ethyl acetate (4 × 3 mL), and the combined extracts were dried (Na_2SO_4) and evaporated to provide **29b** as a light-yellow oil: 0.111 g (94%). RPHPLC (as above, t_R 4.2 min) showed >90% purity and the material was used without further purification.

A solution of crude amino acid **29b** in $POCl_3$ (0.36 mL, 4.0 mmol) was heated at 100 °C and rapidly stirred for 5 min. It was then cooled to 0 °C, and methanol (2.2 mL) was added dropwise over the course of 15 min. After being stirred at 20 °C for 11 h, the reaction mixture was cooled to 0 °C, and half-saturated Na_2CO_3 (18 mL) was added over the course of 25 min. Extraction with dichloromethane (4 × 2.5 mL) provided a combined organic phase which was washed with saturated Na_2CO_3 (2 mL), dried (Na_2SO_4), and evaporated to afford **30b** as an oil (0.27 g) contaminated with $(CH_3O)_3PO$. RPHPLC (as above, **30b**, t_R 11.6 min) showed less than 10% UV active impurity, approximately 2% of which was **32b**.

To crude indoline acetal **30b** in dichloromethane (2.2 mL) and acetone (0.7 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 63.1 mg, 0.28 mmol) in dichloromethane (4.3 mL) with rapid stirring. After 2 h the solvent was evaporated, and the residue was chromatographed (5 g of neutral Al_2O_3, activity III, dichloromethane). Combination of selected fractions gave **32b** as an oil which crystallized under vacuum: 57 mg (61% from **27b**); mp 145–148 °C; t_R (as above, 4.2 min); NMR (90 MHz) δ 2.26 (s, 3 H, CH_3), 2.54 (tt, 2 H, NCH_2CH_2), 3.17 (t, 2 H, $NCH_2CH_2CH_2$, J = 7 Hz), 3.73, 3.80 (2 s, 3 H each, OCH_3), 4.21 (t, 2 H, NCH_2, J = 7 Hz), 5.02 (s, 2 H, Ar CH_2), 7.32 (m, 5 H, 5 Ar H), 10.28 (s, 1 H, CHO); IR (Nujol) 1645, 1524, 1493, 1416, 1285, 1258, 1094, 1014, 845, 755, 700 cm^{-1}; mass spectrum, m/e (relative intensity) 366 (M + 1, 2.4), 365 (M^+, 7.4), 274 (91.6), 57 (100); exact mass calcd for $C_{22}H_{23}NO_4$ 365.1627, found m/e 365.1614 (M^+).

2,3-Dihydro-7-methoxy-6-methyl-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (36). A. From 32a. Vacuum-dried indole aldehyde **32a** (31.2 mg, 0.11 mmol, 0.015 mm, 56 °C, 24 h) in glacial acetic acid (2.7 mL) was cooled with an ice/water bath for 20 min at which time concentrated HNO_3 (2.7 mL, 0 °C) was added dropwise to the pasty solid over the course of 3 min with rapid stirring. Water (10 mL, 5 °C) was added after 30 min followed by a 45-min dropwise addition of 10% $NaHCO_3$ (65 mL). The mixture was extracted with dichloromethane (4 × 15 mL), and the combined extracts were washed with brine. Drying and evaporation provided **36** as an orange solid: 23.2 mg (83% yield, pure by RPHPLC, solvent A, t_R 6.8 min); mp 226–228 °C (lit. mp 224–227 °C,[5] 222–224 °C[9]); R_f (SiO_2, ethyl acetate) 0.60; NMR (250 MHz) δ 2.01 (s, 3 H, CH_3), 2.68 (tt, 2 H, NCH_2CH_2), 3.14 (t, 2 H, $NCH_2CH_2CH_2$, J = 7 Hz), 4.06 (s, 3 H, OCH_3), 4.31 (t, 2 H, NCH_2, J = 7 Hz), 10.38 (s, 1 H, CHO) (lit.[5] NMR δ 1.99, 4.12, 4.34 (t, J = 7 Hz), 10.5); IR (Nujol) 1681, 1642, 1603, 1529, 1506, 1342, 1307, 1285, 1259, 1101, 1020, 995, 956, 922, 898, 806, 742 cm^{-1} (lit.[5] IR (KBr) 1689, 1672, 1647, 1104, 1022 cm^{-1}); UV λ_{max} 217 nm (ϵ 18 290), 246 (9740), 272 (10 430), 280 (10 960), 285 (10 940), 324 (5580), 370–530 (sh; 730 at 415 nm) (lit.[5] UV λ_{max} 216 (ϵ 25 200), 243 (14 900), 272 (14 250), 289 (13 870), 732 (7120)).

B. From 32b. To indole aldehyde **32b** (4.5 mg, 0.012 mmol) in acetonitrile (0.25 mL) was added ceric ammonium nitrate (19.7 mg, 0.036 mmol) in water (0.25 mL) over the course of 1 min. After 50 min water (2.0 mL) was added and the mixture was extracted with dichloromethane (3 × 1.0 mL). The combined organic extract was washed with water (1.0 mL), 10% $NaHCO_3$ (2 × 0.5 mL), water (1.0 mL), and brine (1.0 mL). Drying and evaporation provided crude **36** which was chromatographed (150 mg of SiO_2, ethyl acetate) to yield 2.7 mg (87%) of pure **36**.

Registry No. 5, 2207-57-0; **6**, 81457-00-3; **6b**, 81457-01-4; **7**, 81457-02-5; **9**, 81457-03-6; **10**, 81457-04-7; **11**, 81457-05-8; **13**, 81457-06-9; **14a**, 81457-07-0; **14b**, 81457-08-1; **15**, 81457-09-2; **16**, 81457-10-5; **17**, 81457-11-6; **18**, 81457-12-7; **19**, 81457-13-8; **20**, 81457-14-9; **21**, 19676-67-6; **22**, 81457-15-0; **23**, 81457-16-1; **24**, 81457-17-2; **26**, 81457-18-3; **27a**, 81457-19-4; **27b**, 81457-20-7; **28a**, 81457-21-8; **28b**, 81457-22-9; **29a**, 81457-23-0; **29b**, 81457-24-1; **30a**, 81457-25-2; **30b**, 81457-26-3; **31a**, 81457-27-4; **31b**, 81457-28-5; **32a**, 81457-29-6; **32b**, 81457-30-9; **36**, 3188-25-8; proline methyl ester, 2577-48-2.

Enones with Strained Double Bonds. 7. Precursors for Substituted Bicyclo[3.3.1]nonane Systems[1]

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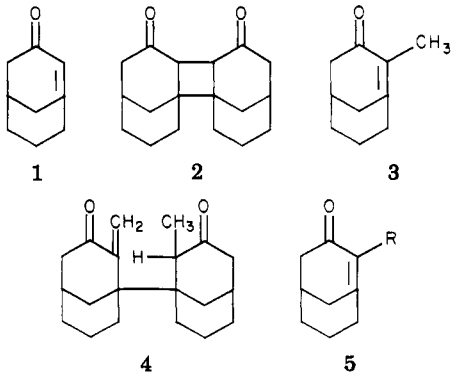
Compounds **11c**, **12**, and **13** have been synthesized as potential precursors for the 2-substituted bicyclo[3.3.1]non-1(2)-en-3-ones **5** (R = Ph and *t*-Bu). The lactone **34** and its derivatives **32** have also been synthesized as potential precursors for the parent bicyclo[3.3.1] enone **1**.

The rapid formation of dimeric 2 + 2 cycloadducts (e.g., **2**) has thus far frustrated our efforts to isolate the parent bicyclo[3.3.1] enone **1** (Scheme I) even when this enone **1** was generated in the absence of favorable reactants such as nucleophiles or dienes.[2] We reasoned that formation of dimeric cycloadducts such as **2** would be sterically impeded if the parent enone system contained α substituents such as the α-methyl enone **3**. In fact, no 2 + 2 cycloaddition products were isolated from solution of the enone **3**, and reaction of enone **3** with furan to form a Diels–Alder adduct was significantly slower than the corresponding reaction of enone **1** with furan.[3] Unfortunately, isolation

Scheme I

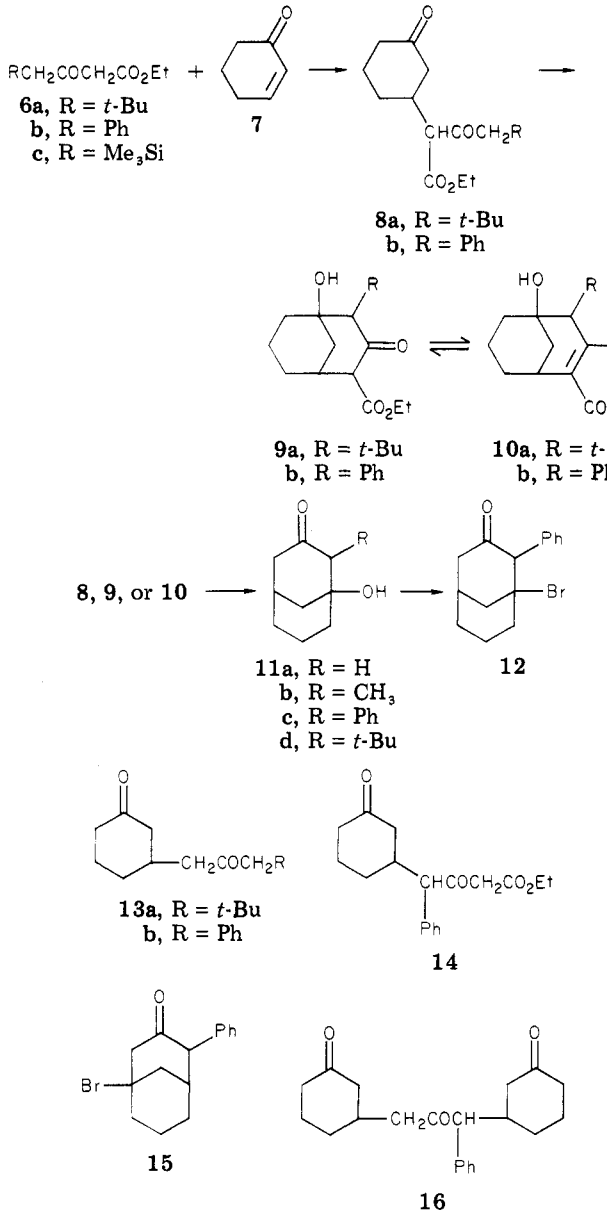


(1) A portion of this research has been supported by Public Health Service Grant R01-GM-20197 from the National Institute of General Medical Science. The execution of this research was also facilitated by Institutional Research Grants from the National Science Foundation for the purchase of a mass spectrometer and an NMR spectrometer.

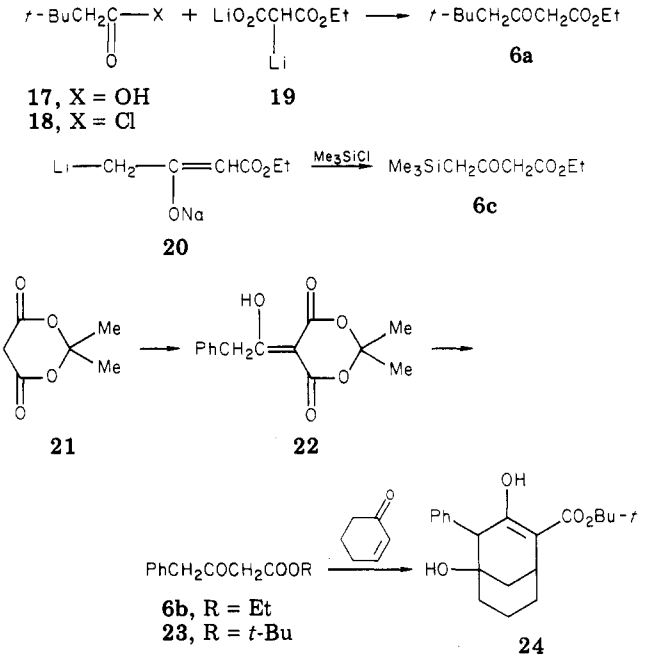
(2) (a) House, H. O.; Kleschick, W. A.; Zaiko, E. J. *J. Org. Chem.* **1978**, *43*, 3653. (b) House, H. O.; DeTar, M. B.; VanDerveer, D. *Ibid.* **1979**, *44*, 3793.

0022-3263/82/1947-2413$01.25/0

Scheme II



Scheme III



of the α-methyl enone **3** was still unsuccessful because a rapid ene reaction of the enone **3** with itself formed the dimeric diketone **4**. Therefore, we could conclude that an enone α substituent with no α-H atom (e.g., **5**, R = *t*-Bu, 1-adamantyl, Me_3Si, or Ph) would be needed as a sterically hindering group. Alternatively, precursors for the parent enone **1** that could be decomposed thermally in the gas phase or photochemically at low temperatures might permit isolation of the enone **1** at temperatures sufficiently low to retard 2 + 2 cycloaddition. This paper describes our synthetic efforts directed toward these bicyclo[3.3.1] enone precursors.

The general synthetic scheme explored for the α-substituted enones **5** involved Michael addition of an appropriate β-keto ester **6** (Scheme II) to cyclohexenone (**7**) to form the adducts **8**. The β-keto esters **6** were formed by the various routes indicated in Scheme III. Since several attempts to use the γ-(trimethylsilyl)-β-keto ester **6c** in the Michael reaction resulted in cleavage of the trimethylsilyl group, work with this β-keto ester **6c** was discontinued. The monocyclic adduct **8a** showed no tendency to form the bicyclic aldol product **9a**, and treatment with KOH in aqueous EtOH formed the monocyclic diketone **13a** rather than the bicyclic ketol **11d**. Although the related ketols **11a**,[2] **11b**,[3] and **11c** have all been prepared by intramolecular aldol reactions, we have not yet found a suitable method for converting the diketone **13a** (or the diketo ester **8a**) to the desired ketol **11d**.

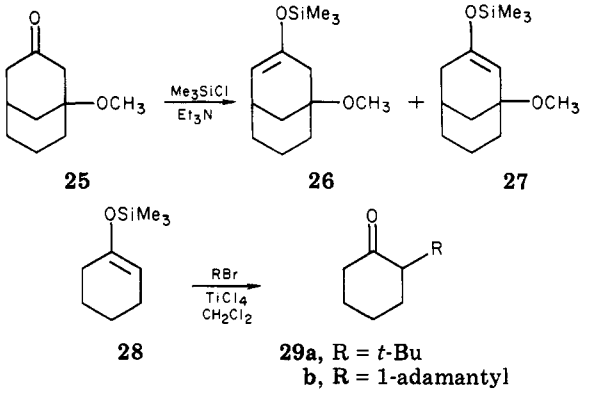
Michael adduct **8b**, formed in the presence of ethanolic NaOEt, cyclized in the reaction mixture to form the enolic keto ester **9b** and/or **10b** as a mixture of two epimers that could be separated by chromatography. A similar mixture of epimers of enolic keto ester **24** was isolated from Michael addition of keto ester **23** to cyclohexenone (**7**). In at least the Michael addition of keto ester **6b** to cyclohexenone (**7**), subsequently described evidence indicates that formation of the Michael adduct **8b** is accompanied by the formation of smaller amounts of the structurally isomeric adduct **14**.

Heating the purified keto ester **9b** or **10b** with aqueous KOH cleaved the carboethoxy function to form a mixture of the diketone **13b** and the ketol **11c** that was separable by chromatography. A similar mixture of **11c** and **13b** was formed by heating the *tert*-butyl ester **24** with TsOH in PhH. When the crude product from the Michael reaction, containing **9b** or **10b**, was heated with KOH in aqueous ethanol, a relatively complex mixture was formed from which the ketol **11c**, the diketone **13b**, and the triketone **16** were isolated by chromatography. The triketone **16** is evidently formed by Michael addition of both activated methylene groups in keto ester **6b** to cyclohexenone acceptors.

The bromo ketone **12** could be prepared by reaction of the purified ketol **11c** with PBr_3 in PhH (cf. ref 1 and 2). However, this preparative route via isolated samples of intermediates **9b** or **10b** and **11c** required either one or two rather tedious chromatographic separations. A less tedious procedure involved first heating the crude Michael reaction product (containing keto ester **9b** and/or **10b**) with KOH in aqueous ethanol to form a mixture containing ketol **11c**, diketone **13b**, and other products. A solution of this crude product in $CHCl_3$ was then saturated with HBr. Subsequent chromatography resulted in the relatively rapid separation of the desired bromo ketone **12** in 19% overall

(3) House, H. O.; DeTar, M. B.; Sieloff, R. F.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3545.

Scheme IV

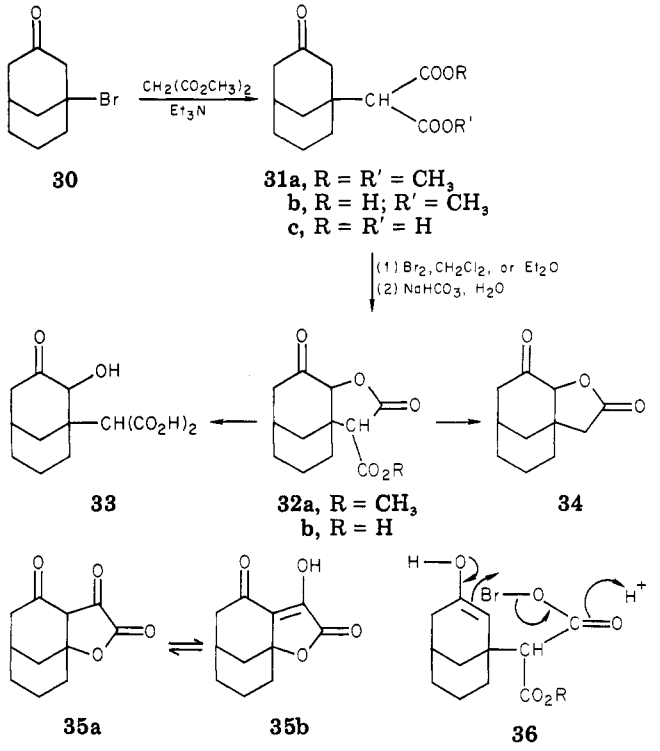


yield based on the starting keto ester **6b**. This chromatography also separated a minor amount (2% overall yield) of the structurally isomeric bromo ketone **15**. The isolation of this ketone **15** indicates the presence of Michael adduct **14** in the crude reaction mixture.

In an alternative approach to a derivative of the α-*tert*-butyl ketol **11d**, the previously described[2] methoxy ketone **25** (Scheme IV) was treated with Me_3SiCl and Et_3N. The product contained a mixture of the structurally isomeric trimethylsilyl enol ethers **26** and **27**; our efforts to separate this mixture have failed. Thus, we have been unable to explore in a meaningful way a Lewis acid catalyzed alkylation analogous to the conversion of silyl enol ether **28** to the α-substituted ketones **29**.[4,5]

Our earlier study[1a] of the α-keto lactone **35** (Scheme V) suggested that thermal decomposition of this material initially formed the bridgehead enone **1** that underwent further thermal rearrangement. Attempts to convert **35** to enone **1** photochemically[1a] led to a very complex mixture, a result that we attribute to the existence of this keto lactone in its enol form **35b**. Since similar derivatives of the lactone **34** would not be expected to be highly enolized, a route to the lactones **32** and **34** was explored. Our synthetic plan was devised with the expectation that initial reaction of keto acid **31b** or **31c** with bromine would form an intermediate acyl hydrobromite that would deliver a bromine atom regioselectively (see structure **36**). In fact successive treatment of either acid **31b** or **31c** with bromine and with aqueous $NaHCO_3$ formed the corresponding lactones **32** that could be converted to the lactone **34** or the ketol diacid **33**. Various chemical transformations of the lactones **32** and **34** are under current study.

Scheme V



Experimental Section[6]

Preparation of the β-Keto Esters 6. A. Trimethylsilyl Derivative 6c. A solution of 15.05 g (115.7 mmol) of ethyl acetoacetate in 30 mL of THF was added, dropwise and with stirring during 10 min, to a cold (0–6 °C) suspension of 3.08 g (128 mmol) of NaH (the residue after washing 5.13 g of a 60% dispersion of NaH in oil with cyclohexane) in 350 mL of THF. After the resulting pale yellow solution of the Na enolate had been stirred at 0 °C for 30 min, a solution of 129.6 mmol of *n*-BuLi in 81 mL of hexane was added, dropwise and with stirring during 15 min. The resulting yellow solution of the dianion was stirred at 0 °C for 15 min and then 16.0 mL (13.7 g, 126 mmol) of Me_3SiCl was added dropwise during 5 min. After the resulting solution had been stirred for 15 min at 0 °C, it was poured into excess aqueous NH_4Cl, and the organic layer was separated. After the organic solution had been washed with aqueous $NaHCO_3$, dried, and concentrated, fraction distillation separated 1.981 of forerun (a mixture of keto ester **6c** and ethyl acetoacetate), bp 40–64 °C (1.4 mm), and 16.59 g (71%) of the crude keto ester **6c**, bp 64–81 °C (1.5–1.6 mm). Redistillation of the later fraction separated 12.89 g of the keto ester **6c**: bp 58–72 °C (0.9–1.1 mm), n^{25}_D 1.4410; IR (CCl_4), 1740 (ester C=O), 1700 (C=O), 1635, 1610 cm^{-1} (enolic β-keto ester); mass spectrum, *m/e* (rel intensity) 202 (M^+, 0.7), 159 (34), 117 (24), 115 (45), 77 (46), 75 (68), 73 (100), 45 (23), 43 (22); ^1H NMR ($CDCl_3$) δ 4.20 (2 H, q, J = 7 Hz, ethoxyl CH_2O), 3.38 (2 H, s, CH_2), 2.35 (2 H, s, CH_2), 1.30 (3 H, t, J = 7 Hz, ethoxyl CH_3), 0.15 (9H, s, Me_3Si); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) δ 199.9 (s), 166.3 (s), 60.6 (t), 50.5 (t), 38.1 (t), 14.0 (q), −1.2 (q, 3 C).

Anal. Calcd for $C_9H_{18}O_3Si$: mol wt, 202.1020. Found: mol wt 202.1060.

B. *tert*-Butyl Derivative 6a. After a mixture of 58.0 g (50 mmol) of acid **17** and 83 g (730 mmol) of $SOCl_2$ had been stirred at 25 °C for 20 h, the mixture was distilled. The fraction boiling in the range 120–130 °C was collected and redistilled to separate 58.1 g (86%) of the acid chloride **18**: bp 126–130 °C (lit.[7] bp 129–130 °C); ^1H NMR ($CDCl_3$) δ 2.83 (2 H, s, CH_2), 1.05 (9 H, s, *t*-Bu). The previously described[8] reaction of 40.0 g (25 mmol) of $CH_2(COOEt)_2$ with 14.0 g (21.3 mmol) of 85% KOH in 300 mL of EtOH yielded 27.7 g (78%) of crude liquid $EtOOCCH_2COOH$ that was used without further purification; ^1H NMR ($CDCl_3$) δ 8.63 (1 H, s, OH), 4.22 (2 H, q, J = 7 Hz, ethoxyl CH_2), 3.40 (2

(4) (a) Chan, T. H.; Paterson, I.; Pinsonnault, J. *Tetrahedron Lett.* **1977**, 4183. (b) Schmerling, L. *J. Am. Chem. Soc.* **1947**, *69*, 1121.

(5) (a) Reetz, M. T.; Maier, W. F.; Schwellnus, K.; Chatziiosifidis, I. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72. (b) Boldt, P.; Militzer, H.; Thielcke, W.; Schulz, L. *Justus Liebigs Ann. Chem.* **1968**, *718*, 101.

(6) 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 299 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 ^1H NMR spectra were determined at 60 mHz with a Varian Model T-60A NMR spectrometer or at 300 mHz with a Bruker Model WM-300 NMR spectrometer. The ^{13}C NMR spectra were determined at 25 mHz with a JEOL Model PFT-100 NMR spectrometer or at 75 mHz with a Bruker Model WM-300 NMR spectrometer. The chemical shift values are expressed in δ values relative to a Me_4Si 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.

(7) Dubois, J. E.; Leheup, B.; Hennequin, F.; Bauer, P. *Bull. Soc. Chim. Fr.* **1967**, 1150.

(8) Breslow, D. S.; Baumgarten, E.; Hauser, C. R. *J. Am. Chem. Soc.* **1944**, *66*, 1286.

H, s, CH_2), 1.27 (3 H, t, J = 7 Hz, ethoxyl CH_3).

Following a general procedure described previously,[9] a solution of 10.5 g (79.5 mmol) of $EtOOCCH_2COOH$ and 10 mg of 2,2-bipyridyl in 250 mL of THF was cooled to −70 °C, and then 114 mL of a hexane solution containing 159 mmol of *n*-BuLi was added, dropwise and with stirring. The reaction temperature was kept below −60 °C until approximately 75% of the *n*-BuLi solution had been added; then the temperature was allowed to rise to −5 °C as the remainder of the *n*-BuLi was added. The resulting solution was recooled to −70 °C, and then 6.50 g (48 mmol) of acid chloride **18** was added, dropwise and with stirring during 5 min. The resulting mixture was stirred at −70 °C for 45 min and then warmed to 25 °C and partitioned between aqueous 2 M HCl and Et_2O. The ethereal layer was washed with aqueous $NaHCO_3$, dried, and concentrated. Distillation of the residual yellow liquid (8.60 g) separated 7.52 g (84%) of the partially enolic keto ester **6a** as a colorless liquid: bp 68–70 °C (1.2 mm); n^{25}_D 1.4341; IR (CCl_4) 1745 (ester C=O), 1720 (C=O), 1652, 1630 cm^{-1} (enolic β-keto ester); ^1H NMR (CCl_4) δ 12.1 (0.3 H, s, enol OH), 4.87 (0.3 H, s, enolic vinyl CH), 4.13 (2 H, q, J = 7 Hz, ethoxyl CH_2), 3.25 (1.4 H, s, $COCH_2CO$), 2.37 (0.6 H, s, CH_2CO of enol), 2.03 (1.4 H, s, CH_2CO of keto form), 1.30 (3 H, t, J = 7 Hz, ethoxyl CH_3), 1.00 (9 H, s, *t*-Bu); mass spectrum, m/e (rel intensity) 186 (M^+, 2), 130 (100), 115 (40), 99 (48), 57 (47), 43 (20).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.49; H, 9.77.

C. Phenyl Derivative 6b from Diethyl Malonate. As described above, 135 mL of a hexane solution containing 205 mmol of *n*-BuLi was added, dropwise and with stirring during 70 min, to a cold (−78 °C) solution of 13.6 g (103 mmol) of $HO_2CCH_2CO_2Et$ and 11 mg of 2,2-bipyridyl (an indicator) in 250 mL of THF. The resulting suspension, whose temperature rose to −5 °C, was recooled to −65 °C, and then 8.77 g (56.7 mmol) of $PhCH_2COCl$ was added, dropwise and with stirring during 5 min. After the resulting mixture had been stirred for 15 min, it was partitioned between Et_2O and aqueous 1 M HCl. The organic layer was washed successively with aqueous $NaHCO_3$ and with H_2O and then dried and concentrated. The residue was distilled in a short-path still to separate 8.31 g of the crude β-keto ester **6b**. Redistillation through a 15-cm Vigreux column separated 6.39 g (55%) of the keto ester **6b** as a colorless liquid: bp 119–120 °C (0.55 mm), n^{25}_D 1.5093 [lit.[8] bp 154–156 °C (9 mm]; IR (CCl_4), 1740, 1720, 1655, 1630 cm^{-1} (partially enolic β-keto ester); ^1H NMR ($CDCl_3$) δ 7.0–7.6 (5 H, m, aryl CH), 4.17 (2 H, q, J = 7 Hz, ethoxyl CH_2), 3.77 (2 H, s, $COCH_2CO$), 3.40 (2 H, s, $PhCH_2CO$), 1.18 (3 H, t, J = 7 Hz, ethoxyl CH_3); mass spectrum, m/e (rel intensity) 206 (M^+, 23), 118 (54), 115 (38), 105 (22), 92 (25), 91 (100), 87 (28), 65 (28), 43 (49).

D. Phenyl Derivatives 6b and 23 from Meldrum's Acid. A previously described[10] procedure was used to prepare Meldrum's acid; recrystallization from H_2O–acetone separated the 1,3-dioxane **21** as colorless needles, mp 93–96 °C dec (lit.[10] mp 94–95 °C dec). This product was acylated by a recently described procedure[11] employing 65.0 mL (0.805 mmol) of anhydrous pyridine, 44.2 g (0.306 mmol) of Meldrum's acid (**21**), 46.9 g (0.303 mol) of $PhCH_2COCl$, and 230 mL of CH_2Cl_2. The crude product was recrystallized from Et_2O–hexane to separate the acylated product **22** as orange prisms: mp 90–92 °C dec (lit.[11] mp 96–97 °C dec); IR (CCl_4), 1743, 1670, 1565 cm^{-1} (enolic β-keto ester); ^1H NMR ($CDCl_3$) δ 14.83 (1 H, br, OH), 7.1–7.5 (5 H, m, aryl CH), 4.40 (2 H, s, CH_2), 1.67 (6 H, s, CH_3).

A solution of 76.9 g of the crude acylated product **22** in 500 mL of anhydrous EtOH was refluxed for 2.5 h and then concentrated under reduced pressure. Fractional distillation of the residual bown liquid through a 50-cm spinning-band column separated 41.7 g (67%) of the β-keto ester **6b** as a colorless liquid, bp 98–102 °C (0.5 mm), n^{25}_D 1.5080, that was identified with the previously described sample by comparison of ^1H NMR spectra.

In a similar manner, a mixture of 2.77 g (10.6 mmol) of the β-keto ester **22** (mp 90–92 °C dec), 2.73 g (36.8 mmol) of *t*-BuOH, and 50 mL of PhH was refluxed for 4 h and then concentrated under reduced pressure. Distillation of the residual red-orange liquid (3.09 g) in a short-path still (100–105 °C and 0.8 mm) separated 2.42 g (98%) of the β-keto ester **23** as a pale yellow liquid: n^{25}_D 1.4956 [lit.[11] bp 112 °C (0.25 mm), mp 36 °C]; ^1H NMR ($CDCl_3$), δ 7.0–7.4 (5 H, m, aryl CH), 3.78 (2 H, s, CH_2), 3.33 (2 H, s, CH_2), 1.43 (9 H, s, *t*-Bu).

Formation of the Michael Adduct 8a. To a solution of NaOEt, prepared from 12 mg (0.52 mg atom) of Na and 35 mL of EtOH, was added 601 mg (3.2 mmol) of the keto ester **6a** and 207 mg (2.1 mmol) of the enone **7**. After the resulting solution had been stirred at 25 °C for 1.5 h, it was acidified with 1 mL of HOAc and then partitioned between H_2O and Et_2O. The ethereal layer was washed with aqueous $NaHCO_3$, dried, and concentrated. Distillation of the residual liquid separated 466 mg (77%) of the Michael adduct **8a** as a colorless liquid: bp 152–155 °C (1 mm); n^{25}_D 1.4674; IR (CCl_4), 1745 (ester C=O), 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.20 (2 H, q, J = 7 Hz, ethoxyl CH_2), 3.40 (1 H, d, J = 8 Hz, COCHCO), 1.2–2.4 (11 H, m, aliphatic CH), 1.25 (3 H, t, J = 7 Hz, ethoxyl CH_3), 1.00 (9 H, s, *t*-Bu); mass spectrum, m/e (rel intensity) 282 (M^+, 3), 184 (40), 183 (20), 130 (28), 99 (100), 97 (24), 71 (20), 57 (71), 41 (24).

Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.04; H, 9.28. Found: C, 68.04; H, 9.37.

Preparation of the Diketone 13a. A mixture of 1.52 g (5.39 mmol) of the keto ester **8a**, 605 mg (9.2 mmol) of 85% KOH, 5 mL of EtOH, and 15 mL of H_2O was stirred at 25 °C for 2 h and then heated on a steam bath for 10 min. After the mixture had been acidified with aqueous 1 M HCl, it was extracted with Et_2O, and the ethereal extract was washed with aqueous $NaHCO_3$, dried, and concentrated. Distillation of the residual yellow liquid in a short-path still (110 °C at 0.8 mm) separated 0.87 g (77%) of the diketone **13a** as a colorless liquid, n^{25}_D 1.4649; IR ($CDCl_4$), 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.1–2.6 (13 H, m, aliphatic CH), 1.00 (9 H, s, *t*-Bu); mass spectrum, m/e (rel intensity) 210 (M^+, 3), 139 (26), 99 (27), 97 (47), 95 (28), 57 (100), 55 (24), 43 (22), 41 (42); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) δ 209.5 (s), 207.8 (s), 55.0 (t), 47.2 (t), 41.0 (t), 34.1 (d or t), 30.8 (s and t or d, 2 C atoms), 29.5 (q, 3 C atoms), 24.9 (t).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.28; H, 10.58.

Formation and Cyclization of the Michael Adduct 8b. A solution of 6.019 g (29.2 mmol) of the keto ester **6b** in 5 mL of EtOH was added, dropwise and with stirring, to a cold (0 °C) solution of NaOEt (from 397 mg or 17.3 mg atom of Na) in 15 mL of EtOH. To the resulting slurry was added, dropwise and with stirring during 10 min, a solution of 2.79 g (29 mmol) of cyclohexenone (**7**) in 5 mL of EtOH. The resulting mixture was stirred at 25 °C for 3.25 h, during which time the solid components dissolved to give an orange-yellow solution. The reaction solution was neutralized with HOAc and then partitioned between Et_2O and H_2O. The organic layer was dried and concentrated to leave 8.28 g of orange liquid. This material was crystallized from cyclohexane to separate 3.28 g (37%) of the crude keto ester **9b** or **10b** as a pale tan solid, mp 85–105 °C. The mother liquors were chromatographed on silica gel with an EtOAc–hexane eluent (1:3 v/v) to separate an additional 1.39 g (total 4.69 g or 53%) of the crude keto ester **9b** or **10b**. Recrystallization from cyclohexane separated a sample of the pure enolic β-keto ester **10b** as colorless needles: mp 114.5–116.5 °C; IR (CCl_4), 1645, 1610 cm^{-1} (enolic β-keto ester); ^1H NMR ($CDCl_3$) δ 12.58 (1 H, s, OH), 7.2–7.5 (5 H, m, aryl CH), 4.12 (2 H, q, J = 7 Hz, ethoxyl CH_2), 3.86 (1 H, s, benzylic CH), 3.18 (1 H, m, bridgehead CH), 0.8–2.4 (12 H, m, OH and aliphatic CH including an ethoxyl CH_3 triplet, J = 7 Hz, at 1.33); mass spectrum, m/e (rel intensity) 302 (M^+, 72), 256 (63), 213 (56), 198 (42), 165 (60), 160 (44), 118 (100), 115 (52), 97 (63), 91 (61), 90 (43), 43 (31); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) δ 172.1 (s), 171.6 (s), 135.9 (s), 129.9 (d, 2 C atoms), 127.7 (d, 2 C atoms), 126.7 (d), 100.7 (s), 70.6 (s), 60.1 (t), 58.4 (d), 41.0 (t), 35.5 (t), 30.0 (d), 27.6 (t), 18.6 (t), 13.9 (q).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.50; H, 7.36.

In a similar experiment, reaction of 6.12 mmol of NaOEt, 4.841 g (23.5 mmol) of keto ester **6b**, and 2.258 g (23.5 mmol) of cyclohexenone in 60 mL of EtOH at 22 °C for 7 h gave, after isolation, 5.913 g of crude product as an orange liquid. A solution

(9) Wierenga, W.; Skulnick, H. I. *J. Org. Chem.* **1979**, *44*, 310.
(10) Davidson, D.; Bernhard, S. A. *J. Am. Chem. Soc.* **1948**, *70*, 3426.
(11) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087.

of this liquid in cyclohexane deposited 2.705 g (38%) of the previously described crude keto ester **9b** or **10b** as a colorless solid, mp 96–105 °C. The mother liquor was chromatographed on silica gel with an EtOAc–hexane eluent (1:3 v/v). Early fractions contained 120 mg of an epimer of keto ester **9b** or **10b**. Recrystallization separated 83 mg (1%) of the pure *minor epimer* as colorless prisms, mp 117–118 °C; IR (CCl_4) 3580 (OH), 1650, 1612 cm^{-1} (enolic β-keto ester); ^1H NMR ($CDCl_3$), δ 12.18 (1 H, s, OH), 7.1–7.6 (5 H, m, aryl CH), 4.28 (2 H, q, J = 7 Hz, ethoxyl CH_2), 3.56 (1 H, s, benzylic CH), 3.20 (1 H, m, bridgehead CH), 0.7–2.2 (12 H, m, aliphatic CH including an ethoxyl triplet, J = 7 Hz, at 1.33); mass spectrum, m/e (rel intensity) 302 (M^+, 74), 256 (66), 213 (69), 211 (33), 198 (48), 173 (20), 165 (66), 160 (42), 137 (27), 118 (100), 115 (30), 105 (29), 97 (45), 91 (61), 90 (34), 77 (20), 55 (20), 43 (27), 41 (22).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.50; H, 7.34.

Preparation of the Ketol 11c. A. By Saponification of the Enolic Keto Ester 10b. A solution of 327 mg (1.08 mmol) of the purified keto ester **10b** and 154 mg (2.33 mmol) of 87% KOH in 6 mL of H_2O was refluxed for 75 min and then neutralized with aqueous 1 M HCl and extracted with Et_2O. After the ethereal extract had been dried and concentrated, the residual yellow oil (199 mg) was chromatographed on silica gel with an EtOAc–hexane eluent (35:65 v/v). Early fractions, containing 127 mg (51%) of the crude diketone **13b** as a yellow liquid, were distilled in a short-path still (140–160 °C at 0.5 mm) to separate 95 mg of the **diketone 13b** as a colorless liquid that solidified on standing as colorless prisms, mp 43.5–46 °C. The spectrometric properties of the diketone **13b** follow: IR (CCl_4), 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.2–7.6 (5 H, m, aryl CH), 3.67 (2 H, s, benzylic CH), 0.9–3.2 (11 H, m, aliphatic CH); mass spectrum, m/e (rel intensity) 230 (M^+, 8), 139 (37), 134 (42), 97 (23), 95 (100), 91 (43), 69 (23), 55 (36), 41 (26); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) δ 209.4 (s), 205.3 (s), 133.2 (s), 128.7 (d, 2 C), 128.1 (d, 2 C), 126.5 (d), 50.3 (t), 47.5 (t), 47.1 (t), 40.9 (t), 34.0 (d), 30.5 (t), 24.7 (t).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.25; H, 7.90.

Later fractions from the chromatography contained 48 mg (19%) of the crude ketol **11c** as a white solid. Recrystallization from a PhH–hexane mixture separated the pure **ketol 11c** as colorless prisms: mp 153.5–154.5 °C; IR ($CHCl_3$), 3570 (OH), 1705 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.0–7.6 (5 H, m, aryl CH), 3.60 (1 H, s, benzylic CH), 0.8–3.0 (12 H, m, OH and aliphatic CH); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) δ 207.5 (s), 132.5 (s), 130.8 (d, 2 C), 127.5 (d, 2 C), 126.8 (d), 73.0 (s), 68.2 (d), 45.9 (t), 41.8 (t), 35.7 (t), 30.9 (t), 30.2 (d), 20.2 (t); mass spectrum, m/e (rel intensity), 230 (M^+, 22), 135 (10), 134 (100), 97 (85), 91 (10).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.25; H, 7.88.

B. From Cyclohexenone (7) and the Keto Ester 6b. A cold (2 °C) solution of NaOEt, from 458 mg (19.9 mg atom) of Na and 90 mL of EtOH, was treated with a solution of 12.31 g (59.7 mmol) of the keto ester **6b** in 10 mL of EtOH. The resulting slurry was treated with a solution of 5.774 g (60.1 mmol) of cyclohexenone (**7**) and then stirred for 45 min at 0–2 °C and for 3 h at 25 °C. After the resulting mixture had been neutralized with HOAc, it was partitioned between Et_2O and H_2O. The organic layer was washed with H_2O, dried, and concentrated to leave 16.79 g of yellow-orange liquid. A solution of this material and 5.129 g (91.4 mmol) of 85% KOH in 50 mL of EtOH and 50 mL of H_2O was refluxed for 6 h and then allowed to stand at 25 °C for 21 h. The resulting yellow solution was extracted with Et_2O. After this ethereal extract had been washed with aqueous NaCl, dried, and concentrated, the residual yellow liquid (11.62 g) was crystallized from PhH to separate 2.049 g (14.9%) of the previously described ketol **11c**. The remaining material recovered from the mother liquors was chromatographed on silica gel with an EtOAc–hexane eluent (2:3 v/v). The early fractions contained (TLC analysis) 2.189 (16%) of the previously described diketone **13b**. Subsequent fractions contained 1.904 g (total yield 3.95 g or 29%) of the ketol **11c**. The final component eluted from the chromatogram was 1.09 g (5.6%) of the crude triketone **16** as a white solid, mp 135–150 °C. Recrystallization from PhH afforded a mixture of the diastereoisomeric **triketones 16** as colorless prisms: mp 152–163.5 °C dec; IR (CCl_4), 1715 cm^{-1} (C=O); ^1H NMR (300 mHz, $CDCl_3$) δ 7.1–7.4 (5 H, m, aryl CH), 3.48 (1 H, d, J = 9.9 Hz, benzylic CH), 2.58–2.8 (1 H, m, aliphatic CH), 2.55 (1 H, d of m, J = 13.5 Hz, aliphatic CH), 1.7–2.5 (11 H, m, aliphatic CH), 1.45–1.70 (4 H, m, aliphatic CH), 0.9–1.45 (2 H, m, aliphatic CH); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) δ 209.2 (s, 2 C), 205.9 (s), 135.2 (s), 128.3 (d, 2 C), 128.0 (d, 2 C), 127.0 (d), 63.8 (d), and a series of partially resolved peaks in the region 24.2–48.9; mass spectrum, m/e (rel intensity) 326 (M^+, 0.5), 139 (43), 130 (60), 97 (22), 95 (100), 91 (55), 69 (22), 55 (62), 41 (54).

Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.28; H, 8.04.

Michael Reaction of Cyclohexenone (7) with the Keto Ester 23. A solution of 1.15 g (4.89 mmol) of the β-keto ester **23** in 5 mL of MeOH was added to a solution of NaOMe prepared from 36 mg (1.57 mg atom) of Na and 10 mL of MeOH. Then a solution of 448 mg (4.66 mmol) of cyclohexenone (**7**) in 3 mL of MeOH was added and the resulting solution was stirred at 25 °C for 3.5 h and then neutralized by addition of saturated aqueous NH_4Cl. The reaction mixture was partitioned between Et_2O and H_2O, and the organic layer was washed with aqueous NaCl, dried and concentrated. The residual orange liquid (1.42 g) was chromatographed on silica gel with an EtOAc–hexane eluent (1:3 v/v) to separate 312 mg (20%) of early fractions containing stereoisomer **A** of the keto ester **24** as a colorless solid, mp 125–127 °C dec. Recrystallization from cyclohexane separated 147 mg (10%) of the keto ester **24** stereoisomer **A** as colorless prisms: mp 131–133 °C dec; IR (CCl_4), 3580 (OH), 1647, 1615 cm^{-1} (enolic β-keto ester); ^1H NMR ($CDCl_3$) δ 12.28 (1 H, s, OH), 7.0–7.4 (5 H, s, aryl CH), 3.45 (1 H, s, benzylic CH), 3.05 (1 H, br, OH), 0.8–2.0 (18 H, m, aliphatic CH including a t-Bu singlet at 1.52); ^{13}C NMR ($CDCl_3$, multiplicity on off-resonance decoupling) δ 175.8 (s, 2 C), 137.4 (s), 129.5 (d, 2 C), 127.9 (d, 2 C), 126.9 (d), 102.4 (s), 81.0 (s), 69.4 (s), 57.0 (d), 40.8 (t), 37.0 (t), 30.5 (d), 28.2 (q and t, 4 C), 18.8 (t); mass spectrum, m/e (rel intensity) 330 (M^+, 0.6), 274 (100), 256 (60), 238 (22), 213 (44), 198 (46), 183 (28), 165 (40), 160 (25), 118 (50), 97 (32), 91 (42), 90 (26), 57 (88), 43 (29), 41 (64).

Later fractions from the chromatograph contained 624 mg (41%) of stereoisomer **B** of the β-keto ester **24** as a colorless liquid that partially solidified on standing; mp 50–70 °C dec; IR (CCl_4), 3580 (OH), 1640, 1610 cm^{-1} (enolic β-keto ester); ^1H NMR ($CDCl_3$) δ 12.62 (1 H, s, OH), 7.1–7.4 (5 H, m, aryl CH), 3.75 (1 H, s, benzylic CH), 3.03 (1 H, br, OH), 0.6–2.2 (18 H, m, aliphatic CH including a t-Bu singlet at 1.50); ^{13}C NMR ($CDCl_3$, multiplicity on off-resonance decoupling), 175.8 (s, 2 C), 135.8 (s), 129.6 (d, 2 C), 127.4 (d, 2 C), 126.3 (d), 101.6 (s), 80.8 (s), 70.7 (s), 58.5 (d), 41.3 (t), 35.8 (t), 30.7 (d), 28.2 (q and t, 4 C), 19.0 (t); mass spectrum, m/e (rel intensity), 330 (M^+, 0.5), 274 (100), 256 (56), 213 (37), 198 (37), 183 (23), 178 (46), 166 (20), 165 (33), 160 (32), 135 (31), 118 (53), 109 (31), 97 (55), 95 (52), 91 (52), 81 (40), 69 (28), 67 (24), 57 (62), 55 (37), 41 (57), 39 (21).

A solution of 188 mg (0.57 mmol) of the keto ester **24** (isomer **B**) and 12 mg of p-TsOH in PhH was refluxed for 3.5 h, then diluted with Et_2O, and washed successively with aqueous $NaHCO_3$ and with aqueous NaCl. After the organic layer had been dried and concentrated, the residual yellow liquid (144 mg) was chromatographed on silica gel with an EtOAc–hexane eluent (1:2 v/v). The early fractions contained 45 mg (34%) of the **diketone 13b**, which was identified by comparison of NMR spectra and TLC R_f values. Later chromatographic fractions contained 48 mg (37%) of the **ketol 11c**, which was also identified by comparison of NMR spectra and TLC R_f values.

Preparation of the Bromo Ketone 12. A. From the Ketol 11c. A mixture of 3.28 g (14.23 mmol) of the ketol **11c** and 1.50 mL (16 mmol) of PBr_3 in 75 mL of PhH was stirred at 25 °C for 6 h, at which time the mixture formed a yellow solution and consumption of the starting ketol **11c** was complete (TLC analysis). The reaction solution was partitioned between H_2O and Et_2O, and the organic layer was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl and then dried and concentrated. The residual crude bromo ketone **12**, 3.603 g of pale yellow liquid, was chromatographed on silica gel with a hexane–EtOAc eluent (3:1 v/v) to separate 3.37 g (81%) of the bromo ketone **12** as a colorless liquid. Crystallization from cy-

clohexane separated 2.88 g (69%) of the pure bromo ketone **12** as colorless prisms: mp 105–110 °C dec; IR (CCl_4), 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$), δ 7.0–7.6 (5 H, m, aryl CH), 3.97 (1 H, s, benzylic CH), 1.4–3.0 (11 H, m, aliphatic CH); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) δ 204.6 (s), 133.7 (s), 131.1 (d, 2 C), 127.1 (d, 3 C), 69.7 (d), 69.0 (s), 47.4 (t), 46.0 (t), 39.2 (t), 32.2 (d), 30.2 (t), 22.1 (t); mass spectrum, *m/e* (rel intensity) 294 (M^+, 1.4), 292 (M^+, 1.5), 213 (63), 195 (21), 169 (63), 129 (42), 115 (29), 91 (100).

Anal. Calcd for $C_{15}H_{17}BrO$: C, 61.45; H, 5.84; Br, 27.25. Found: C, 61.52; H, 5.85; Br, 27.15.

B. From the Crude Michael Adduct 9b. To a solution prepared from 29.64 g (143.7 mmol) of the keto ester **6b**, the NaOEt from 897 mg (39.0 mg atom) of Na, and 250 mL of EtOH was added a solution of 13.82 g (143.8 mmol) of cyclohexenone (**7**) in 10 mL of EtOH. The orange mixture, which became homogeneous after 30 min, was stirred at 25 °C for 16 h and then worked up as previously described to leave 41.7 g of the crude adduct **9b** or **10b** as a tan liquid that partially solidified on standing. A solution of this crude product and 18.96 g (287 mmol) of 85% KOH in 100 mL of EtOH and 100 mL of H_2O was refluxed for 6 h and then stirred at 25 °C for 16 h. After the resulting brown solution had been acidified with HOAc and refluxed for 1 h, it was cooled and partitioned between Et_2O and H_2O. After the organic layer had been dried and concentrated, the residual brown liquid (26.22 g) was dissolved in 350 mL of $CHCl_3$. A slow stream of HBr gas was passed through the solution for 1 h. Then N_2 was bubbled through the cloudy brown solution for 30 min, after which the solution was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl. The organic layer was dried, concentrated, and filtered through a 7.5 × 0.5 cm column of silica gel with an EtOAc–hexane eluent (1:3 v/v) to separate 24.17 g of brown liquid. This material was chromatographed on silica gel with an EtOAc–hexane eluent (1:3 v/v) to separate 682 mg of early fractions as an unidentified yellow liquid followed by 3.19 g of intermediate fractions as a yellow liquid that partially solidified on standing. These intermediate fractions were rechromatographed on silica gel with an EtOAc–hexane eluent (1:9 v/v) to separate 1.59 g of the crude bromo ketone **15** as a pale yellow solid. Recrystallization from cyclohexane afforded 826 mg (2% overall yield) of the **bromo ketone 15** as colorless needles, mp 133.5–134.5 °C dec. Additional recrystallization raised the decomposition point of the bromo ketone **15** to 136–137 °C dec; IR ($CHCl_3$), 1715 cm^{-1} (C=O); ^1H NMR (300 mHz, $CDCl_3$), δ 7.1–7.4 (5 H, m, aryl CH), 3.70 (1 H, d, J = 5.5 Hz, benzylic CH), 3.25 (2 H, s, CH_2CO), 2.77 (1 H, d of m, J = 12.5 Hz, aliphatic CH), 2.63 (1 H, d of m, J = 12.5 Hz, aliphatic CH), 2.38–2.48 (2 H, m, aliphatic CH), 2.31 (1 H, t of d, J = 12.5 and 5.5 Hz, bridgehead CH), 1.2–1.7 (4 H, m, aliphatic CH); mass spectrum, *m/e* (rel intensity) 294 (M^+, 3), 292 (M^+, 2), 213 (42), 185 (46), 129 (27), 117 (28), 115 (28), 91 (100), 81 (29), 67 (33), 41 (32), 39 (27); ^{13}C NMR ($CDCl_3$, multiplicity on off-resonance decoupling) δ 204.4 (s), 136.1 (s), 129.1 (d, 2 C), 127.7 (d, 2 C), 126.5 (d), 62.5 (s), 59.1 (d), 58.0 (t), 46.6 (t), 44.5 (t), 40.4 (d), 24.9 (t), 21.8 (t). The presence of this isomeric bromo ketone **15** indicates that the crude Michael adduct **8b** contains some of the structurally isomerical adduct **14** or a related cyclic form.

Anal. Calcd for $C_{15}H_{17}BrO$: C, 61.45; H, 5.84; Br, 27.25. Found: C, 61.44; H, 5.87; Br, 27.20.

The final fractions from the original chromatography contained 15.21 g of pale yellow liquid that partially solidified on standing. Trituration with hexane separated 9.76 g of the crude bromo ketone **12**, mp 83–100 °C, which was rechromatographed on silica gel and then recrystallized from cyclohexane to separate 7.24 g of the bromo ketone **12** as colorless prisms, mp 105–109 °C dec. The various mother liquors were rechromatographed and recrystallized to separate an additional 0.75 g of bromo ketone **12** (total yield 7.99 or 19% overall), mp 104.5–109 °C dec.

Preparation of the Malonic Acid Derivatives 31. A. Diester 31a. A literature procedure[12] was used to convert 2.65 g (12.2 mmol) of the bromo ketone **30** (mp 83–84 °C) to 2.45 g (75%) of the keto diester **31a** as a colorless liquid [lit.[12] bp 145–148 °C (15 mm), mp 56.6–57.5 °C] after purification by chromatography on silica gel with an EtOAc–hexane eluent (1:1 v/v). The product was identified with an authentic sample by comparison of IR and ^1H NMR spectra.

B. Monoester 31b. A solution of 1.64 g (6.12 mmol) of the diester **31a** and 325 mg (4.93 mmol) of 85% KOH in 30 mL of MeOH was stirred at 25 °C for 36 h. After the mixture has been concentrated under reduced pressure, it was partitioned between CH_2Cl_2 and aqueous 2 M HCl. The organic layer was dried and concentrated, and the residual semisolid was recrystallized from EtOAc to separate 1.25 g (80% based on the starting ester **31a**) of the ester acid **31b** as colorless needles: mp 153–155 °C; IR (CCl_4), 3620, 3480, 2900–3000 (OH), 1750 (sh), 1735 (sh), 1705 cm^{-1} (ester, acid, and ketone C=O); ^1H NMR ($CDCl_3$) δ 10.41 (1 H, s, OH), 3.73 (3 H, s, OCH_3), 3.30 [1 H, s, $CH(COOR)_2$], 1.0–3.1 (13 H, m, aliphatic CH); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 212.4 (s), 170.5 (s), 167.8 (s), 61.1 (d), 52.4 (q), 48.0 (t), 46.1 (t), 39.2 (s), 36.1 (t), 35.8 (t), 31.0 (t), 30.0 (d), 18.7 (t).

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.44; H, 7.17.

C. Diacid 31c. A solution of 5.36 g (20 mmol) of the diester **31a** and 10.56 g (160 mmol) of 85% KOH in 50 mL of H_2O and 50 mL of EtOH was refluxed for 1 h, acidified to pH 4 with aqueous HCl, and extracted with EtOAc. After the organic layer had been dried and concentrated, the residual solid was recrystallized from a MeOH–EtOAc mixture to separate 3.22 g (67%) of the diacid **31c** as colorless needles: mp 170–171 °C; IR (KBr pellet), 2950 (br, assoc. OH), 1750, 1710, 1670 cm^{-1} (C=O and COOH); ^1H NMR ($CDCl_3$ + CD_3SOCD_3) δ 11.82 (2 H, s, OH), 3.22 (1 H, s, ROOCCHCOOR), 1.0–3.2 (13 H, m, aliphatic CH); ^{13}C NMR ($CDCl_3$ + CD_3SOCD_3, multiplicity in off-resonance decoupling) δ 211.9 (s), 169.0 (narrow d), 168.6 (narrow d), 60.9 (d), 47.7 (t), 45.6 (t), 38.1 (s?), 35.3 (t, 2 C?), 30.5 (t), 29.4 (d), 18.3 (t).

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.04; N, 6.75.

Preparation of the Lactone 34. To a solution of 254 mg (1.0 mmol) of the monoester **31b** in 50 mL of CH_2Cl_2 was added a solution of 0.16 g (1.0 mmol) of Br_2 in 25 mL of CH_2Cl_2. The red solution was stirred at 25 °C for 1 h at which time the Br_2 color was abruptly discharged. After the reaction solution had been washed successively with aqueous $NaHCO_3$ and with aqueous NaCl, it was dried and concentrated. The residual yellow oil was chromatographed on silica gel with an EtOAc–hexane eluent to separate 221 mg (88%) of the crude ester lactone **32a** (a mixture of stereoisomers) as a colorless liquid: IR (CCl_4) 1800 (γ-lactone, C=O), 1740 (ester C=O), 1725 cm^{-1} (C=O); ^1H NMR (CCl_4), δ 4.37 (1 H, s, OCHCO), 4.03 (1 H, br, ROOCCHCOOR), 3.72 (3 H, s, OCH_3), 0.6–3.4 (11 H, m, aliphatic CH); mass spectrum, *m/e* (rel intensity) 252 (M^+, 35), 220 (33), 180 (31), 178 (36), 164 (31), 153 (49), 152 (70), 151 (35), 149 (74), 135 (34), 134 (59), 121 (48), 119 (51), 108 (37), 107 (100), 106 (78), 93 (49), 91 (40), 82 (45), 79 (51), 67 (31), 55 (30), 41 (54), 39 (46).

A solution of 1.82 g (7.22 mmol) of the crude ester lactone **32a** and 1.62 g (24.6 mmol) of 85% KOH in 25 mL of MeOH and 25 mL of H_2O was refluxed for 1 h and then cooled, acidified with aqueous HCl, and extracted with EtOAc. After the organic extract had been dried and concentrated, the residual oil crystallized on standing. Recrystallization from EtOAc separated 0.79 g (44%) of the **diacid 33** as colorless needles: mp 146–148 °C; IR (KBr pellet), 3350, 2950 (br, assoc. OH), 1740, 1700 cm^{-1} (carboxyl and ketone C=O); ^1H NMR ($CDCl_3$ + CD_3SOCD_3), δ 10.7 (br, OH), 4.50 (1 H, s, OCHCO), 3.63 (1 H, s, ROOCCHCOOR), 1.0–2.8 (11 H, m, aliphatic CH).

Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.16; H, 6.33.

A mixture of 256 mg (1.00 mmol) of the hydroxy diacid **33**, 21 mg of *p*-TsOH, and 100 mL of PhH was refluxed for 15 h with continuous removal of H_2O. The resulting PhH solution was concentrated, and the residual liquid was chromatographed on silica gel with an Et_2O–cyclohexane eluent (6:4 v/v) to separate in the later fractions the crude crystalline lactone **34**. Recrystallization from a $CHCl_3$–cyclohexane mixture separated 150 mg (77%) of the lactone **34** as colorless needles, mp 94–95 °C; IR ($CHCl_3$), 1795 (γ-lactone C=O), 1725 cm^{-1} (C=O); ^1H NMR ($CDCl_3$), δ 4.23 (1 H, s, OCHCO), 2.3–3.1 (4 H, m, CH_2CO), 1.0–2.2

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(9 H, m, aliphatic CH); mass spectrum, m/e (rel intensity) 194 (M^+, 10), 94 (100), 79 (29), 41 (26), 39 (24).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.95; H, 6.99.

A second component, separated in the early fractions from the chromatography, was isolated as 10 mg of liquid with the following IR absorption ($CHCl_3$): 1805 (lactone C=O), 1725 cm^{-1} (C=O). This material appears to be either a second stereoisomer of the lactone **34** or a structural isomer.

A solution of 2.40 g (10 mmol) of the diacid **31c** in 300 mL of anhydrous Et_2O was treated with 1.60 g (10 mmol) of Br_2. The red Br_2 color was discharged within 5 s. After the resulting solution had been stirred at 25 °C for 30 min, it was extracted with aqueous $NaHCO_3$. The aqueous phase was cooled to 0 °C and then acidified to pH 5–6 with aqueous HCl. This mixture was extracted with EtOAc, and the EtOAc extract was dried and concentrated. The residual liquid, which crystallized on standing, was chromatographed on silica gel with a $CHCl_3$–HCOOH eluent. The white solid separated by chromatography was recrystallized from $CHCl_3$ to separate the crude acid lactone **32b** as colorless needles: mp 161–163 °C; IR ($CHCl_3$), 1795 (lactone C=O), 1725 cm^{-1} (carboxyl and ketone C=O); ^1H NMR ($CDCl_3$–Me_2SO-d_6) δ 10.93 (1 H, s, OH), 4.60 (s), 4.18 (s, together 1 H, OCHCO of stereoisomers), 3.37 (s), 3.20 (s, together 1 H, ROOCCHCOOR of stereoisomers), 0.8–3.0 (11 H, m, aliphatic CH).

In another comparable experiment starting with 2.40 g (10 mmol) of the diacid **31c**, the product isolated after initial treatment with aqueous $NaHCO_3$ was 2.23 g of a solid that appeared to be an intermediate α-bromo ketone diacid. This material was redissolved in 50 mL of saturated aqueous $NaHCO_3$, and the solution was stirred at 25 °C for 3 h. After the material had been acidified, extracted with EtOAc, isolated, and recrystallized, 1.72 g (74%) of the crude acid lactone **32b** was isolated, mp 160–163 °C.

Trimethylsilyl Enol Ethers 26-28. A previously described[2a] procedure was used to convert the bromo ketone **30** to the methoxy ketone **25** as a colorless liquid: bp 90–92 °C (1 mm); n^{25}_D 1.4885 (lit.[2a] n^{25}_D 1.4887). A solution of 3.66 g (22 mmol) of the methoxy ketone **25** and 8.89 g (88 mmol) of Et_3N in 50 mL of DMF was treated with 4.75 g (44 mmol) of Me_3SiCl, and the resulting solution was heated to 70–90 °C under an N_2 atmosphere for 16 h. The reaction mixture was cooled, diluted with 50 mL of pentane, washed with aqueous $NaHCO_3$, dried, and concentrated. Distillation of the residual liquid (4.83 g) separated 4.71 g (89%) of a mixture of approximately equal amounts (NMR analysis) of enol ethers **26** and **27** as a colorless liquid: bp 95–98 °C (1.0 mm); n^{25}_D 1.4389; IR (CCl_4) 1665 cm^{-1} (enol C=C); ^1H NMR (CCl_4) δ 4.4–4.8 (1 H, 2 br peaks, vinyl CH of enol ether), 3.10 (3 H, 2 partially resolved singlets, OCH_3), 1.1–2.8 (11 H, m, aliphatic CH), 0.17 (9 H, 2 partially resolved singlets, Me_3Si); mass spectrum, m/e (rel intensity) 240 (M^+, 10), 198 (17), 196 (100), 181 (22), 73 (28). Our efforts to separate this mixture of enol ethers have thus far been unsuccessful.

The enol ether **28**, a colorless liquid, bp 74–75 °C (20 mm), n^{25}_D 1.4455 (lit.[13] n^{25}_D 1.4451), was used to study various alkylation procedures. Following a modified literature procedure,[4a] a solution of 5.48 g (40 mmol) of t-BuBr in 50 mL of CH_2Cl_2 and a solution of 3.40 g (20 mmol) of the enol ether **28** in 50 mL of CH_2Cl_2 were added consecutively to a cold (−78 °C) solution of 3.80 g (20 mmol) of $TiCl_4$ in 100 mL of CH_2Cl_2. After the resulting dark colored solution had been stirred at −78 °C under an N_2 atmosphere for 2 h, it was warmed to 0 °C and quenched with 100 mL of H_2O. The resulting organic layer was washed with aqueous $NaHCO_3$ and with H_2O and then dried and concentrated. Distillation separated 1.08 g (35%) of the ketone **29a** as a colorless liquid: bp 75 °C (2 mm); n^{25}_D 1.4555 [lit.[4b] bp 62.5 °C (4 mm), n^{25}_D 1.4579]; IR (CCl_4), 1714 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.2–2.5 (9 H, m, aliphatic CH), 0.97 (9 H, s, t-Bu); mass spectrum, m/e (rel intensity) 154 (M^+, 3), 98 (100), 83 (24), 69 (25), 57 (27), 55 (28), 41 (48), 39 (22).

Again following a literature procedure,[5a] a cold (−78 °C) solution of 3.80 g (20 mmol) of $TiCl_4$ in 15 mL of CH_2Cl_2 was added to a cold (−78 °C) solution of 3.50 g (20 mmol) of the enol ether **28** and 4.50 g (20.9 mmol) of 1-bromoadamantane in 60 mL of CH_2Cl_2. After the dark colored reaction solution had been stirred at −78 °C for 1 h, it was warmed to 0 °C and subjected to the usual isolation procedure. Recrystallization of the residual solid from MeOH separated 3.48 g (78%) of the ketone **29b** as colorless needles: mp 84–85 °C (lit.[5a] mp 86 °C); IR (CCl_4), 1712 cm^{-1} (C=O); ^1H NMR ($CDCl_3$), δ 1.0–3.0 (m, aliphatic CH); mass spectrum, m/e (rel intensity) 232 (M^+, 5), 136 (12), 135 (100), 93 (12), 79 (13), 41 (13). So that an alternative procedure could be investigated,[5b] a solution of 4.30 g (20 mmol) of 1-bromoadamantane in 50 mL of CH_3NO_2 was treated with 4.15 g (20 mmol) of $AgClO_4$. After the resulting mixture had been cooled to 0 °C and stirred for 1 h, a solution of 4.08 g (24 mmol) of the enol ether **28** in 15 mL of CH_3NO_2 was added and the resulting mixture was stirred for 3 h at 0 °C. The usual isolation procedure separated a brown liquid, which failed to give a crystalline material and contained (TLC analysis) a complex mixture of products.

Registry No. 6a, 5435-91-6; **6b**, 718-08-1; **6c**, 81408-08-4; **7**, 930-68-7; **8a**, 81408-09-5; **8b**, 81423-12-3; **9b**, 81408-10-8; **10b**, 81408-11-9; **11c**, 81408-12-0; **12**, 81408-13-1; **13a**, 81408-14-2; **13b**, 81408-15-3; **14**, 81408-16-4; **15**, 81408-17-5; **16**, 81408-18-6; 17, 1070-83-3; **18**, 7065-46-5; **21**, 2033-24-1; **22**, 66696-84-2; **23**, 66697-03-8; **24** (isomer 1), 81408-19-7; **24** (isomer 2), 81408-20-0; **25**, 66921-79-7; **26**, 81408-21-1; **27**, 81408-22-2; **28**, 6651-36-1; **29a**, 1728-46-7; **29b**, 41031-34-9; **30**, 66077-98-3; **31a**, 73274-42-7; **31b**, 81408-23-3; **31c**, 81408-24-4; α-Br-**31c**, 81408-25-5; **32a**, 81408-26-6; **32b**, 81408-27-7; **33**, 81408-28-8; **34**, 81408-29-9; ethyl acetoacetate, 141-97-9; diethyl malonate, 105-53-3; monoethyl malonate, 1071-46-1; phenylacetyl chloride, 103-80-0; 1-bromoadamantane, 768-90-1.

(13) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.