

Use of Cyclopropanes and Their Derivatives in Organic Synthesis

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Contents

| | |
|---|-----|
| I. Introduction | 165 |
| 1. Overview | 165 |
| 2. Thermodynamic Considerations/Strain Energy | 165 |
| 3. Bonding in Cyclopropane | 165 |
| 4. The Cyclopropyl Group as a Substituent | 167 |
| 5. Perspective on Cyclopropanes in Synthesis | 168 |
| II. Thermal Ring Fission | 168 |
| 1. Cyclopropyl Carbene Rearrangement | 168 |
| 2. Cyclopropylmethyl Carbene Rearrangement | 169 |
| 3. Vinylcyclopropane Rearrangement | 169 |
| 4. Divinylcyclopropane Rearrangement | 172 |
| 5. Miscellaneous Thermal Fission | 174 |
| III. Oxidative and Reductive Ring Fission | 175 |
| 1. Oxidative Fission | 175 |
| 2. Reductive Fission | 176 |
| IV. Electrophilic and Nucleophilic Ring Fission | 178 |
| 1. Additions to Cyclopropanes | 178 |
| 2. Electrophilic Additions | 179 |
| 3. Cyclopropylcarbinyl Cation and Related Rearrangements | 182 |
| 4. Nucleophilic Addition | 186 |
| 5. Imine-Cyclopropane and Carbonyl-Cyclopropane Rearrangement | 190 |
| V. Miscellaneous Ring Fission | 192 |
| 1. Fission Caused by Irradiation | 192 |
| 2. Transition-Metal-Mediated Ring Fission | 192 |
| 3. Free Radical Reactions of Cyclopropanes | 193 |
| 4. Rearrangement of the Cyclopropylcarbinyl Radical | 194 |
| VI. Summary | 194 |
| VII. Acknowledgment | 195 |
| VIII. References | 195 |

I. Introduction

1. Overview

Under the influence of a variety of chemical reagents (e.g., electrophiles, nucleophiles, radicals) or external physical forces (e.g., heat, light), cyclopropane deriva-

tives undergo a variety of ring-opening reactions. In contrast to normal paraffins, the chemistry of the cyclopropane C-C single bond resembles that of a carbon–carbon double bond. Relief of ring strain provides a potent thermodynamic driving force for these processes. Since numerous methodologies have been developed for the construction of three-membered carbocycles, the chemistry of cyclopropanes has emerged as a versatile tool in organic synthesis. In this section, the theoretical basis for the “unusual” reactivity and properties of cyclopropane is reviewed.

2. Thermodynamic Considerations/Strain Energy

Formation of a cyclopropane ring requires that three $-\text{CH}_2-$ groups be accommodated into a cyclic arrangement with all C–C–C bond angles equal to 60° .^{1,2} These bond angles are considerably less than the ideal 109.5° for sp^3 -hybridized orbitals, resulting in significant angular (Bayer) strain. Further, cyclopropane suffers additional torsional (Pitzer) strain because the coplanar arrangement of the carbon atoms mandates that the C–H bonds be eclipsed. The relief of strain associated with ring opening is often invoked to rationalize the high reactivity of the cyclopropyl group.

However, the strain energies of cyclopropane and cyclobutane are similar: 27.5 and 26.5 kcal/mol, respectively.³ This similarity is also revealed by considering the energy required for homolytic C–C cleavage, $c-(\text{CH}_2)_{n+2} \rightarrow \cdot\text{CH}_2(\text{CH}_2)_n\text{CH}_2\cdot$: 61 kcal/mol⁴ for $n = 1$ and 62.5 kcal/mol for $n = 2$.⁵ In contrast, whereas the chemistry of a cyclopropane ring resembles that of a carbon–carbon double bond (i.e., susceptible to electrophilic attack, easily oxidized, etc.), the chemistry of cyclobutane is unremarkable. Consequently, thermochemical considerations alone are insufficient to explain the unusual reactivity of cyclopropane.

3. Bonding in Cyclopropane

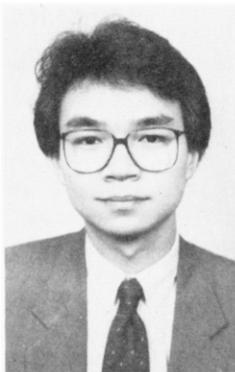
A. The Coulson–Moffitt Model

A popular description of bonding in cyclopropane, advanced by Coulson and Moffitt, imagines the construction of the cyclopropane ring from three sp^3 -hybridized $-\text{CH}_2-$ groups (Figure 1).^{6,7} As such, the sp^3 hybrids are pointed ca. 22° outward from the imaginary line connecting the nuclei, resulting in about 20% less effective overlap than the C–C bond of ethane. For this reason, the bonds are often referred to as “bent”.^{6–9}

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Henry Wong was born in Hong Kong in 1950. He graduated (B.Sc.) at the Chinese University of Hong Kong (1973) and obtained his Ph.D. (1976) from University College London (with the late Franz Sondheimer). After postdoctoral work (1976–1978) at Harvard University (with the late Robert B. Woodward), he returned to University College London as a Ramsay Memorial Fellow (1979–1980). From 1980 to 1982, he was an Associate Research Fellow at the Shanghai Institute of Organic Chemistry, Academia Sinica, China. He finally returned to Hong Kong as a Lecturer of the Hong Kong Polytechnic (1982–1983). He is currently a Senior Lecturer at the Chinese University of Hong Kong. His research interests include synthesis and study of nonnatural as well as natural products.



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This diminished overlap is reckoned to be the source of the angular strain.

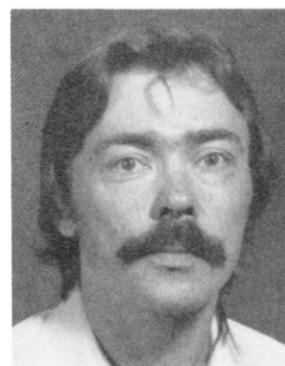
Other formulations of the Coulson–Moffitt model involve utilizing $sp^{2.3}$ - and sp^5 -hybridized orbitals to describe the carbon–hydrogen and carbon–carbon bonds, respectively. The greater p-character in the C–C σ -bonds is frequently invoked to explain the similarity of cyclopropane chemistry to that of olefins. Various physical properties (e.g., $J(^1H–^{13}C)$ and $J(^{13}C–^{13}C)$



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NMR coupling constants) are adequately explained by this deviation from sp^3 hybridization.¹⁰

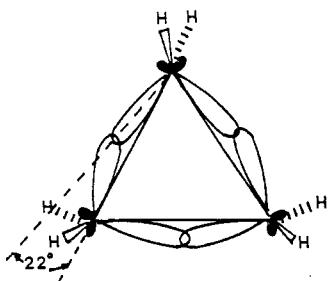


Figure 1. The Coulson-Moffitt model.

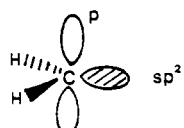


Figure 2.

B. The Walsh Model

The Walsh model¹¹⁻¹³ envisions cyclopropane as being constructed from three sp^2 -hybridized $-CH_2-$'s (Figure 2), arranged such that the sp^2 hybrids are oriented radially toward the center of the cyclopropane ring. The molecular orbital diagram depicted in Figure 3 results from the use of this basis set.¹⁴

By this model, angular strain is also attributed to poor overlap. For example, the overlap of the orbitals comprising ψ_1 is diminished because the lobes of the sp^2 hybrids are oriented inward from the imaginary lines connecting the carbon atoms. Similarly, ψ_2 can be viewed as a distorted π -bond. (This distorted π -bond description of ψ_2 offers an intuitively appealing explanation of the reactivity of cyclopropane toward electrophilic reagents.)

C. The Notion of σ -Aromaticity

The classical approach to organic chemistry has been to treat σ -bonds as localized entities. However, as articulated by Dewar¹⁵ in 1984, this assumption is often lacking. The concept of “ σ -conjugation” provides an especially intriguing explanation of the physical and chemical properties of cyclopropane: the three C-C σ -bonds provide a cyclic array of 6 electrons; by the $4n + 2$ rule, cyclopropane is aromatic. In contrast, cyclobutane, with $4n$ electrons ($n = 1$), is antiaromatic.¹⁵

A slight modification of this approach, advocated by Cremer,¹⁶ utilizes the Walsh basis set and the molecular orbital diagram depicted in Figure 3. σ -Aromaticity is postulated to arise from occupation of the “surface orbital”, ψ_1 , resulting in a three-center,two-electron bond.¹⁶

Several chemical and physical properties of cyclopropane, previously considered anomalous, are easily explained when σ -aromaticity is invoked. Some of these are highlighted below. For additional examples, the interested reader is directed to the original literature.^{15,16}

1. Strain Energy. The strain energy of cyclopropane (27.5 kcal/mol)³ is substantially lower than that calculated from the C-C-C bending force constant obtained from vibrational spectroscopy (104 kcal/mol);^{15,17} part of the discrepancy is attributable to σ -aromaticity. (Note that the same calculation for cyclobutane underestimates the strain energy since eclipsing (Pitzer) interactions are not taken into account.¹⁵)

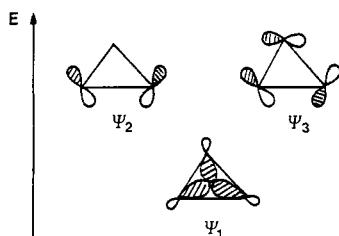


Figure 3. The Walsh model.

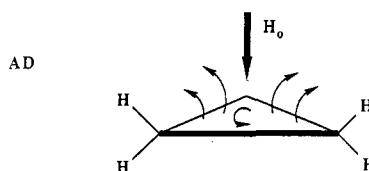
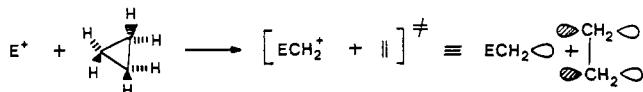


Figure 4. Ring-current effects in cyclopropane.

SCHEME I

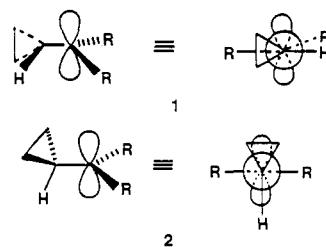


2. NMR Characteristics. Coupling constants (e.g., $J(^1H-^{13}C)$ and $J(^{13}C-^{13}C)$) are explicable by approximate sp^2 hybridization of carbon as explained by either the Coulson-Moffitt or Walsh models (vide supra). Ring-current effects provide a satisfactory explanation for the observed upfield shift of the protons of cyclopropane because its protons are shielded from the applied magnetic field (Figure 4).¹⁵

3. Reactivity of Cyclopropane toward Electrophiles. The high reactivity of cyclopropane toward electrophiles, frequently explained on the basis of a relief of strain, can be better understood on the basis of σ -aromaticity. For the reaction of $c\text{-C}_3\text{H}_6$ with an electrophile (Scheme I), aromaticity is maintained in the transition state (depicted in Scheme I as a methyl cation/ethylene π -complex for clarity).¹⁵ Thus, the fact the cyclopropyl group remains essentially intact in the transition state accounts for its high reactivity. In contrast, the ring strain (thermodynamic) argument would suggest the cyclopropane ring is substantially broken in the transition state.

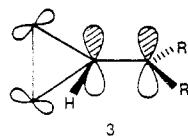
4. The Cyclopropyl Group as a Substituent

When attached to a π -system, a cyclopropyl ring can be characterized as a strong π -donor. The interaction of ψ_2 and ψ_3 (Figure 1) with the π system is maximal when the cyclopropyl ring adopts a bisected (1) rather than a symmetric (2) conformation with respect to the adjacent π -system.¹⁸



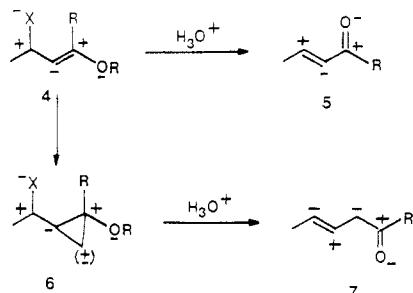
With the Walsh model, this conformational requirement is readily explained by considering the symmetry

of the orbitals involved in a system such as 3.¹⁸ The bisected conformation allows maximum overlap between the p-orbital on the cyclopropyl carbon and the adjacent π -system. In the symmetric conformation, these orbitals are orthogonal.



5. Perspective on Cyclopropanes in Synthesis

The utility of cyclopropanes in organic synthesis arises from the unique characteristics of the three-membered ring and the resemblance of its chemistry to that of a carbon–carbon double bond. Additionally, the incorporation of a cyclopropyl group provides an opportunity, upon reacting, for changes in either the consonant or the dissonant relationships within the carbon framework of the products. For example, hydrolysis of 4 provides enone 5 in which the consonant



relationship of charges has been retained. The incorporation of the odd carbon in the form of a cyclopropane in 6 allows for the cleavage to 7, where the consonance (or dissonance) will be dictated solely on the basis of further use or will depend on additional functionalities surrounding the olefin.¹⁹

This quality becomes important during synthetic design as it allows the addition of only one carbon. The cyclopropane ring can thus be viewed as a “synthetic wedge tool”, which is introduced to disrupt an existing charge parity or to introduce it in current or incipient operations.

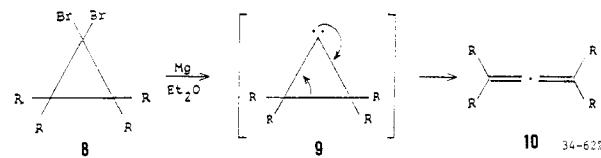
Cyclopropanes and their derivatives have been used in virtually every synthetic sense that befits the utility of alkenes in synthesis. Their preparation is the subject of many reviews²⁰ and their applications in the preparation of organic compounds are extensive.²¹ No attempt is made in this review to describe exhaustively every procedure or transformation. Rather the review should be viewed as a guide to the literature organized by the fundamental reaction types in which cyclopropanes participate. The coverage of the literature is complete through December 1987, and a comprehensive listing of reviews on aspects of cyclopropane chemistry is found in the reference section, irrespective of whether the reviews are mentioned explicitly in the text.²²

II. Thermal Ring Fission

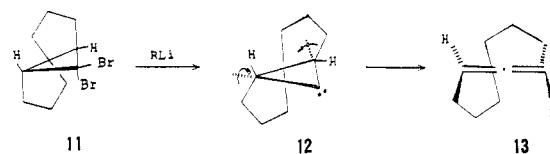
1. Cyclopropyl Carbene Rearrangement

An intriguing rearrangement occurs when 1,1-dibromocyclopropanes are treated with magnesium. The

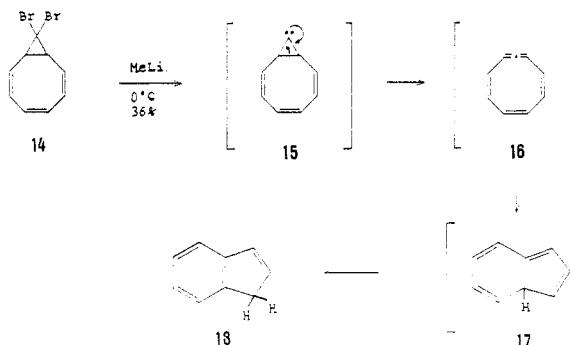
product of this reaction is an allene,^{23,24} which may arise from rearrangement of a cyclopropyl carbenoid.⁹



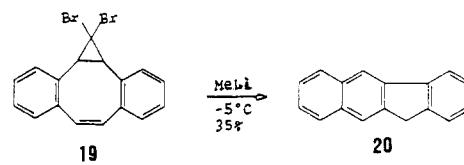
Alkyllithiums are also used to generate cyclopropyl carbenoids.²⁵ For example, treatment of dibromocyclopropane 11 with an alkylolithium yields intermediate 12, which undergoes conrotatory ring opening to give allene 13 in an overall ring expansion.²⁶



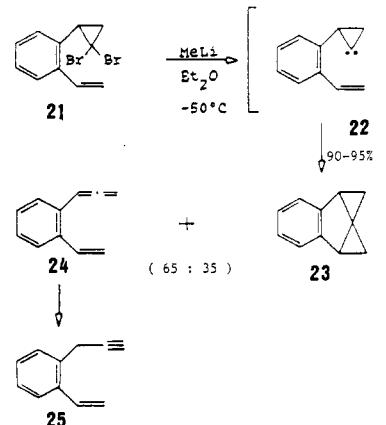
When other suitable functional groups are present in the molecule, the endocyclic allenes react further. Thus, dibromobicyclononatriene 14 reacts with methylolithium to form initially carbenoid 15, which rearranges to the nine-membered cyclic polyene 16 and finally to bicyclic compound 17. [1,5]-Sigmatropic rearrangement of 17 yields indene 18.²⁷



Through a similar series of events, 19 furnished the fused aromatic system 20.²⁷

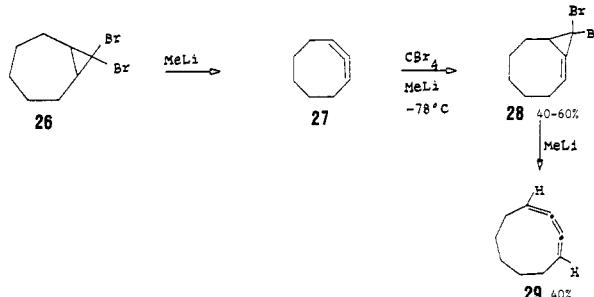


The cyclopropyl carbenoid can be trapped internally, as in the reaction of o-(2,2-dibromocyclopropyl)styrene (21) with methylolithium at -50 °C, which leads to a



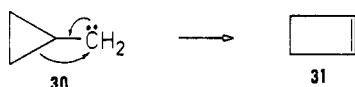
mixture of hydrocarbons, **23** and **24**, in 90–95% yield. At room temperature, the mixture of **23** and **24** is accompanied by a trace of alkyne **25**, formed by the base-induced isomerization of allene **24**.²⁸

Dibromocyclopropane **26** can be converted to 1,2-cyclooctadiene (**27**) by reaction with methylolithium. Treatment of **27** with carbon tetrabromide and methylolithium at -78 °C generates methylenecyclopropane **28**, which is transformed into 1,2,3-cyclononatriene (**29**) by further treatment with methylolithium.²⁹ Various dibromovinylcyclopropanes have also been shown to lead to vinylcyclopropyl carbenes, which rearrange to either vinylallenes or cyclopentadienes.³⁰

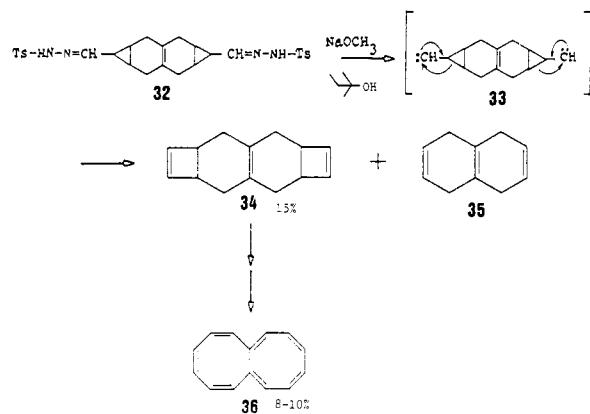


2. Cyclopropylmethyl Carbene Rearrangement

The generation of a carbene at a cyclopropylmethyl carbon results in a ring expansion through a 1,2-migration of the cyclopropyl C–C bond, resulting in formation of a cyclobutene.³¹

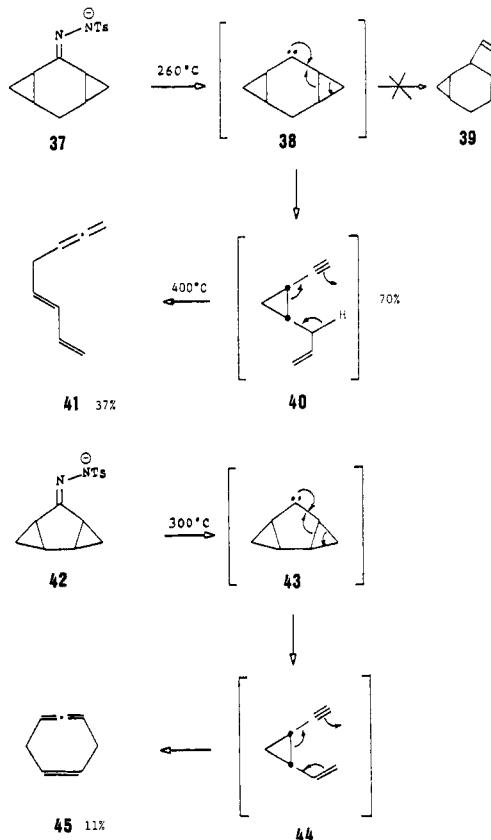


This strategy has been employed successfully in the synthesis of octalene **36**.³¹ When ditosylhydrazone **32** and sodium methoxide in 3-ethyl-3-pentanol were heated at 140 °C, a mixture of **34**, **35**, and other compounds was obtained via the rearrangement of **33**. A 15% yield of **34** was realized, and this triene was then converted to octalene **36** though double electrocyclic ring opening of the cyclobutene rings.³²



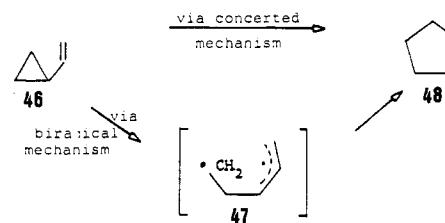
When the intermediate cyclopropylmethyl carbene is constrained so as to prevent rearrangement to cyclobutene, other rearrangements occur. For example, thermolysis of the anion of tosylhydrazone **37** at 260 °C furnished **40**. Because of the ring strain present in **38** and its potential ring-expanded product **39**, tricyclic carbene **38** rearranges with fission of one of the cyclopropyl rings to give **40** in 70% yield.³² When the

thermolysis temperature was raised to 400 °C, **40** underwent a homoene reaction to generate polyene **41** in 37% yield.³² Similarly, treatment of **42** at 300 °C provided 11% of heptatriene **45**, presumably via a consecutive cyclopropyl carbene rearrangement in **43** and a homo-Cope rearrangement of vinylcyclopropane **44**.³³



3. Vinylcyclopropane Rearrangement

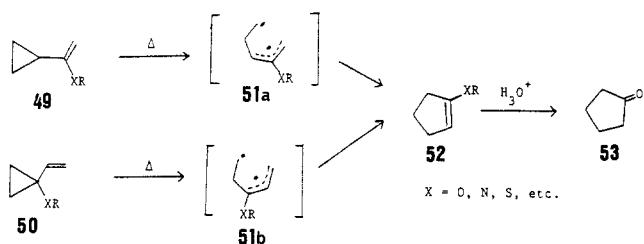
The chemical properties of cyclopropanes are greatly altered by conjugation with adjacent π-systems. Vinylcyclopropane undergoes unimolecular rearrangement to yield cyclopentene upon heating,^{34,35} with an activation energy of 49.7 kcal/mol.^{35,36} The mechanism^{36,37} and stereochemistry³⁸ of this rearrangement have been discussed extensively. The majority of these rearrangements involve biradical intermediates,³⁶ although concerted processes have been proposed in several cases.^{39,40} The versatility of this rearrangement has led to the development of several methodologies concerned with the preparation of functionalized cyclopentenes, and this subject has recently been reviewed.⁴⁵ The following examples show the utility of the vinylcyclopropane–cyclopentene rearrangement in the preparation of substituted or annulated cyclopentenes.



This reaction is particularly useful because vinylcyclopropanes are readily available and cyclopentenes are important structural units of natural products.⁴¹ It

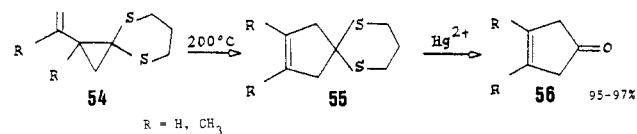
is not surprising that the vinylcyclopropane–cyclopentene rearrangement strategy has been employed extensively in the synthesis of complex natural products.⁴²

This rearrangement is also useful because heteroatoms and other functional groups can be readily introduced at various positions in the starting vinylcyclopropane, resulting in the increased complexity of the cyclopentene obtained after rearrangement. For example, cyclopentanone **53** can be obtained via rearrangement of either vinylcyclopropane **49** or **50**.³⁷

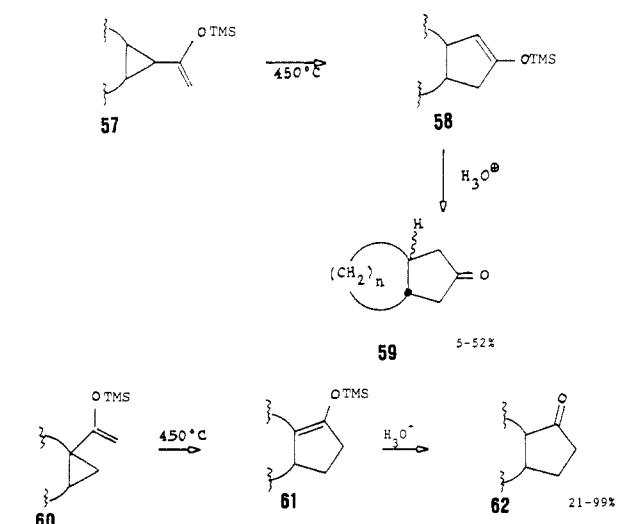


It is interesting to note that methoxy and dimethylamino groups on the cyclopropyl group of the vinylcyclopropane decrease the activation energies of rearrangement to 38.7 and 31.2 kcal/mol, respectively,⁴² while the presence of these groups on the vinyl group has very little effect on the rate of rearrangement.⁴³ Other substituents on the cyclopropane moiety (trimethylsilyl, carbonyl, and imino groups) also have pronounced effects on the rate of the rearrangement as discussed below.

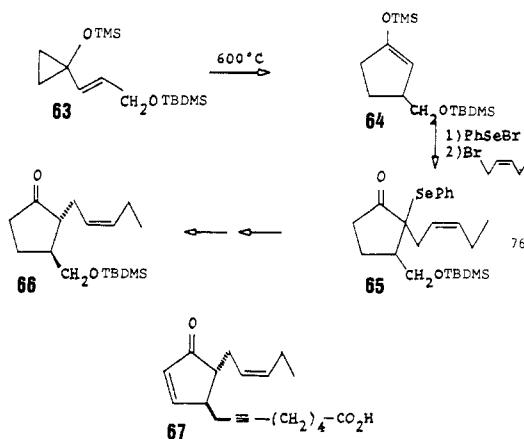
The methods for inducing the vinylcyclopropane–cyclopentene rearrangement range from photolysis or flash pyrolysis to subtle transition-metal catalysis.^{41,44} Thermolysis of vinylcyclopropyl thioketal **54** at 200 °C leads to cyclopentene **55**. Thioketal **55** is converted to substituted cyclopent-3-enone **56** by treatment with mercury(II) solution.⁴⁶



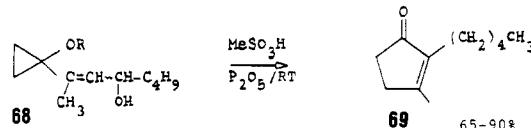
A cyclopentanone annulation methodology utilizing silyl enol ethers was developed by Monti.⁴⁷ For instance, bicyclic trimethylsilyl enol ethers **57** and **60** were heated at 450 °C to produce (after hydrolysis) **59** and **62**, respectively.⁴⁷



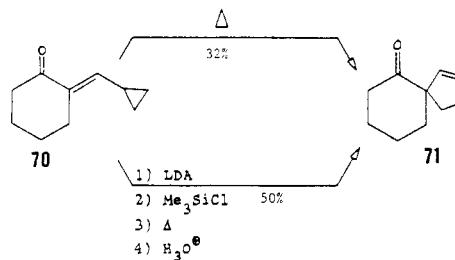
A similar strategy was employed by Salaün, who thermolyzed vinylcyclopropane **63** to furnish trimethylsilyl enol ether **64**.⁴⁸ This enol ether was treated with phenylselenium bromide and alkylated with *cis*-pent-2-enyl bromide to give **65** in 76% yield. This compound was converted to an important intermediate used in the synthesis of (\pm)-dicranenone A (**67**).⁴⁸



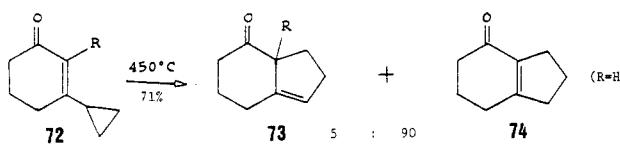
These examples^{47,48} demonstrate that upon pyrolysis, (trimethylsilyl)oxy-substituted vinylcyclopropanes rearrange to ((trimethylsilyl)oxy)cyclopentenes, which can be hydrolyzed to cyclopentanones or subjected to further functionalization. Dihydrojasmine (**69**) was prepared by the acid-catalyzed rearrangement of vinylcyclopropane **68**,⁴⁹ although the mechanism of this reaction does not involve a true vinylcyclopropane–cyclopentene rearrangement.



Thermolysis of β -cyclopropyl enone **70** provides cyclopentene **71** in a facile entry to spirobicyclic systems.⁵⁰ Two procedures for converting **70** to **71** have been described: direct thermolysis of **70** to give a 32% yield of **71**, and the conversion of **70** to the corresponding trimethylsilyl enol ether, which rearranges to **71** in 50% overall yield after hydrolysis.⁵⁰

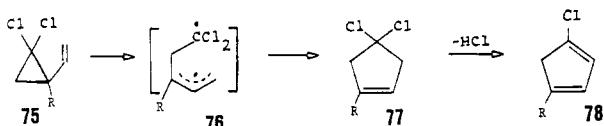


Thermolysis of vinylcyclopropane **72** at 450 °C yielded cyclopentene **73** or **74** (when R = H).⁵¹



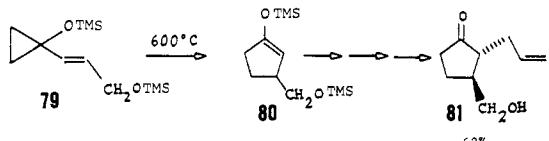
As discussed above in the mechanistic context, the substitution of heteroatoms on the vinylcyclopropane system has also been used extensively in synthetic procedures. Neureiter in his classical paper on the

discovery of the vinylcyclopropane-cyclopentene rearrangement reported that the pyrolysis of 75 yielded cyclopentadiene 78, presumably via the loss of HCl from 77.^{34a}

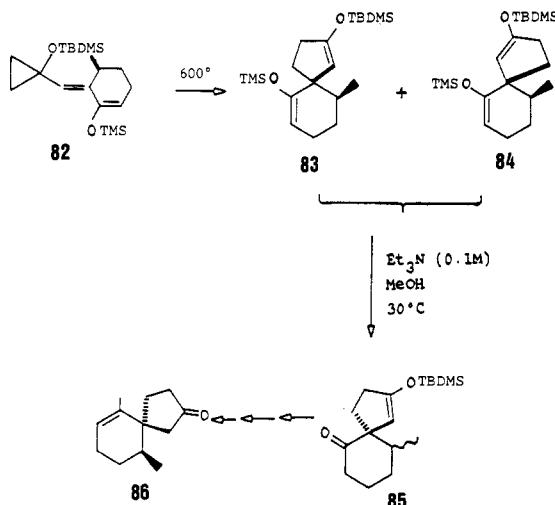


Flash pyrolysis of the trimethylsilyl ether 79 at 600 °C resulted in the isolation of 80, which was transformed to prostaglandin precursor 81.⁵²

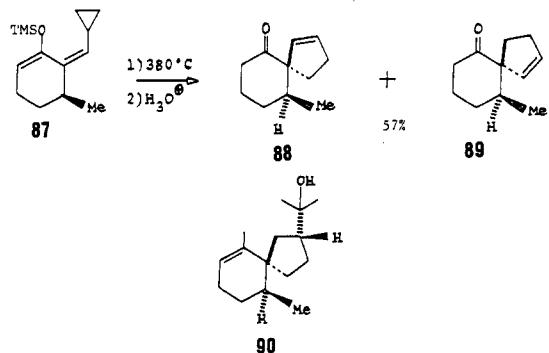
A trimethylsilyl ether accelerated vinylcyclopropane



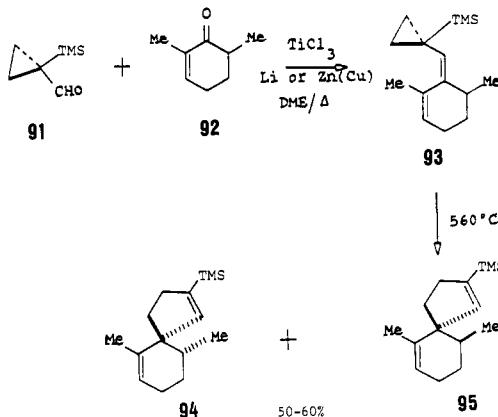
rearrangement was used in the synthesis of spirovetivane 86. Flash thermolysis of 82 gave a 78:22 mixture of 83 and 84. The product mixture was treated without purification with 0.1 M triethylamine in methanol to give the epimeric cyclohexanones 85, which were transformed to 86.⁵³ 2-(Cyclopropylmethylene)-



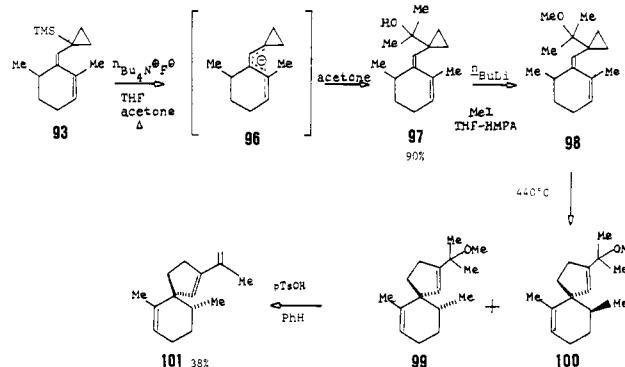
cycloalkenones such as 82 or 87 serve as convenient starting materials for a spiroannulation sequence. Thermolysis of silyl enol ether 87 at 380 °C, followed by acid hydrolysis of the crude thermolysate, afforded a 2.5:1 mixture of the two spiro enones 88 and 89 in a 57% yield.⁵⁴ The structural similarity of the spiro-annulated compounds obtained in this manner to natural products such as hinesol (90) or vetispirene (101) prompted their synthesis through the use of silicon-substituted vinylcyclopropanes.



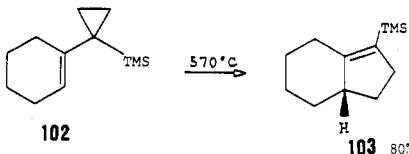
Reductive coupling of 1-(trimethylsilyl)cyclopropane-1-carboxaldehyde (91) and 92 in the presence of low-valent titanium provided 93 in 50–60% yield.⁵⁵ Thermolysis of 93 yielded a 4:1 mixture of spiro vinylsilanes 94 and 95.⁵⁵



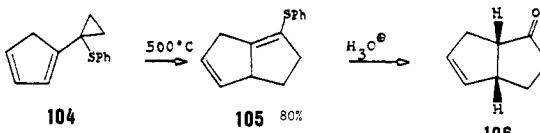
Alternatively, reaction of 93 with anhydrous tetra-*n*-butylammonium fluoride in THF-acetone solution at reflux temperature gave pentadienyl anion 96, which was reacted with acetone to furnish alcohol 97 in 90% yield. Alcohol 97 was protected as its methyl ether 98, which was thermolyzed at 440 °C to produce a separable mixture of 99 and 100 in the ratio of 5:1.⁵⁵ Treatment of 99 with *p*-toluenesulfonic acid in refluxing benzene yielded (\pm)- α -vetispirene (101) in 38% yield.⁵⁵



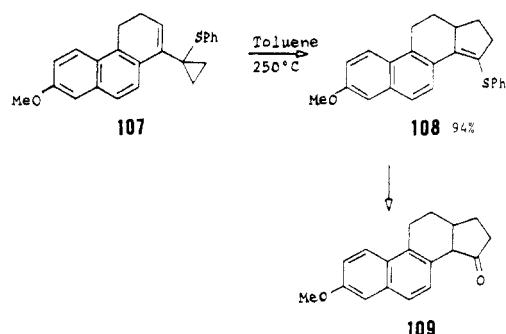
When vinylsilane 102 was passed through a quartz chip packed tube at 570 °C (30–40 Torr), silyl-substituted cyclopentene 103 was obtained in 80% yield.^{56,57}



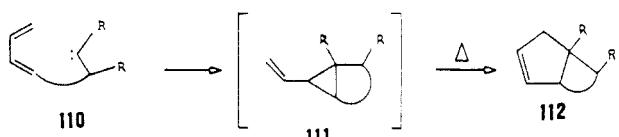
Sulfur-substituted vinylcyclopropanes furnish thienol ethers of cyclopentanones upon thermolysis. Pyrolysis of 104 at 500 °C at 0.2 Torr led to vinyl sulfide 105 in 80% yield. Hydrolysis of 105 provided cyclopentanone 106 in 65% yield.⁵⁸ Similarly, thermolysis



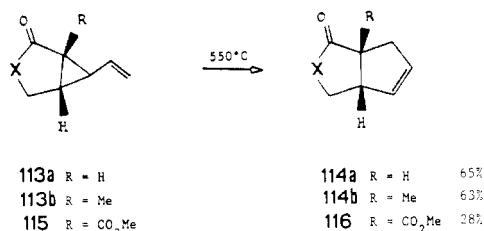
of 107 at 250 °C yielded 108 in 94% yield. The enol ether was then hydrolyzed to 109 in 73% yield.⁵⁹ Cyclopentene-annulated ring systems can be synthesized by intramolecular carbene addition to a 1,3-diene, which



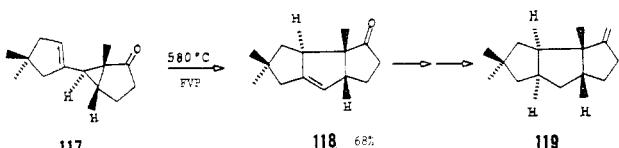
involves a vinylcyclopropane intermediate. Application of this methodology can be illustrated by the following examples.



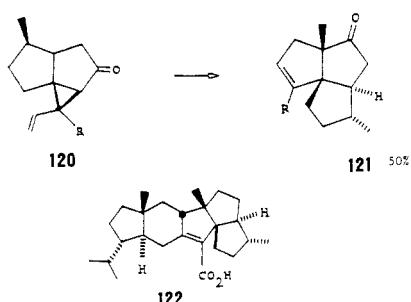
Pyrolytic conversion of 113a and 113b provided 114a⁴⁴ and 114b,⁶⁰ respectively. Similarly, lactone 115 was evaporated under vacuum at 580–600 °C through a Vycor tube to produce 116 in 28% yield.⁶¹



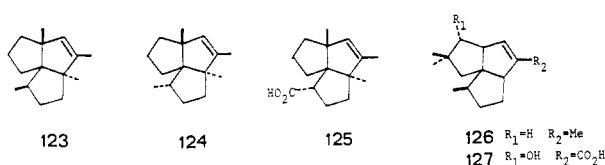
Tricyclic compounds can also be prepared via the vinylcyclopropane–cyclopentene rearrangement. Thus 117 underwent flash vacuum pyrolysis at 580 °C (0.1 Torr) on Vycor glass conditioned with lead carbonate to give tricyclic ketone 118 in 68% yield. This material was converted to hirsutene (119).⁶²



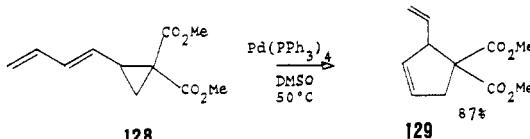
Another example of triquinane synthesis by this method is the formation of 121 in the flash pyrolysis of 120 over a PbCO₃-treated Vycor column.⁶³ This compound served as a potential intermediate in the total synthesis of retigeranic acid (122).⁶³



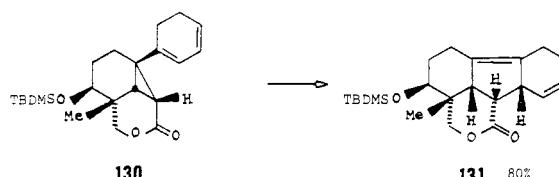
Several triquinane terpenes have been synthesized by this methodology since the publication of the last review.⁴¹ These were epiisocomene (123),⁶⁵ isocomene (124),⁶⁶ isocomenic acid (125),⁶⁷ pentalenene (126),⁶⁸ and pentalenic acid (127).⁶⁹



Transition-metal-catalyzed rearrangements of vinylcyclopropanes have been utilized in synthesis and have been previously reviewed.⁶⁴ In the presence of a Pd(0) catalyst and under mild conditions, dienyl cyclopropanes activated by electron-withdrawing groups rearrange to cyclopentenes.⁷⁰ For example, when a DMSO solution of dienyl cyclopropane 128 was treated with Pd(PPh₃)₄ under an argon atmosphere at 50 °C, vinylcyclopentene 129 was formed.⁷⁰



A critical step in Corey's total synthesis of the (\pm)-antheridium-inducing factor (A_{An}-2) of the fern *Anemia phyllitidis* involved a vinylcyclopropane–cyclopentene rearrangement.⁷¹ Diethylaluminum chloride was used to promote rearrangement of 130 to 131 at 0 °C.⁷¹

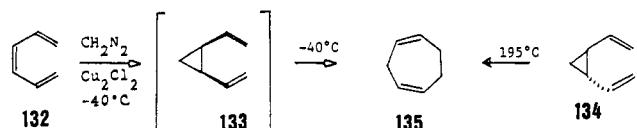


Several other methods for inducing the vinylcyclopropane–cyclopentene rearrangement have recently become available. For example, trimethylsilyl iodide is used in a nucleophilic opening/alkylative reclosure sequence to provide annulated cyclopentenes in good yields (see later).⁷² Other methods involve the anions of oxyvinylcyclopropanes⁷³ or the generation of their radical cations utilizing a stable aminium radical cation salt.⁷⁴ There have been isolated reports of Lewis acid catalyzed vinylcyclopropane–cyclopentene rearrangements involving substrates containing substituents that provide added stabilization to the incipient allylic cation intermediate.⁷⁵ In the case of carbanion-accelerated rearrangements of alkoxyvinylcyclopropanes, excellent stereoselectivity in the production of substituted cyclopentenols was observed, leading to speculation favoring a concerted mechanism for this particular rearrangement.⁷³

Finally, in all of the documented vinylcyclopropane–cyclopentene rearrangements, the only significant competing process seems to be the 1,5-hydrogen shift (or retroene pathway) in any *cis*-alkylvinylcyclopropane. This process is controllable by careful temperature adjustment and is sometimes reversible.⁶⁰

4. Divinylcyclopropane Rearrangement

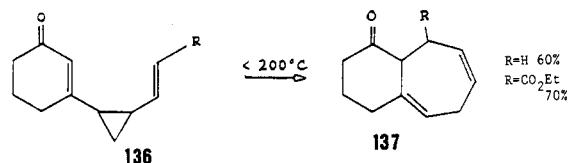
The preparation of seven-membered rings can be realized via thermal rearrangement of divinylcyclopropanes. Cyclopropanation of *cis*-hexatriene (132) with diazomethane in the presence of cuprous chloride at –40 °C resulted in the isolation of 1,4-cycloheptadiene (135).^{36a,76} This result is in complete agreement with



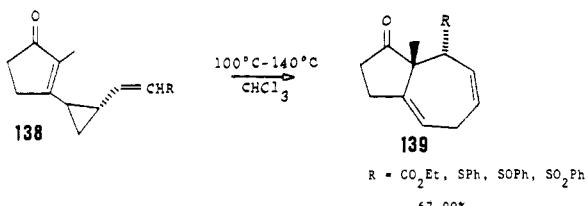
an earlier investigation in which the attempted preparation of *cis*-1,2-divinylcyclopropane unexpectedly yielded 1,4-cyclopentadiene (135).⁷⁷ It appears that the low activation energy for the Cope rearrangement of *cis*-1,2-divinylcyclopropane to 1,4-cycloheptadiene (133 \rightarrow 135) allows this process to take place at lower temperatures. The mechanism of this isomerization has been proposed to be of a biradical nature.^{36a,76}

In contrast, *trans*-1,2-divinylcyclopropane (134) is more stable and requires a temperature of 190°C to isomerize to 1,4-cycloheptadiene.^{36a,76} Allyl-stabilized biradicals are also the presumed intermediates in the *trans* \rightarrow *cis* isomerization of divinylcyclopropanes.

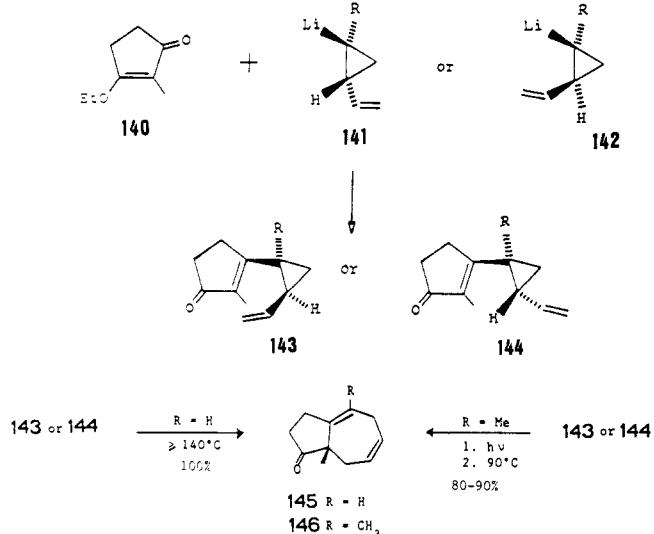
For example, thermolysis of 136 at 200°C gives cycloheptadiene 137 in 60% ($\text{R} = \text{H}$) and 70% ($\text{R} = \text{CO}_2\text{Et}$) yield.^{78,79}



Similarly, 138 undergoes rearrangement at $100\text{--}140^{\circ}\text{C}$ in CHCl_3 (sealed tube) to give hydroazulene 139 in 60% yield.⁷⁹ Bicyclo[5.3.0]decane and bicyclo[5.4.0]undecane skeletons can be prepared via this procedure, and this technique has found application in several natural product syntheses.

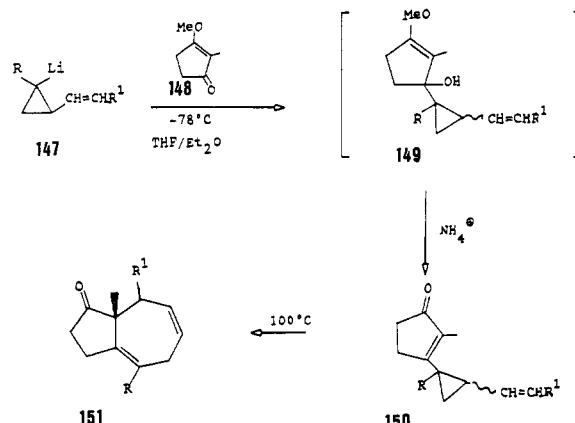


A general method for pseudoguaiane synthesis involving an internal divinylcyclopropane rearrangement has been developed. Cyclopentenone 140 was allowed to react with cyclopropyllithium 141 or 142 to give divinylcyclopropanes 143 or 144, respectively. Ther-

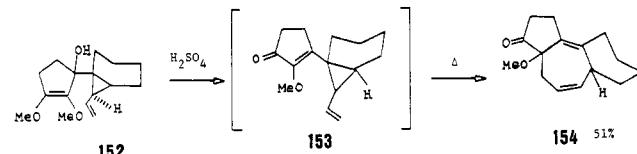


molysis of 143 or 144 at 140°C produced cycloheptadiene 145 in nearly quantitative yield. When $\text{R} = \text{Me}$, photolysis followed by thermolysis of 143 or 144 at 98°C gave cycloheptadiene 146 in 80-90% yield.⁸⁰⁻⁸² A pyrolysis temperature of 140°C is required for the rearrangement of *trans* species 144; the *cis* isomer 143 rearranges spontaneously upon its preparation.

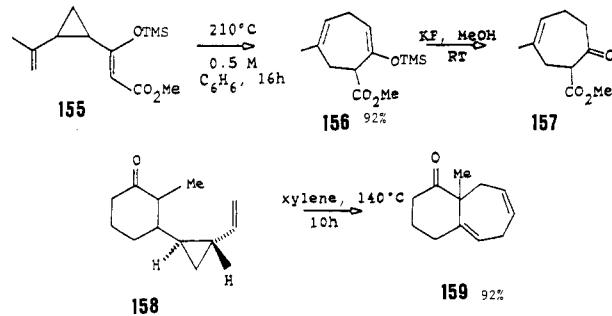
In another example, lithio reagent 147 was added to 2-methyl-3-methoxycyclopentenone (148) at -78°C in THF-ether to give intermediate allylic alcohols 149. Divinylcyclopropane systems 150 were formed after workup of the allylic alcohols with aqueous ammonium chloride. Thermolysis of divinylcyclopropane 150 at 100°C provided the seven-membered-ring annulated hydroazulene 151.⁸³



Similarly, cyclopentene 152 formed divinylcyclopropane 153 on treatment with H_2SO_4 . Thermolysis of 153 provided substituted cycloheptadiene 154.⁸⁴

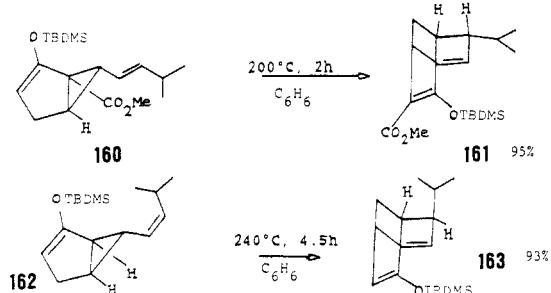


Vinylic substitution of the divinylcyclopropane system is tolerated and is subject to the same restrictions that apply to the vinylcyclopropane-cyclopentene rearrangement. I.e., *cis*-disubstituted vinyl groups retard the rate of rearrangement. Silyl enol ether 155 underwent seven-membered-ring annulation at 210°C (0.5 M in benzene) to furnish 1,4-cycloheptadiene 156 in 92% yield. The enol ether in 156 was then hydrolyzed to give enone 157 in 95% yield.⁸⁵ Bicyclic dienone 159 was obtained in 92% yield on thermolysis of divinylcyclopropane 158 in refluxing xylene.⁸⁶

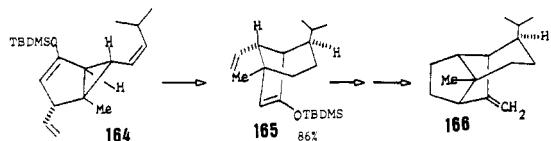


Thermal rearrangement of divinylcyclopropane systems has also been used to produce compounds containing the bicyclo[3.2.1]octane skeleton. For instance,

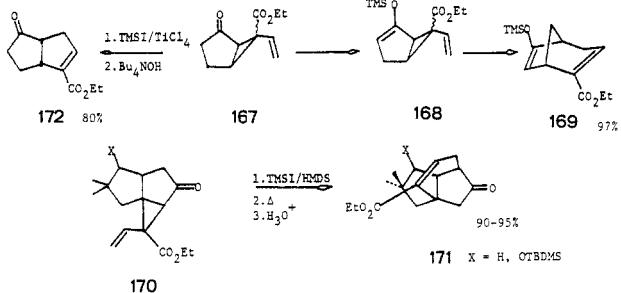
divinylcyclopropyl compound 160 was heated at 200 °C for 2 h in benzene to generate 161 in 95% yield.⁸⁷ For comparison, the cis isomer 162 was also thermolyzed at 240 °C for 4.5 h, furnishing 163 in 93% yield, thus indicating that the isomerization is stereoselective.⁸⁷



The following example illustrates how this method was used in the synthesis of a racemic form of the marine sesquiterpene (\pm)-sinularene (166). Thermal isomerization of 164 furnished 165 in 86% yield.⁸⁸ The conversion of 165 to (\pm)-sinularene (166) has been achieved in several steps.⁸⁸

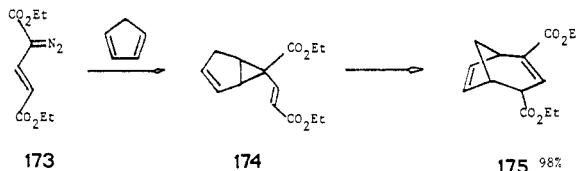


Most recently, the Cope rearrangement of divinylcyclopropanes has been exploited in the synthesis of some functionalized bicyclo[3.2.1]octane systems. Treatment of 167 with TMSI/HMDS at -78 °C pro-



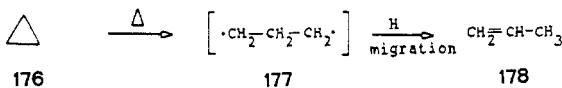
duced the intermediate silyl enol ethers 168. The endo isomer of 168 rearranged to bicyclo[3.2.1]octane 169 between -78 °C and room temperature, while the exo isomer required pyrolysis at 450 °C to produce 169 in 97% yield.⁷² Similarly, the tricyclic ketone 170 was converted to the bridged skeleton 171.^{68,69,72} In this context it should be noted that the silyl enol ethers of keto vinylcyclopropanes such as 167 also provide bicyclo[3.3.0]octanes 172 via the vinylcyclopropane–cyclopentene rearrangement. The endo/exo stereochemistry in 167 allows control over these operations.^{68,69,72}

The addition of unsaturated diazo carbonyl compound 173 to a diene (e.g., cyclopentadiene) generated divinylcyclopropane 174, which upon rearrangement furnished the annulated seven-membered-ring system 175.^{89,90} A mechanistic investigation of this process was reported.⁹⁰



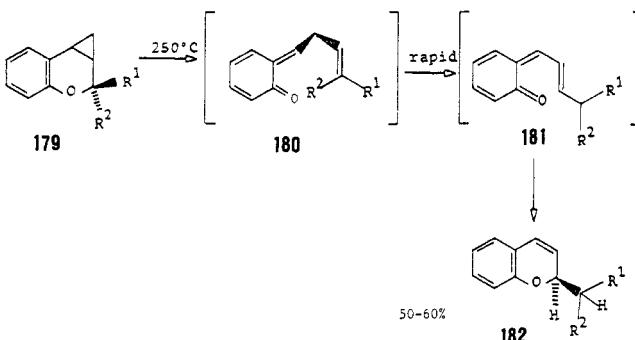
5. Miscellaneous Thermal Fission

The thermal isomerization of cyclopropane to propylene^{91–93} has been discussed in detail.³⁶ The mechanism of the isomerization is thought to involve cleavage

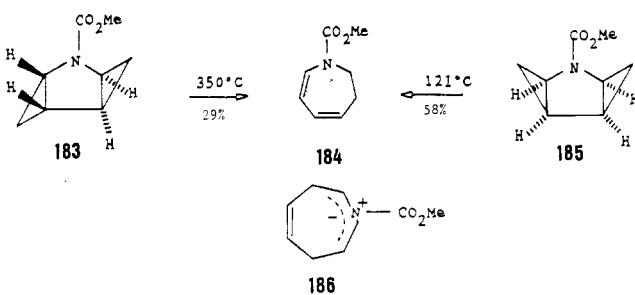


of the three-membered ring to the trimethylene biradical, which undergoes a subsequent hydrogen migration process to yield propylene.⁸⁶ The activation energy of this isomerization has been estimated to be 63.4 kcal/mol at 550–659 °C.⁹¹

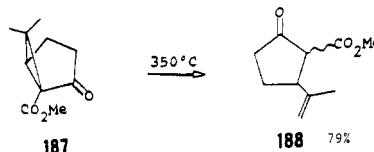
Synthetically, the cyclopropane to propylene isomerization is not generally useful because of the side reactions that accompany the isomerization, especially when other substituents are present.^{36,93,94} In some special cases, however, this rearrangement provides products of practical use and in acceptable yields. Cyclic ether 179 undergoes rearrangement upon heating at 250 °C to provide 182.⁹⁵ Higher temperature was



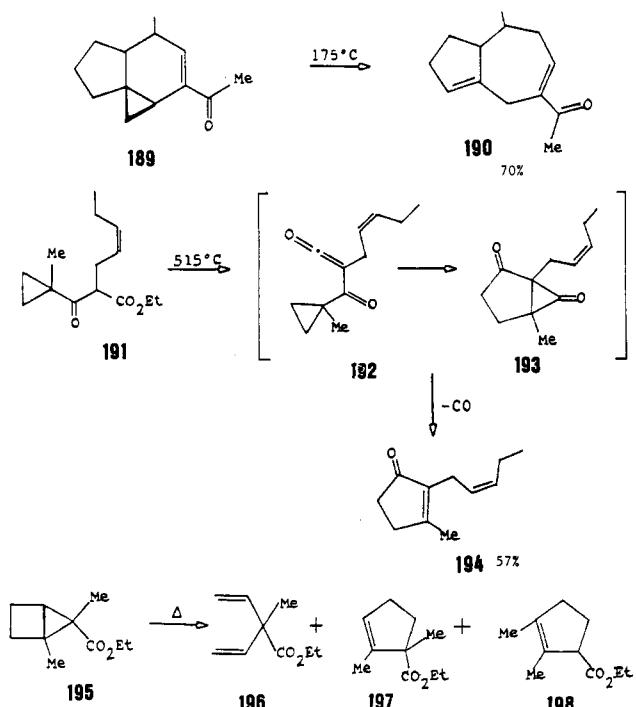
required for the conversion of anti-azotricyclic compound 183 to diene 184 than for syn compound 185; rearrangement of 185 proceeds smoothly at 121 °C to give dihydroazepine 184, whereas the rearrangement of 183 required 350 °C.⁹⁶ This difference in reactivity was rationalized in terms of the ease of the formation of the ylide intermediate 186.⁹⁷ Passing a hexane solution of



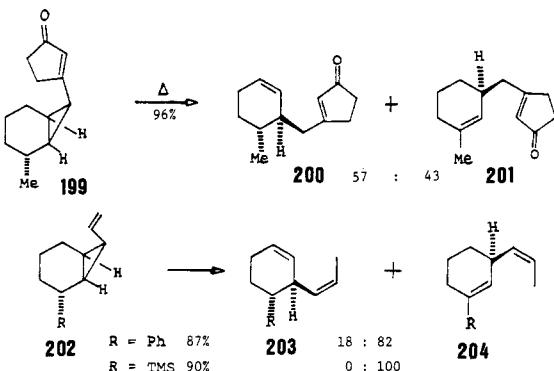
cyclopropyl ketone 187 through a column heated at 350 °C gave keto ester 188 in 79% yield via an ene-type process.⁹⁸ Thermolysis of methyl ketone 189 at 175 °C



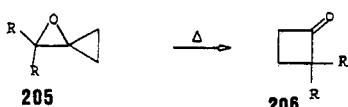
for 2 h yielded hydroazulene 190 in 70% yield.⁹⁹ Thermolysis of 191 at 515 °C gave 194 in 57% yield.¹⁰⁰ Pyrolysis of bicyclopentane 195 gave a high yield of the three isomeric esters 196, 197, and 198 in a ratio of 1:3:4.¹⁰¹



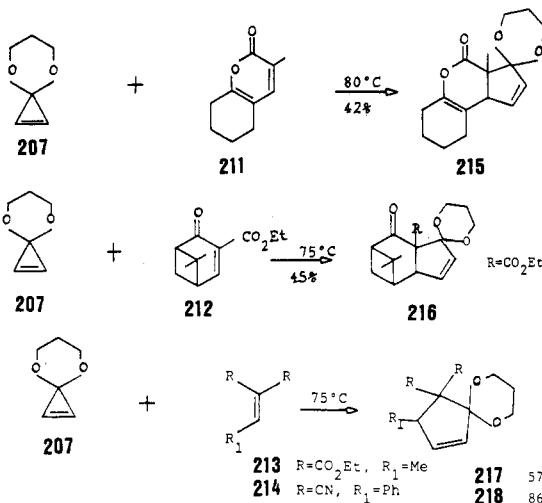
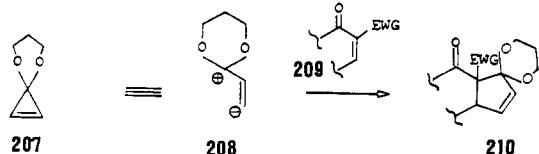
Homo-[1,5]-sigmatropic hydrogen migration was responsible for the rearrangement of 199 to a mixture of 200 and 201.¹⁰² Similarly, 202 upon thermolysis gave 203 and 204.¹⁰² This process occurs readily with *cis*-



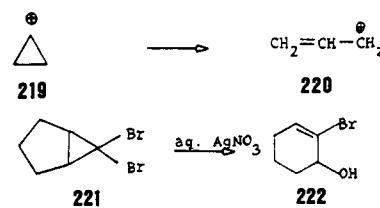
alkylvinylcyclopropanes and has been shown to be reversible.⁶⁰ The thermal rearrangement of oxaspiropentanes 205 to cyclobutanones 206 is well-known and its application has been reviewed elsewhere.¹⁰³



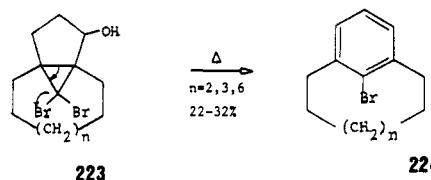
Thermal ring-opening cycloadditions of cyclopropyl derivatives with activated olefins have been reviewed.¹⁰⁴ The following examples illustrate thermal opening of cyclopropene rings and their subsequent cycloadditions with activated olefins.¹⁰⁵ Cyclopropenone ketal 207 was found to be an effective equivalent of 1,3-dipole 208 and undergoes [3 + 2] cycloaddition with activated olefins such as 209 to give five-membered rings of type 210.¹⁰⁵ For instance, reactions of 207 with 211, 212, 213, and 214 provide 215, 216, 217, and 218, respectively.¹⁰⁵



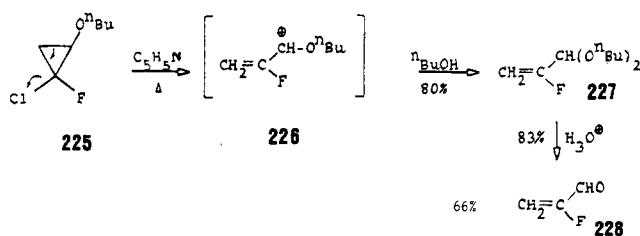
Cyclopropyl carbocations rearrange spontaneously to their corresponding allylic cations. The mechanism of this isomerization is concerted, and the stereochemistry can thus be predicted by orbital symmetry arguments.^{106–108} This rearrangement has been extensively employed to effect ring expansions such as one involving dibromide 221, which was converted to allylic alcohol 222.¹⁰⁹ The synthesis of metacyclophanes 224



was accomplished by thermolysis of the labile 2,2-dibromocyclopropyl carbinol 223, which produced 224 upon ring expansion and elimination.¹¹⁰



It has recently been found that only the *Z* isomer of 225 (cis orientation of fluorine and alkoxy groups) underwent ring opening to allylic cation 226, which could be trapped by 1-butanol, resulting in the isolation of acetal 227.¹¹¹ Hydrolysis of 227 furnished 2-fluoroacrolein (228) in an overall yield of 66% from 225.¹¹¹

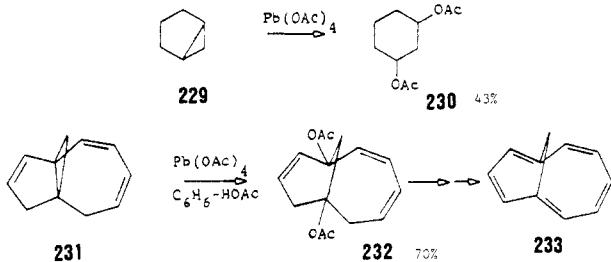


III. Oxidative and Reductive Ring Fission

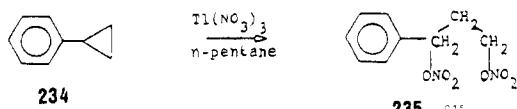
1. Oxidative Fission

Oxidative cleavage of cyclopropanes involves the breakage of a carbon–carbon bond of the cyclopropyl group, followed by the formation of two bonds of higher oxidation state. Steric and electronic effects of sub-

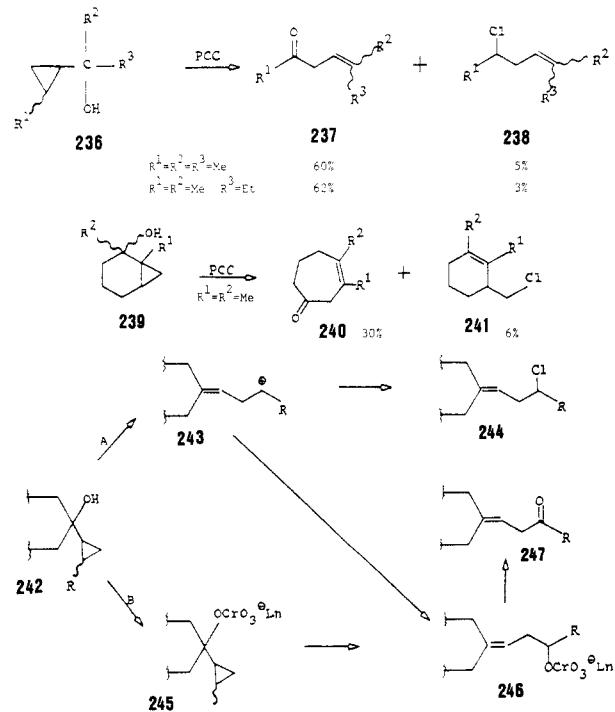
stituents on the ring, as well as the properties of the oxidizing agents, can facilitate regio- and stereospecific opening of the cyclopropane ring. For example, bicyclo[3.1.0]hexane (229) is cleaved by lead tetraacetate to provide diacetate 230.¹¹² Similarly, Scott reported lead tetraacetate oxidation of the cyclopropane ring in 231 to diacetate 232. Further transformations converted 232 to homoazulene 233.¹¹³ Cyclopropanes are



oxidized with thallium(III) nitrate in pentane to give nitrate esters. For example, on treatment with Tl₃(NO₃)₃, cyclopropylbenzene 234 gave exclusively di-nitrate ester 235 in 91% yield.¹¹⁴

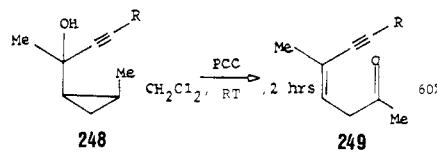


Oxidative rearrangement of *tert*-cyclopropylcarbinols gives β,γ -unsaturated ketones or halides. For example, carbinols 236 were cleaved by pyridinium chlorochromate to give a mixture of β,γ -unsaturated ketone 237 and homoallyl chloride 238.¹¹⁵ Similarly, 239 yielded 240 and 241.¹¹⁵ The proposed mechanism for the 1,4-carbonyl transposition is illustrated below:¹¹⁵



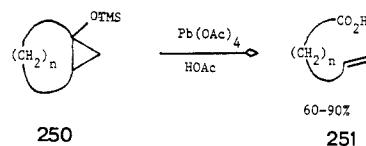
Recently, Holweger utilized this strategy to prepare β,γ -unsaturated ketone 249 in 60% yield.¹¹⁶

When a heteroatom is present on the cyclopropyl ring, the oxidation can proceed with the cleavage of two bonds to furnish olefins in a formal retro carbene addition. For example, Pb(OAc)₄ oxidation of silyl ethers such as 250 gives olefinic acids 251 in excellent



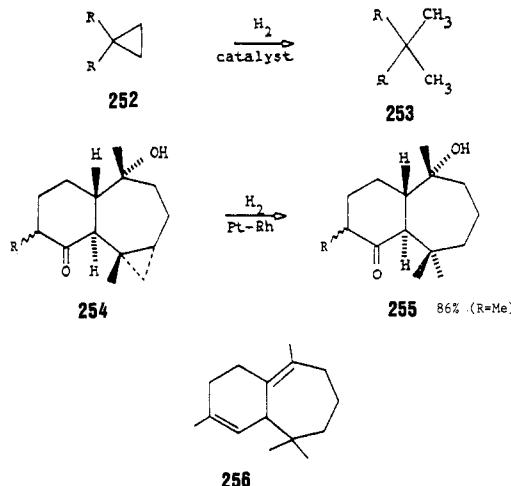
R = H, Me, TMS

yields. This procedure is quite general and has been used effectively to provide a homologous series of unsaturated acids.^{117,118}

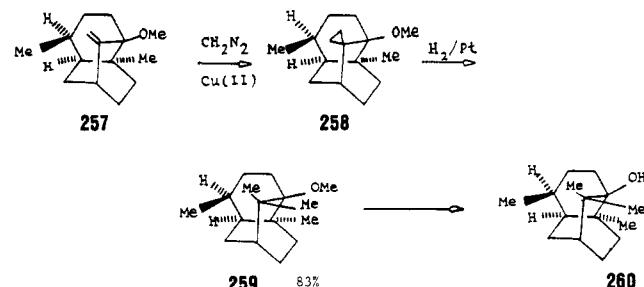


2. Reductive Fission

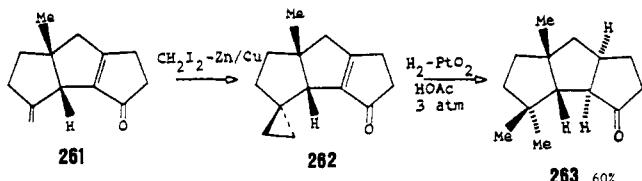
Cyclopropane can be cleaved at the least substituted bond by catalytic hydrogenation in a general synthesis of *gem*-dimethyl groups.¹¹⁹⁻¹²¹ Hydrogenation of cyclopropane 254 over platinum-rhodium catalyst gave rise to ring opening and provided *gem*-dimethyl compound 255, which served as a starting material for the synthesis of β -himachalene (256).¹²²



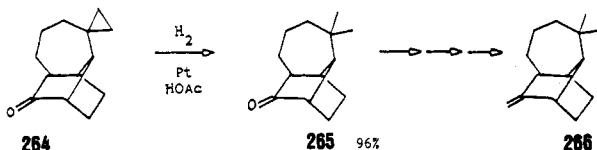
Cyclopropanation of the double bond in allyl ether 257 was achieved by treatment with diazomethane in the presence of a copper chelate and gave a 47% yield of cyclopropane 258. The cyclopropane ring in 258 was catalytically hydrogenated to give (\pm)-patchouli alcohol methyl ether (259) in 83% yield. Ether 259 was then converted under mild conditions to (\pm)-patchouli alcohol (260).¹²³



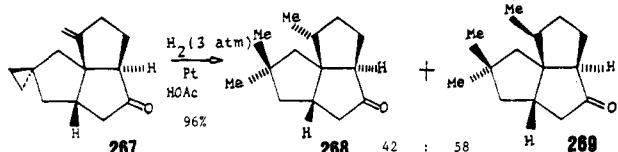
Simmons-Smith reaction of 261 produced cyclopropane 262 in 50% yield. This compound was catalytically hydrogenated over PtO2 in acetic acid at 3 atm to generate 60% of ketone 263.¹²⁴



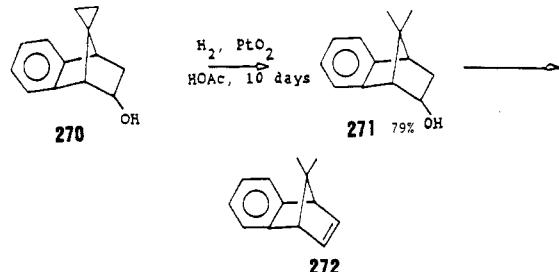
Cyclopropane **264** underwent regioselective hydrogenolysis over Pt in HOAc at room temperature to furnish a 96% yield of ketone **265**, which was converted to (\pm)-longifolene (**266**).¹²⁵



Treatment of **267** with hydrogen in the presence of platinum effected both hydrogenolysis of the cyclopropane ring and hydrogenation of the double bond. A mixture of tricyclic ketones **268** and **269** in a ratio of 42:58 was produced in 96% yield.¹²⁶

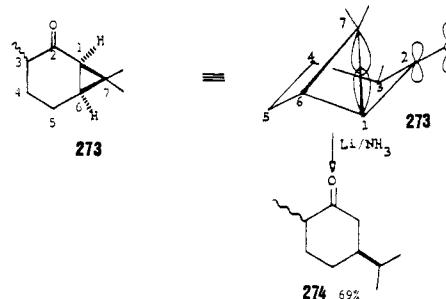


Hydrogenolysis of the spirocyclopropane ring in **270** was achieved in acetic acid solution with a platinum catalyst at ambient pressure. The major product (79%) of this reaction was the *gem*-dimethyl alcohol **271**, which was used to prepare 7,7-dimethylbenzonorbornene (9,9-dimethyl-1,4-methanonaphthalene) (**272**).¹²⁷

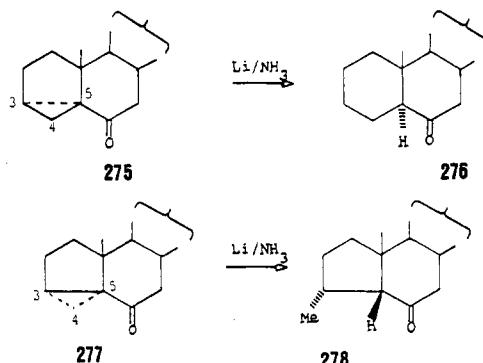


It should be reiterated that catalytic hydrogenation generally cleaves the least hindered bond of the three-membered ring, whereas the bond that breaks in a cyclopropyl ketone upon reduction by alkali metals in liquid ammonia is governed by stereoelectronic effects, specifically the magnitude of overlap between the cyclopropane C-C bond and the p-orbital of the carbonyl group.^{128,129} The introduction of a *gem*-dimethyl group as well as ring enlargement can be realized by reductive fission of three-membered carbocycles. These transformations are both chemo- and stereospecific.

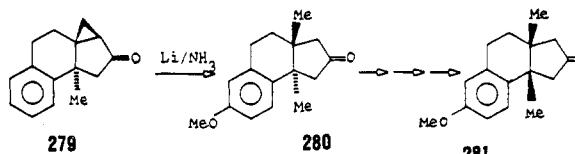
To illustrate the stereoelectronic control of this reduction, competition between various bonds in a cyclopropyl ketone such as **273** has been evaluated.¹²⁹ Because of geometric constraints, the overlap between the internal C₁-C₆ bond and the π -system of the carbonyl group is minimal, whereas the external C₁-C₇ is favorably aligned with the π -system, as illustrated in **273**. Consequently, reduction of **273** with lithium in liquid ammonia results in cleavage of the C₁-C₇ bond, yielding exclusively ketone **274**.¹²⁹



The C₃-C₅ bond in **275** and the C₄-C₅ bond in **277** are better aligned with the π -system of the carbonyl. Under similar reductive conditions, only **276** and **278** were obtained from the reactions of **275** and **277**, respectively.^{129,130} Cyclopropane **279** underwent reductive

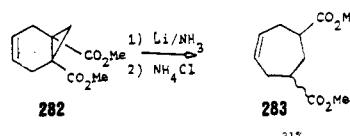


cleavage with Li/NH₃ to generate ketone **280**, which was an intermediate in the total synthesis of triterpenes of the lanostane cycloartane group, represented by **281**.^{131,132}

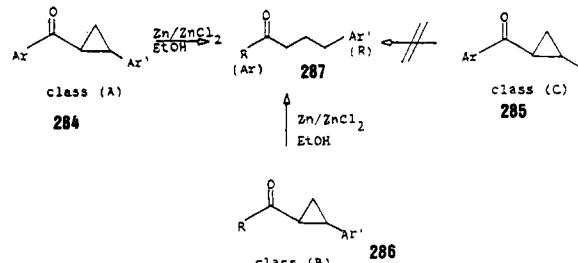


Because of the stereoelectronic control in the reductive fission of cyclopropyl ketones, only bond a in **279** is cleaved, despite the fact that cleavage of bonds b and c would provide more stable intermediates. It is therefore clear that the dissolving-metal reduction of cyclopropyl ketones proceeds under kinetic control.^{131,132}

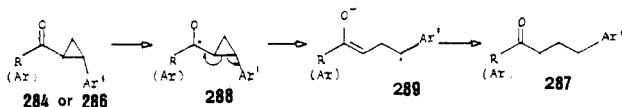
The cyclopropane ring in bicyclic compound **282** was cleaved reductively to **283**.¹³³ Aryl-substituted cyclo-



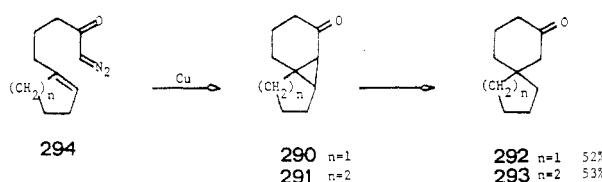
propyl ketones are cleaved to acyclic ketones by zinc or zinc chloride in refluxing ethanol.¹³⁴ Of the three classes of cyclopropyl ketones (**284**, **285**, and **286**), only



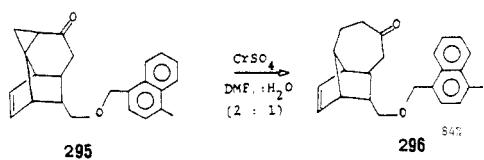
two can undergo reductive cleavage to acyclic ketones such as 287.¹³⁴ The mechanism of this reaction is believed to involve the reduction of the carbonyl to ketyl anion 288 followed by rearrangement to 289.¹³⁴



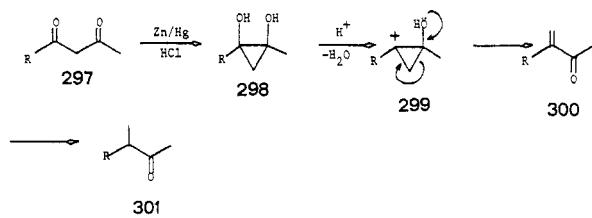
Reductive cleavage of cyclopropyl ketones 290 and 291 produced spiro ketones 292 and 293, respectively, on treatment with lithium in ammonia/ether.¹³⁵ This method is perhaps one of the simplest procedures for the preparation of spirocyclic systems, as the starting substrates can be generated from olefinic diazo ketones 294.¹³⁶



Other methods of cyclopropane saturation are available. For example, exposure of ketone 295 to chromium(II) sulfate in DMF-H₂O (2:1), produced a longifolene-type skeleton 296 in 84% yield.¹³⁷



Fission of an intermediate cyclopropane ring takes place during the Clemmensen reduction of 1,3-diketones. A mechanism for this rather complex process has been postulated and involves an intermediate cyclopropyl cation^{138,139} formed from the pinacol-type coupling of the carbonyls.¹⁴⁰



Reductive ring opening of cyclopropyl ketones has provided a useful method for the total synthesis of polycyclic natural products and has been successfully

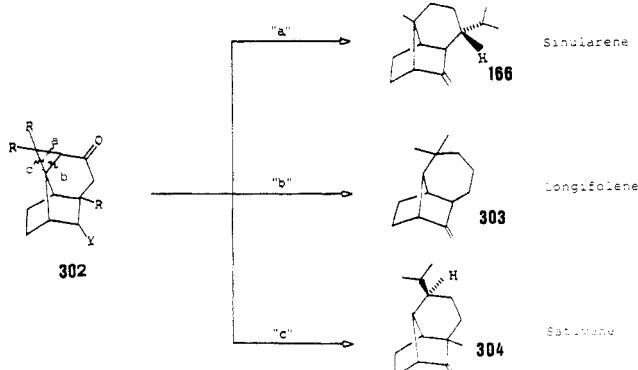
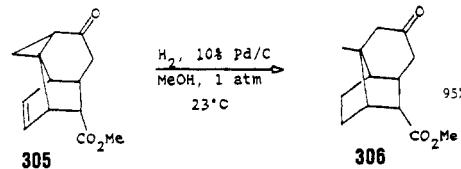


Figure 5.

employed in the stereocontrolled syntheses of (\pm)-hinesol, (\pm)-epihinesol, (-)-acorenene B, (\pm)- α -chamigrene, and (\pm)-sinularene.¹³⁷ After construction of the appropriate tetracyclic precursor, selective cyclopropane bond cleavage (a, b, or c) produced the desired tricyclic ring systems.¹³⁷ For instance, conjugated cyclopropyl ketone 305 was hydrogenated under mild conditions (23 °C, CH₃OH, 10% Pd/C) to give sinularene-type ketone 306 in 95% yield.¹³⁷



IV. Electrophilic and Nucleophilic Ring Fission

1. Additions to Cyclopropanes

Simple fragmentation¹⁴¹ of cyclopropane systems becomes possible when the ring is substituted with functionalities that provide an appropriate reinforcement of unidirectional electron flow (Figure 5). The weakest bond in the cyclopropane can be viewed as the electron pair which is absorbed into the incipient π -system or which leaves behind a cation. This special case of an E₁ or E₂ reaction, which is well-documented in the synthesis of alicyclic or cyclic compounds, is further reinforced in the case of cyclopropanes by the release of ring strain. Additionally, the reacting centers remain connected by the nonparticipating cyclopropane carbon. Depending on the functionalities present, such fragmentation of three-membered-ring carbocycles is an extremely useful method of construction of carbon skeletons resulting in changes in both the structure and the charge parity of products.

In direct analogy to the chemistry of alkenes, cyclopropanes are subject to addition reactions. The only operational difference is the presence of an extra carbon, the "synthetic wedge", which enhances the number of possible rearrangement pathways threefold compared to those available to alkenes. Depending on the substitution of cyclopropane with electron donors or acceptors, any of its three bonds are susceptible to cleavage (Figure 6). Note that either the nucleophile or the electrophile may (or may not) be connected to the cyclopropane (connection indicated by loops in Figure 6). Such connection distinguishes the reactive options of cyclopropanes from those of olefins equipped with similar donors or acceptors, as illustrated in Figure 7. In the case of enone 308, the conceptual "cleavage" of the π -system by the combined effect of donor and acceptor groups leads only to a resonance form of itself. On the other hand, the analogous operation on cyclopropane 310 leads to a new compound by virtue of the connective properties of the extra carbon or "synthetic wedge". All of the ensuing discussion can be reduced to the simple mechanistic representation depicted in Figures 6 and 7. The reactions can generally proceed

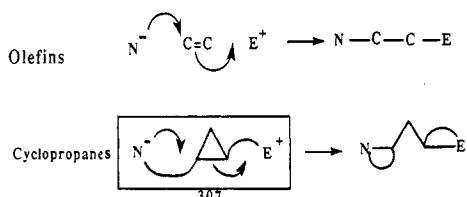


Figure 6.

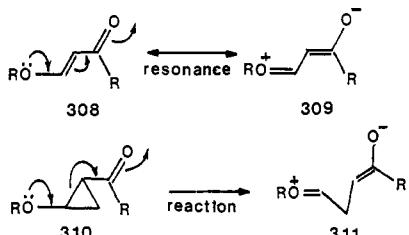
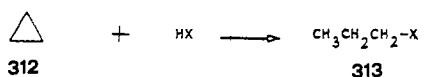


Figure 7.

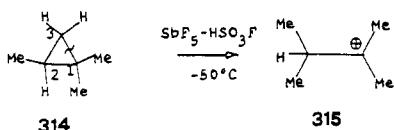
in either acidic or basic media and are organized in order of complexity with respect to the substitution patterns of the cyclopropane and the products.

2. Electrophilic Additions

As the cyclopropane ring behaves much like a carbon–carbon double bond, treatment of a three-membered ring with various electrophiles results in addition of the electrophile with concomitant fission of the ring.^{39,142}

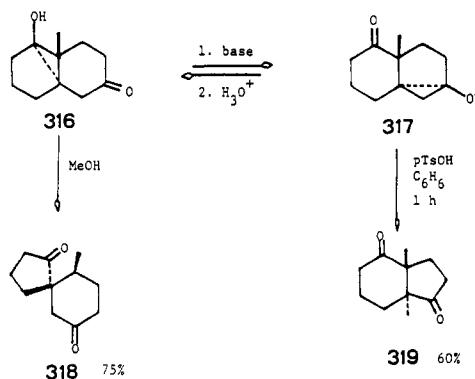


The electrophilic addition follows Markovnikov's rule for substituted cyclopropanes although exceptions have been reported. Addition of $\text{SbF}_5\text{-HSO}_3\text{F}$ to 1,1,2-trimethylcyclopropane (314) at -50°C gave clearly 2,3-dimethyl-2-butyl cation (315).¹⁴³ It appears that the protonation occurred at C-3, to generate the tertiary carbocation 315.¹⁴³

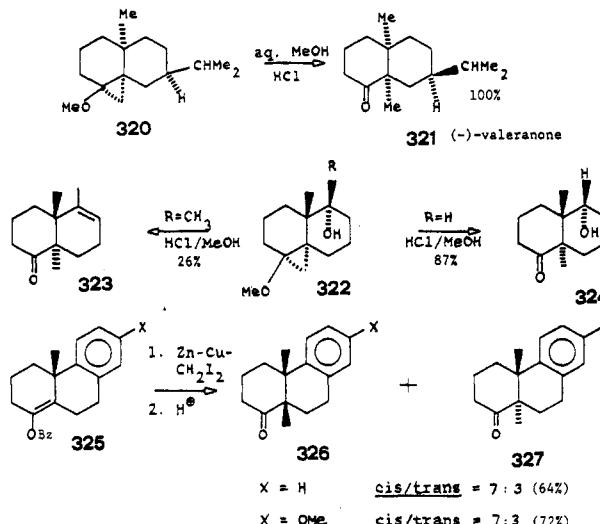


The accepted mechanism for the electrophilic addition to cyclopropane has been briefly reviewed.¹⁴⁴ The electrophile (e.g., H^+) adds to the carbon with the maximum number of protons, generating a cation at the most substituted carbon. The cation is subsequently trapped by its reaction with the nucleophile. As it is possible for the nucleophile to be situated within the same molecule, cleavage of appropriately substituted cyclopropanes would yield compounds containing "angular" methyl groups. The following examples demonstrate these generalizations.

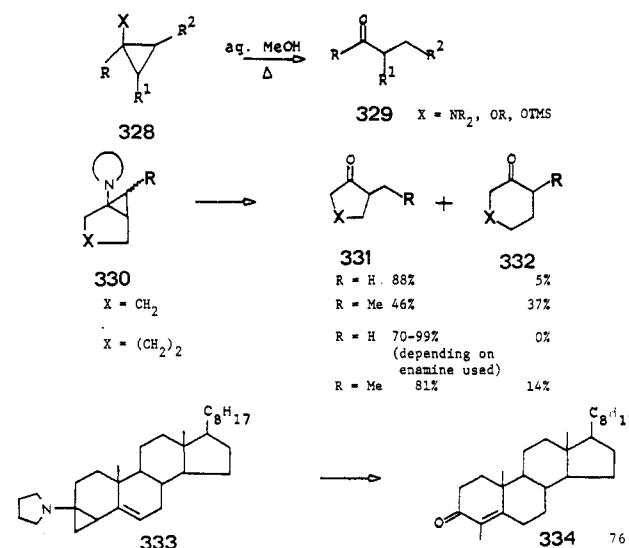
For example, cyclopropanol 317 gave, upon reaction with *p*-toluenesulfonic acid in refluxing benzene for 1 h, a 60% yield of angularly methylated indan 319.¹⁴⁵ Those hydroxycyclopropanes containing suitably situated ketones can exist in equilibrium with their regioisomers. Thus 317 exists in equilibrium with 316, which was transformed to a spiro compound 318 in >75% yield by reaction with methanol.¹⁴⁵



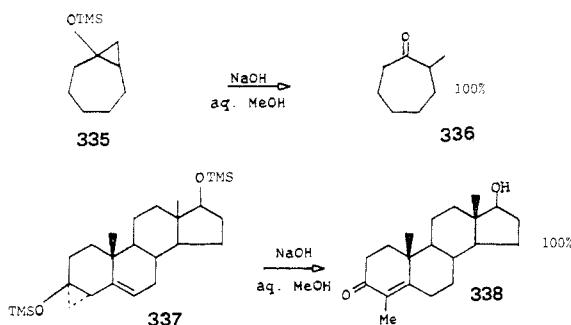
Other examples of introduction of angular methyl groups are shown below. Synthetically, the cyclopropanation of enol ethers followed by cyclopropane opening can be viewed as an alternative to regioselective methylation of ketones.^{146–148}



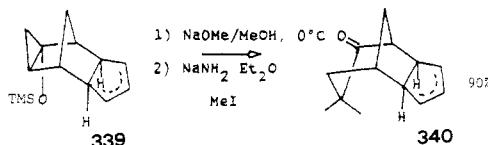
Alkyl and silyl enol ethers as well as enamines have also been used successfully in cyclopropanations leading to systems such as 328. A wide variety of enamines have been transformed, via Simmons–Smith reaction and subsequent protonolysis, to α -methyl ketones in this fashion.¹⁴⁹ Treatment of trimethylsilyl ethers 335



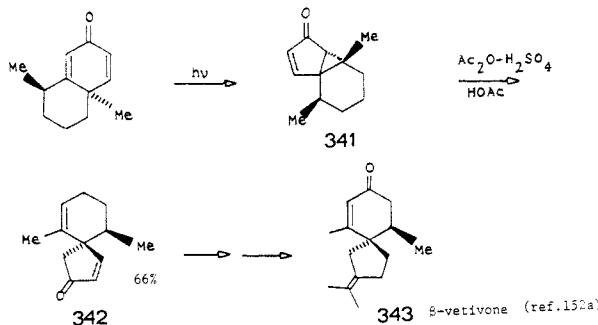
and 337 with NaOH in aqueous MeOH gave α -methylated ketones 336 and 338, respectively, in quantitative yields.¹⁵⁰



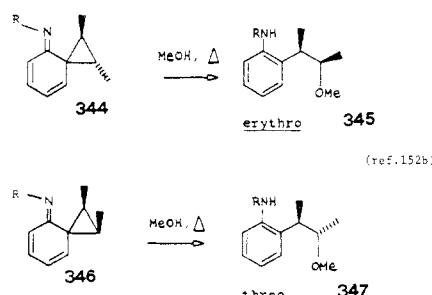
Similarly, trimethylsilyl cyclopropyl ether **339** upon treatment with sodium methoxide in methanol at 0 °C, followed by alkylation of the resulting ketone, provided geminally methylated ketone **340** in 90% yield.¹⁵¹ The



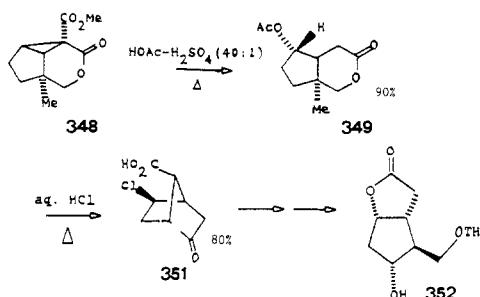
use of silyl ethers allows flexibility in the experimental conditions, as either strong acid, strong base, or nearly neutral fluoride ion catalysis can be employed. Activation of a cyclopropane by an electron-withdrawing group greatly accelerates the ring opening and protonation in analogy to such processes in activated olefins vs simple alkenes. The following examples involving keto cyclopropanes illustrate the utility of this chemistry.¹⁵²



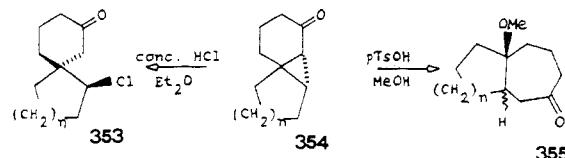
Stereospecific ring opening of *trans*- and *cis*-dimethylcyclopropyl imines **344** and **346** was achieved with inversion of configuration by treatment with methanol to afford erythro and threo products **345** and **347**, respectively.^{152b} Stereospecific cleavage of the



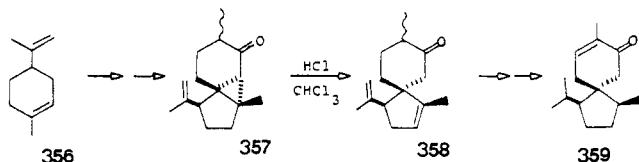
cyclopropyl ring in **348** occurred upon treatment with HOAc-H₂SO₄ (40:1) at 90 °C for 3 h, yielding acetate **349**, which served as a key intermediate in prostaglandin synthesis.¹⁵³ Optically active (+)-tricyclic acid **350** afforded chiral chloro acid **351** in 80% yield on exposure to aqueous HCl in another approach to prostaglandin precursor **352**.¹⁵⁴



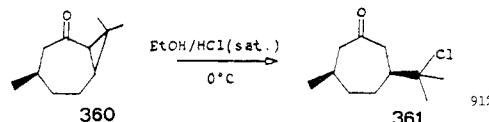
Different modes of ring opening can sometimes be elicited by modifying reaction conditions. Tricyclic ketone **354** was converted to either fused or spiro cyclic systems as shown below.¹⁵⁵



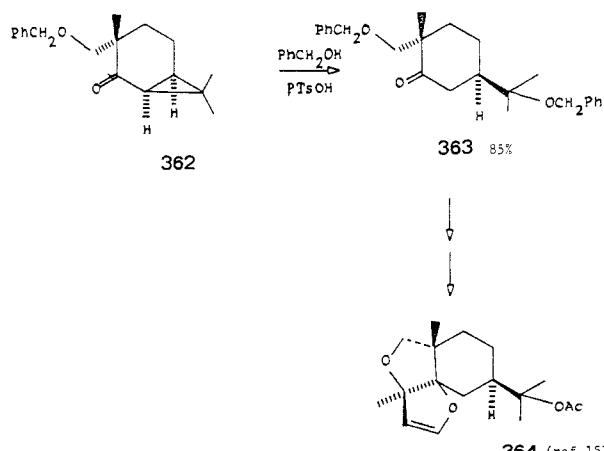
(-)-Acorenone (**359**) was prepared via the ring opening of **357** to **358**, starting from (*R*)-(+)-limonene (**356**).¹⁵⁶



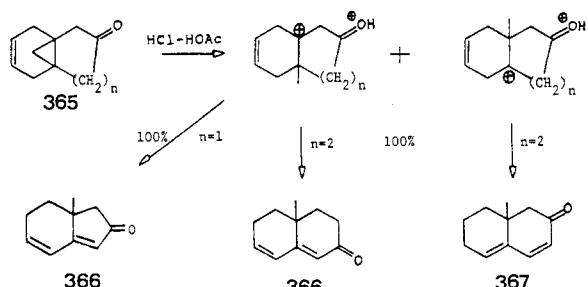
The normal factors governing the trapping of alkyl cations with nucleophiles (S_N1 or S_N2), as opposed to elimination of adjacent protons (E_1 or E_2), operate in keto cyclopropanes as well. Thus, protonation of a cyclopropane can generate a cation stable enough to be trapped by the conjugate base of the original Lewis acid-base pair. The following example illustrates the



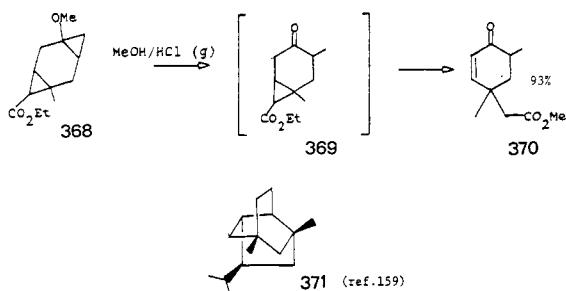
phenomenon and indicates its utility in the design and execution of synthesis of natural products such as (-)-phytuberin (**364**).^{156,157}



Tricyclo[4.3.1.0^{1,6}]dec-3-en-8-one or tricyclo[4.4.1.0^{1,6}]undec-8-en-3-one **365** was treated with hydrochloric acid in acetic acid to give two isomeric ketones, **366** and **367**, quantitatively.¹⁵⁸

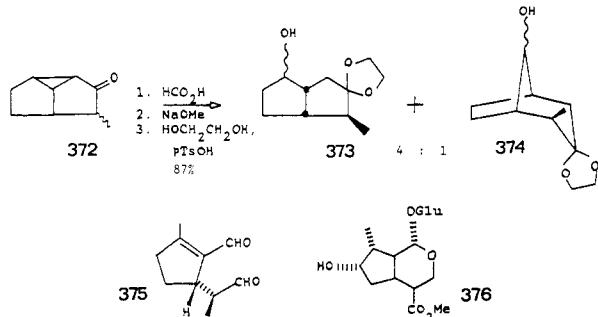


Reaction of tricyclic ester 368 with methanolic HCl produced cyclohexenone derivative 370 in 93% yield. This substance was transformed to (+)-9-pupukeanone (371).¹⁵⁹ The regiocontrol in the opening of keto cy-

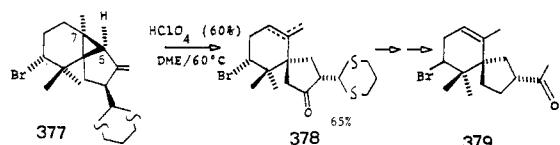


clopropanes was used in general approaches to syntheses of natural products such as the monoterpenes chrysomelidial (375)¹⁶⁰ and loganin (376).¹⁶¹

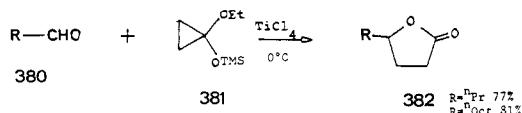
Treatment of 372 with 9% formic acid at 70–80 °C for 30 min followed by methanolysis and ketalization gave 87% of 373 and 374 in a 4:1 ratio.^{160,164} The former substance was converted to chrysomelidial (375) and loganin (376).



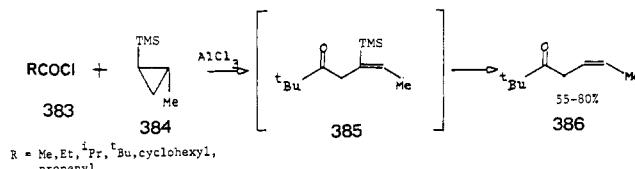
(\pm)-Spirolaurenone (379), an antifungal sesquiterpene isolated from the red algae *Laurencia glandulifera*, was synthesized by a sequence in which the key step was the cyclopropane opening of 377.¹⁶² The acid-catalyzed opening produced a mixture of exo and endo olefins.



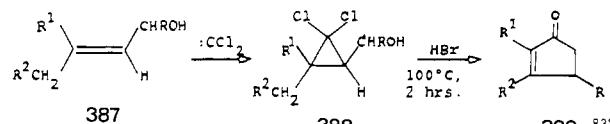
The presence of more than one heteroatom greatly enhances the tendency of cyclopropanes to undergo electrophilic addition. For example, reaction of 1-ethoxy-1-(trimethylsiloxy)cyclopropane (381) with aliphatic aldehydes 380 in the presence of TiCl_4 gave γ -lactones 382 in high yields.¹⁶³ The mechanism is believed to



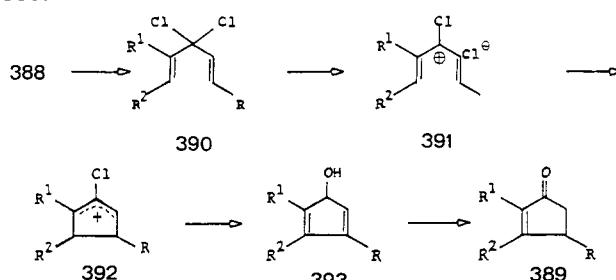
involve electrophilic attack of titanium chloride on the cyclopropane.¹⁶³ Reaction of 1-(trimethylsilyl)-2-methylcyclopropane (384) with acid chlorides 383 in the presence of AlCl_3 in methylene chloride afforded β,γ -unsaturated ketones 386 regio- and stereospecifically.¹⁶⁴



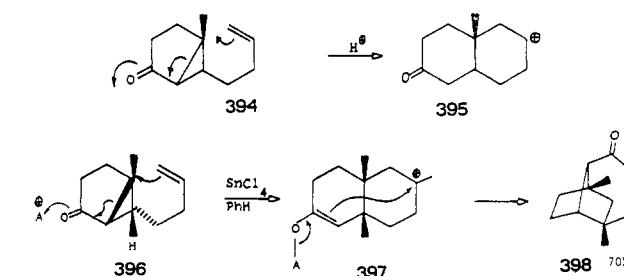
A synthetic method for cyclopentannulation was reported by Hiyama et al.¹⁶⁵ It is based upon one-carbon homologation of allylic alcohols such as 387 with dichlorocarbene to provide 388. Treatment of alcohol 388 with 47% hydrobromic acid at 100 °C gave 389 in 83% yield.¹⁶⁵ The mechanism of the cyclopentenone for-



mation can be rationalized by invoking a Nazarov-type process involving thermal conrotatory ring closure of 391 to produce the cyclopentenyl cation. Deprotonation followed by hydrolysis of the resulting chloro diene gives 389.

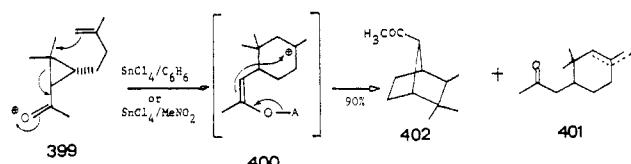


When an acylcyclopropane contains an internal, suitably situated nucleophile, the possibility of multiple C–C bond formation presents itself. For example, acylcyclopropane 394 undergoes acid-catalyzed reaction with a suitably disposed olefinic center leading to the formation of a new ring such as 395.¹⁶⁶ Similarly, treatment of *endo*-bicyclo[3.1.0]hexanone 396 with stannic chloride in benzene afforded tricycle 398 in 70% yield. The cationic intermediate was trapped by the enol generated through acylcyclopropane opening.¹⁶⁷

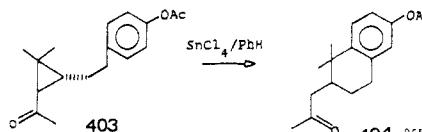


Similar treatment of the nonrigid acylcyclopropane 399 resulted in a >90% yield of a 80:20 mixture of 401 and 402.¹⁶⁸ In contrast, reaction of 399 with 10 equiv of stannic chloride in CH_3NO_2 (25 °C) for 30 min afforded a 20:80 mixture.¹⁶⁸

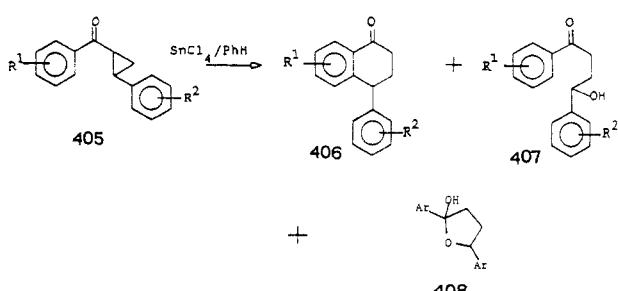
An example involving the annulation of an aromatic ring involves treatment of arene acylcyclopropane 403



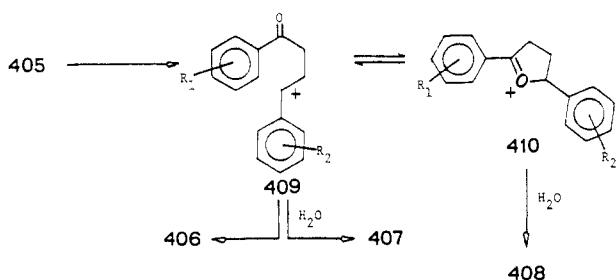
with stannic chloride in benzene, yielding 404 in 85% yield.¹⁶⁸ Cyclization of the activated arylaroylcyclo-



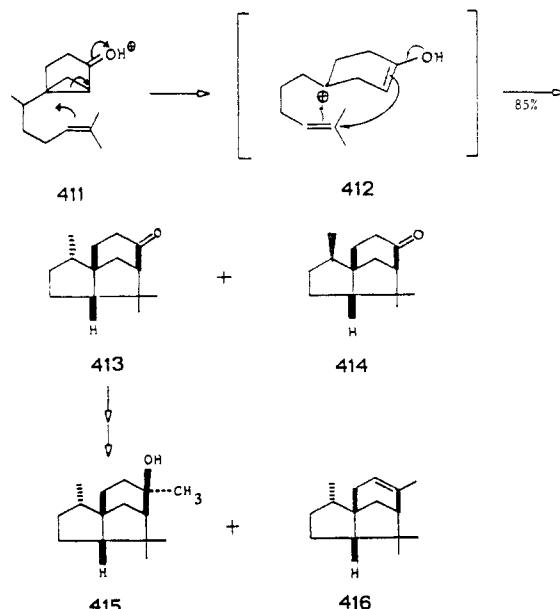
propane 405 was achieved with stannic chloride in benzene at room temperature and afforded mainly tetralone 406.¹⁶⁹ The mechanism of the above trans-



formation involves the formation of benzyl carbocation 409 as illustrated below:¹⁶⁹

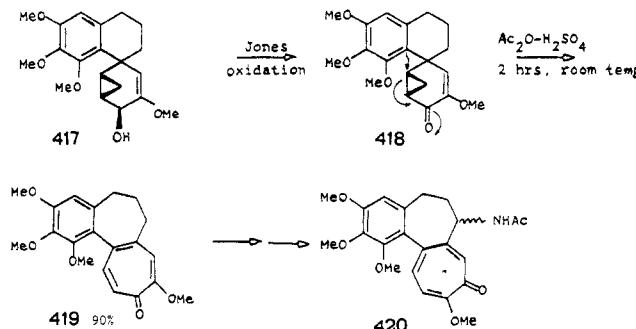


Two elegant examples involving this type of rearrangement are provided by the total syntheses of cedrene and colicine.¹⁷¹ Treatment of a mixture of two diastereomeric forms of 411 with acetyl methane-sulfonate in methylene chloride at -40 °C for 12 h



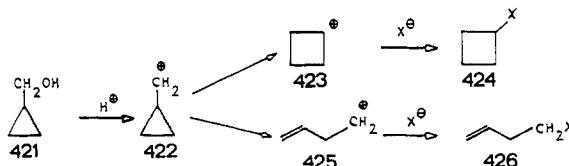
followed by aqueous workup afforded 413 and 414 in an 85% combined yield.¹⁷⁰ Tricyclic ketone 413 was converted to (\pm)-cedrol (415) and (\pm)-cedrene (416).¹⁷⁰

The alkaloid (\pm)-colchicine (420) was synthesized by Tobinaga in a sequence where the key step involved cyclopropyl intermediate 418, which was treated with $\text{Ac}_2\text{O}-\text{H}_2\text{SO}_4$ (2:1) for 2 h at room temperature to give 419 in a one-pot operation involving cyclopropane ring cleavage, aryl migration, and dehydrogenation.¹⁷¹



3. Cyclopropylcarbinyl Cation and Related Rearrangements

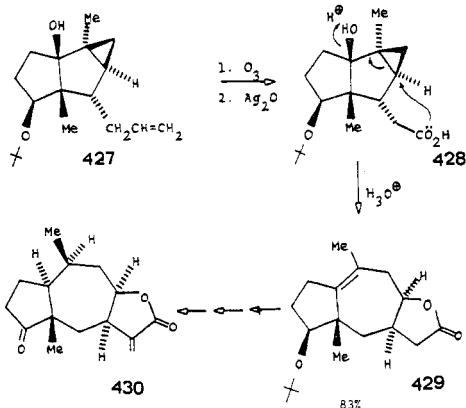
The cyclopropylcarbinyl cation system provides an intriguing example of the number of rearrangements possible for small-ring compounds.³⁹ It is well-known that the intermediates of this rearrangement are either the cyclobutyl cation 423 or the allylcarbinyl cation 425.



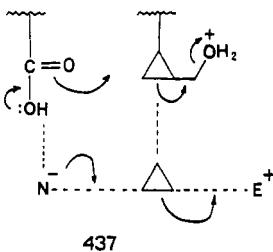
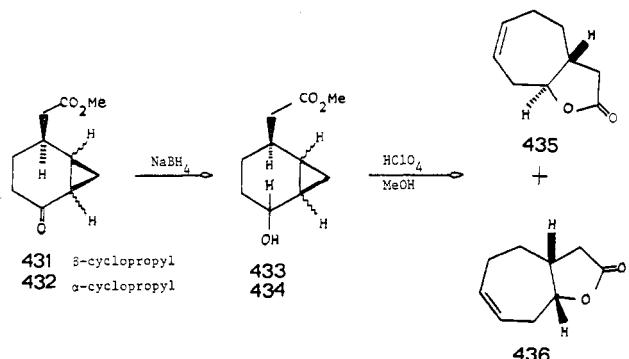
Relief of ring strain and the formation of more stable carbocations are perhaps responsible for the conversion of cyclopropylcarbinyl cation 422 to cyclobutyl cation 423. On the other hand, 422 will also undergo ring fission to furnish allylcarbinyl cation 425. The application of these isomerizations is of particular value to organic synthesis.

The chemistry of this rearrangement has been extensively studied, from both a theoretical and a practical point of view.^{144,172,173} It appears that some degree of control over the two avenues of rearrangement is available; both cyclobutanes and allylic systems can be synthesized in this fashion. Thus, ring-expansion methodology, 1,4-dicarbonyl compounds, γ -unsaturated carbonyl compounds, and their derivatives are all available through the exploitation of this rearrangement. Wenkert¹⁷² and Trost¹⁷³ utilized this rearrangement extensively in the synthesis of terpenoids and cyclobutanones, respectively. Selected examples below illustrate the generality of this process.

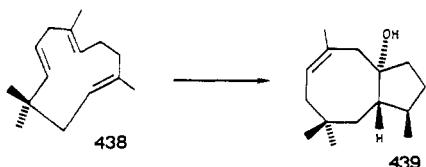
Ozonolysis of the allyl-substituted tricyclic substrate 427 followed by treatment with silver oxide afforded acid 428. Hydroazulene lactone 429 was obtained from 428 upon reaction with aqueous perchloric acid in an overall yield of 80%. This strategy constituted the key step in the total synthesis of confertin (430).¹⁷⁴



Similarly, reduction of a mixture of ketones 431 and 432 with sodium borohydride led to the epimeric alcohols 433 and 434, respectively. This mixture, upon treatment with aqueous perchloric acid in methanol, afforded an 85:15 mixture of the trans and cis lactones 435 and 436.¹⁷⁵ The reactions of the cyclopropylcarbinyl systems in the two aforementioned examples seem to involve the assistance of an internal nucleophile with concomitant ejection of water and cyclopropane bond migration as shown in 437.

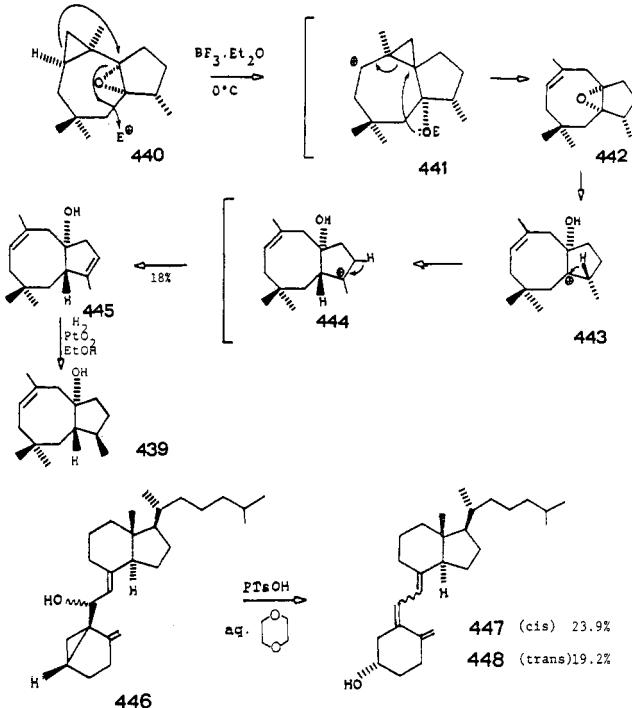


mechanism involving cyclopropylcarbinyl system 441 was proposed to explain the conversion of humulene (438) to dactylo (439).¹⁷⁶ When cyclopropane 440 was

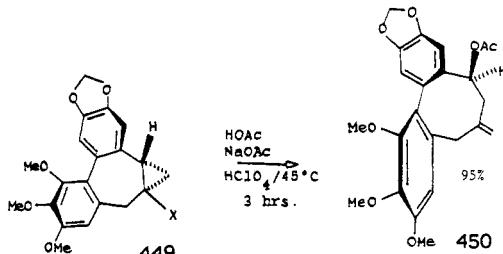


treated with $BF_3 \cdot Et_2O$ at 0 °C, product 445 was produced. This result can be ascribed to opening of cyclopropylcarbinyl cation 441 followed by the epoxide opening, transannular cyclization, and a hydride transfer (443 → 444 → 445). Selective hydrogenation of 445 yielded dactylo (439).¹⁷⁷ Solvolysis of 446 in the presence of *p*-toluenesulfonic acid in aqueous dioxane at 55 °C afforded vitamin D₃ (447) and its trans isomer 448.¹⁷⁸

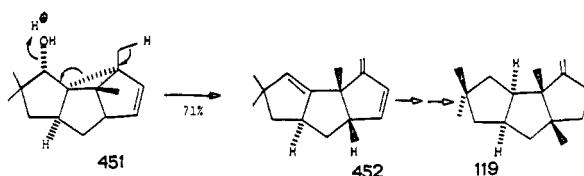
Reaction of cyclopropylcarbinol 449 in acetate buffer



at 45 °C for 3 h gave 450 in 95% yield. Acetate 450 was transformed to (\pm)-steganone, an antileukemic bis-benzocyclooctadiene lignan.¹⁷⁹ Two examples of cy-

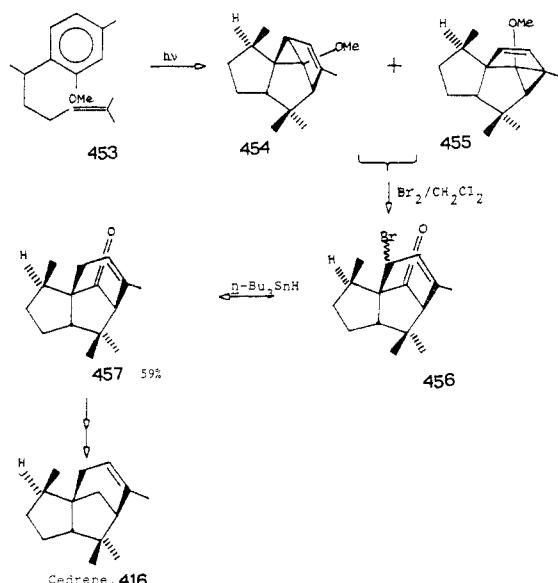


clopropylcarbinyl systems were used by Wender in the synthesis of hirsutene and cedrene.¹⁸⁰ Tetracyclic alcohol 451, prepared by photolysis of the corresponding arene-olefin cyclization, underwent rearrangement with anhydrous 10-camphorsulfonic acid in benzene at room temperature, producing cleanly triene 452 in 71% yield. This triquinane was transformed to (\pm)-hirsutene (119).¹⁸¹

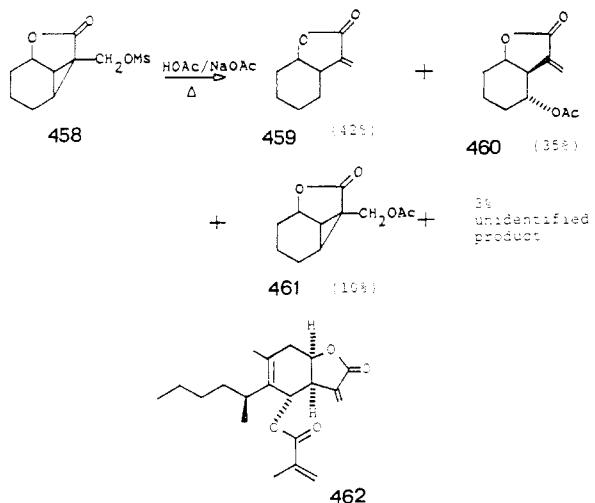


Similarly, a mixture of 454 and 455, prepared from arene-olefin cycloaddition of 453, was treated with bromine (1 equiv in CH_2Cl_2). Electrophilic attack on the double bond induced cleavage of the cyclopropane ring with the assistance of the methoxy group and afforded only 10 α - and 10 β -bromocedren-11-one 456. The bromides were treated immediately with tri-*n*-butyltin hydride to give 457 in 59% overall yield. Wolff-Kishner reduction of this compound provided (\pm)- α -cedrene (416).¹⁸²

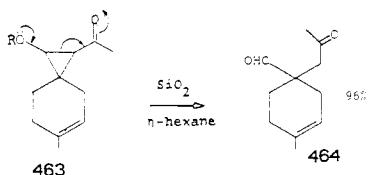
When cyclopropyl lactone 458 was exposed to refluxing glacial acetic acid containing 1.2 equiv of sodium acetate, three substances, 459–461, and an unidentified



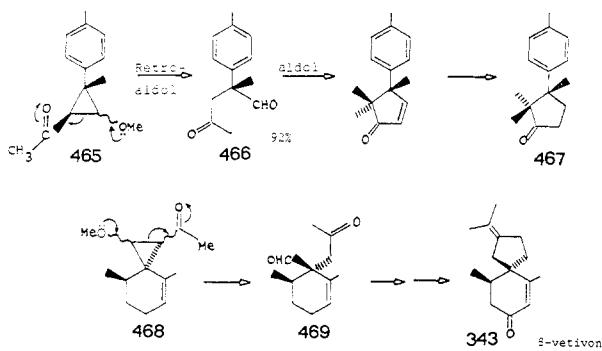
product were isolated.¹⁸³ This synthetic strategy was further employed in the synthesis of eriolanin (462).¹⁸⁴



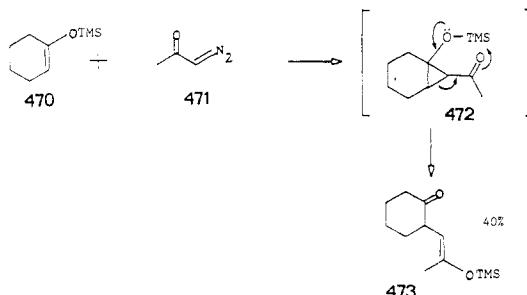
The synthesis of 1,4-dicarbonyl compounds via tandem cyclopropanation–cyclopropylcarbinyl rearrangement has been applied to the preparation of many natural products. Wenkert and others have extensively used this sequence.^{172,185,186} Most recently, this rearrangement has been used in the synthesis of natural products, as in Wenkert's isocomene¹⁸⁵ and Marino's pentalenolactone¹⁸⁶ syntheses. Chromatography of ketone 463 on silica gel promoted the retro-aldol reaction and afforded aldehyde 464 in 96% yield.¹⁸⁷ Sim-



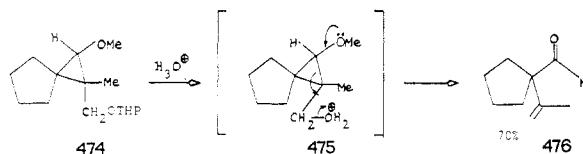
ilar strategy has been used in synthesis of (\pm)- α -cuparenone 467 and β -vetivone (343).¹⁸⁸ In these syntheses, the copper-mediated carbenoid addition of α -diazo ketones and esters to enol acetates led to acetoxy cyclopropyl carbonyl compounds, which upon hydrolysis underwent subsequent retro-aldol ring opening to 1,4-dicarbonyl compounds.^{136,189} More recently, the enol acetates were replaced with silyl enol ethers, which have been found receptive of carbenoids. For example,



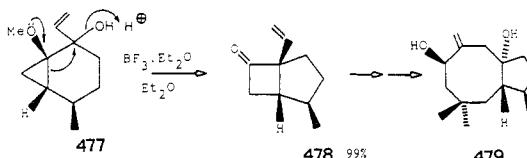
reaction of diazoacetone with 470, in the presence of cupric acetylacetone afforded 472, which underwent subsequent silatropic retro-aldol rearrangement to a masked 1,4-dicarbonyl compound 473.¹⁹⁰ Treatment



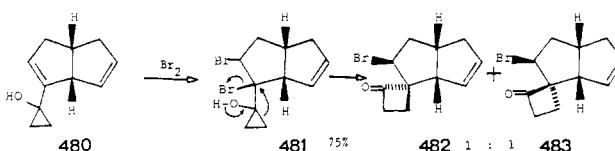
of spiro compound 474 with HCl in aqueous acetone effected the cleavage of the cyclopropane ring with concomitant formation of the isopropenyl moiety to give 476 via intermediate 475.¹⁹¹



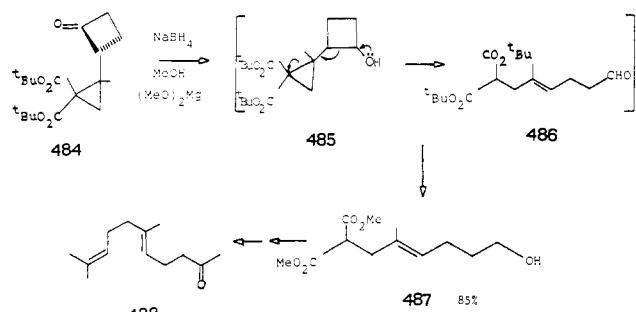
Formation of cyclobutanone 478 was achieved through treatment of norcaranol 477 with 1 equiv of $\text{BF}_3\text{-Et}_2\text{O}$.¹⁹² This compound was an important intermediate in the synthesis of (\pm)-poitediol (479), an unusual sesquiterpene diol isolated from the red seaweed *Laurencia poitei*.¹⁹²



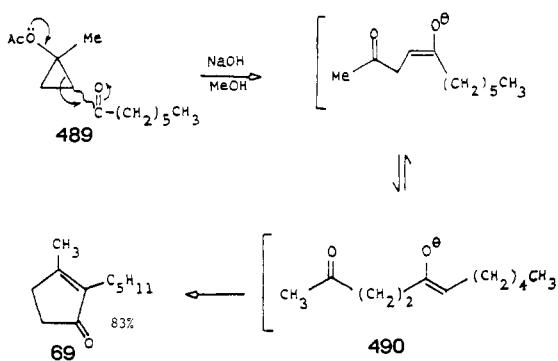
Treatment of vinylcyclopropyl alcohol 480 with bromine afforded an equimolar mixture of spiro ketones 482 and 483.¹⁹³ The mechanism of the ring expansion may involve intermediate dibromide 481 or a bromonium ion.¹⁹³



Treatment of 2-cyclopropylbutanone 484 with a methanolic solution of sodium borohydride and magnesium methoxide at 0 °C, followed by reflux for 40 h, led to an 85% yield of diester 487. This compound is an important precursor to many acyclic terpene units

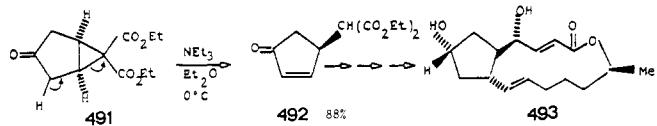


such as (*E*)-geranylacetone 488.¹⁹⁴ A solution of 489 and sodium hydroxide in methanol gave dihydrojasmon (69) in 83% yield through intermediate 490.¹⁸⁸

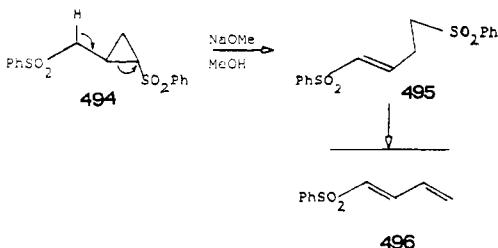


The advantage of a suitably masked cyclopropylcarbinyl system lies in the fact that both acid- and base-catalyzed rearrangements can be effected. The choice depends on the use of acetates or silyl ethers (base deprotection) or allyl ethers (acid catalysis).

Activated cyclopropanes also undergo cleavage under basic conditions. This reaction can be compared mechanistically to either additions to enones (resulting in overall substitution) or to elimination (E_{1cb} or E_2) of β -halocarbonyl groups. In the case of cyclopropanes, the bond that would normally break on departure of a leaving group is either channeled into the π -system of an electron-withdrawing substituent or it becomes a new π -system. The following examples illustrate the utility of the base-induced cyclopropylcarbinyl rearrangement. Treatment of ketone 491 with Et_3N generated a useful precursor 492 for the synthesis of brezelfeldin A (493).¹⁹⁵

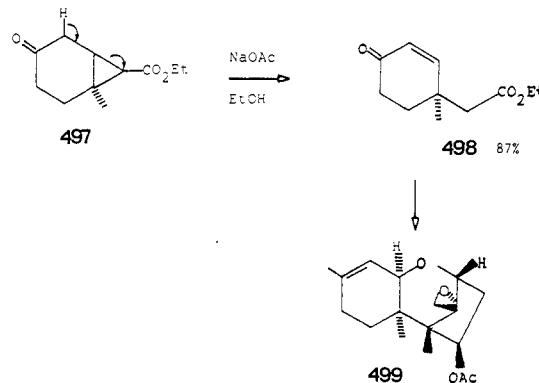


Treatment of cyclopropyl sulfone 494 with ethanolic sodium ethoxide gave 495, which was converted to diene 496 upon elimination of PhSO_2H .¹⁹⁶

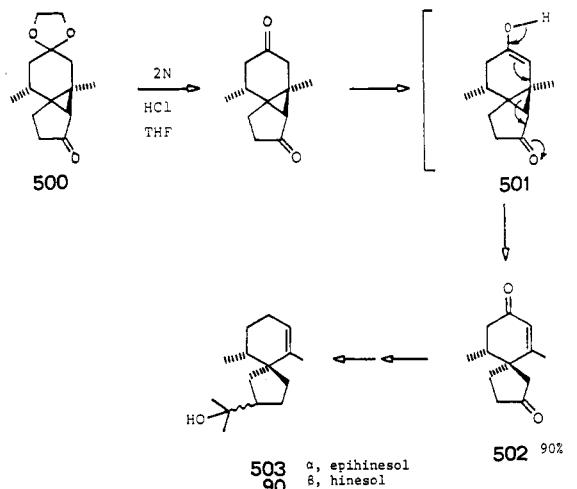


The total synthesis of a phytotoxic trichothecane group sesquiterpene, (\pm)-trichodermin (499), featured

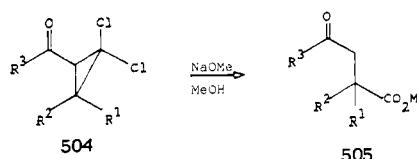
the ring opening of 497 by sodium acetate in ethanol to give 498.^{197,198} The conversion of 497 to 498 exemplifies an extremely useful methodology: the equivalent of a selective γ -alkylation of an enone. The enone is deconjugated by the normal kinetic protonation of its dienolate, the β,γ -unsaturated site is cyclopropaned, and the cyclopropane is opened to provide the γ -alkylated enone selectively.



Treatment of cyclic ketal ketone 500 with 2 N HCl in THF gave spiro enedione 502 via enol intermediate 501. Cyclopropane 501 was then converted to (\pm)-hinesol (90) and (\pm)-epihinesol (503).¹⁹⁹ Treatment of



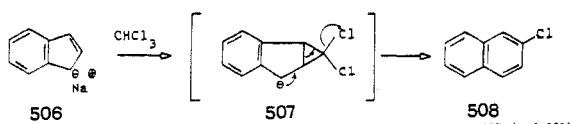
gem-dichlorocyclopropanes 504 with sodium methoxide in methanol afforded ketones 505 in high yields.²⁰⁰



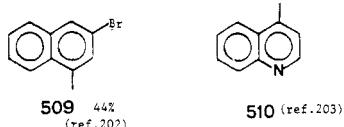
| R^1 | R^2 | R^3 | yield of 505, % |
|-------|---------------------|---------------------|-----------------|
| H | | $-(\text{CH}_2)_3-$ | >94 |
| Me | | $-(\text{CH}_2)_3-$ | >94 |
| H | | $-(\text{CH}_2)_4-$ | >94 |
| H | | $-(\text{CH}_2)_5-$ | >94 |
| Me | Me | Me | 83 |
| | $-(\text{CH}_2)_6-$ | H | 75 |

Reaction of indenylsodium (506) with chloroform results in the formation of 2-chloronaphthalene (65% yield), presumably via rearrangement of 507.²⁰¹

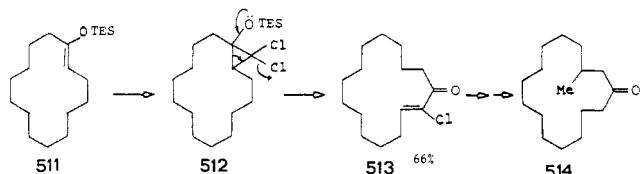
This type of reaction has been used extensively in the preparation of aromatics such as 509.²⁰² This methodology has been extended to synthesis of heterocyclic



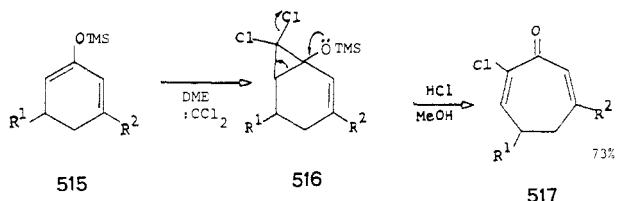
compounds such as **510**,²⁰³ obtained by cyclopropanation and ring expansion of 3-methylindole.²⁰³



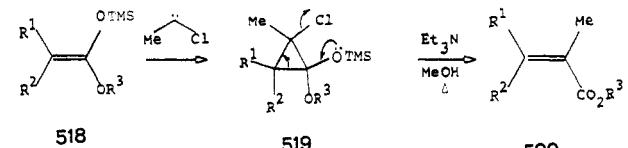
Muscone (**514**) was synthesized via cyclopropanation of triethylsilyl enol ether **511** followed by treatment with 1 N HCl in THF at room temperature for 1 h. Ketone **513** was isolated in 66% yield and was readily converted into (\pm)-muscone (**514**).²⁰⁴ Dichlorocarbene



addition and hydrolysis of dienyl silyl ether **515** gave **516**, which upon treatment with acid rearranged to α -chloro dienone **517** in 73% yield.²⁰⁵ Trimethylsilyl

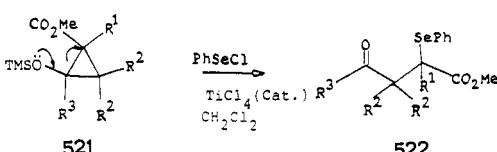


enol ether **518** underwent cycloaddition with chloromethylcarbene to give, after rearrangement of cycloadduct **519**, α -unsaturated ester **520**.²⁰⁶



| R ¹ | R ² | R ³ | yield of 520 , % | E/Z |
|------------------------------------|----------------|--------------------|----------------------------|-------|
| H | H | CH ₂ Ph | 91 | |
| Me | H | Et | 88 | 68/32 |
| Et | H | Et | 94 | 60/40 |
| ⁿ Am | H | Et | 95 | 64/36 |
| ^t Bu | H | Me | 88 | 83/17 |
| Ph | H | Me | 75 | 61/39 |
| Me | Me | Et | 91 | |
| -(CH ₂) ₄ - | | Me | 89 | |
| Ph | Ph | Me | 32 | |
| ^t Bu | H | Me | 94 | 60/40 |

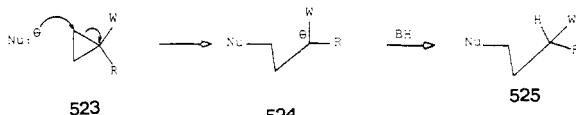
A recent report described the ring opening of trimethylsilyl ether **521** and the trapping of the intermediate with phenylselenium chloride to provide **522**.²⁰⁷ This reaction was used extensively in the preparation of various γ -keto esters.²⁰⁸



| R ¹ | R ² | R ³ | yield of 522 , % |
|----------------|----------------|-----------------|-------------------------|
| H | Me | H | 69 |
| H | Me | Me | 88 |
| H | H | ^t Bu | 85 |
| Me | H | ^t Bu | 82 |

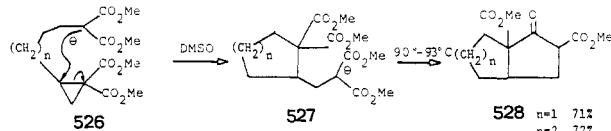
4. Nucleophilic Addition

Cleavage of three-membered carbocycles by nucleophiles is possible only when an electron-withdrawing group (W) is present on the ring.²⁰⁹ This methodology

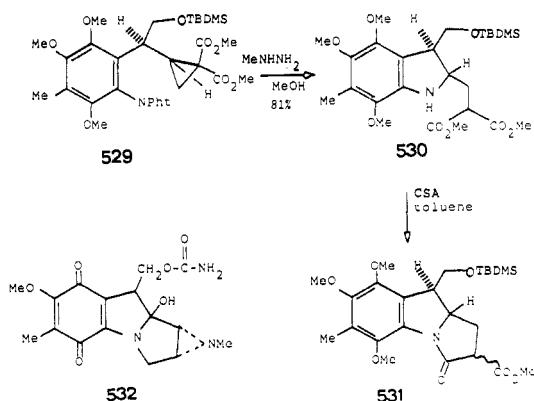


has been widely applied in organic synthesis and is known as the homologous (or 1,5) version of the classical Michael addition.²¹⁰ The following examples demonstrate how this type of reaction has been applied intramolecularly in the preparation of some fused-ring compounds. Central to the approaches to cyclic compounds is the initial nucleophilic attack of an enolate, alkoxide, or amine on an activated cyclopropane, with subsequent intramolecular ring closure.

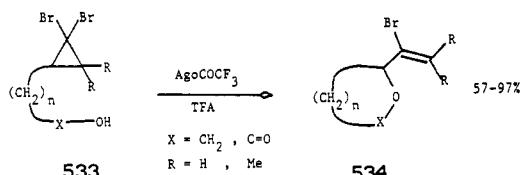
Anions **526** reacted readily at room temperature in DMSO via an intramolecular nucleophilic addition to the cyclopropyl group, yielding **527**. When **527** was heated, a 70% yield of the bicyclic ketones **528** was obtained.²¹¹ Cyclopropane **529** was subjected to hy-



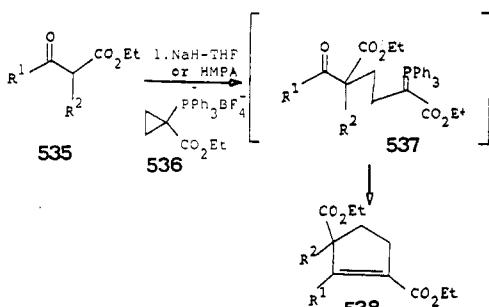
drazinolysis to give an 81% yield of **530**. Heating **530** in the presence of camphorsulfonic acid yielded 50% of lactam ester **531**, which was used in the total synthesis of mitomycin B (**532**).²¹²



The cationic π -cyclization constitutes an important method for the synthesis of an alicyclic and heterocyclic compounds, e.g., **534**. Lactones, tetrahydrofuran, and tetrahydropyran can be synthesized by this method.²¹³

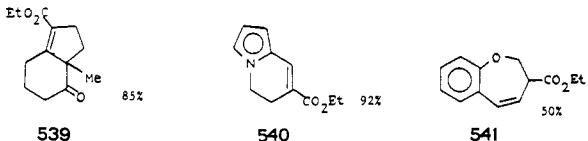


Nucleophilic addition to an activated cyclopropane can also be accomplished *intermolecularly*, although the process requires more activation than its intramolecular counterpart.²⁰⁹ For example, β -keto ester 535 (as its sodium enolate) adds to cyclopropane 536 to produce the phosphorane intermediate 537, which rearranges to cyclopentene diester 538.²¹⁴

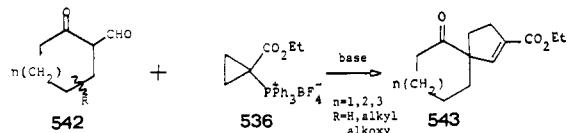


| R ¹ | R ² | yield of 538, % |
|-----------------|-----------------|-----------------|
| CH ₃ | H | 95 |
| Ph | H | 90 |
| CH ₃ | CH ₃ | 88 |

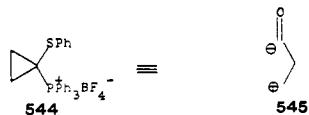
The following examples illustrate the utility of phosphonium salt 536 as a cycloalkenylation reagent. The initiating nucleophile need not be the carbon of an enolate anion as in the reactions leading to 538 and 539; amines and alkoxides also participate in the ring opening of 536, providing entry into heterocyclic systems 540 and 541.²¹⁴ A general synthesis of spirocycles



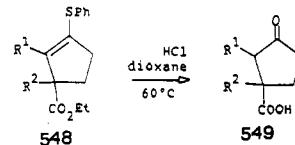
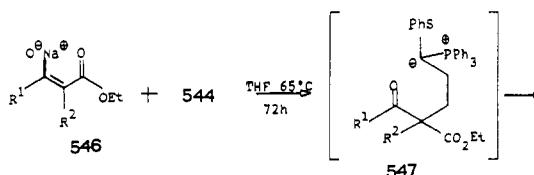
543 was accomplished by reactions of 536 with β -keto esters or symmetrical 1,3-dicarbonyl systems such as 542.²¹⁵ A new compound, (1-(phenylthio)cyclo-



propyl)triphenylphosphonium tetrafluoroborate (544), equivalent to the acyl synthon 545, has been reported.²¹⁶



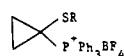
Sodium enolates of β -keto esters 546 were added to 544 to give intermediate phosphonium ylide 547, whose intramolecular Wittig reaction gave rise to vinyl sulfides 548 in good yields. Hydrolysis in 20% HCl-dioxane in 60 °C produced keto acids 549.²¹⁶ Variations in the thioether functionality have also been investigated. Sodium enolates of β -keto ester 546 were added to 544, 550, or 551 to give, after acidic hydrolysis of interme-



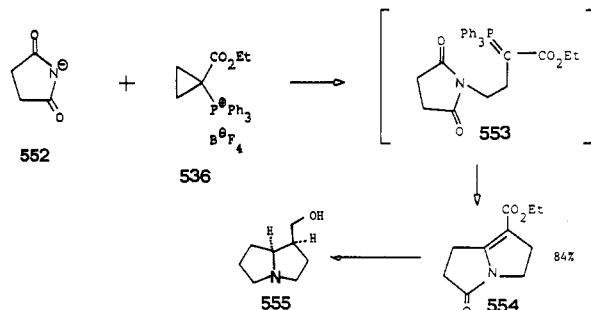
| R ¹ | R ² | yield of 549, % |
|-----------------|--------------------|-----------------|
| CH ₃ | H | 75 |
| CH ₃ | CH ₂ Ph | 80 |
| Ph | H | 75 |

550 R = Me
551 R = iPr

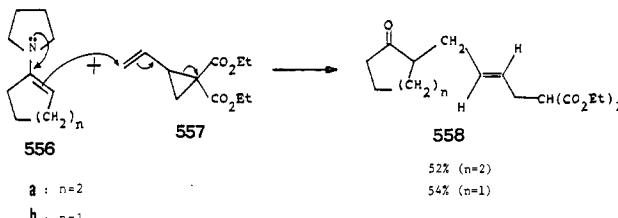
diate thioenol ethers, cyclopentanone carboxylic acids 549 in 80% overall yield.²¹⁷



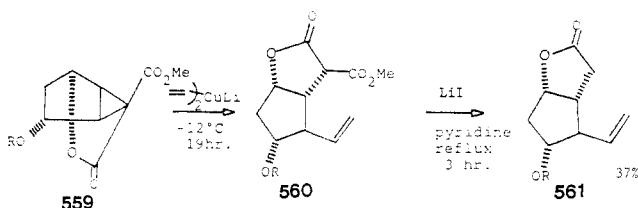
Treatment of phosphorus ylide 536 with succinimide anion (552) yields an intermediate 553, which rearranges to bicyclic N-bridgehead lactam 554 in 84% yield.²¹⁷ This lactam constituted an intermediate in a brief synthesis of isoretronecanol (555).²¹⁸



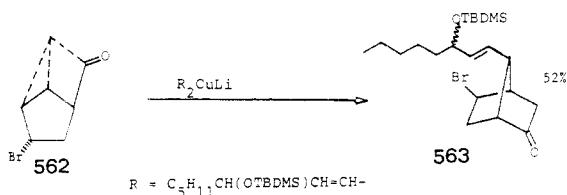
The reaction of enamines 556a and 556b with vinylcyclopropyl diester 557 in *p*-cumene at reflux, followed by mild acid hydrolysis, gave ketones 558a and 558b in 52% and 54% yield, respectively.²¹⁹ This reaction constitutes a vinylogous equivalent of the opening of activated cyclopropanes with carbon nucleophiles.



The reaction of cyclopropyl ketones with organomagnesium and organocupper reagents is well documented.²²⁰ The success of such ring-opening reactions, analogous to 1,4-addition of cuprates to enones, depends on the choice of the organometallic reagent. The following examples offer a glance at the predictable use of these additions in synthesis. Reaction of tricyclic lactone ester 559 with divinylcopper lithium gave lactone ester 560, which was decarboethoxylated with lithium iodide to produce lactone 561 in 37% yield.²²¹

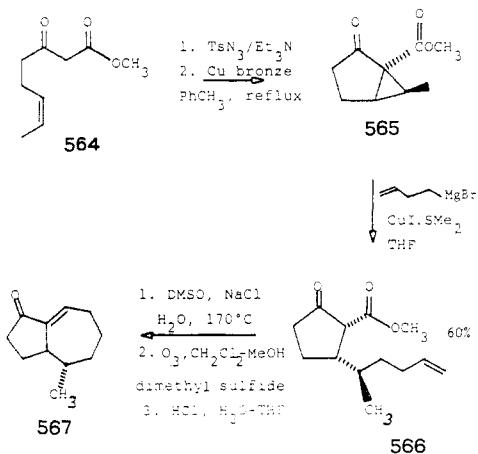


Strained tricyclic ketone **562** reacted efficiently with cuprate reagent to afford the norbornanone **562** in 52% yield. This compound served as a precursor to several prostaglandins.^{222,223} It is important to note that the stereochemistry of **562** dictates that of **563** because the cuprate reagent attacks from the least hindered side.



Compounds such as **562** are easily accessible through the reactions of diazo ketones with olefins.^{41,136,222,223}

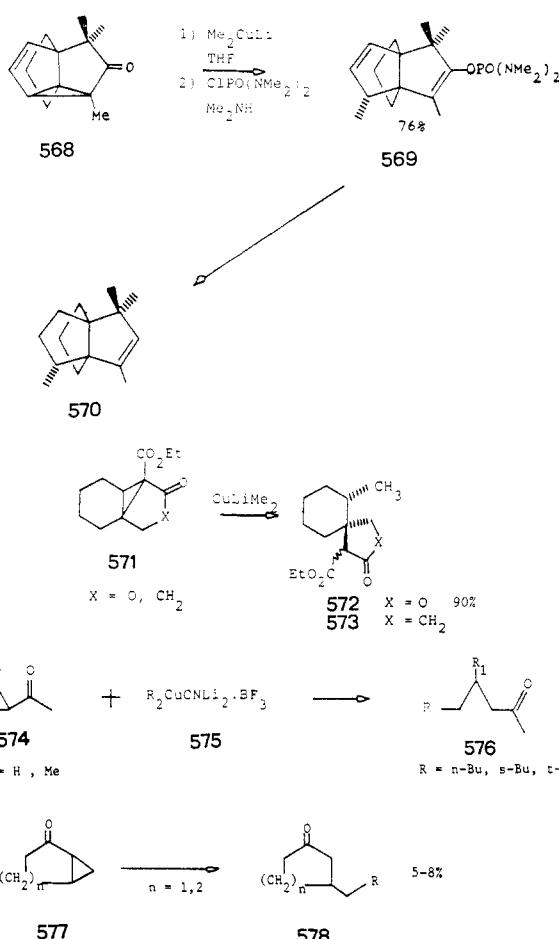
The following example depicts the construction of a bicyclo[3.1.0]hexane system by using a tandem diazo ketone addition to double bond¹³⁶ and the facile cleavage of the strained fused ring system to the desired carbon skeleton. Cyclopropanation of **564** afforded cyclopropyl ketone **565** in 57% yield. Cuprous iodide mediated homoconjugated addition of the Grignard reagent to **565** in THF gave **566** in 60% yield. Decarbomethylation, ozonolysis, and aldol condensation then gave enone **567** in 35% yield.²²⁴



Cyclopropane **568** reacted with 5 equiv of Me₂CuLi stereoselectively to furnish phosphorodiamidate **569** in 76% yield. The phosphonate enol moiety in **569** was then reduced in 93% yield, and the intermediate diolefin was selectively hydrogenated to modhephene (**570**) in quantitative yield.²²⁵ Other examples of cuprate additions to activated cyclopropanes include the preparation of **572** and **573**.²²⁶

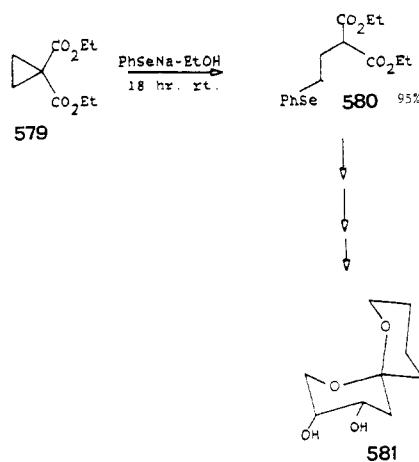
Cyclopropyl ketones such as **574** undergo 1,5-addition at the less substituted carbon with the complex reagent R₂CuCNLi₂·BF₃ (**575**) in moderate to good yields.²²⁷ With fused cyclopropyl ketones such as **577**, the yields are considerably diminished.²²⁷

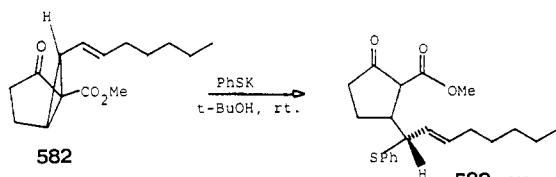
A recent paper by Bertz and Cook²²⁸ discusses several mechanisms that may be operative during the additions of cuprates to activated cyclopropanes. A point of in-



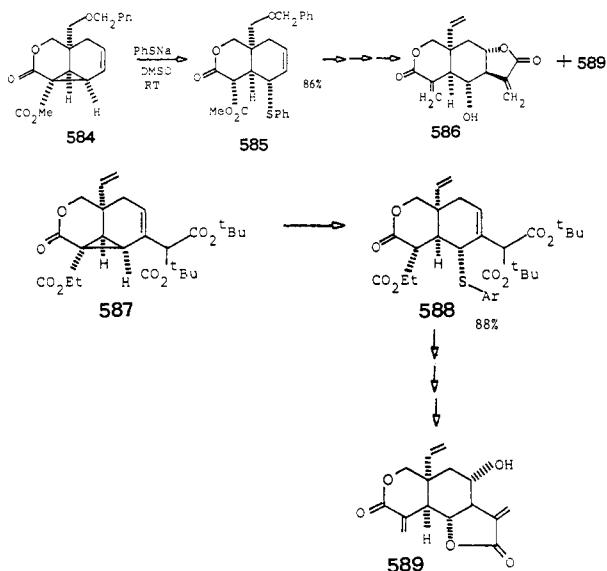
terest that triggered this investigation was the observed difference in reactivity between the propellane intermediates in Cook's synthesis of modhephene.²²⁹ The examples of cuprate additions to cyclopropanes are too numerous to list here, but an appropriate survey of relevant additional examples is available in the reference section.²³⁰⁻²³⁵

Sulfur and selenium nucleophiles also cleave activated cyclopropanes, thus providing convenient departure points for further functionalizations at the side of addition. During the synthesis of talaromycin B (**581**), the reaction of cyclopropane diester **579** with PhSeNa-EtOH afforded alkyl diester **580** in 95% yield.²³⁶ Similarly, the PhSK⁺-induced ring-opening reaction of **582** produced the 2,3-disubstituted cyclopentanone **583** in 89% yield.²³⁷ Similar treatment of **584** with PhSNa



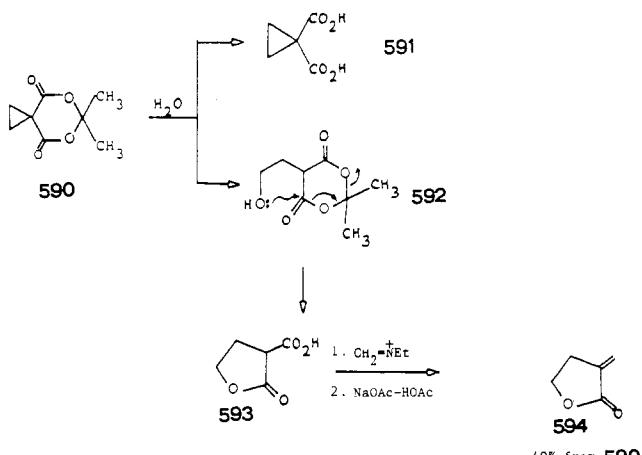


yielded **585**, which was converted to (\pm)-vernolepin (**589**) and (\pm)-vernomenin (**586**).²³⁸

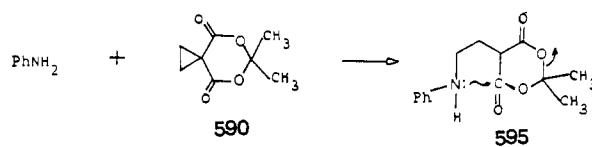


In another approach to vernolepin, opening of the cyclopropane ring in **587** was achieved efficiently by sodium *p*-methoxythiophenolate in THF to afford **588** in 88% yield.²³⁹ Again, release of ring strain played an important role in the building of the extensively substituted bicyclic system. Nitrogen and oxygen nucleophiles have also been used in cyclopropane ring-opening reactions, usually for the purposes of modifying the skeleton or the functionalities of the starting substrates.

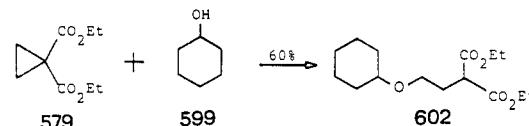
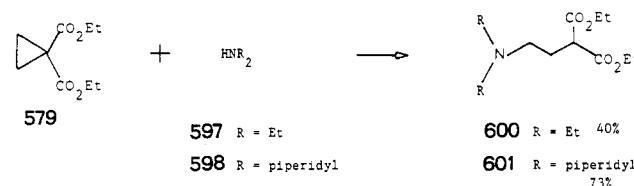
When **590** was heated with 2:1 acetone–water, a 9:1 mixture of 3-carboxybutyrolactone (**592**) and cyclopropane-1,1-dicarboxylic acid (**591**) were obtained. This technology provided synthons such as **593** for conversion to α -methylene lactones **594**.²⁴⁰ Similarly, a



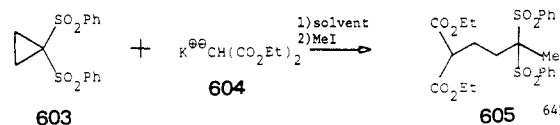
quantitative yield of lactam acid **596** was obtained from treatment of **590** with aniline. A likely pathway involved the formation of the intermediate **595**.²⁴⁰ Ring-opening addition of amines such as **597** and **598** or alcohols such as **599** to diethyl cyclopropane-1,1-



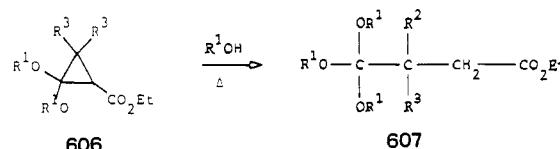
dicarboxylate (**579**) led to 1,1,3-trisubstituted propanes **600**, **601**, and **602**, respectively.²⁴¹ Amine nucleophiles



therefore react in direct analogy to the reaction of cyclopropanes such as 1,1-bis(phenylsulfonyl)cyclopropane (**603**) with the anions of malonic ester, which provided **605** in 64% yield.²⁴² Recently, it has been



reported that the alcoholysis of cyclopropane **606** yields 4,4,4-trialkoxybutanoic ester **607**.²⁴³

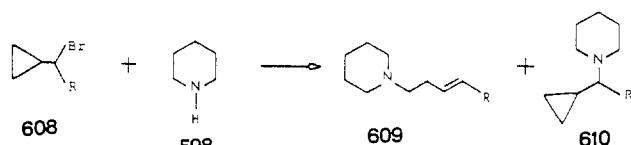


| R ¹ | R ² | R ³ | yield of 607, % |
|----------------|------------------------------------|----------------|-----------------|
| Me | H | H | 73 |
| Et | H | H | 70 |
| Me | Me | H | 72 |
| Et | Me | H | 76 |
| Me | Et | H | 78 |
| Me | Ph | H | 67 |
| Me | Me | Me | 66 |
| Me | -(CH ₂) ₄ - | | 50 |

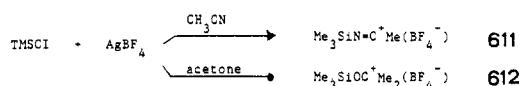
Other variations of the nucleophile-induced ring opening of cyclopropanes involve replacing the activating electron-withdrawing group with $-\text{CR}_2\text{X}$, where X is a leaving group. Departure of X⁻ will lead to the formation of olefins situated 1,3 to the position of nucleophilic opening and is functionally equivalent to a cyclopropylcarbinyl rearrangement.

Reaction of piperidine with 1-bromo-1-cyclopropylalkanes **608** afforded mixtures of products **609** and **610**. Excellent yields of the homoallylic substitution product **609** were achieved when the bromide-bearing carbon was sufficiently sterically hindered.²⁴⁴

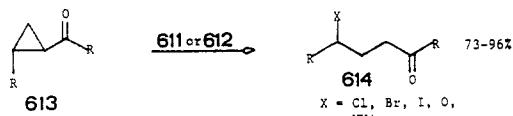
Halides are often used in the nucleophilic opening of activated cyclopropanes.²⁴⁵ A stoichiometric combina-



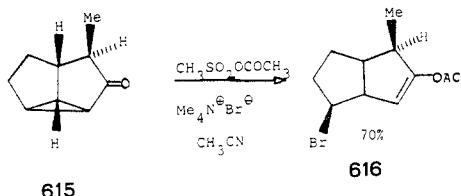
tion of trimethylsilyl chloride and silver tetrafluoroborate in acetonitrile or acetone solution yielded two useful reagents 611 and 612, which were used to convert cyclopropyl carbinols or ketones into homoallyl and γ -substituted ketone derivatives, respectively.²⁴⁶



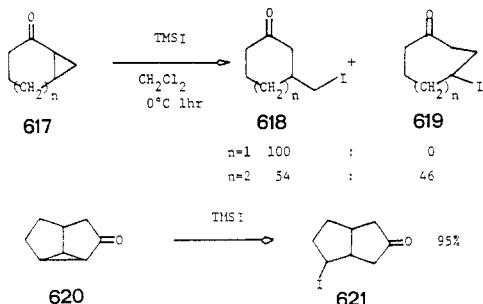
The presence of sodium halides in the reaction mixture resulted in the formation of the corresponding alkyl halides. The presence of water resulted in formation of alcohols ($X = \text{OH}$), while the use of anhydrous 611 in the absence of any additives, followed by aqueous workup, led to acetamides ($X = \text{NHAc}$).²⁴⁶ Tricyclic



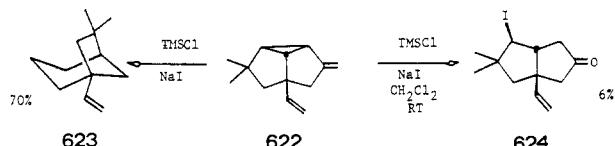
ketone 615 was transformed to 616 in a solution of acetyl methanesulfonate, tetramethylammonium bromide, and acetonitrile.²⁴⁷ Miller has used trimethylsilyl



iodide in a procedure that provided iodo ketones 618, 619, and 621 in excellent yields.²⁴⁸ Iwata reported the

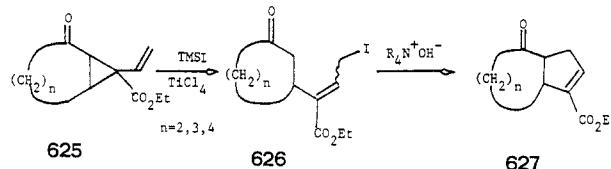


cleavage of ketone 622 to a bridged bicyclo[3.2.1] system 623 in preference to bicyclo[3.3.0]octane 624 with TMSI generated in situ.²⁴⁹



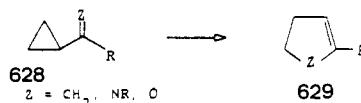
Recently, this methodology has also been found useful in the cyclopentene annulation procedure. Vinylcyclopropanes 625 have been treated with TMSI or TMSI/TiCl₄ to yield, through the allylic S_N2' opening, iodides 626, which were cyclized to cyclopentene-anulated systems 627. Overall, this transformation is equivalent to the vinylcyclopropane-cyclopentene re-

arrangement.⁷² Most recently, a report of the nucleophilic cleavage of cyclopropanes under the conditions of asymmetric induction appeared. Vitamin B_{12a} has been used as the agent of nucleophilic opening of activated cyclopropanes to give moderate induction (24–33% ee) at the site of ring opening.²⁵⁰ Chiral cyclopropyl ketones yielded optically active bromomethylene compounds with trimethylsilyl bromide.²⁵¹

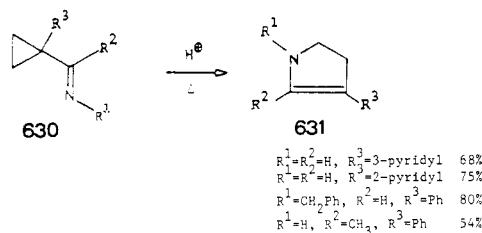


5. Imine-Cyclopropane and Carbonyl-Cyclopropane Rearrangement

Under appropriate conditions, cyclopropanes in conjugation with an unsaturated functional group can undergo the rearrangement (i.e., 628–629) depicted below. The thermal isomerization of vinylcyclopropane to cyclopentene ($Z = \text{CH}_2$) has been discussed. Although these rearrangements represent a heterocyclic variant of the vinylcyclopropane-cyclopentene rearrangement, they need to be treated separately because the mechanistic details can involve not only thermolysis but also protonation of the cyclopropyl ketone followed by either external or internal trapping of the cation. Although no review of these rearrangements is available in the context of the vinylcyclopropane-cyclopentene formalism, the number of examples in the literature certainly warrants one.²⁵² When $Z = \text{NR}$, the resultant dihydropyrrole system can be manipulated to achieve the synthesis of alkaloids. Alternatively, when $Z = \text{O}$ and $\text{R} = \text{OR}'$, hydrolysis leads to the isolation of γ -lactone.

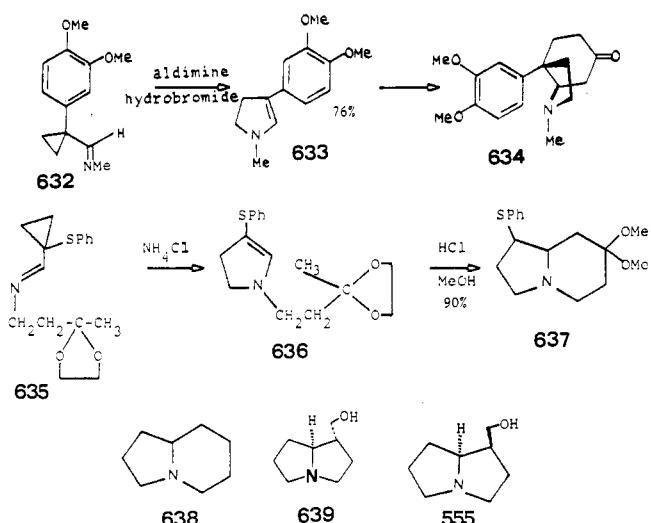


The following examples depict the application of imine-cyclopropane and carbonyl-cyclopropane rearrangement in organic synthesis. The acid-catalyzed thermal rearrangement of cyclopropylimines 630 has been reported as a general method for the synthesis of Δ^2 -pyrrolines 631, which are useful intermediates in alkaloid synthesis.²⁵³



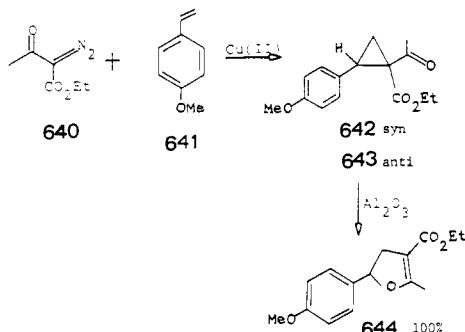
The applications of this reaction have been reviewed.²⁵⁴ An example of this strategy was in the total synthesis of (\pm)-mesembrine (634).²⁵⁵

Rearrangement of the cyclopropylimine 635 afforded pyrroline 636 in 80% yield. Treatment of 636 with methanolic HCl induced cyclization to indolizidine 637 in 90% yield.²⁵⁶ (\pm)- δ -Coniceine 638 was prepared via this route.²⁵⁶

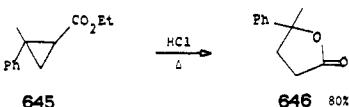


Similarly, the total synthesis of (\pm)-isoretronecanol (555) and trachelanthimidine (639) was executed in an analogous manner.²⁵⁶ It is interesting to note that the parent system, cyclopropylimine, was known since 1929, long before vinylcyclopropane was even isolated.²⁵⁷

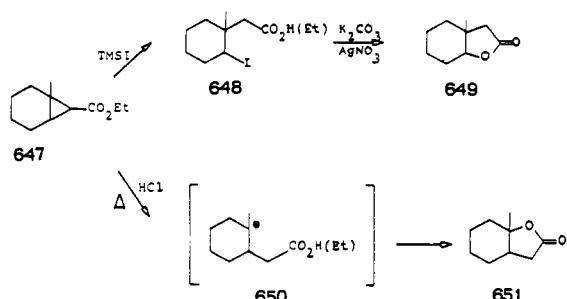
Replacement of nitrogen by oxygen provides an opportunity for a similar rearrangement leading to furanoid derivatives. A syn-anti mixture of cyclopropyl β -keto esters 642 and 643 in 1.9:1 ratio was prepared in 30% yield from the Cu(II)-catalyzed thermolysis of the diazo compound 640 and *p*-methoxystyrene (641). Alumina promoted the rearrangement of 642 and 643 to 644 in nearly quantitative yield.²⁵⁸



Cyclopropyl esters capable of giving stable carbocations upon protonation yield butyrolactones upon heating with acid. Application of this strategy to the cyclopropyl ester 645 afforded an 80% yield of 646.

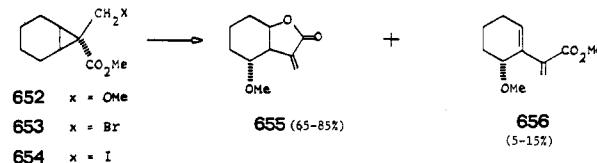


On reaction with trimethylsilyl iodide, 647 yielded lactone 649, whereas HCl-catalyzed lactone formation allowed the reversal of regiospecificity to provide 651.²⁵⁹

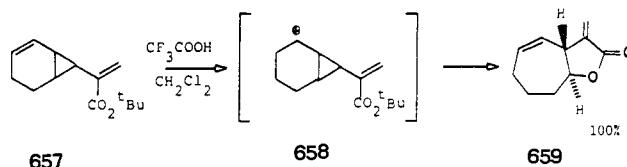


Formation of 649 is attributed to the cleavage of 647 by TMSTI to give iodide 648, which upon treatment with basic Ag⁺ gives 649. On the other hand, protonation of 647 to carbocation 650 is invoked to rationalize the formation of 651.²⁵⁹

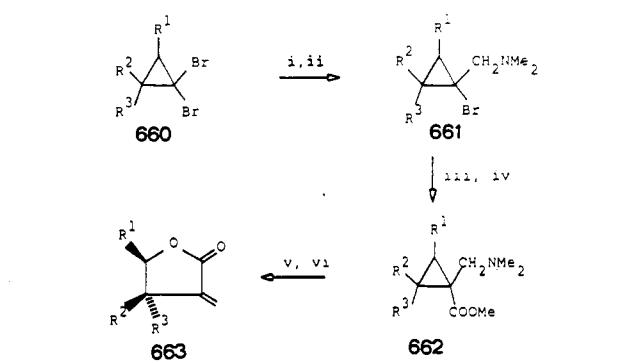
Solvolytic of methoxy ester 652 with LiClO₄ in dioxane provided α -methylene lactone 655 contaminated with 25% of diene ester 656. Bromo ester 653 and iodo ester 654 under AgClO₄ induced rearrangement to give 65–85% of α -methylene lactone 655, contaminated with 5–15% of the diene byproduct.²⁶⁰



Treatment of propenoate 657 with 10% trifluoroacetic acid in methylene chloride led to cation 658, which underwent ring expansion to 659. The α -methylene lactone system (659) was formed quantitatively.²⁶¹



A new method for constructing the α -methylene- γ -butyrolactone moiety under neutral, anhydrous conditions was reported.²⁶² The starting amino ester 662 was prepared from amino bromide 661, which was previously produced from *gem*-dibromocyclopropane 660. When 662 was treated with trimethylsilyl iodide and the crude products were distilled, α -methylene- γ -butyrolactones 663 were obtained with higher regio- and stereoselectivity.²⁶²

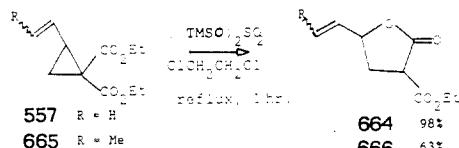


| | | % yield | | | |
|------------------|------------------|------------------|-----|-----|-----|
| R ¹ | R ² | R ³ | 661 | 662 | 663 |
| Ph | H | H | 59 | 73 | 62 |
| ⁿ hex | H | H | 71 | 60 | 58 |
| $-(CH_2)_4-$ | | H | 61 | 61 | 64 |
| ⁿ hex | ⁿ hex | H | | | 67 |
| ⁿ hex | H | ⁿ hex | | | 73 |

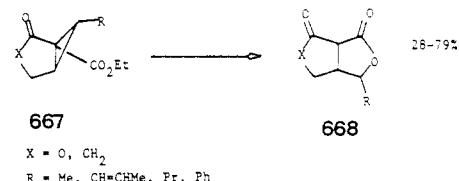
(i) *n*-BuLi, -95 °C, THF, (ii) CH₂=NMe₂⁺I⁻, (iii) *n*-BuLi or *t*-BuLi, -78 °C, THF, (iv) (MeO)₂C=O, (v) Me₃SiI, (vi) distillation.

When a 1,2-dichloroethane solution of 2-vinylcyclopropane-1,1-dicarboxylate (557) was heated to reflux in the presence of bis(trimethylsilyl) sulfone, γ -butyrolactone 664 was produced in 98% yield.²⁶³ The acceleration of this particular rearrangement can be attrib-

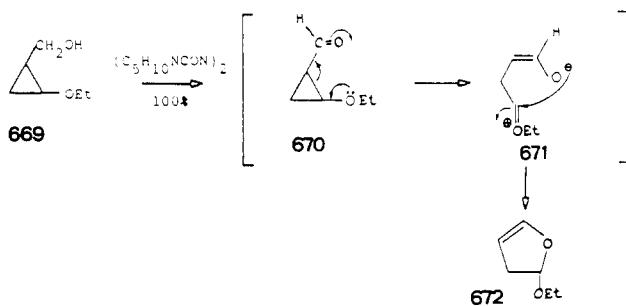
uted to the formation of an allylic cation, which stabilizes the intermediate by ~ 11 kcal/mol. Alkyl-sub-



stituted cyclopropanes 667 gave rise to lactones 668 under identical conditions.²⁶³ This methodology has been applied to several activated cyclopropanes with excellent results. Oxidation of alcohol 669 with azo-



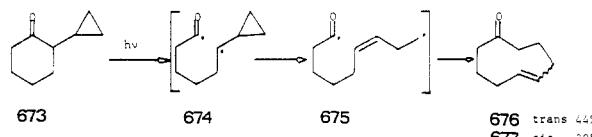
α,α' -bis[piperidine-1-carbaldehyde] led to aldehyde 670, which rearranged spontaneously to the intermediate open-chained ion 671. This intermediate recyclized to form dihydrofuran 672 in almost quantitative yield.²⁶⁴



V. Miscellaneous Ring Fission

1. Fission Caused by Irradiation

The photochemistry of three-membered-ring compounds has been the topic of several previous reviews.^{41,265} The only example discussed here involves 2-cyclopropylcyclohexanone (673), which upon irradiation gave a mixture of *trans*- and *cis*-cyclonon-4-enones 676 and 677 as major products.²⁶⁶ The mechanism presumably involves photochemically induced α -cleavage, followed by rearrangement of the resulting cyclopropylcarbinyl radical 674 and collapse of diradical 675.



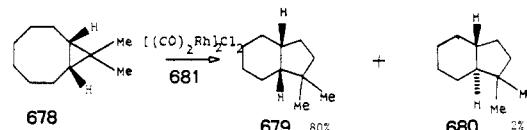
Additional examples of cyclopropane ring isomerization to olefins have been reported.²⁶⁷⁻²⁶⁹ The photochemistry of vinylcyclopropanes has been reviewed.⁴¹

2. Transition-Metal-Mediated Ring Fission

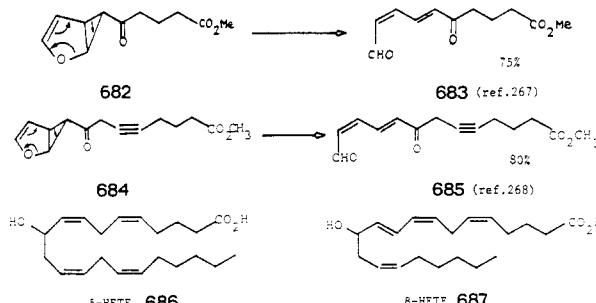
Some aspects of transition-metal-catalyzed ring opening of cyclopropanes have been reviewed.^{41,264} Transition metals can promote the cleavage of cyclopropane derivatives; however, the structures of the resulting products are sometimes unexpected. It is not

always possible to provide reasonable and acceptable mechanisms for such reactions. Cyclopropane derivatives exhibit unusually low oxidation potentials, suggesting electron transfer may be involved in many of these reactions.²⁷⁰ The following examples illustrate the diversity of this process.

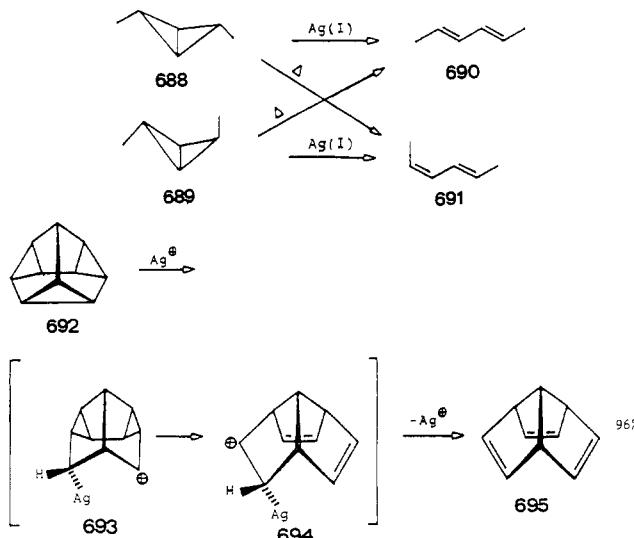
Heating 678 at 190 °C for 30 min in the presence of a catalytic amount of 681 gave a mixture consisting of 80% *cis*-dihydroindene 679 and 2% *trans*-dihydroindene 680.²⁷¹



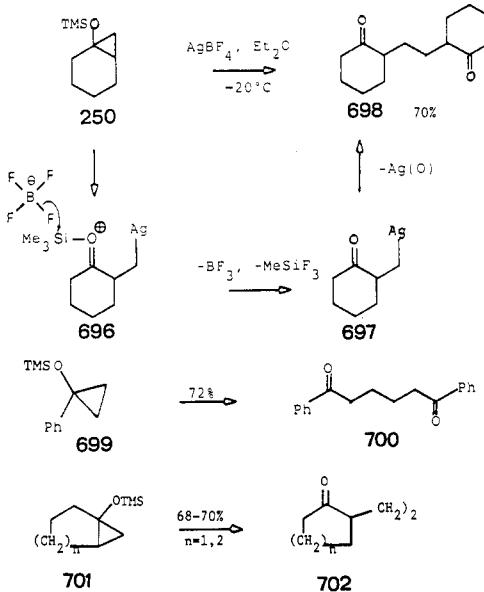
The rearrangement of acylcyclopropyl ethers such as 682²⁷² and 684²⁷³ to keto dienes has been reported. These substrates were formed by the $[\text{Rh}(\text{OAc})_2]_2$ -catalyzed cyclopropanations of furans, although it is not clear whether the rearrangements were solely the result of the action of the rhodium catalyst used in the decomposition of diazo ketones or whether these rearrangements proceeded via thermal or acid-catalyzed mechanisms.^{258,273} The dienes obtained in this fashion were not stereochemically homogeneous, although the *cis,trans* isomers were the major products. These compounds were further transformed to 5-HETE (686),²⁷² 8-HETE (687),²⁷³ and other compounds of this type such as 12-HETE,²⁷⁴ (\pm)-12-HETE,²⁷⁴ and (-)-HETE.²⁷⁴



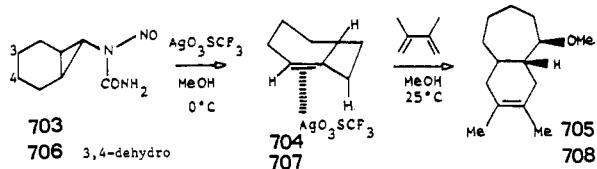
When treated with silver perchlorate in benzene, *exo,exo*- and *endo,exo*-2,4-dimethylbicyclobutanes 688 and 689 rearrange stereospecifically to *trans,trans*- and *cis,trans*-2,2-hexadienes 690 and 691, respectively.²⁷⁵ Treatment of 692 with AgClO_4 in benzene- d_6 affords triquinacene 695 in 96% yield.²⁷⁶



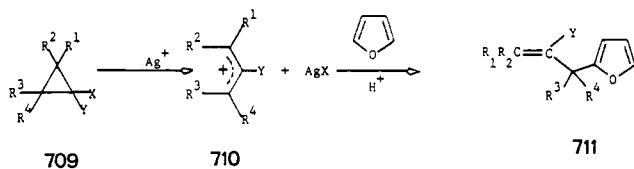
The addition of siloxycyclopropane to a suspension of silver tetrafluoroborate in anhydrous ether (at -20°C under N_2) afforded diketone 698 in 70% yield. It is believed that 696 and 697 are intermediates in this reaction. Other examples of the reaction of siloxycyclopropanes with AgBF_4 are shown below.²⁷⁷ Silver



trifluoromethanesulfonate (triflate) was utilized for the transformation of 703 to 705. Analogously, 706 was converted to 708 in 65% yield.²⁷⁸



Allyl cations 710, generated from electrocyclic ring opening of the corresponding cyclopropyl halide with silver perchlorate in THF/ether, were trapped with furan and afforded 2-allylfuran derivatives 711 in fair to good yields as shown.²⁷⁹ β -Alkoxy cyclopropane-



| 709 | | | | | | conditions | yield of 711, % |
|-----------------|----------------|----------------|----------------|----|----|-------------|-----------------|
| R ¹ | R ² | R ³ | R ⁴ | X | Y | | |
| Me | Me | Me | Me | Br | Br | rt, 1 h | 40 |
| Me | Me | Me | H | Br | Br | rt, 1 h | 76 |
| Me | Me | H | H | Br | Br | reflux, 6 h | 73 |
| Ph | Me | H | H | Br | Br | reflux, 6 h | 73 |
| Ph | H | H | H | Br | Br | reflux, 6 h | 61 |
| ⁿ Pr | H | H | H | Br | Br | reflux, 6 h | 54 |
| Me | Me | Me | Me | Cl | Cl | reflux, 6 h | 60 |
| Ph | H | H | H | Br | H | reflux, 6 h | 37 |

carboxylate ester 712 can be selectively transformed to vinyl ether 713 with various transition-metal catalysts. The product yields obtained with different catalysts are shown.²⁸⁰ When 714 was treated with zinc chloride followed by successive addition of a catalytic amount of $\text{CuBr}\text{-Me}_2\text{S}$ complex, hexamethylphosphoric triamide (HMPA), and the unsaturated carbonyl compound,

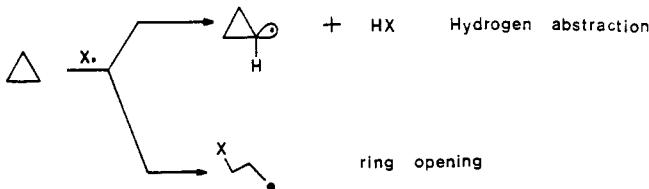


Figure 8.

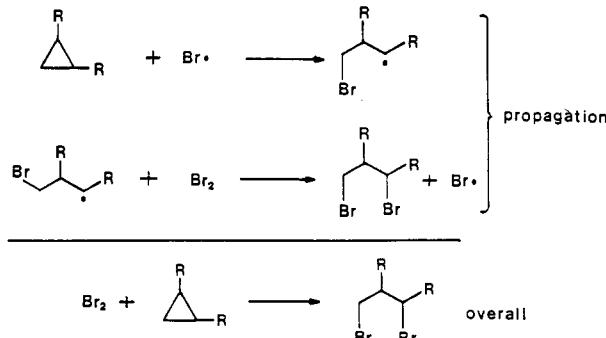
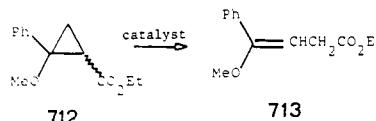
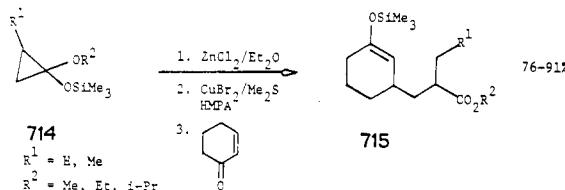


Figure 9.



| catalyst | yield, % |
|---------------------------------------|----------|
| $\text{PtCl}_2\text{-2PhCN}$ | 98 |
| $[\text{Rh}(\text{CO}_2\text{Cl})_2]$ | 98 |
| Cu bronze | 97 |

ester 715 was produced, and the results are shown below.²⁸¹ Recently, a chloropalladation of vinylcyclopropanes has been reported and the kinetics of the process studied.²⁸²



3. Free Radical Reactions of Cyclopropanes

For the reaction of a radical X^{\cdot} with a cyclopropane, two competing pathways are possible: hydrogen abstraction or ring opening (Figure 8).²⁸⁴

Generally, hydrogen abstraction is observed only for extremely reactive radicals (Cl^{\cdot} ,²⁸³ $t\text{-BuO}^{\cdot}$,²⁸³ and imidyl^{283,285}), whereas ring opening is observed for less reactive radicals (I^{\cdot} , Br^{\cdot}).^{286,287} This difference can be accounted for by considering the unusually high bond dissociation energy of a cyclopropyl C–H bond (106 kcal/mol).²⁸⁸

The free radical bromination of alkylcyclopropanes has been studied in detail. The products of the reaction arise from the formal 1,3-addition of Br^{\cdot} . An $\text{S}_{\text{H}}2$ process, wherein Br^{\cdot} attacks the least hindered carbon, to yield the most stable radical, has been proposed (Figure 9).²⁸⁶ Products of hydrogen abstraction (e.g., the corresponding cyclopropyl bromides) have not been reported.

A recent report suggests that cyclopropyl bromides can be synthesized from cyclopropanes by means of

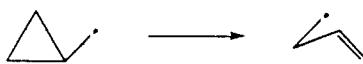
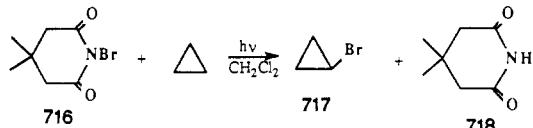


Figure 10.

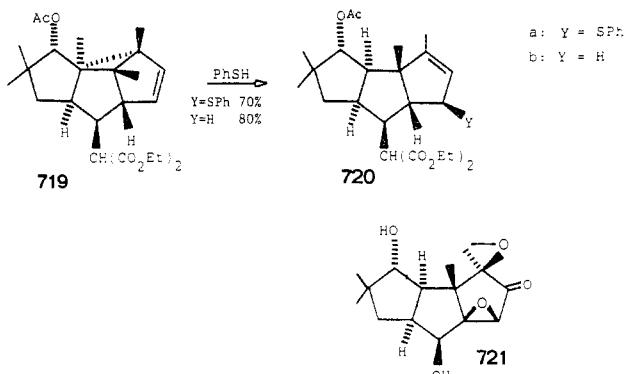
imidyl radical chemistry. For example, the photoinitiated reaction of cyclopropane with 3,3-dimethyl-N-bromoglutaramide (716) yields cyclopropyl bromide in excellent yield. In this reaction, imidyl radical rather than bromine atom is the chain-propagating species.²⁸⁵



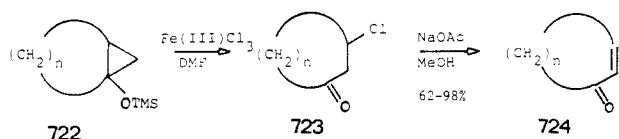
4. Rearrangement of the Cyclopropylcarbinyl Radical

As in the case of the cation, the cyclopropylcarbinyl radical undergoes facile unimolecular rearrangement (Figure 10). The rate constant for this process is $>10^8$ s⁻¹.²⁸⁹ The following examples illustrate the use of this radical-based methodology in organic synthesis.

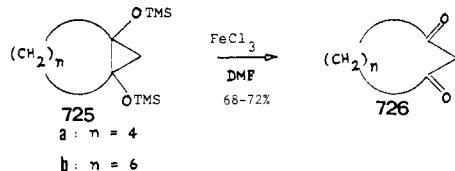
Ring opening of tetracyclic acetate 719 was achieved by heating with 1 equiv of thiophenol at 100 °C. Addition of PhSH• to the double bond, followed by ring opening and trapping by PhSH produced 720a in 70% yield.²⁹⁰ Reductive desulfurization produced 720b in 80% yield. 720b proved to be an important precursor to (\pm)-coriolin (721) and other oxygen-rich natural products.²⁹⁰ Treatment of trimethylsilyl ethers 722 (n



= 3–10) with FeCl₃ in DMF followed by base-induced elimination provided 2-cycloalkenones 724.²⁹¹ Simi-

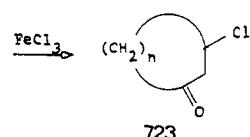
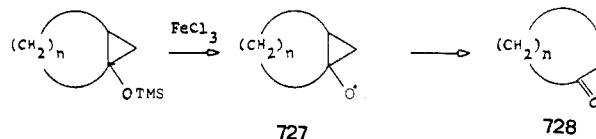


larly, bis(trimethylsiloxy)bicyclo[n.1.0]alkanes 725 were transformed to cycloalkane-1,3-diones 726 by action of FeCl₃ in DMF.²⁹¹

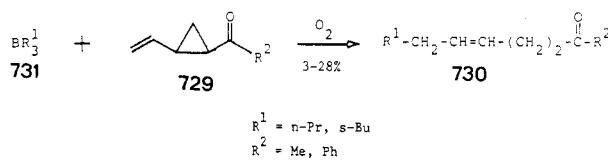


The mechanism of the regioselective ring opening is believed to involve alkoxy radical intermediate 727, which undergoes homolytic scission of the carbon–

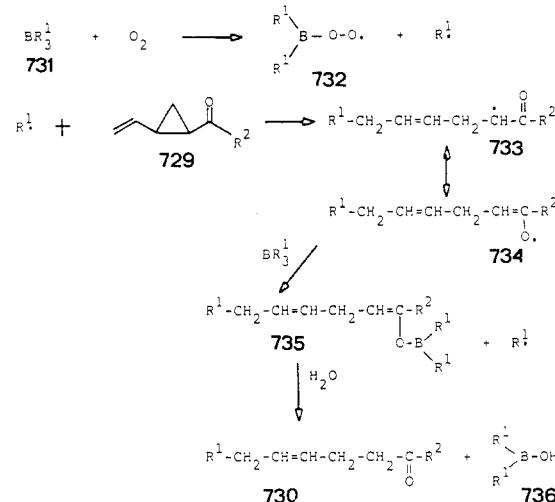
carbon bond (β -scission). Abstraction of chlorine by ring-opened radical 728 yields 3-chlorocycloalkanone 723.²⁹¹ Oxygen-induced reaction of organoborane



reagents 731 with 1-acylcyclopropanes 729 produced 1,6-adducts, which were subsequently hydrolyzed to the corresponding γ,δ -unsaturated ketones 730.²⁹² Since the reaction was inhibited by O₂, a free



radical chain mechanism was proposed for this transformation:²⁹²



VI. Summary

As the syntheses of cyclopropane derivatives can be accomplished by several highly efficient procedures, these derivatives have emerged as important intermediates for the construction of relatively complex molecules. Perhaps more importantly, asymmetric cyclopropanation can be realized in a number of ways. Hence, chiral complex molecules can be obtained via appropriate transformations of these chiral cyclopropane derivatives. This latter aspect has only recently begun to be addressed in detail. Although we have presented several possibilities for the molecular manipulation of three-membered carbocycles, the potential of cyclopropanes has by no means been fully exploited. The underlying theme of this review has been the comparison of the chemistry of alkenes with that of cyclopropanes. The direct result of extrapolating such comparison to synthetic design of complex

molecules has been the explosive growth of new synthetic methodologies. One of the more important aspects of cyclopropane chemistry is the fact that newly established methods that rely on transformation of cyclopropanes are frequently adopted to oxiranes and aziridines in efforts to provide for methodologies in the domain of heterocyclic synthesis. We anticipate that more new strategies will be discovered in the future.

VII. Acknowledgment

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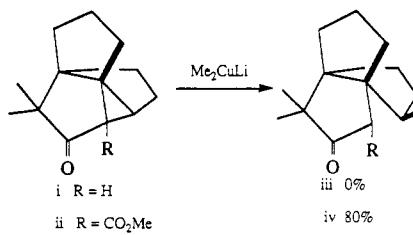
Registry No. Cyclopropane, 75-19-4.

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