Preparation of Cyclohexanones and Cyclopentanones of High Optical Purity

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Cyclization of **3**, prepared from 1-menthol, led to a 1:1 mixture of **4** and **5**. These diastereomeric ketones, readily separated by chromatography, are versatile intermediates for the preparation of alkylated cyclohexanones. The absolute configuration of **5** was assigned by conversion to the known hydroxy ketal **9**. This approach works equally well for the cyclopentane series. Thus, alkylated cyclohexanones and cyclopentanones of known absolute configuration will for the first time be routinely available.

One of the most powerful strategies in synthetic organic chemistry is to use a convergent synthetic plan. Following such a strategy, complex substructures, prepared independently, are combined late in a synthesis. Balanced against the inherent economy of such an approach has been the necessity, where asymmetric centers are involved, of preparing each substructure optically pure. The lack of general methods for the preparation of carbocyclic intermediates with control of absolute stereochemistry has limited the applicability of this approach. We report herein a general method for the preparation of alkylated cyclopentanones and cyclohexanones of high optical purity.

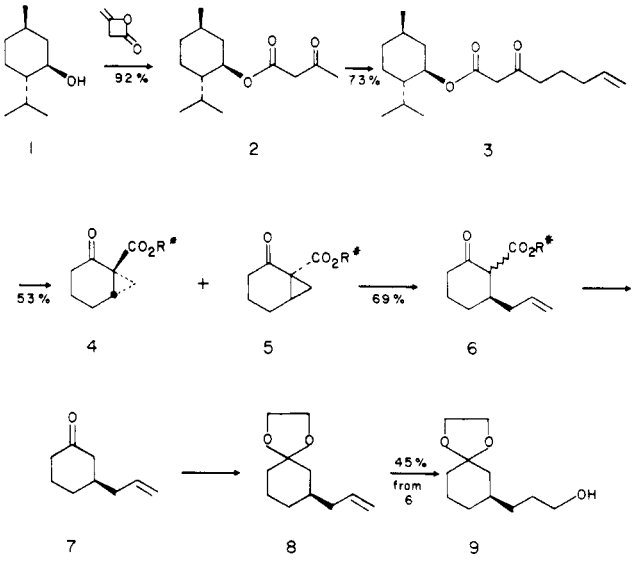
There are three approaches that can be taken in preparing optically pure substances. The first is to use a readily available chiral precursor. Generally such precursors are carbohydrates, with concomitant problems of converting carbon–oxygen to carbon–carbon chirality. While elegant work has been done in this area,[1] this approach is still somewhat cumbersome.

Alternatively, one could prepare the desired material from a prochiral precursor using an appropriate chiral environment or reagent to induce the desired absolute stereochemistry. This approach has been used effectively in controlling carbon–oxygen, carbon–nitrogen, and carbon–carbon chirality.[2]

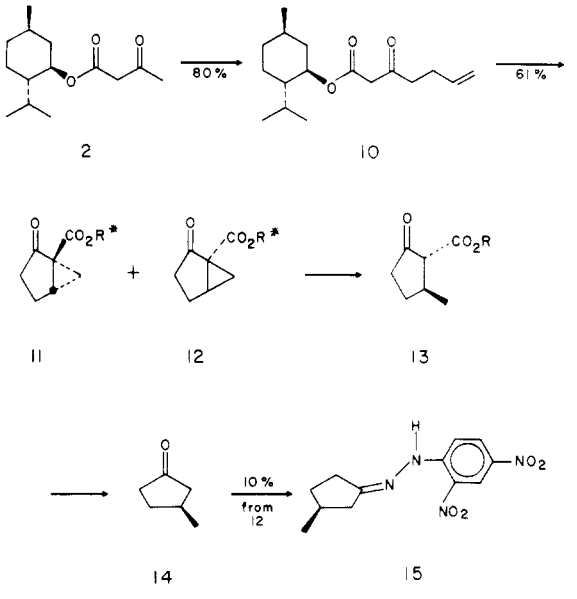
Finally, it is possible to resolve either the desired substructure or, preferably, an early intermediate in its preparation. In recent years the classical technique of fractional crystallization has been augmented by the alternative approach of chromatographic separation of diastereomeric derivatives.[3] We report here the preparation and chromatographic resolution of key intermediates for the preparation of alkylated cyclohexanones and cyclopentanones.

Cyclohexanone Preparation. For the construction of the desired cyclohexane derivatives we chose to use the diazo insertion–homoconjugate addition route (Scheme I) previously used by ourselves[4] and others[5] for cyclopentane construction. This offered the advantage that an early, flexible intermediate, the cyclopropyl ketone, incorporated the key β asymmetric center and so was a candidate for resolution.

Scheme I



Scheme II



Another advantage of this approach was that an optically pure resolving agent could be incorporated directly (Scheme I). Thus, acylation of 1-menthol with diketene[6] yielded menthyl acetoacetate **2**. Alkylation following the procedure of Weiler[7] then proceeded smoothly to give the

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(2) For a review, see: Valentine, D., Jr.; Scott, J. W. *Synthesis* **1978**, 329.

(3) (a) Pirkle, W. H.; Rinaldi, P. L. *J. Org. Chem.* **1978**, *43*, 3803. (b) Meyers, A. I.; Slade, J.; Smith, R. K.; Mihelich, E. D.; Hershenson, F. M.; Liang, C. D. *Ibid.* **1979**, *44*, 2247.

(4) (a) Taber, D. F. *J. Am. Chem. Soc.* **1977**, *99*, 3513. (b) Trost, B. M.; Taber, D. F.; Alper, J. B. *Tetrahedron Lett.* **1976**, 3857.

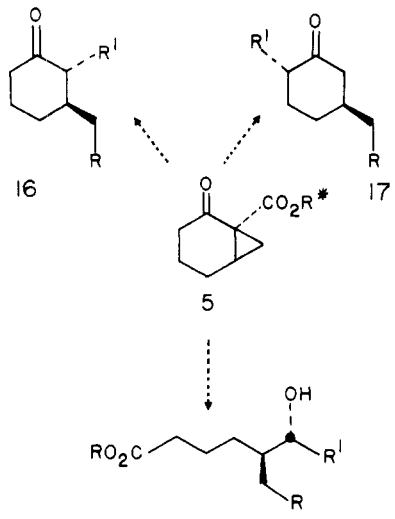
(5) (a) Clark, R. D.; Heathcock, C. H. *Tetrahedron Lett.* **1975**, 529. Kondo, K.; Umemoto, T.; Takakatake, Y.; Tunemoto, D. *Tetrahedron Lett.* **1977**, 113.

(6) Mauz, O. *Justus Liebigs Ann. Chem.* **1974**, 345.

(7) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

0022-3263/80/1945-4699$01.00/0

Scheme III



prochiral olefin **3**. As anticipated, diazo transfer[8] followed by cyclization led to a 1:1 mixture of cyclopropyl ketones **4** and **5**. These were separated by column chromatography.

The absolute configuration of **5** was assigned by conversion to **9**, previously prepared by Nakazaki.[9] Thus, homoconjugate opening with lithium divinylcuprate[10] proceeded to give the enolic β-keto ester **6**.[11] Decarboxylation by the method of Krapcho[12] followed by ketalization and hydroboration[13] then gave **9**, with the absolute stereostructure shown.

Cyclopentanone Preparation. The cyclopentane synthesis (Scheme II) proceeded along the same lines as that for the cyclohexane series. Thus, alkylation of the dianion of **2** with allyl bromide followed by cyclization gave a 1:1 mixture of **11** and **12**, which also were readily separated by column chromatography.

The absolute configuration of **12** was assigned by dissolving-metal reduction[14] and decarboxylation to give 3-methylcyclopentanone (**14**), which was isolated as its 2,4-DNP **15**. Comparison in this case was made to the DNP of the commercially available (+) isomer of **14**. Again, the absolute stereostructure of all intermediates is as shown.

Synthetic Applicability. A wide variety of alkylated cyclohexane derivatives can readily be prepared from the chiral cyclopropyl ketone (Scheme III). For instance, homoconjugate opening followed by alkylation and decarboxylation would give the 2,3-dialkyl derivative **16**. Alternatively, alkylation of the β-keto ester dianion followed by decarboxylation would lead to the 2,5-dialkyl derivative **17**. Finally, control of stereochemistry around the ring could be coupled with ring cleavage to give an acyclic fragment such as **18**, incorporating both carbon–carbon and carbon–oxygen chirality. Thus, with this approach, alkylated cyclohexanones and cyclopentanones of known absolute configuration and high optical purity will for the first time be routinely available.

Ultimately, it would be desirable to convert the prochiral olefin **3** directly into a single chiral cycloalkane. To this end, optical induction by other, sterically more demanding esters is currently under investigation.

Experimental Section

General Methods. ^1H NMR spectra were determined on a JEOLCO MH-100 spectrometer as solutions in $CDCl_3$. Chemical shifts are reported in δ units downfield from the internal reference tetramethylsilane. ^{13}C NMR spectra were determined on a JEOLCO FX-90Q spectrometer as solutions in $CDCl_3$. Shifts are also reported in parts per million downfield from Me_4Si. The multiplicity of a carbon signal is reported when it could be unequivocally assigned. Couplings (J) are in hertz. The infrared spectra (IR) were recorded on a Perkin-Elmer 257 spectrometer as solutions in CCl_4 and are reported in reciprocal centimeters. Mass spectra were determined at 13 eV on an LKB 9000 gas chromatograph–mass spectrometer interfaced with a PDP-12 computer system and are reported as mass per unit charge, with intensities as a percentage of the peak of greatest ion current having $m/z \geq 100$. Rotations were measured on a Rudolph Research Autopol III polarimeter. Organic chemicals were purchased from Aldrich Chemical Co. Organometallics were purchased from Alfa Inorganics and were titrated prior to use. Solvent mixtures (e.g., 5% ethyl acetate/hexane) are volume/volume mixtures. The R_f values indicated refer to thin-layer chromatography on Analtech 2.5 × 10 cm 250-μm analytical plates coated with silica gel GF. Column chromatography was carried out by using the short-column technique,[16-18] modified by running the columns under air pressure (5–20 psig). We have found EM 7747 silica gel to be very effective in this application. Analytical samples were prepared by short-column chromatography followed by bulb-to-bulb distillation. Analyses were performed by Galbraith Laboratories, Inc.

Preparation of Menthyl Acetoacetate 2. The acylation was carried out by following the procedure of Mauz.[6] Thus, to 1-menthol (15.0 g, 96.1 mmol) in 80 mL of acetone in a 250-mL round-bottomed flask was added triethylamine (970 mg, 9.6 mmol) followed by diketene in acetone (50% by weight, 21.14 g, 126 mmol, 1.3 equiv). The mixture was refluxed 2 h, allowed to cool, diluted with dilute aqueous HCl, and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was distilled through a 10-cm Vigreux column to give **2** as an oil: 21.2 g (92%); bp 138–140 °C (0.5 mmHg); ^1H NMR 0.80–1.0 (m, 9 H), 1.0–2.2 (m, 9 H), 2.26 (s, 3 H), 3.44 (s, 2 H), 4.78 (dt, J = 4, 11, 1 H); IR 1715, 780, 775; mass spectrum, m/z (relative intensity) 240 (3.7), 210 (3.5), 137 (100). Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.95; H, 10.07. Found: C, 70.08; H, 9.98.

Preparation of 3. The alkylation was carried out by the method of Weiler.[7] Thus, a flame-dried, 250-mL, three-necked, round-bottomed flask equipped with a magnetic stir bar and maintained under N_2 was charged with 2.60 g (54 mmol) of 50% NaH and 80 mL of THF. The flask was chilled in an ice/water slurry, and then **2** (10.0 g, 41.7 mmol) was added dropwise over 15 min. After an additional 15 min, BuLi (16.5 mL, 2.78 M in hexane, 45.8 mmol, 1.1 equiv) was added in one portion, and stirring was continued an additional 30 min. 4-Iodo-1-butene[22] (11.37 g, 62 mmol, 1.5 equiv) was added in one portion, the cooling bath was removed, and stirring was continued an additional 30 min. The mixture was diluted with a mixture of dilute aqueous

(8) Regitz, M.; Hocker, J.; Liedhegener, A. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 197.
(9) Nakazaki, M.; Naemura, K.; Nakahara, S. *J. Org. Chem.* **1979**, *44*, 2438.
(10) Still, W. C., Columbia University, personal communication.
(11) Cyclohexanone **6** smeared substantially on TLC. This was not the case with cyclopentantone **13**.
(12) Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, 957.
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(16) Hunt, B. J.; Rigby, W. *Chem. Ind. (London)* **1967**, 1869.
(17) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(18) For larger columns (100 g of silica gel or more) we have found it convenient to maintain column flow by the application of aspirator vacuum, using approximately the same ratio of column diameter to column height as for smaller columns. This is easily done by using a large glass-frit filter funnel equipped with a stopcock. The advantages of running chromatography columns under vacuum have recently been noted by others also.[19]
(19) Targett, N. M.; Kilcoyne, J. P.; Green, B. *J. Org. Chem.* **1979**, *44*, 4962.
(20) Prepared by NaI/acetone exchange on the commercially available bromide, bp 128–129 °C (760 mmHg).
(21) Tetravinylstannane was prepared from vinyl bromide and stannic chloride by following the procedure of Still.[10]
(22) House, H. O.; Chu, C. Y.; Wilkins, J. M.; Umen, M. *J. Org. Chem.* **1975**, *40*, 1460.

HCl and brine and extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on 350 g of silica gel with 3% EtOAc/petroleum ether to give 8.90 g (30.3 mmol, 73%) of **3** as a pale yellow oil: R_f (10% EtOAc/hexane) 0.52; ^1H NMR 0.73–1.08 (m, 14 H), 1.08–2.3 (m, 8 H), 2.53 (t, J = 7, 2 H), 3.40 (s, 2 H), 4.70 (dt, J = 4, 11, 1 H), 5.0 (m, 2 H), 5.72 (m, 1 H); IR 1770, 1470, 1310, 950; mass spectrum, m/z (relative intensity) 294 (0.74), 237 (0.74), 155 (56), 137 (100), 114 (15). Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.40; H, 10.27. Found: C, 73.59; H, 10.04.

Preparation of 4 and 5. Diazo transfer was carried out by the method of Regitz.[8] Thus a 250-mL round-bottomed flask equipped with a magnetic stir bar was charged with *p*-toluenesulfonyl azide (6.47 g, 32.9 mmol) and triethylamine (6.03 g, 59.7 mmol). Keto ester **3** (8.78 g, 29.9 mmol) was added, and the mixture stirred at room temperature overnight. The reaction mixture was diluted with 10% aqueous NaOH and extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on 380 g of silica gel with 15% CH_2Cl_2/petroleum ether to give the crude diazo ester as an oil: 9.32 g (97%); R_f (10% EtOAC) 0.64.

This oil was transferred to a 250-mL round-bottomed flask with 80 mL of toluene, copper bronze powder (10.66 g, 2 wt equiv) was added, and the mixture was refluxed 1 h. The cooled mixture was filtered through Celite with Et_2O, and the filtrate concentrated in vacuo. The residue was chromatographed on 240 g of silica gel with 6% EtOAc/petroleum ether. The first 1760 mL was discarded. The next 1020 mL was concentrated in vacuo to give **4** (1.21 g, 14%) as a colorless oil, R_f (10% EtOAc/petroleum ether) 0.21. The next 1020 mL was concentrated in vacuo to give 1.93 g of a mixture of **4** and **5**. The next 1700 mL was concentrated in vacuo to give **5** (1.46 g, 17%) as a colorless oil, R_f (10% EtOAc) 0.18. The combined yield of **4** and **5** was 4.61 g (15.8 mmol, 53% based on **3**).

For **4**: ^1H NMR 0.72–0.94 (m, 11 H), 1.12–2.13 (m, 17 H), 2.26 (m, 1 H), 4.68 (dt, J = 5, 13, 1 H); IR 1710, 1380, 1265, 1180, 1169, 1080; mass spectrum, m/z (relative intensity) 292 (0.26), 154 (100), 137 (67); ^{13}C NMR 15.84 (q, 2) 17.79 (q), 20.93, 21.42, 21.96, 23.04, 25.21, 25.59, 31.38 (t), 34.26 (t), 35.88 (s), 38.32 (t), 40.76 (t), 47.04 (d), 75.21 (d), 169.64 (s), 202.75 (s). Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.92; H, 9.66. Found: C, 74.17; H, 9.89.

For **5**: ^1H NMR 0.73–0.92 (m, 12 H), 1.07–2.12 (m, 16 H), 2.24 (m, 1 H), 4.70 (dt, J = 5, 13, 1 H); IR 1710, 1380, 1270, 1180, 1169, 1080; mass spectrum, m/z (relative intensity) 292 (0.54), 154 (100), 137 (68); ^{13}C NMR 15.62 (q), 16.81 (q), 17.29 (q), 20.44, 21.42, 21.85, 23.46, 24.99, 26.73 (d), 31.28, 34.20 (t), 35.78 (s), 38.27 (t), 40.38 (t), 46.82 (d), 75.16 (d), 169.53 (s), 202.26 (s). Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.92; H, 9.66. Found: C, 74.03; H, 9.73.

Preparation of 6. Vinyllithium was prepared by the method of Still.[10] Thus, a 25-mL round-bottomed flask equipped with a magnetic stir bar and maintained under N_2 was charged with 297 mg (1.5 mmol) of tetravinylstannane[21] and 10 mL of THF. The flask was immersed in an ice/water slurry and the mixture stirred magnetically. BuLi (1.43 mL, 2.78 M in hexane, 4.0 mmol) was added in one portion and the mixture stirred for an additional 15 min. The cooling bath was changed to −35 °C (dry ice/aqueous $CaCl_2$), and CuI·Me_2S[22] (630 mg, 2.5 mmol) dissolved in 5 mL of dimethyl sulfide was added dropwise. After 10 min of additional stirring, ketone **5** (146 mg, 0.5 mmol) in THF (2 mL) was added dropwise. Stirring was continued an additional 10 min. The reaction mixture was diluted with aqueous NH_4Cl and NH_4OH and extracted with petroleum ether. The combined organic extracts were dried over K_2CO_3 and concentrated in vacuo. The residue was chromatographed on 7 g of silica gel with 1% EtOAc/petroleum ether to give ester **6** as an oil: 108 mg (69%); R_f (10% EtOAc/hexane) 0.24; ^1H NMR 0.78–0.94 (m, 11 H), 1.55–2.20 (m, 17 H), 3.13 (d, J = 12, 1 H), 4.76 (dt, J = 4, 11, 1 H), 5.05 (m, 2 H), 5.70 (m, 1 H); IR 1710, 1630, 1250, 1210, 905; mass spectrum, m/z (relative intensity) 320 (1.2), 279 (32), 182 (54), 140 (100). Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.95; H, 10.07. Found: C, 75.06; H, 10.27.

Preparation of 9. Decarboxylation was effected by the method of Krapcho.[12] Thus, a 25-mL round-bottomed flask was charged with Me_2SO (5 mL), NaCl (0.5 g), and water (0.5 mL), ester **6** (346 mg, 1.1 mmol) was added, and the mixture was maintained at 165 °C for 4 h. The cooled mixture was partitioned between petroleum ether and water, and the combined organic extracts were dried over Na_2SO_4.

The petroleum ether was removed by atmospheric pressure distillation through a 10-cm Vigreux column and replaced with 30 mL of dichloroethane. Ethylene glycol (0.5 mL) and *p*-TSOH·H_2O (15 mg) were added, and the mixture was refluxed for 1 h. The cooled mixture was diluted with dilute aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on 8 g of silica gel with 2% EtOAc/hexane to give ketal **8** (131 mg, 67%) as an oil, R_f (10% EtOAc/hexane) 0.33.

This oil was transferred with 2 mL of THF to a 10-mL round-bottomed flask equipped with a magnetic stir bar and maintained under N_2. The flask was cooled in an ice/water slurry, and BH_3[15] (0.5 mL, 1 M in THF, excess) was added. The cooling bath was removed, and stirring was continued for 1 h. The flask was again cooled in an ice/water slurry, and NaOH (1 mL of a cold 50% aqueous solution) was added dropwise. H_2O_2 (1 mL of a cold 30% aqueous solution) was added dropwise, and stirring was continued for 10 min. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with aqueous $Na_2S_2O_3$, dried over K_2CO_3, and concentrated in vacuo. The residue was chromatographed on 6 g of silica gel with 60% ethyl acetate/petroleum ether to give **9** (91 mg, 45% based on **6**, 77%/step) as an oil: R_f (20% EtOAc/hexane) 0.29; ^1H NMR 1.1–1.8 (m, 12 H), 3.60 (t, J = 6, 2 H), 3.90 (s, 4 H); IR 3450, 1440, 1350, 1145, 1070, 940, 925; mass spectrum, m/z (relative intensity) 186 (0.07), 169 (5), 156 (92), 140 (100); $[\alpha]^{28}_D$ +5.6 ± 0.4° (*c* 2.7, EtOH) [lit.[9] $[\alpha]^{28}_D$ +5.3 ± 0.4° (*c* 2.40, EtOH)]. Anal. Calcd for $C_{10}H_{18}H_3$: C, 64.47; H, 9.75. Found: C, 64.37; H, 9.89.

Preparation of 10. Alkylation was carried out as for the preparation of **3** except that 3-bromopropene (7.5 g, 63 mmol) was used as the alkylating agent. The residue after the workup was chromatographed on 300 g of silica gel with 2% EtOAc/petroleum ether to give **10** (9.34 g, 80%) as an oil: R_f (10% EtOAc/hexane) 0.56; ^1H NMR 0.7–1.0 (m, 9 H), 1.0–2.1 (m, 9 H), 2.32 (q, J = 7, 2 H), 2.62 (t, J = 7, 2 H), 3.4 (s, 2 H), 4.70 (dt, J = 4, 11, 1 H), 5.0 (m, 2 H), 5.72 (m, 1 H); IR 1712, 1225, 910; mass spectrum, m/z (relative intensity) 280 (1), 141 (91), 137 (100), 123 (26). Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.80; H, 10.07. Found: C, 72.93; H, 10.21.

Preparation of 11 and 12. Diazo transfer was carried out as for **3** above by starting with 3.0 g (10.7 mmol) of **10**. The residue after workup was chromatographed on 120 g of silica gel with 10% CH_2Cl_2/petroleum ether to give the crude diazo ester (2.78 g, 85%) as an oil, R_f (10% EtOAc/hexane) 0.57.

Cyclization was carried out as above. The residue after the workup was chromatographed on 120 g of silica gel with 6% EtOAc/petroleum ether. The first 1560 mL was discarded. The next 480 mL was concentrated in vacuo to give **11** (651 mg, 22%) as an oil, R_f (10% EtOAc/hexane) 0.26. The next 240 mL was concentrated in vacuo to give **12** (613 mg, 20%) as an oil, R_f (10% EtOAc/hexane 0.23. The combined yield of **11** and **12** was 1.82 (61% based on **10**).

For **11**: ^1H NMR 0.7–1.0 (m, 11 H), 1.0–2.3 (m, 13 H), 2.53 (m, 1 H), 4.71 (dt, J = 4, 11, 1 H); IR 1735, 1450, 1384, 1310, 1260, 1185, 1030, 950; mass spectrum, m/z (relative intensity) 278 (0.3), 140 (66), 137 (100), 122 (13); ^{13}C NMR 15.84 (q) 20.55, 20.71, 20.93, 21.69, 23.04, 25.64 (d), 31.11, 31.97 (d), 33.17 (t), 33.93 (t), 37.51 (s), 40.49 (t), 46.66 (d), 74.62 (d), 167.25 (s), 206.21 (s). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.33; H, 9.42. Found: C, 73.24; H, 9.47.

For **12**: ^1H NMR 0.7–1.0 (m, 11 H), 1.0–2.3 (m, 13 H), 2.57 (m, 1 H), 4.73 (dt, J = 4, 11, 1 H); IR 1735, 1450, 1384, 1310, 1260, 1185, 1030, 950; mass spectrum, m/z (relative intensity) 278 (0.3), 139 (73), 137 (100), 122 (17); ^{13}C NMR 16.38 (q), 20.60, 20.88, 21.36, 21.85, 23.53, 26.29 (d), 31.28, 31.88, 33.45, 34.15, 37.67 (s), 40.65 (t), 46.82 (d), 74.89 (d), 167.52 (s), 206.63 (s). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.33; H, 9.42. Found: C, 73.21; H, 9.48.

Assignment of the Absolute Configuration of 12. Ring cleavage was carried out by the method of Caine.[14] Thus, a three-necked 100-mL, round-bottomed flask equipped with a magnetic stir bar and a dry ice/acetone condensor and maintained under N_2 was charged with NH_3 (20 mL) and Li dispersion (22

mg, 30% in paraffin) to give a deep blue solution. A solution of ketone **12** (100 mg, 0.36 mmol) and *tert*-butyl alcohol (27 mg, 0.36 mmol) in 2 mL of THF was added dropwise over 5 min. After the addition was completed, the NH_3 was evaporated under a stream of N_2. The residue was diluted with dilute aqueous HCl and extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo.

The residue was combined with Me_2SO[12] (3 mL), NaCl (100 mg), and water (10 drops) and maintained at 165 °C for 2 h. The cooled reaction mixture was partitioned between petroleum ether and water. The combined organic extracts were dried over Na_2SO_4. The petroleum ether was removed by atmospheric pressure distillation through a 10-cm Vigreux column, and replaced with 10 mL of absolute EtOH. DNP solution[23] (0.5 mL) was added. After 5 min the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo.

Repeated column chromatography of the residue failed to separate the desired DNP, **15**, from traces of menthol. The partially purified **15** was therefore submitted to preparative high-performance LC.[24] This yielded **15**: 9.8 mg (10% from **12**); R_f (10% EtOAc/hexane) 0.20; ^1H NMR 1.09–1.26 (m, 5 H), 1.6–2.6 (m, 6 H), 7.91 (d, J = 11, 1 H), 8.30 (dd, J = 3, 11, 1 H), 9.12 (d, J = 3, 1 H); IR 3320, 1630, 1330; mass spectrum, m/z (relative intensity) 278 (100), 246 (12), 189 (11), 151 (20), 140 (23); $[\alpha]^{28}_D$ −18.4 ± 1° (*c* 0.98, EtOH). Commercial (+)-3-methylcyclopentanone yielded a DNP that after purification by silica gel chromatography [R_f (10% EtOAc/hexane) 0.20] showed $[\alpha]^{28}_D$ +21.1 ± 1° (*c* 0.80, EtOH).

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Registry No. **1**, 2216-51-5; **2**, 59557-05-0; **3**, 74965-53-0; **3** diazo ester, 74978-09-9; **4**, 75023-17-5; **5**, 74965-54-1; **6**, 74965-55-2; **7**, 74965-56-3; **8**, 74965-57-4; **9**, 74965-58-5; **10**, 74965-59-6; **10** diazo ester, 74965-60-9; **11**, 74965-61-0; **12**, 74985-54-9; **13**, 74965-62-1; **14**, 6672-24-8; **15**, 74965-63-2; diketene, 674-82-8; 4-iodo-1-butene, 7766-51-0; 3-bromopropene, 106-95-6.

(23) Vogel, A. I. "Practical Organic Chemistry", 3rd ed.; Logman: London, 1974; p 344.

(24) This separation was carried out on a Waters semipreparative μ-Porasil column, eluting with 2% EtOAc/petroleum ether.

Prostaglandins and Congeners. 28.[1] Synthesis of 2-(ω-Carbalkoxyalkyl)cyclopent-2-en-1-ones, Intermediates for Prostaglandin Syntheses

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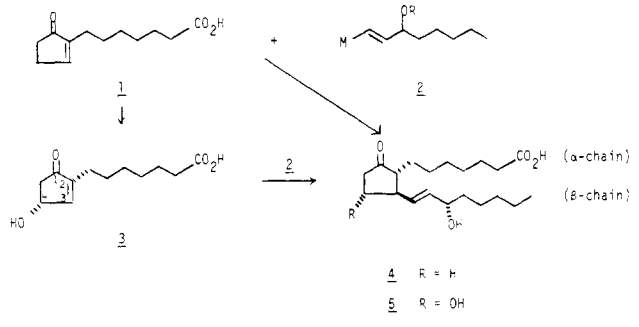
A methodology is described for the synthesis of the 2-substituted cyclopentenone precursors required for the preparation of 11-deoxyprostaglandins by the conjugate addition procedure. Among the cyclopentenones so prepared were some with features designed to inhibit or prevent fatty acid β-oxidative metabolism of the ultimate prostaglandin analogue. These features include methyl, ethyl, phenyl, and fluorine substituents at the α position of the fatty acid side chain and replacement of the β-methylene group with oxygen, sulfur, or *gem*-dimethylmethylene moieties. Cyclopentenones with side chains varying in length from two to nine carbon atoms were also prepared.

For a program aimed at the synthesis of 11-deoxyprostaglandin congeners via the conjugate addition of β-chain organometallic reagents (**1** + **2** → **4**, Scheme I) we required a variety of 2-(ω-carbalkoxyalkyl)cyclopent-2-en-1-ones.[3a] The ω-carbalkoxyalkyl moiety (α chain) of these cyclopentenones was varied with respect to length, substituents, and heteroatom substitution, so that the

Scheme I



effects of these modifications upon the biological activities and metabolism of the derived prostaglandins could be studied. Of particular interest were the preparations of prostaglandin analogues, in which β-oxidative fatty acid metabolism would be blocked or at least hindered. The various cyclopentenones were of further interest, since,

(1) For the previous paper in this series, see S.-M. L. Chen and C. V. Grudzinskas, *J. Org. Chem.*, **45**, 2278 (1980).

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(3) (a) K. F. Bernady and M. J. Weiss, *Tetrahedron Lett.*, 4083 (1972); K. F. Bernady and M. J. Weiss, *Prostaglandins*, **3**, 505 (1973); K. F. Bernady, J. F. Poletto, and M. J. Weiss, *Tetrahedron Lett.*, 765 (1975); John F. Poletto, K. F. Bernady, D. Kupfer, R. Partridge, and M. J. Weiss, *J. Med. Chem.*, **18**, 359 (1975); J. S. Skotnicki, R. E. Schaub, M. J. Weiss, and F. Dessy, *ibid.*, **20**, 1042 (1977); J. S. Skotnicki, R. E. Schaub, K. F. Bernady, G. J. Siuta, J. F. Poletto, M. J. Weiss, and F. Dessy, *ibid.*, **20**, 1551 (1977); J. S. Skotnicki, R. E. Schaub, M. J. Weiss, and F. Dessy, *ibid.*, **20**, 1662 (1977). (b) See K. F. Bernady, M. B. Floyd, J. F. Poletto, and M. J. Weiss, *J. Org. Chem.*, **44**, 1438 (1979), ref 14.

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