD (grade III), NADH (grade III), and DL-α-lipoamide were purchased from Sigma Chemical Co. (St. Louis, MO). Porcine heart diaphorase (EC 1.6.4.3, grade I, control No. 1319322/Sep. 1980) was obtained from Boehringer Mannheim GmbH (Mannheim, West Germany). ^3H_2O (5 Ci/mL) and $Ba^{14}CO_3$ (25 mCi, 55 mCi/mmol) were obtained from International Chemical and Nuclear Corp. (ICN) (Irvine, CA). Lithium triethylborodeuteride (Suber Deuteride, 1M solution in THF) was purchased from Aldrich Chemical Co. (Milwaukee, WI). Silica gel 60 HF 254 + 366 and silica gel 60 (70–230 mesh) (both purchased from E. Merck A. G., Darmstadt, West Germany), were used for thin-layer chromatography and column chromatography, respectively.

Liquid scintillation counting was performed in a Mark II Liquid Scintillation System (Nuclear-Chicago, Des Plaines, IL), using 15 mL of Liquifluor (New England Nuclear, Boston, MA). Thin-layer radiochromatograms were scanned with an Actigraph III (Nuclear-Chicago) or Packard model 7200 radiochromatograph. Analytical gc was performed using a model 3700 gas chromatograph (Varian Associates, Inc., Walnut Creek, CA) fitted with a Varian stainless steel 3% OV-17 Chrom W-HP column (80–100 mesh, 2 m length × 2 mm width).

(1RS) [1–^{3}*H*]-*Octanol.* To $LiBH_4$ (13.4 mmol) in 27.9 mL THF was slowly added 200 μL of ^3H_2O (11.1 mmol, 1 Ci in 5 mL of THF) and the solution was refluxed for 1 h. To the cooled mixture octanal (4.4 g, 34.3 mmol) in 10 mL of diethyl ether was added dropwise. The reaction mixture was stirred for 30 min at room temperature and concentrated *in vacuo*. 1N HCl (13.4 mL) was added to dissolve the inorganic residue and the mixture was briefly warmed. The mixture was neutralized with 1N NaOH (13.4 mL) and extracted with pentane (3 × 30 mL). The pentane was dried (Na_2SO_4) and concentrated *in vacuo* to a colorless liquid; yield of (1*RS*) [1–^{3}H]-octanol (4.04 g; 238 mCi of ^{3}H).

[1–^{3}*H*]-*Octanal* (**1**). To a suspension of 8 g (21 mmole) of pyridinium dichromate[11] in 50 mL of dry CH_2Cl_2 was added 2.3 mL (15 mmole, 79 mCi) of (1*RS*) [1–^{3}H]-octanol. The mixture was stirred at room temp. until gc of an aliquot showed the absence of alcohol (12 h), then dry ether was added (100 mL). The mixture was filtered and the brownish filtrate stored overnight at −20°C. The solution was concentrated under reduced pressure to a small volume and filtered through a column of silica gel (8 g) which was then rinsed sequentially with pentane (50 mL) and ether (50 mL). The combined eluate was concentrated *in vacuo* (below room temp.) to give the aldehyde (**1**) as a colorless oil.

(1S) [1–^{3}*H*]-*Octanol* (**2a**). A solution of HLAD (40 mg) and NAD (160 mg) in 0.2 M potassium phosphate (pH 6.6; 750 mL) was rapidly stirred and flushed with N_2 (30 min.) in a round bottom flask (2L). A solution of sodium dithionite (15 g) in water (125 mL) in a pressure equalization funnel was flushed with N_2 (15 min). The sodium dithionite solution was added dropwise to the enzyme solution while flushing with N_2 continued. Initially the mixture developed a greenish-yellow tinge, which disappeared after a few minutes. The flow of N_2 was discontinued and about half of the synthesized aldehyde was injected into the sealed reactor, followed by injection of the ether washing (0.5 mL) of the syringe. After stirring the mixture at ambient temperature (8 h), a second portion of sodium dithionite (15 g in 100 mL H_2O; flushed with N_2) was added dropwise. The reaction was terminated after *ca.* 27 h, NaCl (100 g) was added and the product recovered with CH_2Cl_2 (5 × 75 mL). The combined CH_2Cl_2 extract was dried (Na_2SO_4) and con-

centrated (*ca.* 10 mL). GC indicated less than 10% aldehyde (**1**) remaining. Two incubation experiments were carried out and the extracts combined. The combined extract was fractionated on a silica gel column (100 g) prepared with pentane. The aldehyde (**1**) was eluted with pentane–ether (99:1) and (1*S*) [1–^{3}H]-octanoll (**2a**) (40 mCi) was eluted with pentane-ether (9:1).

[1–^{14}C]-Octanol was added to (1*S*) [1–^{3}H]-octanol (**2a**) (*ca.* 35 mCi of ^{3}H) and an aliquot of the resulting (1*S*) [1–^{3}H][1–^{14}C]-octanol (**2b**) was converted to octyl-3,5-dinitrobenzoate. The ester showed a [^{3}H: ^{14}C]-ratio of 9.27. The stock (**2b**) was used in subsequent experiments.

(1R) [1–^{3}*H*][1-^{14}*C*]-*Octanol* (**3b**). A mixture of (1*S*) [1–^{3}H][1–^{14}C]-octanol (**2b**) (20 mCi of ^{3}H; *ca.* 2.7 mmole), benzoic acid (500 mg; 4.2 mmole), and diethyl azodicarboxylate (990 μL; 5.2 mmole) in dry THF (5 mL) was stirred, cooled in an ice bath and flushed with N_2. To the cooled mixture, a solution of triphenyl-phosphine (1.64 g; 6.3 mmole) in THF (5 mL) was added dropwise and the reaction stirred at ambient temperature (16 h) in an atmosphere of N_2. Most of the volatile components were removed under reduced pressure and the resulting semisolid residue was leached with pentane (6 × 5 mL). The combined pentane extract was filtered and concentrated. The obtained product was fractionated on a column of silica gel (35 g) which was percolated with pentane (1L) until significant amounts of ^{3}H were detected in the eluate. The solvent was then changed to pentane–ether (99:1) and (1*R*) [1–^{3}H][1–^{14}C]-octyl benzoate (**3a**) (18 mCi of ^{3}H) was eluted (700 mL).

The eluates containing **3a** were concentrated (*ca.* 2 mL) and added to a solution of $LiAlH_4$ (111 mg; 2.9 mmole) in ether (6 mL). The mixture was refluxed (3 h) then more $LiAlH_4$ (40 mg) was added and refluxing continued (1.5 h). The reaction was terminated with water, acidified (6N HCl) and the products recovered with ether (3 × 3 mL). The extract was processed in the conventional manner and concentrated (*ca.* 8 mL). The obtained solution was applied to a column of silica gel (125 g) prepared with pentane. The column was eluted sequentially with pentane–ether (99:1) (5.5 L); pentane–ether (97.5:2.5) (8 L) and pentane–ether (97:3) (2 L) at which time the octanol appeared in the eluate. The octanol was then eluted with the same solvent mixture (4 L) after which benzyl alcohol began to co-elute with the octanol. The eluates containing the (1*R*) [1–^{3}H][1–^{14}C]-octanol (**3b**) were combined and concentrated (*ca.* 5 mL, 11 mCi of ^{3}H).

An aliquot of (**3b**) was converted to octyl 3,5-dinitrobenzoate, which showed a [^{3}H: ^{14}C]-ratio of 8.81.

(1R)-(**4**) *and* (1S)-**5**-[1–^{3}*H*, ^{2}*H*, ^{1}*H*][1–^{14}*C*]-*Octanes*. A 1 M solution of lithium triethylborodeuteride in THF (10 mL) was concentrated under reduced pressure and dry diglyme (9 mL) added under argon. A mixture of the appropriate chiral octanol [(**2a**) or (**3a**)] [*ca.* 1.1 mmole; 7–8 mCi of ^{3}H], triethylamine (450 μL; 3.2 mmole) in dry CH_2Cl_2 (5 mL) was cooled (ice-acetone) under N_2, and a solution of methanesulfonyl chloride (225 μL; 2.9 mmole) in CH_2Cl_2 (1 mL) was added dropwise (10 min.). The reaction was stirred at −20° for 15 min, by which time all the alcohol was consumed, as evidenced by tlc (silica gel; CH_2Cl_2). The plate was scanned for radioactivity and no radioactivity was detected in the octanol zone (R_f 0.15) (R_f of octyl mesylate 0.54).

The mixture was diluted with ether (10 mL), washed with ice cold H_2O (5 mL); 1N HCl; 5% aq. $NaHCO_3$ (2 × 5 mL); brine (5 mL), then dried and concentrated (*ca*). 1 mL).

Ether (5 mL) was added to the mesylate solution [(**2c**) or (**3c**)], followed by lithium triethylborodeuteride in diglyme (8 mL). The mixture was stirred at room temperature (1 h), at which time a trace of mesylate was still detectable (tlc). More lithium triethylborodeuteride in diglyme (1 mL) was added and stirring was continued (30 min) until the mesylate was completely reduced (tlc).

The mixture was cooled in ice and 2.5 N NaOH (4 mL) was added slowly (exothermic reaction), followed by 30% H_2O_2 (3.7 mL) (very exothermic). Ether (5 mL) was added and the mixture distilled through a Vigreux column (15 cm). The ether and residual CH_2Cl_2 were distilled at 35°, then the temperature of the bath was increased and 10 mL of distillate was collected at 75°–100°C. The distillate was saturated with NaCl, transferred to a 25 mL volumetric flask and saturated NaCl added to bring the upper (organic) layer (*ca.* 1 mL) into the neck of the flask. The organic layer was withdrawn and transferred to a 5 mL volumetric flask containing ice cold concentrated H_2SO_4 (2.5 mL). Additional cold concentrated H_2SO_4 was added to bring the octane into the neck of the flask. The sulfuric acid procedure was repeated several times and the obtained octane (95–100 mg; 7.3 mCi per mmole of ^{3}H) was stored in a vial over a few crystals of K_2CO_3.

Determination of the [1–^{3}*H*]-*Octanol Content in* (**2b**). Octanol (250 mg) was added to a solution of (1*S*) [1–^{3}H][1–^{14}C]-octanol (**2b**) (10 μCi of ^{3}H) in acetone (1 mL). The mixture was cooled in an ice bath and *ca.* 1 mL of Jones' reagent was added dropwise. After 3 min. the reaction was brought to room temperature and excess reagent decomposed with 2-propanol. The semisolid residue was extracted with pentane (4 × 3 mL) and the combined pentane extract washed with saturated NaCl (1 × 5 mL) and 1 N NaOH (3 × 3 mL). The combined NaOH solution was washed with 5 mL of pentane, acidified with 6 N HCl and extracted with pentane (3 × 3 mL). The pentane extracts were dried and concentrated to a residue (150 mg).

A solution of the residue in CH_2Cl_2 (1 mL) was added to a solution of DCC (250 mg) and *p*-toluidine (120 mg) in CH_2Cl_2 (2 mL). The mixture was stored overnight and filtered. The filtrate was concentrated and the obtained residue (oil) was crystallized from hexane to constant specific activity. The *p*-toluidide showed a [^{3}H: ^{14}C]-ratio of 0.096 compared to 11.84 for the starting alcohol (counted as the 3,5-dinitrobenzoate). This indicates that more than 99% of ^{3}H was located at C-1 of (**2b**).

[1–^{14}*C*]-*Octanol*. The apparatus consisted of a CO_2 generator connected successively to three traps containing ether solutions of heptyl magnesium bromide, a drying tube filled with KOH pellets, and two traps containing 50% aqueous KOH. Barium carbonate (90 mg, 25 mCi) was placed in the generator. A solution of 6 mmole of heptyl magnesium bromide in ether (10 mL) was distributed among the three traps (5 mL/2.5 mL/2.5 mL), and ether added to cover the inlets of the traps. With N_2 flowing the first trap was cooled in ice–acetone and the other two in ice–water baths. The N_2 flow was reduced to a minimum and conc. H_2SO_4 (3 mL) added dropwise to the $BaCO_3$ (30 min). The generator was then heated to 130°, and finally flamed until the solid was completely dissolved. After cooling, the system was flushed with N_2 for 1.5 h.

The contents of the traps were poured into H_2O (30 mL), and the traps were rinsed with 6 N HCl and ether. The mixture was acidified, the ether separated, and the aqueous layer washed with ether (2 × 5 mL). The combined ether solution was washed with 1N NaOH (4 × 15 mL). The combined NaOH extract was washed with ether (2 × 10 mL), acidified (6 N HCl), and extracted with ether (7 × 10 mL). The combined ether extract was washed, dried ($MgSO_4$), concentrated to 5 mL, and ethereal CH_2N_2 added until a yellow color persisted. The solution was concentrated (5 mL), dried ($MgSO_4$), and diluted with ether to 10.0 mL and counted (23 mCi of ^{14}C).

The solution of the methyl octanoate was cooled in an ice bath, and $LiAlH_4$ (25 mg) added in small portions

with cooling. The mixture was refluxed overnight, quenched with H_2O, and 6 N HCl added until the solids dissolved. The product was recovered with ether and processed in the conventional manner to give an ether solution (10 mL) of [1–^{14}C]-octanol (17 mCi).

An aliquot (3.4 μCi) was added to 104 mg of octanol and converted to octyl 3,5-dinitrobenzoate. All of the ^{14}C was retained in the 3,5-dinitrobenzoate ester.

Culture of the organism

Pseudomonas oleovorans strain TF4-1L (Exxon Research and Engineering Co., Linden, NJ) was grown in 15-L batches in an atmosphere of air saturated with *n*-hexane vapor. The cultivation medium contained, per L of demineralized water, KH_2PO_4 (0.2 g), Na_2HPO_4 (0.8 g), $(NH_4)_2$ (1.5 g), yeast extract (Difco, 0.2 g), $Na_2EDTA \cdot 2\ H_2O$ (20.0 mg), $NiSO_4 \cdot 6H_2O$ (0.1 mg), $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ (0.1 mg), H_3BO_4 (0.1 mg), $AlK(SO_4)_2$ (0.1 mg), $CuSO_4 \cdot 5\ H_2O$ (0.1 mg), $ZnSO_4 \cdot 7\ H_2O$ (1.0 mg), $CoSO_4 \cdot 7H_2O$ (2.0 mg), $CaCl_2 \cdot 2H_2O$ (1.0 mg), $FeSO_4 \cdot 7H_2O$ (2.0 mg), $MnSO_4 \cdot H_2O$ (5.0 mg), and $MgSO_4 \cdot H_2O$ (30.00). Using 10% inocula, typical yields of 2 g of wet cells per L were obtained after 12–15 h from carboys maintained at 24·.

Enzymic hydroxylations

Two sets of (1*R*)- and (1*S*)-octane incubation experiments were carried out using different batches of *P. oleovorans* strain TF4-1L. Harvested cells were suspended in 50 mM potassium phosphate (pH 7.2) at a mass: volume ratio of 1:1 and homogenized (15,000 psi) in a French pressure cell. Homogenates were centrifuged at 4° (30 min) at 35,000 × g, and the supernates used for hydroxylation of chiral octanes.

An aliquot of supernate (2.5 mL), containing *ca.* 90 mg protein was added to 3 mL of 50 mM potassium phosphate containing 0.09 mmol of 4-phenylsemicarbazide-HCl (pH 6.7) and the mixture shaken for 20 min. Hydroxylation was initiated by the addition of NADH (10 μmol in 0.5 mL of 50 mM potassium phosphate, pH 7.2) and 1 μL (45 μCi of ^{3}H) of *chiral octane* in 20 μL of octanol. Reaction mixtures in tightly sealed screw-cap test tubes were vigorously shaken at 26° for 4 h.

Incubations were terminated by saturating the reaction mixtures with NaCl, and the products were recovered with CH_2Cl_2 (3 × 10 mL). The organic phase was washed with 1 N HCl (2 × 10 mL), H_2O (10 mL), brine (10 mL), and dried ($MgSO_4$). To the dried solution unlabelled octanol (200 μL) was added and the solution was concentrated by distillation through a 20-cm Vigreux column to 1–2 mL. The residue was applied to a column of silica gel (11 g) prepared with pentane and eluates (50 mL) collected. The column was washed successively with pentane (100 mL) and ether–pentane (1:9). An aliquot of each eluate was assayed by gc. Octanol, free of contaminating octane generally appeared in fractions 5 through 7 of ether–pentane (1:9). The octanol-containing fractions were pooled and distilled through a Vigreux column, then transferred to a 5 mL volumetric flask. The flask was filled to mark with pentane, and aliquots (25 μL) were counted. The results are summarized in Table 3. The [^{3}H: ^{14}C]-ratios were determined on the derived octyl-3,5-dinitrobenzoates.

Analysis of biosynthesized octanols

Exchange reactions were carried out in parallel using octanols derived enzymically from (1*R*)- and (1*S*)-octane and synthetic (1*RS*) [1–^{3}H][1–^{14}C]-octanol in 10 mL buffer (77 mM potassium phosphate + 3.4 mg $Na_2EDTA \cdot 2H_2O$, pH 8.0) containing ovalbumin (7 mg), NAD (0.62 μ mol), NADH (0.62 μ mol) HLAD (10 mg, 19 U), and porcine heart diaphorase (0.13 mL, 1.3 mg, 180 U assayed as lipoamide dehydrogenase using DL-α-lipoamide).[12,13] The vials were flushed with N_2, and reactions were initiated by injecting the relevant alcohol (20 μL) (see Table 4). Reaction mixtures were vigorously shaken in the dark at 35° for 24 h, then aliquots (1 mL) were withdrawn by syringe and injected into a suspension of NaCl (0.3 g) and octanol (2.5 μL) in ether (5 mL). The suspension was shaken at room temp. (30 min) and the aqueous and organic layers separated by centrifugation. The ether layer was dried ($MgSO_4$) and distilled through a 10-cm Vigreux column to a small volume.

The residue was diluted with dry benzene (3 mL) and 3,5-dinitrobenzoyl chloride (250 mg) added. Following dissolution of the acid chloride, pyridine (2 drops) was added, and the solution refluxed for 90 min. The product was recovered with ether (30 mL) processed in the usual way and the obtained residue was applied to a 20 cm × 20 cm silica gel plate. The plate was developed in benzene–ethyl acetate (150:1), and the band corresponding to octyl-3,5-dinitrobenzoate scraped. The alcohol derivative was eluted from the silica gel with ether, crystallized several times from ethanol and counted.

Octanoic acids from biosynthetic octanols

Biosynthetic octanol (15 μL) in acetone (0.5 mL) was stirred with Jones' reagent (200 μL) at room temperature. The reaction was terminated with 2-propanol. The product was extracted with pentane (4 × 5 mL), the pentane solution washed with brine (2 × 1 mL), and the acidic fraction extracted with 1 N NaOH (4 × 1 mL). The alkaline solution was acidified (conc. HCl) and extracted with pentane (3 × 2 mL). The pentane solution was processed in the usual manner to give an acidic residue. To the residue $SOCl_2$ (0.2 mL) was added and the mixture refluxed (45 min), then more $SOCl_2$ (0.1 mL) added, and refluxing was continued for another 45 min. A solution of *p*-toluidine (100 mg) in dry benzene (1 mL) was added and the mixture refluxed for 30 min.

The reaction mixture was diluted with ether (10 mL), worked up in the conventional manner and the resulting residue applied to a 20 × 40 cm silica gel plate (benzene–ethyl acetate (9:1)). The band corresponding to octanoyl-*p*-toluidide was scraped and the product recovered with ether. Following rechromatography in the same system, the obtained *p*-toluidide was crystallized several times

Table 3. Recovery of octanols from incubations of (1*R*)- and (1*S*)-octane with extracts of *P. oleovorans* strain TF4-1L

EXPERIMENT	CHIRALITY OF OCTANE	[^{3}H:^{14}C] RATIO OF OCTANE	^{3}H-OCTANE INCUBATED	^{3}H-OCTANOL RECOVERED
1	(1R)	8.96	45 µCi	0.56 µCi
	(1S)	8.47	45 µCi	0.75 µCi
2	(1R)	8.96	45 µCi	0.81 µCi
	(1S)	8.47	45 µCi	0.88 µCi

Table 4.

Experiment	Source of Octanol	[^{3}H: ^{14}C] Ratio of Octanol *	[^{3}H: ^{14}C] Ratio of Derived Octanoic Acid **	dpm of ^{3}H-octanol Used for Equilibration X 10^{-3}	[^{3}H: ^{14}C] of Octanol Recovered After 24-h Incubation *
1	(1R)-octane	10.19	7.50	90	8.65
	(1S)-octane	10.10	7.90	125	8.17
	Synthetic (1RS)-octanol	5.76	-	100	2.01
2	(1R)-octane	9.66	6.86	200	7.92
	(1S)-octane	9.07	6.41	200	6.83
	Synthetic (1RS)-octanol	5.98	-	100	1.81

* Counted as the 3,5-dinitrobenzoate ester in 15 ml Liquifluor

** Counted as the p-toluidide in 15 ml Liquifluor

The [^{3}H: ^{14}C]-ratios showed an average variation of ± 0.05 on successive crystallization of the derivatives.

from n-hexane and counted. The results are summarized in Table 4.

Calculation of results

100 (% ^{3}H lost in equilibration) = (% lost from R)x_R + (% lost from S)x_S (eqn 1)

x_R = % *R* alcohol in mixture

X_S = % *S* alcohol in mixture

$X_R = 100 - x_S$

During 24 h equilibration (1*R*)-alcohol lost 100% of ^{3}H

During 24 h equilibration, (1*S*)-alcohol lost *Y*% of ^{3}H

Therefore eqn (1) becomes:

100% (% ^{3}H lost in Equil.) = $(100 - x_S) + Yx_S$ (eqn 2)

Determination of Y from racemic octanol

Data: Initial (1*RS*)-octanol [^{3}H: ^{14}C]: 5.98

After 24 h equilibration: 1.81

% ^{3}H lost: 70

Equation (2) becomes:

100 (70) = 100 (100–50) + *Y* (50)

Y = 40% ^{3}H lost from (1*S*)-alcohol

Determination of x_R *and* x_S *for* (1R)*-octane-derived alcohols* (*Expt.* 2)

Data: Initial biosynthetic alcohol [^{3}H: ^{14}C]: 9.66

After 24 h equilibration: 7.92

Octanoic acid [^{3}H: ^{14}C] 6.86

^{3}H available for exchange: 9.66 − 6.86 = 2.80

$$\% \text{ of available } ^3\text{H lost} = \frac{100\,(9.66 - 7.92)}{(9.66 - 6.86)} = \frac{174}{2.80} = 62\%$$

Equation 2 becomes:

$100\,(62) = 100\,(100 - x_S) + 40x_S$

$x_S = 63\%$

$x_R = 37\%$

Acknowledgment—The work described was supported by a grant from the National Science Foundation (PCM 7800582) and a grant from the National Institutes of Health (AM 12156). We thank Dr. Raam Mohan for the culture of *P. oleovorans* TF4-1L.

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INTRAMOLECULAR CYCLOADDITIONS OF NITRONES JOINED BY AMIDES TO OLEFINS

R. BRAMBILLA, R. FRIARY,* A. GANGULY, M. S. PUAR, B. R. SUNDAY and J. J. WRIGHT
Department of Chemistry, Pharmaceutical Research Division, Schering-Plough Corporation, Bloomfield, N. J. 07003, U.S.A.

and

KAY D. ONAN and ANDREW T. MCPHAIL*
Paul M. Gross Chemical Laboratory, Duke University, Durham, N. C. 27706, U.S.A.

(*Received in USA* 21 *July* 1980)

Abstract—Six nitrones joined by amides to olefins were prepared *in situ* from the related ketones **1–3** with N-methyl- and benzylhydroxylamines. The nitrones added intramolecularly to the olefins, and the cycloadditions gave the 6-lactams **4–9** stereoselectively and regiospecifically. Chemical correlations, CMR spectroscopy and two X-ray crystallographic analyses established that the relative stereochemistries of the six cycloadducts **4–9** were identical.

INTRODUCTION

Discovered by Cope and LeBel,[1–2] intramolecular cycloadditions of nitrones to olefins were developed by the latter and others from a puzzle[2] to a powerful synthetic method.[3–6] C-alkenylnitrones cyclize to carbocycles fused to isoxazolidines,[7–12] and two of these were used to synthesize the α-bisabolols.[13] N-alkenylnitrones ultimately give azacycles like cocaine[14–15] and luciduline.[16–17] When a heteroatomic chain links the cycloaddenda, they give isoxazolidines fused to heterocyclic ethers,[18–19] an amine,[20] a Schiff's base[21] and a thioether from which biotin was synthesized.[22–23]

Were a heteroatomic chain comprising amides of β, γ-unsaturated carboxylic acids and α-aminoketones to link the olefin to the nitrone carbon, cycloadditions should yield isoxazolidines fused to 6-membered lactams. We sought some of these 6-lactams as intermediates.

From ketones **1–3** we prepared six nitrones with N-methyl- and benzylhydroxylamines. We report that these nitrones cyclized *in situ*, giving the 6-lactams **4–9** stereoselectively and regiospecifically (Table 1). The relative stereochemistries of the six cycloadducts were identical. The cycloadditions induced asymmetry at four of the chiral centers of adducts **6–7**, because of prochirality at C_1 of ketone **2**.

Sequential N-demethylation, hydrolysis and hydrogenolysis beginning with **4** yielded the triply functionalized perhydroquinolizine **18**. Hydrogenolyses of **5** and **7** also gave **18**. These changes completed an asymmetric synthesis founded on closure of the C_4–C_5 bonds of 6-lactams by intramolecular cyloadditions of nitrones joined by amides to olefins.

[a]Dedicated to the memory of Robert Burns Woodward, this paper will be included in the Book version of the special Woodward Memorial Supplement.

STARTING MATERIALS

We assembled the starting materials for these cyloadditions from the aminoketal **10** and unsaturated carboxylic acids. To obviate self-condenstation we protected the latent ketone of **10** as the dimethyl ketal, and to provide a variety of amides we chose readily available acids. Ketalization of 2-acetylpyridine with trimethylorthoformate and catalytic reduction of the product gave **10**. It was amidated, and the resulting amideketals were hydrolyzed by dilute aqueous acid to the ketones **1–3** and **11**.

As expected, ketone **1** was a mixture of diastereomers; its CMR spectrum showed 17

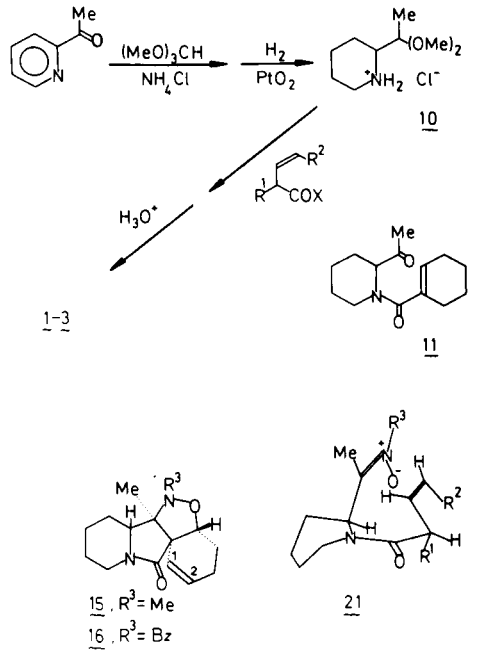
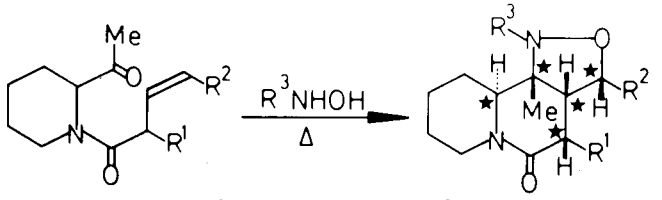
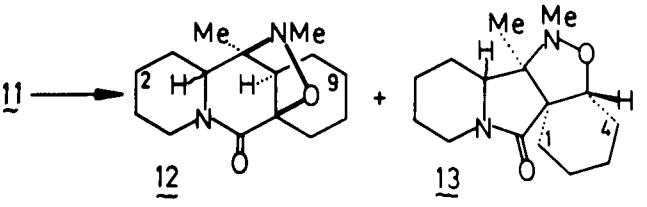


Table 1. Intramolecular cycloadditions of nitrones joined by amides to olefins



KETONE	R^1	R^2	ADDUCT	R^3	YIELD (%)
1	$-(CH_2)_3-$		4	Me	51
	$-(CH_2)_3-$		5	Bz	60[a]
2	$-(CH)_2CH_2-$		6	Me	3
	$-(CH)_2CH_2-$		7	Bz	32[a]
3	H	H	8	Me	45
	H	H	9	Bz	21

[a]Estimated; see Experimental.



resonances. Important, this observation implied we were not predetermining the stereochemistry of **4** and **5** by using only one diastereomer of ketone **1**.

Intramolecular cycloadditions

Excess N-methylhydroxylamine in hot ethanol consumed both diastereomers of ketone **1**, but formed cycloadduct **4** exclusively (tlc). Crystallization routinely isolated pure **4** in a yield of 51%. Although the crude product was sometimes chromatographed lest regio- or stereoisomers be overlooked, none were found.

Gratifying no less because it was foreseen,[4,6] the absence of regioisomers was a premiss of our plan. That of stereoisomers at once emphasized the exquisite discrimination of intramolecular cycloadditions[4,6] and defined the usefulness of these. The structures, acceptable relative stereochemistry, and chemistry of cycloadducts **4** and **8** later proved them to be intermediates we sought. Cycloadduct **8** was prepared like **4**.

We hoped to press other intermediates into service and to exact another diastereoselective response to nitrones larger and smaller than those employed before. We treated N-benzylhydroxylamine[24] with ketones **1** and **3**, and ketone **2** with both N-methyl- and benzylhydroxylamines. Cycloadduct **5** resulted and served as desired. Like the others obtained (**6–7**, **9**), however, it bore the same relative stereochemistry as **4** and **8**.

We made cycloadduct **7** to functionalize its double bond subsequently. At first we obtained only 3% of this substance, a middling yield neither beneath notice nor above contempt. Changing the solvent of cycloaddition from ethanol to benzene increased the yield tenfold, but evidently optimized it. Despite prolonged treatment (119 hr) of **2** with N-benzylhydroxylamine in benzene at 50°, no reaction occurred (tlc). Briefer treatment (23 hr) of **2** with this reagent in boiling toluene gave not **7** but a complex mixture instead (tlc). Indeed, each of the foregoing six reactions was complicated by the formation of impurities.

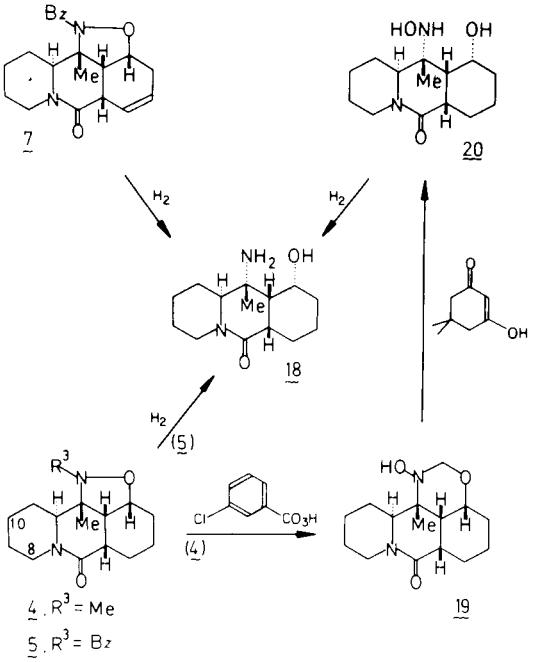
Chromatography isolated four of these impurities: N-benzyl-C-phenylnitrone,[25–26] and cycloadducts **14–16**. This nitrone contaminated adducts **5**, **7** and **9** (PMR). Although we prepared N-benzylhydroxylamine from this nitrone,[24] it did not contaminate the samples of the hydroxylamine used to make cycloadducts **5**, **7** and **9** (tlc, PMR, mp). We speculate that self-condensation of the hydroxylamine formed the nitrone during the cycloadditions.†

Evidently N-methylhydroxylamine also underwent self condensation. The structure of **14**,‡ formed by **2** and this reagent, was formally that of an adduct of N-methylnitrone and **6**.

Cycloadducts **15** and **16** contaminated compounds **6** and **7**. The structures of **15** and **16** implied that one double bond of ketone **2** or of its

†Dehydration of the N-alkylhydroxylamine to the corresponding imine, followed by addition of the hydroxylamine to the imine and elimination of ammonia, would account for the formation of the nitrone.

‡The regioisomeric structure of **14** followed from the frequency (ν 1640, 6-lactam) of its carbonyl absorption and from the three vicinal couplings (9.5, 9.0 and 5.0 Hz) of H_{7a} in it. In the regioisomer of **14**, these couplings would have numbered two. In **14** and **4**, the signals of H_{6a} and H_{2a} were broad 1-proton multiplets at δ4.2–3.9 ppm respectively. These facts allowed us to assign the signals of H_{6a} and H_{7a} in **14**. Its spectrum showed only two signals in this region.



nitrones suffered conjugation to the amide carbonyl. This raises the question of whether we would have detected cycloadducts **12** and **13** in crude **4**.

Had **1** or its N-methylnitrones been isomerized *in situ* to ketone **11** or to its N-methylnitrone, adducts **12** and **13** would have contaminated **4**. They did not, as direct comparison of **12** and **13** to crude **4** showed. We concluded that little isomerization, if any, occurred.

We prepared **12** and **13** from **11** and isolated them by chromatography in a yield of 70% and a ratio of 1:13, respectively. They were distinguishable from **4**, **12** by tlc and **13** by IR. IR spectroscopy not only distinguished **13** from **4** but from **12** as well.

Differentiation of 5- and 6-lactams

In general, IR and CMR spectroscopy distinguished the isomeric 5- and 6-membered lactams (**13**, **15-16** and **12**, **6–7**, respectively). The carbonyls of the former absorbed at higher frequencies and resonated at lower fields than those of the latter. In particular, the signals of the other oxygenated carbons of **12** and of **13** were a singlet (C_{6a}) and a doublet (C_{4a}), respectively. These distinctions were independent of the relative stereochemistries of the cycloadducts.

Assume the illustrated assignment of partial relative stereochemistry to **15** and **16**. Then support for the distinction between them and **6–7** lies in the differential chemical shift ($\nabla\delta$ [H_2–H_1] = 0.8 ppm) of the olefinic protons of **15** and **16**. In stereomodels of the spirocycloadducts **15** and **16**, the planes of the amides and olefins were nearly perpendicular. Consequently anisotropic shielding of H_1 by the carbonyls of **15–16** accounts for the differential chemical shift. Adducts **6–7**, however, should show no such anisotropy. In them, the differential chemical shift of H_4 from H_5 was naught.

The distinction between **15** and **6** was consistent with the differential chemical shift ($\nabla\delta$ = 9 ppm) of the olefinic carbon resonances of **15**. We were unable to assign the olefinic carbon resonances of **15** uniquely, but steric compression of its C_1-carbon by its *cis*, vicinal C_{6a}-methyl group would explain the observed $\nabla\delta$-value. In **6** no effect was observed ($\nabla\delta$ [C_4–C_5] = 1 ppm), and none expected.

Assignments of relative stereochemistry

We assigned the illustrated partial relative stereochemistries to compounds **12–13** and **15–16** for two reasons. Nitrone-olefin cycloadditions are *cis*-stereospecific[28] and other structures manifesting this specificity would be improbably strained. In them the reciprocal fusions of the 5-membered rings and the bridging of the lactam of **12** by its epoxyimino group would be *trans*.

Although we were unable to determine the stereochemistry of spirocycloadducts **15** and **16** at C_{6b}, their comparable CMR chemical shifts were identical. This showed they had the same relative stereochemistry.

So, too, did all six cycloadducts **4–9** have the same relative stereochemistry. Single-crystal X-ray analyses of cycloadduct **4** and of perhydroquinolizinone **17** not only established their complete structures but also demonstrated the identical natures of their common relative stereochemistries. Reduction of **8** with zinc was the source of **17**.

CMR spectroscopy established that the relative stereochemistries of the common chiral centers of **6** and **8** were identical to those of **7** and **9**, respectively. The relevant chemical shifts (Table 2) were within 1 ppm of one another.

We converted cycloadducts **5** and **7** to the same perhydrobenzoquinolizidine **18**, showing the identity of their relative stereochemistries. Oxidative N-demethylation of **4** to **19**,[14–15,27] hydrolysis of **19** to **20**,[27] and hydrogenolysis of **20** also gave **18**. These changes related **5** and **7** to **4**, and they completed elucidation of the relative stereochemistries of **4–9**. From the structural relations of products **4–9**, we inferred that the cycloadditions were indifferent to the nitrones they consumed.

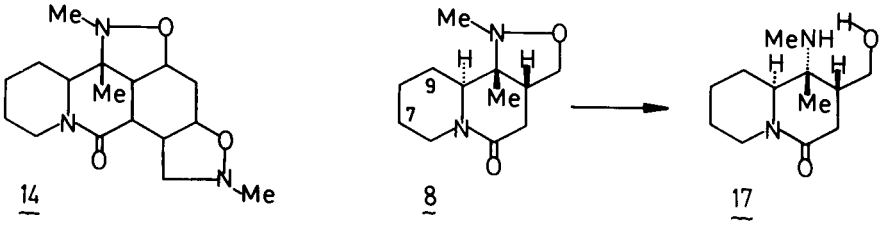


Table 2. ^{13}CMR chemical shifts (δ($CDCl_3$), ppm)[a]

No./C	2a	11c	5a	6	8	9	10	11	11a	11b	Me	3
6	73.7	40.3[b]	48.8	170.8	39.6[b]	22.7[c]	23.8[c]	26.2	58.4	70.0	16.9	20.5
7	73.9	40.2[b]	48.1	169.4	39.3[b]	22.6[c]	23.8[c]	26.2	58.3	70.0	16.5	20.5
	3	3a	4	5	7	8	9	10	10a	10b	Me	
8	71.0	44.8[b]	31.3	168.5	42.4[b]	23.1[c]	24.0[c]	26.7	60.7	66.0	16.5	
9	71.0	45.8[b]	31.8	168.6	42.4[b]	23.1[c]	24.0[c]	26.6	60.6	66.3	17.0	

[a]Assignments were aided by off-resonance spectra. [b,c]Interchangeable.

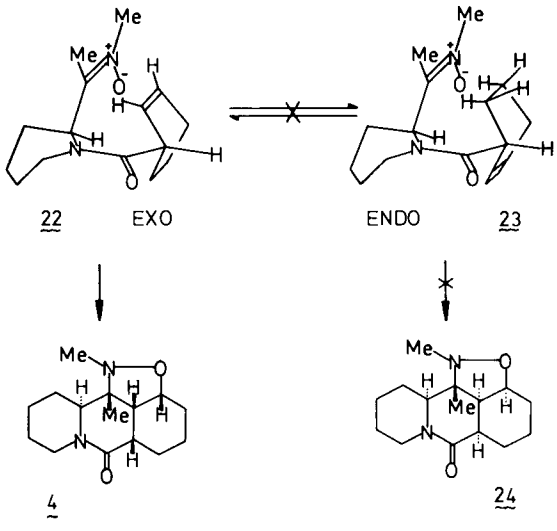
DISCUSSION

Omnivorous, the cycloadditions yielding **4–9** had identical diastereoselectivities. These were independent of the sizes of the N-substituents of the nitrones, of the presence or absence of a cyclohexene and of its size. They implied a common nitrone conformer cyclizing, we presume,† under kinetic control.[29]

We adduce **21** as the nitrone conformer common to the cycloadditions yielding **4–9**. Our inspection of stereomodels suggested that its transition to cycloadducts was least hindered in each series. In stereomodels its variable substituents were remote from the intramolecular site of cycloaddition.

Both diastereomers of **1** were consumed but yielded only half the theoretical amount of cycloadduct **4**. Therefore neither the diastereomers of ketone **1** nor those of its N-methylnitrones were interconverted.

If both diastereomeric nitrones of **1** formed, relatively slow cycloaddition of one would explain the absence of any diastereomeric adduct. Inspection of stereomodels suggested that the cycloadditions of the diastereomeric nitrone conformers **22** and **23** were the least hindered of the respective series. Leading to a sterically disfavored *endo* transition state,[30] **23** may consequently cyclize more slowly than **22**. A less crowded *exo* transition state corresponds to **22**. Uncyclized to the *trans*-fused **24**, unepimerized and unisolated, **23** may have been destroyed rapidly by another (unknown) reaction.



We defer to another report an account of how the structures and stereochemistry of these cycloadducts served. Save for an exposition of the crystallographic findings, we conclude divulging that the diastereoselectivity of these cycloadditions frustrated our greatest hope. *Woodward's Epigram* describes this plight: "...bad planning on Nature's part."‡

X-*ray crystallography*

The crystal structures of cycloadduct **4** and of perhydroquinolizinone **17** were solved by direct methods by use of MULTAN 76.[31] Atomic positional and thermal parameters (anisotropic C, N, O; isotropic H) were refined by full-matrix least-squares calculations to R $(=\Sigma||F_0|-|F_c||/\Sigma|F_0|)$ values of 0.050 for **4** over 1185 reflections and 0.049 for **17** over 1189 reflections. Final atomic positional and thermal parameters are in Tables 3 and 4. Figures 1 and 2 provide views of the solid-state conformations as well as the atom numbering scheme; bond lengths and angles are reported in Figs. 3 and 4.

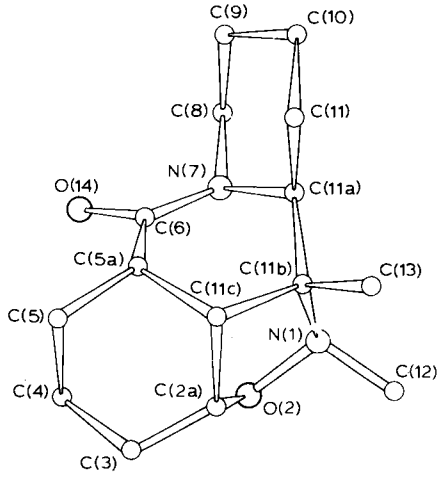


Fig. 1. Molecular structure and conformation of **4**.

†For example, cycloadduct **4** could be distilled under atmospheric pressure at 220° (temp. of Kofler block).

‡R. B. Woodward (6.XII.1971, Basel, Switzerland) firmly postponing—not abandoning—a scheme to synthesize $PGF_{2\alpha}$ (*cf* I. Ernest, *Angew. Chem.* Int. Ed. **15**, 207 (1976)).

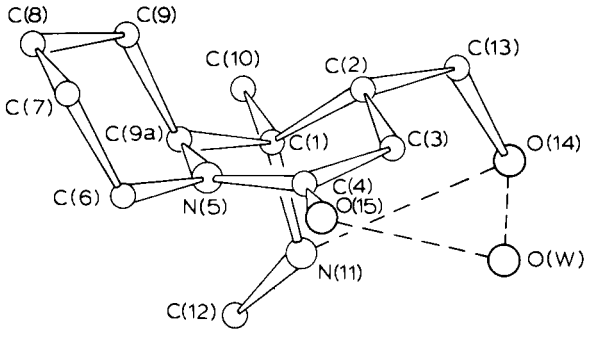


Fig. 2. Molecular structure and conformation of **17**; broken lines denote hydrogen bonds.

Crystals of **4** contain discrete molecules separated by normal van der Waals distances. Molecules of **17**, however, in addition to having an intramolecular N–H...O (N_{11}...O_{14} 2.98 Å) H-bond, are associated further in the solid state through H-bonds involving the water molecule [O_{14}...O_W 2.77 Å; O_{15}...O_W (at x, y, $1+z$) 2.71 Å; O_{14}...O_W (at $(1/2)-x$, $1-y$, $(1/2)+z$) 2.62 Å].

Endocyclic torsion angles characterizing the ring conformations in **4** and **17** are in Table 5. The piperidine rings in both compounds adopt slightly distorted chair conformations in which the means

Table 3. Fractional atomic co-ordinates (x10^4; x10^3 for hydrogen atoms) and thermal parameters (x10^3) for **4**, with estimated standard deviations in parentheses. Hydrogen atoms bear the same labels as the atoms to which they are bonded. Anisotropic thermal parameters are in the form: $\exp[-2\pi^2(U_{11}h^2a^{*2}+U_{22}k^2b^{*2}+U_{33}l^2c^{*2}+2U_{12}hka^*b^*+2U_{13}hla^*c^*+2U_{23}klb^*c^*]$

Atom	*x*	*y*	*z*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	7545(3)	5910(2)	3054(2)	55(2)	37(1)	36(1)	-10(1)	1(1)	-1(1)
O(2)	8469(2)	5053(2)	2970(2)	56(1)	45(1)	55(1)	-6(1)	7(1)	4(1)
C(2a)	8636(4)	4681(3)	4219(3)	52(2)	49(2)	57(2)	-6(2)	-22(2)	01(2)
C(3)	9361(4)	3654(3)	4191(5)	38(2)	65(2)	106(3)	2(2)	-14(2)	11(2)
C(4)	8518(4)	2778(3)	3716(3)	49(2)	42(2)	59(2)	8(2)	2(2)	9(2)
C(5)	7257(4)	2708(3)	4454(4)	66(2)	37(2)	72(2)	8(2)	10(2)	18(2)
C(5a)	6433(3)	3707(2)	4350(3)	53(2)	34(1)	45(2)	1(1)	17(2)	11(1)
C(6)	5703(3)	3768(2)	3126(3)	42(2)	28(1)	54(2)	-5(1)	6(2)	-8(1)
N(7)	5184(3)	4696(2)	2814(2)	46(1)	30(1)	33(1)	-3(1)	1(1)	-5(1)
C(8)	4031(4)	4724(3)	1998(3)	52(2)	48(2)	44(2)	-6(2)	-3(2)	-3(2)
C(9)	2777(4)	4734(3)	2784(4)	49(2)	64(2)	60(2)	-5(2)	4(2)	6(2)
C(10)	2817(4)	5614(3)	3738(4)	56(2)	62(2)	59(2)	13(2)	17(2)	3(2)
C(11)	4073(4)	5609(3)	4503(3)	72(2)	42(2)	47(2)	7(2)	18(2)	-5(1)
C(11a)	5277(4)	5611(2)	3631(3)	60(2)	25(1)	29(1)	1(1)	5(1)	-2(1)
C(11b)	6681(3)	5702(2)	4170(3)	64(2)	27(1)	26(1)	-6(1)	1(2)	-3(1)
C(11c)	7233(4)	4680(3)	4724(3)	69(2)	43(2)	21(1)	2(2)	-4(1)	-1(1)
C(12)	8335(5)	6866(3)	3099(4)	105(3)	42(2)	75(2)	-31(2)	12(3)	6(2)
C(13)	6702(4)	6571(3)	5144(3)	90(3)	48(2)	42(2)	-7(2)	-1(2)	-20(1)
O(14)	5504(3)	2986(2)	2487(3)	68(2)	38(1)	111(2)	-3(1)	-18(2)	-33(1)

Atom	*x*	*y*	*z*	*U*	*Atom*	*x*	*y*	*z*	*U*
H(2a)	912(4)	521(3)	475(4)	74(12)	H(10α)	268(4)	629(3)	329(4)	73(12)
H(3α)	1025(3)	370(3)	386(3)	59(10)	H(10β)	205(3)	561(3)	426(3)	56(10)
H(3β)	958(4)	352(4)	520(4)	87(14)	H(11α)	409(4)	621(3)	503(4)	75(12)
H(4α)	830(3)	285(3)	285(3)	48(9)	H(11β)	416(4)	499(3)	505(4)	71(12)
H(4β)	899(3)	209(2)	380(3)	35(8)	H(11a)	513(2)	626(2)	310(2)	18(6)
H(5α)	673(3)	218(3)	424(3)	45(9)	H(11c)	716(4)	476(3)	556(4)	71(12)
H(5β)	757(4)	270(3)	539(4)	79(13)	H(12A)	884(4)	688(4)	236(4)	77(14)
H(5a)	565(3)	360(2)	493(3)	31(7)	H(12B)	769(4)	746(3)	305(4)	76(11)
H(8α)	409(4)	535(3)	153(3)	63(11)	H(12C)	897(5)	689(4)	387(4)	104(12)
H(8β)	411(4)	414(3)	145(4)	69(12)	H(13A)	762(3)	666(3)	544(3)	54(10)
H(9α)	193(3)	484(3)	225(3)	59(11)	H(13B)	618(4)	639(3)	579(3)	58(10)
H(9β)	264(4)	401(4)	312(4)	93(14)	H(13C)	629(4)	729(3)	477(4)	76(13)

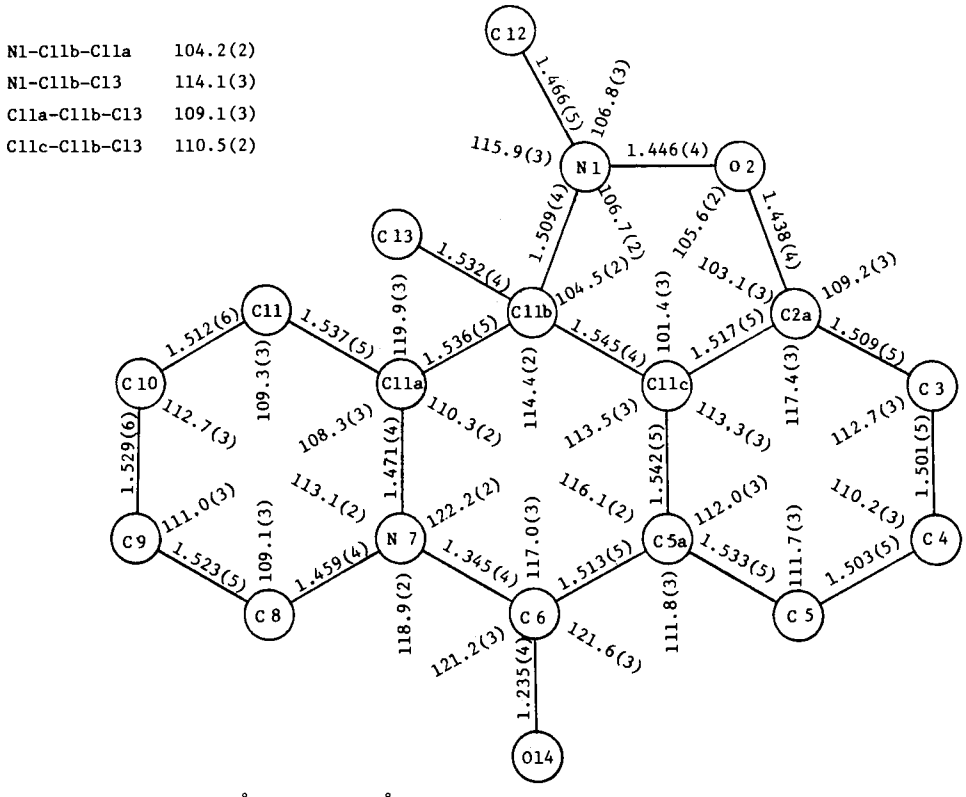


Fig. 3. Bond lengths (Å) and angles (°) in **4**, with estimated standard deviations in parentheses.

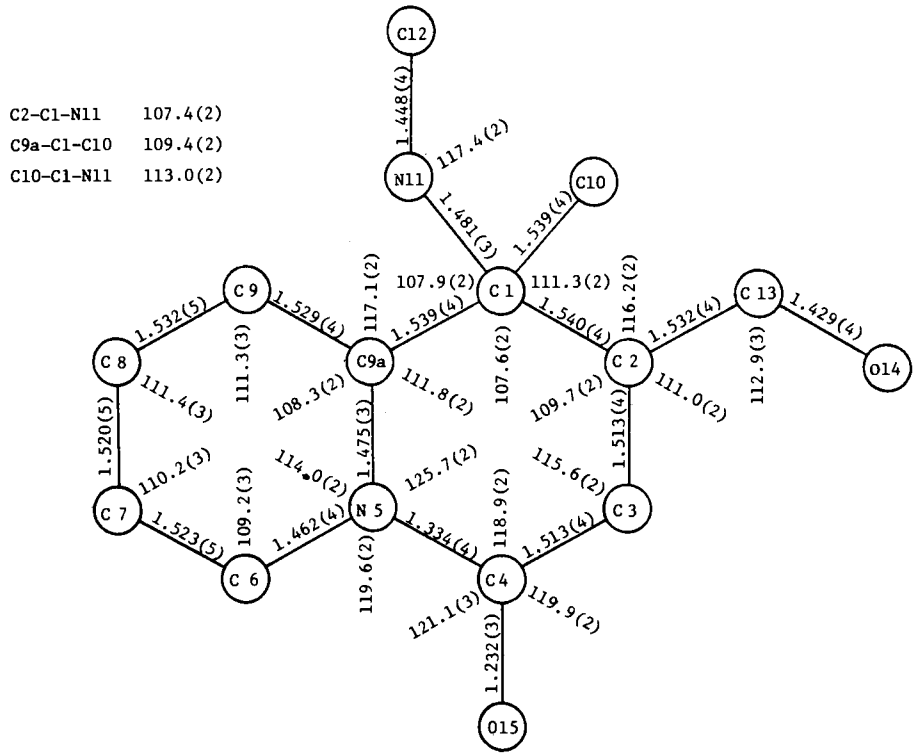


Fig. 4. Bond lengths (Å) and angles (°) in **17**, with estimated standard deviations in parentheses.

Table 4. Fractional atomic co-ordinates ($\times 10^4$; $\times 10^3$ for hydrogen atoms) are thermal parameters ($\times 10^3$) for **17**, with estimated standard deviations in parentheses. Hydrogen atoms bear the same labels as the atoms to which they are bonded. Anisotropic thermal parameters are in the same form as those reported in Table 3

Atom	*x*	*y*	*z*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	1531(2)	2346(2)	3203(3)	36(1)	44(1)	30(1)	-2(1)	-3(1)	-1(1)
C(2)	887(3)	3130(2)	4045(4)	37(1)	42(1)	40(1)	0(1)	0(1)	4(1)
C(3)	1605(3)	3376(2)	5576(3)	42(1)	38(1)	36(1)	0(1)	5(1)	-2(1)
C(4)	2032(2)	2617(2)	6630(3)	39(1)	44(1)	33(1)	-6(1)	4(1)	-2(1)
N(5)	1948(2)	1806(1)	6034(3)	43(1)	39(1)	33(1)	-5(1)	-7(1)	1(1)
C(6)	2134(3)	1058(2)	7125(4)	63(2)	41(1)	43(1)	-1(1)	-12(2)	7(1)
C(7)	880(4)	602(2)	7404(4)	74(2)	46(1)	52(2)	-5(2)	7(2)	9(2)
C(8)	308(3)	331(2)	5776(5)	67(2)	48(1)	59(2)	-17(1)	0(2)	4(2)
C(9)	210(3)	1109(2)	4599(4)	50(1)	49(1)	46(2)	-14(1)	-3(1)	-2(1)
C(9a)	1478(3)	1567(2)	4395(3)	40(1)	37(1)	32(1)	0(1)	-1(1)	-5(1)
C(10)	860(3)	2100(2)	1598(4)	53(2)	63(2)	35(1)	-7(1)	-9(1)	-1(1)
N(11)	2868(2)	2581(2)	2958(3)	38(1)	47(1)	36(1)	-3(1)	3(1)	-1(1)
C(12)	3617(3)	2006(2)	1943(4)	45(1)	68(2)	48(2)	5(1)	8(1)	-6(2)
C(13)	649(3)	3936(2)	2969(5)	60(2)	48(1)	59(2)	6(1)	-9(2)	7(2)
O(14)	1782(2)	4359(1)	2464(3)	75(1)	46(1)	45(1)	-4(1)	10(1)	5(1)
O(15)	2447(2)	2755(2)	8015(3)	89(2)	55(1)	31(1)	-16(1)	-11(1)	-5(1)
O(W)	2988(3)	4305(1)	-542(3)	103(2)	44(1)	63(1)	-9(1)	13(2)	-6(1)

Atom	*x*	*y*	*z*	*U*	*Atom*	*x*	*y*	*z*	*U*
H(2)	0(3)	295(2)	446(4)	40(8)	H(10A)	-8(3)	212(2)	177(5)	56(8)
H(3α)	233(2)	366(2)	525(3)	32(7)	H(10B)	120(3)	154(2)	118(4)	51(8)
H(3β)	105(2)	376(2)	619(3)	33(6)	H(10C)	110(3)	254(2)	71(4)	49(12)
H(6α)	275(3)	62(2)	660(4)	52(8)	H(11)	291(3)	314(2)	267(4)	45(10)
H(6β)	251(3)	129(2)	806(4)	49(8)	H(12A)	442(3)	227(2)	187(5)	62(10)
H(7α)	90(3)	10(2)	823(4)	65(10)	H(12B)	329(3)	190(2)	105(4)	60(9)
H(7β)	31(3)	109(2)	790(4)	51(9)	H(12C)	366(3)	141(2)	248(4)	58(9)
H(8α)	93(3)	-16(2)	522(4)	55(9)	H(13A)	11(3)	438(2)	364(5)	64(10)
H(8β)	-56(4)	10(3)	587(6)	104(15)	H(13B)	15(3)	378(2)	191(4)	61(10)
H(9α)	-10(2)	86(2)	354(4)	37(7)	H(14)	222(-)	434(-)	138(-)	55(8)
H(9β)	-32(2)	155(2)	488(5)	64(10)	H(OWA)	279(-)	373(-)	-108(-)	70(12)
H(9a)	212(3)	113(2)	389(4)	42(7)	H(OWB)	308(-)	482(-)	-130(-)	70(12)

of the moduli of the endocyclic torsion angles are 57.0 and 56.7°, respectively. Fusion of the cyclohexane ring to the isoxazolidine and 2-piperidone rings in **4** results in a significantly flattened chair form wherein the torsion angles range from 38.1 to 61.1° with a mean value of 49.3°. The isoxazolidine ring in **4** has an envelope conformation with C_{2a} as the out-of-plane atom. Non-bonded interactions between the nearly eclipsed N_1-and C_{11b}-methyl substituents associated with this particular envelope conformation are accomodated by a combination of bond lengthening (N_1–C_{11b} at 1.509 Å is significantly longer than the mean of 1.465 Å for the other three non-lactam C–N single bonds in **4** and **17**) and bond angle deformations [C_{11b}–N_1–C_{12} (115.9°) is much larger than C_{12}–N_1–O_2 (106.8°), and N_1–C_{11b}–C_{13} (114.1°) is greater than tetrahedral]. Although the C–C–N–C lactam moieties are nearly planar in both compounds, the conformations adopted by the 2-piperidone rings are distinctly different. In **17**, where the ring conformation in the solid state is undoubtedly influenced to some extent by hydrogen bonding, a form approximating to a half-chair with a C_2 axis bisecting the C_4–C_5 and C_1–C_2 bonds is found. Constraints imposed by the multiple ring fusions in **4** force the 2-piperidone ring to adopt a distorted boat form.

EXPERIMENTAL

Uncorrected m.ps were determined on a Kofler block (Thomas Model 40), IR spectra (CH_2Cl_2) on a Perkin–Elmer 727B spectrophotometer, PMR and CMR (TMS in $CDCl_3$) on Varian CFT-20 or XL-100 instruments, and medium-resolution mass spectra on a Varian CH5 spectrometer. For tlc, commercial silica gel (F-254, E. Merck) and alumina (GF, Analtech) plates were used; developed plates were visualized in I_2 vapor. For column chromatography, silica gel (0.063–0.200 mm, E. Merck) and basic alumina (Woelm; deactivated with H_2O to grade IV) were purchased. Although all chiral compounds prepared were racemic, only one enantiomer is depicted.

2 - (1, 1 - *Dimethoxyethyl*) - *pyridine*. 2 - Acetylpyridine (180g), trimethylorthoformate (246ml), NH_4Cl (24g) and MeOH (1.8 l) were boiled 60 hrs under reflux. cooled, mixed with Na_2CO_3 (47g) and evaporated. The residue was extracted from H_2O with CH_2Cl_2, dried ($MgSO_4$) and distilled giving the ketal (92.9g, 37%), b.p. 44–53°/0.1 mm after redistillation. PMR: 8.74–8.55 (m, 1H), 7.79–7.52 (m,

Table 5. Endocyclic torsion angles (°) in **4** and **17**, with estimated standard deviations in parentheses

(a) Compound 4			
Cyclohexane ring		Piperidine ring	
C(11c)-C(2a)-C(3)-C(4)	44.4(3)	C(11a)-N(7)-C(8)-C(9)	-61.5(3)
C(3)-C(2a)-C(11c)-C(5a)	-38.1(3)	C(8)-N(7)-C(11a)-C(11)	63.8(3)
C(2a)-C(3)-C(4)-C(5)	-54.6(4)	N(7)-C(8)-C(9)-C(10)	53.4(3)
C(3)-C(4)-C(5)-C(5a)	61.1(3)	C(8)-C(9)-C(10)-C(11)	-51.9(3)
C(4)-C(5)-C(5a)-C(11c)	-55.1(3)	C(9)-C(10)-C(11)-C(11a)	53.6(3)
C(5)-C(5a)-C(11c)-C(2a)	42.4(3)	C(10)-C(11)-C(11a)-N(7)	-57.6(3)
2-Piperidone ring		Isoxazolidine ring	
C(11c)-C(5a)-C(6)-N(7)	-35.8(3)	C(11b)-N(1)-O(2)-C(2a)	-27.9(3)
C(6)-C(5a)-C(11c)-C(11b)	27.2(3)	O(2)-N(1)-C(11b)-C(11c)	1.9(2)
C(5a)-C(6)-N(7)-C(11a)	-1.8(3)	N(1)-O(2)-C(2a)-C(11c)	43.0(3)
C(6)-N(7)-C(11a)-C(11b)	44.0(3)	O(2)-C(2a)-C(11c)-C(11b)	-40.1(3)
N(7)-C(11a)-C(11b)-C(11c)	-48.4(3)	N(1)-C(11b)-C(11c)-C(2a)	22.9(3)
C(11a)-C(11b)-C(11c)-C(5a)	14.3(3)		
(b) Compound 17			
2-Piperidone ring		Piperidine ring	
C(9a)-C(1)-C(2)-C(3)	62.5(2)	C(9a)-N(5)-C(6)-C(7)	-61.7(3)
C(2)-C(1)-C(9a)-N(5)	-50.9(2)	C(6)-N(5)-C(9a)-C(9)	60.2(2)
C(1)-C(2)-C(3)-C(4)	-43.1(2)	N(5)-C(6)-C(7)-C(8)	56.6(3)
C(2)-C(3)-C(4)-N(5)	11.2(3)	C(6)-C(7)-C(8)-C(9)	-53.9(3)
C(3)-C(4)-N(5)-C(9a)	0.6(3)	C(7)-C(8)-C(9)-C(9a)	53.6(3)
C(4)-N(5)-C(9a)-C(1)	20.6(2)	C(8)-C(9)-C(9a)-N(5)	-54.4(3)

2H), 7.34–7.07 (m, 1H), 3.23 (s, OMe, 6H), 1.65 (s, Me, 3H); MS: 136 (M–OMe, 36), 122 (22), 104 (100).

2-(1,1-*Dimethoxyethyl*)-*piperidine hydrochloride* (**10**). The filtrate from hydrogenation (20.5 hr, 25°. 60 psi of H_2, Paar shaker) of the foregoing ketal (32.0 g) with PtO_2 (6.2 g) in MeOH (600 ml) and trimethylorthoformate (21 ml) containing NH_4Cl (10.3 g) was concentrated to 100 ml and colorless **10** (36.7 g, 92%), m.p. 140.0–142.0°, pptd. with Et_2O. (Found: N.E. 207; Calc. ($C_9H_{20}ClNO_2$): 210.) Crystallization did not change the m.p. but acceptable microanalytical data could not be obtained. IR (KBr): 2720; PMR (DMSO-d_6): 9.9–7.7 (br, 2H), 3.6–2.6 (br), 3.18 (s, OMe) and 3.14 (s, OMe), 1.70 (br, 6H), 1.36 (s, CMe); MS: 173 (M, free base), 84.

2-*Cyclohexenyl*-1-*carbonyl chloride*. This was prepared according to Pearlman[32] from fresh oxalyl chloride and 2-cyclohexenyl-1-carboxylic acid[33] in benzene (25°) and was used without purification.

Vinylacetic anhydride. After being stirred overnight at 25°, the mixture from vinylacetic acid (28.4 g containing 10 mole % crotonic acid (PMR)), dicyclohexylcarbodiimide (34.1 g) and CH_2Cl_2 (125 ml) was filtered and concentrated; the product, b.p. 105–110°/35 mm (lit.[34] b.p. 98–100°/17 mm) was usually used without purification.

1,4-*Dihydrobenzoic anhydride*. Like vinylacetic anhydride, this was prepared from the corresponding acid[33] and dicyclohexylcarbodimide in CH_2Cl_2, and was used without purification.

Preparation of the amideketals. Equivalent amounts of **10**, $(i\text{-}Pr)_2NEt$ and the corresponding acid chlorides or anhydrides in CH_2Cl_2 (0–5° for 1–2 hr, then 25° overnight) gave these compounds. Lest *both* ketal *and* amide be hydrolyzed, the aqueous work-up was kept basic. When purification was deemed necessary, the crude products were chromatographed on silica gel and eluted with 1–5% MeOH in $CHCl_3$; otherwise the crude products were used directly.

2 - (1,1 - *Dimethoxyethyl*) - *piperidine* 2 - *cyclohexenyl* - 1 - *carboxamide*. A sample of this was distilled, b.p. 120–122°/0.05 mm; PMR: 5.99–5.41 (br m, 2H), 4.98–4.75 (m, 1H), 3.75–3.09 (en), 3.27 (s) and 3.26 (s) (2 OMe) (8H), 2.52–1.00 (en) and 1.31 (s, CMe) (16H); MS: 281, 90.

2 - (1,1 - *Dimethoxyethyl*) - *piperidine* 1,4 - *dihydrobenzamide*. This was prepared from the corresponding anhydride and was used directly.

2 - (1,1 - *Dimethoxyethyl*) - *piperidine* 1 - *cyclohexenyl* - 1 - *carboxamide*. This was prepared from commercial 1 - cyclohexenyl - 1 - carbonyl chloride. IR: 1610, 1430.

2 - (1,1 - *Dimethoxyethyl*) - *piperidine vinylacetamide*. A sample was distilled, b.p. 91–97°/0.05 mm. IR: 1620, 1430; PMR: 6.3–5.7 (m), 5.25–4.95 (m), 4.0–2.9 (br), 3.25 (s, OMe), 2.1–1.1 (en), 1.33 (s, CMe). Samples of this compound were contaminated by small amounts of the corresponding crotonamide which was inseparable by chromatography or distillation.

Preparation of the Amideketones (**1–3** and **11**). Compounds **1** and **2** were best prepared from the corresponding ketals by careful hydrolysis (dil aq HCl, 0–5°, 30–60 min, Et_2O; then aq $NaHCO_3$ workup). Some samples of the ketals contained an unidentified basic impurity, and acidification (to pH 2 with a minimum of conc HClaq) was necessary lest the ketals be recovered. Exposure to HClaq was minimized *lest the amide bonds be hydrolyzed*; Et_2O served this purpose better than THF. When purification was deemed necessary, the crude products were chromatographed on silica gel and eluted with 0.5–2% MeOH in $CHCl_3$; otherwise the crude products were used directly.

2 - *Acetylpiperidine* 2 - *cyclohexenyl* - 1 - *carboxamide* (**1**). The crude ketal (from 0.283 mole of the acid) in cold Et_2O (180 ml) was filtered, the unidentified ppt. discarded, the filtrate mixed with cold 0.1N HCl (300 ml), acidified (pH 2, conc HCl) and stirred 1 hr at 0–5°. Extraction (Et_2O), washing (1N $NaHCO_3$, H_2O, brine), drying (Na_2SO_4) and evaporating gave **1** (45.7 g,

61%). A chromatographed, distilled sample, b.p. 120–125°/0.05 mm was a yellow liquid. IR: 1710, 1630, 1420; PMR: 5.89 (br d, 11) and 5.60 (br d, 11) (2H), 5.24 (s, $W_{h/2}=9$, COCH), 3.87 (br d, 11, NCH), 3.57–2.89 (en, 2H), 2.51–1.13 (en) and 2.12 (s, COMe) (15H); CMR: 207.2 (COMe), 171.4 (CON), 129.7, 125.1 and 124.6 (olefin C, unequal intensities), 59.0 (NCH), 44.1 (NCH_2), 38.9 and 38.6 (equal intensity, COCH), 26.9, 25.8, 25.5, 24.9, 24.7, 21.1, 21.0, 20.7 (CH_2 and COMe); MS: 235 (M), 192, 84 (100).

2 - *Acetylpiperidine* 1,4 - *dihydrobenzamide* (**2**). This compound was prepared from 1,4-dihydrobenzoic anhydride similarly to **3**; a sample of the crude product (31.1 g, 27% from 0.491 mole of the acid) crystallized, m.p. 83.0–85.5° (Et_2O), after chromatography on silica gel. (Found: C, 72.07; H, 8.07; N, 6.07. Calc. ($C_{14}H_{19}NO_2$): C, 72.07; H, 8.21; N, 6.00%). IR: 1720, 1640, 1420; PMR: 6.20–5.53 (m, 4H, vinyl), 5.26 (br, s, 1H, CHCON), 4.27–3.87 (br m, 2H, CH_2N), 3.17 (br t, 12, 1H, CHCOMe), 2.72 (br d, 9, 1H, CH_2 (vinyl)$_2$), 2.14 (s, 3H, COMe), 1.67–1.12 (en, 6H, (CH_2); MS: 190 (M–C_2H_3O, 75), 84 (100).

2 - *Acetylpiperidine* 1 - *cyclohexenyl* - 1 - *carboxamide* (**11**). The crude ketal (9.27 g) in THF (27 ml) and 1N HCl (54 ml) was acidified (pH 2, conc HCl) and stirred 2 hrs at 0–5°; extraction (Et_2O), washing (H_2O, 1N Na_2CO_3, brine) and evaporating gave crude, oily **11** (5.80 g, 74%). IR: 1720, 1620, 1420; PMR: 5.79 (br m, 1H), 4.25–3.67 (br, 1H), 3.17–2.72 (br, 1H), 2.67–1.89 (br) and 2.16 (s) (9H), 1.90–1.11 (br m, 9H); MS: 235, 192, 109 (100).

2 - *Acetylpiperidine vinylacetamide* (**3**). The crude ketal (32.4 g) in THF (100 ml) and 0.1N HCl (200 ml) was stirred 2.5 hrs at 33°; basic aq work-up similar to that for **1** gave **3** (16.8 g, 68%). Chromatographed **3** was distilled, b.p. 100–110°/0.05 mm. IR: 1720, 1640, 1430; PMR: 6.2–5.7 (m, 1H), 5.3–5.0 (m, 2H) (vinyl), 3.74 (br d, 13, $1H_2$), 3.20 (d of t, 6.0, 1.2, $COCH_2$) and 3.3–2.9 (br, overlapping, CH_2N) (4H), 2.13 (s, 3H, COMe), 1.95–1.10 (en, 6H); MS: 152 (M-43), 83 (100).

1,11β - *Dimethyl* - 2aβ,3,4,5,5aβ,8,9,10,11aα, 11b, 11cβ - *dodecahydro* - 2H - *isoxazolo* [5,4,3-kl] *benzo* [b] *quinolizin* - 6 - *one* (4). Crude **1** (24.3 g), MeNHOH HCl (17.2 g), (i-Pr)$_2$NEt (36.0 ml) and EtOH (115 ml) were boiled 34 hr under reflux, evaporated, diluted with H_2O (450 ml) and extracted ($CHCl_3$). Chromatography of the extract (Al_2O_3, elution with Et_2O, or silica gel and elution with 1% MeOH–$CHCl_3$) followed by crystallization (Et_2O) gave **4** (13.94 g, 51%), m.p. 111–114°; alternatively, washing the extract with 1N HCl, basifying (pH 11, 50% aqNaOH), extracting ($CHCl_3$) and crystallizing (Et_2O) gave 4, m.p. 108–110°, without chromatography. Recrystallization gave colorless prisms, m.p. 109.5–111.5° (Et_2O–hexanes). (Found: C, 68.10; H, 9.43; N, 10.62. Calc. ($C_{15}H_{24}N_2O_2$): C, 68.15; H, 9.15; N, 10.60%). IR: 1640, 1460, 1440; PMR: 4.54 (br d, 13, H_{8eq}) and 4.28 (br, H_{2a}) (2H), 3.32 (br dd, 10 and 2, H_{11a}), 2.84–2.25 (en) and 2.64 (s, NMe) (7H), 2.08–1.06 (en) and 1.24 (s, CME) (14H); H_{8eq} suffered the greatest deshielding in the presence of Eu(fod)$_3$; CMR: 171.7 (s, C_6), 74.9 (d, C_{2a}), 65.6 (s, C_{11b}), 61.9 (d, C_{11a}), 48.4 (d, C_{11c}), 44.2 (t, C_8), 38.4 (q, NMe), 35.0 (d, C_{5a}), 27.5 (t, C_{11}), 25.5, 24.5, 24.0, 23.0, 18.6 (q, CMe), 16.2 (t); MS: 264 (25), 152 (100).

Reaction of **1** *and* BzNHOH. Ketone **1** (2.86 g), BzNHOH[24] (3.00 g, freshly crystallized) and C_6H_6 (25 ml) were boiled 71 hr under reflux, concentrated and chromatographed on silica gel. Elution with 0.5% MeOH–$CHCl_3$ gave an oily mixture (3.26 g) of **5** (PMR) and N-benzyl-α-phenylnitrone, inseparable by crystallization or by rechromatography on silica gel or Al_2O_3 with many eluants; the mixture was hydrogenolyzed to **16**. Calculating the square root of the overall yield of **16** from **1** gave an estimate of the yield of **5**.

Reaction of **2** *and* MeNHOH. Ketone **2** (10.0 g), MeNHOH HCl (7.17 g), (i-Pr)$_2$NEt (15.0 ml) in EtOH (50 ml) were boiled 21 hr under reflux in N_2, and worked-up (neutral conditions) as described for 4; chromatography (Al_2O_3, elution with Et_2O) gave a yellow oil (1.65 g, two components (tlc)) which was reserved for rechromatography.

4b, 5, 9 - *Trimethyl* - 1, 2, 3, 4, 4a, 4b, 4c, 6a, 7, 7a, 9, 10, 10a, 10b - 11H - *tetradecahydrodiisoxazolo* [5, 4, 3-k, 1:4, 5-h] benzo [b] quinolizin - 11 - *one* (**14**). Continued elution (Et_2O) gave a yellow oil crystallizing to pure **14** (0.413 g, 3%), m.p. 93–94° (Et_2O). (Found: C, 63.18; H, 8.48; N, 13.20; Calc. ($C_{17}H_{27}N_3O_3$): C, 63.52; H, 8.47; N, 13.07%). IR: 1640, 1440; PMR: 4.25 (br sextet, 9.5, 9.0, 5.0, H_{7a}), 4.2–3.9 (en, $1H_{6a}$), 3.76–2.26 (en), 2.75 (s, NMe) and 2.56 (s, NMe) (12H), 2.26–1.02 (en) and 1.18 (s, CMe) (13H); MS: 321 (9), 56 (100).

1, 11β - *Dimethyl* - 2aβ, 3, 5aβ, 8, 9, 10, 11, 11aα, 11b, 11cβ - *decahydro* - 2H - *isoxazolo* [5, 4, 3-k,1] *benzo* [b] *quinolizin* - 6 - *one* (**6**). Rechromatography on silica gel of the reserved 1.65-g sample and elution with 2.5% MeOH–$CHCl_3$ gave the less polar isomer **6** (0.387 g, 3%) crystallizing from Et_2O, m.p. 88.0–89.0°. (Found: C, 68.95; H, 8.76; N, 11.09; Calc. ($C_{15}H_{22}N_2O_2$): C, 68.67; H, 8.45; N, 10.68%.) IR; 1640, 1440; PMR: 5.89 (complex m, H_4 and H_5), 4.65 (d of t, $J_{2a-11c}=8$, $J_{2a-3\alpha}=J_{2a-3\beta}=5$, H_{2a}), 3.74–2.87 (en, H_{11a}) (4H), 2.74 (dd, 8 and 10, H_{11c}) and 2.64 (s, NMe) (4H), 2.28 (m, 2H), 2.09–1.06 (en, $2H_9$, $2H_{10}$ and $2H_{11}$) and 1.18 (s, Me) (9H); CMR: 127.1 (d, C_4 or C_5), 126.1 (d, C_5 or C_4), 39.3 (NMe); MS: 262 (7), 56 (100).

6, 6a - *Dimethyl* - 3, 4, 6, 6a, 6b, 7, 8, 9 - *octahydro* - 10H, 12H - *indolizino* [3, 2-c] *indoxazin* - 12 - *one* (**15**). Continued elution of the foregoing column with Et_2O gave the more polar isomer **15** (0.715 g, 6%) crystallizing from Et_2O, m.p. 131.5–133.0°. (Found: C, 68.45; H, 8.51; N, 10.62%; Calc. ($C_{15}H_{22}N_2O_2$).) IR: 1680, 1440; PMR: 6.21 (d of t, $J_{2-3\alpha}=J_{2-3\beta}=4.5$, $J_{2-1}=9$, H_2), 5.38 (br d, 9, H_1), 4.35–4.02 (overlapping m of H_{10eq}) and 4.26 (t, 4, H_{4a}), 3.16 (dd, 12, 3, H_{6b}), 2.78 (br d, 12.5, H_{10ax}), 2.59 (s, NMe), 2.34–0.83 (en) and 0.97 (s, CMe) (13H); CMR: 173.3 (C_{12}), 133.2 (C_2 or C_1), 124.6 (C_1 or C_2), 78.3 (C_{4a}), 71.7 (C_{6a}), 63.6 (C_{6b}), 61.0 (C_{12a}), 40.8 (C_{10}), 36.2 (NMe), 29.4 (C_7), 25.6, 24.8, 24.4, 20.0, 11.0; MS: 262 (6), 56 (100).

Reaction of **2** *and* BzNHOH. Ketone **2** (11.8 g, *ca* 80% purity), BzNHOH[24] (9.97 g) in C_6H_6 (75 ml) were boiled under reflux, evaporated and chromatographed on silica gel.

N - *Benzyl* - C - *phenylnitrone*. Elution with 0.75% MeOH–$CHCl_3$ gave an oil (10.6 g) crystallizing from Et_2O to give the nitrone (2.03 g, 24%), m.p. 82.0–82.5° (lit.[25-26] m.p. 81.5–83.5°, 82–83°). (Found: C, H, and N within 0.2%; Calc. ($C_{14}H_{13}NO$).)

1 - *Benzyl* - 11bβ-*methyl* - 2aβ, 3, 5aβ, 8, 9, 10, 11, 11aα, 11b, 11cβ - *decahydro* - 2H - *isoxazolo* [5, 4, 3-k, 1] *benzo* [b] *quinolizin* - 6 - *one* (**7**). Continued elution, rechromatography on silica gel of selected pooled fractions and elution with 1%MeOH–$CHCl_3$ gave a small oily sample of the less polar isomer **7** (containing 10 wt% of the nitrone (PMR)). IR: 1640, 1430; PMR: 7.5–7.2 (m, C_6H_5), 5.90 (m, vinyl), 4.68 (d of t, $J_{2a-11c}=8.5$, $J_{2a-3\alpha}=J_{2a-3\beta}=5$, H_{2a}), 3.95 (s, CH_2Ph), 3.78–3.20 (en) and 3.29 (br d, 10 and 2, H_{11a}) (4H), 2.84 (dd, 8.5 and 8.5, H_{11c}), 2.28 (m, 2H), 2.15–1.20 (en) and 1.24 (s, CMe) (9H); CMR: 128.6, 128.3, 127.0, 126.8, 126.3, 55.0 (CH_2Ph); MS: 338 (4), 91 (100). Four crystallizations ((Et_2O, EtOAc–hexanes) gave a nitrone-free (tlc, PMR) sample, m.p. 108–122°. (Found: c, 74.56; H, 8.03; N, 8.02; Calc. ($C_{21}H_{26}N_2O_2$): C, 74.52; H, 7.74; N, 8.28%.) More **7** (pure by tlc or PMR) was gleaned by repeated rechromatography and recrystallization; the estimated yield of **7** was 32%.

6 - *Benzyl* - 6a - *methyl* - 3, 4, 4a, 6a, 6b, 7, 8, 9, 10, 11a - *decahydro* - 10H, 12H - *indolizino* [3, 2-c] *indoxazin* - 12 - *one* (**16**). Rechromatography on Al_2O_3 of selected pooled fractions and elution with 75% Et_2O–hexanes gave the more polar isomer **16**, m.p. 162.5–163.5° (Et_2O). (Found: C, 74.46; H, 7.83; N, 8.24%; Calc. ($C_{21}H_{26}N_2O_2$).)

IR: 1680, 1450; PMR: 7.5–7.1 (m, C_6H_5), 6.20 (d of t, $J_{2-3\alpha} = J_{2-3\beta} = 4.5$, $J_{2-1} = 10$, H_2), 5.40 (br d, 10, H_1), 4.38–3.99 (overlapping m of H_{10eq}) and 4.25 (t, 4, H_{4a}) (2H), 3.85 (s, CH_2–Ph), 3.24 (dd, 13, 2, H_{6b}), 2.69 (br t, 12, H_{10ax}), 2.25–0.81 (en) and 1.04 (s, CMe); CMR: 173.4 (C_{12}), 138.2, 133.3 (C_2 or C_1), 128.3, 128.0, 127.1, 124.6 (C_1 or C_2), 78.4 (C_{4a}), 71.7 (C_{6a}), 63.7 (C_{6b}), 60.9 (C_{12a}), 53.5 (CH_2–Ph), 40.8 (C_{10}), 29.2 (C_7), 23.5, 24.7, 24.4, 20.3, 12.2; MS: 338 (4), 91 (100).

11, N - *Dimethyl* - 6a, 11-*epoxyimino* - 1, 3, 4, 6, 6a, 7, 8, 9, 10, 10a, 11, 11a - *dodecahydro* - 2H - *benzo* [b] quinolizin - 6 - one (**12**). Ketone **11** (5.80 g), MeNHOH HCl (8.10 g), $(i\text{-}Pr)_2NEt$ (17.2 ml) and EtOH (25 ml) were boiled 19 hrs under reflux, evaporated, worked-up (neutral conditions) as described for **4**, and chromatographed on silica gel. Elution with 2% MeOH–$CHCl_3$ and crystallization gave the less polar isomer **12** (0.346 g, 5.3%), m.p. 168.5–170.5° (Et_2O). (Found: C, 68.28; H, 9.32; N, 10.62%; Calc. ($C_{15}H_{24}N_2O_2$).) IR: 1640, 1440; PMR: 4.63 (br q, 12, 2.5, H_{4eq}), 3.09–2.89 (overlapping m) and 2.83 (s, NMe) (4H), 2.57–0.75 (en) and 1.22 (s, CMe) (19H); CMR: 169.4 (s, C_6), 77.9 (s, C_{6a}), 67.9 (d, C_{11a}), 65.8 (s, C_{11}), 48.9 (d, C_{10a}), 42.7 (t or q, C_4 or NMe), 41.7 (q or t, NMe or C_4), 26.1, 25.5, 24.8, 24.3, 24.1, 24.0, 21.1 (t), 13.6 (q, CMe); MS: 264 (16), 56 (100).

6, 6a - *Dimethyl* - 1, 2, 3, 4, 4a, 6a, 6b, 7, 8, 9, 10, 11a - *dodecahydro* - 10H, 12H - *indolizino* [3, 2-c] *indoxazin* - 12 - *one* (**13**). Continued elution of the foregoing column gave the more polar isomer **13** (4.22 g, 64.7%) as a yellow oil crystallizing from hexanes, m.p. 78.0–79.5°. (Found: C, 68.21; H, 9.27; N, 10.79%; Calc. ($C_{15}H_{24}N_2O_2$).) IR: 1670, 1450; PMR: 4.30–3.95 (overlapping m, H_{10eq} and H_{4a}), 3.23 (dd, 11, 3, H_{10ax}), 2.86–2.48 (overlapping m, H_{6b}) and 2.63 (s, NMe) (4H), 2.70–2.14 (en) and 1.10 (s, CMe) (17H); CMR: 174.2 (s, C_{12}) 78.5 (d, C_{4a}), 71.0 (s, C_{6a}), 60.4 (s, C_{12a}), 59.8 (d, C_{6b}), 40.5 (t, C_{10}), 36.5 (q, NMe), 28.9 (t, C_7), 25.7, 24.8, 24.7, 24.4, 18.5, 17.7, 11.6 (q, CMe); MS: 264 (36), 56 (100).

1, 10bβ-*Dimethyl* - 3, 3aβ, 4, 5, 7, 8, 9, 10, 10aα, 10b - *decahydro* - 1H - *isoxazolo* [5, 4-a] *quinolizin* - 5 - *one* (**8**). Chromatographed **3** (17.0 g), MeNHOH HCl (21.8 g) $(i\text{-}Pr)_2NEt$ (45.6 ml) and EtOH (129 ml) were boiled under reflux in N_2 for 25 hr and evaporated; the residue in H_2O (300 ml) was extracted ($CHCl_3$), and the extract chromatographed on silica gel. 5% MeOH–$CHCl_3$ eluted oily **8** (7.80 g, 40%); rechromatography of a forerun gave another 0.93 g (5%) of **8** IR: 1630, 1440; PMR: 4.47–4.00 (overlapping m, H_{8eq}) and 4.26 (t, 8, $H_{3\alpha}$ or $H_{3\beta}$), 3.56 (t, 8, $H_{2\beta}$ or $H_{3\alpha}$) and 3.35 (br dd, 10, 2, H_{10a}) (3H), 3.05–2.40 (overlapping m, H_{3a} (irradiation at 2.8 affected $H_{3\alpha}$ and $H_{3\beta}$), J_{7ax}, $2H_4$) and 2.61 (s, NMe) (7H), 2.10–1.30 (en, 6H), 1.19 (s, CMe); CMR: 39.0 (NMe); MS: 224 (15), 84 (100).

1 - *Benzyl* - 10bβ - *methyl* - 3, 3aβ, 4, 5, 7, 8, 9, 10, 10aα, 10b - *decahydro* - 1H - *isoxazolo* [5, 4-a] *quinolizin* - 5 - *one* (**9**). Crude **3** (3.00 g), BzNHOH[24] (3.79 g) and EtOH (23 ml) were boiled 4 days under reflux, concentrated, and chromatographed on silica gel. Elution with 2% MeOH–$CHCl_3$, rechromatography on silica gel and elution with 1% MeOH–$CHCl_3$ gave pure (tlc), oily **9** (0.968 g, 21%). IR: 1640, 1440; PMR: 7.31 (br s, C_6H_5), 4.64–4.21 (overlapping m, H_{7eq}) and 4.16 (t, 8, $H_{3\alpha}$ or $H_{3\beta}$) (2H), 3.50 (t, 8, $H_{3\beta}$ or $H_{3\alpha}$) and 3.34 (br, overlapping dd, 10, 2, H_{10a}) (2H), 3.00–2.38 (en, H_{3a}, $2H_4$, H_{7ax}) (4H), 2.10–1.02 (en, $-(CH_2)_3-$) and 1.26 (s, CMe) (9H); CMR: 138.2, 128.5, 128.4, 127.2, 55.4 (CH_2Ph); MS: 300 (3), 91 (100).

1 - *Hydroxy* - 12bβ - *methyl* - 1, 2, 3aβ, 4, 5, 6, 6aβ, 9, 10, 11, 12, 12aα, 12b, 12cβ - *tetradecahydrooxazino* [6, 5, 4-k, 1] benzo [b] - *quinolizin* - 2 - *one* (**19**). After 1 hr at 0–5°, a soln of mCPBA (1.64 g, 80–90%), **4** (2.14 g) and CH_2Cl_2 (75 ml) was chromatographed on silica gel. $CHCl_3$–MeOH-conc. aq. NH_3 (97.5–2.25–0.25) eluted **19** (1.30 g, 57%), m.p. 226.5–228.0° (MeOH). (Found: C, 64.39; H, 8.83; N, 9.96; Calc. ($C_{15}H_{24}N_2O_3$): C, 64.26; H, 8.63; N, 9.99%). IR (Nujol): 3225, 1620; PMR: 7.88 (s, ex, OH), 4.42 (br d, 12, H_{9eq}), 4.21 (d, 9.5) and 4.18 (d, 9.5) ($2H_2$), 3.93 (br q, H_{3a}), 3.48 (br d, 11, H_{12a}), 2.3–1.1 (en), 1.20 (s, CMe); MS: 280 (13), 84 (100).

10α - *Hydroxy* - 11α - *hydroxylamino* - 11β - *methyl* - 1, 3, 4, 6, 6aβ, 7, 8, 9, 10, 10aβ, 11, 11aα - *dodecahydro* - 2H - *benzo* [*b*] *quinolizin* - 6 - *one* (**20**). After 18.5 hr at 25°, the mixture from **19** (0.800 g), dimedone (0.841 g) and 50% aq EtOH (16 ml) was filtered, the ppt crystallized giving dimedone-formaldehyde (0.77 g, 92%), m.p. 188.0–191.0° (MeOH) (lit.[35] 191–191.5°), and the filtrate chromatographed on silica gel. $CHCl_3$–MeOH-conc aq NH_3 (95–4.5–0.5) eluted **20** (0.487 g, 64%), m.p. 208–212° (EtOAc–MeOH). (Found: C, 62.86; H, 9.17; N, 10.28; Calc. ($C_{14}H_{24}N_2O_3$): C, 62.66; H, 9.01; N, 10.44%.) IR (KBr): 3420, 3250, 1610; PMR (DMSO-d_6): 4.48 (br d, 13, H_{4eq}), 4.12 (br s, H_{10}), 3.20–1.00 (en), 1.18 (s, CMe); MS: 268 (8), 84 (100).

11α - *Amino* - 10α - *hydroxy* - 11β - *methyl* - 1, 3, 4, 6, 6aβ, 7, 8, 9, 10aβ, 11, 11aα - *dodecahydro* - 2H - *benzo* [b] *quinolizin* - 6 - *one* (**18**)

A. From **5**. The mixture from hydrogenolysis (2 days, 25°, 60 psi of H_2, Paar shaker) of crude **5** (3.20 g) with 20% $Pd(OH)_2$ on C (2.6 g) in EtOH (50 ml) was filtered and the concentrated filtrate crystallized giving **18** (1.11 g, 36% (2 steps)), m.p. 196.0–198.0° (EtOAc). (Found: C, 67.03; H, 9.91; N, 11.24. Calc. ($C_{14}H_{24}N_2O_2$): C, 66.63; H, 9.59; N, 11.10%.) IR: 3600, 3400, 1630, 1440; PMR: 4.64 (br d, 12, H_{4eq}), 4.36 (br s, $W_{h/2} = 6$, H_{10a}), 3.34 (br d, 11,2, H_{11a}), 2.74–0.78 (en), 1.45 (s, ex, NH_2) and 1.24 (s, CMe) (21H); CMR: 172.5 (s, C_6), 67.2 (d, C_{10}), 65.3 (d, C_{11a}), 51.7 (s, C_{11}), 50.6 (d, C_{6a}), 43.2 (dd, C_4), 35.2 (d, C_{10a}), 34.1 (t, C_1), 26.7, 26.2, 25.9, 25.2, 24.8, 16.3 (t); MS: 252 (4), 84 (100).

B. *From* **7**. The filtered, concentrated product from hydrogenolysis (2 days, 25°, 60 psi of H_2, Paar shaker) of **7** (1.21 g) with 20% $Pd(OH)_2$ on C (1.2 g) in EtOH (100 ml) was chromatographed on silica gel. $CHCl_3$–MeOH-conc aq NH_3 (90-9-1) eluted **18** (0.169 g, 23%), identified by tlc, IR and PMR.

C. *From* **20**. The filtered, concentrated product from hydrogenolysis (69 hr, 25°, 60 psi of H_2, Paar shaker) of **20** (0.40 g) with 20% $Pd(OH)_2$ on C (0.40 g) in EtOH (25 ml) was crystallized (EtOAc) giving **18** (0.181 g, 48%), m.p. 193–196.5°, identified by tlc, IR, PMR, and m.m.p. (191.5–193.5°).

2α - *Hydroxymethyl* - 1β - *methyl* - 1α - *methylamino* - 1, 2, 3, 4, 6, 7, 8, 9aα - *octahydro* - 9H - *quinolizin* - 4 - *one* (**17**). Reduction of **8** (0.612 g) with excess Zn in HOAc-H_2O at 75°, basifying (pH 11, 50% aq NaOH), and extracting ($CHCl_3$) gave oily **17** (0.521 g, 84%) crystallizing from Et_2O–CH_2Cl_2, m.p. 106–109°. (Found: C, 63.90; H, 9.96; N, 12.51. Calc. ($C_{12}H_{22}N_2O_2$): C, 63.88; H, 9.80; N, 12.38%.) IR ($CHCl_3$): 3300 (intramolecularly H-bonded (dilution experiments)), 1620; PMR: 4.78 (br d, $J_{6eq-6ax} = 13.5$, H_{6eq}), 4.09 (dd, $J_{gem} = 11.5$, $J_{2ax-CH(H)OH} = 3$, CH(H)OH), 3.70 (dd, $J_{gem} = 11.5$, $J_{2ax-CH(H)OH} = 3$, CH(H)OH), 3.88 (dd, $J_{9a-9ax} = 10.5$, $J_{9a-9eq} = 3$, H_{9a}), 2.88 (dd, $J_{gem} = 18.6$, $J_{3ax-2ax} = 12.6$, H_{3ax}), 2.65–2.20 (en, H_{3eq}, H_{6a} and OH) and 2.34 (s, NMe) (6H), 2.00 (complex m, H_2), 1.85–1.20 (en) and 1.25 (s, CMe) (9H) (the assignments of H_{6eq}, CH_2OH, H_{9a}, H_{3ax} and H_2 were made or confirmed by reciprocal double resonance experiments); CMR: 168.7 (s, C_4), 62.9 (t, CH_2OH), 62.3 (d, C_{9a}), 56.0 (s, C_1), 45.0 (dd, C_6), 37.9 (d, C_2), 30.8 (t, C_3), 29.2 (t, C_9), 27.6 (q, NMe), 25.4 (C_7 or C_8), 25.5 (C_8 or C_7), 20.1 (q, CMe); MS: 226 (1), 84 (100).

Crystal data.–$C_{15}H_{24}N_2O_2$ (**4**), $M = 264.4$, Orthorhombic, $a = 10.094(5)$, $b = 12.845(6)$, $c = 10.776(5)$ Å, $U = 1397$ Å^3, $Z = 4$, $D_c = 1.257$ g cm^{-3}, $F(000) = 576$. Cu–K_α radiation, $\lambda = 1.5418$ Å; $\mu(\text{Cu}-K_\alpha) = 6.7$ cm^{-1}. Space group $P2_12_12_1(D_2^4)$ uniquely from systematic absences: $h00$ when $h \neq 2n$, $0k0$ when $k \neq 2n$, $00l$ when $l \neq 2n$.

$C_{12}H_{22}N_2O_2 \cdot H_2O$ (**17**), $M = 244.3$, Orthorhombic, $a = 10.645(5)$, $b = 15.266(7)$, $c = 8.166(4)$ Å, $U = 1327$ Å^3, $Z =$

4, $D_c = 1.223\ g\ cm^{-3}$, $F(000) = 536$. $\mu(Cu\text{-}K_\alpha) = 7.2\ cm^{-1}$. Space group $P2_12_12_1(D_2^4)$ uniquely as for (**4**).

Crystallographic measurements. Preliminary unit-cell parameters and space group information were obtained from oscillation and Weissenberg photographs (Cu-K_α radiation) and from precession photographs (Mo-K_α radiation, $\lambda = 0.7101$ Å). Crystals of dimensions *ca* $0.28 \times 0.30 \times 0.54$ mm (**4**) and $0.20 \times 0.40 \times 0.50$ mm (**17**) were then oriented in turn on an Enraf–Nonius CAD-3 automated diffractometer (Ni-filtered Cu-K_α radiation) for intensity measurements, and one octant to $\theta = 67°$ was surveyed by means of the θ-2θ scanning technique as described previously.[36] From totals of 1448 (**4**) and 1378 (**17**) independent intensity measurements, only those 1185 and 1189, respectively, with $I > 2.0\sigma(I)$ [$\sigma^2(I)$ = scan count + total background count] were used in the structure analysis after the usual Lorentz and polarization corrections had been applied. Refined unit-cell parameters were derived by least-squares treatment of the diffractometer setting angles for 40 reflections widely separated in reciprocal space.

Structure analysis. Initial structure models for both compounds were obtained by use of the MULTAN76 series of programs.[31] Refinement of non-hydrogen atom positional and thermal parameters by full-matrix least-squares calculations proceeded smoothly to R values of 0.125 (**4**) and 0.119 (**17**). Hydrogen atom positional and isotropic thermal parameters, save those on the hydroxy group and water molecule in crystals of **17**, were included as variables in the subsequent least-squares iteration which converged to $R = 0.050$ for **4** and 0.049 for **17**. Final atomic positional and thermal parameters are in Tables 3 and 4.

Atomic scattering factors used in all structure-factor calculations were those for C, N, and O from Ref. 37 and for H from Ref 38. In the least-squares calculations, $\Sigma w\Delta^2$ ($\Delta = \|F_0| - F_c\|$) was minimized; the weighting scheme used, $\sqrt{w} = 1$ when $|F_0| < K$ and $\sqrt{w} = K/|F_0|$ when $|F_0| > K$(K = 10.0 for **4**, and K = 7.0 for **17**), showed only random variations of $\langle w\Delta^2 \rangle$ when analyzed in ranges of $|F_0|$ and $\sin\theta$.

Acknowledgements—We thank the staff of Analytical Research Services of Schering-Plough Corporation for microanalyses and spectra. Indebted to Messrs. I. Berger, M. Cohen, and R. Runkle for preparing supplies, to Mrs. JoAnn O'Dell for typing, and to Dr. B. A. Pearlman for detailed procedures, we thank them especially.

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A CHEMICAL AND THERMOCHEMICAL STUDY OF NON-OBSERVED SYMMETRY ALLOWED REACTIONS†

S. RANGANATHAN*, D. RANGANATHAN*, P. V. RAMACHANDRAN, M. K. MAHANTY and S. BAMEZAI
Department of Chemistry, Indian Institute of Technology, Kanpur-208016, India

(*Received in the UK* 12 *October* 1980)

Abstract—A variety of reactions, whilst predicted to be symmetry allowed, are not observed experimentally. Several such non-observed yet allowed reactions have been studied in order to understand them and to possibly bring about, with suitably modified substrates, their observation. For example, although ozone adds to π-bonds, the isoelectronic nitro group does not, due to a high activation energy barrier. This reaction is of the type $A \rightleftarrows B \rightarrow C$. Molecular orbital calculations of a series of 1,3-dipolar species reveal a correlation of the π bond order with their effectiveness in $[4+2]$-additions. Based on this, the nitro group as well as ozone should be considered as poor dipolar agents. The exceptionally high ΔH_f° of ozone ($+34.00$ kcal mol^{-1}) as compared with that of nitrobenzene ($+3.8$ kcal mol^{-1}) could possibly explain the reactivity of the former. This is reflected in an estimated ΔH° value of -45.5 kcal mol^{-1} for the ethylene–ozone addition as compared with $+7.5$ kcal mol^{-1} for the *non-occurring* ethylene–nitrobenzene addition. Thermochemical calculations demonstrate that the nitrogroup is more prone to undergo addition as a 2π partner than as a 1,3-dipolar reagent.

The thermal, nitro group—olefin addition has been examined using a variety of electrophilic nitrobenzenes with tetracyclone as the common substrate. The extent of cyclo-addition was assessed on the basis of the isolation of 2-benzoyl-3,4,5-triphenylfuran. 4-Nitro-4′-methyl diphenyl sulfone and 4,4′-dinitro diphenyl sulfone have been identified as efficient reagents for these reactions. The former compound has been found to add to even non-conjugated olefins.

The clean thermal transformation of crystalline 7,7-dimethyl-bicyclo[2.2.1]heptane-1-nitrile oxide to the corresponding isocyanate is an example of the observable $A \rightleftarrows B \rightarrow C$ change. In this case, the oxazirine corresponding to B, arising from conrotatory cyclisation, undergoes irreversible rupture ($B \rightarrow C$). Such transformations are not observed with the stereochemically more favoured nitrones since these belong to the type $A \rightleftarrows B$.

The $\pi^4s + \pi^2s$ addition of carboxylates to olefins would lead to a carbon base at the expense of an oxygen one. This is clearly unfavourable and is not observed. On the other hand, the reverse of this reaction, namely, the fragmentation of ketal conjugate bases to carboxylates would be expected to be facile. This is indeed so and the process has been shown to be concerted. Ketals from p-nitrobenzaldehyde are shown to undergo fragmentation with 1,5-diazabicyclo[3.4.0]nonene-5 (DBN) to olefins. The carboxylate–olefin addition belongs to the general category $\pi + A^- \rightleftarrows B^-$, that encompasses cycloadditions, electrocyclic reactions and sigmatropic shifts. An equation $\Delta G^\circ = [1.4(pK_a^{BH} - pK_a^{AH}) + X]$ kcal mol^{-1}, wherein X is dependent on the reaction type has been derived for predicting the ΔG° for these $\pi + A^- \rightleftarrows B^-$ processes.

Of practical interest is the development of perturbed $\pi + A_1^- \rightleftarrows B_1^-$ systems that are predicted to occur in the forward direction, where the parent type $\pi + A^- \rightleftarrows B^-$ is not favoured. Although no worthwhile synthon may be devised that might simulate either the carboxylate–olefin addition, or the enolate–olefin addition, the perturbation of the allyl anion is possible, principally by substitution with electron-withdrawing substituents at 2 position. Thus, the anions derived from propenes that carry $-CN$, $-NO_2$, $-SO_2Ph$, $-SO_2CF_3$, $-COO^tBu$, $-CO^tBu$ and $-N_2^+$ as 2-substituents are predicted to add to olefins thereby providing novel routes to functionalised cyclopentanes.

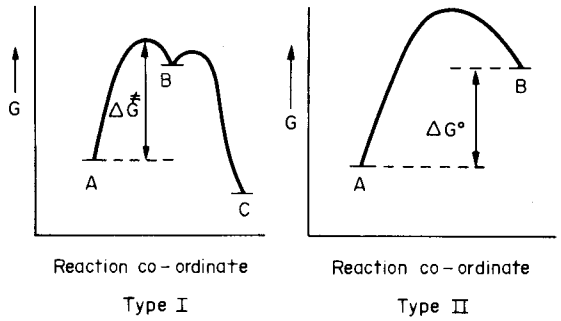
In preliminary investigations, the 2-nitropropene anion unit, generated *via* the collapse of nitrocyclopropane-9,9′-fluorene conjugate base, underwent rapid nitrite elimination leading to allene, thus precluding cycloaddition to added styrene. A preference for [2,3] shift over [3,3] is exhibited by oxime–O–allyl ethers as predicted by the above equation. Several observed and non-observed symmetry allowed reactions have been rationalised using the pK_a concept.

Highly unfavourable $\pi + A^- \rightleftarrows B^-$ changes can be, in principle, realised via the strategy $\pi + A^- \rightleftarrows B^- \rightarrow C^-$. This is possible by appropriate incorporation of weak bonds such as N–O, S–S and O–O with the B^- unit. Endeavours to illustrate this with an unusual oxadiazolinone carrying a particularly fragile N–O bond and with 3-lithiomethyl benzisoxazole are presented.

The principle of the conservation of orbital symmetry[1] enables a prediction of the feasibility of a concerted process. However, a variety of reactions, whilst predicted to be symmetry allowed, are not observed experimentally. In the present work, using experiment and theory, several such non-observed, allowed reactions have been studied in order to understand them and to possibly bring about, with suitably modified substrates, their observance.

As a first step, non-observed allowed reactions can be separated into two categories, namely, I: $A \rightleftarrows B \rightarrow C$ and II: $A \rightleftarrows B$.

†We respectfully dedicate this work to the memory of Professor R. B. Woodward. This paper will be included in the Book version of the special Woodward Memorial Supplement.



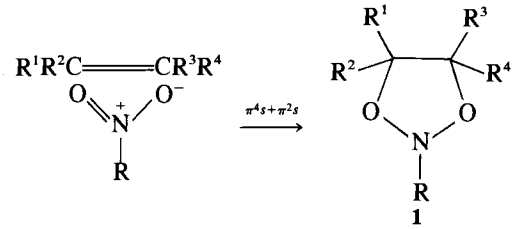
The non-observance of a symmetry allowed A ⇄ B change can be either due to the absence of B in the reaction mixture or because the amount present may be so small that it cannot be detected by the probe employed.

A reaction of the Type I: A ⇄ B → C, offers a method to differentiate the two possibilities mentioned above. In this category, compound B is expected to be rapidly converted to C either on the basis of its preparation by other means or on the basis of reaction mechanisms. If, even after incorporation of such a step, the allowed reaction is not observed, it could be concluded that in the A ⇄ B change, the barrier, which normally is moderate for allowed reactions, is overwhelmingly large. On the other hand, formation of C could be an indication of the presence of B and therefore a demonstration of the occurrence of the symmetry allowed A ⇄ B change.

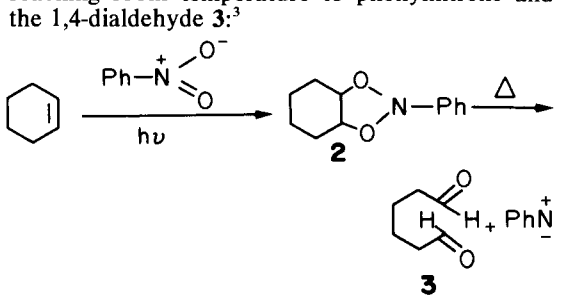
In spite of a surmountable activation energy barrier and the stability of A and B, an allowed reaction of the Type II may not be observed because of highly unfavourable equilibrium. Each of these types are further discussed below.

Type I: A ⇄ B → C where A ⇄ B. Cycloadditions involving the nitro group

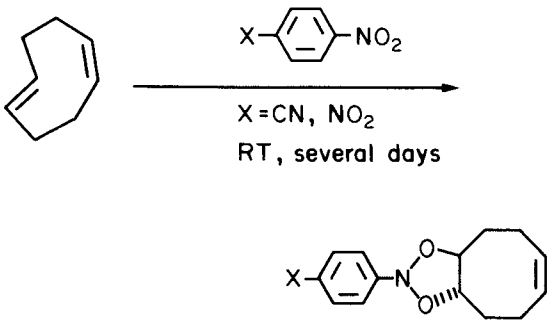
The nitro group being isoelectronic with ozone can be expected to add to olefins leading to **1**:



However such additions, potentially of great practical significance, are not generally observed.[2] Adducts related to **1** prepared by non-concerted additions are thermally unstable. Thus, the cyclohexene–nitrobenzene adduct **2** decomposes on reaching room temperature to phenylnitrene and the 1,4-dialdehyde **3**:[3]



The ready change **2**→**3** should enable the identification of the thermal olefin–nitro group addition, even though the adduct **2** is formed in extremely small amounts. The complete absence of any reaction on refluxing a variety of 2π-components in nitrobenzene[4] indicates a high barrier to the addition. This conclusion finds support from a study of the cycloaddition of nitro-aromatic compounds to the highly strained *E,Z*-cyclo-octadiene.[5] The latter compound undergoes totally stereospecific nitrogroup cycloaddition with aromatic nitro compounds carrying electron-withdrawing substituents leading to 1,3-dioxazolidines:



With nitrobenzene, however, the addition is sluggish and competes with the dimerisation of *E,Z*-cyclo-octadiene itself. Interestingly, this addition is not effective with *E*-cyclooctene for which the "addition strain" has been estimated to be ~12 kcal mol^{-1} lower than the *E,Z*-diene. Of this strain factor, only about 25% contributes to the transition state. Thus, the transition state involving nitro group-olefin cycloaddition is closer to the starting materials. The importance of this observation is discussed later (*vide infra*).

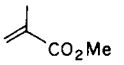
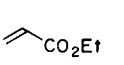
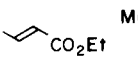
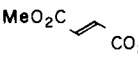
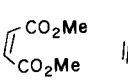
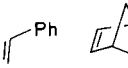
Over the past decade, we have examined diverse aspects of the thermal addition of the nitro group to π systems. Unlike ozone and nitrone, the isoelectronic nitro group does not participate in 1,3-dipolar cycloadditions. To rationalise this experimental reality, efforts were made to correlate observed reactivities in 1,3-dipolar cycloadditions to π-bond order (b.o.) and π-electron densities of the 1,3-dipolar species. Such a correlation should also enable a theoretical evaluation of perturbed nitro systems as potential partners in cycloadditions. We have found that there exists a correlation between the second order rate constants (k_2) of several [4+2]-additions and the 1,3-dipolar contribution of the 4π component, as reflected in the π. b.o. computed from Huckel–Molecular Orbital Theory.[6a] the contributing structures are:

$$a = b^+ - c^- \longleftrightarrow a^+ - b - c^-$$

π b.o.	1	0

Thus in Table 1 are presented k_2 values, all converted to 25° using the Arrhenius equation, for the cycloaddition of seven 2π components of diverse character to five 1,3-dipolar components, each one having a central sp nitrogen. The calculated π b.o. are also given. These data have

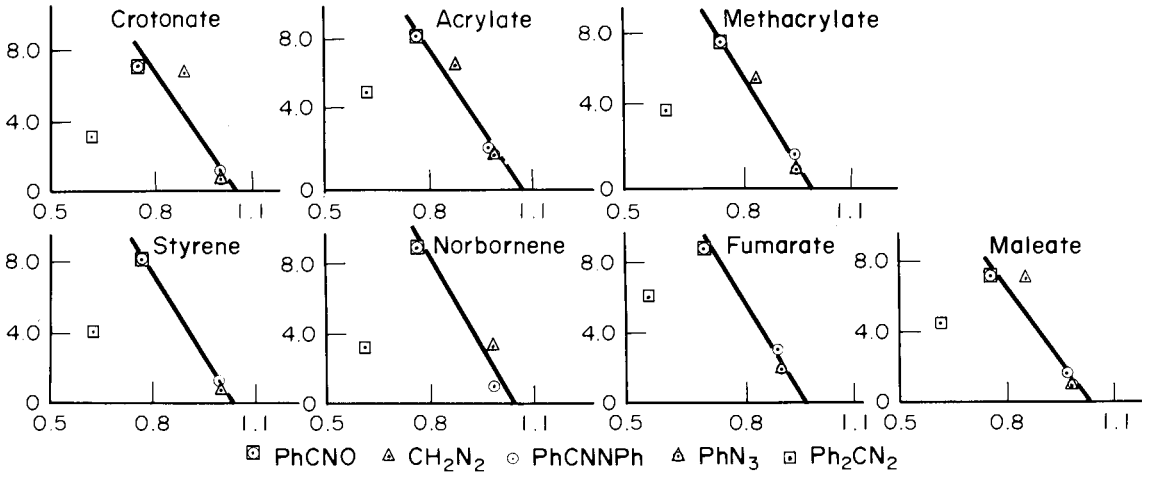
Table 1. Second order rate constants in $1\,mol^{-1}\,s^{-1}$ ($k_2 \times 10^8$), all converted to 25°, for the addition of 1,3-dipolar systems with 2π components

1, 3 dipolar system	π b.o.							
$Ph-\overset{+}{C}\equiv\overset{+}{N}-\overset{-}{O}$[a]	0.769	2.72×10^8	7.81×10^8	0.12×10^8	11.12×10^8	0.19×10^8	1.10×10^8	11.48×10^8
$H_2C=\overset{+}{N}=\overset{-}{N}$[b]	0.873	1.6×10^6	23×10^6	0.19×10^6	—	14×10^6	—	—
$Ph_2C=\overset{+}{N}=\overset{-}{N}$[c]	0.617	3.45×10^4	55.1×10^4	0.344×10^4	203×10^4	4.76×10^4	0.0798×10^4	0.169×10^4
$Ph-C\equiv\overset{+}{N}-\overset{-}{N}-Ph$[d]	0.981	2.42×10^2	8.65×10^2	0.0881×10^2	37×10^2	1.03×10^2	0.154×10^2	0.339×10^2
$Ph-N=\overset{+}{N}=\overset{-}{N}$[e]	0.997	7.2	98.5	2.7	85	3.4	4	1880

[a]R. Huisgen, R. Grashey and J. Sauer, *Chemistry of Alkenes* (Edited by S. Patai), p. 739–953; [b]A Ledwith and Y. Shih-Lin, *J. Chem. Soc.* (B), 83 (1967); THF; [c]R. Huisgen, H. Stangl, H. J. Sturm and H. Wagenhofer, *Angew. Chem.* **73**, 170 (1961); DMF; [d]A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, D. Grashey and E. Spindler, *Chem. Ber.* **100**, 2192 (1967); [e]R. Huisgen, G. Szeimies and L. Mobius, *Chem. Ber.* **100**, 2494 (1967); CCl_4.

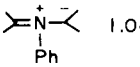
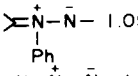
been presented in Chart 1 wherein $\log k_2$ values are plotted against the calculated π b.o. The reasonably good correlation that is found, in spite of the great divergence in the nature of the 2π component is noteworthy.[6b] These correlations bring out the contribution of the 1,3-dipolar character to the kinetic parameters. It should be possible, in principle to isolate the energy factors from the overall interactions that are reflected in the π b.o. We feel, however, that since the utility of this relationship is only to assess the efficacy of a given 1,3-dipole, this simple representation is adequate. It must be pointed out that in all the figures in Chart 1, diphenyldiazomethane exhibits a lower rate than predicted. This must be related to the increased steric crowding in the transition state.

Chart 1. π bond order vs $8 + \log K_2$ for the addition of 1,3-dipolar systems with 2π components (see Table 1).



In Table 2 diverse 1,3-dipolar systems are

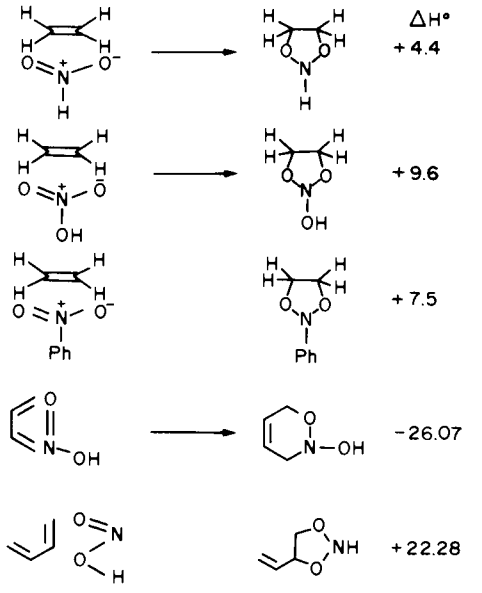
Table 2.

System	π b.O.	System	π b.O.	System	π b.O.	System	π b.O.
$N\equiv\overset{+}{N}-\overset{-}{C}<$	0.873		0.819		1.042	$-N=\overset{+}{O}-\overset{-}{N}-$	0.763
$-C\equiv\overset{+}{N}-\overset{-}{O}$	0.903		1.262		1.058	$>=\overset{+}{O}-\overset{-}{N}-$	0.865
$-C\equiv\overset{+}{N}-\overset{-}{C}<$	1.107			$-N=\overset{+}{N}-\overset{-}{N}-$ (Ph)	1.109	$>=\overset{+}{O}-\overset{-}{O}$	0.899
$-C\equiv\overset{+}{N}-\overset{-}{N}-$	1.113			$-N=\overset{+}{N}-\overset{-}{O}$ (Ph)	1.165	$>=\overset{+}{O}-<$	1.060
$N\equiv\overset{+}{N}-\overset{-}{N}$	1.147					$-N=\overset{+}{O}-\overset{-}{O}$	1.105
$N\equiv\overset{+}{N}-\overset{-}{O}$	1.330					$O=\overset{+}{O}-\overset{-}{O}$	1.250

arranged in the order of their π b.o. Although needed kinetic data are not available, a cursory examination of Table 2 brings out, again, a correlation between the calculated π b.o. and the reactivity of the 1,3-dipolar system in cycloaddition. From Table 2 it would be predicted that ozone should be a poor 1,3-dipolar agent just as the nitro group. This conclusion is certainly in error! Ozone has a special feature that makes it a good 1,3-dipolar agent. The exceptionally high heat of formation (ΔH_f°, ° referring to the standard state of 1 M or 1 atm, 25°C) + 34.00 kcal mol^{-1} of ozone compared with a ΔH_f° of +3.80 kcal mol^{-1} for nitrobenzene[7a] might be making an important contribution, particularly since, in such additions, the transition state is closer to starting materials. To test this, ΔH° for the ethylene–ozone addition as well as that of ethylene to nitrobenzene, nitric acid and nitrous acid were estimated employing group addition methods developed by Benson *et al.*[7b] The important result that whilst the ΔH° estimated for the *occurring* ethylene–ozone addition is −45.5 kcal mol^{-1}, that for the *non-occurring* addition of ethylene to nitrobenzene, nitric acid and nitrous acid are respectively +7.5, +9.6 and +4.4 kcal mol^{-1} (Table 3).

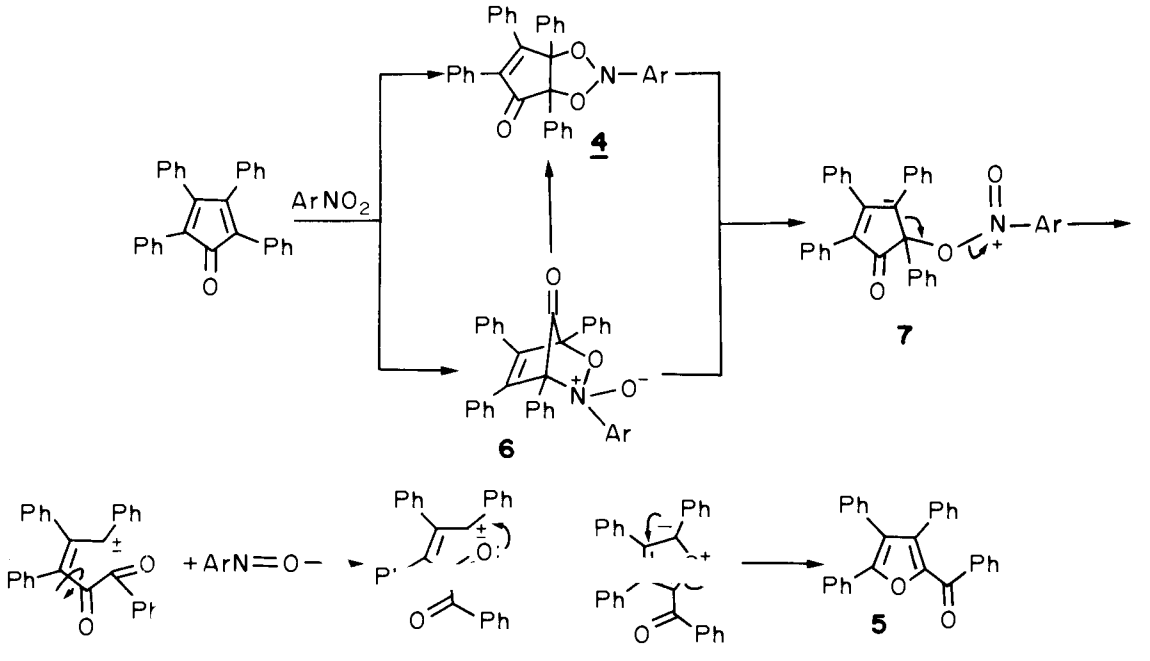
Parenthetically, such calculations demonstrate that the nitro group is more prone to undergo cycloaddition as a 2π partner than as a 1,3-dipolar agent (Table 3). The experimental realisation of $ArNO_2$–*E,Z*-cyclo-octadiene cycloaddition at room temperature suggests that the energy barrier to nitro group cycloaddition can be overcome with perturbed nitro systems. We have calculated the π b.o. for a variety of such perturbed systems. None of them was predicted to be an effective reagent. Simultaneously, however, the cycloaddition of the nitro group to π systems was explored with a wide variation of both the components.

Table 3. Estimated ΔH° values in kcal mol^{-1}



Of great significance in this context was the transformation of tetraphenylcyclopentadienone (tetracyclone) to pentaphenylpyrrole in boiling nitrobenzene discovered by Dilthey in 1941![8] We examined this reaction extensively and our results demonstrate that the primary interaction of the two components leads to the formation of the key adduct **4** (Chart 2). This then fragments to nitrosobenzene and 3,4,5-triphenyl-2-benzoylfuran **5**. The adduct **4** might also result by further transformation of the initially formed [4+2]-adduct **6**. The possibility that the oxygen transfer takes place by initial Michael addition of $PhNO_2$ leading to **7** can be ruled out since $PhNO_2$ can not parti-

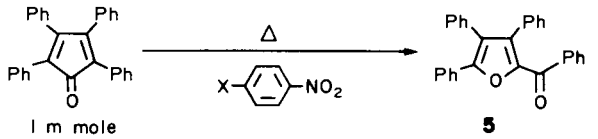
Chart 2



cipate in such processes. Indeed that is the reason for its use as a solvent in Friedel–Craft reactions! The yield of the crystalline furan **5** is then a measure of the extent of addition involving nitrobenzene and tetracyclone. We have examined the yield of the furan **5** as a function of substitution of nitrobenzene. Our results are presented in Table 4.

As in the photochemical cycloadditions, the carbonyl components present were complex. The isolation of azo-compound from reaction of tetracyclone with aromatic nitro compounds (see experimental) clearly establishes the intermediacy of nitrenes. The formation of **8** is not surprising since it is a good substrate for nitrene insertion.

Table 4.



X	Reagent (m moles)	Condition	% Yield of 5
H	excess	$PhNO_2$ reflux; 15 hr	6
CN	10	o-dichlorobenzene reflux; 48 hr	22
CN	10	200°; 7 hr	20
NO_2	10	200°; 7 hr	18
T_s	1	200°; 10 hr	48
N_2^+	1	200°; 6 hr	—

As anticipated, substitution of the nitrobenzene with electron withdrawing groups does increase the furan formation. The fact that a 50% yield of **5** could be realised with equivalent amounts of the reagent 4-nitro-4′-methyl diphenyl sulfone was indeed satisfying.

With a view to clearly establish a thermal nitro group-2π cycloaddition, 4-nitro 4′-methyl diphenyl sulfone, a good reagent for conversion of tetracyclone into **5** change, was reacted with equivalent amounts of acenaphthylene, tolan, maleic anhydride, and indene at 200°C. No reaction was observed. However, 4-nitro 4′-methyl diphenyl sulfone in dicyclopentadiene was rapidly consumed at 150°C and work-up gave a 32% yield of the insertion product **8**.

The formation of the nitrene *via* addition to monomeric cyclopentadiene and fragmentation is excluded from blank experiments. The versatility of 4-nitro 4′-methyl diphenyl sulfone in cycloadditions is being further examined.

The crystalline and stable *p*-nitrophenyl diazonium fluoborate **9** was also reacted with a number of π components. However, there was no evidence for the involvement of the nitro group. The major pathway was coupling leading to azo-compounds. Thus, the reaction of freshly cracked cyclopentadiene with **9** in refluxing methanol gave the bright yellow crystalline **11** in 96% yields! The structural assignment for **11** is supported by analysis, IR, NMR, MS, UV, UV(H^+), UV(OH^-) and its formation rationalized in Chart 3.

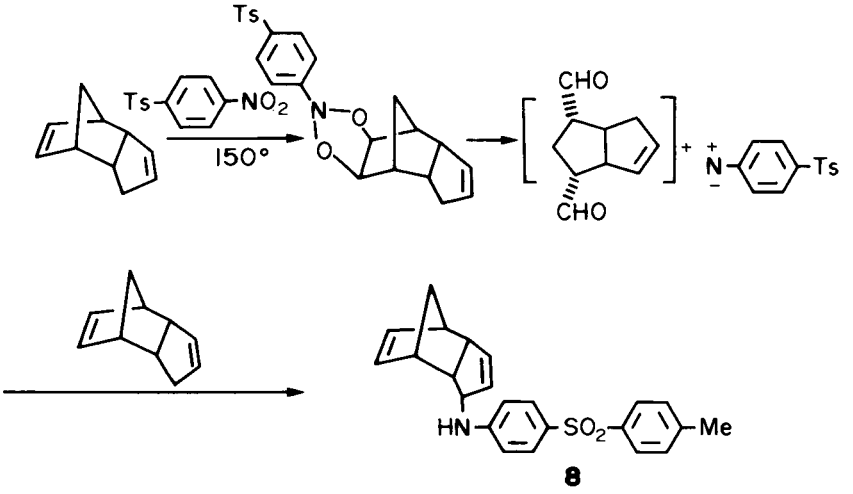
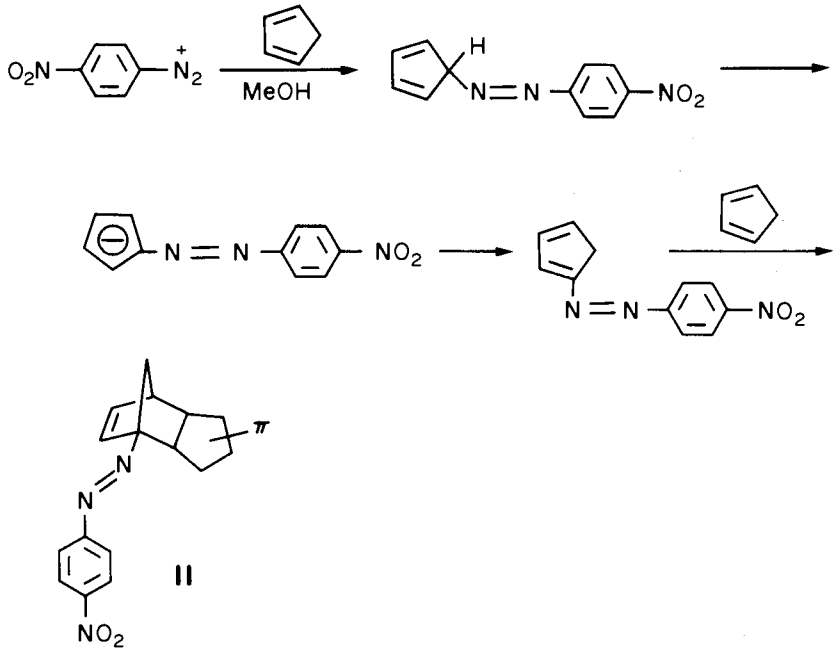


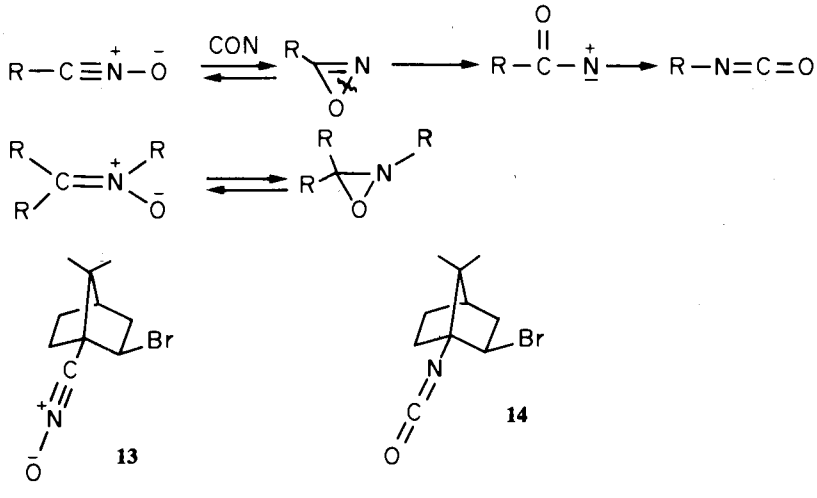
Chart 3



Type I: $A \rightleftarrows B \rightarrow C$. *The nitrile oxide⟶isocyanate rearrangement*

Nitrile oxides which do not dimerize are converted thermally to isocyanates. This change is concerted as evident from studies with labelled substrates[9] and from our own observation[10] of the smooth transformation of the stable bridgehead nitrile oxide **13** to the corresponding isocyanate **14**. The rearrangement therefore, must be taking place *via* a conrotatory cyclization followed by an irreversible oxazirine opening and Curtius rearrangement (Chart 4). The occurrence of the cyclization is discernable because of the irreversible removal of the intermediate oxazirine. Thus this change belongs to the type I: $A \rightleftarrows B \rightarrow C$. Interestingly, the related nitrone ⟶ oxazirane change, although stereochemically more favourable, is not observed.[11] Indeed, the observed transformation is oxazirane ⟶ nitrone.[12] The reaction is not observed since it belongs to the type $A \rightleftarrows B$ wherein the forward change is not favoured (Chart 4).

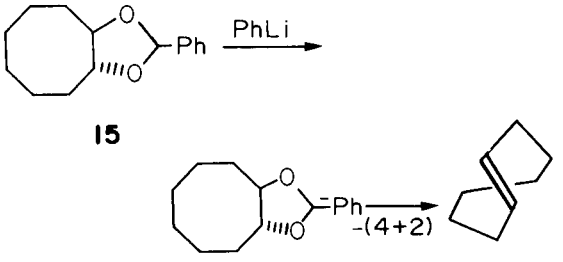
Chart 4



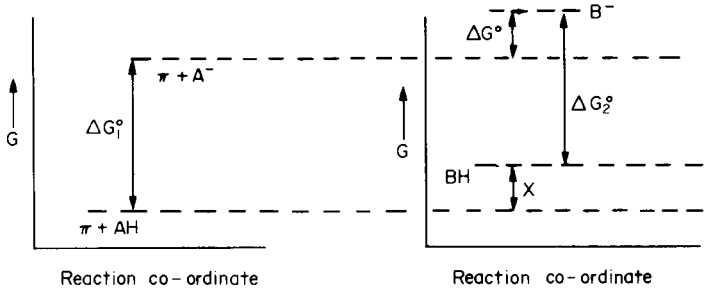
Type II: $A \rightleftarrows B$. $\pi + A^- \rightleftarrows B^-$ *cycloadditions*

A surprisingly large number of reactions involve the concerted transformation of an electron excess species ($\pi + A^-$) to another (B^-) wherein the process $\pi + A^- \rightleftarrows B^-$ is not complicated by irreversible side reactions. In such cases, provided the kinetic barrier is surmountable the direction of a symmetry "allowed" reaction will be dictated by $\Delta G°$ factors. This rationalization finds much support in numerous examples that have come up recently. The (4+2) addition of carboxylates and enolates to olefins, *inter alia*, represents an important class of non-observed allowed, $\pi +$

$A^- \rightleftarrows B^-$ reactions. In these and related systems, the $B^- \rightarrow A^- + \pi$ change takes place with great ease and has become a useful method in organic synthesis. Such a fragmentation can be clean and must be proceeding in a concerted manner as evidenced by the formation of *E*-cyclooctene in 85% yield from ketal conjugate base generated from **15**:[13]

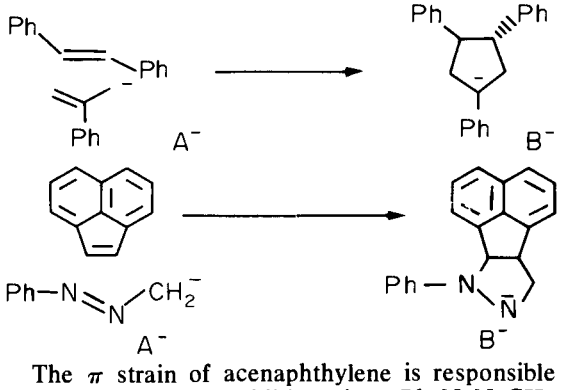


We have derived a relationship that correlates $\Delta G°$ of a $\pi + A^- \rightleftarrows B^-$ change with the pK_a of the respective conjugate acids AH and BH. The genesis of this relationship, represented by eqn (1) becomes apparent with the following illustration:



$$\Delta G_2^\circ - \Delta G_1^\circ + X = \Delta G^\circ$$
$$= [1.4(pK_a^{BH} - pK_a^{AH}) + X](\text{kcal mol}^{-1}) \quad (1)$$

Since the pK_a of AH and BH are available or could be approximated,[20] the realization of the magnitude of X would enable the estimation of the $\Delta G°$ that is responsible for the non-observance of a symmetry allowed reaction. Fortunately, in cycloaddition reactions, a fair idea of the importance of X can be extracted from experimental observations. That this is modest is brought out by the following observed reactions where the pK_a differences are very marginal.[14,15]

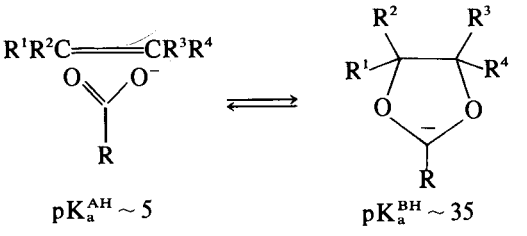


The π strain of acenaphthylene is responsible for the above cycloaddition since Ph–N=N–CH_2^- does not add to normal double bonds. Thus, it could be concluded that the allowed $\pi + A^- \rightleftarrows B^-$ change would be observed if the first term of the right hand side of eqn (1) is not very unfavourable. We feel that eqn (1) could be used with great advantage and this aspect is illustrated below.

THE APPLICATION OF EQN (1) TO ALLOWED $\pi + A^- \rightleftarrows B^-$ REACTIONS

Cycloaddition reactions

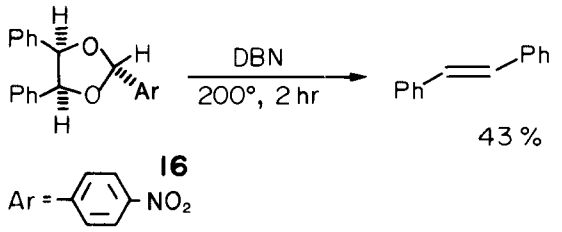
Carboxylate–olefin cycloaddition. The $\pi^4s + \pi^2s$ addition of carboxylate to olefins leads to a ketal conjugate base:



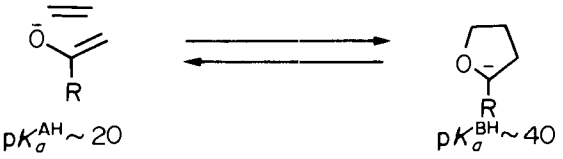
$$\Delta G° \cong 1.4(35 - 5) + X = [42 + X]\ \text{kcal mol}^{-1}$$

One could readily see that the free energy difference here is truly formidable and the great propensity for the reverse fragmentation is understandable. It can also be concluded that the reaction would proceed in the forward direction in the event the product carbon acid is stronger than the starting oxygen acid. It is difficult to suggest such an example with uncomplicated substrates and therefore we hold little hope of designing a carboxylate that would add to olefins. However, the reverse process could be exploited for the transformation, *vic*-diols to olefins.

The fragmentation of ketal conjugate bases is complicated in the case of substrates having other similar acidic sites. Thus, *meso* hydrobenzoin–benzaldehyde ketal gave only 6% *trans* stilbene from complex mixture arising from treatment with ^{n}BuLi.[16] We felt that an enhancement of the acidity of the proton involved in ketal fragmentation would enable the reaction to proceed well and therefore *p*-nitrobenzaldehyde could be a useful reagent for the transformation of *vic* diols to olefins. In the event, the ketal from *p*-nitro-benzaldehyde and *meso* hydrobenzoin **16** resisted fragmentation under mild conditions, where the initially formed *cis* stilbene is stable. However a 43% yield of *trans* stilbene was obtained on treatment of the ketal at 200°C for 2 hr with DBN.

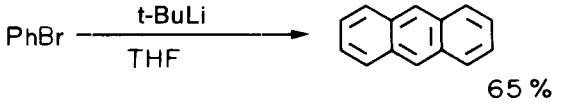


Enolate–olefin cycloadditions



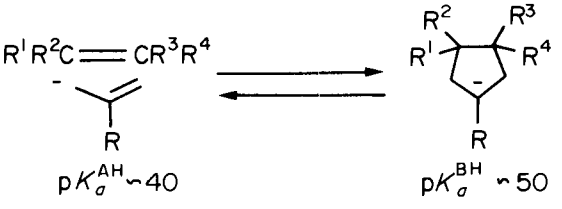
$$\Delta G^\circ \cong [28 + X] \text{ kcal mol}^{-1}$$

As in the previous case, this reaction is also highly unfavourable and as anticipated, the reverse process is exceedingly facile. Conjugate bases of tetrahydrofurans readily fragment to enolates and indeed this method has been exploited for the clean generation of enolates.[17] The ubiquitous nature of this fragmentation is best illustrated with the following fascinating transformation:[18]



In view of the highly unfavourable ΔG° associated with the enolate + π system, it is difficult to tailor perturbed simple synthons that would take the reaction in the forward direction.

Allyl anion–olefin cycloadditions. It should be noted that in the above reaction one carbon base is



$$\Delta G^\circ \cong [14 + X] \text{ kcal mol}^{-1}$$

transformed to another and, in contrast to the previous cases, the allyl anion system presents maximum versatility for perturbation leading to observable $\pi + A^- \rightleftarrows B^-$ reactions. Indeeed, the only $\pi + A^- \rightleftarrows B^-$ reactions, thus far observed, belongs to this type, wherein an initially formed carbon base is transformed either to a more stabilized carbanion or a nitrogen equivalent.[19] In both cases, the ΔG° can be predicted to be favourable (Chart 5). We feel that the allyl anion-olefin cycloaddition with perturbed substrates can be used to advantage in organic synthesis. A few of the possibilities, each predicted [20] on the basis of eqn (1) to take place, are presented in Chart 6.

An excellent method for the generation of 2-substituted propenyl carbanions envisaged in Chart 6 is *via* collapse of appropriate cyclo-

Chart 5

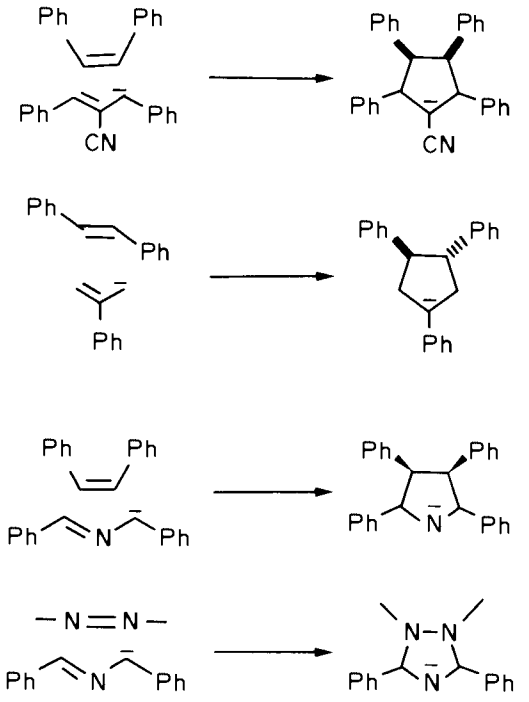
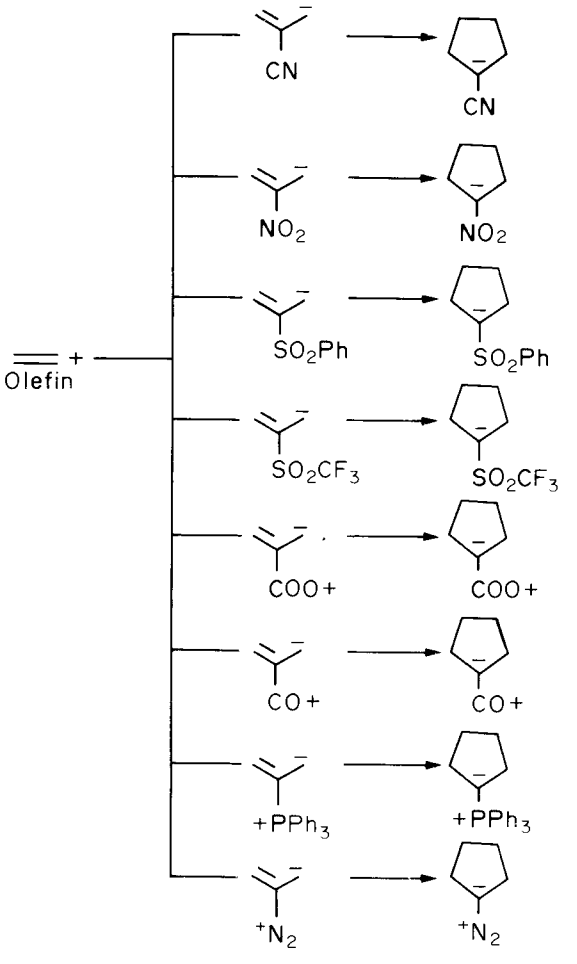
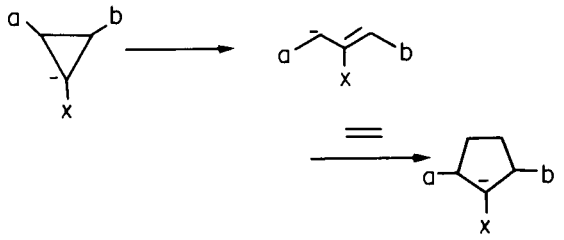
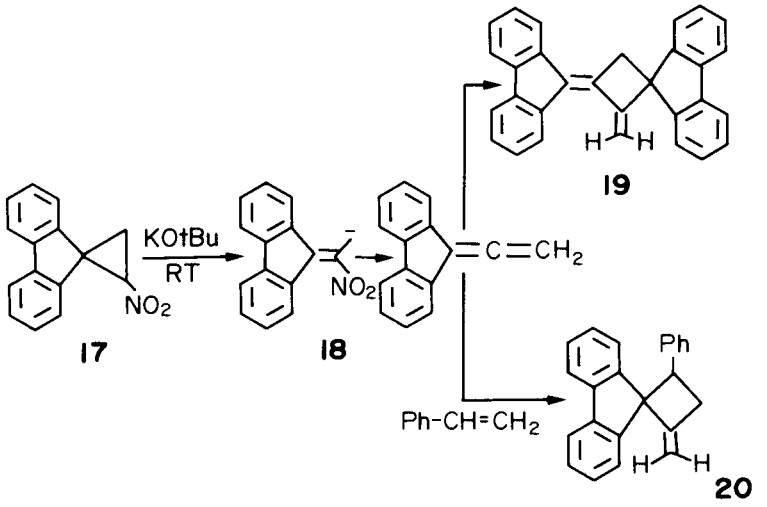


Chart 6





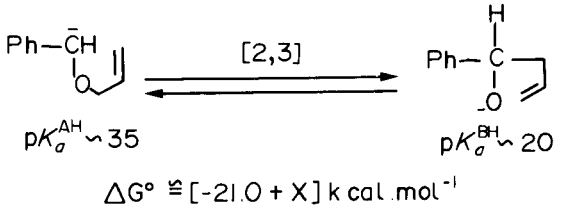
propane anions.[21] In this approach the cyclopropane strain is exploited to generate a stronger carbon base. Employing this strategy we generated the 2-nitropropenyl anion **18** by collapse of nitronate generated from the nitrospiro compound **17**:[22]



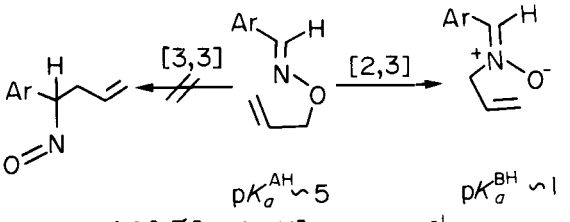
Unfortunately, at room temperature, **18** eliminated nitrite leading to allene which partly dimerised to **19** and partly underwent [2+2]-addition with styrene, introduced to capture **18** to give **20**. Modified conditions to curb the tendency of compounds related to **18** to eliminate and the generation of several species presented in Chart 6 are being explored.

Sigmatropic reactions

The pK_a considerations represented by eqn (1) become even more significant in the area of sigmatropic reactions of the type $A^- \rightleftarrows B^-$ since the value of X now principally associated with the activation energy ceases to be a major consideration. Thus the facile [2,3] shift represented by the following can be readily rationalized:[23]

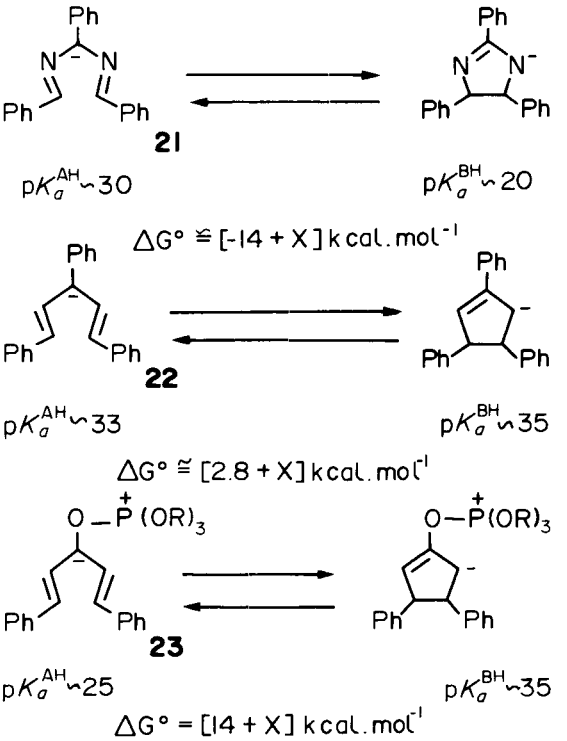


Indeed a great majority of the [2,3] shifts can be analysed in terms of such favoured $A^- \rightleftarrows B^-$ changes.[24] Our earlier unexpected finding that oxime–O–allyl ethers undergo [2,3] sigmatropic shift in preference to [3,3] can now be rationalised:[25]

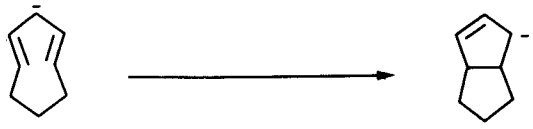


Electrocyclic reactions

Equation (1) provides a ready rationalisation for the fact that whilst **21** undergoes ready cyclisation[26] such a process does not take place either with **22** or with **23**.[27]



Nearly all treatises on Woodward–Hoffmann rules cite the following as a typical disrotatory cyclisation:[1]

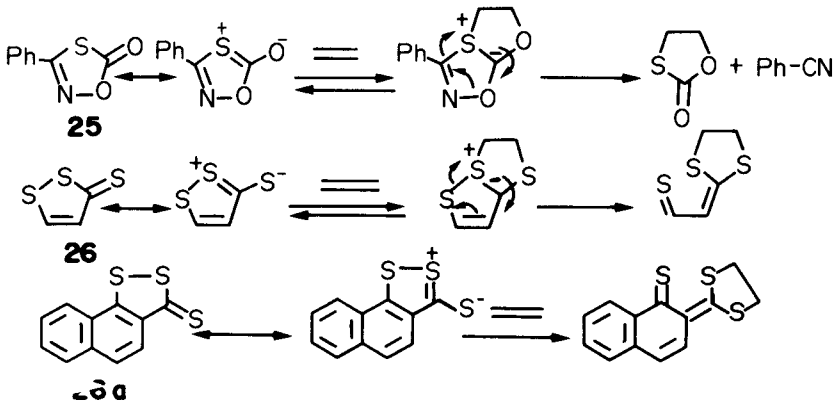


24

The above reaction represents a cyclopentadiene anion–allyl anion type cyclisation which according to eqn (1) would be predicted to be unfavourable. A ready explanation that seems to have been overlooked thus far was provided in the original paper itself.[28] Models, confirmed by NMR studies, clearly show that the five-centred dienide ion cannot achieve coplanarity. The best conformation associated with the observed cyclisation is one where the middle carbon is lifted from the plane by as much as 30°. The cyclisation then transforms a relatively destabilized carbanion to a stable allyl anion. This has been clearly pointed out by Bates,[28] who estimated the $\Delta G°$ for this change to be $-3\,\text{kcal mol}^{-1}$. Indeed, he has made the interesting prediction that when the ring size that incorporates the penta-dienide anion unit is increased, the cyclised form would be destabilized and therefore, the reaction may not take place. The cyclo-octadiene anion cyclisation is not an electrocyclic process in the normal sense.

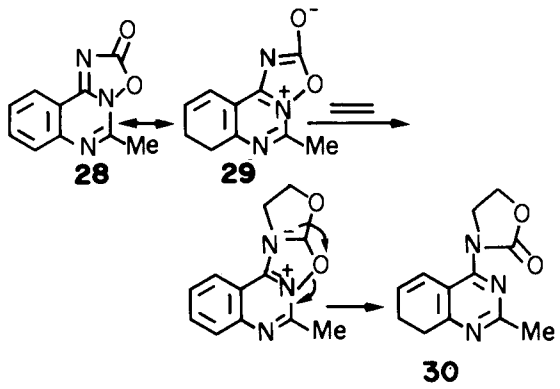
THE DEMONSTRATION OF A ⇄ B → C REACTIONS BY INCORPORATION OF WEAK BONDS

As stated earlier it is, in principle, possible to demonstrate the occurrence of non-observable A ⇄ B change by incorporating the feature A ⇄ B → C. For example in the nitrile oxide → isocyanate change the key step is the rupture of the weak N–O bond of oxazirine arising from con-rotatory cyclisation. Even the most unfavourable carboxylate–olefin cycloaddition may be, accomplished by this strategy. Thus, the weak bonded systems **25**,[29] **26**[30] and **26a**[31] could be considered as masked equivalents of the thiocarboxylate in cycloadditions:



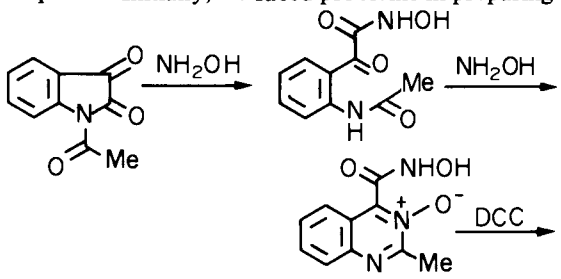
26a

We have examined the unusual oxadiazolinone **28** as a carboxylate equivalent in cycloadditions. Because of the major contributing structure **29** it should lead to the quinoxaline **30** *via* a facile N–O bond rupture.

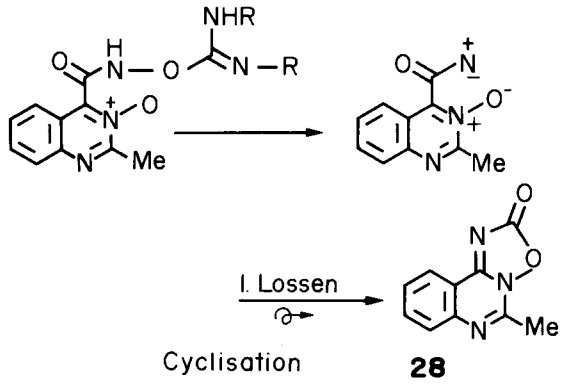


28 **29** **30**

Although **28** is known,[32] details relating to its preparation as well as yields are not available. It arises from N-acetylisation *via* the interesting sequence. Initially, we faced problems in preparing



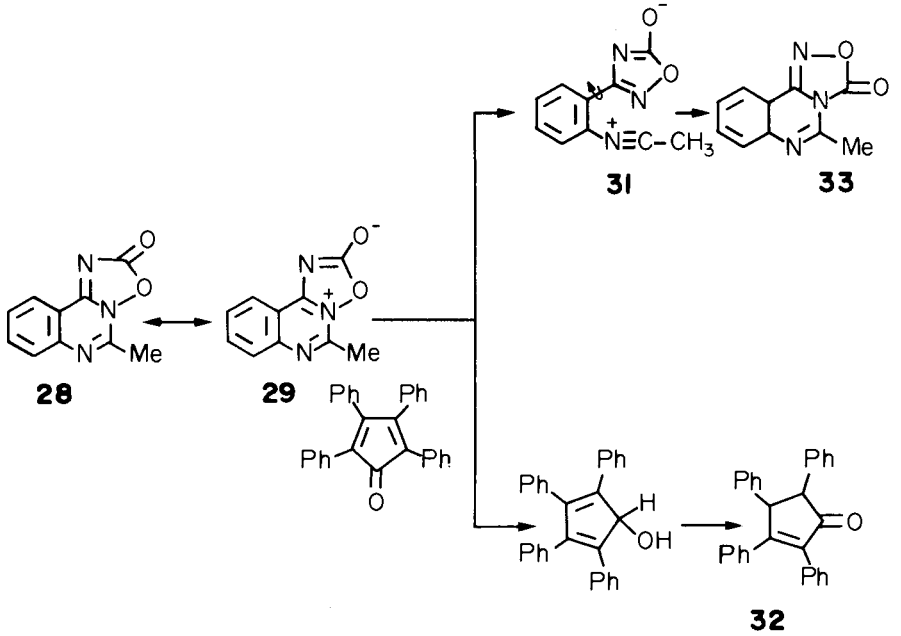
27



Cyclisation **28**

27 as well as **28**. However, they can now be obtained by precise procedures presented in the experimental section. The thermal reaction of **28** with tetraphenylcyclopentadienone at 200° for 6 hr gave a 50% yield of the isomeric oxadiazolinone

33,[33,34] and a 20% yield of cyclopentenone **32**. The formation of **33** and **32** are rationalized *via* novel pathways outlined below highlighting the importance of the contributing structure **29**:



A systematic study of **28** in cycloadditions is in progress.

The weak N–O bond of isoxazoles can be advantageously used to promote allyl anion–olefin type cycloaddition reactions. The versatility of this approach is illustrated in Chart 7 with 3,5-dimethylisoxazole. The conjugate base of 3-methylbenzisoxazole presents an unusual combination and illustrates the possible transformation of a strong carbon base to a very weak phenolate *via* cycloaddition and N–O bond rupture. (Chart 8).

3-Methylbenzisoxazole[35] was prepared by an improved procedure. Deuterium exchange experiments showed that NaH in dimethoxyethane

Chart 7

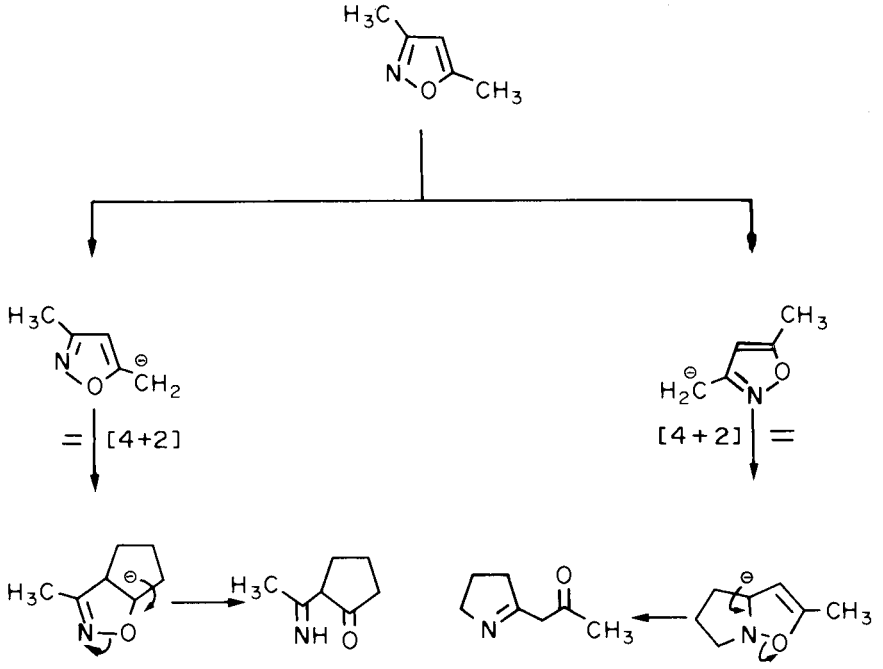
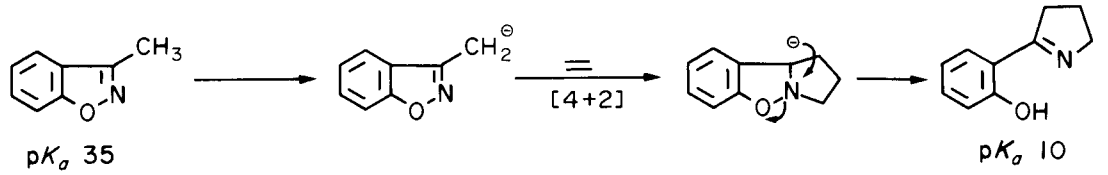
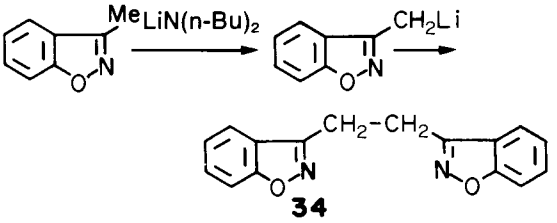


Chart 8



was ineffective. However, the involvement of 3-lithiomethylbenzisoxazole was clearly demonstrated with lithium di-n-butylamide by isolation of dimer **34**.



The versatility of 3-lithiomethylbenzisoxazole in cycloadditions is under study.

An understanding of a wide variety of non-observed symmetry allowed reactions, an untapped facet of Woodward–Hoffmann rules, has been attempted in this study. Further efforts in this direction could lead to the identification of new reagents, new reaction types and useful synthetic strategies.

EXPERIMENTAL

Melting points and boiling points are uncorrected. IR spectra were recorded on Perkin–Elmer Model 377 and 580 spectrophotometers as neat liquids or solids as KBr discs. NMR spectra were obtained on approximately 10–15% solutions mostly in $CDCl_3$ on A-60D and R-90 spectrometers. The chemical shifts are reported in ppm downfield from TMS at 0.00 as internal standard. Mass spectra were obtained from a Jeol instrument. Elemental analysis were carried out in Coleman automatic C, H and N analysers. Silica gel (Acme) was used for tlc and column chromatography was done on silica gel (Acme, 100–200 mesh). Reactions were monitored, wherever possible, by tlc.

Reaction of tetracyclone in boiling nitrobenzene: isolation of pentraphenylpyrrole, tetraphenyl N-phenyl 2-oxo 4-pyrroline, 2-benzoyl triphenyl furan (5) and benzanilide

A solution of tetracyclone (3.84 g, 0.01 mole) in nitrobenzene (25 ml) was refluxed for 15 h. Excess nitrobenzene was removed *in vacuo*, the residue steam distilled to remove nitrosobenzene formed in the reaction, extracted with benzene, the organic layer dried ($MgSO_4$), solvents evaporated and the residue chromatographed over silica gel. Elution with benzene:hexane (1:1) followed by benzene gave 0.81 g (18%) of pentaphenylpyrrole, mp 283–84° [lit[8] m.p. 283–84°; IR: ν_{max}(KBr) cm^{-1}: 1590], followed by 0.93 g (20%) of tetraphenyl N-phenyl 2-oxo 4-pyrroline m.p. 158–59° [lit[36] m.p. 158–59°; IR: ν_{max}(KBr) cm^{-1}; 1710 (>C=O], and 0.24 g(6%) furan **5**, m.p. 166–67° [lit[37] m.p. 166–67°; IR: ν_{max}(KBr) cm^{-1}: 1635(>C=O]. All compounds were identified on the basis of comparison of their spectra with authentic samples.

Reaction of tetracyclone with p-*cyano nitrobenzene in boiling* o-*dichlorobenzene: isolation of* **5**, *tetraphenyl N-p-cyanophenyl 2-oxo 4-pyrroline and 4,4'-dicyanoazobenzene*

Under nitrogen, a solution of tetracyclone (0.38 g, 0.001 mole) and *p*-cyano-nitrobenzene[38] (1.5 g, 0.01 mole) in *o*-dichlorobenzene was refluxed for 48 hr. Solvents were evaporated under reduced pressure, excess *p*-cyano-nitrobenzene removed by vacuum sublimation, triturated with benzene (10 ml), the resulting extract evaporated and the residue chromatographed over silica gel. Elution with benzene: ethyl acetate (1:1) gave 0.09 g (22%) of **5**, m.p. 164–66°, 0.16 g (33%) of tetraphenyl N-p-cyanophenyl 2-oxo 4-pyrroline, m.p. 213–15° [Calc. C, 86.06; H, 4.91; N, 5.73; Found C, 85.86; H, 5.02; N, 5.95%; IR: ν_{max}(KBr) cm^{-1}: 2200(CN), 1730(>C=O)] and 0.01 g (5%) of 4,4'-dicyanoazobenzene m.p. 263–66° (lit.[39] m.p. 268–70°, Calc. C, 72.41; H, 3.44; N, 24.13; Found C, 72.58; H, 3.55; N, 24.06%; IR: ν_{max}(KBr) cm^{-1}: 2200(CN)].

Neat thermal reaction of tetracyclone with p-*cyanonitrobenzene*

A mixture of tetracyclone (3.84 g, 0.01 mole) and *p*-cyanonitrobenzene (14.8 g, 0.1 mole) under N_2 was held at 200–210°C for 7 h in a sealed tube. Excess *p*-cyanonitrobenzene was removed by sublimination and work up as described above gave 0.81 g (20%) furan **5**, m.p. 166–167°C, 1.47 (30%) of the 2-oxo-4-pyrroline m.p. 215–218°C, 0.22 g (10%) of 4-cyanobenzanilide, m.p. 160–162° and 0.11 g (5%) 4,4'-dicyanoazobenzene, m.p. 263–266°.

Neat thermal reaction of tetracyclone with p-*dinotrobenzene*

An intimate mixture of tetracyclone (0.384 g, 0.001 mole) and *p*-dinitrobenzene (1.68 g, 0.01 mole) was held at 200° for 7 h. under N_2 in a sealed tube. The reaction mixture was triturated with benzene and the organic extract of chromatography over silica gel gave 0.7 g (18%) of furan **5** on elution with benzene.

Neat thermal reaction of tetracyclone with 4-nitro-4'-methyl diphenyl sulfone

4-Nitro-4'-methyl diphenyl sulfone was prepared by an improved procedure. Under nitrogen, a mixture of *p*-dinitrobenzene[40] (5 g, 0.0297 mole) and sodium *p*-toluene sulfinate[41] (6 g, 0.0337 mole) in dry dimethylsulfoxide was left stirred at room temperature for 18 h, poured into ice water, the precipitated solid collected and crystallised from absolute alcohol to give 7.5 g (91%) of 4-nitro-4'-methyl diphenyl sulfone, m.p. 170° (lit[42] m.p. 170–71°). Calc. C, 56.32; H, 3.97; Found C, 56.58; H, 3.38%; IR: ν_{max}(KBr) cm^{-1}: 1535, 1350(NO_2), 1305, 1160, 1100(SO_2); NMR: $\delta_{(CDCl_3)}$: 8.06(q, 2H, 3H), 7.73(d, 2'H), 7.26(d,3'H), 2.32(S,CH_3).

In a sealed tube, an intimate mixture of tetracyclone (1.884 g, 0.0049 mole) and 4-nitro-4'-methyl-diphenyl-sulfone (1.108 g, 0.004 mole) was held at 200° for 10 h. The reaction mixture was triturated with benzene and the organic extract on chromatography over silicagel gave 0.770 g (48%) of furan **5** m.p. 164–65° on elution with benzene and 0.921 g (37%) of pale yellow tetraphenyl N-p-tosylphenyl-2-oxo 4-pyrroline m.p. 244° on further elution with benzene: ethylacetate (19:1) Calc. C, 79.74; H, 5.02; N, 2.27; Found C, 79.84; H, 5.20; N, 2.27%; IR: ν_{max}(KBr) cm^{-1}: 1730(>C=O), 1305, 1150, 1105(SO_2); NMR: $\delta_{(CDCl_3)}$: 7.8–6.7(m, aromatic protons); 2.28(s, CH_3).

Reaction of 4-nitro-4'-methyl-diphtnyl sulfone with dicyclopentadiene: isolation of nitrene insertion product **8**

A solution of 4-nitro-4'-methyl diphenyl sulfone (2.0 g, 0.0072 mole) in dicyclopentadiene (25 ml) was heated at 150° for 3 h, diluted with hexane, decanted and the residue chromatographed on silica gel. Elution wth ethyl acetate: benzene (1:19) gave 0.891 g (32%) of **8** as a foam. IR: ν_{max}(KBr) cm^{-1}: 3400(NH), 1305, 1160, 1105(SO_2); NMR: $\delta_{(CCl_4)}$: 9.5(m, N$\underline{H}$), 7.55(d, 2H, 3H), 7.1(m, 2'H), 6.75(b, 3'H), 5.5(m, olefinic), 2.25(s, C$\underline{H}_3$). In addition to **8**, a carbonyl containing compound was also isolated.

Reaction of p*-nitrobenzene diazonium fluoborate with cyclopentadiene: isolation of adduct* **11**

Freshly cracked cyclopentadiene (10 ml) was added, in drops, to a refluxing solution of *p*-nitrobenzene diazonium fluoborate[40] (1.1 g, 0.0046 mole) in methanol (75 ml). The reaction was complete after 1 h reflux (tlc). Solvents were evaporated, the residue washed with benzene and chromatographed on silica gel. Elution with hexane: benzene (1:9) gave 1.25 g (96%) of **11** as a yellow solid which was crystallised from dilute ethanol m.p. 175–178°. Calc. C, 64.2; H, 5.35% (hydrate). Found. C, 64.6; H, 4.8; *m/e*: 281(M$^+$); IR: ν_{max}(KBr) cm^{-1}: 1510, 1325(NO_2); NMR: $\delta_{(CDCl_3)}$: 7.95(d, J = 9 Hz), 6.9(d, J = 9 Hz, π isomer a), 6.85(d, J = 9 Hz, π isomer b), 5.9(m, olefinic).

Reaction of meso*-hydrobenzoin 4-nitrobenzaldehyde acetal with DBN: isolation of* trans*-stilbene*

A solution of *meso*-hydrobenzoin-4-nitrobenzaldehyde acetal[43] (0.35 g, 0.001 mole) m.p. 110–11° in DBN (2 ml) was held at 200° for 2 h, triturated with water (30 ml), decanted, the residue extracted with benzene (20 ml), solvents evaporated and chromatographed over silica gel. Elution with hexane gave 0.08 g (44%) of *trans*-stilbene m.p. 118–21°.

Reaction of 2-nitrospirocyclopropane 1,9'-fluorene (**17**) *with potassium t-butoxide: attempted cyclo-addition of 2-nitropropenyl anion* **18** *with styrene: isolation of allene dimer* **19** *and allene-styrene adduct* **20**

Under nitrogen and stirring, to a heterogeneous solution of KO^{t}Bu (0.61 g, 0.0054 mole) in dry benzene (15–20 ml) was added **17**[22] (1.2 g, 0.005 mole), soon followed by a dry benzene solution of freshly prepared styrene (5.2 g, 0.05 mole). The resulting yellowish red reaction mixture was left stirred for 4 h, cooled (ice), acidified with 2 ml of 1N H_2SO_4, diluted with water, extracted with benznee, washed with saturated NaCl, dried ($MgSO_4$), solvents evaporated and the residue (1.3 g) chromatographed on silica gel. Elution with hexane: benzene (1:9) gave 0.09 g (6.2%) of **20**: m.p. 83–84°: Calc. C, 93.87; H, 6.12%; Found C, 93.88; H, 6.35%; NMR: $\delta_{(CDCl_3)}$: 7.8–6.4(m, aromatic), 4.82(t, *exo*-CH_2), 4.5(t, *exo*-CH_2), 4.25(d, benzylic), 3.42(m, ring CH_2).

Further elution with hexane: benzene (1:4) gave 0.26 g (13%) of the yellow allene dimer **19**. m.p. 247°. Calc. C, 94.73; H, 5.26; Found C, 94.60; H, 5.13%; NMR: $\delta_{(CDCl_3)}$: 8.15–6.82(m, aromatic), 6.2(d, highly shielded aromatic), 5.38(s, *exo*-C$\underline{H}^a_2$), 4.75(s, *exo*-C$\underline{H}^b_2$), 2.6(s, ring C$\underline{H}_2$).

Preparation of Oxadiazolinone **28**

2-Methyl-3-N-oxidoquinazoline-4-hydroxamic acid **27**. Sodium acetate (2 g) and hydroxylaminehydrochloride (1 g, 0.014 mole) were separately dissolved in the minimum amount of water, mixed, and added to N-acetylisatin[44] (1 g, 0.0056 mole). Ethanol was added gradually and with stirring to the mixture until a clear solution was obtained (~30 ml EtOH), then refluxed for 0.5 h, concentrated to half the volume and left overnight in the refrigerator. The white crystalline **27** was collected, washed with alcohol: water (1:1) and crystallised from hot ethanol m.p. 239–40°. (lit[32] m.p. 240°); yield 0.66 g (57%); Calc. C, 54.79; H, 4.11; N, 19.1; Found C, 54.60; H, 4.00; N, 18.8%; IR: ν_{max}(KBr) cm^{-1}: 3120, 1655, 1600, 1538, 1490; NMR: $\delta_{(DMSO)}$: 7.9–7.55(m, aromatic), 6.15(b, N$\underline{H}$O$\underline{H}$), 2.72(S, C$\underline{H}_3$).

Lossen rearrangement followed by cyclisation of **27**: *preparation of oxadiazolinone* **28**

A mixture of the hydroxamic acid **27** (2 g, 0.009 mole) and dicyclohexylcarbodiimide (2 g, 0.009 mole) in dry dioxan (50 ml) was refluxed for 1 hr, the clear solution left aside at room temperature overnight, dicyclohexyl urea was filtered off, washed with ethylacetate, the combined filtrates evaporated *in vacuo* and the residue on crystallisation from hot ethyl acetate gave 1.10 g (60%) of **28** as colourless needles m.p. 230–231° (lit[32] m.p. 232–233°); Calc. C, 59.7; H, 3.48; N, 20.09; Found C, 60.02; H, 3.08; N, 19.80%; *m/e* 201(M$^+$); UV: λ^{MeOH}_{max} 330, 316, 284, 274, 260 nm; IR: ν_{max}(KBr) cm^{-1}: 1810, 1790, 1620, 1560, 1530, 1460; NMR: $\delta_{(DMSO)}$: 8.3–7.5(m, aromatic), 2.72(s, C$\underline{H}_3$).

The filtrate on concentration gave a gummy residue which was chromatographed on a column of silica gel. Elution with EtOAc: benzene (15:85) gave the isomeric oxadiazolinone **33** (0.16 g, 9%) which on crystallisation from methanol yielded colourless prisms m.p. 189–90° (lit[32] m.p. 195–97°); Calc. C, 59.7; H, 3.48; N, 20.09; Found C, 59.73; H, 3.45; N, 19.5%; *m/e* 201(M$^+$); UV: λ^{MeOH}_{max}: 318, 306, 295, 285, 250, 243, 235 nm; IR: ν_{max}(KBr) cm^{-1}: 1825(shoulder), 1795, 1635, 1610, 1590, 1480, 1460; NMR: $\delta_{(CDCl_3)}$ (500 MHz): 8.08(d, 1H), 7.77(t, 1H), 7.7(d, 1H), 7.55(t, 1H) (aromatic protons), 2.85(s, 3H, C$\underline{H}_3$).

Thermal reaction of oxadiazolinone with tetracyclone: isolation of cyclopentenone **32** *and the isomeric oxadiazolinone* **33**

In a sealed tube a mixture of **28** (0.201 g, 0.001 mole) and tetracyclone (0.384 g, 0.001 mole) was held at 200° for 10 h, cooled, extracted with ethylacetate, solvents evaporated and the residue chromatographed on silica gel. Elution with benzene gave unchanged tetracyclone (0.15 g), and with benzene: ethylacetate (19:1) 0.075 g (20%) of **32**, m.p. 163–64° (lit[45] m.p. 162°) *m/e*: 386(M$^+$); UV: λ^{MeOH}_{max}: 295 nm; IR: ν_{max}(KBr) cm^{-1} 1680, 1620, 1600, 1490, 1348.

Further elution with ethyl acetate: benzene (3:7) gave 0.1 g (50%) of the isomeric oxadiazolinone **33**, m.p. 189–90°.

Attempted cycloaddition of 3-lithiomethylbenzisoxazole with styrene: isolation of dimer **34**

3-Methylbenzisoxazole was prepared from *o*-hydroxyacetophenone by an improved procedure. Sodium acetate (2.5 g) and hydroxylamine hydrochloride (2 g) were separately dissolved in minimum amount of water, mixed and added to *o*-hydroxyacetophenone (3.4 g, 0.025 mole). Ethanol was then added until a clear solution was obtained, the reaction mixture refluxed for 0.5 h, concentrated to half the volume, cooled, poured into crushed ice (~200 g), the white crystals collected, washed with cold water and dried *in vacuo* to give 3.2 g (85%) of *o*-hydroxyacetophenone oxime m.p. 112–15°. *o*-Hydroxyacetophenone oxime (1 g; 0.0066 mole) was admixed with acetic anhydride (3 ml) and the clear solution left stirred at room temperature for 1 h. The precipitated N-acetoxy derivative was washed with petroleum ether and crystallised from benzene m.p. 141–43°, 0.96 g (75%). The N-acetoxy oxime (5 g, 0.026 mole) was held at 170–80° for 1 h, then at 100° for 1 h. The dark residue on distillation gave 3 g (87%) of 3-methylbenzisoxazole b.p. 89–90°/10 mm.

Under nitrogen and stirring, n-dibutyl amine (11.4 g, 0.088 mole) was gradually added to a solution of *n*-BuLi prepared at 0°C from Li(0.63 g, 0.09 mole) and *n*-BuBr

(12.3 g, 0.09 mole) in dry ether (50 ml), followed by, in drops, a solution of 3-methylbenzisoxazole (2 g, 0.015 mole) in dry ether (10 ml). After 0.5 h, freshly distilled styrene (2 g, 0.019 mole) was added, the reaction mixture left stirred for 5 h, poured into cold, saturated aqueous ammonium chloride adjusted to pH 2 (dil. H_2SO_4), extracted with ether (3 × 200 ml), washed with water, dried ($MgSO_4$), solvents evaporated and the residue chromatographed on silica gel. Elution with benzene : ethyl acetate (3 : 1) gave 0.05 g (5%) of **34** which was crystallised from ethylacetete–benzene; yellow needles. m.p. 215–18°; *m/e*: 264(M^+); IR: ν_{max}(KBr) cm^{-1}: 1610, 1593, 1530, 1500, 1452, 1430, 1380.

Acknowledgments—We are most grateful to the referee and to Prof. N. Sathyamurthy, IITK, for valuable suggestions.

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