Preparation of Methyl 5,11,14,17-Eicosatetraenoate-8,8,9,9-d_4

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For studies of incorporation, elongation and desaturation of fats in humans and animals, methyl 5,11,14,17-eicosatetraenoate-8,8,9,9-d_4 was prepared by Wittig coupling, in the presence of sodium *bis*(trimethylsilyl) amide, of 6,9,12-pentadecatrienal-3,3,4,4-d_4 and 4-carboxybutyltriphenylphosphonium bromide. The all-*cis* isomer was separated from *trans* isomers and other impurities by silver resin chromatography. Location and configuration of the double bonds and deuterium atoms were affirmed by nuclear magnetic resonance and mass spectrometry.
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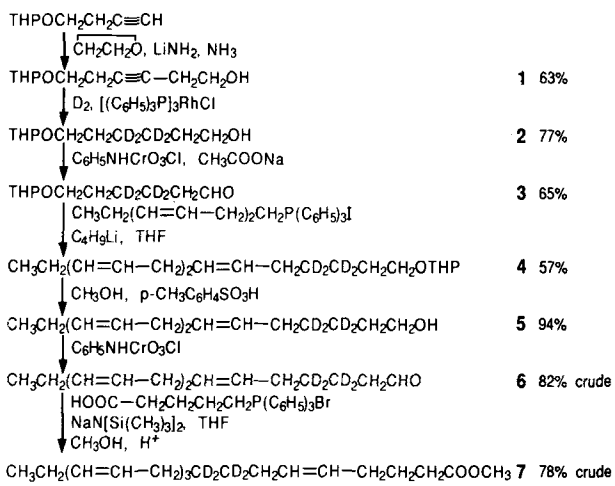
For studies of incorporation, elongation and desaturation of fats in humans and animals (1,2), we have synthesized various monoenoic (3), dienoic (4) and tri- and tetraenoic (5–7) fatty acid esters labeled with deuterium in various positions. In this paper we describe the synthesis of methyl 5,11,14,17-eicosatetraenoate-8,8,9,9-d_4 (5,11,14,17-20:4-d_4) which is potentially an intermediate in the conversion of linolenate (9,12,15-18:3) to eicosapentaenoate (5,8,11,14,17-20:5). The 5,11,14,17-20:4-d_4 has been synthesized to study the proposed pathway (8) that involves the action of a Δ8 desaturase. The results of the biochemical investigation will be published separately.

RESULTS AND DISCUSSION

The original plan was to generate methyl 5,11,14,17-20:4-d_4 by Wittig coupling of 3,6-nonadienyltriphenylphosphonium iodide with methyl 11-oxo-5-undecenoate-8,8,9,9-d_4. The synthesis of the nine carbon phosphonium salt has been described previously (6,7). An improved preparation of 1-bromo-2-pentyne, the first intermediate in the synthesis of the phosphonium salt, is presented in this paper. The required aldehyde ester was to be obtained by oxidation of methyl 11-hydroxy-5-undecenoate-8,8,9,9-d_4. We thought this hydroxy ester should be accessible through Wittig reaction of 3,3,4,4-tetradeutero-6-hydroxyhexyltriphenylphosphonium iodide and methyl 5-oxopentanoate. However, the reaction did not yield the desired Wittig coupling product. A hydroxyphosphonium salt reacts with a simple aldehyde to give the expected Wittig coupling product but, according to Ohta *et al.* (9), the principal product (about 35% yield) of the reaction of a hydroxyphosphonium salt and an aldehyde ester is a macrocyclic lactone rather than the Wittig coupling product. In an effort to avoid this unwanted reaction, we prepared the tetrahydropyranyl (THP) ether of 6-hydroxyhexyltriphenylphosphonium bromide but were unable to obtain it in crystalline form. We were unsuccessful in our attempts to isolate a Wittig product from the reaction between the viscous phosphonium salt and the five-carbon aldehyde ester.



SCHEME 1

We then decided to approach the synthesis from the other end of the molecule (Scheme 1). This would involve coupling, *via* a Wittig reaction, 3,6-nonadienyltriphenylphosphonium iodide with the THP ether of 6-hydroxyhexanal-3,3,4,4-d_4, **3**, to yield, after hydrolysis, 6,9,12-pentadecatrienol-3,3,4,4-d_4, **5**.

For the synthesis of compound **3**, we condensed the THP ether of 3-butynol with ethylene oxide in the presence of lithium amide in liquid ammonia to give the mono-THP ether of 3-hexyne-1,6-diol, **1**. This compound was treated with deuterium gas in the presence of *tris*-(triphenylphosphine)chlororhodium to give the mono-THP ether of 1,6-hexanediol-3,3,4,4-d_4, **2**. Oxidation of this intermediate with pyridinium chlorochromate in the presence of sodium acetate (10) produced the THP ether of 6-hydroxyhexanal-3,3,4,4-d_4, **3**. Compound **3** was coupled with 3,6-nonadienyltriphenylphosphonium iodide and butyl lithium to give the THP ether of pentadecatrienol-3,3,4,4-d_4, **4**, which was then hydrolyzed to **5**. The pentadecatrienol-d_4, **5**, could be converted to the phosphonium iodide through the bromide. The phosphonium iodide could then be coupled with methyl 5-oxopentanoate to give 20:4-d_4. Alternatively, compound **5** could be oxidized to the corresponding aldehyde and coupled with 4-carboxybutyltriphenylphosphonium bromide (which is commercially available) to give 20:4-d_4. We chose the latter route. Accordingly, pentadecatrienol-d_4, **5**, was oxidized to pentadecatrienal-d_4, **6**, with pyridinium chlorochromate. With unsubstituted phosphonium salts, the Wittig reaction with butyl lithium as base yields about 10–15% *trans* in the coupled product. With carboxybutyltriphenylphosphonium bromide and nonanal we found that the Wittig reaction with butyl lithium gave about 30% *trans*

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Abbreviations: DHP, dihydropyran; EE, diethyl ether; GC, gas chromatography; NMR, nuclear magnetic resonance; PE, petroleum ether (35–60°C); *p*-TSA, *p*-toluenesulfonic acid; THF, tetrahydrofuran; THP, tetrahydropyranyl.

isomer, and the yield was poor due to the formation of the aldol condensation product from the nonanal. We investigated other bases and settled on sodium *bis*(trimethylsilyl)amide (11) because it gave the desired product with only about 10% *trans*, and without the formation of the aldol product. Therefore we used sodium *bis*(trimethylsilyl)amide to condense pentadecatrienal-d_4, **6**, with 4-carboxybutyltriphenylphosphonium bromide to give compound **7**. The all-*cis* isomer of **7** was isolated on a 75% Ag/Na XN1010 column using 2–5% concentrations of acetonitrile in methanol as eluant.

EXPERIMENTAL PROCEDURES

Reagents. Butyl lithium, triphenylphosphine, dihydropyran, 4-carboxybutyltriphenylphosphonium bromide, 3-butynol, sodium *bis*(trimethylsilyl)amide and pyridinium chlorochromate were obtained from Aldrich Chemical Company (Milwaukee, WI). 2-Pentynol was purchased from Farchan Laboratories (Gainsville, FL), and *tris*(triphenylphosphine)chlororhodium was obtained from Strem Chemicals (Newburyport, MA). Silica gel (60–200 mesh) and Florisil (100–200 mesh) were purchased from J.T. Baker (Jackson, TN), and Silica Gel 60 A (70–230 mesh) was from American Scientific Products (McGaw Park, IL).

Methods. A 30 m × 0.25 mm SP2340 fused silica capillary column (Supelco, Inc., Bellefonte, PA) was used for analyzing binary mixtures of geometric isomers. For other analyses, a 6 ft × 4 mm column packed with 3% EGSS-X on 100/120 GasChrom Q or a 5 m × 0.53 mm HP-1 column (Hewlett-Packard Co., Avondale, PA) was employed.

^{13}C Nuclear magnetic resonance (NMR) spectra were recorded with a Bruker (Billerica, MA) WM 300 WB pulsed Fourier transform spectrometer operating at 75.5 MHz. Typically, 2500 transients were collected from solutions in $CDCl_3$, which served as both internal lock and secondary reference, using 5-mm tubes. Sweep widths of 200 ppm and 8 K real data points limited acquisition time to 0.54 s and were used to obtain chemical shift values within ± 1.85 Hz, *i.e.*, ±0.05 ppm. A pulse width of 3 μs (40°) was employed with no delay between pulses. Decoupling power was held to *ca.* 1 W to provide adequate broadband decoupling power while minimizing sample heating (27°C probe temperature). The signal from carbons bearing two deuterium atoms or one deuterium atom and a double bond is diminished to such an extent that it is usually not detected.

Mass spectra were obtained on a Finnigan (San Jose, CA) 4500 mass spectrometer using isobutane chemical ionization with data processing of the isotope distribution against standards (12).

The macroreticular resin used for the separations was Rohm and Haas (Philadelphia, PA) XN1010 sulfonic acid resin ground to the mesh size indicated. Preparation of the silvered columns has been described (13–15).

Improved preparation of 1-bromo-2pentyne. Triphenylphosphine (171.5 g, 655 mmol) was dissolved in methylene chloride (325 mL) in a 1-L, three-necked flask equipped with a mechanical stirrer, a low temperature thermometer and a burette or dropping funnel. A slow stream of N_2 was maintained through the apparatus as it was cooled in an ice bath. Bromine (102.8 g, 33.2 mL, 643 mmol) was added dropwise over 50 min while the temperature was kept between 3 and 15°C by intermittent cooling. 2-Pentynol (50.1 g, 595 mmol) in CH_2Cl_2 (50 mL) was added to the off-white slurry over 30 min at 4 to 8°C. The ice bath was removed and 15 min later petroleum ether (PE) (400 mL) was added. The mixture was filtered with suction and the precipitate was washed with PE (2 × 100 mL). A column (3 × 50 cm) was packed with Baker silica gel (100 g), and 900 mL of solution was passed through the dry column followed by two 250 mL portions of PE. Solvent was removed from the eluate on a rotary evaporator at about 15°C and about 100 torr to yield 103 g of residue. The residue was distilled through a jacketed Vigreux column to yield the title compound (77.59 g, 88.7% yield, 98% pure by gas chromatography (GC) b.p. 63–80°C at 90 torr). In contrast to previously described preparations, this sample of 1-bromo-2-pentyne was not a lachrymator.

Preparation of 6-(2-tetrahydropyranyloxy)-3-hexynol (**1**) (16). Liquid ammonia (*ca.* 400 mL) was charged to a 1-L, three-necked flask equipped with a mechanical stirrer and a dry ice-cooled condenser and surrounded by Vermiculite insulating material. Ferric nitrate (0.4 g) was added followed by the slow addition of metallic lithium (2.62 g, 328 mmol). After the slurry had turned gray, a solution of the THP ether of 3-butynol (45.5 g, 295 mmol) in diethyl ether (EE) (25 mL) was added. Liquid ethylene oxide (35.28 g, 40 mL, 802 mmol) was added in one portion and stirring was continued for 8 h. The Vermiculite insulating material was removed, and the ammonia was permitted to vent overnight through a tube containing KOH pellets. The next morning, aqueous NH_3 (5 mL) and water (100 mL) were added. The reaction mixture was extracted with EE (1 × 100, 2 × 50 mL), and the combined EE layers were washed with saturated NaCl solution (100 mL) and dried (Na_2SO_4). Distillation through a jacketed Vigreux column gave a forerun (5.12 g) b.p. 45–80°C at 0.35 torr containing principally unreacted THP ether of 3-butynol and then the title compound, **1**, (36.53 g, 62.6% yield, 94% pure by GC) b.p. 93–130°C at 0.3 to 0.5 torr. ^1H NMR ($CDCl_3$; ppm): δ 1.41–1.73 (*m*, 6H, $CH_2CH_2CH_2$), 2.28-2.40 (*m*, 4H, $CH_2C{\equiv}CCH_2$), 2.76 (*t*, 1H, OH), 3.39–3.48 (*m*, 2H, CH_2O), 3.53–3.60 (*m*, 2H, $THPOCH_2$), 3.66–3.78 (*m*, 2H, CH_2OH), 4.54 (*m*, 1H, OCHO). ^{13}C NMR (ppm): C-1, 61.0; C-2, 22.9; C-3, 77.7; C-4, 78.9; C-5, 20.0; C-6, 65.8; THP group: C-2, 98.6; C-3, 30.4; C-4, 19.3; C-5, 25.2; C-6, 62.1.

Preparation of 6-(2-tetrahydropyranyloxy)hexanol-3,3,4,4-d_4, (**2**). Compound **1** (26.1 g, 132 mmol) in benzene (1 L) was treated with deuterium gas in the presence of *tris*-(triphenylphosphine)chlororhodium (3 g) in the manner previously described (3). Benzene was removed on the rotary evaporator, and the red liquid remaining was diluted with PE (100 mL), filtered and passed through a column (3 × 50 cm) containing Silica Gel 60 (100 g) in PE. Elution with increasing concentrations of EE in PE (0 to 50%) yielded fractions which were combined (26 g) and distilled through a jacketed Vigreux column to yield a forerun (0.39 g), b.p. 50–100°C at 0.5 torr containing all the impurities and a main fraction (20.84 g, 76.8% yield), b.p. 120–123°C at 0.6 torr containing the title compound, **2**, (98% pure by GC). Deuterium distribution: 2.3% d_3, 96.7% d_4, 1.0% d_5, 0.1% d_6. ^1H NMR ($CDCl_3$; ppm): δ 1.44–1.76 (*m*, 10H, $CH_2CH_2CH_2$ and $CH_2CD_2CD_2CH_2$), 2.08 (*s*, 1H, OH), 3.30–3.37 (*m*, 2H, CH_2O), 3.54–3.58 (*m*,

2H, THPOCH_2), 3.64–3.72 (*m*, 2H, CH_2OH), 4.51 (*m*, 1H, OC*H*O). ^{13}C NMR (ppm): C-1, 62.6; C-2, 32.3; C-5, 29.3; C-6, 67.4; THP group: C-2, 98.7; C-3, 30.6; C-4, 19.6; C-5, 25.4; C-6, 62.3.

Preparation of 6-(2-tetrahydropyranyloxy)hexanal-3,3,4,4-d_4, (3). Pyridinium chlorochromate (38.9 g, 183 mmol) and sodium acetate (3 g, 36.6 mmol) were suspended in methylene chloride (170 mL) in a 500-mL, three-necked flask equipped with a mechanical stirrer and a thermometer. A stream of nitrogen was maintained through the apparatus. A solution of compound 2 (18.8 g, 91.3 mmol) in CH_2Cl_2 (10 mL) was added in one portion. The reaction mixture turned black, and the mildly exothermic reaction was maintained between 25 and 30°C by intermittent use of an ice bath. Ninety minutes later, EE was added to the stirred mixture. The EE layer was decanted, and the black residue was stirred with two fresh portions (100 mL each) of EE and decanted. The combined EE layers were passed through a column containing Florisil (40 g) to yield a pale green liquid (17.83 g). This material may be used without further purification or it may be passed through a column (3 × 50 cm) containing Silica Gel 60 (100 g) in PE. The title compound, 3, (12.13 g, 65% yield, 89% pure by GC) elutes with mixtures containing up to 15% EE in PE. ^{1}H NMR ($CDCl_3$; ppm): δ 1.43–1.78 (*m*, 8H, CH_2CH_2CH_2 and CH_2CD_2), 2.37 (*s*, 2H, CH_2CHO), 3.28–3.47 (*m*, 2H, CH_2O), 3.64–3.83 (*m*, 2H, THPOCH_2), 4.49–4.51 (*m*, 1H, OC*H*O), 9.70–9.71 (*t*, 1H, C*H*O). ^{13}C NMR (ppm): C-1, 202.5; C-2, 43.5; C-5, 29.1; C-6, 67.1; THP group: C-2, 98.9; C-3, 30.7; C-4, 19.6; C-5, 25.4; C-6, 62.3.

Preparation of 2-(3',3',4',4'-tetradeutero-6',9',12'-pentadecatrienyloxy)tetrahydropyran, (4). 3,6,-Nonadienyltriphenyl phosphonium iodide (33.5 g, 65.4 mmol) was slurried in tetrahydrofuran (150 mL) in a 500-mL, three-necked flask equipped with a mechanical stirrer, a thermometer and a $CaCl_2$ drying tube. While a stream of nitrogen was maintained through the apparatus, the slurry was cooled to 5°C, and butyl lithium (2.5 M, 30 mL, 75 mmol) was added. A dark red solution was formed. Fifteen minutes later, compound 3 (12.13 g, 59.5 mmol) in tetrahydrofuran (THF) (15 mL) was added. The color of the reaction remained red due to the presence of excess phosphonium salt. The ice bath was removed, and 1 h later GC analysis of a sample of the reaction mixture (after reaction with saturated NaCl solution) showed absence of aldehyde and presence of a new component. Thirty minutes later saturated NaCl solution (100 mL) was added and the layers were separated. Solvent was removed from the organic layer on the rotary evaporator to give a liquid and solid (38.7 g). This mixture was extracted with PE (4 × 50 mL), and the combined PE layers were dried (Na_2SO_4). After removal of the drying agent and solvent, the residue was placed on a column (3 × 50 cm) containing silica gel 60 (100 g) in PE. The title compound, 4, (13.44 g, 57% yield, 90% pure by GC) was obtained by elution with PE containing 2 or 5% diethyl ether. ^{1}H NMR ($CDCl_3$; ppm): δ 0.96 (*t*, 3H, CH_3), 1.49–1.80 (*m*, 6H, CH_2CH_2CH_2), 2.01–2.08 (*m*, 4H, C=CH-CH_2), 2.78 (*t*, 4H, C=CHCH_2CH=C), 3.32–3.39 (*m*, 2H, OCH_2), 3.68–3.75 (*m*, 2H, THPOCH_2), 4.54–4.56 (*m*, 1H, OC*H*O), 5.27–5.41 (*m*, 6H, *H*C=C*H*). ^{13}C NMR (ppm): C-1, 67.5; C-2, 29.4; C-5, 26.9; C-6, 130.1; C-7, 127.7; C-8, 25.6; C-9,10, 128.2; C-11, 25.5; C-12, 127.0; C-13, 131.9; C-14, 20.5; C-15, 14.2; THP group: C-2, 98.7; C-3, 30.7; C-4, 19.6; C-5, 25.5; C-6, 62.2.

Preparation of 6,9,12-pentadecatrienol-3,3,4,4-d_4, (5). Compound 4 (4.55 g, 14.7 mmol) was dissolved in methanol (125 mL). *p*-Tbluenesulfonic acid (0.5 g) was added, and the flask was flushed with nitrogen and capped. The next morning, solid $NaHCO_3$ was added, and the solvent was removed on the rotary evaporator. The residue was dissolved in saturated $NaHCO_3$ solution (25 mL) and extracted into EE (2 × 25 mL). The EE solution was dried (Na_2SO_4), and after removal of the drying agent, there was obtained the title compound, 5, (3.11 g, 94% yield, 87% pure by GC). Deuterium distribution: 0.1% d_0, 0.4% d_2, 3.9% d_3, 93.4% d_4, 1.6% d_5, 0.3% d_6. ^{1}H NMR ($CDCl_3$; ppm): δ 0.93–0.98 (*t*, 3H, CH_3), 1.45–1.65 (*m*, 3H, O*H*, CH_2CH_2OH), 2.05 (*m*, 4H, CH_2C=C), 2.77 (*m*, 4H, C=CCH_2C=C), 3.60 (*t*, 2H, CH_2OH), 5.35 (*m*, 6H, C*H*=C*H*). ^{13}C NMR (ppm): C-1, 62.8; C-2, 32.4; C-5, 26.9; C-6, 130.0; C-7, 127.8; C-8, 25.6; C-9,10, 128.2; C-11, 25.5; C-12, 127.0; C-13, 131.9; C-14, 20.5; C-15, 14.2.

Preparation of 6,9,12-pentadecatrienal-3,3,4,4-d_4, (6). Pyridinium chlorochromate (40.7 g, 189 mmol) was suspended in methylene chloride (170 mL) in a 500-mL, three-necked flask equipped with a mechanical stirrer and a thermometer. A flow of nitrogen was maintained through the apparatus and 6,9,12-pentadecatrienol-d_4, 5, (21.4 g, 94.7 mmol) was added in one portion. The mildly exothermic reaction was controlled by intermittent cooling with an ice bath. One hour later, EE (100 mL) was added to the black viscous reaction mixture and stirring was continued for 10 min. Liquid was decanted and two fresh portions of EE (100 mL each) were stirred with the tar for about 10 min each and liquid was decanted. The combined decantates were passed through a column (2 × 30 cm) containing dry Florisil (40 g). The column was flushed with EE (50 mL), and the combined eluates were concentrated on the rotary evaporator to yield a slightly colored liquid (17.4 g, 82% crude yield, 84% pure by GC on HP-1). This liquid was used without further purification in the Wittig reaction with carboxybutyltriphenylphosphonium bromide. An analytical sample was obtained by elution through a SepPak (Waters, Milford, MA). ^{1}H NMR ($CDCl_3$; ppm) : δ 0.93–0.99(*t*, 3H, CH_3), 2.01–2.10 (*m*, 4H, CH_2C=C), 2.40 (*s*, 2H, CH_2CHO), 2.80 (*m*, 4H, C=CCH_2C=C), 5.30–5.40 (*m*, 6H, C*H*=C*H*), 9.74 (*t*, 1H, C*H*O). ^{13}C NMR (ppm): C-1, 202.4; C-2, 43.5; C-5, 26.7; C-6, 129.4; C-7, 128.0; C-8, 25.6; C-9,10, 128.4; C-11, 25.5; C-12, 127.0; C-13, 131.9; C-14, 20.5; C-15, 14.2.

Preparation of methyl 5,11,14,17-eicosatetraenoate-8,8,9,9-d_4, (7). Carboxybutyltriphenylphosphonium bromide (29.36 g, 66 mmol) was slurried in THF (125 mL) in a 500-mL, three-necked flask equipped with a mechanical stirrer, a thermometer and a septum inlet. While a stream of nitrogen was passed through the apparatus, sodium *bis*(trimethylsilyl)amide (1M, 133/mL) was added over a period of about 10 min. The mildly exothermic reaction was kept at 23–30°C by intermittent use of an ice bath. The septum inlet was replaced with a reflux condenser, and the red-orange reaction mixture was heated at the reflux temperature for 1.5 h. The reaction mixture was cooled in an ice bath, and compound 6 (14.8 g, 66 mmol) in THF (10 mL) was added and the color changed to tannish-orange. One hour later, water (25 mL) was added to the slurry. The resulting cherry red solution was cooled

in an ice bath as it was acidified with 5N H_2SO_4 (70 mL). The organic layer was separated, washed with saturated NaCl solution and dried (Na_2SO_4). Removal of the drying agent and solvent left an amber liquid (43.67 g). Methanol (200 mL) and concentrated sulfuric acid (1 mL) were added, and the reaction mixture was heated at reflux temperature for 2 h. The acid was neutralized with solid $NaHCO_3$. Solvent was removed on the rotary evaporator to give a mixture of solid and liquid (47 g). This was extracted with hexane (2 × 50 mL and 1 × 25 mL), and the solvent was removed to give a residue (23.15 g). The title compound was obtained by purification on a column (3 × 45 cm) containing Baker silica gel (100 g) in PE. Elution with up to 5% EE in PE gave a product (16.81 g, 78% crude yield, about 70% pure by GC on SP2340). The all-*cis* isomer was isolated by silver resin chromatography on a 62% Ag/Na XN1010 resin column using 2% acetonitrile in methanol as eluant. Deuterium distribution. 0.3%d_1, 0.7%d_2, 2.8%d_3, 94.8%d_4, 1.3%d_5, 0.2%d_6, 0.1%d_8 (Ave. No. deuteriums=3.97). ^{1}H NMR ($CDCl_3$; ppm): δ 0.96 (*t*, 3, CH_3), 1.67 (*m*, 2H, CH_2CH_2COO), 1.91-2.1 (*m*, 8H, $C{=}CCH_2$), 2.3 (*t*, 2H, CH_2COO), 2.78 (*m*, 4H, $C{=}CCH_2C{=}C$), 3.65 (*s*, 3H, OCH_3), 5.32-5.36 (*m*, 8H, $CH{=}CH$). ^{13}C NMR (ppm): C-1, 174.0; C-2, 33.4; C-3, 24.9; C-4,7 and 10, 26.5 or 26.9; C-5, 130.9; C-6, 128.4; C-11, 130.1; C-12, 127.7; C-13, 25.6, C-14,15, 128.2; C-16, 25.5; C-17, 127.1; C-18, 131.9; C-19, 20.5; C-20, 14.3. Chemical shift assignments are consistent with data published by Gunstone *et al.* (17) and Gunstone (18) for similar compounds.

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