minum oxide chromatography. Optical purity was determined by proton NMR using the chiral shift reagent tris[3-((trifluoromethyl)hydroxymethylene)-*d*-camphorato]europium (III)[13] and showed no detectable amounts of the other enantiomer.

In summary, we have shown that CoA and acetyl-CoA can be used to generate millimole quantities of product using enzyme-catalyzed carbon–carbon bond-forming and esterification reactions. While recycle numbers of 11 800 have been achieved, the high cost of CoA requires further optimization of this system except for very high valued products (>$100/mol). Further studies are in progress to apply this method to the production of fatty acids and polyketide-derived natural products.

Experimental Section

Proton NMR were recorded on a 300-MHz Bruker instrument. A coaxial NMR tube (Wilmad) was used to record the spectra. The inner 5 mm tube was filled with the reaction mixture in water and the outer 10 mm tube with D_2O as the locking solvent. A Waters HPLC instrument with reverse phase C-18 column was used to monitor the reaction and assay the enzymes.

Oxaloacetic acid, DL-carnitine, and tris[3-((trifluoromethyl)-hydroxymethylene)-*d*-camphorato]europium(III) were purchased from Aldrich. Acetyl phosphate, phosphotransacetylase, citrate synthase, and carnitine acetyltransferase were purchased from Sigma. PAN was prepared by a reported procedure.[7]

Acetyl-CoA Recycling: Synthesis of Citric Acid (Scheme I). A typical small scale reaction was carried out as follows: Acetyl phosphate K^+, Li^+ salt (55 mg, 0.3 mmol) and oxaloacetic acid (40 mg, 0.3 mmol) [each dissolved separately in 0.5 mL of 0.5 M Tris buffer of pH 7.5 and neutralized with 2 M Tris base to pH 7.8] were added in small aliquots (0.1 mL) to the reaction mixture consisting of CoA (1.24×10^{-5} mmol), dithiothreitol (6×10^{-4} mmol), ammonium sulfate (1×10^{-2} mmol), and the enzymes phosphotransacetylase (E.C. 2.3.1.8) (500 U) and citrate synthase (E.C. 4.1.3.7) (200 U) in Tris buffer pH 7.5 at 40 °C. (Final volume of the reaction was 1.5 mL). The reaction was carried out under N_2 at 40 °C. The presence of CoA was followed by HPLC,[14] and the progress of the reaction was monitored by the formation of citrate using ^1H NMR. After 7 days, 0.147 mmol of citrate was formed as determined from ^1H NMR using methanol as an internal standard. This corresponds to a recycling number of 11 800 for acetyl-CoA. The reaction was repeated on a larger scale by using acetyl phosphate (0.9 g, 5.0 mmol), oxaloacetate (0.66 g, 5.0 mmol), CoA (7.3×10^{-3} mmol), 1500 U of phosphotransacetylase, and 500 U of citrate synthase in a total volume of 40 mL of 0.5 M Tris buffer pH 7.8. After 7 days citric acid (0.86 g, 4 mmol) was formed corresponding to a recycling of 560 for acetyl-CoA. Citric acid was purified from the reaction mixture as follows: The reaction mixture was acidified to pH 1 and lyophilized to a white powder which was extracted with ethyl acetate (4 × 20 mL). Ethyl acetate was removed under reduced pressure to give an oil containing 80% citric acid as determined by ^1H NMR. The remaining material consisted entirely of Tris base.

Acetyl-CoA Recycling Using Immobilized Enzymes. The above procedure was repeated using PAN immobilized[7] phosphotransacetylase (50 U) and citrate synthase (50 U). Acetyl-CoA was recycled 400 times to furnish 80 mg of citric acid after 3 days of reaction. At the end of the reaction, the enzyme activity was recovered by centrifuging the gel and washing with 0.5 M Tris buffer pH 7.4. The enzymes were assayed using HPLC[14] and immobilized PTA retained 80% of its activity after 3 days in the reaction mixture at 4 °C and 15 days storage at 0–4 °C.

Acetyl-CoA Recycling: Synthesis of L-Acetylcarnitine (Scheme III). DL-Carnitine (1 g, 5 mmol) and acetyl phosphate (0.5 g, 2.7 mmol) [each dissolved separately in 1 mL of 0.5M Tris buffer of pH 7.5 and neutralized with 2 M Tris base of pH 7.8 at 25 °C] were added to CoA (3.3×10^{-3} mmol), dithiothreitol (0.03 mmol), manganese sulfate (0.01 mmol), and the enzymes phosphotransacetylase (200 U) and carnitine acetyltransferase (2.3.1.7, 160 U) in 0.5 M Tris buffer in a round-bottomed reaction flask (total volume 3.3 mL). The reaction mixture was purged with argon and stirred at 40 °C. After 12 h, the reaction reached equilibrium with 60% conversion of L-carnitine to L-acetylcarnitine as determined from the 300-MHz proton NMR. The trimethylammonium protons of carnitine appears at 3.0 ppm and those of acetylcarnitine at 2.96 ppm. The ratio of these peaks for the conversion corresponds to a recycling number of 420 for acetyl coenzyme A. A similar small scale reaction with lesser amounts of coenzyme A and kept for longer periods has furnished a recycling number of 2500 for acetyl coenzyme A. L-Acetylcarnitine was purified from DL-carnitine by aluminum oxide preparative chromatography developed with 14:5:1 methylene chloride/methanol/ammonium hydroxide. Its optical purity was confirmed by proton NMR using the chiral shift reagent, tris-[3-((trifluoromethyl)hydroxymethylene)-*d*-camphorato]europium(III). When an equimolar quantity of the chiral shift reagent was added to DL-acetylcarnitine, resolution of the two enantiomers was observed on the proton NMR. The acetyl group appears as a doublet at 2.06 ppm and the trimethylammonium group as a doublet at 3.4 ppm. Addition of the chiral shift reagent to the acetylcarnitine purified from the above reaction showed only one isomer in the proton NMR.

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Registry No. 1, 328-42-7; 2, 77-92-9; 4, 406-76-8; 5, 3040-38-8; PTA, 9029-91-8; CoA, 85-61-0; CoA-SAc, 72-89-9; E.C.6.2.1.1, 9012-31-1; E.C.4.1.3.7, 9027-96-7; E.C.2.3.1.7, 9029-90-7.

(13) McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038.

(14) HPLC was done on a Versapack C-18, 10-μm column using potassium phosphate (0.22 M), 12% methanol buffer, pH 4 as th eluant.

Carbon–Carbon Bond Fragmentation through Oxidative Electrolysis of Carboxylic Acids and Its Application to the Synthesis of Malyngolide

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The pioneering work of Corey[1] established a paradigm for oxidative electrolysis of γ-hydroxy acid **1** which proceeds through initial carbonium ion formation followed by fragmentation to form an oxygen stabilized cation **2**. Loss of a proton, then gives keto olefin **3** (Scheme I).

This paradigm and the expectation that ketals should exert a stronger carbocation stabilizing effect led us to examine the oxidative electrolysis of γ-ketal carboxylic acid **4** to olefinic ester **5** (Scheme II).

We now wish to report the success of this design which represents the first case in which a ketal stabilized carbocation participates in an electrolytically induced carbon–carbon bond fragmentation.

The desired substrate **4** was readily prepared from 3-methoxybenzoic acid (**6**). Reductive alkylation[2] with 1-bromononane gave acid **7**, which upon distillation cyclized to lactone **8** in 82.8% overall yield. Hydrogenation, methanolysis, and ketalization secured ester **9** in 98.0% yield. Basic hydrolysis gave acid **4** in 98.8% (Scheme III).

With acid **4** in hand we examined the electrolysis under a variety of conditions. Experimentally, all electrolysis reactions were run at 50 applied V DC at 0.5 ampere be-

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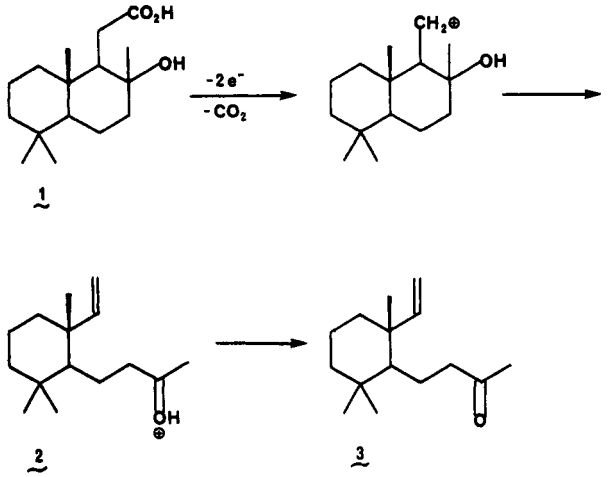
Scheme I



Scheme II

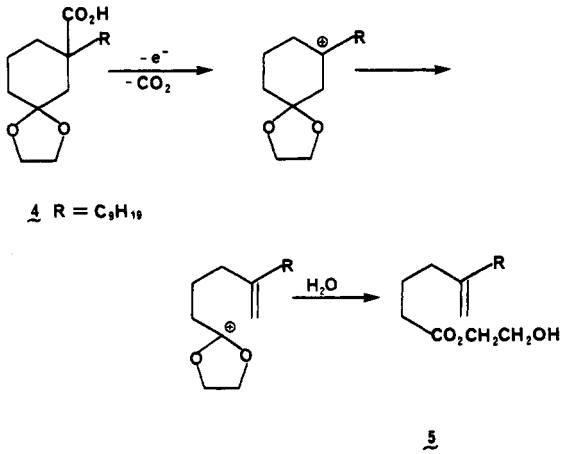


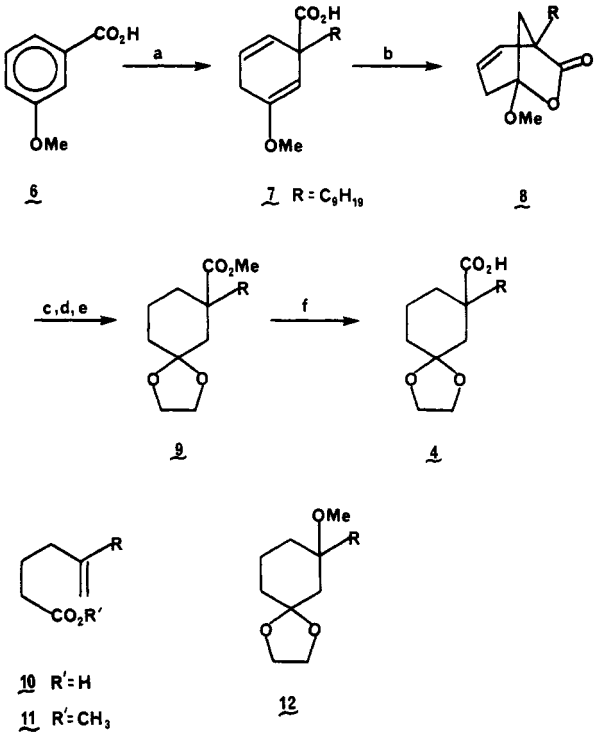
Table I

conditions	isolated yields, % 5	10	12	11
anhydrous MeOH, Pt electrodes	16.4	10.0	39.1	
anhydrous MeOH, carbon stick electrodes	24.1	13.1	0.0	
anhydrous MeOH, carbon plate electrodes followed by KOH/H_2O; CH_2N_2				78.6

cause it is well-known that carbonium ion formation is favored by the use of high applied voltage with carbon electrodes in akaline media.[3] From Table I it is clear that the type of electrode material is of considerable importance for achieving a high yield of the desired fragmentation product. The softer porous carbon plate electrodes[4] give the best yield of ester while the harder carbon stick electrodes[5] produce the desired fragmentation products in an exiguous yield of 37.2%. The use of platinum electrodes results in formation of considerable quantities of methyl ether 12 along with the desired fragmentation products. With regard to solvent we found that the use of CH_2Cl_2, CH_3CN, and $MeOH/H_2O$ failed to produce product. Anhydrous methanol proved to be the solvent of choice. In all cases only esters or acids were isolated rather than the mixed ortho esters as would be expected by trapping of the intermediate carbonium ion with methanol. This is presumably due to the presence of adventitious water. It should be noted that chemical means to effect a similar fragmentation were entirely unsuccessful. Treatment of the acid 4 with lead tetraacetate[6] gave only olefinic products without a trace of the desired fragmentation product, thus placing the electrochemical approach in a unique position.

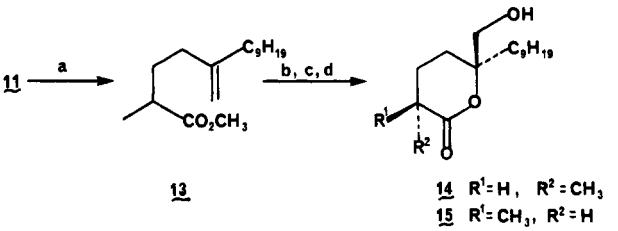
Having realized success in the desired fragmentation we turned our attention to the synthesis of malyngolide (14).[7] Ester 11 was alkylated with MeI in 92% yield and oxidized

Scheme III[a]



[a] (a) Li/NH_3; $C_9H_{19}Br$; (b) distillation, 144–146 °C (0.5 torr); (c) H_2, Pd, MeOH; (d) MeOH, TsOH, Δ; (e) $(CH_2OH)_2$, TsOH, PhH, Δ; (f) KOH, EtOH, Δ.

Scheme IV[a]



[a] (a) LDA, HMPA, THF; MeI; (b) OsO_4, NMO, H_2O, H_2O, *t*-BuOH; (c) KOH, EtOH; (d) HCl, $CHCl_3$.

(1) (a) Corey, E. J.; Sauers, R. R. *J. Am. Chem. Soc.* **1957**, *79*, 3925. (b) Corey, E. J.; Sauers, R. R.; Swann, S., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 5826. (c) Corey, E. J.; Sauers, R. R. *J. Am. Chem. Soc.* **1959**, *81*, 1739, 1743. (d) Bauld, N. L. Ph.D. Dissertation, University of Illinois, Urbana, 1959. (e) Corey, E. J.; Bauld, N. L.; La Londe, R. T.; Casanova, J., Jr.; Kaiser, E. T. *J. Am. Chem. Soc.* **1960**, *82*, 2645.

(2) Nelson, N. A.; Fassnacht, J. H.; Piper, J. U. *J. Am. Chem. Soc.* **1961**, *83*, 206.

(3) Koehl, W. J., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 4686. Parker, V. D. *J. Chem. Soc., Chem. Commun.* **1968**, 1164. For an excellent discussion of the factors favoring carbonium ion formation, see: Eberson, L.; Utley, J. H. F. In *Organic Electrochemistry*; Baizer, M. M., and Lund, H., Eds.; Marcel Dekker: New York, 1983; Chapter 14.

(4) These were obtained from Prof. H. J. Schäfer of the Organisch-Chemisches Institut der Wesfalischen Wilhelms-Universitat, Munster, West Germany.

(5) Purchased from Alfa Inorganics.

(6) Corey, E. J.; Casanova, J., Jr., *J. Am. Chem. Soc.* **1963**, *85*, 165. Birladeanu, L.; Hanafusa, T.; Winstein, S. *J. Am. Chem. Soc.* **1966**, *88*, 2315.

(7) Cardellina, J. H., II; Moore, R. E.; Arnold, E. V.; Clardy, J. *J. Org. Chem.* **1979**, *44*, 4039.

to a mixture of diastereomeric diols (Scheme IV). Treatment of the diols with HCl in $CHCl_3$ cleanly gave malyngolide in 63% yield along with 35% of its epimer, which was conveniently separated by chromatography. Infrared and NMR spectra of malyngolide and epimalyngolide were identical with those reported in the literature.[8] The unexpected 2:1 ratio of isomers achieved in the osmium oxidation indicates that the methyl group exerts a significant influence on the facial selectivity in the addition reaction. This effect is particularly unusual in that the center of chirality is significantly removed from the site of reactivity.

From these results it is clear that a ketal may readily serve as a terminator in an oxidatively induced carbon–carbon bond fragmentation initiated by electrolysis of a γ-ketal carboxylic acid. This process should be applicable to a wide variety of substrates.

Experimental Section

^1H NMR spectra were obtained on a Varian T-60 spectrometer and a Bruker WM-360 spectrometer. Carbon-13 NMR spectra were obtained on a Jeol FX-90Q spectrometer. Infrared spectra were recorded on a Beckman Accu Lab 1 and a Nicolet DX FT spectrophotometer. Melting points are uncorrected. Solvents and reagents were commercially available unless otherwise noted and were used directly. *n*-Bromononane, ethylene glycol, and methyl iodide were dried and distilled before use. Methanol was dried over magnesium and distilled before use. Tetrahydrofuran was distilled from sodium/benzophenone ketyl and HMPA was distilled from calcium hydride before use. Microanalyses were performed by Spang Microanalytical Laboratory and Galbraith Labs., Inc. The DC power supply was a B. K. Precision Model 1601.

1-Methoxy-5-nonyl-7-oxabicyclo[3.2.1]-3-octen-6-one (8). Into a suspension of 9.32 g (60.0 mmol) of 3-methoxybenzoic acid and 75 mL of tetrahydrofuran, cooled in a dry ice/acetone bath, was condensed 250 mL of liquid ammonia. Lithium (1.0 g, 144 mmol) was added in small pieces until a blue color persisted. When lithium addition was complete, the solution was stirred for an additional 25 min, and then 17.4 mL (18.83 g, 90.0 mmol) of *n*-bromononane was added over a period of 10 min, whereupon the color turned from orange to yellow and eventually white. Stirring was continued for another 15 min, and then ammonium chloride (9.64 g, 180 mmol) was carefully added. Ammonia was then removed in a slow stream of argon and finally in vacuo. The remaining material was dissolved in 120 mL of water and the solution washed with ether. The aqueous layer was cooled to −5 °C and acidified to pH 5 with cold concentrated hydrochloric acid. The product was immediately extracted with ether three times. The ether extracts were dried over anhydrous magnesium sulfate and concentrated to give the crude 3-methoxy-1-nonyl-2,5-cyclohexadienecarboxylic acid (7): IR (film) 3200, 2920, 2850, 2620 (br), 1780, 1690, 1650, 1585, 1460, 1380, 1270, 1220, 1180, 1130, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) 5.80 (m, 2 H), 4.75 (s, 1 H), 3.64 (s, 3 H), 2.70 (m, 2 H), 1.30 (s, 16 H), 0.88 ppm (t, 3 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) 181.9, 154.3, 127.7, 127.5, 124.0, 95.1, 53.9, 50.0, 40.4, 31.9, 29.9, 29.6, 29.3, 28.7, 24.2, 22.7, 14.1 ppm. Distillation [144–146 °C (0.5 mmHg)] of the crude acid afforded 14.77 g (52.7 mmol, 87.8%) of 1-methoxy-5-nonyl-6-oxabicyclo[3.2.1]-3-octen-6-one (8): IR (film) 3050, 2930, 2860, 1780, 1650, 1470, 1360, 1250, 1140, 1060, 930, 900, 800, 690 cm^{-1}; ^1H NMR ($CDCl_3$) 5.84 (dd, 1 H, J = 9.3, 3.5 Hz), 5.70 (dd, 1 H, J = 9.3, 1.9 Hz), 3.51 (s, 3 H), 2.67 (m, 2 H), 2.24 (d, 1 H, J = 10.8 Hz), 1.86 (d, 1 H, J = 10.8 Hz), 1.27 (s, 16 H), 0.88 ppm (t, 3 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) 175.7, 132.1, 127.8, 107.7, 50.8, 50.7, 40.5, 35.8, 33.9, 32.9, 31.8, 29.9, 29.4, 29.3, 24.7, 22.7, 14.1 ppm. Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.07. Found: C, 72.81; H, 10.20.

Methyl 1-Nonyl-3-oxocyclohexanecarboxylate Ethylene Ketal (9). A mixture of 3.85 g (13.7 mmol) of 1-methoxy-5-nonyl-6-oxabicyclo[3.2.1]-3-octen-6-one (8), 30 mL of methanol, and 300 mg of 5% palladium on activated carbon were placed under an atmosphere of hydrogen and stirred overnight. At the end of hydrogenation, palladium was removed by filtration through Celite and methanol removed under reduced pressure. Ether was added to the oil and the solution washed with water (2x) and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated. The residue was distilled [144–145 °C (0.3 mmHg)] to give crude saturated bicyclic lactone. The crude lactone and 0.5 g of *p*-toluenesulfonic acid monohydrate were dissolved in 80 mL of methanol and then heated to reflux overnight. The solution was cooled and methanol removed under reduced pressure. Ether was added to the residue and the solution washed successively with two 50-mL portions of 10% sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated to give an ester. A solution of this ester, 1.28 g (20.6 mmol) of ethylene glycol, and 0.4 g of *p*-toluenesulfonic acid monohydrate in 60 mL of benzene was heated to reflux with continuous removal of water for 18 h. The reaction mixture was cooled and washed three times with 60 mL of saturated sodium bicarbonate solution and then with water. The aqueous layer was extracted with ether and the combined organic layer dried over anhydrous magnesium sulfate. Purification by flash chromatography over silica gel with 40% ethyl acetate/hexane followed by Kugelrhor distillation [135–136 °C (0.2 mmHg)] gave 4.40 g (13.5 mmol, 98.0%) of methyl 1-nonyl-3-oxo-cyclohexanecarboxylate ethylene ketal (9): IR (film) 2925, 2860, 1735, 1460, 1380, 1290, 1210, 1170, 1125, 1080, 1060, 1020, 960 cm^{-1}; ^1H NMR ($CDCl_3$) 3.99–3.82 (m, 4 H), 3.67 (s, 3 H), 1.85–1.48 (m, 8 H), 1.23 (s, 16 H), 0.88 ppm (t, 3 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) 176.4, 108.4, 64.2, 63.8, 51.1, 47.2, 42.2, 41.5, 35.1, 31.8, 31.6, 29.9, 29.4, 29.2, 23.9, 22.6, 20.6, 14.0 ppm. Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 69.98; H, 10.53.

1-Nonyl-3-oxocyclohexanecarboxylic Acid Ethylene Ketal (4). A solution of 4.14 g (12.6 mmol) of methyl 1-nonyl-3-oxo-cyclohexanecarboxylate ethylene ketal (9), 1.07 g (19.0 mmol) of potassium hydroxide, and 25 mL of ethanol was heated to reflux under argon for 8 days. After the solution was cooled, ethanol was removed, and 100 mL of water was added. The mixture was cooled to −5 °C and acidified to pH 5 with 3 M sulfuric acid. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with water and dried over anhydrous magnesium sulfate. Solvent was removed and the residue recrystallized from ether/hexane to give 3.89 g (98.8 % yield) 1-nonyl-3-oxocyclohexanecarboxylic acid ethylene ketal (4): mp 47–48 °C; IR (KBr) 3300–2500, 2960, 2930, 2850, 1705, 1450, 1120, 1080, 780 cm^{-1}; ^1H NMR ($CDCl_3$) 3.90 (s, 4 H), 2.32–1.50 (m, 8 H), 1.24 (s, 16 H), 0.87 ppm (t, 3 H, J = 6.6 Hz); ^{13}C NMR: ($CDCl_3$) 182.4, 108.3, 64.3, 63.8, 47.0 41.8, 41.4, 35.2, 31.8, 31.3, 29.9, 29.4, 29.1, 23.9, 22.6, 20.6, 14.0 ppm. Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.19; H, 10.34.

Methyl 5-Nonyl-5-hexenoate (11). In a divided electrolytic cell equipped with carbon plate electrodes were added 2.2 g (7.0 mmol) of 1-nonyl-3-oxocyclohexanecarboxylic acid ethylene ketal (4), 250 mL of anhydrous methanol, and potassium carbonate (2.2 g). Fifty DC volts at 0.5 amperes were applied. Due to resistive heating the cell was cooled with cold water. When thin-layer chromatography showed complete reaction, 250 mL of H_2O was added. The reaction mixture was extracted with ether, washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated to give the crude ester. The crude electrolytic product, 0.69 g (10.5 mmol) of potassium hydroxide, and 30 mL of ethanol were heated to reflux under argon overnight. After cooling, ethanol was removed, and 30 mL of water was added; the mixture was then cooled to −5 °C and acidified to pH 5 with 3 M sulfuric acid. The aqueous layer was extracted

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with ethyl acetate and the combined organic layers were washed with water and dried over anhydrous magnesium sulfate. Solvent removal gave crude 5-nonyl-5-hexenoic acid, which was esterified with diazomethane. Medium-pressure column chromatography over silica gel with 10% ethyl acetate/hexane followed by Kugelrhor distillation [94–96 °C (0.03 mmHg)] gave 1.4 g (5.5 mmol, 78.6%) of methyl 5-nonyl-5-hexenoate (11): IR (film) 3070, 2920, 2850, 1745, 1650, 1465, 1460, 1440, 1370, 1150, 890 cm^{-1}; ^1H NMR ($CDCl_3$) 4.71 (d, 2 H, J = 8.8 Hz), 3.67 (s, 3 H), 2.30 (t, 2 H, J = 7.5 Hz), 2.01 (quintet, 4 H, J = 8.0 Hz), 1.77 (quintet, 2 H, J = 7.0 Hz), 1.27 (s, 14 H), 0.88 ppm (t, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) 173.9, 148.8, 109.4, 51.3, 35.9, 35.4, 33.5, 31.9, 29.6, 29.4, 27.8, 23.0, 22.7, 14.0 ppm. Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89. Found: C, 75.67; H, 11.79.

Methyl 2-Methyl-5-nonyl-5-hexenoate (12). A solution of 25 mL of anhydrous THF, 25 mL of anhydrous HMPA, and 1.33 g (13.1 mmol) of diisopropylamine was cooled to −78 °C in dry ice/acetone bath and treated with 10 mL (13.1 mmol, 1.34 M) of n-BuLi. After the mixture was stirred for 1 h, 2.67 g (10.5 mmol) of methyl 5-nonyl-5-hexenoate (11) was added dropwise. After 1 h methyl iodide (12 g, 84 mmol) was added, and the solution was stirred for 5 h at −50 °C. The mixture was acidiifed and the product isolated with ether, dried over $MgSO_4$ solution, and concentrated. Medium-pressure column chromatography over silica gel with 10% ethyl acetate/hexane followed by Kugelrhor distillation [80–82 °C (0.05 mmHg)] afforded 2.60 g (9.69 mmol, 92.3%) of methyl 2-methyl-5-nonyl-5-hexenoate (12): IR (film) 3060, 2910, 2840, 1735, 1645, 1460, 1430, 1380, 1260, 1200, 1160, 1100, 1020, 890, 800 cm^{-1}; ^1H NMR ($CDCl_3$) 4.70 (d, 2 H, J = 6.7 Hz), 3.67 (s, 3 H), 2.45 (sextet, 1 H, J = 6.9 Hz), 1.99 (m, 4 H), 1.83 (m, 1 H), 1.56 (m, 1 H), 1.26 (s, 14 H), 1.16 (d, 3 H, J = 7.0 Hz), 0.88 ppm (t, 3 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) 177.1, 149.1, 1090.1, 51.4, 39.0, 36.0, 33.5, 31.9, 29.6, 29.4, 27.8, 22.7, 17.0, 14.1. Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02. Found: C, 76.13; H, 11.98.

Methyl 2-Methyl-5-hydroxy-5-(hydroxymethyl)tetradecanoate. A solution of 0.75 g (5.5 mmol) of N-methylmorpholine N-oxide, 2.5 mL of water, 2.5 mL of *tert*-butyl alcohol, 0.05 g of osmium tetraoxide, and 1.34 g (5.0 mmol) of methyl 2-methyl-5-nonyl-5-hexenoate (13) was stirred under argon at room temperature for 44 h. Sodium bisulfite (0.6 g), Celite (1.0 g), and water (2 mL) were added to the solution. The slurry was stirred 15 min and filtered and the filtrate acidified to pH 2. The crude diol was isolated with ethyl acetate. Medium-pressure column chromatography over silica gel with 50% ethyl acetate/hexane followed by Kugelrhor distillation [100–103 °C (0.01 mmHg)] afforded 1.40 g (4.63 mmol, 92.5%) of methyl 2-methyl-5-hydroxy-5-(hydroxymethyl)tetradecenoate as a mixture of diastereomers: IR (film) 3440 (br), 2970, 2940, 2860, 1745, 1470, 1460, 1440, 1420, 1385, 1265, 1120 (br), 800 (br) cm^{-1}; ^1H NMR ($CDCl_3$) 3.67 (s, 3 H), 3.46 (s, 2 H), 2.55 (m, 2 H), 2.10–1.45 (m, 5 H), 1.27 (s, 16 H), 1.17 (dd, 3 H, J = 7.0 1.7 Hz), 0.88 ppm (t, 3 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) 177.2, 175.5, 74.5, 67.9, 67.7, 51.6, 39.7, 35.9, 35.7, 35.2, 33.1, 31.9, 30.3, 30.0, 29.6, 29.3, 27.4, 27.2, 25.5, 23.3, 22.7, 17.3, 17.1, 14.1 ppm. Anal. Calcd for $C_{17}H_{34}O_4$: C, 67.51; H, 11.33. Found: C, 67.54; H, 11.49.

Malyngolide (14). A solution of 0.32 g (1.05 mmol) of methyl 2-methyl-5-hydroxy-5-(hydroxymethyl)tetradecanoate, 0.09 g (1.59 mmol) of potassium hydroxide, and 5.0 mL of absolute ethanol was heated to reflux under argon for 38 h. After the solution was cooled, ethanol was removed, and 5 mL of water was added; the mixture was cooled to −5 °C and acidified to pH 5 with 2 M sulfuric acid. The aqueous phase was extracted with ethyl acetate, and the combined organic layers were washed with water and dried over anhydrous magnesium sulfate. Solvent removal gave the crude acid. The crude acid, 10 mL of chloroform, and one drop of concentrated HCl were stirred for 4 h. The mixture was poured into 10% $NaHCO_3$ and isolated with $CHCl_3$. Medium-pressure column chromatography over silica gel with 50% ethyl acetate/hexane followed by Kugelrhor distillation [108–110 °C (0.5 mmHg)] gave 0.18 g (0.66 mmol, 62.9%) of malyngolide (14): R_f 0.41 (50% EtOAc/hexane). Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 71.14; H, 11.23.

The remaining material from the chromatography consisted of epimalyngolide (15), which was Kugelrohr distilled [148–150 °C (0.06 mmHg)] to give 0.10 g (0.37 mmol, 35.2%): R_f 0.27 (50% EtOAc/hexane). Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 71.14; H, 11.23. Both malyngolide and epimalyngolide had spectroscopic characteristics identical with those reported in the literature.[8]

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Synthesis of 2,7-Dibromopyrene

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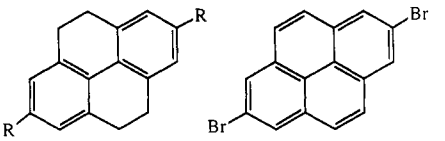
In connection with a program to prepare the active metabolites of polycyclic aromatic hydrocarbons for carcinogenesis research, we required 2,7-dibromopyrene (2) as a starting compound. Pyrene is known to undergo electrophilic substitution preferentially in the 1,6- and 1,8-positions.[1,2] The most convenient synthetic strategy for the introduction of groups into the 2- and 7-positions involves conversion of pyrene to a biphenyl aromatic ring system by regiospecific catalytic hydrogenation in the 4,5- and 9,10-positions.[3] Electrophilic reactions of 4,5,9,10-tetrahydropyrene (1a) are known to take place predominantly in the 2- and 7-positions.[2,4] However, direct bromination of 1a reportedly failed to afford 2-bromo-4,5,9,10-tetrahydropyrene, and 2-bromopyrene has been prepared only in low yield from 2-aminopyrene by means of the Sandmeyer reaction.[5] As far as we are aware, 2 has not been previously prepared.



1a: R = H
b: R = Br

2

We now report convenient synthesis of 2 involving bromination of 1a to yield 2,7-dibromo-4,5,9,10-tetrahydropyrene (1b)[6] followed by dehydrogenation by an unusual method. Bromination of 1a with 2 equiv of bromine in an aqueous medium in the presence of $FeCl_3$ as a catalyst took place smoothly at room temperature to afford 1b in quantitative yield. Analogous reaction of 1a with 1 equiv of bromine gave a mixture of mono and dibromo compounds along with unreacted 1a. The 500-MHz NMR spectrum of 1b was in good agreement with the assigned structure, exhibiting a benzylic singlet at δ 2.82 and an aromatic singlet at δ 7.20 in a 2:1 ratio. Attempted dehydrogenation of 1b with DDQ afforded mixtures of

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