Synthesis of Some Bioactive Acetylenic Alcohols, Components of the Marine Sponge *Cribrochalina vasculum*

B. A. Kulkarni, S. Chattopadhyay, A. Chattopadhyay, and V. R. Mamdapur*

Bio-Organic Division, Modular Laboratory, Bhabha Atomic Research Centre, Bombay-400 085, India

Received March 3, 1993•

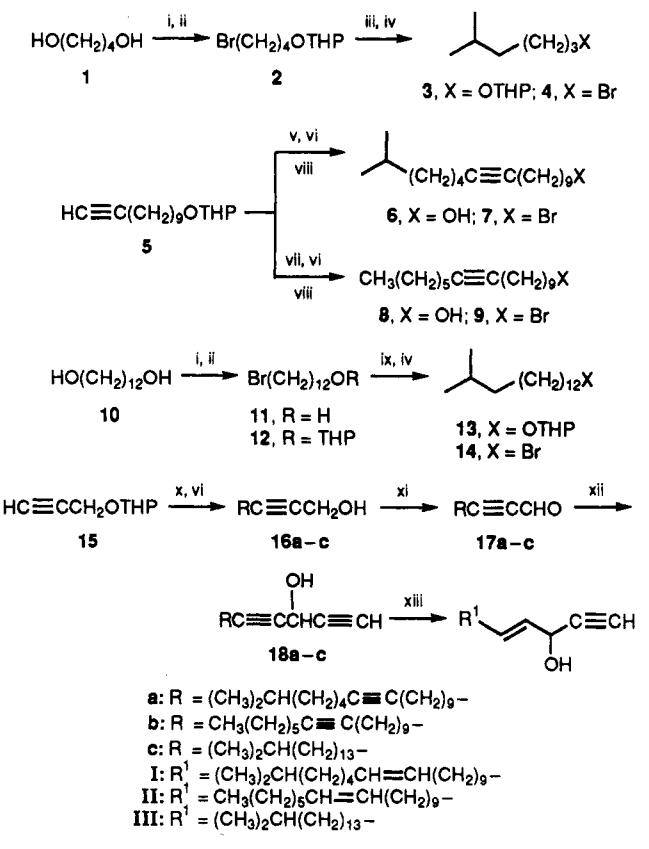
Grignard coupling of isopropylmagnesium bromide with 4-(tetrahydropyranyloxy)bromobutane (**2**) and subsequent bromination gave **4**. Alkylation of 1-(tetrahydropyranyloxy)undec-10-yne (**5**) with **4** and 1-bromohexane, acidic hydrolysis, and bromination furnished **7** and **9**, respectively. Likewise, coupling of isobutylmagnesium bromide with 12-(tetrahydropyranyloxy)bromododecane (**12**) followed by bromination afforded **14**. Alkylation of 1-(tetrahydropyranyloxy)-2-propyne (**15**) with **7**, **9**, and **14** and oxidation of the respective products afforded the alkynals **16a-c**. These on reaction with lithium acetylide and subsequent chemoselective *trans* reduction of the internal alkynes led to the target compounds **I-III**.

The current upsurge in marine research has rejuvenated natural product chemistry. Recently, Gunasekera and Faircloth[1] have isolated a series of acetylenic alcohols from the marine sponge *Cribrochalina vasculum*. Their potential *in vitro* immunosuppressive and antitumor activities and 1,4-enyn-3-ol skeleton provided an attractive challenge for synthesis. In a continuation of our recent efforts[2-4] in this direction, we report the first synthesis of three of those structurally related enynic alcohols (**I-III**).

We envisaged that the common structural feature of **I-III** can be constructed by a sequence of reactions on the required propargylic alcohols **16 a-c** (Scheme I). Hence, the initial task was the preparation of those synthons using commercially available starting materials and operationally simple facile reactions.

The bromo alcohol derivative **2** obtained by monobromination[5] of **1** and subsequent pyranylation was coupled with isopropylmagnesium bromide to furnish **3**. Its bromination with $PPh_3 \cdot Br_2$[6a] gave compound **4**.[7] Further, easily accessible 10-undecynoic acid[8] was converted to the OTHP derivative (**5**) *via* esterification, LAH reduction, and pyranylation. Alkylation of **5** with **4** and 1-bromohexane gave **6** and **8**, respectively. Likewise, the known bromo ether **12**[9] prepared from dodecanediol (**10**) on coupling with isobutylmagnesium bromide furnished **13**. Compounds **6**, **8**, and **13** were converted[6b] to their corresponding bromides **7**, **9**, and **14**. Alkylation of the propargyl alcohol derivative (**15**) with these bromides followed by depyranylation of the resultant products led to the respective alcohols **16a-c**. Oxidation with PCC[10] gave the aldehydes **17a-c** which on reaction with lithium acetylide afforded the triacetylenic alcohols **18a-c**. Regio- and stereoselective *trans* reduction of the internal alkyne groups with sodium in liquid ammonia without a proton donor respectively afforded **I**, **II**, and **III** of 96-98% purity (GLC).

Scheme I[a]



a: R = $(CH_3)_2CH(CH_2)_4C{\equiv}C(CH_2)_9-$
b: R = $CH_3(CH_2)_5C{\equiv}C(CH_2)_9-$
c: R = $(CH_3)_2CH(CH_2)_{13}-$
I: R^1 = $(CH_3)_2CH(CH_2)_4CH{=}CH(CH_2)_9-$
II: R^1 = $CH_3(CH_2)_5CH{=}CH(CH_2)_9-$
III: R^1 = $(CH_3)_2CH(CH_2)_{13}-$

[a] (i) HBr/PhH; (ii) DHP/H^+; (iii) $(CH_3)_2CHMgBr, Li_2CuCl_4$/THF; (iv) $Ph_3P \cdot Br_2$; (v) n-BuLi/HMPA/THF, **4**; (vi) MeOH/H^+; (vii) n-BuLi/HMPA/THF/1-bromohexane; (viii) $Ph_3P \cdot Br_2$/Py; (ix) $(CH_3)_2CHCH_2MgBr/Li_2CuCl_4$/THF; (x) n-BuLi/HMPA/THF, **7**/**9**/**14**; (xi) PCC/CH_2Cl_2; (xii) LiC≡CH/THF/NH_3, (**I**); (xiii) Na/NH_3 (**I**).

The spectral data of **I-III** were in agreement with those reported.[1] The (*E*)-geometry of the 3-hydroxy-4-en-1-yne unit was confirmed by the PMR spectra showing a dd (4H) at δ 5.5-5.6 (J = 15-16 and 6-8 Hz) and a dt (5H) at δ 5.8-6.0 (J = 15-16 and 6-8 Hz). The isolated olefin signals in **I** and **II** appeared at δ 5.3-5.4 with a signal

• Abstract published in *Advance ACS Abstracts*, September 15, 1993.

(1) Gunasekera, S. P.; Faircloth, G. T. *J. Org. Chem.* **1990**, *55*, 6223.
(2) Kulkarni, B. A.; Chattopadhyay, A.; Mamdapur, V. R. *Synth. Commun.* **1992**, *22*, 2921.
(3) Kulkarni, B. A.; Chattopadhyay, S.; Mamdapur, V. R. *Org. Prep. Proc. Int.* **1993**, *25*, 193.
(4) Kulkarni, B. A.; Chattopadhyay, S.; Chattopadhyay, A.; Mamdapur, V. R. *Synthesis*, in press.
(5) Kang, K.; Kim, W. S.; Moon, B. H. *Synthesis* **1985**, 1161.
(6) (a) Sonnet, P. E. *Synth. Commun.* **1976**, *6*, 21. (b) Wiley, G. A.; Hershlowitz, R. I.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 964.
(7) Mori, K.; Ebata, T. *Tetrahedron* **1986**, *42*, 3471.
(8) Vogel, A. I. Text Book of Practical Organic Chemistry; English Language Book Society/Longman: Birmingham, 1986, p 346.
(9) Iyer, R. R.; Mamdapur, V. R. *Ind. J. Chem. (Sect. B)* **1989**, *28B*, 728.
(10) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

0022-3263/93/1958-5964$04.00/0

width of 18–20 Hz, thereby indicating the (*E*)-geometry. The overall (*E*)-geometry of **I-III** was further confirmed by the ^{13}C-NMR spectra which exhibited signals for the allylic carbons at δ 32 ppm, characteristic of internal (*E*)-alkenes.[11,12]

Experimental Section

All bps are uncorrected. Anhydrous reactions were carried out under argon atmosphere using freshly dried solvents. Unless otherwise mentioned, the organic extracts were dried over anhydrous Na_2SO_4.

4-(Tetrahydropyranyloxy)-1-bromobutane (2). Butane-1,4-diol (20.0 g, 0.22 mol) was monobrominated[5] with 48% HBr (27.7 mL) in 54.8% (18.5 g) yield and the resultant bromo alcohol (18.0 g, 0.118 mol) pyranylated with dihydropyran (12.9 mL) in CH_2Cl_2 (200 mL) in the presence of PPTS (0.1 g) to furnish **2** (26.34 g, 95%): bp 84–86 °C/0.3 mm; IR 1085, 1050, 990, 810 cm^{-1}; ^1H-NMR δ 1.3 (m, 4H), 1.7 (m, 6H), 3.2–3.8 (m, 6H), 4.6 (s, 1H).

5-Methyl-1-(tetrahydropyranyloxy)hexane (3). To a stirred solution of isopropylmagnesium bromide [prepared from isopropyl bromide (5.0 g, 0.041 mol) and Mg turnings (1.1 g, 0.045 mol) in THF (30 mL)] was added **2** (9.52 g, 0.04 mol) in THF (40 mL) followed by Li_2CuCl_4 (2.5 mL, 0.1 M solution in THF). After 3 h, the reaction was quenched with aqueous 10% NH_4Cl and the mixture extracted with ether (100 mL). The organic phase was separated, the aqueous portion extracted with ether (3 × 50 mL), and the combined organic extract washed with water and brine. Removal of solvent and column chromatography (SiO_2, 0–10% ether/hexane) of the residue gave **3** (5.44 g, 67%): IR 1390, 1370, 1080, 1020, 900 cm^{-1}; ^1H-NMR δ 0.86 (d, J = 6.4 Hz, 6H), 1.1–1.8 (m, 13H), 3.2–3.8 (m, 4H), 4.5 (s, 1H). Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.73; H, 12.29. Found: C, 71.95; H, 12.08.

5-Methyl-1-bromohexane (4). Compound **3** (5.4 g, 0.027 mol) was brominated with triphenylphosphine (8.5 g, 0.032 mol) and Br_2 (1.67 mL, 0.032 mol) in CH_2Cl_2 (20 mL) to give the bromide **4**[6] (3.42 g, 71%): bp 80–82 °C/20 mm; IR 1390, 1370 cm^{-1}; ^1H-NMR δ 0.86 (d, J = 6.6 Hz, 6H), 1.1–1.5 (m, 7H), 3.6 (t, J = 6.5 Hz, 2H).

16-Methyl-10-heptadecyn-1-ol (6). To a stirred solution of **5** (4.78 g, 0.019 mol) in THF (30 mL) at −78 °C was added *n*-BuLi (12.7 mL, 1.5 M in hexane, 0.019 mol). It was then brought to −50 °C, and HMPA (10 mL) was added followed by **4** (3.4 g, 0.019 mol) in THF (20 mL). After being stirred for 5 h, the reaction mixture was poured into excess cold (0 °C) aqueous NH_4Cl solution and extracted with ether (4 × 50 mL). The organic extract was washed with water and brine and finally dried. The product obtained on removal of solvent was taken in MeOH (200 mL) containing concd HCl (1 drop) and refluxed for 6 h. Most of the solvent was removed in vacuo and the residue taken up in ether (100 mL). The extract was washed with water and dried. After concentration, the product was purified by column chromatography (SiO_2, 0–20% EtOAc/hexane) to give **6** (3.2 g, 63%): IR 3340, 2210, 1370, 1390 cm^{-1}; ^1H-NMR δ 0.87 (d, J = 6 Hz, 6H), 1.1–1.7 (m, 21H), 1.9–2.4 (m, partially D_2O exchangeable, 5H), 3.57 (t, J = 7 Hz, 2H). Anal. Calcd for $C_{18}H_{34}O$: C, 81.13; H, 12.86. Found: C, 81.22; H, 12.84.

1-Bromo-16-methyl-10-heptadecyne (7). To a stirred solution of PPh_3 (3.5 g, 0.014 mol) in CH_2Cl_2 (20 mL) was added bromine (2.45 mL, 5.5 M in CCl_4, 0.014 mol). After 0.5 h, a solution of **6** (3.0 g, 0.011 mol) and pyridine (1.0 mL, 0.013 mol) in CH_2Cl_2 (20 mL) was added to it over a period of 20 min. Stirring was continued for 6 h, the reaction mixture concentrated and diluted with hexane, and the supernatant passed through a pad of silica gel to furnish pure **7** (2.68 g, 73%) after removal of solvent: IR 2100, 1390, 1370 cm^{-1}; ^1H-NMR δ 0.86 (d, J = 6.6 Hz, 6H), 1.3 (m, 21H), 2.1–2.4 (m, 4H), 3.5 (t, J = 6.5 Hz, 2H). Anal. Calcd for $C_{18}H_{33}Br$: C, 65.51; H, 10.39; Br, 24.08. Found: C, 65.64; H, 10.10; Br, 24.26.

10-Heptadecyn-1-ol (8): bp 125–128 °C/0.5 mm; IR 3350, 2220 cm^{-1}; ^1H-NMR δ 0.9 (br t, 3H), 1.1–1.5 (m, 22H), 1.7 (br s, 1H, D_2O exchangeable), 1.9–2.3 (m, 4H), 3.7 (t, J = 6 Hz, 2H). Anal. Calcd for $C_{17}H_{32}O$: C, 80.64; H, 12.86. Found: C, 80.88; H, 12.78.

1-Bromoheptadec-10-yne (9): bp 179–181 °C/1 mm; IR 2220 cm^{-1}; ^1H-NMR δ 0.9 (br t, 3H), 1.2–1.6 (m, 22H), 1.8–2.2 (m, 4H), 3.4 (t, J = 6 Hz, 2H). Anal. Calcd for $C_{17}H_{31}Br$: C, 64.92; H, 10.10; Br, 25.15. Found: C, 64.75; H, 9.91; Br, 25.34.

12-(Tetrahydropyranyloxy)bromododecane (12): bp 169–171 °C/3 mm; IR 1080, 1050, 990, 800 cm^{-1}; ^1H-NMR δ 1.3 (m, 20H), 1.6 (m, 6H), 3.2–3.9 (m, 6H), 4.6 (s, 1H).

1-(Tetrahydropyranyloxy)-14-methylpentadecane (13): IR 1390, 1370, 1080, 1020 cm^{-1}; ^1H-NMR δ 0.81 (d, J = 6.5 Hz, 6H), 1.2–1.4 (m, 25H), 1.5–1.6 (m, 6H), 3.3–3.9 (m, 4H), 4.54 (s, 1H). Anal. Calcd for $C_{21}H_{42}O_2$: C, 77.02; H, 12.79. Found: C, 77.23; H, 12.97.

14-Methyl-1-bromopentadecane (14): bp 170–172 °C/6.0 mm; IR 1390, 1370 cm^{-1}; ^1H-NMR δ 0.85 (d, J = 6.8 Hz, 6H), 1.34 (m, 25H), 3.4 (t, J = 6 Hz, 2H). Anal. Calcd for $C_{16}H_{33}Br$: C, 62.86; H, 10.78; Br, 26.35. Found: C, 62.94; H, 10.89; Br, 26.17.

19-Methyleicosa-2,13-diyn-1-ol (16a). As described for **6**, alkylation of **15** (1.10 g, 8.0 mmol) with **7** (2.6 g, 8.0 mmol) using *n*-BuLi (5.3 mL, 1.5 M solution in hexane, 8.0 mmol) as the base and subsequent depyranylation (MeOH/H$^+$) of the product furnished **16a** (1.58 g, 66%): IR 3300, 2290, 1385, 1375 cm^{-1}; ^1H-NMR δ 0.86 (d, J = 6.8 Hz, 6H), 1.1–1.6 (m, 21H), 1.9–2.2 (m, 6H), 2.3 (br s, D_2O exchangeable, 1H), 4.1 (t, J = 2 Hz, 2H). Anal. Calcd for $C_{21}H_{36}O$: C, 82.68; H, 11.68. Found: C, 82.83; H, 11.92.

Eicosa-2,13-diyn-1-ol (16b): IR 3310, 2280, 2200 cm^{-1}; ^1H-NMR δ 0.85 (br t, 3H), 1.1–1.7 (m, 22H), 1.9–2.3 (m, 6H), 2.5 (br s, 1H, D_2O exchangeable), 4.13 (t, J = 2 Hz, 2H). Anal. Calcd for $C_{20}H_{34}O$: C, 82.54; H, 11.96. Found: C, 82.69; H, 11.80.

17-Methyloctadec-2-yn-1-ol (16c): IR 3350, 2290, 2220, 1390, 1375 cm^{-1}; ^1H-NMR δ 0.86 (d, J = 6.8 Hz, 6H), 1.3 (m, 25H), 1.7 (br s, D_2O exchangeable, 1H), 1.9–2.3 (m, 2H), 4.12 (t, J = 2 Hz, 2H). Anal. Calcd for $C_{19}H_{36}O$: C, 81.54; H, 12.84. Found: C, 81.36; H, 12.94.

19-Methyleicosa-2,13-diyn-1-al (17a). To a stirred suspension of PCC (1.6 g, 7.0 mmol) in CH_2Cl_2 (10 mL) was added **16a** (1.5 g, 5.0 mmol) in CH_2Cl_2 (10 mL) in one lot. The mixture was stirred for 3 h, and **17a** (0.99 g, 67%) (pure, TLC) was isolated following the known procedure.[10] The compound was sufficiently pure and hence used as such for the next step: IR 2720, 2290, 2200, 1700, 1390, 1375 cm^{-1}; ^1H-NMR δ 0.86 (d, J = 6.6 Hz, 6H), 1.1–1.5 (m, 21H), 2.0–2.2 (m, 6H), 9.2 (s, 1H).

Eicosa-2,13-diyn-1-al (17b): IR 2740, 2290, 2200, 1700 cm^{-1}; ^1H-NMR δ 0.86 (br t, 3H), 1.1–1.6 (m, 22H), 2.1–2.4 (m, 6H), 9.2 (s, 1H).

17-Methyloctadec-2-yn-1-al (17c): IR 2730, 2290, 2210, 1700, 1390, 1370 cm^{-1}; ^1H-NMR δ 0.86 (d, J = 6.6 Hz, 6H), 1.2–1.4 (m, 25H), 2.1–2.3 (m, 2H), 9.17 (s, 1H).

3-Hydroxy-21-methyldocosa-1,4,15-triyne (18a). To a stirred suspension of lithium acetylide (9.0 mmol) in liquid NH_3 (75 mL) was added **17a** (0.91 g, 3.0 mmol) in THF (20 mL) with continuous passage of acetylene gas. After 3 h, NH_4Cl (s) was added and the reaction mixture left overnight for the removal of NH_3 (g). Then cold water (0 °C) (200 mL) was added in the reaction flask and the mixure extracted with ether (4 × 50 mL). The ether layer was washed successively with water and aqueous saturated NH_4Cl. The dried extract was concentrated under reduced pressure and the residue purified by column chromatography over silica gel (0–20% EtOAc in hexane) to give **18a** (0.68 g, 71.5%): IR 3400, 3310, 2290, 2200, 2110, 1390, 1370 cm^{-1}; ^1H-NMR δ 0.83 (d, J = 6.3 Hz, 6H), 1.1–1.4 (m, 21H), 1.9–2.2 (m, 6H), 2.54 (d, J = 2 Hz, 1H), 3.1 (br s, D_2O exchangeable, 1H), 4.80 (s, 1H). Anal. Calcd for $C_{23}H_{36}O$: C, 84.08; H, 11.05. Found: C, 84.22; H, 11.06.

3-Hydroxydocosa-1,4,15-triyne (18b): IR 3450, 3300, 2260, 2200, 2100 cm^{-1}; ^1H-NMR δ 0.9 (br t, 3H), 1.1–1.6 (m, 22H), 1.8–2.15 (m, 6H), 2.51 (d, J = 2 Hz, 1H), 3.0 (br s, 1H, D_2O exchangeable), 4.8 (s, 1H). Anal. Calcd for $C_{22}H_{34}O$: C, 84.18; H, 11.10. Found: C, 84.02; H, 10.90.

3-Hydroxy-19-methyleicosa-1,4-diyne (18c): IR 3400, 3320, 2260, 2210, 1390, 1370 cm^{-1}; ^1H-NMR δ 0.83 (d, J = 6.4 Hz, 6H), 1.1-1.5 (m, 25H), 2.0–2.1 (m, 2H), 2.5 (br s, D_2O exchangeable,

(11) Ciminello, P.; Fattorusso, E.; Magno, S.; Mangoni, A.; Lalenti, A.; Di Rosa, M. *Experientia* **1991**, *47*, 739.

(12) Vysotaskii, M. V.; Imbas, A. B.; Popkov, A. A.; Latyshev, N. A.; Svetashev, V. I. *Tetrahedron* Lett. **1990**, *31*, 4367.

1H), 2.54 (d, J = 2 Hz, 1H), 4.80 (s, 1H). Anal. Calcd for $C_{21}H_{36}O$: C, 82.83; H, 11.92. Found: C, 82.71; H, 11.77.

3-Hydroxy-21-methyldocosa-4(*E*),15(*E*)-dien-1-yne (I). To a stirred solution of Na (0.33 g, 14.6 mg. atm) in liquid NH_3 (100 mL) was added **18a** (0.60 g, 1.8 mmol) in ether (50 mL) dropwise over a period of 0.5 h. After the solution was stirred for 8 h, NH_4Cl (s) (1.0 g) and ice–water were added. The mixture was extracted with ether (3 × 30 mL) and the combined extract washed with water and brine and dried. Removal of solvent and column chromatography over silica gel (0–10% EtOAc in hexane) furnished **I** (0.45 g, 76.0%): GLC (3% OV-17, 40 mL of N_2/min, 200-250 °C, 4°/min), t_R = 20.31 min; IR 3400, 3300, 2110, 1390, 1370, 970 cm^{-1}; ^{1}H-NMR δ 0.87 (d, J = 6.5 Hz, 6H), 1.1–1.5 (m, 21H), 1.8 (br s, D_2O exchangeable, 1H), 2.0–2.1 (m, 6H), 2.54 (d, J = 2 Hz, 1H), 4.82 (d, J = 5.5 Hz, 1H), 5.3–5.4 (m, 2H), 5.59 (dd, J = 15.3 Hz, 6.2 Hz, 1H), 5.9 (dt, J = 15.3 Hz, 6.8 Hz, 1H). ^{13}C-NMR 22.6, 27.0, 27.3, 27.9, 28.9, 29.2, 29.4, 29.5, 29.7, 29.92, 30.0, 31.9, 39.0, 62.6, 73.7, 83.4, 128.3, 129.5, 134.4; MS 332 (M^+). Anal. Calcd for $C_{23}H_{40}O$: C, 83.22; H, 12.30. Found: C, 83.06; H, 12.12.

3-Hydroxydocosa-4(*E*),15(*E*)-dien-1-yne (II): GLC (3% OV-17, 40 mL of N_2/min, 200–250 °C, 4°/min), t_R = 18.57 min; IR 3450, 3300, 2120, 980 cm^{-1}; ^{1}H-NMR δ 0.88 (br t, 3H), 1.3–1.6 (m partially D_2O exchangeable, 23H), 1.9–2.15 (m, 6H), 2.54 (d, J = 2Hz, 1H), 4.82 (d, J = 6Hz, 1H), 5.3–5.4 (m, 2H), 5.59 (dd, J = 15.2 Hz, 5.9 Hz, 1H), 5.90 (dt, J = 15.2 Hz, 6.8 Hz, 1H); ^{13}C-NMR δ 14.0, 22.5, 28.5, 29.1, 29.2, 29.4, 29.5, 29.7, 31.3, 32.0, 62.7, 73.8, 80.2, 128.4, 129.8, 134.4; MS 318 (M^+). Anal. Calcd for $C_{22}H_{38}O$: C, 82.78; H, 12.18. Found: C, 82.95; H, 12.02.

3-Hydroxy-19-methyleicos-4(*E*)-en-1-yne (III): GLC (3% OV-17, 40 mL of N_2/min, 200–250 °C, 4°/min), t_R = 12.05 min; IR 3400, 3310, 2110, 1385, 1360, 980 cm^{-1}; ^{1}H-NMR δ 0.86 (d, J = 6.4 Hz, 6H), 1.15–1.4 (m, 25H), 2.0–2.1 (m, 2H), 2.3 (br s D_2O exchangeable, 1H), 2.55 (d, J = 2 Hz, 1H), 4.82 (d, J = 5.9 Hz, 1H), 5.59 (dd, J = 15.3 Hz, 5.8 Hz, 1H), 5.9 (dt, J = 15.3 Hz, 6.8 Hz, 1H); ^{13}C-NMR 22.6, 27.0, 27.3, 27.9, 28.9, 29.2, 29.4, 29.5, 29.7, 29.92, 30.0, 31.9, 39.0, 62.6, 73.7, 83.4, 128.3, 134.4; MS 306 (M^+). Anal. Calcd for $C_{21}H_{38}O$: C, 82.48; H, 12.78. Found: C, 82.28; H, 12.50.

Supplementary Material Available: Experimental details pertaining to the synthesis of II and III (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.