Convenient Construction of Cyclopentanones via "Cyclopentannulation" of Carbonyls

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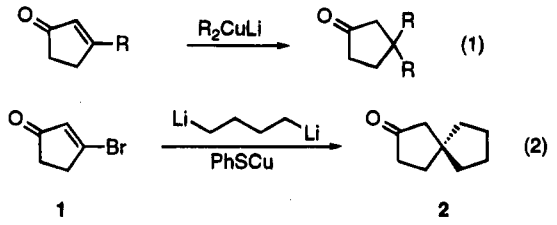
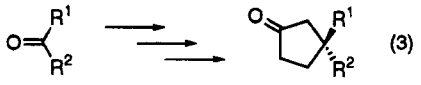
Received June 3, 1994

The cyclopentanone moiety is prevalent in organic chemistry.[1] Typically, the large number of commercially available quinanes obviates the need for their preparation in the laboratory. However, recent work in our group indicated that the currently known methods for the preparation of 3,3-disubstituted cyclopentanones were not amenable to our needs.[2] Specifically, these compounds have previously been prepared by the addition of cuprates to an appropriately functionalized enone (eq 1).[3] In an interesting extension, Wender has shown



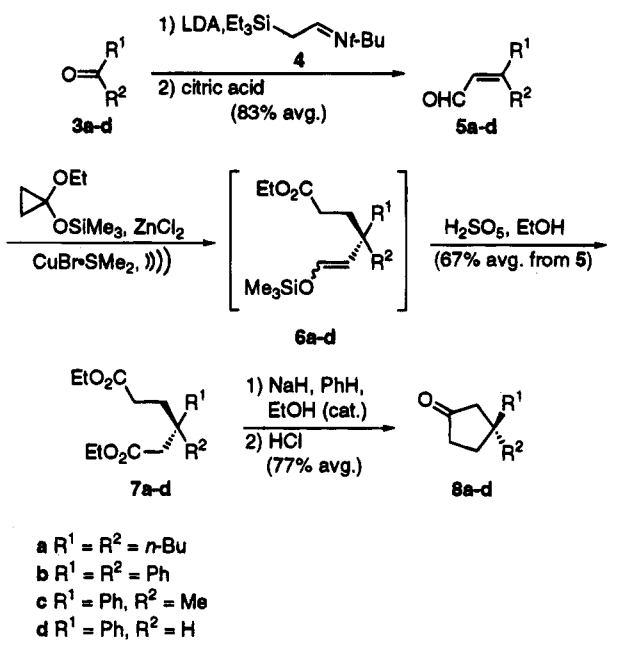
that spiroalkanones could be prepared in this fashion utilizing α,ω-bisorganocuprates (eq 2).[4]

Given that not all side chains are viable as cuprates, we sought to develop a general method in which the cyclopentanone could be prepared with properly functionalized side chains. The ease with which ketones can be prepared coupled with their ready availability led us to develop a general synthetic route to cyclopentanones from these compounds as well as aldehydes. In a formal sense, then, we needed to execute a "cyclopentannulation" about the carbonyl, as illustrated in eq 3.

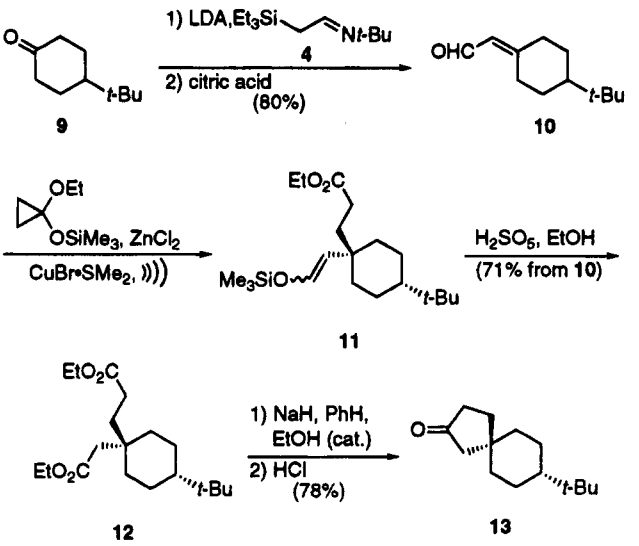


In the synthetic sense, Peterson olefination of the ketones **3** with silyl imine **4** led to the corresponding enals **5** upon mild acidic workup in an average yield of 83% (Scheme 1).[5] Copper-catalyzed addition of the zinc homoenolate derived from [(1-ethoxycyclopropyl)oxy]trimethylsilane[6,7] to **5** generated the silyl enol ethers **6**, which were not isolated but were treated with a solution of Caro's acid in ethanol to give the diesters **7**.[8] Dieckmann condensation followed by hydrolysis and decarboxylation finally afforded the desired cyclopentanones **8** in reasonable yield.

Scheme 1



Scheme 2



In order to evaluate the general synthetic utility of this transformation and to verify its effectiveness in the preparation of spiroalkanones, we performed our cyclopentannulation on a cyclohexanone (Scheme 2). The reactions proceeded as in the acyclic case to yield spiroalkanone **13** as a single compound.[9]

It should be noted that it was necessary to perform these additions on the enals as indicated, as addition to the corresponding esters did not occur to an appreciable extent.[10] The subsequent oxidation can be performed under milder conditions (such as with sodium chlorite)[11]

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(4) Wender, P. A.; White, A. W. *J. Am. Chem. Soc.* **1988**, *110*, 2218.
(5) For a similar addition, see: Schlessinger, R. H.; Poss, M. A.; Richardson, S.; Lin, P. *Tetrahedron Lett.* **1985**, *26*, 2391.
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(7) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056. For recent reviews of homoenolate chemistry, see: Kuwajima, I.; Nakamura, E. *Top. Curr. Chem.* **1990**, *155*, 1. Crimmins, M. T.; Nantermet, P. G. *Org. Prep. Proc. Int.* **1993**, *25*, 41.
(8) Nishihara, A.; Kubota, I. *J. Org. Chem.* **1968**, *33*, 2525.
(9) While we are certain that **13** is a single isomer by NMR, we have not rigorously proven the stereochemical outcome of the addition to the enal. It should be noted, however, that the structure shown above is that which would be expected to arise via equatorial attack followed by Dieckmann cyclization via the less hindered enolate. Additions to **9** typically occur in this fashion. For example, see: Nakamura, E.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1986**, *108*, 3745.

0022-3263/94/1959-5496$04.50/0

following liberation of the corresponding aldehyde.[2] This allows for considerable flexibility in the side chains that can be utilized.[2] Typically the Caro's acid oxidation is preferred, however, as it decreases the number of manipulations required in the overall synthesis.

In summary, we have developed a concise and generally applicable method for the synthesis of cyclopentanones with a variety of substituents at the 3-position. Given the facility with which these transformations can be realized, the carbonyl can thus be considered a viable retron for cyclopentanones. Work is underway in our laboratories to further explore this reaction and its use in the synthesis of natural and unnatural products.

Experimental Section

All compounds were obtained from Aldrich Chemical Co. and were used without further purification except where noted. Ether and THF were distilled under nitrogen from sodium and benzophenone. Benzene was distilled under nitrogen from calcium hydride. Diisopropylamine was distilled from potassium hydroxide. Analytical thin-layer chromatography was performed with E. Merck 250-μm precoated F-254 silica gel 60 plates. Flash chromatography was run under air pressure using 230–400 mesh silica gel supplied by E. Merck (Darmstadt).[12] The solution of butyllithium was standardized by titration with diphenylacetic acid. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$. J values are given in Hz. Infrared spectra were recorded as neat films on sodium chloride plates. Melting points are corrected. Microanalyses were performed by MHW Laboratories, Phoenix, AZ.

Silyl Imine 4. A solution of diisopropylamine (42.3 mL, 0.302 mol) in dry THF (600 mL) was cooled with stirring to −78 °C in a flame-dried round-bottomed flask under nitrogen, and butyllithium (125 mL, 2.30 M in hexanes, 0.287 mol) was added dropwise. The mixture was stirred for an additional 10 min, and a solution of *N-tert*-butylacetaldimine[13] (28.2843 g, 0.287 mol) in dry THF (15 mL) was added slowly. The mixture was stirred at −78 °C for an additional 30 min, and triethylsilyl chloride (48.0 mL, 0.287 mol) was added. The solution was allowed to warm to 0 °C over 3 h and then poured into water (700 mL) and extracted with ether. The combined extracts were washed with saturated brine and dried over potassium carbonate. The solution was filtered and concentrated on a rotary evaporator to a light yellow oil. Purification via vacuum distillation (100–105 °C at 18 mm) gave **4** as a colorless oil (54.8824 g, 90%). ^{1}H NMR: δ 0.58 (q, J = 7.9, 6 H), 0.96 (t, J = 7.9, 9 H), 1.16 (s, 9 H), 1.87 (d, J = 6.4, 2 H), 7.66 (t, J = 6.4, 1 H). ^{13}C NMR: δ 3.5, 7.1, 24.2, 29.7, 56.2, 156.2. Anal. Calcd for $C_{12}H_{27}NSi$: C, 67.53; H, 12.75; N, 6.56. Found: C, 67.61; H, 12.84; N, 6.70.

General Procedure for the Synthesis of Enals 5. A solution of diisopropylamine (2.02 mL, 14.4 mmol) in dry THF (25 mL) was cooled with stirring to 0 °C in a flame-dried round-bottomed flask under nitrogen, and butyllithium (5.95 mL, 2.40 M in hexanes, 14.3 mmol) was added dropwise. The mixture was stirred for an additional 10 min, and a solution of freshly distilled **4** (3.06 g, 14.3 mmol) in dry THF (5 mL) was added dropwise. The red solution was stirred at 0 °C for an additional 15 min and then cooled to −78 °C. A solution of carbonyl **3** (6.34 mmol) in dry THF (5 mL) was added, and the resulting mixture was warmed to room temperature over 3 h. The reaction was acidified to pH 4 with 20% aqueous citric acid and then was stirred under nitrogen overnight at room temperature. The mixture was poured into saturated brine (70 mL) and extracted with ether. The combined organic extracts were washed with saturated sodium bicarbonate and dried over magnesium sulfate. The mixture was filtered and the solvent removed on a rotary evaporator to give a yellow oil. Purification by flash chromatography produced the desired enals.

5a. 5-Nonanone (505.9 mg, 3.50 mmol) was treated as above to give **5a** as a colorless oil (525.4 mg, 89%). ^{1}H NMR: δ 0.93 (t, J = 7.3, 3 H), 0.94 (t, J = 7.3, 3 H), 1.35 (m, 4 H), 1.47 (m, 4 H), 2.22 (dt, J = 1.1, 7.6, 2 H), 2.56 (t, J = 7.8, 2 H), 5.85 (d, J = 8.2, 1 H), 9.99 (d, J = 8.2, 1 H). ^{13}C NMR: δ 13.8, 13.8, 22.4, 22.7, 29.5, 31.1, 31.7, 37.7, 127.1, 168.9, 191.1. IR: 1680 (s), 1630 (m), 1570 (m) cm^{-1}. Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.36; H, 12.09.

5b. Benzophenone (1.0152 g, 5.57 mmol) was treated as above to give **5b** as a yellow oil (899.0 mg, 78%). ^{1}H NMR: δ 6.60 (d, J = 8.0, 1 H), 7.37 (m, 10 H), 9.53 (d, J = 8.0, 1 H). ^{13}C NMR: δ 127.2, 128.3, 128.6, 128.6, 129.4, 130.4, 130.7, 136.6, 139.7, 162.2, 193.5. IR: 1660 (s), 1590 (m), 1560 (m), 1490 (m), 1445 (m), 1390 (m), 1340 (m), 1240 (m) cm^{-1}.

5c. Acetophenone (762.2 mg, 6.34 mmol) was treated as above to give **5c** (obtained as a colorless oil) as a mixture of isomers (801.3 mg, 86%). ^{1}H NMR: major δ 2.13 (d, J = 1.1, 3 H), 6.14 (dd, J = 1.3, 8.2, 1 H), 7.30 (m, 2 H), 7.41 (m, 3 H), 9.47 (d, J = 8.2, 1 H); minor δ 2.57 (d, J = 1.3, 3 H), 6.39 (dd, J = 1.2, 7.8, 1 H), 7.41 (m, 3 H), 7.55 (m, 2 H), 10.18 (d, J = 7.6, 1 H). Mixture ^{13}C NMR: δ 16.3, 26.4, 126.2, 127.2, 128.3, 128.3, 128.7, 129.1, 129.1, 130.0, 138.4, 140.5, 157.5, 162.0, 191.1, 193.3. IR: 1650 (s), 1615 (m), 1490 (m), 1440 (m), 1390 (m), 1370 (m), 1140 (s) cm^{-1}. Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 81.92; H, 7.00.

5d. Benzaldehyde (503.9 mg, 4.71 mmol) was treated as above to give **5d** as a colorless oil (482.0 mg, 78%). ^{1}H NMR: δ 6.72 (dd, J = 7.7, 16.0, 1 H), 7.43 (m, 3 H), 7.48 (d, J = 16.0, 1 H), 7.56 (m, 2 H), 9.70 (d, J = 7.7, 1 H). ^{13}C NMR: δ 128.4, 128.5, 129.0, 131.2, 133.9, 152.7, 193.6.

General Procedure for the Synthesis of Diesters 7. A solution of [(1-ethoxycyclopropyl)oxy]trimethylsilane (3.00 mL, 14.8 mmol) in dry ether (35 mL) was stirred at room temperature in a flame-dried round-bottomed flask under argon, and a solution of zinc chloride (10.9 mL, 1.0 M, 10.9 mmol) in ether was added. The mixture was heated to reflux with sonication in an ultrasonic bath for 2 h and then was cooled to 0 °C. Following addition of cuprous bromide–dimethyl sulfide complex (614.8 mg, 2.97 mmol), a solution of **5** (5.94 mmol) in dry THF (35 mL) was added dropwise, and then HMPA (2.60 mL, 14.8 mmol) was added. The resulting solution was stirred at 0 °C for 5 min and then was warmed to room temperature with stirring for 3 h. Saturated ammonium chloride (15 mL) was added, and the mixture was washed with half-saturated ammonium chloride until the aqueous layer was no longer blue. The aqueous layer was back-extracted with ether, and the combined organic layers were washed with saturated brine and dried over potassium carbonate. The solution was filtered and the solvent removed on a rotary evaporator to give a colorless oil. This crude oil was dissolved in absolute ethanol (15 mL) and cooled to 0 °C under nitrogen, and Caro's acid [prepared from potassium persulfate (1.7557 g, 6.5 mmol) in concentrated sulfuric acid (5.3 g)] was added dropwise. The reaction was stirred at 0 °C for 6 h and poured into saturated brine (25 mL). The mixture was extracted with ether, and the combined organic layers were washed with brine and dried over potassium carbonate. The solution was filtered and concentrated on a rotary evaporator to give a yellow oil. Purification by flash chromatography provided the desired diesters.

7a. **5a** (316.5 mg, 1.88 mmol) was treated as above to give **7a** as a colorless oil (421.7 mg, 71%). ^{1}H NMR: δ 0.90 (t, J = 7.0, 6 H), 1.24 (m, 12 H), 1.65 (m, 2H), 2.19 (s, 2 H), 2.27 (m, 2 H), 4.10 (q, J = 7.1, 2 H), 4.12 (q, J = 7.2, 2 H). ^{13}C NMR: δ 14.1, 14.1, 14.2, 23.4, 25.2, 28.8, 31.5, 36.2, 38.0, 41.2, 59.9, 60.3, 171.9, 174.0. IR: 1740 (s) cm^{-1}. Anal. Calcd for $C_{18}H_{34}O_4$: C, 68.75; H, 10.90. Found: C, 68.87; H, 10.87.

7b. **5b** (1.5020 g, 7.20 mmol) was treated as above to give **7b** as a yellow oil (1.1092 g, 44%). ^{1}H NMR: δ 0.92 (t, J = 7.1, 3 H), 1.20 (t, J = 7.1, 3 H), 2.11 (m, 2 H), 2.62 (m, 2 H), 2.69 (m, 2 H), 2.56 (t, J = 7.8, 2 H), 3.08 (s, 2 H), 3.83 (q, J = 7.1, 2 H), 4.04 (q, J = 7.1, 2 H), 7.16 (m, 6 H), 7.27 (m, 4 H). ^{13}C NMR:

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δ 13.8, 14.1, 29.7, 32.7, 43.0, 48.2, 60.1, 60.3, 126.3, 127.6, 128.0, 146.3, 170.9, 173.4. Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.78; H, 7.31.

7c. **5c** (444.4 mg, 3.04 mmol) was treated as above to give **7c** as a colorless oil (619.1 mg, 70%). ^{1}H NMR: δ 1.07 (t, J = 7.3, 3 H), 1.20 (t, J = 7.1, 3 H), 1.49 (s, 3 H), 2.12 (m, 4 H), 2.59 (d, J = 13.9, 1 H), 2.70 (d, J = 13.9, 1 H), 3.97 (t, J = 7.1, 2 H), 4.05 (q, J = 7.1, 2 H), 7.20 (m, 1 H), 7.31 (m, 4 H). ^{13}C NMR: δ 14.0, 14.1, 24.0, 29.6, 37.1, 39.9, 47.2, 60.0, 60.3, 126.0, 126.2, 128.2, 145.0, 171.1, 173.6. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.89; H, 8.38.

7d. **5d** (629.1 mg, 4.76 mmol) was treated as above to give **7d** as a colorless oil (1.0730 g 81%). ^{1}H NMR: δ 1.13 (t, J = 7.1, 3 H), 1.20 (t, J = 7.1, 3 H), 1.91 (m, 1 H), 2.05 (m, 1 H), 2.14 (m, 2 H), 2.61 (m, 2 H), 3.11 (m, 1 H), 4.04 (m, 4 H), 7.20 (m, 3 H), 7.29 (m, 2 H). ^{13}C NMR: δ 14.0, 14,1, 24.3, 31.0, 32.2, 41.6, 60.2, 60.2, 126.7, 127.4, 128.5, 142.6, 171.9, 173.1. IR: 1730 (s), 1720 (s), 1450 (m), 1370 (m), 1150 (m) cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.87; H, 7.96.

General Procedure for the Synthesis of Cyclopentanones 8. A flame-dried round-bottomed flask was charged with sodium hydride (24.9 mg, 50% oil dispersion, 0.52 mmol) under nitrogen, and the solid was washed with pentane (3 × 5 mL). Dry benzene (2 mL) was added, followed by a solution of **7** (0.354 mmol) in dry benzene (1 mL) and absolute ethanol (0.15 mL). The mixture was heated to reflux under argon for 5 h, and a mixture of 6 N hydrochloric acid (4 mL) and THF (3 mL) was added. The mixture was heated to reflux overnight and then was cooled and extracted with ether. The combined organic extracts were washed with water and saturated brine and dried over magnesium sulfate. The mixture was filtered, and the solvent was removed on a rotary evaporator to give a light oil. Purification by flash chromatography gave the desired cyclopentanones.

8a. **7a** (493.2 mg, 1.57 mmol) was treated as above to give **8a** as a colorless oil (260.8 mg, 85%). ^{1}H NMR: δ 0.91 (t, J = 7.1, 6 H), 1.3 (m, 12 H), 1.79 (t, J = 8.0, 2 H), 1.96 (s, 2 H), 2.24 (t, J = 7.9, 2 H). ^{13}C NMR: δ 14.0, 23.3, 26.3, 33.1, 36.4, 37.4, 42.1, 51.1, 220.2. IR: 1745 (s) cm^{-1}. Anal. Calcd for $C_{13}H_{24}O\cdot 0.1H_2O$: C, 78.81; H, 12.31. Found: C, 78.58; H, 12.47.

8b. **7b** (125.3 mg, 0.354 mmol) was treated as above to give **8b** as a colorless oil (50.1 mg, 60%). ^{1}H NMR: δ 2.28 (t, J = 7.5, 2 H), 2.71 (t, J = 7.5, 2 H), 3.00 (s, 2 H), 7.18 (m, 2 H), 7.27 (m, 8 H). ^{13}C NMR: δ 35.3, 36.5, 51.8, 126.4, 126.7, 128.5, 146.5, 217.3.[14]

8c. **7c** (207.0 mg, 0.708 mmol) was treated as above to give **8c** as a colorless oil (99.8 mg, 81%). ^{1}H NMR: δ 1.38 (s, 3 H), 2.34 (m, 4 H), 2.47 (d, J = 17.3, 1 H), 2.65 (d, J = 17.6, 1 H), 7.28 (m, 5 H). ^{13}C NMR: δ 29.4, 35.7, 36.7, 43.8, 52.2, 125.4, 126.3, 128.5, 148.4, 218.5.[15]

8d. **7d** (306.9 mg, 1.08 mmol) was treated as above to give **8d** as a colorless oil (136.2 mg, 80%). ^{1}H NMR: δ 1.96 (m, 1 H), 2.19 (m, 2 H), 2.43 (m, 2 H), 2.64 (dd, J = 7.7, 18.2, 1 H), 3.39 (m, 1 H), 7.22 (m, 3 H), 7.30 (m, 2 H). ^{13}C NMR: δ 31.0, 38.7, 42.0, 45.6, 126.5, 126.6, 128.5, 142.9, 218.1.[16]

Enal 10. A solution of diisopropylamine (1.60 mL, 11.3 mmol) in dry THF (20 mL) was cooled with stirring to 0 °C in a flame-dried round-bottomed flask under nitrogen, and butyllithium (4.65 mL, 2.40 M in hexanes, 11.2 mmol) was added dropwise. The mixture was stirred for an additional 10 min, and a solution of freshly distilled **4** (2.39 g, 11.2 mmol) in dry THF (5 mL) was added dropwise. The red solution was stirred at 0 °C for an additional 15 min and then cooled to −78 °C. A solution of **9** (750 mg, 4.86 mmol) in dry THF (5 mL) was added, and the resulting mixture was warmed to room temperature over 3 h. The reaction was acidified to pH 4 with 20% aqueous citric acid and then was stirred under nitrogen overnight at room temperature. The mixture was poured into saturated brine (50 mL) and extracted with ether. The combined organic extracts were washed with saturated sodium bicarbonate and dried over magnesium sulfate. The mixture was filtered and the solvent removed on a rotary evaporator to give a yellow oil. Purification by flash chromatography produced **10** as a colorless oil (698 mg, 80%). ^{1}H NMR: δ 0.88 (s, 9 H), 0.95 (m, 1 H), 1.26 (m, 3 H), 2.02 (m, 3 H), 2.44 (dt, J = 4.4, 13.3, 1 H), 3.42 (m, 1 H), 5.81 (d, J = 8.3, 1 H), 10.01 (d, J = 8.3, 1 H). ^{13}C NMR: δ 27.5, 28.8, 29.0, 29.3, 32.4, 37.9, 47.8, 124.9, 168.1, 190.6.

Diester 12. A solution of [(1-ethoxycyclopropyl)oxy]trimethylsilane (0.790 mL, 3.95 mmol) in dry ether (10 mL) was stirred at room temperature in a flame-dried round-bottomed flask under argon, and a solution of zinc chloride (2.90 mL, 1.0 M, 2.90 mmol) in ether was added. The mixture was heated to reflux with sonication in an ultrasonic bath for 2 h and then was cooled to 0 °C. Following addition of cuprous bromide–dimethyl sulfide complex (163 mg, 0.790 mmol), a solution of **10** (282 mg, 1.58 mmol) in dry THF (10 mL) was added dropwise, and then HMPA (0.690 mL, 3.95 mmol) was added. The resulting solution was stirred at 0 °C for 5 min and then was warmed to room temperature with stirring for 3 h. Saturated ammonium chloride (15 mL) was added, and the mixture was washed with half-saturated ammonium chloride until the aqueous layer was no longer blue. The aqueous layer was back-extracted with ether, and the combined organic layers were washed with saturated brine and dried over potassium carbonate. The solution was filtered and the solvent removed on a rotary evaporator to give a colorless oil. This crude oil was dissolved in absolute ethanol (15 mL) and cooled to 0 °C under nitrogen, and Caro's acid [prepared from potassium persulfate (1.07 g, 3.95 mmol) in concentrated sulfuric acid (3.2 g)] was added dropwise. The reaction was stirred at 0 °C for 6 h and poured into saturated brine (20 mL). The mixture was extracted with ether, and the combined organic layers were washed with brine and dried over potassium carbonate. The solution was filtered and concentrated on a rotary evaporator to give a yellow oil. Purification by flash chromatography provided **12** as a colorless oil (367 mg, 71%). ^{1}H NMR: δ 0.85 (s, 9 H), 0.96 (m, 1 H), 1.15 (m, 4 H), 1.25 (t, J = 7.1, 6 H), 1.64 (m, 6 H), 2.30 (s, 2 H), 2.37 (m, 2 H), 4.12 (q, J = 7.1, 4 H). ^{13}C NMR: δ 14.2, 14.2, 22.4, 27.5, 28.8, 32.4, 35.3, 36.2, 36.8, 37.5, 48.1, 60.0, 60.2, 172.2, 174.1. Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 70.10; H, 10.53.

Spiroalkanone 13. A flame-dried round-bottomed flask was charged with sodium hydride (76.0 mg, 50% oil dispersion, 1.58 mmol) under nitrogen, and the solid was washed with pentane (3 × 5 mL). Dry benzene (5 mL) was added, followed by a solution of **12** (386 mg, 1.18 mmol) in dry benzene (3 mL) and absolute ethanol (0.15 mL). The mixture was heated to reflux under argon for 5 h, and a mixture of 6 N hydrochloric acid (8 mL) and THF (6 mL) was added. The mixture was heated to reflux overnight and then was cooled and extracted with ether. The combined organic extracts were washed with water and saturated brine and dried over magnesium sulfate. The mixture was filtered, and the solvent was removed on a rotary evaporator to give a light oil. Purification by flash chromatography gave **13** as a white solid (191 mg, 78%). Mp: 43.5–45.5 °C. ^{1}H NMR: δ 0.84 (s, 9 H), 1.03 (m, 3 H), 1.33 (m, 2 H), 1.64 (m, 4 H), 1.75 (d, J = 8.0, 2 H), 2.12 (s, 2 H), 2.27 (t, J = 8.0, 2 H). ^{13}C NMR: δ 24.1, 27.5, 32.4, 36.4, 37.4, 37.8, 40.1, 48.0, 48.2, 220.1. Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.80; H, 11.70.

Acknowledgment. This work was funded in part by the Committee on Research at the University of California and the University of California Cancer Research Coordinating Committee. In addition, acknowledgment is made to the donors of the Petroleum Research Fund (ACS-PRF no. 28001-G1), administered by the American Chemical Society, for partial support of this research. D.P.P. is grateful to the Eastman Kodak Co. for a Kodak fellowship.

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