give 82.2 g of crude **5** as an oil. A 80.9-g portion was distilled rapidly through a short-path apparatus to give 75.5 g of epoxide **5** (92%) as a colorless oil: bp 108–110 °C (0.08 mm); IR (film) 1260 and 1280 cm^{-1} (epoxide); NMR ($CDCl_3$) δ 2.58 (s, 2, methylene), 1.25 (s, 3, C_2-methyl), and 0.88 (d, 12, J = 6 Hz, methyls). Anal. Calcd for $C_{19}H_{38}O$: C, 80.78; H, 13.56. Found: C, 81.09; H, 13.49.

7-Hydroxy-7,11,15,19-tetramethyleicosane-2,4-dione (6). To a suspension of sodium hydride (30.0 g of 57% dispersion, 0.72 mol, washed free of oil with hexane) in THF (500 mL) at 0 °C was added dropwise over 30 min a solution of 2,4-pentanedione (71.0 g, 0.71 mol) in THF (150 mL). After stirring for 20 min at 0 °C, butyllithium (260 mL of 2.5 M solution in hexane, 0.65 mol) was added over 30 min at 0–5 °C. The epoxide **5** (40.0 g, 0.142 mol) in THF (50 mL) was added in one portion and the solution was stirred 17.5 h at room temperature. The solution was cooled to 0 °C and poured into a vigorously stirred mixture of ice (2 kg) and concentrated HCl (114 mL). Saturated ammonium chloride (100 mL) was added and the product was isolated with ether to give a crude oil which was further evaporated at 30–35 °C (0.3 mm) for 2.5 h to give 73.5 g of crude diketone **6** as an oil. A 0.36-g sample was purified for analysis by preparative TLC to give 0.20 g of pure diketone **6** (75%) as a light-yellow oil: IR (film) 3460 (hydroxyl), 1710 and 1620 cm^{-1} (ketone and enol); UV max (2-propanol) 274 nm (ϵ 5265); NMR ($CDCl_3$) δ 5.51 (s, C_3H, enol form), 4.30 (br, 1, hydroxy), 2.81 (m, C_3H, keto form), 2.20 (s, 3, C_1 methyl), 2.02 (s, 3, C_7 methyl), 0.86 (d, 12, J = 6 Hz, methyls). Anal. Calcd for $C_{24}H_{46}O_3$: C, 75.34; H, 12.12. Found: C, 75.06; H, 12.03.

Dimethyl 2-Hydroxy-4-methyl-6-(3-hydroxy-3,7,11,15-tetramethylhexadecanyl)benzene-1,3-dicarboxylate (7). To a solution of the crude diketone **6** (72.5 g) and dimethyl acetonedicarboxylate (29.6 g, 0.17 mol) in methanol (190 mL) at 0 °C was added a solution of sodium methoxide in methanol (90 mL) (from 2.44 g sodium (0.106 mol)). The solution was stirred 44 h at room temperature and concentrated on a rotary evaporator to remove ca. 100 mL of methanol. The residue was poured onto ice (500 g) and 20% HCl (45 mL) and the product was isolated as usual with ether to give 91.7 g of crude **7** as an orange oil. A 90.2 g-portion of the oil was redissolved in ether and washed free of excess dimethyl acetonedicarboxylate with 20% potassium carbonate, and then washed with brine, dried, and concentrated to give 83.1 g of crude **7**. Chromatography on 2.45 kg of silica gel eluting with 20–30% ether in hexane gave 30.83 g (43% yield from **5**) of **7** as a colorless oil: IR ($CHCl_3$) 3605 (hydroxyl), 1726 and 1660 cm^{-1} (ester C=O); UV max (2-propanol) 214 (ϵ 24 230), 251 (ϵ 9900), and 314 nm (ϵ 5200); NMR ($CDCl_3$) δ 11.67 (s, 1, phenol OH), 6.56 (s, 1, aromatic), 3.89 (s, 6, $COOCH_3$), 2.67, and 1.66 (AA'BB', 4, J = 8 Hz, C_1 and C_2 methylenes), 2.42 (s, 3, methyl, and 0.83 (d, 12, J = 6 Hz, methyls). Anal. Calcd for $C_{31}H_{52}O_6$: C, 71.50; H, 10.07. Found: C, 71.51; H, 9.93.

2,3,6-Trimethyl-5-(3-hydroxy-3,7,11,15-tetramethylhexadecanyl)phenol (8). To a solution of diester **7** (5.17 g, 9.93 mmol) in xylene (25 mL) at 10 °C was added sodium dihydrobis(2-methoxyethoxy)aluminate (20 mL of a 70% solution in benzene, Red-Al (69.2 mmol)) over 10 min with occasional cooling to keep the temperature at 10 °C. After stirring 10 min, the solution was heated to reflux for 1.5 h, cooled to 10 °C, and poured cautiously into cold 20% H_2SO_4 (100 mL). The product was isolated as usual with ether to give 4.29 g of crude **8** which was chromatographed on silica gel, eluting with ether in petroleum ether to give 3.19 g of **8** (74%) as a colorless oil: IR ($CHCl_3$) 3610 cm^{-1} (hydroxyl); UV max (2-propanol) 204 (ϵ 46 750) and 224 nm (ϵ 9335); NMR ($CDCl_3$) δ 6.52 (s, 1, aromatic), 4.85 (br s, 1, phenol OH), 2.54 and 1.67 (AA'BB', 4, J = 8 Hz, C_1 and C_2 methylene), 2.14, 2.11, and 2.07 (3 s, 9, aromatic methyls), 1.18 (s, 3, C_3-methyl), and 0.81 (d, 12, J = 6 Hz, methyls). Anal. Calcd for $C_{29}H_{52}O_2$: C, 80.49; H, 12.11. Found: C, 80.40; H, 12.42.

Fremy's Salt Oxidation of 8 with Varying Amounts of Tricaprylylmethylammonium Chloride (10) (Table I). A solution of Fremy's salt was prepared by dissolving 8.5 g of the sodium carbonate slurry[9b] in 52 mL of 15% sodium carbonate followed by adding 0.5 g of solid sodium carbonate. The concentration of the solution was determined by measuring the absorbance at 440 nm where pure Fremy's salt has ϵ 14.5.[9b] The solution of Fremy's salt, phenol **8**, ammonium salt **10**, and 2 mL of benzene were combined as indicated in Table I and the reaction was followed by TLC.

Tocopherylquinone (9). To a 1.6 g-portion of the sodium carbonate slurry of Fremy's salt was added 10 mL of 15% sodium carbonate and a solution of 0.29 g (ca. 0.72 mmol) of tricaprylylmethylammonium chloride (**10**) in benzene (4 mL). The phenol **8** (0.30 g, 0.69 mmol) in benzene (8 mL) was added and the mixture was stirred for 2.5 h. The mixture was poured into water (5 mL), extracted with petroleum ether, washed twice with water (10 mL), dried (Na_2SO_4), and concentrated to give the crude quinone **9**. Chromatography on 7.0 g of silica gel, eluting with ether–petroleum ether, gave 0.2 g of oily quinone **9** (93% yield, corrected for UV assay): UV max (2-propanol) 268 nm (ϵ 15 340) (lit.[15] for crystalline **9**: UV max (ethanol) 268 nm (ϵ 17 816)); IR ($CHCl_3$) 1640 cm^{-1}; NMR ($CDCl_3$) δ 2.49 (m, 2, C_1 methylene), 1.98 and 1.95 (3 s, 9, quinone methyls), 1.69 (br s, 1, hydroxyl), 1.18 (s, 3, C_3 methyl), and 0.80 (d, 12, J = 6 Hz, methyls).

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Registry No. **4**, 502-69-2; **5**, 69371-89-7; **6**, 69371-90-0; **7**, 69371-88-6; **8**, 69371-91-1; **9**, 72657-56-8; 2,4-pentanedione, 123-54-6; dimethyl acetonedicarboxylate, 1830-54-2.

Syntheses of 10-(Carboxymethyl)-*trans*-decal-2-one

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10-(Carboxymethyl)-*trans*-decal-2-one (**2**) has been prepared by two routes. The first involves homologation of compounds derived from the known 10-(carboethoxy)-*trans*-decal-2-one (**5**) via cyanide displacement on 10-tosyloxymethyl or 10-mesyloxymethyl derivatives of *trans*-decal-2-one. The second is based on Robinson annulation of 2-(carbomethoxymethyl)cyclohexanone (**6**), which affords a low yield of lactone **20**. Hydrogenation of enone acid **21** or its anion **22** leads exclusively to 10-(carboxymethyl)-*cis*-decal-2-one (**24**). Hydrogenation of enone ester **18** also leads to a preponderance of cis ring fusion, but affords some of the methyl ester (**19**) of **2**. The most efficient synthesis of **2** proceeds from **5** via **16** in 38% overall yield.

As part of a study of proton abstraction α to carbonyl groups and derived iminium ions,[1,2] we required decalin-carboxylic acids **1** and **2** so that we could assess the effective concentration[3] of carboxylate anions in processes

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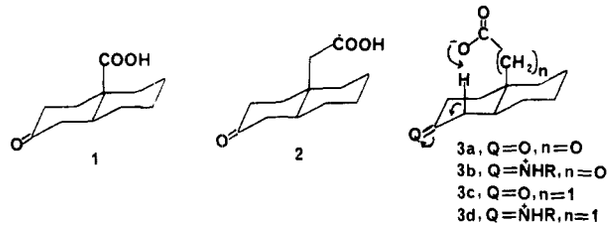
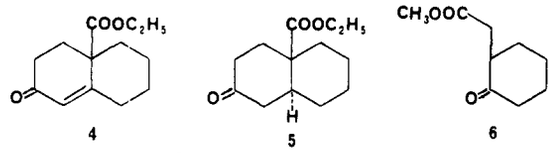


3a–d by comparison with appropriate intermolecular analogues.

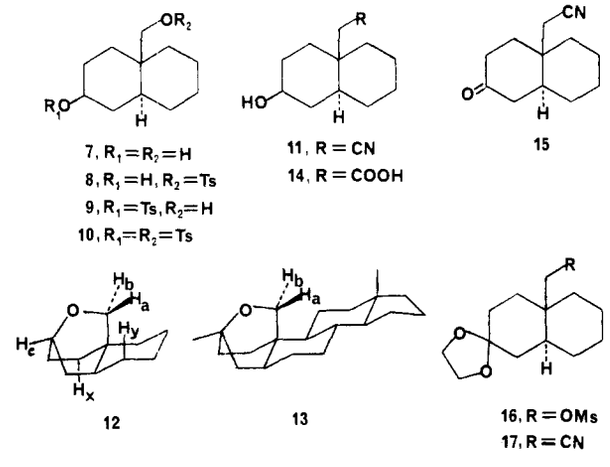
The known acid **1** was prepared by a slight modification of the previously published procedure of Dreiding and Tomasewski,[4] involving hydrogenation of enone ester **4** to



trans keto ester **5**.[5] Synthesis of **2** is described in this paper. Two basic approaches were used: homologation of the angular substituent of compounds derived from **5** and Robinson annulation of 2-(carbomethoxymethyl)-cyclohexanone (**6**).[6]

Arndt–Eistert homologation of **1** was attempted first. Hindered acid chlorides have been reported to be resistant to reaction with diazomethane,[7] but there has been at least one successful conversion to a diazo ketone of an acid chloride with a fully substituted α carbon.[8] In a few attempts, however, we were unable to isolate a diazo ketone from the reaction of the acid chloride derived from **1** with diazomethane.

Attention was next turned to displacement by a carbon nucleophile of a derivative of the 10-hydroxymethyl group of diol **7**, a known reduction product of keto ester **5**.[9] This



approach was encouraged by Mander's report[10] of efficient displacement of the tosylate of 10-(hydroxymethyl)-*trans*-decalin with cyanide ion and by the fact that it is possible to effect highly selective tosylation of primary hydroxyl groups in the presence of secondary ones.[11] Unfortunately, such selectivity was not found with the neopentyl hydroxyl group of **7**. Treatment of **7** with 1 equiv of *p*-toluenesulfonyl chloride, at a variety of concentrations and temperatures ranging from ambient to −78 °C, afforded after separation by high-performance LC a maximum of 32% of the desired monotosylate **8**, plus 27% of the 2β-monotosylate **9**, 19% of ditosylate **10**, and 19% of recovered **7**. The overall efficiency of preparation of **8** was improved by reconversion of **9** and **10** to **7** by sodium in ammonia reduction.[12]

According to the procedure of Mosher et al. for effecting displacement on neopentyl tosylate without rearrangement,[13] **8** was treated with sodium cyanide in hexamethylphosphoramide at 130–140 °C for 36 h to afford 64% of the desired hydroxy nitrile **11**. This reaction also produced 30% of intramolecular displacement product, tricyclic ether **12**, a structure suggested earlier by Dreiding and Tomasewski,[4] undoubtedly correctly, for an uncharacterized oil obtained from a different reaction.

Structure **12** was confirmed by the distinctive ^{1}H NMR signals of H_a and H_b, which are consistent with those of the analogous protons in steroidal ether **13**.[14] The protons on carbons next to oxygen in **12** appear as follows: H_c is a multiplet at δ 3.69; H_b is a doublet at δ 3.33 (J = 8.8 Hz); and H_a is a doublet of doublets at δ 4.15 (J = 8.8 and 2.4 Hz). The 2.4-Hz splitting of H_a is due to long-range "W" coupling to H_x,[14] and the deshielding of H_a is caused by steric compression[15,16] with H_y. The only difference between the H_a and H_b signals of **12** and **13** is a relative deshielding of H_b in **13** (δ 3.74), presumably caused by steric compression with the C11β proton of **13**.

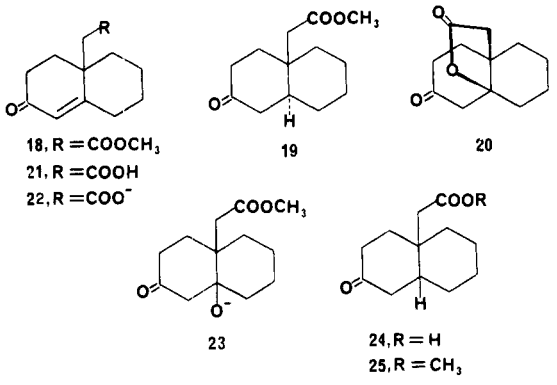
Conversion of **11** to **2** was first attempted by hydrolysis to hydroxy acid **14** followed by Jones' oxidation. Surprisingly, however, neither basic nor acidic hydrolysis of **11** gave a good yield of **14**, for reasons which remain obscure.[17] The alternative sequence of initial oxidation to keto nitrile **15** followed by hydrolysis to **2** worked better, affording the desired keto acid, mp 117.5–118.5 °C. Although the yield of crude **2** from this hydrolysis was excellent, as judged by the IR spectrum and TLC, the keto acid could be obtained crystalline in 64% yield only with difficulty. Interestingly, the IR spectrum of **2** as a solid (KBr pellet), but not in solution ($CHCl_3$), shows a carbonyl stretching vibration at an unusually low frequency (1640 cm^{-1}), presumably a consequence of hydrogen bonding.[18]

In view of the low yield of the desired tosylate **8** and the formation of byproduct **12** in its reaction with cyanide ion,

(1) Review: T. A. Spencer, "Bioorganic Chemistry", Vol. 1, E. E. van Tamelen, Ed., Academic Press, New York, 1977, Chapter 13, p 313.
(2) H. E. Ferran, Jr., R. D. Roberts, J. N. Jacob, and T. A. Spencer, *J. Chem. Soc., Chem. Commun.*, 49 (1978).
(3) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, 1969, p 10.
(4) A. S. Dreiding and A. J. Tomasewski, *J. Am. Chem. Soc.*, **77**, 411 (1955).
(5) The yield of **5** from **4** is improved by using ethyl acetate as the solvent for the hydrogenation (J. A. Nelson and G. C. Lamb, unpublished results in this laboratory; cf. W. L. Meyer, R. A. Manning, E. Schindler, R. S. Schroeder, and D. C. Shew, *J. Org. Chem.*, **41**, 1005 (1976)).
(6) E. R. DeWaard, R. Neeter, U. K. Pandit, and H. O. Huisman, *Recl. Trav. Chim. Pays-Bas*, **87**, 572 (1968).
(7) W. E. Bachmann and W. S. Struve, *Org. React.*, **1**, 45 (1942).
(8) C. R. Engel and G. Just, *Can. J. Chem.*, **33**, 1515 (1955).
(9) A. S. Hussey, H. P. Liao, and R. H. Baker, *J. Am. Chem. Soc.*, **75**, 4727 (1953). It is worth noting that the stereochemistry of **7** is incorrectly assigned in this reference; cf. A. S. Dreiding and A. J. Tomasewski, *ibid.*, **77**, 168 (1955), and L. S. Minckler, A. S. Hussey, and R. H. Baker, *ibid.*, **78**, 1009 (1956).
(10) L. N. Mander, R. H. Prager, and J. V. Turner, *Aust. J. Chem.*, **27**, 2645 (1974).
(11) W. S. Johnson, J. C. Collins, Jr., R. Pappo, M. B. Rubin, P. J. Kropp, W. F. Johns, J. E. Pike, and W. Bartmann, *J. Am. Chem. Soc.*, **85**, 1409 (1963).
(12) D. B. Denney and B. Goldstein, *J. Org. Chem.*, **21**, 479 (1956).
(13) B. Stephenson, G. Solladié, and H. S. Mosher, *J. Am. Chem. Soc.*, **94**, 4184 (1972).
(14) A. Guzmán, E. Diáz, and P. Crabbé, *J. Chem. Soc., Chem. Commun.*, 1449 (1969).
(15) W. Nagata, T. Terasawa, and K. Tori, *J. Am. Chem. Soc.*, **86**, 3746 (1964).
(16) B. V. Cheney, *J. Am. Chem. Soc.*, **90**, 5386 (1968).
(17) It is a curious fact that basic hydrolysis of either **11** or cyano ketal **17** is much slower than that of cyano ketone **15**.
(18) The displacement of 70 cm^{-1} for the C–O stretch in **2** vs. **15** (1710 cm^{-1}) indicates a strong hydrogen bond (K. Nakanishi, "Infrared Absorption Spectroscopy-Practical", Holden-Day, San Francisco, 1962, p 42). A highly favorable intramolecular hydrogen bond can form if the carbonyl-bearing ring of **2** adopts a twist-boat conformation.

an alternate homologation was pursued via ketal mesylate **16**, which had previously been prepared from **5** by successive ketalization, reduction, and mesylation.[4] Reaction of **16** with cyanide under the same conditions used with **8** proceeded smoothly to afford ketal nitrile **17** in 95% yield. Hydrolysis of the protecting group then afforded the familiar keto nitrile **15** quantitatively.

Since both of these homologation routes to **2** involved several steps, a more direct route was sought through Robinson annulation of **6**. If the normal annulation product **18** could be obtained, it was anticipated, incorrectly as it turned out, that hydrogenation would lead to **19**, and hence to **2**, just as hydrogenation of **4** yields **5**.[4,5]



Reaction of **6** with methyl vinyl ketone (MVK) under a variety of conditions produced, not unexpectedly, a complex mixture. The reaction product obtained using essentially the conditions of Ross and Levine[19] (**6**:MVK = 1.6:1) was distilled to afford an oil from which precipitated ca. 15% of lactone **20**, mp 133–134 °C. In solution, **20** is in equilibrium with its β elimination product, enone acid **21**,[20] a fact which makes isolation of **20** by chromatography impractical. In base, **20** is converted completely to carboxylate anion **22**.[20] Formation of **20** from **6** and MVK could occur either through ring closure of putative Robinson annulation intermediate **23**[21] or via closure of **21** formed by reaction of **18** with hydroxide ion produced in the reaction.[22]

Direct hydrogenation of anion **22** or the **20** $\rightleftarrows$ **21** mixture using palladium on carbon as catalyst led exclusively to a keto acid, mp 133.5–135 °C, isomeric with **2**, assumed to be the cis-fused **24**. This result is perhaps not too surprising, since the carboxyl or, especially, the carboxylate group might direct the stereochemistry of hydrogenation through coordination to the catalyst.[23]

Accordingly, attention was returned to hydrogenation of enone ester **18**. Preparation of **18** was achieved in 81% yield by converting lactone **20** to enone carboxylate **22** in methanolic sodium methoxide, neutralizing to form free acid **21**, and trapping **21** with diazomethane before it reformed **20**. This procedure worked much better than alkylation of **22** with methyl iodide.[24]

Hydrogenation of **18** using palladium on carbon in ethyl acetate gave a mixture of saturated keto esters which was separated by liquid chromatography to afford 25% of trans-fused **19** and 51% of cis-fused **25**. Hydrolysis to **2** served to identify **19**, and **25** was obtained when cis-keto acid **24** was treated with diazomethane.

Numerous other hydrogenation catalysts and solvents were tried (see Experimental Section) in the hope of finding conditions which would lead selectively to the trans isomer **19**, but the results were disappointing. Only Wilkinson's catalyst[25] gave **19** as the major isomer, and hydrogenation using this catalyst was extremely slow. Enone ester **4** is obviously not a good model for predicting the stereochemistry of hydrogenation of **18**, whose tendency to give cis product is reminiscent of other octalones with sp^3-hydridized angular substituents.[26]

The most efficient synthesis of **2** is clearly via ketal mesylate **16**. The overall yield of crystalline **2** from **5** via **16** is 38%, based on the use of isolated, purified intermediates at each stage in prior[4] and present work.

Experimental Section

Melting points were determined in a Thomas-Hoover apparatus in unsealed capillaries and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 137, 257, or 599 spectrophotometer. IR spectra were taken as KBr pellets for solids, or as neat liquids on NaCl plates. Ultraviolet (UV) spectra were recorded on a Unicam SP800B spectrophotometer or on a Varian Cary 219 spectrophotometer in 1-cm quartz cuvettes. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ solution on a Perkin-Elmer R-24 instrument (60 MHz ^1H) or on a JEOL FX-60Q multinuclear Fourier transform NMR spectrometer (60 MHz ^1H and 15 MHz ^{13}C). Chemical shifts are reported in parts per million downfield from Me_4Si. Low-resolution mass spectra were determined with the assistance of D. Deuring, C. Hill, or M. Killoran on a Finnigan Model 4000 gas chromatograph–mass spectrometer. Preparative thin-layer chromatography (TLC) was performed on 20 × 20 cm plates coated with 1.45 mm thick layers of silica gel $PF_{(254+366)}$ (Brinkmann Instruments Inc., Westbury, NY). UV light was used to visualize TLC plates. Qualitative TLC plates were coated with 0.25 mm thick layers of silica gel $PF_{(254+366)}$ and were sprayed with a 5% isopropyl alcohol solution of phosphomolybdic acid (Eastman Kodak) and heated briefly at 110 °C. Preparative high-performance liquid chromatography (LC) was carried out on a Waters Associates liquid chromatograph Model 6000-A. Analytical LC was carried out on a Perkin-Elmer Series 3 liquid chromatograph using a reverse-phase ODS-CH-Sil-X-1 column. High-performance low-pressure chromatography was carried out on an apparatus assembled by Mr. P. D. Kutzenco and Dr. G. W. Gribble of the type developed by Dr. A. I. Meyers at Colorado State University. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. The term "normal workup" means that the organic extracts were washed with saturated aqueous sodium chloride solution, dried over $MgSO_4$, and concentrated under reduced pressure.

Tosylation of 10β-(Hydroxymethyl)-*trans*-decal-2β-ol (7). Keto ester **5** was prepared according to a slight modification[5] of the method of Dreiding and Tomasewski.[4] Reduction of **5** to diol **7**, mp 141–142 °C, was effected with lithium aluminum hydride.[9] To a solution of 3.73 g (0.020 mol) of **7** in 15 mL of dry pyridine (distilled from barium oxide) at 0 °C was added 3.83 g (0.020 mol) of *p*-toluenesulfonyl chloride (recrystallized from hexane). The reaction was stirred at 4 °C overnight with protection from moisture. After the addition of 3 mL of ethyl acetate and stirring at 0 °C for 5 min, 10 mL of 5% $NaHCO_3$ solution was added. After 10 min, the reaction mixture was diluted to a volume of 50 mL with 5% $NaHCO_3$ solution and extracted with ethyl acetate (3 × 50 mL). Normal workup afforded 7.79 g of clear oil. Separation by LC (ethyl acetate) afforded (in order of elution) 1.53

(19) N. C. Ross and R. Levine, *J. Org. Chem.*, **29**, 2341 (1964).
(20) Catalysis of the interconversions of **20** with **21** and **22** by general acids and bases and via iminium ion formation is being studied in this laboratory by B. J. Mayer.
(21) T. A. Spencer, K. K. Schmiegel, and K. L. Williamson, *J. Am. Chem. Soc.*, **85**, 3785 (1963).
(22) There was invariably isolated from annulations of **6** some 2-(carboxymethyl)cyclohexanone, presumably produced by reaction of **6** with hydroxide ion. In practice, in order to promote formation of **20** (for example, via **18** → **21** → **20**), the whole annulation mixture was saponified before workup (see Experimental Section).
(23) H. W. Thompson and R. E. Naipawer, *J. Am. Chem. Soc.*, **95**, 6379 (1973).
(24) F. S. Alvarez and A. N. Watl, *J. Org. Chem.*, **33**, 2143 (1968).
(25) Hydrogenation of α,β-unsaturated ketones using Wilkinson's catalyst is described by C. Djerassi and J. Gutzwiller, *J. Am. Chem. Soc.*, **88**, 4537 (1966).
(26) R. L. Augustine, "Catalytic Hydrogenation", Marcel Dekker, New York, 1965, p 61.

g (16%) of ditosylate **10**, 1.82 g (27%) of 2β-tosylate **9**, 2.14 g (32%) of 10β-tosylate **8**, and 0.71 g (19%) of **7** as gummy solids. Analytical samples of the three tosylates were prepared by recrystallization from ether.

Pure **10** has mp 136–137 °C; IR 1600 cm^{-1}; NMR δ 1.0–2.2 (m, 15), 2.45 (s, 6), 4.06 (s, 2), 4.5 (m, 1), and 7.54 (q, 8). Anal. Calcd for $C_{25}H_{32}O_6S_2$: C, 60.95; H, 6.55. Found: C, 61.14; H, 6.50.

Pure **9** has mp 117–118 °C; IR 3400–3300 and 1590 cm^{-1}; NMR δ 1.0–2.2 (m, 15), 2.44 (s, 3), 3.74 (s, 2), 4.50 (m, 1), and 7.56 (q, 4). Anal. Calcd for $C_{18}H_{26}O_4S$: C, 63.89; H, 7.74. Found: C, 63.88; H, 7.63.

Pure **8** has mp 116.5–118 °C; IR 3500, 3400, and 1590 cm^{-1}; NMR δ 1.0–2.2 (m, 15), 2.45 (s, 3), 3.61 (m, 1), 4.14 (s, 2), and 7.56 (q, 4, J = 8 Hz). Anal. Calcd for $C_{18}H_{26}O_4S$: C, 63.89; H, 7.74. Found: C, 63.78; H, 7.75.

Mixtures of unpurified **9** and **10** were reconverted to diol **7** in ca. 50% yield (after separation by LC using ethyl acetate) by reduction with sodium in ammonia–dioxane following the procedure of Denney and Goldstein.[12]

10β-(Cyanomethyl)-*trans*-decal-2β-ol (11) and Tricyclo[6.2.2.0$^{1,6\text{-}trans}$]-10-oxadodecane (12). According to a procedure of Mosher et al.,[13] 1.26 g (3.73 mmol) of **8** was dissolved in 20 mL of freshly distilled (but not dried) hexamethylphosphoramide, and 0.55 g (11.5 mmol) of sodium cyanide (Baker) was added in three portions over a period of 60 min. The reaction was stirred for 36 h at 130–40 °C. The reaction was followed by TLC using 1:1 ethyl acetate:hexane until all of **8** had disappeared. The reaction was allowed to come to room temperature, 40 mL of ice water was added, and the reaction mixture was extracted with benzene (3 × 50 mL). Normal workup afforded 0.98 g of pale yellow oil. Column chromatography on 25 g of silicic acid using hexane/ethyl acetate afforded 0.311 g of a clear oil containing tricyclic ether **12**, which was purified by distillation (Kugelrohr) to afford 0.185 g (30%) of **12**: bp 84–88 °C (10 mm); IR 1040 cm^{-1}; ^1H NMR δ 1.0–2.2 (m, 13), 3.3 (d, 1, J = 8.8 Hz), 3.7 (m, 1), and 4.1 (dd, 1, J = 8.8 and 2.4 Hz); ^{13}C NMR δ 21.9, 25.8, 26.7, 30.5, 30.9, 34.2, 34.5, 35.3, 36.2, 65.2, and 68.5; MS, m/e 166 (M^+) (calcd for $C_{11}H_{18}O$, m/e 166). Anal. Calcd: C, 79.46; H, 10.91. Found: C, 79.22; H, 10.71.

Further elution afforded 0.46 g (64%) of **11** as a pale yellow oil, slightly impure by TLC. Distillation (Kugelrohr) afforded 0.297 g (42%) of **11** as a clear oil: bp 135–140 °C (0.8 mm); IR 3400 and 2240 cm^{-1}; NMR δ 1.0–2.2 (m, 15), 2.5 (s, 2), 3.7 (m, 1), and 4.1 (s, 1). Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91. Found: C, 74.76; H, 9.82.

10-(Cyanomethyl)-*trans*-decal-2-one (15). To a solution of 0.203 g (1.05 mmol) of **11** in 20 mL of acetone at 0 °C was added 30 drops of Jones' reagent.[27] The reaction was stirred at 0 °C for 10 min and isopropyl alcohol was added to consume the excess Jones' reagent. The reaction was diluted with 20 mL of water and extracted with ethyl acetate (3 × 20 mL). Normal workup afforded 0.201 g (100%) of **15**, mp 98–102 °C. Three recrystallizations from ether afforded 0.119 g (59%) of pure **15**: mp 107.5–108.5 °C; IR 2240 and 1710 cm^{-1}; NMR δ 1.0–2.5 (m, 15) and 2.65 (s, 2); MS, m/e 191.1 (M^+) (calcd for $C_{12}H_{17}NO$, m/e 191.3). Anal. Calcd: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.47; H, 8.96; N, 7.31.

10-(Carboxymethyl)-*trans*-decal-2-one (2). To a solution of 0.088 g (0.46 mmol) of **15** dissolved in 25 mL of ethanol was added 0.077 g of potassium hydroxide in 5 mL of water. The reaction was stirred at reflux for 16 h. The reaction was cooled to room temperature, and the ethanol was removed under reduced pressure. To the residue was added 20 mL of water, and the mixture was extracted with ethyl acetate (3 × 20 mL). Normal workup afforded 0.098 g of clear oil. Crystallization from ether afforded 0.062 g (64%) of **2**, mp 102–109 °C. The mother liquors from other, lower yielding, preparations of **2** were subjected to preparative TLC (8% acetic acid in chloroform) and molecular distillation, but the total yield of solid **2** never exceeded ca. 65%. Recrystallization from ether afforded pure **2**: mp 117.5–118.5 °C; IR (KBr) 3500–2500, 1725, and 1640 cm^{-1}; IR ($CHCl_3$) 3600–2400, 1735, and 1710 cm^{-1}; NMR δ 1.44, 2.07, and 2.21 (most intense peaks). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.59; H, 8.67.

10-(Cyanomethyl)-*trans*-decal-2-one Ethylene Ketal (17). Mesylate **16** was prepared by the method of Dreiding and Tomasewski.[4] In our hands, **16** was never obtained in the form reported with mp 133–136 °C.[4] In one preparation of enone ester **4** en route to **16**, cyclization to **4** was inadvertently incomplete, and the overall sequence afforded as a byproduct, 2-(mesyloxymethyl)-2-(3-oxobutyl)cyclohexanone bis(ethylene ketal), mp 99–100 °C, after recrystallization from ether, cyclohexane, or acetone: IR 1360 and 1175 cm^{-1}; NMR δ 1.2–1.8 (m, 15), 2.90 (s, 3), 3.92 (s, 8), and 4.20 (d, 2, J = 4 Hz); MS, m/e 349 (calcd for $C_{16}H_{28}SO_7 - CH_3 = 364 - 15 = 349$) and 87 (calcd for $C_4H_7O_2$, 87). Anal. Calcd: C, 52.73; H, 7.74; S, 8.80. Found: C, 52.77; H, 7.83; S, 8.72.

To a solution of 2.04 g (6.71 mmol) of **16**, mp 105–106 °C, in 15 mL of freshly distilled (but not dried) hexamethylphosphoramide was added 0.986 g (20.1 mmol) of sodium cyanide. This mixture was stirred at 130–140 °C for 40 h, while disappearance of **16** was monitored by TLC using 3:1 ether:hexane. The mixture was cooled to 0 °C, stirred with 30 mL of added ice water for 10 min, and extracted with benzene (3 × 40 mL). The benzene extracts were washed with water and brine, passed through a 5-g column of activity I basic alumina, and concentrated to afford 1.91 g of a yellow crystalline mass. Recrystallization from ether yielded 1.16 g (74%) of **17**, mp 127–128 °C. An additional 0.339 g of **17**, mp 108–125 °C, was obtained from the mother liquors for a total of 1.50 g (95%). An analytical sample prepared by recrystallization from ether had mp 127–128 °C; IR 2240 cm^{-1}; NMR δ 1.0–2.2 (m, 15), 2.50 (s, 2), and 3.93 (s, 4); MS, m/e 235 (M^+) (calcd for $C_{14}H_{21}NO_2$, m/e 235). Anal. Calcd: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.55; H, 8.98; N, 5.85.

Conversion of 17 to 15. To a solution of 1.00 g (4.26 mmol) of **17**, mp 127–128 °C, in 25 mL of methanol was added 20 mL of 10% hydrochloric acid and the mixture was heated on a steam bath for 10 min, cooled, concentrated to ca. 20 mL under reduced pressure, diluted with 20 mL of water, and extracted with ether (4 × 25 mL). Normal workup afforded 0.828 g (102%) of **15**, mp 105–107.5 °C.

Tricyclo[4.4.3.0^{1,6}]-11-oxa-3,12-dioxotridecane (20). The annulation of 2-(carbomethoxymethyl)cyclohexanone (**6**)[6] was attempted with numerous ratios of **6**, methyl vinyl ketone, and sodium methoxide. The most successful procedure is described below. The acid-catalyzed method of Heathcock and McMurry[28] and annulation of 2-(carboxymethyl)cyclohexanone[29] were also tried[30] with negligible success. To a solution of 4.6 g (0.20 mol) of freshly cut sodium in 50 mL of methanol which had been distilled from sodium was added a solution of 33.7 g (0.198 mol) of **6** in 100 mL of anhydrous ether. The mixture was stirred at 0 °C for 15 min under nitrogen, and then a solution of 10 mL (8.64 g, 0.123 mol) of freshly distilled methyl vinyl ketone in 75 mL of anhydrous ether was added dropwise over 1 h. The resulting mixture was stirred at 0 °C for 2 h and at room temperature for 10 h. The mixture was then treated with 10 mL of water and heated at 60–70 °C for 1 h and then cooled to room temperature and extracted with ether (2 × 75 mL). Evaporation of these ether layers yielded negligible material. The aqueous layer was cooled to 0 °C, acidified with concentrated hydrochloric acid, stirred at room temperature for 3 h, and extracted with ether (3 × 100 mL). Normal workup afforded 33.55 g of red tarry material.

Distillation of this crude product afforded two fractions. The first was 10.00 g, bp 128–160 °C (0.15–0.20 mm), which solidified and was identified as 2-(carboxymethyl)cyclohexanone (32%); after recrystallization from ether: mp 69–72 °C (lit.[29] mp 73–74 °C); IR 3300–2500 and 1730–1720 cm^{-1}; NMR δ 1.0–2.9 (m, 11) and 10.6 (s, 1). The material was identical with that, mp 72–73 °C, obtained by hydrolysis of **6**.[30]

The second fraction was 10.56 g of viscous yellow oil, bp 165–230 °C (0.15–0.20 mm), which was induced to crystallize by trituration with 5 mL of ether, affording 4.89 g (19% based on MVK; 12%

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(30) These experiments were performed by B. J. Mayer.

based on 6) of lactone **20**, mp 133–134 °C. A second crop, 0.77 g of **20**, mp 129–131.5 °C, was obtained from the mother liquors. The remaining oil (6.46 g) was redistilled and the fraction (1.69 g) with bp 160–180 °C (0.05–0.10 mm) afforded 0.56 g of **20**, mp 115–125 °C, for a total yield of 6.22 g (24% based on MVK; 15% based on 6) of crystalline **20**. An analytical sample of **20**, prepared by recrystallization from ether, had mp 133.5–134 °C; IR 1770 and 1720 cm^{-1}; ^1H NMR δ 1.2–2.4 (m, 14) and 2.59 (d, J = 1.3 Hz, 2); ^{13}C NMR δ 20.5, 21.7, 31.5, 32.1, 34.1 36.7, 40.1, 40.8, 50.1, 90.7, 175.0, and 206.3; MS m/e 208.2 (M^+) (calcd for $C_{12}H_{16}O_3$, m/e 208.3). Anal. Calcd: C, 69.21; H, 7.74. Found: C, 69.13; H, 7.76.

10-(Carboxymethyl)-$\Delta^{1(9)}$-octal-2-one (21). To a solution of 0.104 g (0.50 mmol) of **20** in 10 mL of methanol was added a solution of 0.08 g of potassium hydroxide in 2 mL of water and the mixture was heated at reflux for 1.5 h. The methanol was removed under reduced pressure and the residue was diluted with 10 mL of water. After extraction with ether (2 × 10 mL), the aqueous solution was acidified with concentrated hydrochloric acid and extracted with ether (3 × 10 mL). Normal workup afforded 0.098 g (94%) of **21**: mp 111–119 °C; IR 3300–2500, 1720, and 1630 cm^{-1}; NMR δ 5.8 (s, 1) and 11.1 (s, 1). On attempted recrystallization or on long standing **21** reverted to **20**.

10-(Carboxymethyl)-*cis*-decal-2-one (24). To a solution of 0.691 g (3.32 mmol) of lactone **20** in 145 mL of ethyl acetate was added a solution of 0.209 g (3.6 mmol) of potassium hydroxide in 5 mL of ethanol and 0.111 g of 10% palladium on carbon. This mixture was stirred under an atmosphere of hydrogen and the reaction was monitored by observing the decrease in absorbance at 247 nm as enone acid anion 22 was reduced. After 12 h the chromophore was gone, the system was flushed with nitrogen and the catalyst removed by filtration. The filtrate was diluted with 1 M hydrochloric acid and the organic layer was separated. The aqueous layer was saturated with sodium chloride and extracted with ethyl acetate (2 × 25 mL). Normal workup afforded 0.696 (100%) of crude solid **24**. Recrystallization from ether–hexane gave 0.538 g (78%) of **24**: mp 133.5–135 °C; IR 1720 and 1680 cm^{-1}; ^1H NMR δ 1.0–2.5 (m, 15) and 2.6 (s, 2); ^{13}C NMR δ 21.2, 24.4, 28.5, 30.1, 33.5, 35.7, 37.3, 42.0, 42.9, 43.8, 177.4 and 211.1; MS m/e 210.1 (M^+) (calcd for $C_{12}H_{18}O_3$, m/e 210.3). Anal. Calcd: C, 68.55; H, 8.63. Found: C, 68.54; H, 8.57.

Hydrogenation of **20** in 5:1 ethyl acetate:1 M hydrochloric acid using 10% palladium on carbon also afforded only **24**.

Cis keto acid **24** could also be obtained by hydrogenation in base, as above, of the crude Robinson annulation product from **6**, followed by column chromatography on silicic acid using chloroform containing 1–2% acetic acid. The overall yield from **6** of **24**, mp 131–133 °C, was 13%.

10-(Carbomethoxymethyl)-$\Delta^{1(9)}$-octal-2-one (18). To a solution of 1.04 g (5.00 mmol) of **20** in 100 mL of methanol was added 0.81 g (15.0 mmol) of sodium methoxide (Fisher) and this mixture was stirred for 45 min. The mixture was then acidified with concentrated hydrochloric acid, and ethereal diazomethane generated from *N,N'*-dimethyl-*N,N'*-dinitrosoterephthalimide[31] was immediately distilled directly into it. When a yellow color persisted for 10 min, the mixture was titrated with 1 M hydrochloric acid until colorless, and excess ethereal diazomethane was added again. The titration and addition of diazomethane were repeated and the mixture was stirred at room temperature for 3 h. The solvents were removed under reduced pressure and the residue was partitioned between 100 mL of ether and 20 mL of water. Normal workup afforded 0.903 g (81%) of **18** as an oil, homogeneous by TLC (3:1 ether:hexane). An analytical sample of **18** was prepared by distillation (Kugelrohr) and had bp 135–140 °C (0.8 mm); UV (H_2O) λ_{max} 245 nm (ϵ 14 500); IR 1740, 1670, and 1620 cm^{-1}; NMR δ 3.63 (s, 3) and 5.68 (s, 1); MS m/e 222 (M^+) (calcd for $C_{13}H_{18}O_3$, m/e 222). Anal. Calcd: C, 70.24; H, 8.16. Found: C, 70.27; H, 8.23.

Lactone **20** was also converted to **18** by treatment with sodium bicarbonate and methyl iodide in dimethylacetamide,[24] but the yield was only ca. 20%.

10-(Carbomethoxymethyl)-*cis*-decal-2-one (25) and 10-(Carbomethoxymethyl)-*trans*-decal-2-one (19). To a solution of 0.307 g (1.38 mmol) of **18** in 25 mL of ethyl acetate was added 0.03 g of 10% palladium on carbon. The reaction was stirred under an atmosphere of hydrogen. The theoretical volume of hydrogen was taken up in 1 h. The catalyst was removed by filtration and the filtrate was evaporated to afford 0.296 g of a mixture of **19** and **25**, which were incompletely separated by TLC. Separation by high-performance low-pressure chromatography using 1:1 ether:hexane afforded 0.076 g (25%) of the trans keto ester **19**, mp 46–48 °C, followed by 0.157 g (51%) of oily cis keto ester **25**.

An analytical sample of **19** was prepared by recrystallization from ether/hexane and had mp 54–55 °C; IR 1750 and 1725 cm^{-1}; ^1H NMR δ 1.0–2.6 (m, 17) and 3.68 (s, 3). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.65; H, 9.09.

An analytical sample of **25** was prepared by distillation (Kugelrohr) and had bp 118–123 °C (0.2 mm); IR 1740 and 1720 cm^{-1}; NMR δ 1.0–2.6 (m, 17) and 3.67 (s, 3); MS m/e 224 (M^+) (calcd for $C_{13}H_{20}O_3$, m/e 224). Anal. Calcd: C, 69.61; H, 8.99. Found: C, 69.52; H, 8.94.

The following hydrogenation conditions were also used to reduce **18**, for 1 h unless otherwise specified, and the ratio of **25** to **19** obtained in each experiment as determined by analytical LC using 7:13 methanol–water, or the yield isolated by preparative LC, is given in parentheses: 10% Pd–C, ethyl acetate, as described above (1.3:1); 10% Pd–C, water (1.4:1); 10% Pd–C, dimethylacetamide (1.6:1); 10% Pd–C, ethanol (1.3:1); 5% Pd–C, ethanol (2.3:1); 5% Pt–C, ethanol (overreduction); 5% Ru–C, ethanol, 1.25 h (1:1); 5% Rh–C, ethanol (45% **25**, 33% **19**); $Rh(PPh_3)_3Cl$, 1:1, ethanol–benzene, 7 days (15% **25**, 35% **19**); $Rh(PPh_3)_3Cl$, 1:1, ethanol–benzene, 13 days (50% **19**).

Treatment of **19** with potassium hydroxide in ethanol–water at reflux for 1 h afforded **2**, mp 116.5–118.5 °C.

Treatment of **24** with ethereal diazomethane afforded **25** which had an IR spectrum identical with that of **25** obtained from hydrogenation of **18** (and different from that of **19**).

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Registry No. **2**, 72542-02-0; **5**, 1209-32-1; **6**, 41302-34-5; **7**, 72542-03-1; **8**, 72542-04-2; **9**, 72542-05-3; **10**, 72558-81-7; **11**, 72542-06-4; **12**, 72542-07-5; **15**, 72542-08-6; **16**, 72542-09-7; **17**, 72542-10-0; **18**, 18963-05-8; **19**, 72542-11-1; **20**, 72542-12-2; **21**, 72542-13-3; **24**, 72542-14-4; **25**, 72542-15-5; 2-[(mesyloxy)methyl]-2-(3-oxobutyl)-cyclohexanone bis(ethylene ketal), 72542-16-6; 2-(carboxymethyl)-cyclohexanone, 1438-96-6.

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