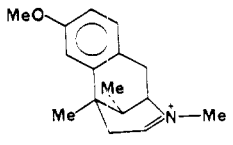
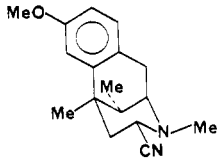
The possibility that iminium intermediate 8 might undergo isomerization to the less strained compound 9, thereby leading to nitrile 10, was ruled out by an independent synthesis of this regioisomer.[11]



9



10

The route to C-2 functionalized benzomorphans conceivably can be applied to the morphinans and opiates for preparation of C-9 substituted congeners.

Experimental Section

Melting points were determined by using a Mel-Temp capillary apparatus and are uncorrected. Infrared spectra were taken with a Perkin-Elmer Model 281 instrument. NMR spectra were obtained (Me_4Si, internal standard) with Varian T-60 and FT-80 instruments. An AE1 MS-30 spectrometer (70 eV) was employed for mass spectra. Normetazocine was obtained from Sterling-Winthrop Research Institute.

4-[2-(Dimethylamino)ethyl]-*cis*-3,4-dimethyl-6-methoxy-3,4-dihydronaphthalene (3). (2α,6α,11α)-1,2,3,4,5,6-Hexahydro-6,11-dimethyl-2,6-methano-3-benzazocine (normetazocine,[12] 21.7 g, 0.1 mol) and methyl iodide (125 mL, 2.0 mol) were dissolved in a solution of NaOH (9.0 g, 0.23 mol) in methanol (550 mL). After the mixture was stirred at 25 °C for 15 h and refluxed for 1 h, the volatile components were removed in vacuo. The mixture (68.9 g) of the quaternary salt 2 and NaI which was obtained was dissolved in 10% aqueous NaOH (350 mL) and heated on a steam bath for 2.5 h. Extraction with methylene chloride, washing with water, drying (Na_2SO_4), and removal of solvent gave 3 as an oil (24.6 g, 95%): R_f 0.51 (chloroform/methanol/ammonia, 4:1:0.2); NMR (CCl_4) δ 6.73 (m, 3 H, aromatic), 6.27 (d, 1 H, J = 10 Hz, vinyl), 5.72 (m, 1 H, J = 10 Hz, vinyl); mass spectrum, m/e 259 (M^+). Anal. Calcd for $C_{17}H_{25}NO$: C, 78.76; H, 9.65; N, 5.40. Found: C, 78.76; H, 10.08; N, 5.31.

4-[2-(((2,2,2-Trichloroethoxy)carbonyl)methylamino)-ethyl]-*cis*-3,4-dimethyl-6-methoxy-3,4-dihydronaphthalene (4). The amine 3 (44.6 g, 0.15 mol) in benzene (1.4 L) was refluxed with 2,2,2-trichloroethyl chloroformate (80.5 g, 0.3 mol) and K_2CO_3 (26 g, 0.19 mol) for 44 h. The reaction mixture was then stirred with 5% aqueous KOH (250 mL) for 30 min to decompose excess reagent. The organic phase was separated, washed with water, and dried (Na_2SO_4), and the solvent was removed to give 84 g of crude carbamate mixed with bis(2,2,2-trichloroethyl) carbonate. This material was chromatographed on a silica gel column (chloroform/petroleum ether, 1:20) to yield 64.5 g of pure 4 as an oil (91%): R_f 0.66 ($CHCl_3$/EtOAc, 2:1); IR (neat) 1725 cm^{-1} (carbamate); NMR (CCl_4) δ 4.5 (s, 2 H, OCH_2CCl_3), 2.7 (s, 3 H, NCH_3); mass spectrum, m/e 419 (M^+). Anal. Calcd for $C_{19}H_{24}O_3NCl_3$: C, 54.41; H, 5.72; N, 3.34; Cl, 25.41. Found: C, 54.49; H, 5.89; N, 3.08; Cl, 25.27.

4-[2-(((2,2,2-Trichloroethoxy)carbonyl)methylamino)-ethyl]-*cis*-3,4-dimethyl-6-methoxy-3,4-dihydro-2(1*H*)-naphthalenone (5). A methylene chloride solution (300 mL) of carbamate 4 (20.8 g, 0.05 mol) was cooled to 5 °C and a solution of *m*-chloroperbenzoic acid (14.85 g, 0.07 mol) in chloroform (140 mL) was added dropwise over a period of 30 min. After being stirred at 25 °C for 2.5 h, the reaction mixture was extracted with cold 5% NaOH and washed with water. After drying of the solution (Na_2SO_4) and removal of the solvent 26.3 g of an oil was obtained. This oil was refluxed in absolute ethanol (210 mL) containing 1.7 g of HCl for 20 min. The ethanol was removed in vacuo and the residue was redissolved in methylene chloride. The solution was washed with aqueous $NaHCO_3$ and then water. Drying (Na_2SO_4) and removal of the solvent gave an oil (19.56 g) which was purified on a silica gel column (chloroform/petroleum ether, 3:2) to provide the ketone 5 (10.19 g, 52%): R_f 0.64 (EtOAc/C_6H_6, 1:1); IR (neat) 1725 (carbamate), 1710 cm^{-1} (ketone). NMR (CCl_4) δ 4.5 (s, 2 H, OCH_2CCl_3), 3.66 (s, 2 H, CH_2Ar); mass spectrum, m/e 435 (M^+). Anal. Calcd for $C_{19}H_{24}O_4NCl_3$: C, 52.17; H, 4.81; N, 3.20. Found: C, 52.09; H, 4.89; N, 2.95.

(2α,6α,11α)-1,2,3,4,5,6-Hexahydro-2-hydroxy-8-methoxy-3,6,11-trimethyl-2,6-methano-3-benzazocine (7). The tetralone 5 (5 g, 0.01 mol) was dissolved in a mixture of THF (100 mL), acetic acid (30 mL), and water (15 mL) and then stirred with Zn dust (1.5 g) for 1 h at 15 °C. The unreacted Zn was removed and the THF was evaporated in vacuo. The residue was redissolved in water, acidified with dilute HCl, and extracted with ether to remove neutral materials. The aqueous layer was basified and extracted with methylene chloride. Drying (Na_2SO_4) and removal of the solvent gave 2.37 g of solid which was crystallized from ethyl acetate/petroleum ether (1:1) to afford 7 (1.2 g, 40%): mp 164–166 °C; R_f 0.56 ($CHCl_3$/CH_3OH/ammonia, 4:1:0.02); NMR (CD_2Cl_2) δ 3.5 (s, 3 H, OCH_3), 2.85 (d, 1 H, J = 16 Hz, benzylic), 2.40 (d, 1 H, J = 16 Hz, benzylic); mass spectrum, m/e 261 (M^+). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.81; N, 5.36. Found: C, 73.94; H, 9.14; N, 5.05.

(2α,6α,11α)-1,2,3,4,5,6-Hexahydro-2-cyano-8-methoxy-3,6,11-trimethyl-2,6-methano-3-benzazocine (8). A solution of carbinolamine 7 (1.31 g, 5 mmol) in methanol (40 mL) and water (50 mL) was refluxed with KCN (0.6 g, 9.2 mmol) for 40 h, after adjusting to pH 5.5 with dilute HCl. Basification and extraction gave 1.30 g of an oil which was purified on a silica gel column (EtOAc/$CHCl_3$, 9:1) to provide 8 as oil (0.98 g, 75%): R_f 0.61 ($CHCl_3$/EtOAc, 3:2); NMR ($CDCl_3$) δ 6.90 (m, 3 H, aromatic), 3.86 (s, 3 H, OCH_3), 3.38 (d, 1 H, J = 18 Hz, benzylic), 3.04 (d, 1 H, J = 18 Hz, benzylic), 2.72 (s, 3 H, NCH_3), 2.03 (m, 5 H, C_{11}-H, C_4 and C_5 methylene protons), 1.50 (s, 3 H, C_6-CH_3), 1.23 (d, 3 H, C_{11}-CH_3); IR (neat) 2220 cm^{-1} (weak, CN); mass spectrum, m/e 270 (M^+). Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.55; H, 8.15; N, 10.37. Found: C, 75.42; H, 8.25; N, 10.15.

Acknowledgment. We thank Dr. A. E. Soria, Sterling Winthrop Research Institute, Rensselaer, NY, for the gift of normetazocine. This work was supported by NIDA research Grant DA 02220.

Registry No. 1, 74752-75-3; 3, 74752-76-4; 4, 74752-77-5; 5, 74752-78-6; 7, 74752-79-7; 8, 74763-40-9; *cis*-normetazocine, 16603-67-1; 2,2,2-trichloroethyl chloroformate, 17341-93-4.

(10) M. Toda, Y. Hirata and S. Yamamura, *J. Chem. Soc. D*, 1597 (1970).
(11) P. S. Portoghese, M. Essawi, W. C. Groutas, *Synth. Commun.*, in press.
(12) E. M. Fry and E. L. May, *J. Org. Chem.*, 24, 116 (1959).

Lactone Formation via Oxidative Cyclization of an Unsaturated Carboxylic Acid: Application to the Stereoselective Synthesis of (±)-Malyngolide, an Antibiotic from the Marine Blue-Green Alga *Lyngbya majuscula* Gomont

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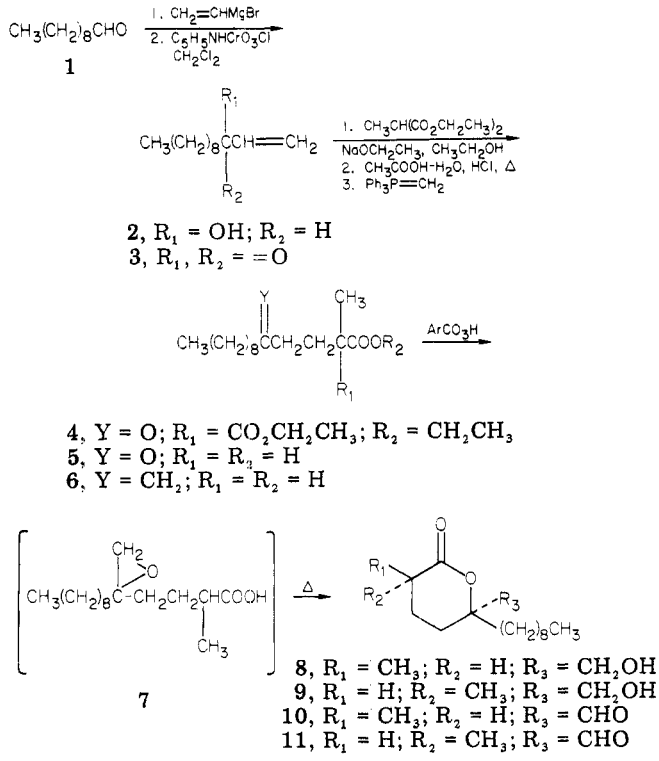
Recently the isolation and structure determination of malyngolide (8), an antibiotic effective against *Mycobacterium smegmatis* and *Streptococcus pyogenes*, was reported.[1] In view of its activity and to further confirm the assigned structure, we set out to develop a convenient route for total synthesis of this marine natural product. In this note we report such a method, one that should also be adaptable to preparation of other similarly functionalized

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

0022-3263/80/1945-4241$01.00/0

Scheme I



δ-valerolactones and γ-butyrolactones.

In planning the route to lactone **8**, unsaturated carboxylic acid **6** (Scheme I) seemed to be the most attractive intermediate. Once synthesized, it can be treated with a peroxy acid to afford the corresponding epoxide (**7**) which hopefully can be subsequently isomerized to the desired hydroxy lactone (**8**). Although an isolated example of an analogous transformation has been reported,[2] this potentially useful synthetic methodology has not been further exploited.

The key step in the synthesis of carboxylic acid **6** involved a Michael reaction[3] between diethyl methylmalonate[4] and 1-dodecen-3-one (**3**).[5] The latter compound was in turn readily obtained in 61% overall yield by addition of vinylmagnesium bromide[6] to decyl aldehyde (**1**),[4] followed by oxidation[7] of the resultant allylic alcohol (**2**)[8] with pyridinium chlorochromate.[4] Subsequent treatment of the Michael adduct (**4**) with a mixture of acetic acid and aqueous hydrochloric acid under reflux effected hydrolysis–decarboxylation to afford keto acid **5**[9] in 89% yield. The desired unsaturated carboxylic acid (**6**) was obtained in 77% yield by treatment of the latter ketone (**5**) with the ylide derived from methyltriphenylphosphonium bromide.[4]

The synthesis of (±)-malyngolide (**8**) was completed by epoxidation of olefinic acid **6** using *m*-chloroperbenzoic acid[4] in a mixture of toluene–cyclohexane. Since we were able to demonstrate[10] that the intermediate oxirane (**7**) was stable under these reaction conditions, it was necessary to heat the mixture at reflux to effect its isomerization to the desired hydroxy lactone (**8**).[11] The IR and NMR spectral properties of the latter product (**8**) were virtually identical[12] with those previously reported[1] for the marine natural product.

In order to confirm the stereochemical homogeneity of our final product, it was oxidized to the corresponding aldehyde (**10**) with dimethyl sulfoxide and dicyclohexylcarbodiimide in the presence of pyridinium trifluoroacetate according to the procedure previously described[1] for (−)-malyngolide. NMR analysis of our aldehyde product indicated the presence of only one component, identical with the aldehyde (**10**) obtained by oxidation of the marine natural product. Since aldehyde **10** and its C-2 epimer (**11**) can be readily differentiated[1] by the NMR absorption observed for the aldehydic proton, the cyclization of oxirane **7** to afford hydroxy lactone **8** appears to be a highly stereoselective process.[13] In view of the few steps required overall, the method reported in this note is a convenient one for synthesis of (±)-malyngolide and structural analogues.

Experimental Section

General. Reactions were carried out under a nitrogen atmosphere. The isolation of reaction products was accomplished by extracting them with the specified solvent. The extracts were washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was removed by using a rotary evaporator under reduced pressure. Evaporative distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. The NMR spectra were recorded with a Varian EM-360 spectrometer, and infrared spectra were obtained by using a Beckman Acculab 1 spectrophotometer. Vapor-phase chromatography (VPC) was performed on a Hewlett-Packard 5750 chromatograph, using a 6 ft × 0.125 in. SE-30 column. Where indicated, percentages refer to peak areas without correction for response factors relative to an internal standard. Microanalyses were performed by Micro-Tech Laboratories, Skokie, IL.

1-Dodecen-3-ol (2). A solution of 4.18 g (26.6 mmol) of decyl aldehyde (**1**)[4] in 10 mL of anhydrous ether was added dropwise over a period of 5 min to 45 mL of 1.4 M vinylmagnesium bromide–tetrahydrofuran solution,[6] cooled to 0 °C in an ice water bath. After this mixture had been stirred at 0 °C for 20 min, the reaction was quenched by dropwise addition of 10 mL of saturated aqueous NH_4Cl solution and subsequently diluted with 350 mL of saturated brine. Extraction of the product with ether, followed by evaporative distillation, afforded 3.65 g (75%) of allylic alcohol **2**:[8] bp 82–95 °C (bath temperature, 0.25 mm) [lit.[8] bp 122–122.5

(2) Berti, G. *J. Org. Chem.* **1959**, *24*, 934. This paper reported direct conversion of certain aromatic olefinic carboxylic acids to hydroxy lactones, without any evidence for formation of an intermediate epoxide, by use of perbenzoic acid.

(3) For examples of analogous transformations, see: Spencer, T. A.; Newton, M. D.; Baldwin, S. W. *J. Org. Chem.* **1964**, *29*, 787; Johnson, W. S.; McCarry, B. E.; Markezich, R. L.; Boots, S. G. *J. Am. Chem. Soc.* **1980**, *102*, 352.

(4) Available from Aldrich Chemical Co., Inc., Milwaukee, WI.

(5) Prestwich, G. D.; Kaib, M.; Wood, W. F.; Meinwald, J. *Tetrahedron Lett.* **1975**, 4701.

(6) Available from Ventron Corporation, Alfa Division, Danvers, MA.

(7) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(8) This compound has previously been prepared in 51% yield by addition of nonylmagnesium bromide to propenal. See: Püschel, F.; Kaiser, C. *Ber.* **1964**, *97*, 2917–25.

(9) This compound has previously been prepared by a different route. See: Prome, J. C.; Asselineau, C. *Bull. Soc. Chim. Fr.* **1964**, 2665–70.

(10) If the reaction was allowed to proceed at room temperature for 24 h, followed by destruction of the excess peroxy acid using aqueous sodium sulfite and recovery of the product using ether for the extraction and the general experimental isolation procedure, NMR analysis indicated the presence of only *m*-chlorobenzoic acid and the intermediate epoxide (**7**) [characterized by a broad singlet at δ 2.46 (oxirane CH_2)]. No trace of the corresponding hydroxy lactone (**8**) could be detected.

(11) The cyclization product (**8**) was homogeneous by TLC and VPC analysis. Treatment of it with 1,5-diazabicyclo[5.4.0]undec-5-ene in refluxing toluene, in an attempt to achieve epimerization at C-2, failed to change any of the product's spectral properties.

(12) The only discrepancy was the appearance of the ^1H NMR absorption pattern for the methylene adjacent to the hydroxyl. If toluene was used to remove all traces of ether and moisture from the sample prior to taking the NMR spectrum, this pattern was quite broad (the largest peak centered at δ 3.60 and possessing a shoulder at δ 3.54; very broad smaller peaks at δ 3.80 and 3.34). However, when no rigorous effort was made to remove traces of moisture from the sample, the pattern was considerably sharper and was virtually identical with that previously reported[1] for the natural product.

(13) (−)-Malyngolide (**8**) was reported[1] to be more stable than its C-2 epimer (**9**) since epimerization at C-2 was not observed under basic reaction conditions. Since our cyclization process (i.e., conversion of **7** to **8**) occurs under equilibrating conditions, the observed stereoselectivity is not as unusual as it first appears.

°C (10 mm)]; IR ν_{max} (film) 3360 (OH), 1645 (C=C), 1055, 995, 920 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 6.1–5.55 (complex pattern, C**H**=CH_2), 5.3–4.87 (complex pattern, CH=C**H**$_2$), 3.98 (br q, J = 6 Hz, C**H**OH), 2.32 (s, OH), 1.28 (br, 16 H), 0.88 (br t, J = 5 Hz, CH_3). VPC analysis (oven temperature 180 °C, flow 15 mL/min) indicated the product (retention time 5.9 min) to be >98% pure.

1-Dodecen-3-one (3). A solution of 1.042 g (5.66 mmol) of 1-dodecen-3-ol (**2**) in 10 mL of dichloromethane was added dropwise rapidly to 4.69 g (21.7 mmol) of pyridinium chlorochromate[4] in 20 mL of dichloromethane. After this mixture was stirred vigorously at room temperature for 90 min, it was transferred with 120 mL of ether and 150 mL of 1 M aqueous NaOH to a separatory funnel. After separation of the layers, the organic layer was washed thoroughly with 1 M aqueous sodium hydroxide solution, 2 M aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, and saturated brine in successive order. Isolation of the product from the organic extract in the usual manner, followed by evaporative distillation, afforded 837 mg (81%) of enone **3**:[5] bp 55–70 °C (bath temperature, 0.07 mm); IR ν_{max} (film) 1695 (C=O), 1620 (C=C), 1465, 1405, 1378, 1203, 1130, 1088, 990, 963, 725 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 6.19 (d, J = 8 Hz, 1 vinyl H), 6.15 (d, J = 4 Hz, 1 vinyl H), 5.66 (dd, J_1 = 8 Hz, J_2 = 4 Hz, C**H**=CH_2), 2.48 (t, J = 6 Hz, CH_2C=O), 0.88 (br t, J = 5 Hz, CH_3). VPC analysis (oven temperature 190 °C, flow 15 mL/min) indicated the product (retention time 3.9 min) to be >96% pure.

Diethyl Methyl-(3-oxododecyl)propanedioate (4). To a dilute solution of sodium ethoxide (prepared in situ by using 10 mg of sodium metal) in 4.0 mL of absolute ethanol were added 1.0 mL (5.8 mmol) of diethyl methylmalonate[4] and 799 mg (4.38 mmol) of 1-dodecen-3-one (**3**). After being stirred at room temperature for 22 h, the mixture was diluted with 40 mL of 0.05 M aqueous hydrochloric acid and the product was isolated in the usual manner by extraction with dichloromethane. Fractional[14] evaporative distillation afforded 1.29 g (83%) of diester **4**: bp 115–135 °C (bath temperature, 0.08 mm); IR ν_{max} (film) 1730 (br, C=O), 1460, 1375, 1295, 1255, 1170, 1110, 1020 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 4.10 (q, 4 H, J = 7 Hz, OC**H**$_2$CH$_3$), 1.32 (s, CH_3), 1.25 (t, 6 H, J = 7 Hz, OCH$_2$C**H**$_3$), 0.88 (br t, J = 5 Hz, $CH_2CH_2CH_3$). VPC analysis (oven temperature 215 °C, flow 20 mL/min) indicated the product (retention time 27.5 min) to be >98% pure.

Anal. Calcd for $C_{20}H_{38}O_5$: C, 67.38; H, 10.18. Found: C, 67.60; H, 10.13.

2-Methyl-5-oxotetradecanoic Acid (5). A mixture of 1.02 g (2.86 mmol) of diester **4**, 4.0 mL of glacial acetic acid, and 4.5 mL of 2 M aqueous hydrochloric acid was heated at reflux for 68 h. The crude product was isolated by dilution of this mixture at room temperature with 100 mL of 1:1 (v/v) water–saturated brine and extraction with dichloromethane. Further purification of the reaction product was accomplished by thoroughly washing an ether solution of the crude material (765 mg) with 0.5 M aqueous sodium hydroxide solution. The combined base washes were extracted with dichloromethane to remove traces of any nonacidic components and then subsequently were acidified by using 2 M aqueous hydrochloric acid. Extraction of the acidified aqueous layer with ether afforded 651 mg (89%) of keto acid **5**:[9] mp (after recrystallization from 1:1 (v/v) hexane–cyclohexane) 58–60 °C (lit.[9] mp 59–60 °C); NMR δ_{Me_4Si} ($CDCl_3$) 10.43 (br s, COOH), 2.08–2.75 (m, 5 H, CHCOOH, C**H**$_2$C(O)C**H**$_2$), 1.20 (d, J = 7 Hz, CHC**H**$_3$), 0.88 (br t, J = 5 Hz, CH_2CH_3).

2-Methyl-5-nonyl-5-hexenoic Acid (6). A mixture of 281 mg (7.13 mmol) of 61% sodium hydride (washed with hexane to remove the mineral oil) and 9 mL of anhydrous dimethyl sulfoxide was heated at 70 °C (bath temperature) for 30 min or until hydrogen evolution had ceased. The mixture was then cooled to room temperature and 2.60 g (7.28 mmol) of methyltriphenylphosphonium bromide[4] was added. After this mixture was stirred at room temperature for 20 min to ensure formation of the ylide a solution of 350 mg (1.36 mmol) of ketone **5** in 4.0 mL of anhydrous dimethyl sulfoxide was added dropwise and the ensuing reaction mixture was stirred vigorously at room temperature for an additional 4 h. The product was isolated by dilution of this mixture with 125 mL of 0.1 M aqueous hydrochloric acid followed by thorough extraction with 1:1 (v/v) hexane–ether. The combined extracts were washed thoroughly with water and saturated brine, after which the aqueous washes were discarded. The organic layer was then washed thoroughly with 0.5 M aqueous sodium hydroxide solution, after which the combined base washes were extracted with dichloromethane to remove traces of any nonacidic components. Subsequent acidification of the aqueous layer using 2 M hydrochloric acid, followed by extraction with ether in the usual manner, afforded 265 mg (77%) of unsaturated acid **6**: bp 115–130 °C (bath temperature, 0.10 mm); IR ν_{max} (film) 1705 (C=O), 1642 (C=C), 1460, 1413, 1378, 1290, 1240, 1185, 935, 885 cm^{-1}; NMR δ_{Me_4Si} (CCl_4) 10.9 (br s, COOH), 4.66 (br s, C=C**H**$_2$), 2.38 (m, C**H**COOH), 1.19 (d, J = 7 Hz, CHC**H**$_3$), 0.87 (br t, J = 5 Hz, CH_2CH_3).

Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89. Found: C, 75.79; H, 12.00.

Preparation of (±)-Malyngolide (8). A mixture of 126 mg (0.50 mmol) of unsaturated acid **6** and 137 mg of 85% *m*-chloroperbenzoic acid[4] in 1.5 mL of cyclohexane and 0.5 mL of toluene was stirred at room temperature for 6 h. The mixture was then filtered through a micro Büchner funnel in order to remove *m*-chlorobenzoic acid, which had been produced during the epoxidation. The solid acid was washed[15] with five 1.0-mL portions of cyclohexane, and the filtrate and combined washes were subsequently heated at reflux for 24 h. After this solution was cooled to room temperature, it was diluted with 20 mL of ether. The organic layer was then washed thoroughly with 2:1 (v/v) 1 M aqueous sodium hydroxide solution–saturated brine, followed by the operations described in the general experimental isolation procedure. Removal of the solvent, followed by chromatography on silica gel (10 mL, elution with hexane–60% ether) afforded 67 mg (50%) of (±)-malyngolide (**8**), >99% pure by VPC analysis (oven temperature 215 °C, flow 20 mL/min, retention time 21.3 min). The IR and NMR spectral properties of this hydroxy lactone (**8**) were virtually identical[12] with those previously reported[1] for the naturally occurring (–)-malyngolide (**8**).

Acknowledgment. We thank Professor Richard E. Moore of the University of Hawaii for comparing the IR and NMR spectra of our synthetic (±)-malyngolide with those of the natural product. The assistance of Dr. David S. Crumrine of Loyola University of Chicago in determining the ^{13}C NMR spectrum of our synthetic malyngolide is also gratefully acknowledged.

Registry No. 1, 112-31-2; 2, 4048-42-4; 3, 58879-39-3; 4, 74684-33-6; 5, 74742-18-0; 6, 74709-66-3; 8, 74742-19-1; diethyl methylmalonate, 609-08-5; vinyl bromide, 593-60-2.

(14) The unreacted diethyl methylmalonate was collected at 50–75 °C (bath temperature, 2.5 mm).

(15) On a larger scale, considerably smaller amounts of cyclohexane should be used during this step to minimize dissolution of the *m*-chlorobenzoic acid, which is sparingly soluble in cyclohexane. The presence of this latter acid in the reaction mixture during the lactonization can lead to a competing intermolecular reaction between the epoxide **7** and *m*-chlorobenzoic acid. This was demonstrated by a similar experiment in which the initial epoxidation mixture was diluted, without filtering off the aromatic acid, with 5 mL of cyclohexane prior to refluxing the reaction mixture to induce the cyclization. Under such conditions, the yield of malyngolide was only 34%.

Constraints on Long-Range Aryl Migration.[1] Solvolysis of *exo*-3,3-Fluorenylidenetricyclo[3.2.1.0^{2,4}]oct-*anti*-8-yl Tosylate and 6,6-Diphenylbicyclo[3.1.0]hex-*exo*-3-yl Tosylate

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The solvolytic rearrangement shown in eq 1 involves both aryl migration and cyclopropyl ring opening.[3] The

