SYNTHESIS OF ETHYL ω-$^2H_5$-DOCOSA-4, 7, 10, 13, 16, 19-HEXAENOATE

Douglass F. Taber* and Kamfia You
Department of Chemistry & Biochemistry, University of Delaware, Newark, DE 19716 USA

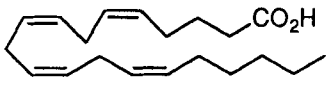
SUMMARY

The preparation and subsequent Wittig reaction of phosphonium salt **4**, a useful synthon for the preparation of polyunsaturated fatty acids, are reported. Salt **4** is a key intermediate for the synthesis of ethyl ω-$^2H_5$-docosa-4,7,10,13,16,19-hexaenoate (**3**).

Key words: Deuterated, fatty acid, phosphonium, polyene, Wittig

INTRODUCTION

Elucidation of the physiological role of arachidonic acid **1** and especially of its oxygenated metabolites has depended critically on the availability of stable-isotope labelled material (1). In brain, the dominant polyunsaturated fatty acid is all Z-4,7,10,13,16,19-docosahexaenoic acid **2**. A linear synthesis of **2** was recently reported (2).We report here the preparation of phosphonium salt **4** (3) and the use of **4** in a convergent synthesis of ethyl ω-$^2H_5$-docosa-4,7,10,13,16,19-hexaenoate **3**.



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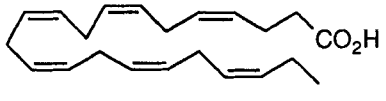

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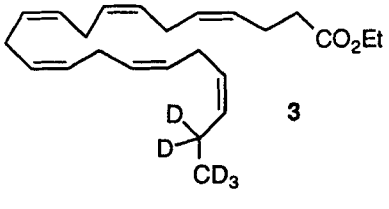

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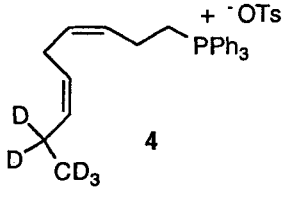

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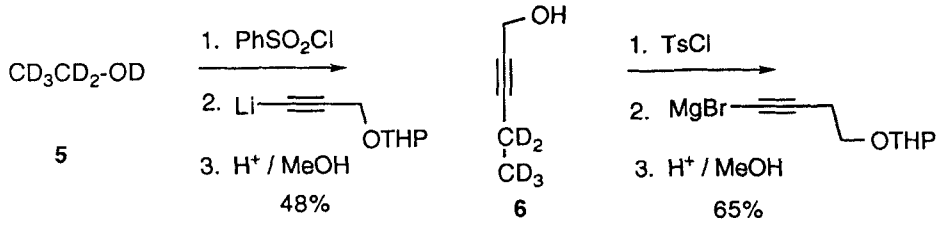
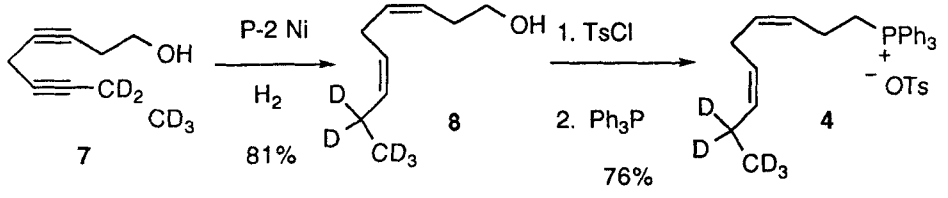
Alcohol **8** (**Scheme 1**), the immediate precursor to phosphonium salt **4**, was prepared from the relatively inexpensive ethanol-d6. Coupling of the derived benzenesulfonate with the lithium salt of protected propargyl alcohol (4), followed by acid hydrolysis, then gave **6**. Activation of **6** as the tosylate followed by coupling with protected butynol completed the carbon skeleton. For the most part, phosphonium salts have been prepared from alcohols via the corresponding bromides. There are scattered reports (5) of the use of phosphonium tosylates. Employing this variant, with the obvious advantage that primary alkyl tosylates are much more easily purified by silica gel chromatography than the corresponding bromides, we secured phosphonium salt **4.**

Scheme 1

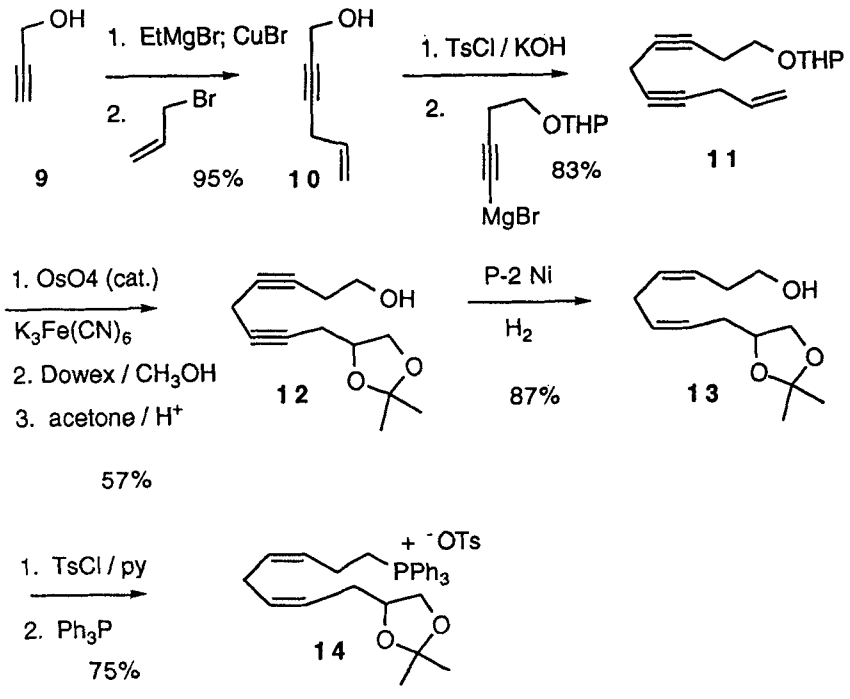




A key aspect of this synthetic strategy is the use of an acetonide as a masked aldehyde equivalent, that can be unveiled under conditions such that the proximal alkene is not brought into conjugation. The requisite phosphonium salt was then **14** (**Scheme 2**) (6). The corresponding alcohol **13**, not previously described, was prepared by iterative homologation of propargyl alcohol. Again, the phosphonium salt was most efficiently prepared as the tosylate.

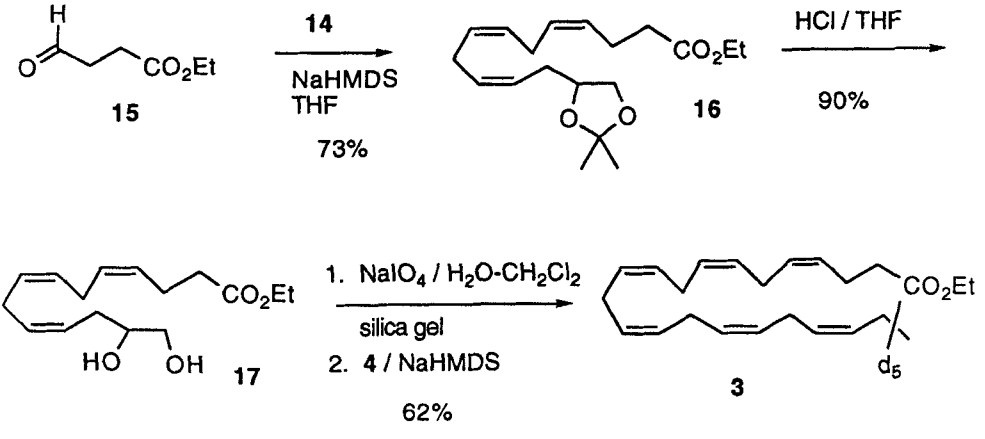
The key to this approach was the cleavage of diol **17** (**Scheme 3**), to give the very unstable β, γ-unsaturated aldehyde. In the past, such a cleavage has been effected with lead tetraacetate. We speculated that sodium periodate might be more convenient, especially if conditions could be found such that the crude aldehyde could be used directly in the subsequent Wittig condensation. In fact, the Vo-Quang (7)modification allowed rapid cleavage (room temperature, 5 min). Filtration of the resultant CH_2Cl_2 solution directly into a solution of the pre-prepared phosphorane (THF, -78°) led to ethyl ω-d5-docosa-4,7,10,13,16,19-hexaenoate (**3**) in 62 % yield.

Scheme 2



Phosphonium salt **4** allows an assembly of ω-d5-skipped conjugation polyenes that is convergent, rather than linear, and thus more amenable to scale-up. We have already used the procedures outlined here to prepare gram quantities of the ω–deuterated ethyl ester.

Scheme 3



EXPERIMENTAL

General: ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AM-250 spectrometer. Chemical shifts are reported relative to tetramethylsilane at 0.0 ppm. Infrared spectra were determined on a Nicolet 5DXB System FT IR and are reported in wavenumbers (cm^{-1}). High resolution mass spectrometry (HRMS) was performed on a Fison Autospec Q Double-focusing Mass Spectrometry. Low resolution mass spectra (LRMS) were obtained on a Hewlett Packard 5890 Gas Chhromatograph-Mass Spectrometer (GC-MS). Thin layer chromatography (TLC) were run using Analtech 2.5 x 10 cm, 250 micron analytical plates coated with silica gel GF. Column chromatography was carried out with TLC-mesh silica gel, using the procedure we have described(8). The solvent mixtures indicated for TLC are volume/volume mixture. THF and ether were purified by distillation from Na/benzophenone. Unless otherwise specified, all reactions were carried out in flame-dried glassware under an atmosphere of N_2.

d5-Ethyl benzenesulfonate: Pyridine (110 mL), benzenesulfonyl chloride (20.5 mL, 0.16 mol), and 4-dimethylaminopyridine (1.41 g, 11.5 mmol) were added sequentially to an ice cold solution of ethanol-d_6 (6.0 g, 0.115 mol) in methylene chloride (120 mL). After stirring for 48 h, the reaction mixture was diluted with 10% aqueous HCl and saturated aqueous NaCl. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extract was concentrated, dried (Na_2SO_4), and chromatographed to give the desired product (6.19 g, 67% yield) as a cloudy white oil, TLC R_f = 0.31 (20% ethyl acetate/petroleum ether). ^{1}H NMR (δ) : 7.55- 7.96 (m, 5H). ^{13}C NMR (δ): d=127.8, 129.2, 133.6; u=136.5. IR(cm^{-1}, neat): 3067, 2938, 2875. MS (m/z, %): 191(10), 141(27), 77(100). HRMS calcd for $C_8H_5D_5O_3S$:191.0665; found:191.0665.

2-Pentyn-1-ol-4,5-d5 **6:** A mixture of propargyl alcohol (10.0 g, 0.178 mol) and dihydropyran (30.0 g, 0.36 mol) in 400 mL of dry CH_2Cl_2 containing p-toluenesulfonic acid (4.3 g, 17.1 mmol) was maintained at 0° for 10 h. The reaction mixture was then washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), concentrated, and distilled bulb-to-bulb (bath$_{10\ mm}$ = 77-85°) to give tetrahydropyranyloxy-2-propyne (23.4 g, 0.167 mmol, 94% yield) as a colorless oil. ^{1}H NMR (δ): 1.51-2.0 (m, 6H), 2.42 (t, J=2.4 Hz, 1H), 3.55 (m, 1H), 3.84 (m, 1H), 4.26 (dddd, J=2.4 Hz, 13.3 Hz, 2.4 Hz, 2.6 Hz, 2H), 4.82 (t, J=3.0, 1H).

n-BuLi (21.3 mL; 2.265 M in hexane) was added to a solution of the above THP ether (7.23 g; 51.56 mmol) in dry THF (20 mL) at -75°. After stirring for 0.5 h, d5-ethyl benzenesulfonate (6.0 g, 32.2 mmol) in DMSO (60 mL) was added and the mixture was allowed to warm to rt over 10 h. The reaction mixture was

quenched with saturated aqueous NH4Cl, and the aqueous layer was extracted with ethyl acetate/petroleum ether (3:7). The combined organic extract was dried ($MgSO_4$) and concentrated to give the crude alkylated THP ether. Hydrolysis of the THP ether was completed in 10 h by the addition of 0.8 g Dowex 50 x 8 - 100 ion-exchange resin to a stirring solution of the crude THP ether in methanol (50 mL) The reaction mixture was concentrated and chromatographed to give the product alcohol **6** (2.05 g, 23.0 mmol, 71% yield from ethyl benzenesulfonate-d5) as a pale yellow oil, TLC Rf = 0.22 (10% ethyl acetate/ petroleum ether). ^1H NMR(δ): 2.07-2.21(br, s, 1H), 4.25 (d, J=6.4 Hz, 2H). ^{13}C NMR (δ): u= 51.16, 77.67, 87.65. IR(cm^{-1}, neat):3361 (br), 2207, 1040. MS (m/z, %): 89(M^+, 10), 88(10), 71(41), 55(100), 39(93). HRMS calcd for $C_5H_3D_5O$: 89.0889; found: 89.0889.

3,6-Nonadiyn-1-ol-8,9-d5 **7:** p-Toluenesulfonyl chloride (21.2 g, 0.11 mol) and potassium hydroxide (10.1 g, 0.18 mol) were added to 2-pentyn-1-ol-4,5-d5 **6** (8.0 g, 89.9 mmol) in dry ether (210 mL) at -50°. The mixture was stirred for 6 h with warming to rt. The mixture was quenched with 10% aqueous HCl and the aqueous phase was extracted with ether (3x50 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give the tosylate (19.9 g, 91% yield) as a cloudy white oil, TLC Rf = 0.38 (10% ethyl acetate/ petroleum ether). ^1H NMR (δ): 2.43 (s, 3H), 4.66 (s, 2H), 7.22 (d, J=9.1Hz, 2H), 7.78 (d, J=9.1Hz, 2H).

3-Butyn-1-ol (10.0 g, 0.143 mol) and dihydropyran (24.0 g, 0.285 mol) in 120 mL of dry CH_2Cl_2 containing 2 mol % p-toluenesulfonic acid were maintained at 0° for 10 h. The reaction mixture was then washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), concentrated, and distilled bulb-to-bulb (bath$_{10mm}$=85-90°) to give the protected alcohol (20.1 g, 92% yield) as a colorless oil. ^1H NMR (δ): 1.21-1.90 (m, 3H), 2.02 (t, J=2.0 Hz, 1H), 2.52 (m, 2H), 3.41-3.60 (m, 2H), 3.80-3.98 (m, 2H), 4.63 (t, J=4.7 Hz, 1H).

Ethyl magnesium bromide (15 mL, 1.56 M in THF) was added to an ice cold solution of 1-tetrahydropyranloxy-3-butyne (4.88 g, 31.63 mmol) in dry THF (50 mL) . The reaction mixture was heated to reflux for 30 min, then chilled to 0°. Copper (I) bromide-dimethyl sulfide complex (0.31 g, 1.51 mmol) was added to the reaction mixture, followed by 1-tosyloxy-2-pentyn-4,5-d5 (5.38 g, 22.6 mmol) in THF (5 mL). The reaction mixture was allowed to warm to rt over 13 h. Saturated aqueous NH4Cl (10 mL) was added. The organic layer was separated and the aqueous layer was extracted with ether (3x30 mL). The combined organic phase was dried (Na_2SO_4) and concentrated. The crude alkylated product was hydrolyzed with Dowex 50 x 8 - 100 ion-exchange resin(0.5 g) in 30 mL methanol. The reaction mixture was concentrated and chromatographed to give the product **7** (2.06 g, 14.6 mmol, 65% yield from **6**) as a pale yellow oil, TLC Rf= 0.31. ^1H

NMR (δ) : 1.81 (br, s, 1H), 2.45 (m, 2H), 3.16 (t, J=2.2 Hz, 2H), 3.71 (t, J=6.5 Hz, 2H); ^{13}C NMR (δ): u= 10.0, 23.2, 61.1, 73.4, 76.8; IR(cm^{-1}, neat): 3349 (br), 2216, 1490.

(Z, Z)-3, 6-Nonadien-1-ol-8,9-d5 **8:** The reduction was carried out by the method of Brown (9). Sodium borohydride (0.44 g, 7.3 mmol) was added to a suspension of nickel acetate tetrahydrate (1.21 g, 4.87 mmol) in ethanol (40 mL). The mixture instantly turned black. Then, ethylenediamine (2.5 mL) and 3,6-nonadiyn-1-ol-d5 (4.81 g, 34.08 mmol) were added sequentially. The reaction mixture was stirred vigorously under an atmosphere of hydrogen at rt. After the uptake of hydrogen ceased (11 h), the reaction mixture was filtered through a pad of celite and the ethanolic filtrate was concentrated. The crude diene was dissolved in ether (50 mL) and the ether layer was washed with saturated NaCl (60 x 2 mL), dried over $MgSO_4$, concentrated and chromatographed to give the desired product **8** (4.02 g, 27.7 mmol, 81% yield) as a pale yellow oil, TLC Rf = 0.15 (10% ethyl acetate/ petroleum ether). ^1H NMR(δ) : 1.45 (s, br, 1H), 2.31 (q, J=6.8 Hz, 2H), 2.80 (t, J=5.4 Hz, 2H), 3.69 (t, J=6.8 Hz, 2H), 5.21-5.60 (m, 4H). ^{13}C NMR(δ): d=125.3, 126.4, 131.4, 132.0; u= 25.6, 30.8, 62.2. IR(cm^{-1}, neat): 3310 (br), 1660, 965. MS (m/z, %): 145 (M^+, 25), 127 (M^+-H_2O, 28), 114 (100). HRMS calcd for $C_9H_{11}D_5O$: 145.1515; found: 145.1516.

(Z,Z)-3,6-Nonadienyl Triphenylphosphonium Tosylate-8,9-d5 **4:** Pyridine (2.8 mL, 34 mmol) and p-toluenesulfonyl chloride (4.90 g, 25.7 mmol) were added sequentially with stirring to a ice cold solution of (Z,Z)-3,6-nonadien-1-ol-8,9-d5 **8** (2.4 g, 17.1 mmol) in CH_2Cl_2 (60 mL).The mixture was stirred at rt overnight, then was quenched with 10% aqueous HCl (40 mL) and extracted with CH_2Cl_2 (2 x 40 mL). The organic extract was dried (Na_2SO_4), concentrated and chromatographed to give the tosylate (4.0 g, 81% yield) as a cloudy white oil, TLC R_f = 0.43 (10% ethyl acetate/petroleum ether). ^1H NMR (δ): 2.35 (q, J=7.1 Hz, 2H), 2.44 (s, 3H), 2.81 (t, J=5.6 Hz, 2H), 3.90 (t, J=7.1 Hz, 2H), 5.22-5.59 (m, 4H), 7.38 (d, J=9.1 Hz, 2H), 7.82 (d, J=9.1 Hz, 2H).

Triphenylphosphine (5.02 g, 19.2 mmol) was added to a solution of the above tosylate (2.82 g, 9.6 mmol) in acetonitrile (6 mL). The reaction mixture was maintained at reflux for 13 h. The mixture was diluted with methylene chloride, concentrated, and chromatographed to give **4** (5.03 g, 9.0 mmol, 76% yield from **8**) as a white powder, TLC R_f = 0.60 (10% MeOH/CH_2Cl_2). ^1H NMR (δ): 2.30 (s, 3H), 2.33-2.65 (m, 4H), 3.66 (m, 2H), 5.05-5.51 (m, 4H), 7.04 (d, J=9.1 Hz, 2H), 7.51-7.89 (m, 17H). ^{13}C (δ): d= 21.2, 50.5, 126.2, 126.3, 126.5, 128.2, 130.3, 130.5, 131.9, 132.1, 133.5, 134.9; u=20.2, 20.6, 22.4, 25.3, 117.6, 118.9, 138.3, 144.5. IR (neat, cm^{-1}) 3059, 2922, 2195, 1697, 1589, 1438.

5-Hexen-2-yn-1-ol **10:** Ethyl magnesium bromide (78 mL, 1.5 M in THF) was added dropwise to a solution of propargyl alcohol (3.0 g, 53.5 mmol) in dry THF (55 mL) at 0°. The mixture was heated at 50° for 40 min, then chilled again to 0°. A catalytic amount of copper(I) bromide-dimethyl sulfide complex (0.82 g, 4.1 mmol) was added to the mixture, followed by allyl bromide (5.6 mL, 64 mmol). The reaction mixture was stirred for 13 h with warming to rt. The mixture was then was quenched sequentially with water (10 mL), saturated aqueous NH_4Cl (50 mL), and 10% aqueous HCl (10 mL). The aqueous phase was extracted with ether (3 x 50 mL). The combined organic extract was dried (Na_2SO_4), filtered and concentrated. The residue was distilled bulb-to-bulb (bath 0.5 mm = 86-89°) to give alcohol **10** (4.9 g, 95% yield) as a colorless oil. ^1H NMR (δ): 1.69 (br, s, 1H), 3.01 (m, 2H), 4.33 (m, 2H), 5.16 (dq, J=1.6 Hz, 8.4 Hz, 1H), 5.35 (dq, J=1.6 Hz, 16.9 Hz, 1H), 5.8-5.9 (m, 1H). ^{13}C NMR (δ): d= 132.2; u= 23.0, 51.3, 80.6, 83.0, 116.3. IR (cm^{-1}, neat): 3432 (br), 3086, 2919, 2236, 2337, 1642. MS(m/z, %): 96 (M^+, 12), 95 (100), 81 (66), 67 (72), 65 (55), 53 (89), 41 (48), 27 (43). HRMS calcd for C_6H_8O: 96.0575; Found: 96.0578. Anal. calcd for C_6H_8O: C, 74.97; H, 8.39. Found C, 74.99; H, 8.45.

1-Tetrahydropyranyloxydeca-9-en-3,6-diyne **11:** p-Toluenesulfonyl chloride (13.4 g, 70 mmol) and potassium hydroxide (3.9 g, 70 mmol) were added to a solution of alcohol **10** (4.5 g, 46.9 mmol) in dry ether (150 mL) at -78°. After warming to rt (4 h), the reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with ether (3 x 50 mL), and the combined organic extract was dried (Na_2SO_4), concentrated and chromatographed to give the tosylate (11.0 g, 94% yield) as a cloudy white oil, TLC R_f = 0.44 (10% ethyl acetate/petroleum ether). ^1H NMR (δ): 2.40 (s, 3H), 2.88 (m, 2H), 4.73 (t, J=1.9 Hz, 2H), 5.0-5.31 (m, 2H), 5.62-5.78 (m, 1H), 7.21(d, J=9.1 Hz, 2H), 7.78 (d, J=9.1 Hz, 2H).

Ethyl magnesium bromide (15.6 mL, 21.1 mmol) was added dropwise to a solution of 1-tetrahydropyranyloxy-3-butyne (3.25 g, 21.1 mmol) in 30 mL of dry THF at 0° over 10 min. The reaction mixture was maintained at 50° for 30 min, then was cooled again to 0°. Copper(I) bromide-dimethyl sulfide complex (0.31 g, 1.5 mmol) was added. The reaction mixture was stirred for 5 min, then 1-tosyloxy-5-hexen-2-yne (4.40 g, 17.58 mmol) in 10 mL of dry THF was added dropwise over 10 min. After warming to rt over 10 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 x 50 mL). The combined organic phase was dried (Na_2SO_4), concentrated and chromatographed to give the desired product **11** (3.58 g, 83% yield from **10**) as a clear pale yellow oil, TLC R_f = 0.73 (20% ethyl acetate/petroleum ether). ^1H NMR(δ):1.41-1.89 (m, 6H), 2.50 (m, 2H), 2.92 (m, 2H), 3.16 (m, 2H), 3.50-3.57 (m, 2H), 3.81-3.92 (m, 2H), 4.65 (t, J=3.8 Hz, 1H), 5.11 (dq, J= 2.1 Hz, 11.8 Hz, 1H), 5.30 (dq, J=2.1 Hz, 16.1 Hz, 1H), 5.70-5.94

(m, 1H). ^{13}C NMR (δ): d=98.6, 132.6; u=9.7, 19.3, 20.1, 22.9, 25.3, 30.4, 62.0, 65.7, 75.2, 76.6, 76.9, 77.2, 115.8. IR (cm^{-1}, neat): 3346, 3086, 2945, 2355, 2348, 2207, 1722, 986. MS (m/z, %) 232 (M^+, 15), 231 (35), 153 (100), 147 (24). HRMS calcd for $C_{15}H_{20}O_2$ 232.1374; Found: 232.1379.

9,10-O-Isopropylidenedeca-3,6-diyn-1-ol **12**: Osmylation was carried out following the procedure of Yamamoto (10). $K_3Fe(CN)_6$ (26.2 g, 81.4 mmol), K_2CO_3 (11.3 g, 81.4 mmol), and OsO_4 solution (6.92 mL, 12.5 mg/mL in tBuOH, 0.35 mmol) were added sequentially to a solution of **11**(6.3 g, 27.1 mmol) in t-butyl alcohol (130 mL) and water (130 mL). The yellowish brown reaction mixture was stirred for 48 h at rt. Solid Na_2SO_3 (21.0 g, 0.17 mol) was added, and stirring was continued for an additional 2 h. The organic (upper) layer was then separated, and the dark blue aqueous layer was extracted with ethyl acetate (3 x 60 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to give a crude diol.

The crude dihydroxy tetrahydropyranyl ether in methanol (100 mL) was stirred with 2.0 g of Dowex 50 x 8 - 100 ion-exchange resin at rt for 13 h. The reaction mixture was filtered, concentrated, and chromatographed to give recovered deca-3,6-diyn-9-en-1-ol (0.79 g, 5.3 mmol), TLC R_f = 0.18 (10% ethyl acetate/petroleum ether), followed by the desired triol (3.41 g, 70% yield) as a clear yellow oil, TLC R_f = 0.23 (5% methanol/CH_2Cl_2). ^1H NMR (δ): 2.40-2.48 (m, 4H), 3.15 (m, 2H), 3.58-3.80 (m, 4H), 3.70 (br s, 1H), 3.80-3.93 (m, 1H).

Concentrated H_2SO_4 (two drops) was added to a mixture of the triol (3.41 g) in dry acetone (70 mL), anhydrous Na_2SO_4 (4.0 g) and 4A molecular sieve (2.0 g). After stirring for 13 h at rt, solid $NaHCO_3$ (6.0 g) was added, and stirring was continued for an additional 1 h. The mixture was filtered through a pad of celite topped with a layer of $MgSO_4$. The filtrate was concentrated and chromatographed to give the desired acetonide **12** (3.41 g, 57% from **11**) as a viscous cloudy white oil, TLC R_f = 0.14 (20% ethyl acetate/petroleum ether). ^1H NMR (δ): 1.38 (s, 3H), 1.47 (s, 3H), 2.13 (s, br, 1H), 2.40-2.61 (m, 4H), 3.18 (m, 2H), 3.72 (t, J=7.4 Hz, 2H), 3.70-3.77 (dd, J=7.1 Hz, 8.2 Hz, 1H), 4.15-4.23 (dd, J=7.4 Hz, 8.2 Hz, 1H), 4.14-4.30 (m, 1H). ^{13}C NMR (δ): d= 26.0, 27.4, 74.5 ; u=10.0, 23.1, 24.2, 61.3, 68.8, 76.6, 76.9, 78.0, 78.8, 110.2. IR (cm^{-1}, neat): 3422 (br), 2934, 2333, 2213, 1558, 1589, 847. MS (m/z, %): 207 (45, M^+ - CH_3), 147 (12), 101 (100). HRMS calcd for $C_{12}H_{15}O_3$ (M^+-CH_3) : 207.1021 ; Found 207.1027. Anal calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found C, 70.11; H, 8.13.

9,10-O-Isopropylidenedeca-3,6-dien-1-ol **13**: Following the established protocol (9), sodium borohydride (0.08 g, 1.41 mmol) was added to a suspension of nickel acetate

tetrahydrate (0.23 g, 0.94 mmol) in ethanol (7.0 mL). The green suspension instantly turned black with gas evolution. Then ethylenediamine (0.5 mL) in 1.0 mL of ethanol and **12** (1.26 g, 5.68 mmol) in 3.0 mL of ethanol were added sequentially. The black reaction mixture was stirred vigorously under an atmosphere of hydrogen at 23°. After hydrogen uptake ceased (5 h), the reaction mixture was filtered through a pad of celite and the ethanol filtrate was concentrated in vacuo. The crude diene was dissolved in ether (40 mL), and the ether layer was washed with saturated aqueous NaCl (2 x 40 mL), dried over $MgSO_4$, concentrated and chromatographed to give **13** (1.11 g, 87% yield) as a pale yellow oil, TLC R_f = 0.18 (20% ethyl acetate/petroleum ether). ^1H NMR (δ): 138 (s, 3H), 1.46 (s, 3H), 2.21-2.45 (m, 4H), 2.86 (t, J=6.2 Hz, 2H), 3.57 (dd, J=8.1 Hz, 6.5 Hz, 1H), 3.76 (t, J=6.9 Hz, 2H), 4.03 (dd, J=6.5 Hz, 7.4 Hz, 1H), 4.14-4.20 (m, 1H), 5.31-5.60 (m, 4H).^{13}C NMR (δ) : d= 25.1, 26.9, 75.4, 124.1, 126.0, 130.0, 130.9; u=25.7, 30.8, 31.6, 61.5, 68.7, 108.2. IR (cm^{-1}, neat): 3440 (br), 2985, 2931, 2862, 1660. MS (m/z, %): 211 (M^+-CH_3, 29), 101 (100). HRMS calcd for $C_{12}H_{19}O_3$ (M^+ - CH_3) 211.1334; Found: 211.1341.

(Z,Z)-8-(2,2-Dimethyl-1,3-dioxolan-4-yl)-3,6-octadienyl Triphenylphosphonium Tosylate **14**: p-Toluenesulfonyl chloride (1.51g, 7.7 mmol) and pyridine (7mL) were added to a solution of **13** (1.16 g, 5.1 mmol) in methylene chloride (35 mL) at 0° with warming to rt for 8 h.The mixture was washed with 10% aqueous HCl and the aqueous phase was extracted with methylene chloride (3x30 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to afford the desired tosylate (1.59 g, 82% yield), TLC R_f = 0.44 (20% ethyl acetate/petroleum ether).^1H NMR (δ) =1.18 (s, 3H), 1.20 (s, 3H), 2.23-2.42 (m, 4H), 2.50 (s, 3H), 2.74 (t, J=6.1 Hz, 2H), 3.56 (t, J=7.1 Hz, 1H), 3.99-4.22 (m, 4H), 5.21-5.62 (m, 4H), 7.41 (d, J=9.1 Hz, 2H), 7.80 (d, J=9.1 Hz, 2H).

Triphenylphosphine (1.42 g, 5.4 mmol) and calcium carbonate (0.14 g) were added to a solution of tosylate (1.03 g, 2.7 mmol) in 4.5 mL of acetonitrile. The reaction mixture was warmed to reflux at 90° for 48 h. The mixture was diluted with methylene chloride (50 mL), filtered, concentrated, and chromatographed to give **14** (1.58 g, 75% from **13**) as a clear pink glass, TLC R_f = 0.41 (10% MeOH/CH_2Cl_2). ^1H NMR (δ): 1.36 (s, 3H), 1.45 (s, 3H), 2.0-2.57 (m, 6H), 2.31 (s, 3H), 3.57 (t, J=7.6 Hz, 1H), 3.72 (m, 2H), 3.93-4.11 (m, 2H), 5.22-5.58 (m, 4H), 7.11 (d, J=9.1 Hz, 2H), 7.49-7.90 (m, 17H). ^{13}C NMR (δ): d=21.2, 25.5, 26.9, 75.3, 124.7, 126.2, 126.8, 126.9, 128.2, 129.6, 129.9, 130.3, 130.5, 133.6, 133.7, 134.9; u=20.8, 21.3, 22.3, 25.6, 31.5, 68.9, 108.1, 117.7, 119.1, 138.3, 144.5. IR (cm^{-1}, neat): 3058, 2984, 2932, 1646, 1439, 1368.

Ethyl 13,14-O-Isopropylidenetetradeca-4,7,10-trienoate **16**: The phosphonium salt **14** was dissolved in dry THF (60 mL). To this solution, sodium

bistrimethylsilylamide (16.5 mL, 1.0 M in THF) was added slowly at -5°, causing the mixture to turn from pale yellow to bright orange. After stirring at 0° for 10 min, ethyl-4-oxo-butanoate **15** (11) (2.80 g, 21.5 mmol) in 4 mL of dry THF was added to the mixture at -78°. The brick red reaction mixture was allowed to warm up to rt over 3 h. At rt the reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), and the aqueous layer was extracted with ether (4 x 30 mL). The extract was dried (Na_2SO_4), concentrated and chromatographed to give **16** (3.47 g, 73% yield from **3**) as a clear pale yellow oil, TLC R_f = 0.46 (10% ethyl acetate / petroleum ether). ^1H NMR(δ): 1.24 (t, J=7.2 Hz, 3H), 1.38 (s, 3H), 1.48 (s, 3H), 2.21-2.56 (m, 6H), 2.90 (t, J=5.5 Hz, 4H), 3.57 (dd, J=7.2 Hz, 6.9 Hz, 1H), 3.99-4.20 (m, 4H), 5.35-5.53 (m, 6H). ^{13}C NMR(δ): d=14.2, 25.6, 26.8, 75.5, 124.4, 127.9, 128.0, 128.2, 129.1, 130.6; u=22.8, 25.6, 25.8, 31.5, 34.2, 60.3, 69.0, 108.9, 173.4. IR (cm^{-1}, neat): 2982, 1736, 1448, 1369, 1213, 1157, 1018, 850. MS(m/z, %): 307(M^+-CH_3, 20), 264(11), 219(36), 159(19), 105(27), 101(100). HRMS calcd for $C_{19}H_{30}O_4$: 322.2144; Found: 322.2147.

Ethyl 13,14-Dihydroxytetradeca-4,7,10-trienoate **17**: Hydrolysis of the acetonide **16** (2.41 g, 7.5 mmol) was carried out with 4N HCl (1 mL) in 30 mL of THF containing methylene blue (0.01 g). After stirring for 30 min, the reaction mixture was neutralized with $CaCO_3$ (1.6 g). The $CaCO_3$ was rinsed with ethyl acetate (3 x 10 mL). The combined organic rinse was dried (Na_2SO_4), concentrated and chromatographed to give **17** (1.92 g, 90% yield) as a clear colorless oil, TLC R_f = 0.17 (10% MeOH/CH_2Cl_2). ^1H NMR(δ): 1.24 (t, J=7.3 Hz, 3H), 2.11-2.53 (m, 6H), 2.88 (t, J=5.4 Hz, 4H), 3.50 (m, 1H), 3.57-3.80 (m, 2H), 4.16 (q, J=7.3 Hz, 2H), 5.31-5.60 (m, 6H). ^{13}C (δ): d=14.2, 71.8, 124.9, 127.8, 127.9, 128.3, 129.2, 131.1; u= 22.9, 25.6, 25.8, 31.4, 34.2, 60.4, 66.2, 173.4. IR (cm^{-1}, neat): 3397 (br), 2931, 1732, 1373, 1182, 1037. MS (m/z, %): 282 (M^+, 3), 264 (M^+-H_2O, 100), 222 (57), 159 (33), 105 (84). HRMS calcd for $C_{16}H_{26}O_4$: 282.1831; Found: 282.1835.

Ethyl Docosa-4,7,10,13,16,19-hexaenoate-21,22-d_5 **3**: A solution of $NaIO_4$ (2.1 mL, 0.8 M in H_2O) was added dropwise to a suspension of 60-200 mesh SiO_2 (4.0 g) in CH_2Cl_2 (11.0 mL) at rt. After the mixture was thoroughly stirred, diol **17** (0.19 g, 0.64 mmol) was added to the SiO_2 suspension. After stirring for 5 min, this suspension was filtered directly into a solution of ylide made from the addition of sodium bistrimethylsilylamide (1.65 mL, 1.0 M in THF) to phosphonium salt **4** (0.75 g, 1.35 mmol) in 10 mL of dry THF at -75°. The reaction mixture was allowed to warm to rt over 4 h. The mixture was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with ether (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed to give 0.138 g of a colorless oil, TLC R_f = 0.75 (10% ethyl acetate/petroleum ether). This material was then chromatographed on Analtech octadecyl modified 35-75 micron

Unibond silica gel, eluting with 1% CH_2Cl_2/CH_3CN, to give the product **3** (0.125 g, 58% yield from **17**). ^1H NMR (δ): 1.31 (t, J=7.1 Hz, 3H), 2.18- 2.42 (m, 4H), 2.71-3.0 (m, 10H), 4.11 (q, J=7.1 Hz, 2H), 5.23-5.60 (m, 12H). ^{13}C NMR (δ): d=14.3, 30.9, 127.1, 127.9, 128.0, 128.1, 128.2, 128.3, 128.6, 129.2, 132.0; u= 22.6, 25.5, 25.6, 34.3, 60.3, 173.1. IR (cm^{-1}, neat): 3011, 2962, 2931, 1735, 1176, 1035. MS (m/z, %): 220 (20), 180 (17), 159 (27), 145 (35), 131 (52),119 (90),.105 (100). HRMS calcd for $C_{24}H_{31}D_5O_2$ = 361.3029; Found: 361.3045. The ^1H and ^{13}C NMR data were consistent with the authentic ethyl ester (prepared from the commercially available docosahexaenoic acid), and also with those reported (12) for the methyl ester. The unlabelled d_0 impurity was found to be less than 0.5 ppt.

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