Enones with Strained Double Bonds. 5. The 2-Methylbicyclo[3.3.1]non-1-en-3-one System[1]

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Reaction of the bromo ketone 8 with Et$_3$N resulted in the generation of solutions containing the strained enone 9. Enone 9 could be trapped with furan to form Diels–Alder adducts 10 and 11. However, enone 9 was consumed more rapidly in a reaction that formed the dimeric diketone 12. This dimeric product 12 is believed to be formed by an ene reaction (see structure 14) that occurs under mild conditions.

Our earlier efforts to isolate the unsubstituted bicyclo-[3.3.1]nonenone 1 (Scheme I) were thwarted by the tendency of this enone 1 to form 2 + 2 cycloadducts (e.g., 2) when other more favorable reactants such as nucleophiles or dienes were absent.[2,3]

In an effort to impede the cycloaddition reaction 1 → 2 so that isolation of the strained enone can be pursued, we have undertaken the syntheses of several bicyclo[3.3.1] enones 4 with substituents R at the β-carbon atom. This paper describes the outcome of those studies when the substituent R was a methyl group.

The synthetic route used to generate the methyl substituted enone 9 is summarized in Scheme II. The presence of the enone 9 in solutions formed from the bromo ketone 8 and Et$_3$N was demonstrated by trapping the enone 9 as its furan adducts 10 and 11. The structure and stereochemistry of the major furan adduct 10 were established by X-ray crystallographic analyses as illustrated in Figure 1. It will be noted that the adduct 10 has the same stereochemistry as the major adduct 3 formed from furan and the unsubstituted enone 1.

The reaction of enone 9 with furan to form adducts 10 and 11 was clearly less favorable than the corresponding reaction with the unmethylated enone 1, since even in the presence of excess furan, the adducts 10 and 11 were formed slowly along with a dimeric diketone 12. This same dimeric diketone 12 was formed along with ketol 7 (presumably from the enone 9 + H$_2$O) when bromo ketone 8 was allowed to react with Et$_3$N. The structure and stereochemistry of dimeric diketone 12 were established by

Scheme I

1

3 (major product)

4

2 (major product)

+ other 2 + 2 cycloadducts
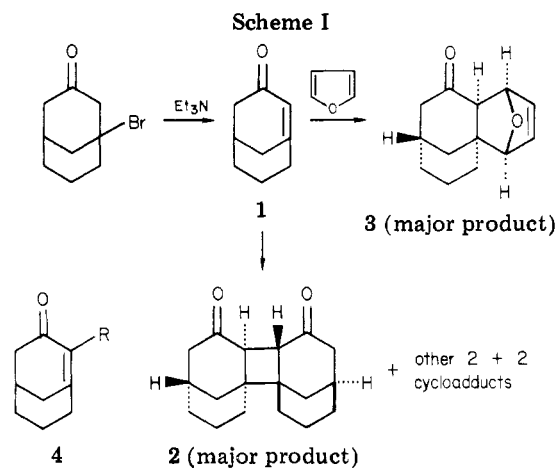
X-ray crystallographic analyses, as illustrated in Figure 2. We found no indication of the formation of a dimeric product of the type 13 (Scheme III) analogous to major 2 + 2 cycloadduct 2 formed from enone 1. Furthermore, the different bridgehead stereochemical relationships in dimers 12 and 13 indicate that the isolated product 12 is not formed from the 2 + 2 cycloadduct 13. Instead the stereochemistry of the dimeric product 12 corresponds to that expected from a concerted ene reaction (see structure 14) between two molecules of the bicyclic enone 9.

We utilized Allinger's molecular mechanics program for molecules containing conjugated π systems (MMPI)[4,5] to gain
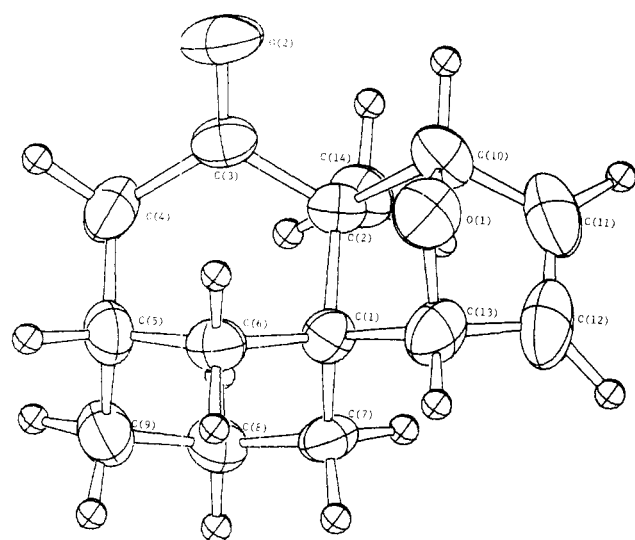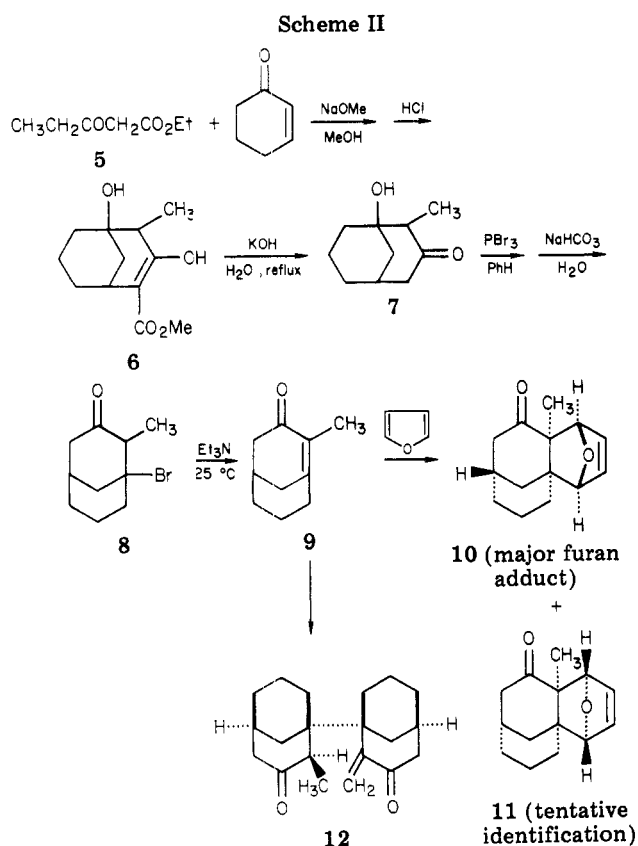
(1) This research has been supported by Public Health Service Grant R01-GM-20197 from the National Institute of General Medical Science. The execution of this research was also assisted by Institutional Research Grants from the National Science Foundation for the purchase of a mass spectrometer and a Fourier transform NMR spectrometer.

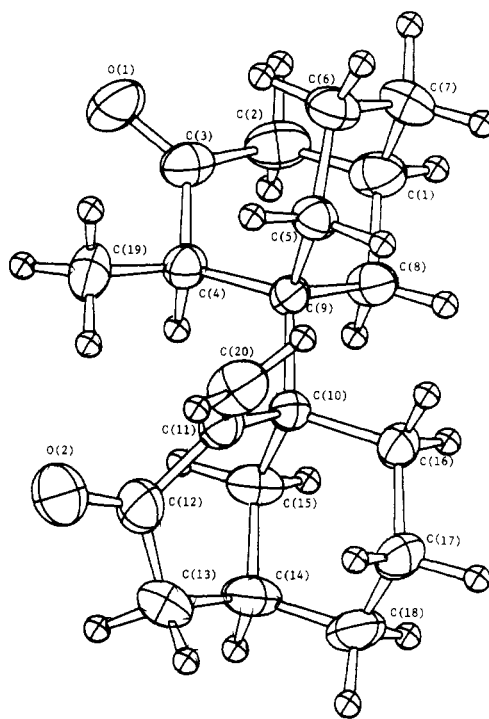(2) House, H. O.; DeTar, M. B.; Van Derveer, D. *J. Org. Chem.* 1979, 44, 3793.

(3) House, H. O.; Sieloff, R. F.; Lee, T. V.; DeTar, M. B. *J. Org. Chem.* 1980, 45, 1800.

(4) Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* 1973, 95, 3893.

(5) (a) Allinger, N. L.; Tribble, M. T.; Miller, M. A.; Wertz, D. H. *J. Am. Chem. Soc.* 1971, 93, 1637. (b) Allinger, N. L.; Sprague, J. T.; Liljefors, T. *Ibid.* 1974, 96, 5100. (c) Wertz, D. H.; Allinger, N. L. *Tetrahedron* 1974, 30, 1579. A summary of the minimization techniques is given in ref 5a and force-field parameters are listed in ref 5c. Calculations were performed on an IBM 370 system. We are most grateful to Professor Allinger and his associates and to the University of Georgia Computer Center for allowing us to use the current version of the MMPI program for these calculations.

Scheme II

5

6

7

8 **9** **10 (major furan adduct)**

+

12

11 (tentative identification)

Scheme III

13 **12**

14 **15**

Figure 2. Perspective view of the molecular structure of dimeric diketone **12**. (For clarity, the H atom thermal parameters have been reduced.)
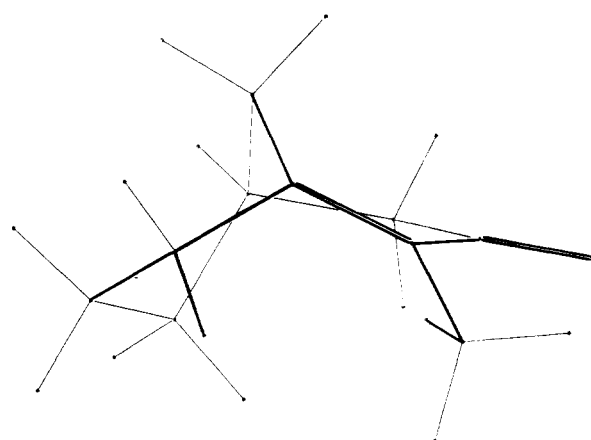
Figure 3. MMPI energy-minimized conformation of enone **9** (calculated steric energy 24.6 kcal/mol).

information about the favored conformation of the bicyclic enone **9**. The calculated steric energies were 29.8 kcal/mol for a planar conformation and 24.6 kcal/mol for a nonplanar conformation. A perspective drawing of the more stable nonplanar conformation of enone **9** is presented in Figure 3;[6] this conformation resembles very closely the favored conformation calculated[3] for the unsubstituted enone **1**. By use of the numbering scheme presented in partial structure **15**, the calculated dihedral angles for this favored conformation of enone **9** are the following: C1–C2–C3–C4, 14°; C1–C2–C3–C5, 132°; C4–C3–C2–C6, 176°; C5–C3–C2–C6, 31°. The calculated deviation of C3 from the plane defined by C2, C4, and C5 is 0.243 Å.

On the basis of these studies it appears that the presence of an α substitutent R in the bicyclo[3.3.1]nonenone system **4** will impede both 2 + 4 cycloadditions of dienes to the

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enone and the formation of 2 + 2 cycloadducts such as structure 2. However, the remarkable ease with which the enone 9 undergoes an ene reaction (see structure 14) indicates that the substituent R to be selected should not have an α C–H bond if isolation of a representative enone 4 is desired. Further work to test this idea is in progress.

Experimental Section[7]

Preparation of Keto Ester 6. To a solution of NaOMe, prepared from 1.55 g (67.5 mmol) of Na and 100 mL of MeOH, was added 9.32 g (64.7 mmol) of ethyl propionylacetate (5). After the resulting solution had been cooled to 0 °C, 6.34 g (66.0 mmol) of cyclohexenone was added dropwise and with stirring during 6 min. The resulting yellow solution was refluxed for 46 h, then concentrated, and partitioned between Et_2O and aqueous 0.4 M HCl. The ethereal solution was dried and concentrated to leave 16.8 g of brown liquid. A 1.86-g aliquot of this liquid was chromatographed on silica gel with an EtOAc–hexane eluant (1:4 v/v) to separate 126 mg of one stereoisomer of the enolic β-keto ester 6 as colorless plates: mp 82–83 °C; IR (CCl_4) 3610 (OH), 1655, 1612 cm^{-1} (enolic β keto ester); UV max (95% EtOH) 258 nm (ε 9770); ^{1}H NMR ($CDCl_3$) δ 12.3 (1 H, s, OH), 3.78 (3 H, s, OCH_3), 3.05 (br, 1 H, bridgehead CH), 2.37 (1 H, q, J = 7 Hz, CHMe), 1.3–2.1 (9 H, m, OH and CH), 1.25 (3 H, d, J = 7 Hz, CH_3); mass spectrum, m/e (relative intensity) 194 (13), 151 (20), 98 (42), 97 (100), 55 (36), 44 (64), 43 (30), 41 (32), 39 (22); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 175.5 (s), 171.3 (s), 98.3 (s), 69.4 (s), 51.2 (q), 45.0 (d), 42.0 (t), 36.2 (t), 30.1 (d), 28.4 (t), 18.9 (t), 15.0 ppm (q).

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.75; H, 8.02.

Preparation of Ketol 7. To a cold (0 °C) solution of NaOMe, prepared from 2.52 g (106 mmol) of Na and 130 mL of MeOH, were added 11.9 g (82.5 mmol) of ethyl propionylacetate (5) and 10.0 mL (106 mmol) of cyclohexenone. The resulting solution, which became dark brown in color, was refluxed for 72 h, then cooled, and diluted with a solution of 11.6 g of KOH in 100 mL of H_2O. The resulting mixture was refluxed for 10 h, then concentrated under reduced pressure, and extracted with Et_2O. After the ethereal extract had been dried and concentrated, the residual orange liquid was chromatographed on silica gel with an Et-OAc–hexane eluant (2:3 v/v) to separate 11.62 g (84%) of the crude ketol 7 as a pale yellow solid, mp 138–141 °C. Recrystallization from hexane separated one stereoisomer (stereochemistry not established) of ketol 7 as colorless plates: mp 142–143 °C; IR (CCl_4) 3605, 3460 (OH), 1710 cm^{-1} (C=O); UV max (95% EtOH) 280 nm (ε 46); ^{1}H NMR ($CDCl_3$) δ 2.95 (1 H, s, OH), 2.2–2.7 (4 H, m, aliphatic CH), 0.9–2.2 (11 H, m, aliphatic CH including a CH_3 doublet, J = 7.7 Hz, at 1.12); mass spectrum, m/e (relative intensity) 168 (M$^+$, 3), 98 (10), 97 (100), 55 (11), 43 (10), 41 (12); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 212.0 (s), 72.9 (s), 55.5 (d), 45.7 (t), 43.0 (t), 34.6 (t), 30.6 (t), 30.4 (d), 19.8 (t), 7.5 ppm (q).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.20; H, 9.59.

Preparation of Bromo Ketone 8. A solution of 3.423 g (20.6 mmol) of ketol 7 in 100 mL of PhH was treated with 2.00 mL (21.2 mmol) of PBr$_3$. The mixture, which became yellow and separated into two phases, was stirred at 25 °C for 4 h and then washed successively with H_2O, aqueous NaHCO$_3$, and H_2O. The organic solution was filtered and concentrated under reduced pressure.

The residual pale orange liquid was distilled [83 °C (0.07 mm)] to separate 3.420 g (72%) of bromo ketone 8 that crystallized as colorless plates: mp 33–35 °C; IR (CCl_4) 1712 cm^{-1} (C=O); UV max (95% EtOH) 283 nm (ε 58); mass spectrum, m/e (relative intensity) 232 (M$^+$, 1), 230 (M$^+$, 1), 151 (73), 109 (65), 107 (46), 97 (100), 81 (46), 79 (28), 67 (43), 55 (22), 41 (31), 39 (19); ^{1}H NMR ($CDCl_3$) δ 2.86 (1 H, q, J = 7.8 Hz, COCHMe, established by decoupling experiment), 1.1–2.7 (14 H, m, aliphatic CH including a CH_3 doublet, J = 7.8 Hz, at 1.38); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 207.3 (s), 70.3 (s), 57.6 (d), 47.0 (t), 45.8 (t), 39.1 (t), 32.3 (d), 29.9 (t), 21.3 (t), 10.9 ppm (q).

Anal. Calcd for $C_{10}H_{15}BrO$: C, 51.96; H, 6.54; Br, 34.57. Found: C, 51.97; H, 6.54; Br, 34.57.

Generation of Enone 9. A. In the Presence of Furan. A solution of 3.16 g (18.8 mmol) of ketol 7 in 110 mL of anhydrous PhH was treated with 7.2 g (26.8 mmol) of PBr$_3$. The resulting mixture, which separated into two phases, was stirred at 25 °C for 5 h and then washed successively with H_2O and aqueous NaHCO$_3$. After the organic layer had been dried and concentrated, the residual liquid bromide 8 was mixed with 75 mL of anhydrous furan and 10 mL (72 mmol) of Et$_3$N. The resulting mixture, from which a colorless precipitate slowly separated, was stirred at 25 °C for 125 h and then concentrated under reduced pressure. After the residue had been partitioned between H_2O and CH_2Cl_2, the organic layer was washed successively with aqueous 1 M HCl and H_2O, then dried, and concentrated under reduced pressure. The residual yellow oil, which partially crystallized on standing, was dissolved in 3.5 mL of warm CH_2Cl_2 and chromatographed on silica gel with an EtOAc–hexane eluant (1:4 v/v). The fractions separated, in order of elution, contained 43 mg (1%) of bromide 8 (identified by comparison of IR and NMR spectra), 33 mg (0.8%) of a component believed to be furan adduct 11, 197 mg (4.7%) of furan adduct 10, 1.362 g (48%) of dimer 12, 26 mg of an unknown component, and 321 mg (10%) of ketol 7 (identified by comparison of IR spectra). The fraction containing furan adduct 10 was recrystallized from a CH_2Cl_2–hexane mixture to separate 102 mg of adduct 10 as colorless plates: mp 104.5–105.5 °C; IR (CCl_4) 1711 cm^{-1} (C=O); UV max (95% EtOH) 289 nm (ε 30); mass spectrum, m/e (relative intensity) 218 (M$^+$, 3), 150 (100), 122 (96), 108 (37), 107 (23), 96 (59); ^{1}H NMR ($CDCl_3$) δ 6.48 (2 H, br s, vinyl CH), 5.28 (1 H, br s, allylic CH–O), 4.28 (1 H, br s, allylic CH–O), 1.1–2.7 (11 H, m, aliphatic CH), 1.02 (3 H, s, CH_3); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 213.4 (s), 135.8 (d), 133.2 (d), 86.9 (d), 82.1 (d), 56.2 (s), 45.7 (s), 39.8 (t), 38.9 (t), 31.3 (t), 29.7 (t), 28.1 (t), 19.2 (t), 17.7 ppm (q).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.78; H, 8.37.

The fraction containing the dimeric diketone 12 was recrystallized from hexane to separate 978 mg of the dimer 12 as colorless plates, mp 158–160 °C, that was identified with a subsequently described sample by a mixture melting point determination and by comparison of IR spectra. The crude product thought to be the furan adduct 11 exhibited the following mass spectrum: m/e (relative intensity) 218 (M$^+$, 1), 150 (97), 122 (70), 108 (42), 107 (27), 97 (100), 96 (44), 93 (20), 79 (27). The crude unknown component eluted after the dimer 12 exhibited broad IR absorption (CCl_4) at 1705–1735 cm^{-1}, with an NMR multiplet ($CDCl_3$) in the range 1.0–3.8 and the following mass spectrum: m/e (relative intensity) 192 (64), 164 (21), 151 (20), 150 (88), 135 (22), 123 (24), 122 (55), 121 (30), 119 (28), 117 (30), 109 (53), 108 (54), 107 (46), 97 (86), 96 (100), 95 (70), 94 (24), 93 (37), 91 (37), 86 (33), 84 (78), 82 (21), 81 (43), 80 (27), 79 (68), 77 (29), 68 (22), 67 (45), 55 (54), 53 (24), 43 (22), 41 (66), 39 (42).

B. In Et$_3$N Solution. Reaction of 3.12 g (18.6 mmol) of ketol 7 in 140 mL of anhydrous PhH with 4.3 g (16 mmol) of PBr$_3$ as previously described formed the crude bromide 8. This crude bromide 8, a colorless liquid, was mixed with 30 mL of Et$_3$N and stirred at 25 °C for 72 h. During this period, the mixture initially separated into two phases and then a colorless precipitate (Et$_3$NHBr) separated. The resulting mixture was concentrated under reduced pressure and then partitioned between H_2O and CH_2Cl_2. After the organic layer had been dried and concentrated, the residual yellow liquid was chromatographed on silica gel with an EtOAc–hexane eluant (1:4 v/v). The components separated, in order of elution, were 1.32 g (31%) of bromide 8, 442 mg (16%)

(7) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated MgSO$_4$ was employed as a drying agent. The IR spectra were determined with a Perkin-Elmer Model 257 infrared recording spectrophotometer fitted with a grating. The UV spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The proton NMR spectra were determined at 60 MHz with a Varian Model T-60A NMR spectrometer and the ^{13}C NMR spectra were determined at 25 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in δ values (parts per million) relative to a Me$_4$Si internal standard. The mass spectra were obtained with either a Hitachi (Perkin-Elmer) Model RMU-7 or a Varian MAT Model 112S mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

of dimeric diketone 12, 655 mg (21%) of ketol 7, and 41 mg of an unidentified component. Ketol 7 was identified with previously described material by comparison of IR spectra and bromide 8 was identified by comparison of IR and NMR spectra. The dimeric diketone 12 was recrystallized from a CH_2Cl_2-hexane mixture to separate the dimer 12 as 310 mg of colorless plates, mp 157.5–159.3 °C. After an additional recrystallization the dimer 12 melted at 157.2–159 °C: IR (CCl_4) 1702 (C=O), 1691 (conjugated C=O), 882 cm^{-1} (C=CH$_2$); UV max (CH_3CN) 233 nm (ϵ 2900), 322 (41); mass spectrum, m/e (relative intensity) 300 (M$^+$, 62), 258 (20), 257 (100), 151 (26), 137 (22), 121 (20), 109 (31), 108 (26), 107 (36), 97 (73), 95 (24), 94 (20), 93 (26), 91 (27), 81 (28), 79 (41), 67 (35), 55 (30), 44 (27), 43 (24), 41 (53), 40 (42), 39 (20); ^{1}H NMR ($CDCl_3$) δ 5.83 (1 H, d, J = 0.5 Hz, vinyl CH), 5.18 (1 H, d, J = 0.5 Hz, vinyl CH), 2.1–3.0 (6 H, m, aliphatic CH), 1.1–2.1 (17 H, m, aliphatic CH), 0.92 (3 H, d, J = 7 Hz, CH$_3$); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 213.1 (s), 205.7 (s), 153.7 (s), 121.0 (t), 49.8 (d), 47.1 (s), 46.4 (s), 46.0 (t), 43.7 (t), 35.5 (t), 34.6 (t), 31.7 (t), 31.6 (t), 31.4 (t), 30.6 (d), 27.2 (t and d, 2 C), 19.4 (t), 19.1 (t), 10.1 ppm (q).

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.88; H, 9.42.

Preparation of Keto Ester 5. By a general procedure described previously,[8] dropwise addition of a solution of 160 g (1.0 mol) of $CH_2(COOEt)_2$ in 80 mL of absolute EtOH to a mixture of 25.0 g (1.02 mol) of Mg, 25 mL of absolute EtOH, and 1 mL of CCl_4 followed by refluxing for 4 h formed the ethoxymagnesium enolate of diethyl malonate. This mixture was diluted with 300 mL of Et$_2$O and then a solution of 96 mL (1.08 mol) of CH_3C-H_2COCl in 80 mL of Et$_2$O was added dropwise and with stirring. The resulting mixture was refluxed for 30 min, then cooled to 10 °C and treated with a solution of 80 mL of concentrated H_2SO_4 in 360 mL of H_2O. The resulting mixture was extracted with Et$_2$O and the ethereal layer was washed with aqueous 1 M H_2SO_4, dried, and concentrated. The residual liquid was mixed with 16 g of naphthalene-2-sulfonic acid and heated to 200 °C for 30 min. During this heating period CO_2 was evolved and 34 mL of liquid (a mixture of EtOH and $EtOOCCH_2CH_3$) was allowed to distill from the mixture through a 15-cm Vigreux column. The residual liquid was diluted with 250 mL of Et$_2$O, then washed with aqueous 0.6 M NaHCO$_3$, dried, and concentrated. Distillation of the residue separated the following fractions: (1) 3.2 g, bp 30–120 °C (25 mm); (2) 48.6 g, bp 120–130 °C (25 mm), n^{25}_D 1.4221; (3) 19.0 g, bp 130–145 °C (25 mm), n^{25}_D 1.4248; (4) 43.4 g, bp 145–167 °C (25 mm), n^{25}_D 1.4350; (5) 32.2 g, bp 60–70 °C (0.3 mm), n^{25}_D 1.4295. Fraction 5, mainly $CH_3CH_2COCH(CO_2Et)_2$, was again heated with 8 g of naphthalene-2-sulfonic acid and the crude product was subjected to the same workup procedure. The various fractions containing keto ester 5 were fractionally distilled to separate a mixture containing keto ester 5 (ca. 80%) and CH_2-$(COOEt)_2$ (ca. 20%). A solution of 28 g of the crude product in 160 mL of EtOH was added to a solution (pH 4.5) prepared from 18.2 g of $CuSO_4 \cdot 2H_2O$, 500 mL of H_2O, 20 mL of aqueous 28% NH$_3$, and 10 mL of HOAc. The mixture was shaken vigorously and then cooled to 5 °C. Filtration followed by washing with cold (0 °C) EtOH separated 35.2 g of the Cu(II) complex of the keto ester 5 as a green solid, mp 141–143 °C. This Cu(II) complex (30.6 g) was shaken with a mixture of Et$_2$O and aqueous 4 M H_2SO_4. The ethereal layer was dried, concentrated, and distilled to separate 9.48 g (13%) of the keto ester 5 as a pale yellow liquid: bp 132 °C (28 mm); n^{25}_D 1.4224 [lit.[9] bp 67–72 °C (5 mm), n^{20}_D 1.4230]; IR (CCl_4) 1745 (ester C=O), 1722 cm^{-1} (C=O); NMR (CCl_4) δ 4.13 (2 H, q, J = 7 Hz, ethoxyl CH$_2$), 3.35 (2 H, s, COCH$_2$CO), 2.51 (2 H, q, J = 7 Hz, CH$_2$), 0.8–1.4 (6 H, m, overlapping CH$_3$ signals).

Crystal Structure of Dimeric Diketone 12. A. Data Collection. A crystal of the dimer 12 with approximate dimensions 0.8 × 0.4 × 0.1 mm was mounted on a glass fiber with epoxy cement such that the longest crystal dimension (0.8 mm) was approximately parallel to the fiber axis. Unit cell parameters

and the orientation matrix were determined on a Syntex P2$_1$ four-circle diffractometer equipped with a graphite monochromator (Bragg 2θ angle = 12.2°), using Mo K$_\alpha$ radiation at a takeoff angle of 6.75°. Fifteen reflections whose 2θ values ranged from 12.94° to 21.04° were machine-centered and used in least-squares refinement of the lattice parameters and orientation matrix. Unit cell parameters obtained were a = 10.847 (3) Å,[10] b = 10.432 (1) Å, c = 15.677 (6) Å, β = 115.71 (2)°, and V = 1598.4 (7) Å^3. The calculated density of 1.245 g cm^{-3} for 4 formula units per unit cell agrees with the experimental density of 1.242 g cm^{-3} measured by the flotation method using a mixture of pentane and CCl_4. ω scans of several low 2θ angle reflections gave peak widths at half-height of less than 0.19°, indicating a satisfactory mosaic spread for the crystal. Axial photographs indicated that the crystal belonged to the monoclinic system. Intensity data for zero and upper levels were collected at a rapid scan rate and the intensities examined carefully for systematic absences. The absence of $h0l$ ($l = 2n + 1$) and $0k0$ ($k = 2n + 1$) reflections is consistent with only space group $P2_1/c$ (No. 14).[11]

Intensity data were collected by using θ–2θ scans with X-ray source and monochromator settings identical with those used for determination of the unit cell parameters. A variable scan rate of from 2.02 to 29.30°/min was used and a scan width of 2° was sufficient to collect all of the peak intensity. Stationary background counts were measured at the beginning (bgd1) and at the end (bgd2) of each scan with a total background to scan time ratio, TR, of 1.0. No significant fluctuations were observed in the intensities of three standard reflections (006, 060, 600) monitored every 97 reflections. Intensities were calculated from the total scan count (CT) and background counts by the relationship I = CT – (TR)(bdg1 + bdg2). The intensities were assigned standard deviations according to the formula $\sigma(I)$ = [CT + (TR)^2(bdg1 + bdg2)]$^{1/2}$ from a total of 2836 reflections collected in a complete quandrant of data out to 2θ = 50 °C; 2144 were accepted as statistically above background on the basis that F was greater than $3\sigma(F)$. Lorentz and polarization corrections were made in the usual way.

B. Solution and Refinement of the Structure. Computations were performed by using standard programs;[12] all computations were carried out on the CDC Cyber 74 System. For structure factor calculations the scattering factors were taken from Cromer and Mann's tabulation.[13] The agreement factors are defined in the usual way as R = $(\sum ||F_o| - |F_c||)/(\sum |F_o|)$ and R_w = $[\sum (|F_o| - |F_c|)(w^{0.5})]/[\sum (|F_o|)(w^{0.5})]$. In all least-squares refinements, the quantity minimized was $w(|F_o| - |F_c|)^2$. A weighting scheme based on counting statistics ($w = 1/[\sigma(F)^2 + 0.01F^2]$) was employed for calculating R_w and in least-squares refinement.

The structure was solved by using the automatic centrosymmetric direct methods program SHELX-76. The total number of parameters varied were 215 for 2144 observations. Parameters varied included a scale factor, coordinates of all atoms except hydrogens, anisotropic thermal parameters for all atoms except H atoms, and isotropic thermal parameters for H atoms. Hydrogen atoms were refined in the riding mode. The full-matrix least-squares refinement converged at R = 0.061 and R_w = 0.082. The final atomic coordinates and thermal parameters are available as supplementary material in Table 2 and the list of calculated and observed structure factors are available from us as Table 3; the list of bond angles and bond distances is available as supplementary material in Table 1.

Crystal Structure of Furan Adduct 10. A. Data Collection. A crystal of the adduct 10 with approximate dimensions 0.3 × 0.4 × 0.7 mm was mounted on a glass fiber with epoxy cement such that the longest crystal dimension (0.7 mm) was approximately parallel to the fiber axis. Unit cell parameters were determined as described above. Fifteen reflections whose 2θ values ranged from 11.34° to 24.25° were machine-centered and used

(8) (a) Riegel, B.; Lilienfeld, W. M. *J. Am. Chem. Soc.* **1945**, *67*, 1273. (b) Lund, H.; Voigt, A. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. 2, p 594.

(9) Kost, A. N.; Gents, F. *Zh. Obshch. Khim.* **1958**, *28*, 2773; *Chem. Abstr.* **1959**, *53*, 9197.

(10) Numbers in parentheses here and elsewhere in this paper indicate estimated standard deviations in the least significant digit(s).

(11) "International Tables for X-Ray Crystallography", Kynoch Press: Birmingham, England, 1952; Vol. I.

(12) Programs utilized were Sheldrick's SHELX-76 program and Johnson's ORTEP program.

(13) "International Tables for X-Ray Crystallography", Kynoch Press: Birmingham, England, pp 72–98; Vol. IV.

in least-squares refinement of the lattice parameters and orientation matrix. Unit cell parameters obtained were a = 8.439 (4) Å,[10] b = 7.423 (2) Å, c = 18.032 (9) Å, and V = 1129.5 (8) Å^3. The calculated density of 1.199 g cm^{-3} for 4 formula units per unit cell agrees with the experimental density of 1.198 g cm^{-3} measured by the flotation method using a mixture of pentane and CCl$_4$. ω scans of several low 2θ angle reflections gave peak widths at half-height of less than 0.19°, indicating a satisfactory mosaic spread for the crystal. Axial photographs indicated that the crystal belonged to the orthorhombic system. Intensity data for zero and upper levels were collected at a rapid scan rate and the intensities examined carefully for systematic absences. The absence of $h00$ ($h = 2n + 1$), $0k0$ ($k = 2n + 1$), and $00l$ ($l = 2n + 1$) reflections is consistent with only space group $P2_12_12_1$ (No. 19).[11]

Intensity data were collected by using θ–2θ scans with X-ray source and monochromator settings identical with those used for determination of the unit cell parameters. A variable scan rate from 2.02 to 29.3°/min was used and a scan width of 2° was sufficient to collect all of the peak intensity. Stationary background counts were measured at the beginning (bdg1) and at the end (bgd2) of each scan with a total background to scan time ratio, TR, of 1.0. No significant fluctuations were observed in the intensities of three standard reflections (008, 200, 020) monitored every 97 reflections. Intensities were calculated as described above. From a total of 1186 reflections collected in a complete octant of data out to 2θ = 50°, 1006 were accepted as statistically above

background on the basis that F was greater than $3\sigma(F)$. Lorentz and polarization corrections were made in the usual way.

B. Solution and Refinement of the Structure. Computations were performed as described above. In all least-squares refinements, the quantity minimized was $w(|F_o| - |F_c|)^2$. A weighting scheme based on counting statistics ($w = 1.0/[\sigma(F)^2 + 0.037F^2]$) was employed for calculating R_w and in least-squares refinement.

The structure was solved by using the multisolution tangent refinement direct methods program SHELX-76. The total number of parameters varied were 156 for 1006 observations. The full-matrix least-squares refinement converged at R = 0.0548 and R_w = 0.0691. The final atomic coordinates and thermal parameters are available as supplementary material in Table 5 and the list of calculated and observed structure factors are available from us as Table 6; the list of bond angles and bond distances is available as supplementary material in Table 4.

Registry No. 5, 4949-44-4; 6, 74262-50-3; 7, 74262-51-4; 8, 74262-52-5; 9, 74262-53-6; 10, 74262-54-7; 11, 74345-29-2; 12, 74262-55-8; cyclohexenone, 930-68-7; diethyl malonate, 510-20-3; propionyl chloride, 79-03-8; furan, 110-00-9.

Supplementary Material Available: Tables of atomic coordinates and thermal parameters (Tables 2 and 5) and tables of bond distances and bond angles (Tables 1 and 4) (6 pages). Ordering information is given on any current masthead page.

Preparation of β-Hydroxy-α-phenylthio Esters via Condensation of Aldehydes with α-Phenylthio Ester Enolate Anions

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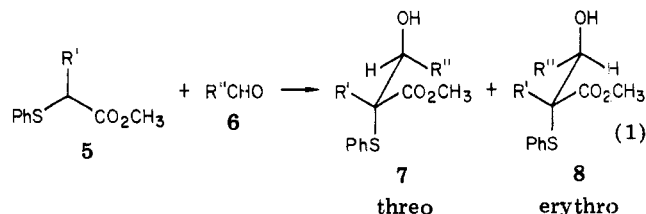*Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455*
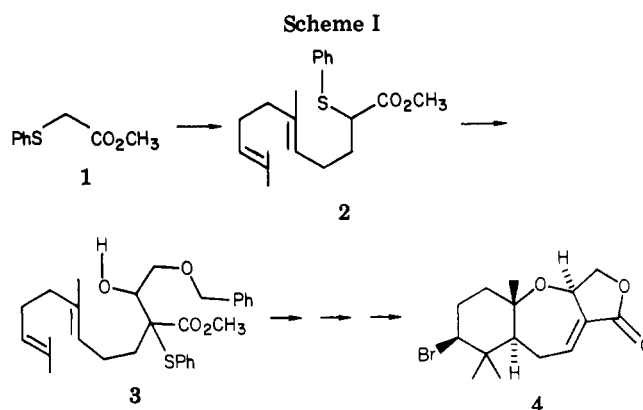
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The lithium enolates of α-phenylthio esters **5** react with aldehydes **6** to give good yields of diastereomeric aldol products **7** and **8** provided that anhydrous zinc chloride is first added to the enolate solution. The threo or erythro nature of several of the aldol products (**7** and **8**) was determined by transforming them stereospecifically to Z and E olefins **15** through a net trans elimination of the elements of PhSOH. α-(Phenylthio)-γ-butyrolactone (**16**) also takes part in the aldol reaction.

The use of α-sulfenylated carbonyl compounds in organic synthesis is well documented.[1] We recently invoked the sequential alkylation and aldolization of methyl α-(phenylthio)acetate (1) to prepare the β-hydroxy ester 3 (Scheme I), a key intermediate in a synthesis of *dl*-aplysistatin (4).[2] We have examined the aldol portion of that sequence (i.e., 2 → 3) in some detail and now report the results of that study.

Initial attempts to condense the lithium enolates of α-sulfenylated esters of general structure 5 (R′ = alkyl) with aldehydes 6 (eq 1) at −78 °C or room temperature in tetrahydrofuran met with limited success. In the best case

Scheme I

$$
\underset{\textbf{5}}{\text{PhS}\diagdown\text{CO}_2\text{CH}_3} \overset{R'}{\underset{}{|}} + \underset{\textbf{6}}{\text{R''CHO}} \longrightarrow \underset{\textbf{7}}{\underset{\text{threo}}{\text{R'}\diagup\diagdown\text{CO}_2\text{CH}_3}} + \underset{\textbf{8}}{\underset{\text{erythro}}{\text{R'}\diagup\diagdown\text{CO}_2\text{CH}_3}} \quad (1)
$$

(that leading to **7d** and **8d**; see Table I, entry 4), a 30% yield[3] of β-hydroxy-α-phenylthio esters 7 and 8 was obtained. In most instances, however, little if any quantity of aldol products could be detected by NMR analysis of the crude reaction mixtures, and the starting esters 5 were recovered. These results were surprising in view of the

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(1) Trost, B. M. *Chem. Rev.* **1978**, *78*, 363.
(2) Hoye, T. R.; Kurth, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 5065.

(3) All yields refer to chromatographed or recrystallized material.