Synthesis of Cholesta-8(14),24-dien-3β-ol[1a,2]

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It has been suggested[3] that $\Delta^{8(14)}$ compounds are produced during the biological conversion of lanosterol to cholesterol when the methyl group on C_{14} is removed. Cholest-8(14)-en-3β-ol (rat skin),[4] stigmasta-8(14),22-dien-3β-ol (rayless goldenrod),[5] and 4-methylcholesta-8(14),24-dien-3β-ol (yeast)[6] have been isolated from natural sources. Lee et al.[7] have found that [3α-^{3}H]cholest-8(14)-en-3β-ol is converted to cholesterol in intact rats and rat liver homogenates incubated aerobically. Cholesta-8(14),24-dien-3β-ol (**1**) may be a cholesterol biosynthetic intermediate, especially in brain where the Δ^{24} path predominates.[8] Consequently, its synthesis was undertaken by the procedure in Scheme I.

3β-Acetoxy-23,24-dinorchol-5-en-22-oic acid methyl ester (**2**) was converted to 3β-acetoxy-23,24-dinorchola-5,7-dien-22-oic acid methyl ester (**3**) by allylic bromination with *N*-bromosuccinimide (NBS) followed by dehydrohalogenation with trimethyl phosphite.[9,10] Isomerization of **3** in SO_2 was carried out by the method used for isomerization of ergosterol acetate.[11,12] The crude product was reduced with lithium aluminum hydride ($LiAlH_4$) to 23,24-dinorchola-6,8(14)-dien-3β,22-diol (**4**; after heating for 5 min) or 23,24-dinorchola-8,14-dien-3β,22-diol (**5**; after heating for 45 min). Ultraviolet absorptions of **4** and **5** agree with those of ergosterol isomerization products.[13]

Raney nickel W-2[14] and hydrogen reduced both **4** and **5** to 23,24-dinorchol-8(14)-ene-3β,22-diol (**6**). The Castells and Meakins' test,[15] when applied to the reduction product, indicates that the double bond is in the $\Delta^{8(14)}$ position. Partial acetylation of **6** gave 22-acetoxy-23,24-dinorchol-8(14)-en-3β-ol (**7**), the diacetate, and a trace amount of 3β-acetoxy-23,24-dinorchol-8(14)-en-22-ol. Compound **7** was converted to 22-acetoxy-3β-benzoyloxy-23,24-dinorchol-8(14)-ene (**8**), which was partially saponified to 3β-benzoyloxy-23,24-dinorchol-8(14)-en-22-ol (**9**).

Table I. Molecular Rotations of Two Cholestenols and Synthetic Cholesta-8(14),24-dien-3β-ol

	λ					
	400	280	250	235	230	225
1. cholest-8(9)-en-3β-ol[a]		+116	+548	−332	−243	+321
2. cholest-8(14)-en-3β-ol[a]	+7	−28	−154	−665	−924	−399
3. cholesta-8(14),24-dien-3β-ol	−5	−56	−192	−633	−916	−407

[a] Produced by the reduction of cholesta-8,14-dien-3β-ol with Raney nickel W-2/hydrogen at 1 atm in EtOH.

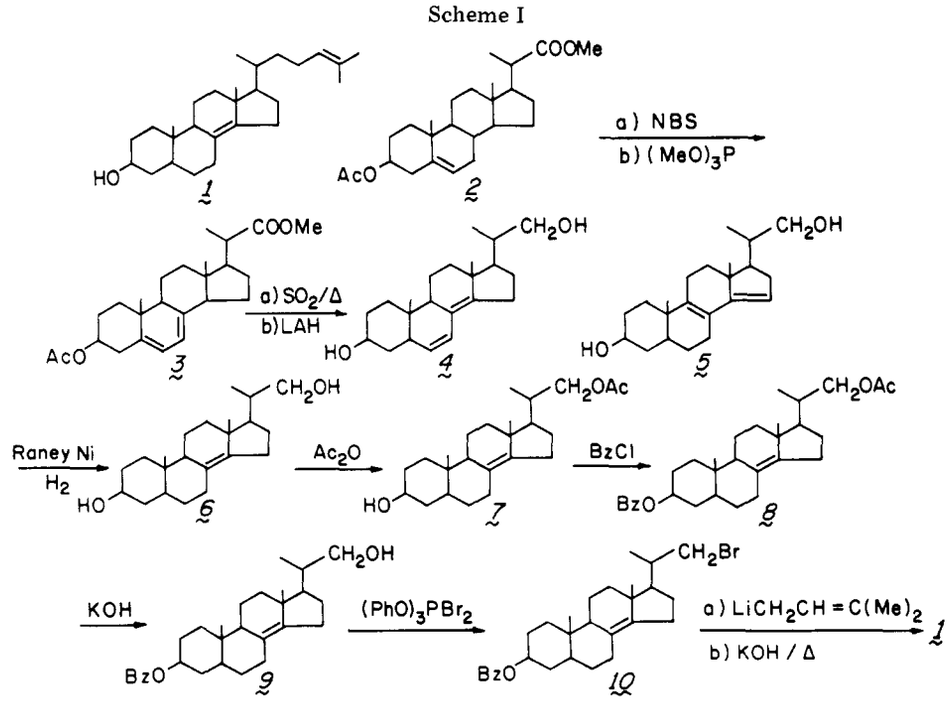
Compound **9** was converted to 3β-benzoyloxy-22-bromo-23,24-dinorchol-8(14)-ene (**10**) by the method of Black et al.[16] for the conversion of allenic or acetylenic alcohols to bromides. Compound **10** was coupled with dimethylallyllithium in a manner previously used for the production of desmosterol.[17] Just as in the preparation of desmosterol, a minor byproduct results from allylic rearrangement.

The positions of the angular methyl group protons in the proton magnetic resonance spectrum of **1** agree with the calculated values,[18] and the molecular rotations of **1** and cholest-8(14)-en-3β-ol show concordance (Table I). The infrared absorption in the characteristic 700–1000 cm^{-1} region is that of a $\Delta^{8(14)}$ steroid.[19]

Experimental Section

Melting points were determined on a Hoover Uni-Melt apparatus under vacuum and are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 521 spectrophotometer equipped with a KBr micropellet attachment. Ultraviolet spectra were determined on a Beckman DU spectrophotometer. High-resolution mass spectra were recorded on an A.E.I. MS 30. The ^{1}H NMR spectra were determined on a Bruker 270-MHz instrument in Me_2SO-d_6 (**4**) or $CDCl_3$ (**1**), and the chemical shifts are reported downfield from the Me_4Si internal standard. Optical rotatory dispersion data were recorded in MeOH on a Cary 60. Gas–liquid chromatographic separations were conducted on a Packard Model 7300 series single FID gas chromatograph with a nitrogen flow of 29 mL min^{-1}. The 6 ft × 2 mm glass column packed with 1% Supelco SP-2401 on Supelcoport was heated to 195 °C. Polarimeter readings were determined in $CHCl_3$ on a Perkin-Elmer 241

Scheme I



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at the sodium D line. Microanalyses were carried out by M-H-W Laboratories, Phoenix, Ariz.

3β-Acetoxy-23,24-dinorchola-5,7-dien-22-oic Acid Methyl Ester (3). Compound **2**[20] (1.18 g, 2.94 mmol) was converted to compound **3** by the method of Fryberg et al.[9] The oily yellow product was chromatographed on Alumina F-20 (Alcoa, 80–100 mesh, 300 g) in benzene and benzene–EtOAc (95:5, v/v), and the effluent was monitored by ultraviolet absorption. The fractions containing product were rechromatographed on silicic acid–Super-Cel (Johns-Manville)–$AgNO_3$[21] (285 g) in benzene–hexanes (50:50, v/v), and the product was eluted with benzene. The crude solid (295 mg) was recrystallized from MeOH to yield plates: 247 mg, 0.61 mmol, 21%; mp 149–151 °C (lit.[22] mp 147 °C); IR (KBr) 1733, 1729, 1248 cm^{-1}; UV λ_{max} (EtOH) 271 nm (ε 12 800), 281 (13 137), 293 (7579). Anal. Calcd for $C_{25}H_{36}O_4$: M^+, *m/e* 400.2613. Found: M^+, *m/e* 400.2553.

23,24-Dinorchola-6,8(14)-diene-3β,22-diol (4).[23] Compound **3** (0.43 g, 1.08 mmol) was isomerized in liquid SO_2 for 5 min using a modification of the method of Hudgell et al.[11] The crude product was reduced with $LiAlH_4$ in dry THF, acetylated, and chromatographed on silicic acid–Super-Cel–$AgNO_3$[21] (138 g) in benzene–hexanes (80:20, v/v). The diacetate was saponified in 2% methanolic KOH (5 mL), and H_2O (10 mL) was added. The precipitate which formed was filtered, and part of the product (226 mg, 0.68 mmol, 63%) was recrystallized from MeOH to form long needles subliming at 256.5–258.5 °C: $[\alpha]_D$ −46° (*c* 0.05, $CHCl_3$); IR (KBr) 1080, 1050 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 606 (q, $J_{6,7}$ = 10 Hz, $J_{5,6}$ = 2 Hz), 5.24 (d, $J_{6,7}$ = 10 Hz); UV λ_{max} (EtOH) 247 nm (ε 21 699), 250 (22 773), 252 (23 203). Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.79; H, 10.44.

23,24-Dinorchol-8(14)-ene-3β,22-diol (6).[24] Compound **4** (209 mg, 0.63 mmol) in EtOH (150 mL) was reduced with Raney nickel W-2[14] (5 g) at 1 atm of hydrogen for 4.5 h. The mixture was filtered, and the solvent was removed under a stream of nitrogen, leaving a white product (202 mg, 0.61 mmol, 97%). An analytical sample was recrystallized from MeOH to form needles subliming at 237–241 °C: $[\alpha]_D$ + 18.1° (*c* 0.04, $CHCl_3$); IR (KBr) 1085, 1051 cm^{-1}. Anal. Calcd for $C_{22}H_{36}O_2$: C, 79.47; H, 10.91. Found: C, 79.69; H, 11.07.

22-Acetoxy-23,24-dinorchol-8(14)-en-3β-ol (7). Ac_2O (43.2 mg, 0.42 mmol) was added to compound **6** (70 mg, 0.21 mmol) in dry pyridine (2.84 g). The mixture was stirred for 21 h at room temperature, and the pyridine and Ac_2O were removed with nitrogen. The product was chromatographed on silicic acid–Super-Cel[25] (63 g) on benzene–EtOAc (95:5, v/v). 3β,22-Diacetoxy-23,24-dinorchol-8(14)-ene (25.1 mg, 0.06 mmol, 76–77 °C), 3β-acetoxy-23,24-dinorchol-8(14)-en-22-ol (trace), and **7** (49.5 mg, 0.13 mmol, 62.9%) were eluted in that order, and unreacted starting material (7.25 mg, 0.02 mmol) was eluted with EtOAc. An analytical sample was rechromatographed on silcic acid–Super-Cel–$AgNO_3$[26] (18.9 g) in benzene–hexanes (75:25, v/v) and recrystallized from hexanes (49–50 and 94–95.5 °C depending on the concentration): IR (KBr) 3520, 3340, 1740, 1720, 1240, 1045 cm^{-1}. Anal. Calcd for $C_{24}H_{38}O_3$: M^+, *m/e* 374.2820. Found: M^+, *m/e* 374.2803.

22-Acetoxy-3β-benzoyloxy-23,24-dinorchol-8(14)-ene (8). Benzoyl chloride (90 mg, 0.64 mmol) was added to compound **7** (44.65 mg, 0.11 mmol) in dry pyridine (0.44 g). After 11 h at room temperature, Et_2O (80 mL) and H_2O (10 mL) were added. The organic layer was washed with 2% HCl (2 × 10 mL, v/v) and H_2O (10 mL). The crude product was chromatographed on silicic acid–Super-Cel[25] (56 g) in benzene–hexanes (50:50, v/v) followed by benzene alone. The product (43 mg, 0.09 mmol, 90%) was rechromatographed on silicic acid–Super-Cel–$AgNO_3$[26] (13.5 g) in benzene–hexanes (30:70, v/v) and recrystallized from MeOH to form crystals melting at 107–108 °C; IR (KBr) 1735, 1711, 1284, 1241, 716 cm^{-1}. Anal. Calcd for $C_{31}H_{42}O_4$: M^+, *m/e* 478.3083. Found: M^+, *m/e* 478.3048.

3β-Benzoyloxy-23,24-dinorchol-8(14)-en-22-ol (9). Compound **8** (43 mg, 0.09 mmol) was dissolved in MeOH (23 mL), and 0.1 M KOH in MeOH (1.6 mL, 0.16 mmol) was added. The solution was stirred at room temperature for 20.5 h, and Et_2O (80 mL) and H_2O (40 mL) were added. The aqueous layer was washed with Et_2O (40 mL), and the organic layers were combined. The crude product was chromatographed on silicic acid–Super-Cel[25] in benzene followed by benzene–EtOAc (95:5, v/v) (27.8 mg, 0.064 mmol, 71%). The product was recrystallized from distilled hexanes and formed rosettes of needles which sublimed at 179–181 °C: IR (KBr) 1710, 1329, 1314, 1277, 1119, 702 cm^{-1}. Anal. Calcd for $C_{29}H_{40}O_3$: M^+, *m/e* 436.2978. Found: M^+, *m/e* 436.3016.

3β-Benzoyloxy-22-bromo-23,24-dinorchol-8(14)-ene (10). The reaction is similar to one described previously,[17] except that slightly more pyridine was used (2 mol). Obtained from compound **9** (27.8 mg, 0.064 mmol) dissolved in benzene (10 mL), compound **10** (21.65 mg, 0.043 mmol, 68%) was recrystallized from MeOH to yield needles: mp 179.5–180.5 °C with sublimation; IR (KBr) 1710, 1275, 1110, 710, 588 (Br) cm^{-1}. Anal. Calcd for $C_{29}H_{39}O_2Br$: M^+, *m/e* 498.2134. Found: M^+, *m/e* 498.2106.

Cholesta-8(14),24-dien-3β-ol (1). The coupling reaction has been described.[17] Compound **10** (41.35 mg, 0.083 mmol) was coupled with dimethylallyllithium to form cholesta-8(14),24-dien-3β-ol (7.5 mg, 0.02 mmol, 24%), which was recrystallized from MeOH to form needles: mp 108–109 °C; $[\alpha]_D$ +16.6° (*c* 0.122, $CHCl_3$); IR (KBr) 1135, 1088, 1045, 973 sh, 968, 942, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (s), 0.69 (s). Anal. Calcd for $C_{27}H_{44}O$: M^+, *m/e* 384.3391. Found: M^+, *m/e* 384.3371.

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Registry No.—**1**, 68129-47-5; **2**, 6556-99-6; **3**, 60543-39-7; **4**, 68129-48-6; **5**, 68129-58-8; **6**, 68129-49-7; **7**, 68129-50-0; **8**, 68129-51-1; **9**, 68129-52-2; **10**, 68129-53-3; 3β-acetoxy-23,24-dinorchola-6,8(14)-dien-22-oic acid methyl ester, 68129-54-4; 23,24-dinorchola-6,8(14)-diene-3β,22-diol diacetate, 68129-55-5; 23,24-dinorchola-8(14)-ene-3β,22-diol diacetate, 68129-56-6; 23,24-dinorchol-8(14)-ene-3β,22-diol 3-acetate, 68129-57-7; dimethylallyllithium, 50585-10-9.

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(12) It should be noted that although 3β-acetoxyergosta-8,14,22-triene was produced in 86% yield when ergosterol acetate was isomerized in SO_2 for 18 h, extended periods of isomerization produced a tar from **3**.
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(20) Compound **2**, which can be formed from the commercially available acid, was recrystallized from MeOH and melted at 131–134 (plates) or 156.5–157 °C (needles). A previously published melting point for **2** was 138–139 °C: E. Fernholz, *Justus Liebigs Ann. Chem.*, **507**, 128 (1933).
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(23) Compound **5** is produced by this procedure if the isomerization is conducted for 45 min. From **3** (342 mg, 0.855 mmol), **5** (278 mg) was produced which

contains two unidentified impurities by GC. Recrystallized from MeOH, **5** sublimes at 208–210 °C: $[\alpha]_D$ −27.9° (*c* 0.03, $CHCl_3$); IR (KBr) 3284–3263, 3056, 1102, 1080, 1049, 1032, 972, 799 cm^{-1}; UV λ_{max} (EtOH) 250 nm (17 717). The retention times for **4** and **5** on an SP-2401 GC column are 8.4 and 7.4 min when cholesterol emerges at 7.7 min.

(24) Compound **5** is also reduced to compound **6** by this procedure.
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Synthesis of (±)-Helenynolic Acid[1]

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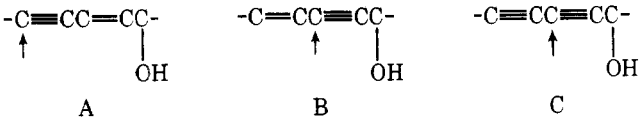
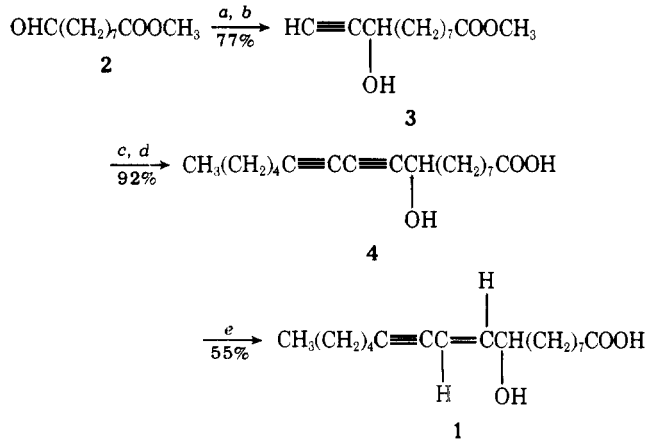
Helenynolic acid (**1**) occurs naturally in the seeds of *Helichrysum bracteatum* family of compositae.[2] The structure and stereochemistry of this unusual enynolic fatty acid were determined by degradation and spectroscopy.[3,4] An elegant conversion of natural crepenyic acid to **1** has been reported but is impractical for providing **1** in useful quantity.[5]

As part of our studies of naturally occurring acetylenes of biogenetic importance, we have developed an efficient synthesis of ±−1 as shown in Scheme I. This sequence provides **1** in good yield and displays two useful synthetic steps. The Chodkiewicz–Cadiot coupling reaction between **3** and 1-bromoheptyne in the presence of cuprous chloride occurs readily in the presence of the unprotected hydroxy function.[6] Reduction of **4** with lithium aluminum hydride occurs both stereoselectively and regioselectively to give ±−1. Stereoselectivity is common for propargyl alcohol reduction but regioselectivity in conjugated systems is not as well documented.[7] Accordingly, conjugated enynolic systems A,[9] which is converted to an allenic system, and B[9] are reduced with specificity for the acetylenic bond. The diynolic system C, however, shows reduction selectively for the acetylenic bond nearest the hydroxy function. These findings hold importance for the design of selective synthesis for other enynolic systems.[10]



A B C

Scheme I



[a] HC≡CH, KOH. [b] CH_2N_2. [c] $CH_3(CH_2)_7C{\equiv}CBr$, CuCl. [d] KOH. [e] $LiAlH_4$, THF.

Experimental Section

Methyl 9-oxononanoate (2) was obtained by ozonolysis of methyl oleate as described by Pryde.[11] Reaction workup to produce the aldehyde was best effected with the use of acetic acid, water, and amberlite MB-3 resin.

Methyl 9-Hydroxyundec-10-ynoate (3). A modification of the procedure described by Stansbury and Proops[12] was used in which a mixture of 30 g of fused potassium hydroxide and 140 mL of anhydrous 1,2-dimethoxyethane was ground in a Waring blender for 0.5 h. A container of dry ice–2-propanol suspended above the blender blades cooled the mixture to 20–30 °C while the blender was operating. The resulting suspension of potassium hydroxide was transferred to a 500-mL, three-necked, round-bottomed flask fitted with a 100-mL pressure equalizing addition funnel, a gas diffusion tube, and a mechanical stirrer. The mixture was cooled to −5 °C, 1.0 mL of absolute ethanol was added, and the suspension was saturated with dry acetylene. A solution of methyl 9-oxononanate (12.9 g, 0.7 mol) in 13 mL of 1,2-dimethoxyethane and 1.0 mL of absolute ethanol was added dropwise over 0.5 h while the slow addition of acetylene was continued. The mixture was poured into cold ice water, acidified, and extracted with benzene–ether (1:1). The dried extracts were concentrated on a rotary evaporator. The crude acid product was esterified with diazomethane and distilled at 100–123 °C (0.15 mm) to give 11.5 g (77%) of pure ester: IR (CCl_4) 3600–3500 cm^{-1} (OH), 3310 (C≡CH), 2125 (C≡C), 1735 (C=O), and 1165 (C—O); NMR (CCl_4) δ 4.25 (m, 1 H, CH of alcohol), 3.6 (s, 3 H, CH_3), 2.7–3.1 (broad, 1 H, –OH), 2.3 (d, 1 H, C≡CH), 2.2 (m, 2 H, CH_2 C=O), 1.2–1.8 (broad, 12 H, aliphatic). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.92: H, 9.43. Found: C, 67.67; H, 9.33.

Attempts to prepare **3** by reaction of **2** with sodium acetylide were unsuccessful.

1-Bromo-1-heptyne was obtained in 67% yield from bromination of 1-heptyne in KOH–dimethoxyethane as described by Brandsma:[13] IR (CCl_4) 2250 cm^{-1} (C≡CBr); NMR (CCl_4) δ 2.2 (m, 2 H, $-CH_2C{\equiv}C$), 1.4 (m, 6 H, CH_2), 0.95 (m, 3 H, CH_3).

9-Hydroxyoctadeca-10,12-diynoic Acid (4). A mixture of **3** (1.06 g, 4 mmol), methanol (12 mL), cuprous chloride powder (10 mg), 33% isopropylamine (1.4 mL), and hydroxylamine hydrochloride (10 mg) was treated with 1-bromo-1-heptyne (0.88 g, 5 mmol) with stirring during 0.5 h. Small amounts of hydroxylamine hydrochloride were added to discharge the blue color which developed. A solution of potassium cyanide (25 mg) in 5 mL of water was added. Extraction with ether gave after drying and concentration a nearly quantitative yield of crude methyl 9-hydroxyoctadeca-10,12-diynoate which was purified by conversion to the acid with methanolic potassium hydroxide: 1.88 g (92%); IR (CCl_4) 3570 (OH), 3500–2800 (COOH), 2220 (C≡CC≡C), 1680 cm^{-1} (C=O); NMR (CCl_4) δ 87.4 (b, 1 H, COOH), 4.35 (m, 1 H, CH of alcohol), 2.3 (m, 4 H, CH_2), 1.8–1.2 (m, 18 H, aliphatic). Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.97; H, 9.59. Found: C, 74.04; H, 9.30.

9-Hydroxyoctadec-*trans*-10-en-12-ynoic Acid (Helenynolic Acid, 1). A mixture of **4** (0.7 g), tetrahydrofuran (25 mL), and lithium aluminum hydride (0.3 g) was heated at reflux for 24 h. Moist ether was added to destroy the excess $LiAlH_4$. Water was added and the mixture was extracted with ether. The dried ($MgSO_4$) ether extract was concentrated to give a crude oil which was chromatographed on silica gel G (300 μm) with 2,2,4-trimethylpentane–2-propanol–ether–formic acid (200:40:1:1). The product was collected at R_f 0.11 (0.38 g; 55%): IR (neat) 3600–3200 (OH) 3200–2500 (COOH), 2250 (C≡C), 1710 (C=O), 1705 cm^{-1} (C=C); UV (CH_3OH) 228, 235 nm; NMR (CCl_4) δ 6.3–6.9 (two doublets, 1 H, C=CH), 5.8–5.5 (m, 1 H, C≡CC=C), 4.4 (m, 1 H, CH), 2.3 (m, 5 H, CH_2C=O, $CH_2C{\equiv}C$, COH), 1.35 (m, 18 H, CH_2), and 0.9 (m, 3 H, CH_3).

Acid **1** was converted quantitatively to methyl helenynoate by reaction with diazomethane. IR, NMR, and UV analysis were identical with spectra reported in the literature:[3] IR (neat) 3600–3200 (OH), 2250 (C≡C), 1735 (C=O), 1625 (C=C), 953, 718 cm^{-1}; NMR (CCl_4) δ 6.3–5.9 (two doublets, 1 H, C=CHCO), 5.8–5.5 (m, 1 H, C≡CCH=C), 4.4 (m, 1 H, CHO), 3.7 (s, 3 H, CH_3), 2.4–2.0 (m, 5 H, CH_2C=O, $CH_2C{\equiv}C$, OH), 1.4 (m, 18 H, $-CH_2-$), and 0.95 (m, 3 H, CH_3); UV (CH_3OH) 228, 235 nm. Anal. Calcd for $C_{19}H_{31}O_3$: C, 74.26; H, 10.10. Found: C, 74.11; H, 9.96.

Registry No.—**1**, 68538-95-4; **2**, 1931-63-1; **3**, 68475-05-8; **3** acid, 68475-07-0; **4**, 68475-06-9; methyl helenynoate, 68538-96-5; acetylene, 74-86-2; 1-bromo-1-heptyne, 19821-84-2.

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