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Facial Selectivity in Cycloadditions of a Chiral Ketene Acetal under Microwave Irradiation in Solvent-Free Conditions. Configurational Assignment of the Cycloadducts by NOESY Experiments and Molecular Mechanics Calculations

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(*R*)-4-Phenyl-2-methylene-1,3-dioxolane (**1**) undergoes 1,3-dipolar and Diels–Alder cycloadditions under microwave irradiation within 3 min with excellent yields, a simple purification procedure, and an interesting facial selectivity. The stereochemistry of these cycloadducts has been inferred by NOESY experiments and molecular mechanics calculations. X-ray structure determination was required in one case. Thermal isomerization of the cycloadducts was performed affecting only the spiro-carbon. The Diels–Alder adducts in the presence of a slight amount of acid yield the corresponding open chain esters.

Introduction

It is well known that the participation of a chiral and optically active diene or dienophile in a cycloaddition reaction affords a facially selective addition. The use of cycloaddition reactions for the enantioselective preparation of complex molecules involves, in many cases, the intervention of a chiral auxiliary attached to the dienophile.[1] Ideally, the auxiliary blocks one face of the dienophile and a face-selective cycloaddition takes place.

In 1989 enantiomerically pure cyclic vinylketene acetals were employed in Diels–Alder reactions as chiral dienes,[2] a less often way of inducing facial selectivity. However, ketene acetals[3] and thioacetals[4] have been used in most cases in asymmetric cycloadditions as dienophiles or dipolarophiles. Likewise, in 1994 an asymmetric 1,3-dipolar cycloaddition of nitrones with achiral ketene acetals catalyzed by chiral oxazaborolidines has been described.[5]

We have recently reported a simple and useful method of performing cycloaddition reactions of achiral cyclic ketene acetals with several dienes and 1,3-dipoles under microwave irradiation in solvent-free conditions.[6] Now, we have tested the use of a chiral and enantiomerically pure cyclic ketene acetal as asymmetric reagent in 1,3-dipolar and [4 + 2] cycloadditions to induce facial selectivity in these reaction conditions. When a nitrone is employed as 1,3-dipole, isoxazolidine derivatives are obtained. Isoxazolidines have found widespread application in the synthesis of biotin, aminoglycosides, alkaloids, amino acids, β-lactams, and herbicide compounds.[7] These cycloadducts can be easily transformed into 5-isoxazolidinones or 3-amino alcohols, 3-amino acids, and 3-amino esters. 3-Amino acids are very attractive compounds and their preparation has been recently reviewed.[8] If a 1-oxa 1,3-diene is used, the cycloadducts bear a dihydropyran ring, which is structurally related with many natural products such as carbohydrates, talaromycines, avermectins, pheromones, and other natural substances.[9]

Microwave irradiation in solvent-free conditions has well demonstrated his utility in 1,3-dipolar,[6,10] Diels–Alder,[6,11] and [2 + 2][12] cycloadditions along the last years. In this paper we will analyze the facial selectivity induced by (*R*)-4-phenyl-2-methylene-1,3-dioxolane (**1**) with N,α-diphenyl nitrone and chalcone.

Results and Discussion

Compound **1** and *N*,α-diphenyl nitrone react in solvent-free conditions under microwave irradiation within 3 min (450 W, domestic oven) to yield the 1,3-dipolar cycloadducts in 98% yield. In the same reaction conditions, compound **1** and chalcone lead to the Diels–Alder adducts in 96% yield. Reaction times are dramatically reduced, yields are excellent and products are isolated directly from the crude reaction by column chromatography. The time/temperature relationship is 30 sec/78, 1 min/113, 1.5 min/115, 2 min/116, 2.5 min/120 and 3 min/124 °C in the 1,3-dipolar cycloaddition, and 30 sec/

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§ Chimie Structurale Biomoléculaire.
® Abstract published in *Advance ACS Abstracts,* June 1, 1995.

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(6) Díaz-Ortiz, A.; Díez-Barra, E.; De la Hoz, A.; Prieto, P.; Moreno, A. *J. Chem. Soc., Perkin Trans I* **1994**, 3595–3598.
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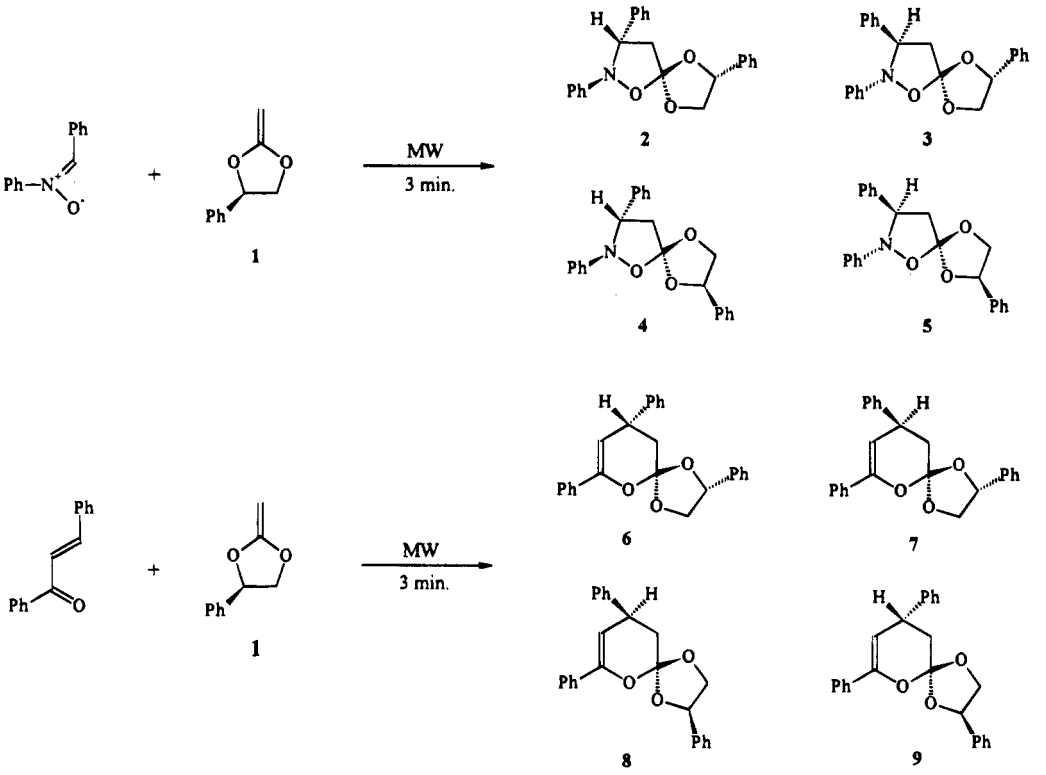
Scheme 1



80, 1 min/99, 1.5 min/108, 2 min/115, 2.5 min/129, and 3 min/120 °C in the Diels–Alder reaction. The temperature is uniform within the mixture in both reactions. Since in a domestic oven the irradiation is not focused, stirring of the sample is not neccesary. In absent of solvent, the microwave irradiation absorbed is directly proportional to the quantity of reagents and the reaction conditions reported above are optimal for the lab-scale. In preparative scale (50–500 g) the time or power of the irradiation should be diminished.

In order to check any specific effect of the microwave irradiation in these reactions, the cycloadditions were also performed with classical heating in solvent-free conditions, finding that with 3 min at 120–124 °C in an oil bath, yields decrease to 3–4%. These results suggest that the excellent yields achieved under microwave irradiation perhaps are not exclusively due to the rapid heating of the reaction mass. Typical procedures reported in the literature[3b,13] (toluene/reflux, 14 h, inert atmosphere) produce the 1,3-dipolar and Diels–Alder adducts in 40 and 49% yield, respectively. To test other reaction conditions, cycloadditions were carried out without solvent using other energy sources such as an ultrasonic cleaning bath (55 Hz, 200 W) during 1 h at room temperature or 30 min at 75 °C. However, yields are always below 65%.

In both cycloadditions with compound **1** four diastereomers can be obtained resulting from the four different approaches of the reagents (Scheme 1). However, due to the chirality of the system, approaches of the diene from the "bottom" face of **1** have minor steric hindrance than approaches from the "top" face raising the transition state energy of the latter. Consequently, net diastereomeric excess is achieved.

The diastereomeric ratios, determined by ^{1}H-NMR, are **2/3**: 38/36; **4/5**: 18/8 in the 1,3-dipolar cycloaddition and **6/7**: 43/37; **8/9**: 14/6 in the Diels–Alder reaction. The former analysis implies, as expected, that the predominant couple of diastereomers comes in both cases by approach from the "bottom" face of **1**. Facial selectivity is 2.8:1 with *N*,α-diphenyl nitrone and 4:1 with chalcone. Significant changes in the facial selectivity were not observed either in thermal reaction conditions[10b] or under ultrasound irradiation. Compounds **2** and **6**, the major isomer in each cycloaddition, are insoluble in methanol and easily isolated from the reaction mixture. Other diastereomers were separated by preparative thin layer chromatography.

In order to get energetic insight as an aid to analyze the relative stability of the transition states (TS) in the cycloaddition of compound **1** with chalcone, the four TSs **A**–**D** (Figure 1) have been minimized and their relative energy was calculated using the MMX-type force field,[14] which has proved to be a reliable method[15] in calculation of TS in Diels–Alder reactions of 1-oxa-1,3-butadienes. The program uses the atom types C*, C#, O#, and C• to define a transition state of Diels–Alder reaction for calculations and the bond orders C#–O# and C*–C* are recommended to be set at 0.3 giving a good correlation with Houk[16] for the resulting structure in the cycloaddition of butadiene and ethylene. Nevertheless, it seems more appropriate to set these bond orders at 0.1 and 0.7, respectively, according to the transition state semiempirically calculated.[15]

(13) (a) Huisgen, R.; Grashey, R.; Seild, H.; Hauck, H. *Chem. Ber.* **1968**, *101*, 2559–2567. (b) Gruseck, U.; Heuschmann, M. *Chem. Ber.* **1990**, *123*, 1905–1909.

(14) Molecular mechanics calculations (MMX) were performed using the program PCModel (version 4.0) from Serena Software on a PC Compatible 486 machine at 50 MHz. For each structure, the minimum energy was determined after reminimization.

(15) Tietze, L. F.; Geissler, H.; Fennen, J.; Brumby, T.; Brand, S.; Schulz, G. *J. Org. Chem.* **1994**, *59*, 182–191.

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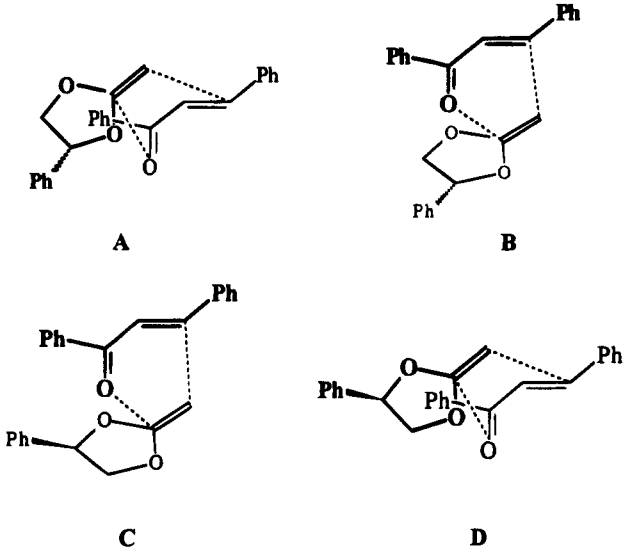

Figure 1. A–D Transition states resulting from the four approaches in the Diels–Alder cycloaddition.

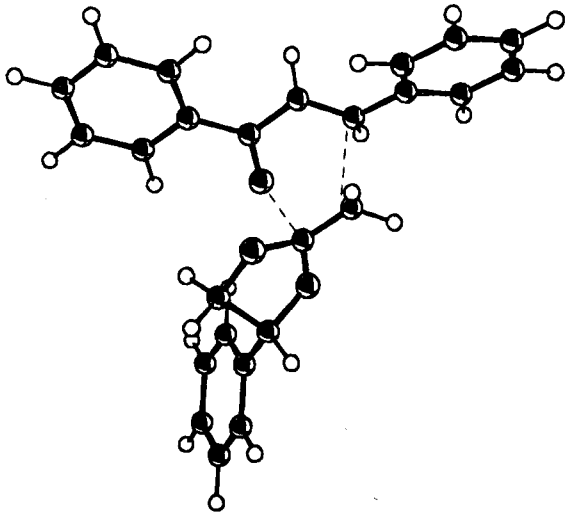

Figure 2. Optimized geometry of the transition state **D**.

Table 1. Structure and Energy Comparison between MMX Calculation with Different Bond Orders C#–O# = 0.1 and C*–C* = 0.7 for TS A–D in the Diels–Alder Reaction of 1 with Chalcone

	A	B	C	D
C*–C*(pm)	176	175	175	175
C#–O#(pm)	258	265	262	264
C•–C•–C*–C* (deg)	−67.3	−76.5	−74.4	−75.8
O#–C•–C•–C* (deg)	−0.8	0.0	+1.0	−0.1
energy (kcal mol^{-1})	34.05	27.91	29.51	27.74

The calculations of the TS (Table 1) are in a good agreement with the experimental data; thus, the isomer **9** (6%) can be formed via the TS **A** (energy: 34.05 kcal/mol), whereas **7** (37%) is formed via the TS **B** (energy: 27.91 kcal/mol), **8** (14%) is formed via the TS **C** (energy: 29.51 kcal/mol), and **6** (43%) is formed through the TS **D** (energy: 27.74 kcal/mol). The slight difference between the stability of transition states **B** and **D** is in agreement with the difference between the yields of **7** and **6**; besides, the less favourable TS **A** drives to the minor isomer **9**.

Forced field calculations with equal bond orders for bonds C#–O# and C*–C*, and set to 0.3, resulted in a smaller difference in the energy of the transition states,

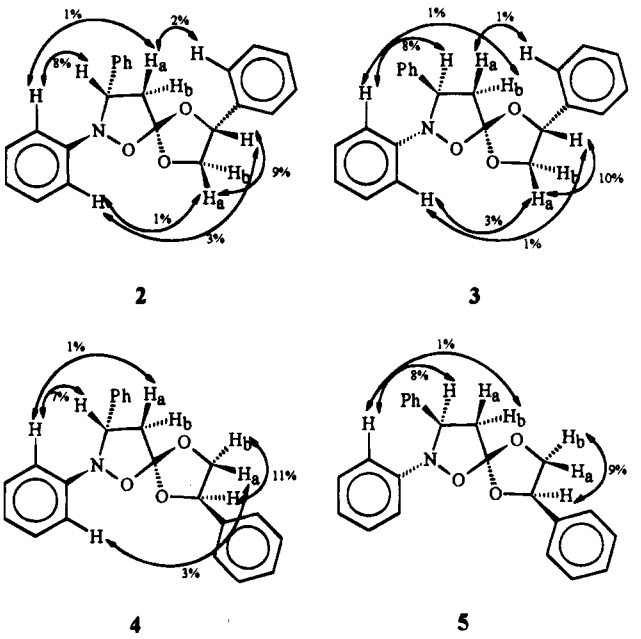

Figure 3. Selected NOEs for the 1,3-dipolar cycloadducts **2–5**.

which should cause a much worse selectivity; nevertheless, the order of stability is not modified.[17]

Then, we tried to infer the stereochemical configuration of the four adducts in each cycloaddition. The absolute configuration of their chiral carbons in the 1,3-dipolar adducts **2–5** was assigned by the 1D-NOE difference and NOESY[18] (nuclear Overhauser enhancement and exchange spectroscopy) experiments shown in Figure 3. The structural disposition of the dioxolane ring in the adducts **2** and **3** was inferred from the NOE values observed between *ortho*-H 4′-Ph and H-4. The stereochemistry at C-3 was determined by irradiation at *ortho*-H PhN: compound **2** shows a NOE with H-3, H-4a, and H-4′ while compound **3** shows NOEs with H-3, H-4b, and H-5′a. In the case of adducts **4** and **5** NOE between *ortho*-H 4′-Ph and H-3 or H-4 is not observed; however, when *ortho*-H PhN are irradiated, an NOE with H-3, H-4a and H-5′a is observed in compound **4**, while in adduct **5** it was found only with H-3 and H-4b.

Some isoxazolidine derivatives have been described as relatively unstable compounds which undergo to decomposition[19] or retro-1,3-dipolar cycloadditions[20] when heated at high temperatures. In order to check the thermal stability of these cycloadducts bearing a cyclic acetal group attached to the isoxazolidine ring, compounds **2–4** were heated in an high boiling solvent. Thus, unexpectedly, we found that when adduct **2** is heated in dimethyl sulfoxide or *o*-dichlorobenzene for 2 h, a mixture of **2** and **4**, 54:46, is obtained. On the same conditions, compound **3** afforded a mixture **3/5**, 57:43, without side-reactions; compound **4** produced a mixture **4/2**, 53/47; compound **10** gave a mixture **10/11**, 80:20; and compound **12** afforded a mixture **12/13**, 64:36 (Scheme 2). Prolongation

(17) Energies when bond orders C#–O# and C*–C* equal 0.3 are the following: 28.57 kcal/mol for **A**, 26.86 kcal/mol for **B**, 26.96 kcal/mol for **C** and 25.12 kcal/mol for **D**.

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(19) Delpierre, G. R.; Lamchen, M. *Proc. Chem. Soc.* **1960**, 386–387.

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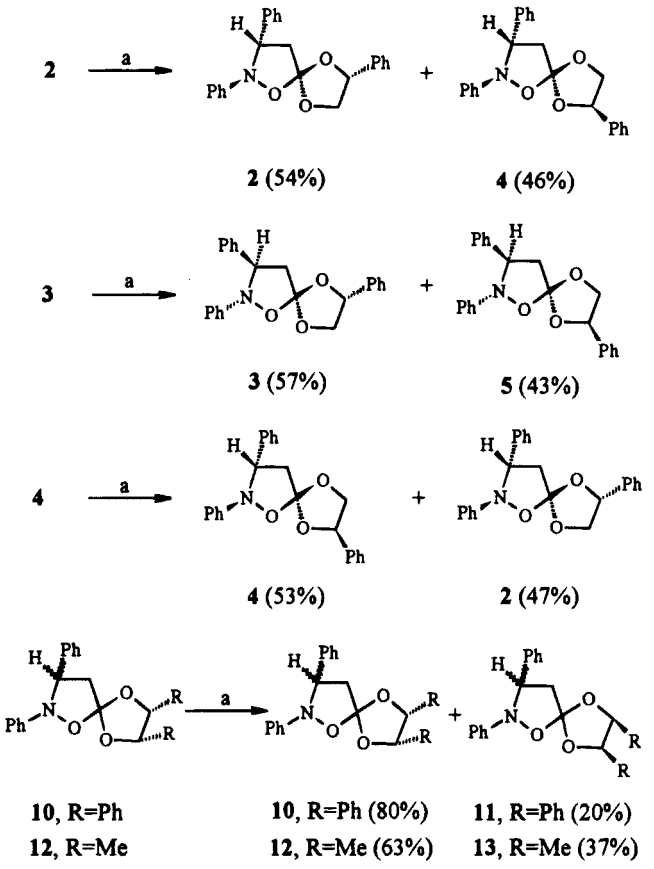
Scheme 2



[a] Conditions: (a) DMSO, 150 °C, 2 h.

of the heating time does not change the isomer proportions but produces decomposition of the mixture. In all cases the isomerization occurs with retention of the configuration at C-3 and C-4′ carbons. This was confirmed through the following experiment: Addition of adduct **4** to the mixture, resulting of the isomerization of adduct **2**, does not produce any splitting in the ^{1}H-NMR when (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol is added as shift reagent. However, addition of racemic compound **2** (prepared from a racemic ketene acetal) to the above mixture produces a splitting of their signals, with, obviously, unequal enantiomer proportions. Finally, optical rotations of the isomerized products, $[\alpha]_D$ −139° for **2** and $[\alpha]_D$ −41° for **4**, proved their stereochemistry.

The isomerization process may implicate a retro-1,3-dipolar cycloaddition, an epimerization at C-3 or C-4′ carbons, or a stereochemical change at C-5. If the cycloadducts revert to the nitrone and ketene acetal reactants, the isomerization mixture would be composed by the four possible diastereomers, not two in each case. Nevertheless, in order to confirm that the isomerization do not occur in the microwave oven during the cycloaddition process, pure adducts **2**, **3**, **6**, and **7** were irradiated at 780 W for 10 min (the final temperature was up to 100 °C in all the cases) and isomerization was not observed. Any epimerization process was discarded by the shift reagent experiment described above. The homolytic cleavage of the N−O bond, which, as reported in isoxazolidine-5-spirocycloalkane compounds,[21] rearranges to several products, has been also discarded:

(21) Brandi, A.; Cordero, F. M.; De Sarlo, F.; Goti, A.; Guarna, A. *Synlett* **1993**, 1−8.

Table 2. Force Field Calculated Relative Energies

compound	MM + energy[a]	ΔE[a]	% in equilibrium
2	10.04		54
4	9.27	0.77	46
10	7.58		80
11	8.33	−0.75	20
12	14.48		64
13	15.07	−0.59	36
6	5.58		61
9	4.20	−1.38	39
7	6.60		65
8	5.24	−1.36	35

[a] Kcal mol^{-1}.

thermal isomerization occurs at a similar rate in the presence of benzophenone or topanol. Finally, since the isomerization can be performed in dimethyl sulfoxide or *o*-dichlorobenzene, this process cannot be a solvent effect. Therefore, we conclude that the isomerization must occur by bond breaking, rotation, and subsequent formation of a C−O bond. C−O Acetal bonds are usually cleaved in the presence of a mineral or Lewis acid.[22] However, the breaking of this bond at neutral or basic pH has also been reported.[23] The factors that facilitate an uncatalyzed ionization are a good leaving group, a relatively stable intermediate carbonium ion, or a weak C−O bond. In our case, we cannot atribute the isomerization to only one factor, but to the particular chemistry of ortho-esters.[24]

The structure of compounds **2**, **4**, and **6**−**13** were minimized and their energies were calculated. Molecular mechanics calculations were performed with the program HyperChem.[25] The geometry of a given molecule was optimized at the empirical level using an MM+ molecular mechanics routine. The Polak−Ribiere conjugate gradient algorithm was employed, and all calculations converged and had final gradients of less than 0.01. In each case, the isomer proportions are in agreement with the calculated energies (Table 2); the most stable adduct is present in higher proportion in the thermodynamic equilibrium.

The stereochemical assignment in the Diels−Alder cycloadducts **6**−**9** was more difficult and cannot be done exclusively by NOESY experiments. The adducts **6** and **7**, as their 1,3-dipolar analogues **2** and **3**, show a NOE between *ortho*-H 4′-Ph and H-5. Compounds **8** and **9** do not show it. However, due to the planarity of C-2, the stereochemistry at C-4 cannot be assigned by irradiation at *ortho*-H 2-Ph protons. The values obtained are summarized in Figure 4. The stereochemical assignment at C-4 carbon was done finally through isomerization experiments and theoretical calculations, and then confirmed by the single crystal X-ray structure determination of **6**.[30] This compound crystallized from methanol as long needles. The diffraction data was recorded as described in the Experimental Section. This led to the structure depicted in Figure 5. Only the two relevant hydrogens, important for the stereochemical determination, are reported, though all of them were located on Fourier-difference syntheses.

(22) Schmitz, E.; Eichorn, I. *The Chemistry of the Ether Linkage*; Patai S., Ed.; Wiley: New York, 1967; Chapter 7.

(23) (a) Fife, T. H.; Brod, L. H. *J. Am. Chem. Soc.* **1970**, *92*, 1681−1684. (b) Anderson, E.; Fife, T. H. *J. Am. Chem. Soc.* **1969**, *91*, 7163−7166.

(24) (a) Johnson, W. S.; Werthemann, L.; Barlett, W. R.; Brocksom, T. L.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741−743. (b) Takahashi, T.; Miyazawa, M.; Sakamoto, Y.; Yamada, H. *Synlett* **1994**, 902−904.

(25) HyperChem is a product of Autodesk Inc.

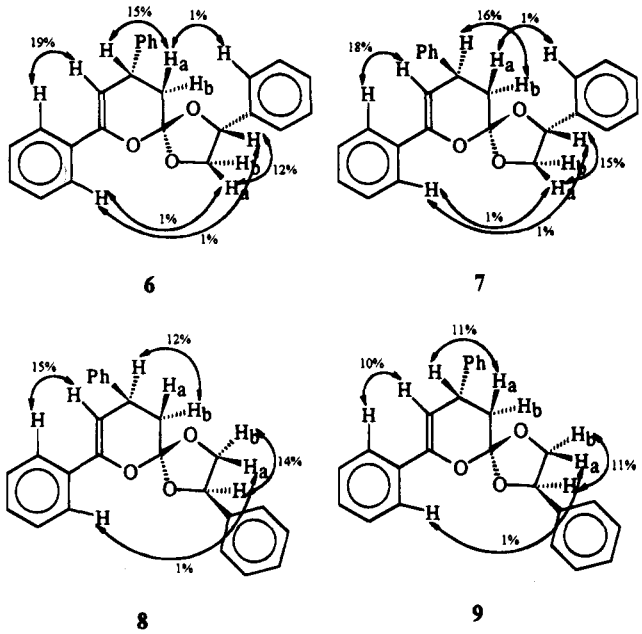


Figure 4. Selected NOEs for the Diels–Alder cycloadducts **6–9**.

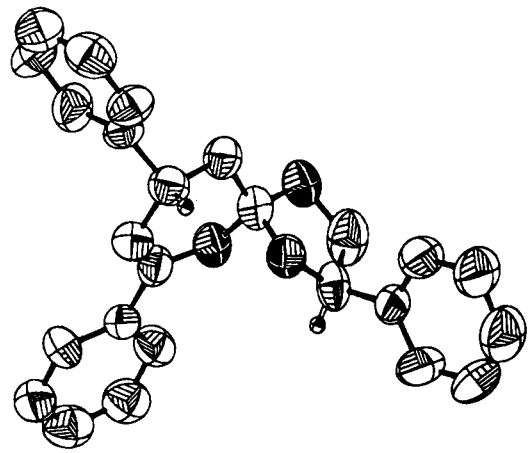


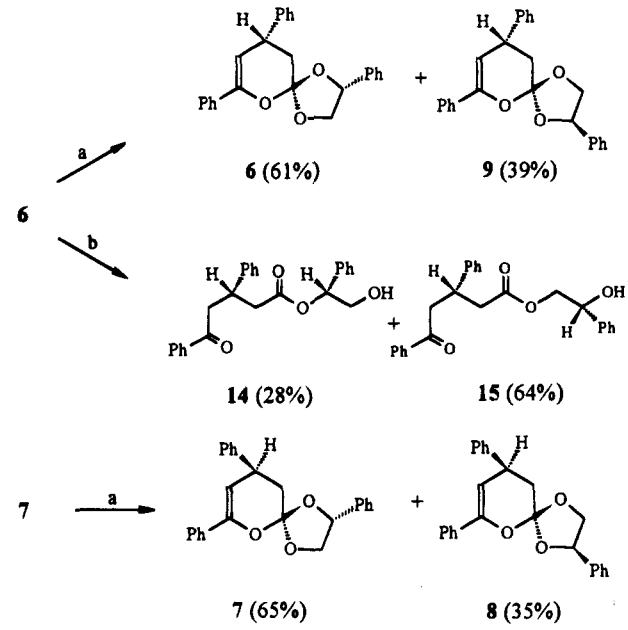
Figure 5. ORTEP view of the X-ray crystal structure of **6**.

Thermal reactivity of these Diels–Alder cycloadducts in a high boiling solvent was also analyzed. We found, as in the 1,3-dipolar adducts, that when heated in DMSO or *o*-dichlorobenzene at 150 °C during 45 min, adduct **6** provided a mixture **6/9**, 61:39, without side-reactions. On the same conditions, adduct **7** afforded a mixture **7/8**, 65:35 (Scheme 3). An increase of the reaction time led to a rapid decomposition of the mixture. The adducts ratio in these isomerizations are not in agreement with their calculated energies (Table 2). A higher proportion of **9** and **8** was expected, however, the observed ratio can be perhaps due to the shorter reaction time that does not allow thermodynamic equilibrium.

All mechanistic considerations exposed above in the 1,3-dipolar isomerizations are valid again, and we must conclude that this process is due to a C–O bond breaking with ring opening, rotation, and subsequent ring closure. Only the spiranic carbon is affected in these experiments. Thus, the stereochemistry at C-4 carbon in **8** and **9** is confirmed to be as the one indicated in Scheme 1, since the stereochemistry in adduct **6** had been unequivocally determined by single crystal X-ray.

When adduct **6** was heated in *o*-dichlorobenzene at 150 °C for 45 min in the presence of a slight amount of an acid ion-exchange resin, we obtained, as expected, the enantiomerically pure esters **14** and **15**, in 28 and 64% yield, respectively. These interesting compounds, useful as highly functionalized chiral synthons, were separated by preparative TLC. The transformation is simply an acid-catalyzed hydrolysis of the orthoester function, widely reported in the literature.[22] However, on similar reaction conditions, adduct **2** did not afford the corresponding esters but led rapidly to a complete decomposition. Milder hydrolytic conditions (shorter reaction times and lower temperatures) did not avoid a complex decomposition mixture, either.

Scheme 3



[a] Conditions: (a) DMSO, 150 °C, 45 min; (b) *o*-dichlorobenzene, Dowex 50 (H^+), 150 °C, 2 h.

Conclusions. Microwave irradiation in solvent-free conditions has again proved its utility to induce cycloaddition reactions of chiral cyclic ketene acetals with 1,3-dipoles or hetero-1,3-dienes, providing an excellent procedure to obtain diastereoselectively five- or six-membered heterocyclic compounds. These reactions are completed in 3 min with easy workup, almost quantitative yields, and an interesting facial selectivity resulting from the chirality of the acetal. Heating these adducts in a high boiling solvent does not produce retrocycloadditions, N–O bond cleavage, or other reported processes, but rather isomerization at the spiro-carbon through a C–O bond cleavage, rotation, and C–O bond formation. The adducts ratio obtained in the cycloaddition and isomerization reactions is in agreement with molecular mechanics calculations performed with PCModel and HyperChem programs, respectively.

Experimental Section

All mps were determined on a Gallenkamp apparatus and are uncorrected. Optical rotations were measured with a Perkin Elmer 241 polarimeter. IR spectra were measured on a Perkin Elmer 883 infrared spectrophotomer. ^{1}H NMR spectra were recorded at 300 MHz on a Varian Unity 300 NMR spectrophotometer. ^{13}C NMR spectra were recorded at 75 MHz on a Varian Unity 300 NMR spectrophotometer. Chemical shifts were reported in ppm (δ) using Me_4Si as standard, and coupling constants were expressed in hertz. Percentage NOE enhancement was obtained by integrating the affected reso-

nance relative to the irradiated resonance in the difference spectrum in each case. Elemental analysis was performed on a Perkin Elmer PE2400 CHN elemental analyser. Column chromatography was carried out with SiO_2 (silica gel, Merck type 60 70–230 and 230–400 mesh). Preparative TLC was developped on glass plates coated with silica gel (Merck type 60 PF_{254}) of 2 mm thickness. Microwave irradiations were conducted in a Miele Electronic M720 domestic oven. Reagents were purchased from commercial suppliers or prepared by literature methods.

1,3-Dipolar Cycloaddition of Compound 1 with *N*-(Benzylidene)phenylamine *N*-oxide. A mixture of (*R*)-4-phenyl-2-methylene-1,3-dioxolane (**1**) (0.67 g, 4.1 mmol) and *N*-(benzylidene)phenylamine *N*-oxide[26] (0.81 g, 4.1 mmol) was placed in the microwave oven and irradiated at 450 W for 3 min (final temperature 124 °C). The crude reaction mixture was purified by flash chromatography (silica gel, petroleum ether–ethyl acetate 7:1). This gave a mixture of cycloadducts **2**, **3**, **4** and **5** (1.44 g, 98%) in proportions of 38, 36, 18 and 8%, respectively.

A suspension of this cycloadducts mixture in methanol (40 mL) was stirred at room temperature for 15 min and then filtered off to obtain the compound **2** as a white solid. Cycloadducts **3**–**5** were separated by preparative TLC (silica gel, carbon tetrachloride–dichloromethane 8:1).

Data for **2**: mp 148–149 °C (from methanol); $[\alpha]_D$ −143° (*c* 0.1, $CHCl_3$); IR (KBr) 3036, 2897, 1595, 1326, and 1054 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.84 (1 H, dd, J = 13.2, 8.0 Hz), 3.10 (1 H, dd, J = 13.2, 8.5 Hz), 3.91 (1 H, t, J = 7.0 Hz), 4.58 (1 H, t, J = 7.0 Hz), 4.77 (1 H, t, J = 8.2 Hz), 5.42 (1 H, t, J = 7.0 Hz), 6.93 (1 H, m), 7.00 (2 H, m), 7.17 (2 H, m), 7.30–7.38 (6 H, m), 7.35 (2 H, m), 7.52 (2 H, m); ^{13}C NMR (CD_3SOCD_3) δ 43.5, 68.8, 71.4, 76.5, 114.9, 121.6, 137.9, 141.1, 151.2, 126.2, 126.6, 127.3, 127.4, 128.2, 128.4, 128.5. Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.9; H, 5.85; N, 3.9%. Found: C, 76.8; H, 5.95; N, 3.8%.

Data for **3**: mp 94.5–95.5 °C (from hexane:ethyl acetate); $[\alpha]_D$ +37.5° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.90 (1 H, dd, J = 13.2, 8.9 Hz), 3.07 (1 H, dd, J = 13.2, 8.0 Hz), 3.90 (1 H, dd, J = 7.8, 6.3 Hz), 4.55 (1 H, t, J = 7.8, 6.8 Hz), 4.73 (1 H, t, J = 8.9, 8.0 Hz), 5.46 (1 H, t, J = 6.8, 6.3 Hz), 6.96 (1 H, m), 7.00 (2 H, m), 7.20 (2 H, m), 7.34 (2 H, m), 7.36 (2 H, m), 7.52 (2 H, m), 7.30–7.40 (4 H, m); ^{13}C NMR (CD_3SOCD_3) δ 43.6, 68.7, 70.6, 77.3, 115.0, 121.8, 139.0, 140.9, 151.0, 126.0, 126.7, 127.2, 127.5, 128.1, 128.4, 128.5. Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.9; H, 5.85; N, 3.9%. Found: C, 76.7;H, 5.85; N, 3.85%.

Data for **4**: mp 123–124 °C (from methanol); $[\alpha]_D$ −44° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.85 (1 H, dd, J = 12.9, 9.2 Hz), 3.00 (1 H, dd, J = 12.9, 7.7 Hz), 4.05 (1 H, dd, J = 9.5, 8.6 Hz), 4.43 (1 H, dd, J = 8.6, 6.6 Hz), 4.92 (1 H, dd, J = 9.2, 7.7 Hz), 5.23 (1 H, dd, J = 9.5, 6.6 Hz), 7.02 (2 H, m), 7.17–7.46 (9 H, m), 7.60 (4 H, m); ^{13}C NMR (CD_3SOCD_3) δ 43.3, 68.6, 70.4, 78.9, 114.3, 121.4, 138.2, 141.3, 151.6, 126.5, 126.6, 127.5, 127.6, 128.3, 128.5, 128.6. Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.9; H, 5.85; N, 3.9%. Found: C, 76.8; H, 5.75; N, 3.85%.

Data for **5**: colorless oil, ^1H NMR (CD_3SOCD_3) δ 2.63 (1 H, dd, J = 13.4, 7.6 Hz), 3.10 (1 H, dd, J = 13.4, 8.9 Hz), 3.88 (1 H, t, J = 9.0, 8.3 Hz), 4.57 (1 H, dd, J = 8.3, 6.3 Hz), 4.85 (1 H, t, J = 8.9, 7.6 Hz), 5.24 (1 H, dd, J = 9.0, 6.3 Hz), 6.98 (2 H, m), 7.21–7.47 (9 H, m), 7.52 (2 H, m), 7.56 (2 H, m); ^{13}C NMR (CD_3SOCD_3) δ 44.6, 69.1, 70.9, 78.5, 116.6, 122.7, 138.0, 140.4, 150.1, 126.6, 127.0, 127.3, 127.6, 128.3, 128.5, 128.6.

Diels–Alder Cycloaddition of Compound 1 with Chalcone. A mixture of (*R*)-4-phenyl-2-methylene-1,3-dioxolane (**1**) (0.61 g, 3.7 mmol) and chalcone (0.78 g, 3.7 mmol) was placed in the microwave oven and irradiated at 450 W for 3 min. The final temperature is 120 °C. The crude reaction mixture was purified by flash chromatography (silica gel, toluene). This gave a mixture of cycloadducts **6**, **7**, **8** and **9** (1.33 g, 96%) in proportions of 43, 37, 14, and 6%, respectively.

When this product mixture was stirred in methanol (40 mL) at room temperature for 15 min, the cycloadduct **6** could be separated by filtration as a white solid. Cycloadducts **7**–**9** were separated by preparative TLC (silica gel, carbon tetrachloride–dichloromethane 25:1).

Data for **6**: mp 112–113 °C (from methanol); $[\alpha]_D$ −11° (*c* 0.1, $CHCl_3$); IR (KBr) 3059, 1729, 1649 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (1 H, t, J = 12.9, 12.3 Hz), 2.51 (1 H, ddd, J = 12.9, 6.4, 1.3 Hz), 4.03 (1 H, t, J = 7.4 Hz), 4.08 (1 H, ddd, J = 12.3, 6.4, 2.4 Hz), 4.80 (1 H, t, J = 7.4 Hz), 5.53 (1 H, t, J = 7.4 Hz), 5.54 (1 H, m), 7.40 (2 H, m), 7.42 (2 H, m), 7.68 (2 H, m), 7.30–7.46 (9 H, m); ^{13}C NMR (CD_3SOCD_3) δ 36.9, 37.8, 71.8, 76.7, 101.4, 124.4, 126.6, 127.5, 119.8, 126.7, 128.3, 128.5, 128.6, 134.6, 138.5, 143.8, 148.8. Anal. Calcd for $C_{25}H_{22}O_3$: C, 81.1; H, 5.95%. Found: C, 81.1; H, 6.0%.

Data for **7**: colorless oil; $[\alpha]_D$ −67.5° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.34 (1 H, t, J = 13.0 Hz), 2.48 (1 H, ddd, J = 13.0, 6.4, 1.2 Hz), 4.01 (1 H, dd, J = 7.8, 5.6 Hz), 4.02 (1 H, ddd, J = 12.6, 6.4, 2.3 Hz), 4.63 (1 H, t, J = 7.8, 7.4 Hz), 5.53 (1 H, m), 5.66 (1 H, dd, J = 7.4, 5.6 Hz), 7.35 (2 H, m), 7.37 (2 H, m), 7.65 (2 H, m), 7.22–7.38 (9 H, m); ^{13}C NMR (CD_3SOCD_3) δ 36.9, 37.9, 70.9, 77.4, 101.2, 124.4, 126.0, 127.4, 119.8, 126.2, 128.2, 128.4, 128.5, 134.6, 139.4, 143.7, 148.8. Anal. Calcd for $C_{25}H_{22}O_3$: C, 81.1; H, 5.95%. Found: C, 80.95; H, 5.85%.

Data for **8**: mp 95–96 °C (from methanol); $[\alpha]_D$ −29° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.26 (1 H, t, J = 12.7, 11.8 Hz), 2.40 (1 H, ddd, J = 12.7, 6.5, 1.2 Hz), 4.04 (1 H, ddd, J = 11.8, 6.5, 2.5 Hz), 4.30 (1 H, dd, J = 9.3, 8.3 Hz), 4.57 (1 H, dd, J = 8.3, 6.9 Hz), 5.31 (1 H, dd, J = 9.3, 6.9 Hz), 5.58 (1 H, m), 7.35 (2 H, m), 7.38 (2H, m), 7.61 (2 H, m), 7.25-7.41 (9 H, m); ^{13}C NMR (CD_3SOCD_3) δ 37.0, 37.6, 71.4, 78.4, 101.3, 124.2, 126.2, 127.5, 119.7, 126.6, 128.0, 128.2, 128.3, 128.5, 128.6, 134.3, 138.7, 143.8, 148.3. Anal. Calcd for $C_{25}H_{22}O_3$: C, 81.1; H, 5.95%. Found: C, 81.0, H, 5.95%.

Data for **9**: colorless oil; ^1H NMR ($CDCl_3$) δ 2.30 (1 H, t, J = 12.9, 12.5 Hz), 2.40 (1 H, ddd, J = 12.9, 6.3, 1.2 Hz), 4.06 (1 H, ddd, J = 12.5, 6.3, 2.3 Hz), 4.11 (1 H, dd, J = 9.8, 8.5 Hz), 4.49 (1 H, dd, J = 8.5, 6.6 Hz), 5.30 (1 H, dd, J = 9.8, 6.6 Hz), 5.53 (1 H, m), 7.35 (2 H, m), 7.40 (2 H, m), 7.64 (2 H, m), 7.19–7.40 (9 H, m); ^{13}C NMR (CD_3SOCD_3) δ 37.1, 37.8, 70.5, 79.2, 101.6, 124.2, 126.6, 127.4, 119.8, 126.3, 128.2, 128.3, 128.4, 128.5, 128.6, 134.6, 138.5, 143.7, 148.8. Anal. Calcd for $C_{25}H_{22}O_3$: C, 81.1; H, 5.95%. Found: C, 81.2; H, 5.95%.

Thermal Isomerization of the Cycloadducts. General Procedure. A disolution of the appropiate adduct (0.2 mmol) in deuterated dimethyl sulfoxide (0.8 mL) was heated at 150 °C for 2 h with the 1,3-dipolar adducts or 45 min with the Diels–Alder adducts. The resulting products mixture was directly analyzed by ^1H-NMR.

Isomerization of the 1,3-Dipolar Adduct 2. From the adduct **2** (0.072 g) a mixture **2/4**, 54:46, respectively, was obtained.

Isomerization of the 1,3-Dipolar Adduct 3. From the adduct **3** (0.072 g) a mixture **3/5**, 57:43, respectively, was obtained.

Isomerization of the 1,3-Dipolar Adduct 4. From the adduct **4** (0.072 g) a mixture **4/2**, 53:46, respectively, was obtained.

Isomerization of the Diels–Alder Adduct 6. From the adduct **6** (0.070 g) a mixture **6/9**, 61:39, respectively, was obtained.

Isomerization of the Diels–Alder Adduct 7. From the adduct **7** (0.070 g) a mixture **7/8**, 65:35, respectively, was obtained.

Isomerization of the 1,3-Dipolar Adduct 10. From the adduct **10**[6] (0.087 g) a mixture **10/11**, 80:20, respectively, was obtained.

Isomerization of the 1,3-Dipolar Adduct 12. From the adduct **12**[6] (0.062 g) a mixture **12/13**, 64:36, respectively.

Hydrolysis of the Diels–Alder Cycloadduct 6. To a solution of the compound **6** (0.35 g, 1 mmol) in *o*-dichlorobenzene (2 mL) a Dowex 50(H^+) ion exchange resin (15 mg) was added. The mixture was vigorously stirred at 150 °C for 2 h. The solvent was evaporated at reduced pressure and the residue purified by preparative TLC (silica gel, petroleum ether–ethyl acetate 5:1) to obtain the esters **14** (0.11 g, 28%) and **15** (0.25 g, 64%).

Data for **14**: mp 101–102 °C (from petroleum ether–ethyl acetate); $[\alpha]_D$ -32.5° (*c* 0.1, $CHCl_3$); IR (KBr) 3533, 3059, 1713,

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1685, 1591, 1267, and 1220; ^{1}H NMR ($CDCl_3$) δ 2.80 (1 H, dd, J = 15.6, 8.1 Hz), 2.97 (1 H, dd, J = 15.6, 7.0 Hz), 3.31 (1 H, dd, J = 16.9, 7.3 Hz), 3.38 (1 H, dd, J = 16.9, 6.6 Hz), 3.67 (1 H, dd, J = 12.2, 7.8 Hz), 3.75 (1 H, dd, J = 12.2, 3.9 Hz), 3.94 (1 H, m), 5.78 (1 H, dd, J = 7.8, 3.9 Hz), 7.19–7.91 (15 H, m); ^{13}C NMR ($CDCl_3$) δ 37.5, 40.7, 44.7, 65.8, 77.0, 126.4, 126.9, 127.2, 128.0, 128.1, 128.4, 128.5, 128.7, 133.1, 136.7, 136.8, 143.2, 171.1, 198.3. Anal. Calcd for $C_{25}H_{24}O_4$: C, 77.3; H, 6.25%. Found: C, 77.2; H, 6.2%.

Data for **15**: mp 128–129 °C (from petroleum ether–ethyl acetate); $[\alpha]_D$ -8.5° (c 0.1, $CHCl_3$); IR (KBr) 3520, 3056, 1706, 1684, 1592, 1277, 1213 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.75 (1 H, dd, J = 15.0, 8.1 Hz), 2.88 (1 H, dd, J = 15.0, 7.0 Hz), 3.37 (2 H, d, J = 7.0 Hz), 3.91 (1 H, m), 4.02 (1 H, dd, J = 11.5, 8.6 Hz), 4.21 (1 H, dd, J = 11.5, 3.0 Hz), 4.77 (1 H, dd, J = 8.6, 3.0 Hz), 7.26–7.93 (15 H, m); ^{13}C NMR ($CDCl_3$) δ 37.6, 40.8, 44.6, 69.4, 72.0, 126.0, 126.9, 127.2, 127.9, 128.0, 128.4, 128.5, 128.6, 133.1, 136.7, 139.5, 143.2, 171.8, 198.2. Anal. Calcd for $C_{25}H_{24}O_4$: C, 77.3; H, 6.25%. Found: C, 77.15; H, 6.2%.

Single Crystal X-ray Structure Determination of 6. Crystal Data. $C_{25}H_{22}O_3$, M = 370. Orthorhombic, a = 19.754(3), b = 10.605(3), c = 9.477(3) and Z = 4. V = 1985.3[3] (by least square refinement on diffractometer angles for 25 random reflections within the range $15 \leq \theta \leq 35°$), space group $P2_12_12_1$, D_x = 1.238, crystals as colorless needles with dimensions 0.6 × 0.1 × 0.05 mm.

Data Collection and Processing. Philips PW1100 diffractometer, $\theta/2\theta$ step-scan mode, Cu Kα radiation, graphite-monochromated; 5223 reflections measured ($2 \leq \theta \leq 63°$, $\pm h,k,l$) reduced as a unique set of 2105 (merging R = 0.043 after decomposition correction) with $I \geq 3\sigma(I)$. Room temperature.

Structure Analysis and Refinement. Solved by direct methods.[27] Full-matrix least squares refinement[28] in two blocks: (i) with all non-hydrogens atoms isotropic, followed by an empirical absorption correction,[29] (ii) with non-hydrogen atoms anisotropic. Hydrogens located on Fourier-difference maps and introduced with isotropic thermal factors equal to that of the bonded carbons. Hydrogen position not refined. Final R and Rw (with a weighting scheme $w = 1/[\sigma^2(F_o) + 0.002F_o^2]$ values are 0.068, 0.066. No peak above 0.2 eÅ^{-3} in the last Fourier-difference map.

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Supplementary Material Available: ^{1}H and ^{13}C NMR data of cycloadducts **2–9** with peak assignments (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(29) Walter, N.; Stuart, D. *Acta. Crystallogr. Sect. A* **1983**, *39*, 158–166.
(30) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.