New Synthon for the Convergent Construction of Skipped Conjugation Polyenes: Synthesis of Ethyl Docosa-4,7,10,13,16,19-hexaenoate

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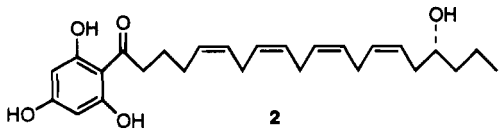
The preparation and subsequent Wittig reaction of the (*Z,Z*)-phosphonium salt **4**, a useful synthon for the preparation of skipped conjugation polyenes, are reported. Salt **4** is a key intermediate for the synthesis of ethyl docosa-4,7,10,13,16,19-hexaenoate (**3b**).

A variety of physiologically active natural products, illustrated by the antimicrobial leucettamol A (**1**),[1] the cytotoxic acylphloroglucinol **2**,[2] and docosahexaenoic acid (**3a**), the dominant fatty acid in brain,[3,4] have extended systems of *all-Z* skipped conjugation polyenes. We report a useful synthon **4** for the construction of such polyene arrays. The utility of this synthon is illustrated by the first convergent assembly of ethyl docosahexaenoate **3b**.[5]

1



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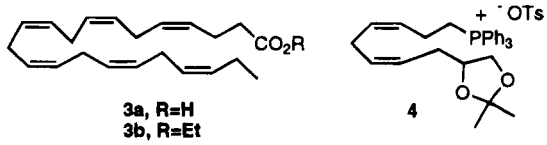


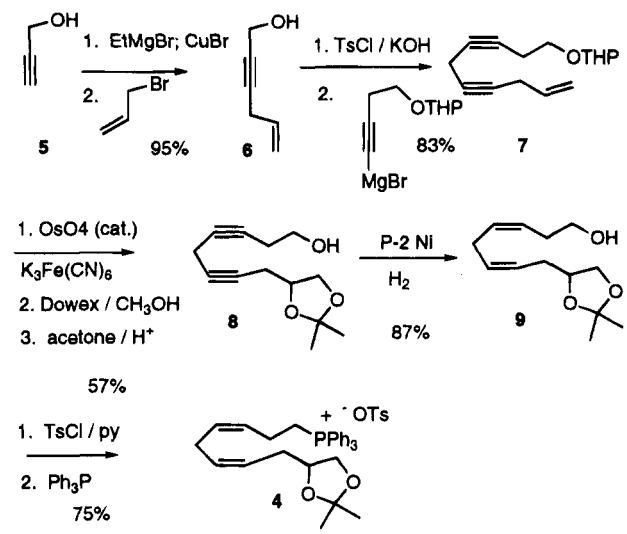
3a, R=H
3b, R=Et

4

In general, skipped conjugation polyenes have been prepared by iterative alkyne homologation, followed by catalytic hydrogenation. Such a linear synthesis of **3a** was recently communicated.[5] A limitation of this approach is that when the hydrogenation of a polyalkyne is effected, the desired *all-Z* product is necessarily contaminated with significant amounts of the alternative geometric isomers. We thought to minimize this problem by preparing polyunsaturated phosphonium salts of substantial geometric purity.

Alcohol **9** (Scheme 1) was prepared as shown. For the most part, phosphonium salts have been prepared from alcohols via the corresponding bromides. There are scattered reports[7] 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 are the corresponding bromides, we secured phosphonium salts **4** (Scheme 1) and **13**[8] (Scheme 2).

Scheme 1



We next needed to establish the geometric purity of **4** and **13**. Here, the literature on ^{13}C NMR of fatty acids was very helpful. It has been observed[9] that the chemical shift of the doubly allyic methylene is sensitive to alkene geometry: a methylene flanked by two trans alkenes resonates at about 35 ppm, a methylene flanked by a cis and a trans alkene resonates at about 30 ppm, and a methylene flanked by two cis alkenes resonates at about 25 ppm. In fact, the ^{13}C spectra of **4** and **13** were quite clean.[10]

Aldehyde **10**[11] (Scheme 2) condensed smoothly with the phosphorane derived from **4** to give the acetonide **11**.

[⊗] Abstract published in *Advance ACS Abstracts,* December 15, 1994.

(1) Kong, F.; Faulkner, D. J. *J. Org. Chem.* **1993**, *58*, 970.

(2) Kusumi, T.; Ooi, T.; Uchimura, H. *Tetrahedron Lett.* **1994**, *35*, 3127.

(3) (a) Pullarkat, R. K.; Reha, H. *J. Chromatogr. Sci.* **1976**, *14*, 25. (b) Moore, S. A.; Yoder, E.; Murphy, S.; Dutton, G. R.; Spector, A. A. *J. Neurochem.* **1991**, *56*, 518.

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(5) For the only previous total synthesis of **3a** or its esters, see: Vos, A.; Reinhart, M.; Sankarappa, S.; Sprecher, H. *J. Biol. Chem.* **1991**, *266*, 19995.

(6) (a) For a convenient three-carbon synthon for unsaturated fatty acid synthesis, see: Viala, J.; Santelli, M. *Synthesis* **1988**, 395. (b) For a six-carbon synthon for polyunsaturated fatty acid synthesis, see: Viala, J.; Sandri, J. *Tetrahedron Lett.* **1992**, *33*, 4897.

(7) Yoshioka, M.; Nakai, S.; Ohno, M. *J. Am. Chem. Soc.* **1984**, *106*, 1133.

(8) Wong, J. W.; Palaniswamy, P.; Underhill, E. W.; Steck, W. F.; Chisholm, M. D. *J. Chem. Ecol.* **1984**, *10*, 1579.

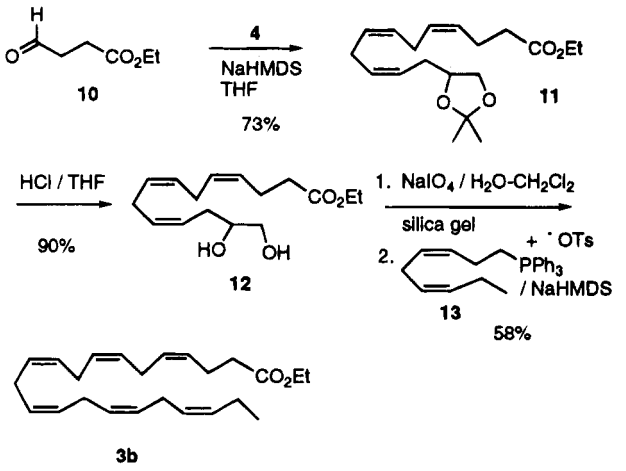
(9) Gunstone, F. D.; Pollard, M. R.; Scrimgeour, C. M.; Vedanayagam, H. S. *Chem. Phys. Lipids* **1977**, *18*, 115.

(10) Phosphonium salt **13** has a methylene that resonates at 25.4 ppm (*Z, Z*), with nothing at 30.6 ppm (*Z, E*) or 35.7 ppm (*E, E*). Phosphonium salt **4** has a resonance at 25.6 ppm (*Z, Z*), with less than 5% impurity at 30.6 ppm (*Z, E*). Although neither phosphonium salt was highly crystalline, the geometric impurities, if present, had partitioned away on routine purification.

(11) Kuehne, M. E.; Pitner, J. B. *J. Org. Chem.* **54**, *1989*, 4553.

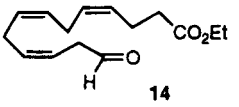
0022-3263/95/1960-0139$09.00/0

Scheme 2



Hydrolysis of **11** (THF/water/HCl) then set the stage for the synthesis of **3b**.

The key to this approach was the cleavage of diol **12** to give the very unstable β,τ-unsaturated aldehyde **14**.



14

We speculated that it might be possible to effect this cleavage with sodium periodate, 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[12] modification allowed rapid cleavage (room temperature, 5 min). Filtration of the resultant CH_2Cl_2 solution directly into a solution of the preprepared phosphorane (THF, −78 °C) led to ethyl docosa-4,7,10,13,16,19-hexaenoate (**3b**) in 58% yield. The ^1H and ^{13}C NMR data were exactly consistent with those for the authentic ethyl ester that we prepared from commercially available docosahexaenoic acid, and also with those reported[13] for the methyl ester.

Phosphonium salt **4** allows an assembly of 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 derivatives of ester **3b**. In addition, the new method described for the generation and subsequent reaction of a β,τ-unsaturated aldehyde without concomitant isomerization should be of general utility in organic synthesis.

Experimental Section[14]

5-Hexen-2-yn-1-ol (6). 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 °C. The mixture was heated at 50 °C for 40 min and then chilled again to 0 °C. 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). After being warmed to rt and stirred for 13 h, the reaction mixture 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 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was distilled bulb-to-bulb (bath 0.5 mm = 86−89 °C) to give alcohol **6** (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): down = 132.2; up = 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-(Tetrahydropyranyloxy)dec-9-ene-3,6-diyne (7). 3-Butyn-1-ol (10.0 g, 0.14 mol) and dihydropyran (24.0 g, 0.3 mol) in 120 mL of dry CH_2Cl_2 containing *p*-toluenesulfonic acid (4.3 g, 17.1 mmol) were maintained at 0 °C 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 = 85−90 °C) 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).

1-(Tosyloxy)-5-hexen-2-yne was prepared from **6** (4.5 g, 46.9 mmol) with 1.5 equiv of *p*-toluenesulfonyl chloride (13.4 g, 70 mmol) and 1.5 equiv of potassium hydroxide (3.9 g, 70 mmol) in dry ether (150 mL) at −78 °C. After being warm to rt (4 h), the reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with ether (3 × 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).

Ethylmagnesium bromide (15.6 mL, 21.1 mmol) was added dropwise to a solution of the THP ether (3.25 g, 21.1 mmol) in 30 mL of dry THF at 0 °C over 10 min. The reaction mixture was maintained at 50 °C for 30 min and then cooled again to 0 °C. Copper(I) bromide−dimethyl sulfide complex (0.31 g, 1.5 mmol) was added. The reaction mixture was stirred for 5 min, and then 1-(tosyloxy)-5-hexen-2-yne (4.4 g, 17.6 mmol) in 10 mL of dry THF was added dropwise over 10 min. After being warmed 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 × 50 mL). The combined organic phase was dried (Na_2SO_4), concentrated, and chromatographed to give the desired product **7** (3.58 g, 85% yield from **6**) 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): down = 98.6, 132.6; up = 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 (8). $K_3Fe(CN)_6$ (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 of tBuOH, 0.35 mmol) were added sequentially to a solution of **7** (6.3 g, 27.1 mmol) in *tert*-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 × 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 × 8 − 100 ion-exchange resin at rt for 13 h. The reaction mixture was filtered, concentrated, and chromatographed to give recovered dec-9-ene-3,6-diyn-1-ol (0.79 g, 5.3 mmol), TLC R_f = 0.18 (10%

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(13) Gunstone, F. D. *Chem. Phys. Lipids* **1990**, *56*, 227.

(14) For general experimental procedures, see: Taber, D. F.; Houze, J. B. *J. Org. Chem.* **1994**, *59*, 4004.

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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). ^{1}H 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 sieves (2.0 g). After the mixture was stirred 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 **8** (3.41 g, 57% from **7**) as a viscous cloudy white oil, TLC R_f = 0.14 (20% ethyl acetate/petroleum ether). ^{1}H 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): down = 26.0, 27.4, 74.5; up = 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 (9). Following the established protocol,[12] 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 **8** (1.26 g, 5.7 mmol) in 3.0 mL of ethanol were added sequentially. The black reaction mixture was stirred vigorously under an atmosphere of hydrogen at 23 °C. 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 × 40 mL), dried over $MgSO_4$, concentrated, and chromatographed to give **9** (1.11 g, 87% yield from **8**) as a pale yellow oil, TLC R_f = 0.18 (20% ethyl acetate/petroleum ether). ^{1}H 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): down = 25.1, 26.9, 75.4, 124.1, 126.0, 130.0, 130.9; up = 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 (4). The tosylate was prepared from 9 (1.16 g, 5.1 mmol) with 1.5 equiv of *p*-toluenesulfonyl chloride (1.5 g, 7.7 mmol) and 2.0 equiv of pyridine in methylene chloride at 0 °C for 8 h. Aqueous workup and chromatography afforded the desired tosylate (1.59 g, 82% yield), TLC R_f = 0.44 (20% ethyl acetate/petroleum ether). ^{1}H 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 (1.4 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 °C for 48 h. The mixture was diluted with methylene chloride (50 mL), filtered, concentrated, and chromatographed to give **4** (1.58 g, 75% from **9**) as a clear pink glass, TLC R_f = 0.41 (10% MeOH/CH_2Cl_2). ^{1}H 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): down = 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; up = 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 (11). The phosphonium salt **4** was dissolved in dry THF (60 mL). To this solution, sodium bis(trimethylsilyl)amide (16.5 mL, 1.0 M in THF) was added slowly at −5 °C, causing the mixture to turn from pale yellow to bright orange. After the mixture was stirred at 0 °C for 10 min, ethyl 4-oxobutanoate **10**[11] (2.8 g, 21.5 mmol) in 4 mL of dry THF was added to the mixture at −78 °C. The brick red reaction mixture was allowed to warm 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 × 30 mL). The extract was dried (Na_2SO_4), concentrated, and chromatographed to give **11** (3.47 g, 73% yield from **4**) as a clear pale yellow oil, TLC R_f = 0.46 (10% ethyl acetate/petroleum ether). ^{1}H 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): down = 14.2, 25.6, 26.8, 75.5, 124.4, 127.9, 128.0, 128.2, 129.1, 130.6; up = 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 (12). Hydrolysis of the acetonide **11** (2.41 g, 7.5 mmol) was carried out with 4 N HCl (1 mL) in 30 mL of THF containing methylene blue (0.01 g). After being stirred for 30 min, the reaction mixture was neutralized with $CaCO_3$ (1.6 g). The $CaCO_3$ was rinsed with ethyl acetate (3 × 10 mL). The combined organic rinse was dried (Na_2SO_4), concentrated, and chromatographed to give **12** (1.92 g, 90% yield from **11**) as a clear colorless oil, TLC R_f = 0.17 (10% MeOH/CH_2Cl_2). ^{1}H 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): down = 14.2, 71.8, 124.9, 127.8, 127.9, 128.3, 129.2, 131.1; up = 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.

(*Z*,*Z*)-3,6-Nonadienyltriphenylphosphonium Tosylate (13). Pyridine (2.8 mL, 34 mmol) and *p*-toluenesulfonyl chloride (4.90 g, 25.7 mmol) were added sequentially with stirring to an ice-cold solution of (*Z*,*Z*)-3,6-nonadien-1-ol[8] (2.4 g, 17.1 mmol) in CH_2Cl_2 (60 mL). After being stirred at rt for 13 h the mixture was quenched with 10% aqueous HCl (40 mL) and extracted with CH_2Cl_2 (2 × 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). ^{1}H NMR : 0.95 (t, J = 7.6 Hz, 3H), 2.08 (m, 2H), 2.35 (q, J = 6.9 Hz, 2H), 2.44 (s, 3H), 2.84 (t, J = 6.7 Hz, 2H), 3.90 (t, J = 7.6 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 **13** (5.03 g, 9.0 mmol, 76% yield from the alcohol) as a white powder (mp = 197 °C after recrystallization from 30% Et_2O/CH_2Cl_2), TLC R_f = 0.60 (10% MeOH/CH_2Cl_2). ^{1}H NMR (δ): 0.88 (t, J = 7.5 Hz, 3H), 1.86 (m, 2H), 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): down = 14.1, 21.2, 126.2, 126.4, 126.7, 128.1, 130.3, 130.5, 132.2, 133.5, 133.7, 134.8, 134.8, 134.9; up = 20.3, 20.3, 20.4, 21.7, 22.4, 25.4, 117.7, 119.1, 138.2, 144.7. IR (neat, cm^{-1}): 3059, 2922, 2195, 1697, 1589, 1438.

Ethyl Docosa-4,7,10,13,16,19-hexaenoate (3b). 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 **12** (0.190 g, 0.64 mmol) was added to the SiO_2 suspension. After being stirred for 5 min, this suspension was filtered directly into a solution of ylide made from the addition of sodium bis(trimethylsilyl)amide (1.65 mL, 1.0 M in THF) to phosphonium salt **13** (0.75 g, 1.35 mmol) in 10 mL of dry THF at −75 °C. 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 × 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 μm Unibond silica gel, eluting with 1% CH_2Cl_2/CH_3CN, to give **3b** (0.128 g, 58% yield from **12**) as a colorless oil, TLC R_f = 0.45 (100% CH_3CN). ^1H NMR (δ): 0.99 (t, J = 7.5 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 2.0–2.17 (m, 2H), 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): down = 14.3, 127.0, 127.9, 128.0, 128.1, 128.2, 128.3, 128.6, 129.2, 132.0; up = 20.6, 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 (18), 180 (28), 159 (40), 119 (100), 105 (99). HRMS: calcd for $C_{24}H_{36}O_2$ 356.2715, found 356.2720. The ^1H and ^{13}C NMR data were exactly consistent with those for the authentic ethyl ester that we prepared from the commercially available docosahexaenoic acid and also with those reported[13] for the methyl ester of that acid.

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Supplementary Material Available: Copies of ^1H and ^{13}C spectra for compounds **3b**, **4**, **6**, **7**, **8**, **9**, **11**, **12**, and **13** (19 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.

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