erature ^1H NMR and ^{13}C NMR data.[27]

Photolysis at 254 nm of 2t. A C_6D_6 (0.5 mL, 0.1 M) solution of **2t** in a quartz NMR tube was sealed under vacuum after three freeze–thaw–degas cycles. The sample was then irradiated at 254 nm in a Vycor sleeve and the reaction progress was monitored by ^1H NMR of the characteristic NCH_3 singlets. A major product with an NMR singlet at δ 3.12 was assigned as the cis azo isomer **2c** on the basis of its photochemical behavior. The NMR spectrum of **2c** was obtained on the IBM 300-MHz spectrometer in the following way. A 0.1 M solution of **2t** in C_6D_6 was irradiated for a short period at 254 nm. A difference NMR spectrum was then generated from the "before" and "after" irradiation spectra. **2c**: ^1H NMR (C_6D_6) δ 1.24 (m, 1 H), 1.82 (m, 1 H), 2.03 (m, 1 H), 2.92 (m, 1 H), 3.12 (s, 3 H).

Quantum Yields. Light intensities were based on the chemical actinometer 2,3-diazabicyclo[2.2.1]hept-2-ene which evolves nitrogen with unit efficiency. Gas yields were measured using a Töpler pump and gas buret. Each product (except styrene) had an NCH_3 singlet in the NMR which allowed us to follow product concentrations as a function of irradiation time. All quantum yields are based on initial slopes of such concentration vs. time plots.

Thermolysis of 2t and 3t. Solutions of **2t** (0.04 M) and **3t** (0.1 M) in C_6D_6 were degassed and sealed in NMR tubes. The samples were then suspended in an oil bath regulated at 141 °C and were periodically removed for NMR analysis. Concentration vs. thermolysis time plots were then constructed as described above. Theoretical concentration vs. time plots were prepared by modifying the computer program EPFIT[20] to model this system. Both azocyclopropanes were assumed to form a single biradical which then partitions itself among the two azoalkanes and the pyrazoline **1**. Formation of **1** was assumed to be irreversible based on its thermal stability at 141 °C. The curves thus generated from EPFIT were then compared visually with the experimental curves. Changes in the rate constants were made and the new curves again compared to the experimental curves. This process was repeated until a single set of rate constants which gave the "best fit" to the experimental curves was obtained.

Acknowledgment. We thank the National Science Foundation and the Robert A. Welch Foundation for financial support. G.A.B. gratefully acknowledges the ARCS Foundation for a fellowship.

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Total Synthesis of 8(*S*)-, 9(*S*)-, 11(*S*)-, and 12(*S*)-HETE Methyl Esters

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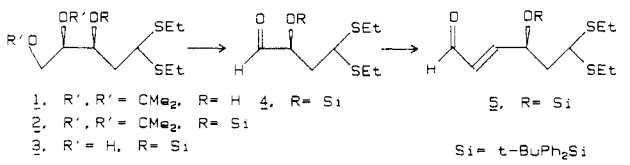
Starting from D-arabinose, the total syntheses of methyl 8(*S*)-, 9(*S*)-, 11(*S*)-, and 12(*S*)-hydroxyeicosatetraenoates are described.

Enzymic oxidation of arachidonic acid leads to a multitude of biochemically important products that include not only prostaglandins and their transformation products such as thromboxane and prostacycline but also lipoxygenase-derived hydroperoxides (HPETE's) and alcohols (HETE's).[1]

The oxidation of the (*Z*,*Z*)-1,4-diene system characteristic of arachidonic acid (Figure 1) is thought to proceed via radical **B**, itself probably generated by abstraction of an electron from the double bond followed by loss of a proton. This radical **B** may then add oxygen, a superoxide anion, or superoxide to give **C1–3**, which may be further reduced to the HETE's. Six of these intermediates can be produced in theory, and five of them have either been isolated or are postulated to be key intermediates in the biosynthesis of eicosanoids. Thus, the biosynthesis of prostaglandins is thought to proceed via the 11(*S*)-peroxy radical of type **C1**. The related 11-HETE[3] is a key compound in the search for biosynthetically patterned prostaglandin syntheses. 12-HETE, generated from arachidonic acid by 12-lipoxygenase enzyme, is found in human

Scheme I



platelets[4] and skin keratinocytes.[5] It has also been detected in high concentrations in psoriatic lesions[6] and shown to possess both chemotactic and chemokinetic properties. 8-HETE has recently been found to appear, among the various HETE's, as the only biologically active metabolite of arachidonic acid in starfish oocytes.[7] Its 8(*S*) stereochemistry has just been determined.[8] In order to facilitate the study of the biological and biochemical properties of these arachidonic acid metabolites, significant quantities of these HETE's are required. An efficient synthesis of 5-HETE[9] and an enzymatic preparation of

(1) Samuelsson, B. In *Progress in Lipid Research*; Holman, R. T., Ed.; Pergamon: Oxford, 1981; Vol. 20, pp 23 and references cited therein.
(2) (a) Borgeat, P.; Hamberg, M.; Samuelsson, B. *J. Biol. Chem.* **1976**, *251*, 7816. See correction: *J. Biol. Chem.* **1977**, *252*, 8772. (b) Hamberg, M.; Svensson, J.; Wakabayaski, T.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 345 and references cited therein. (c) Hamberg, M.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 3400. (d) Bryant, R. W.; Bailey, J. M. In *Progress in Lipid Research*; Holman, R. T., Ed.; Pergamon: Oxford, 1981; Vol. 20, pp 279 and references cited therein.
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(9) Corey, E. J.; Albright, J. O.; Barton, A. E.; Hashimoto, S. *J. Am. Chem. Soc.* **1980**, *102*, 1435.

0022-3263/86/1951-4796$01.50/0

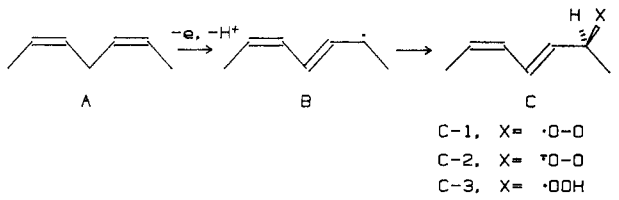


Figure 1.

15-HETE[10] provide convenient access to these natural products. We describe a general and practical way to make the four other HETE's available as either the *R* or *S* enantiomers.

A retrosynthetic analysis[11] indicates that either enantiomer of 8-, 9-, 11-, and 12-hydroxyeicosatetraenoic acids can, in principle, be constructed from intermediate **5**, which is available from D- or L-arabinose in either chirality and phosphoranes **6**, **7**, **17**, and **20**. Phosphoranes **6** and **17** are readily available; **20** and **7** have been described.[12,13] The phosphorane **20** can also be built rapidly by the method recently developed in our laboratory.[14] The availability of both enantiomers is relatively important since no solution has yet been found for the synthesis of enantiomerically pure HPETE's.

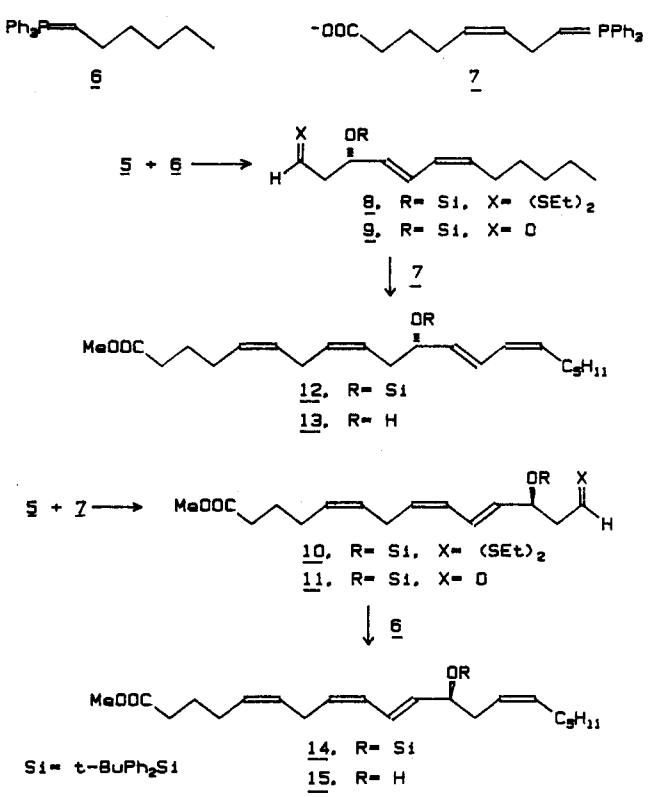
Results

In the following, we describe the detailed synthesis of 8(*S*)-, 9(*S*)-, 11(*S*)-, and 12(*S*)-HETE methyl esters. The synthesis of the key intermediate **5** (Scheme I) utilized the D-2-deoxypentose dithioacetal **1**, easily prepared in large scale by the method of Wong and Gray[15] from D-arabinose. Transformation to its *tert*-butyldiphenylsilyl ether **2**, followed by acidic hydrolysis with trifluoroacetic acid–tetrahydrofuran (THF)–water gave the diol **3**. Oxidative cleavage of the diol **3** by sodium periodate in THF–acetone–water afforded an unstable aldehyde **4**. Treatment of the aldehyde **4** with (formylmethylene)triphenylphosphorane in dry benzene gave the key compound **5**, which was quite stable and could be stored at 0–10 °C for weeks.

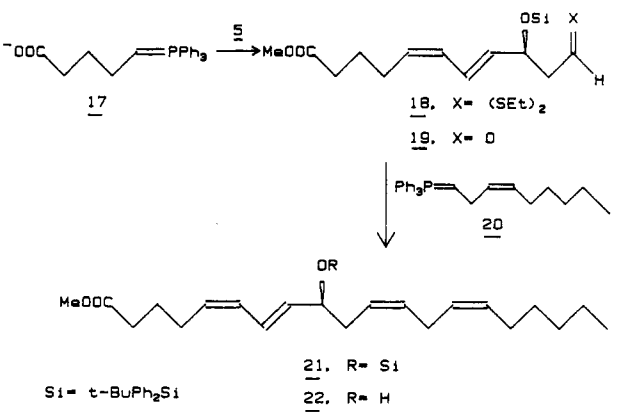
The synthesis of 11(*S*)-HETE methyl ester **13** (Scheme II) was accomplished in the following manner. Condensation of the aldehyde **5** with 1-hexylidenetriphenylphosphorane **6** gave dithioacetal **8**. Hydrolysis of the thioacetal function[16] by treatment of *N*-chlorosuccinimide (NCS) and silver nitrate ($AgNO_3$) provided highly unstable aldehyde **9**, which was immediately treated with the phosphorane **7**, followed by esterification with dimethyl sulfate in situ, to give the ester **12** and its olefinic isomers. Hydrolysis of the silyl protecting group of **12** and its isomers with tetra-*n*-butylammonium fluoride gave, after purification by HPLC, optically pure 11(*S*)-HETE methyl ester **13**.

Conversely, condensation of the aldehyde **5** with the phosphorane **7**[13] gave, after quenching with dimethyl sulfate, the ester **10**. Coupling of the aldehyde **11**, generated from the ester **10** by hydrolysis of its thioacetal function with NCS–$AgNO_3$, with the phosphorane **6** yielded the protected 12(*S*)-HETE **14**. Removal of the silyl protecting group of **14** gave, after HPLC purification, the optically pure 12(*S*)-HETE methyl ester **15**.[17]

Scheme II



Scheme III



For the synthesis of 9(*S*)-HETE methyl ester (Scheme III), the aldehyde **5** was coupled with the phosphorane **17**, and the reaction mixture was treated with dimethyl sulfate to provide the ester **18**. Hydrolysis of the thioacetal function with NCS–$AgNO_3$ gave the aldehyde **19**. A conventional Wittig reaction of the aldehyde **19** with the phosphorane **20**[18] in THF containing HMPA gave the adduct **21** in only 20% yield (*E*:*Z* at $\Delta^{11} \sim 1{:}1$). However, when HMPA was omitted, the adduct **21** was obtained in 75% yield (*E*:*Z* at $\Delta^{11} \sim 98{:}2$). Removal of the silyl protecting group with tetra-*n*-butylammonium fluoride gave 9(*S*)-HETE methyl ester **22**.

(10) Crawford, C. G.; Van Alphen, G. W. H. M.; Lands, W. E. M. *Life Sci.* **1978**, *23*, 1255.
(11) Just, G.; Wang, Z. Y. *Tetrahedron Lett.* **1985**, 2993.
(12) Corey, E. J.; Arai, Y.; Mioskowski, C. *J. Am. Chem. Soc.* **1979**, *101*, 6748.
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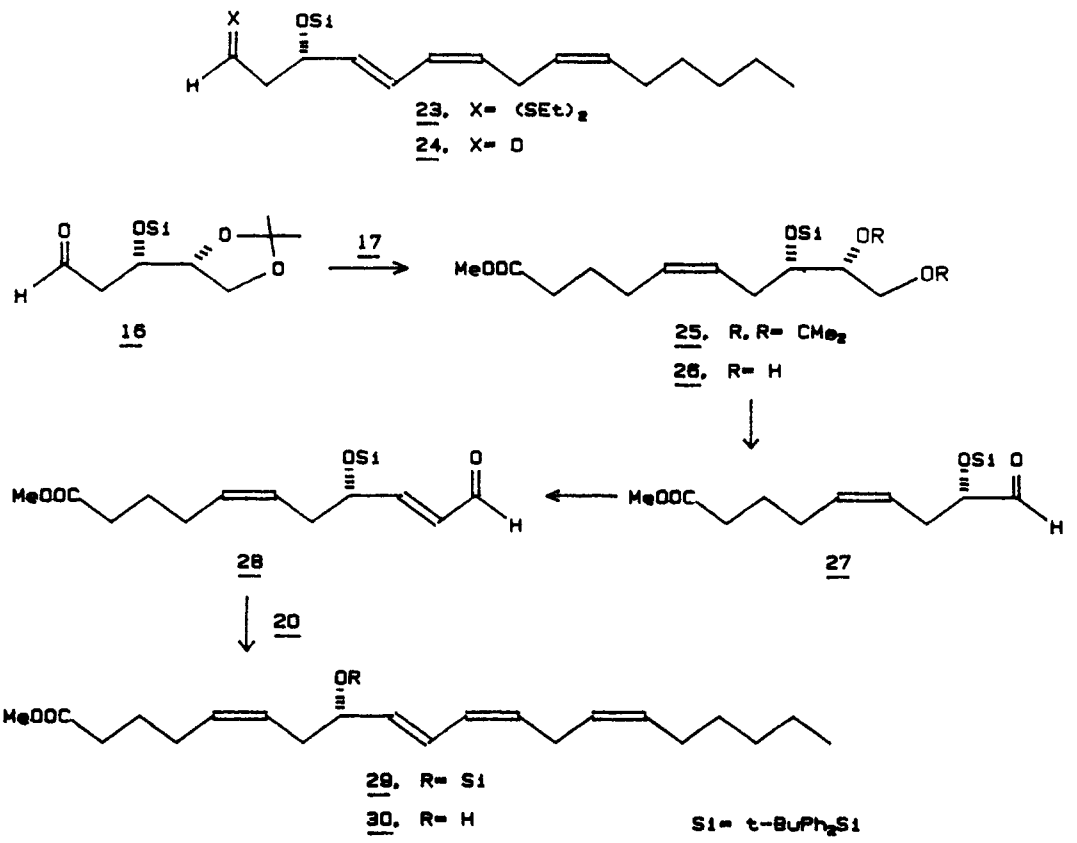
(16) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.
(17) $[\alpha]_D$ +1.5° (*c* 0.2, $CHCl_3$). Literature values: $[\alpha]_D$ +1.3° (*c* 0.3, $CHCl_3$) [Corey, E. J.; Niwa, H.; Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942], $[\alpha]_D$ +13° (*c* 1.5, acetone) [Leblanc, Y.; Fitzsimmons, B. J.; Adams, J.; Perez, F.; Rokach, J. *J. Org. Chem.* **1986**, *51*, 789].
(18) Cohen, N. C.; Banner, B. L.; Lopresti, R. J.; Wong, F.; Rosenerger, M.; Liu, Y.-Y.; Thom, E.; Liebmoan, A. A. *J. Am. Chem. Soc.* **1983**, *105*, 3661.

Scheme IV



On our first approach to the synthesis of 8(*S*)-HETE methyl ester (Scheme IV), the Wittig adduct **23** was obtained from the reaction of the aldehyde **5** with the ylide corresponding to **20**, generated by a one-pot reaction[14] of pentyllithium–CuBr·SMe_2–acetylene–vinyltriphenylphosphonium bromide. Hydrolysis of the dithioacetal function of **23** with NCS–$AgNO_3$ provided the highly unstable aldehyde **24** in 20–30% yield. Attempts to couple with the ylide **17** gave only the product of β-elimination of the aldehyde **24** in nearly quantitative yield. Since all attempts to affect the Wittig reaction proved futile, due to the instability of the aldehyde **24**, we next investigated an alternate sequence. The aldehyde **16** earlier obtained from the dithioacetal **3** was treated according to the procedure of Zamboni et al.[19] with the phosphorane **17**. Esterification of the reaction product with diazomethane gave the ester **25** which was hydrolyzed to the diol **26**. Cleavage of the resulting diol with sodium periodate afforded the aldehyde **27**, which was then homologated by treatment with (formylmethylidene)triphenylphosphorane to give α,β-unsaturated aldehyde **28**. Condensation of the aldehyde **28** with the ylide **20** gave the adduct **29**. Deprotection and further purification by HPLC afforded the optically pure 8(*S*)-HETE methyl ester **30**. Since the proton NMR spectra of the 8-, 9-, 11-, and 12-HETE are very similar and many signals overlap, a 2D homocorrelation (COSY) experiment was undertaken for 8(*S*)- and 12(*S*)-HETE methyl esters. This allowed also for the interpretation of the other two HETE spectra.

Starting with the H_8 signal (at 4.23 ppm), which shows clearly correlation with two other protons, the olefinic protons were easily assigned (Figure 2a). The signals of H_5, H_6, H_{12}, H_{14}, and H_{15} overlap; the other olefinic protons (H_9, H_{10}, H_{11}) appear at different chemical shifts. A first complete assignment of ^1H NMR spectra of 12(*S*)-HETE methyl ester was made. The ambiguous signals[20] of H_3/H_{17} and H_4/H_{16} were clearly assigned from its 2D NMR spectrum (Figure 2b).

Experimental Section

General Methods. Melting points (mp) were measured on a Gallenkamp block and are uncorrected. Ultraviolet spectra (UV) were recorded on a SP800 ultraviolet spectrophotometer. Optical rotations were measured with the indicated solvent and concentration in a 1-dm cell on a Jasco DIP-140 digital polarimeter. Thin-layer chromatography (TLC) was performed on Merck silica gel $60F_{254}$ aluminum-backed plates. Flash chromatography was done on Woelm Silica (32–63 μm). Infrared (IR) spectra were recorded on a Perkin-Elmer 257 spectrophotometer. The NMR spectra were recorded on Varian XL-200 and XL-300 spectrometers. Mass spectra (MS) were obtained on HP 5984A or LKB 9000 spectrometers, in the direct-inlet mode unless indicated otherwise. High-resolution mass spectra (HRMS) were obtained on a Du Pont 21-492B instrument.

Tetrahydrofuran (THF) was distilled from sodium and benzophenone immediately prior to use. Hexamethylphosphoramide (HMPA) was dried over a 3-Å molecular sieves. All reactions were carried out under an inert atmosphere of nitrogen or argon and were monitored by TLC.

2-Deoxy-3-*O*-(*tert*-butyldiphenylsilyl)-4,5-*O*-isopropylidene-D-*erythro*-pentose Diethyl Dithioacetal (2). A solution of the alcohol **1** (0.280 g, 1 mmol), *tert*-butylchlorodiphenylsilane (1.1 equiv, 0.32 mL), and imidazole (2.2 equiv, 0.150 g) in dry DMF was heated at 75–80 °C for 18 h. After cooling, water (20 mL) was added and the resulting mixture was extracted with ether (3 × 50 mL). The combined ether extracts were washed with water (3 × 10 mL) and dried over anhydrous sodium sulfate. Removal of solvent in vacuo and purification by flash chromatography (60:1 (v/v) petroleum ether–ethyl acetate) gave the pure silyl ether **2**: 0.480 g (92.6%); IR (neat, cm^{-1}) 3050; ^1H NMR (200

(19) Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1982**, 4752.

(20) See ^1H NMR spectral data for 12(*S*)-HETE methyl ester previously published by E. J. Corey et al. and J. J. Rokach et al.

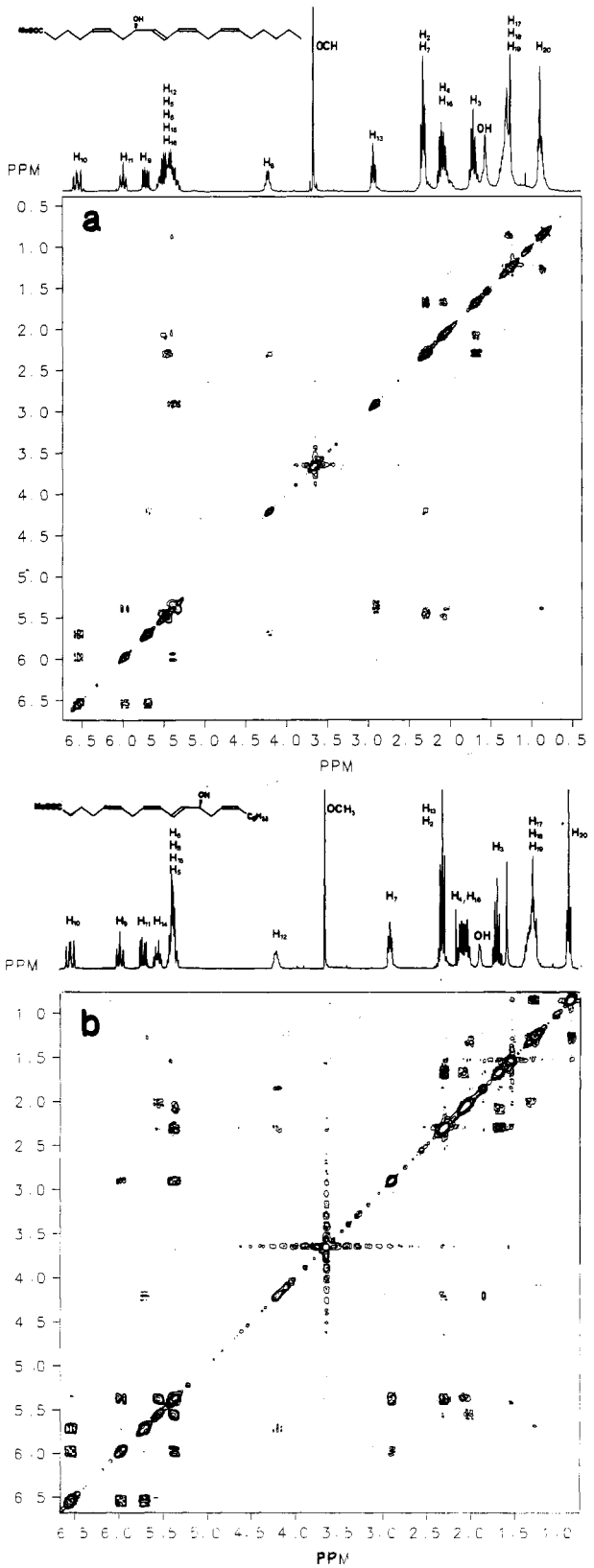


Figure 2. ^{1}H HOMCOR (COSY) spectra of (a) 8(*S*)-HETE methyl ester in $CDCl_3$ and (b) 12(*S*)-HETE methyl ester, recorded on a Varian XL-300 spectrometer.

MHz, $CDCl_3$) δ 1.10 [s, 9 H, $C(CH_3)_3$], 1.19 (t, 6 H, SCH_2CH_3), 1.29 and 1.31 [2 s, 6 H, $C(CH_3)_2$], 1.70–2.60 (m, 6 H, SCH_2CH_3, $CHCH_2CHS$), 3.50–4.20 (m, 5 H, CH_2CHS, $OCH_2CHCHOSi$), 7.30–7.80 (m, 10 H, Ar H).

2-Deoxy-3-*O*-[(*tert*-butyldiphenylsilyl)oxy]-4,5-dihydroxy-D-*erythro*-pentose Diethyl Dithioacetal (3). The solution of the acetonide **2** (5.70 g, 0.011 mol) in 38 mL of trifluoroacetic acid–THF–water (1:2:1 (v/v), 1 mL/0.15 g of **2**) was stirred at room temperature for 6 h and neutralized by addition of sodium hydroxide solution (1 N) at 0 °C, and the THF was removed at reduced pressure. The residue was diluted with water (150 mL), and the resulting mixture was extracted with ether (3 × 150 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, and the solvent was removed at reduced pressure. Flash chromatography of the residue (20% ethyl acetate in hexanes) yielded the diol **3**: 4.52 g (86%); $[\alpha]^{20}_D$ +24.7° (*c* 3.0, $CHCl_3$); IR (neat, cm^{-1}) 3440, 2930, 2940, 2860, 1740, 1430, 1110, 710; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10 [s, 9 H, $(CH_3)_3CSi$], 1.15 and 1.30 (t, 6 H, SCH_2CH_3), 1.90–2.10 (, 2 H, CH_2CHS), 2.40 (m, 5 H, SCH_2CH_3, OH), 3.65 (m, 3 H, $C_{4,5}$ H), 3.80 (q, *H*COSi), 4.15 (m, 2 H, $HCSCH_2$, OH), 7.45 (m, 6 H, *p,m*-Ar-H), 7.75 (m, 4 H, OArH).

2(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-4,4-bis(ethylthio)-butanal (4). To a well-stirred solution of the diol **3** (180 mg, 0.377 mmol) in THF (1 mL) at room temperature was added sodium periodate (282 mg, 3.5 equiv) in water (1.5 mL) and acetone (0.5 mL). The resulting mixture was stirred for 15 min, then diluted with ether (20 mL), and filtered through Celite. The residue was washed with ether a few times. The combined ethereal phases were washed with brine (20 mL) and dried over anhydrous magnesium sulfate. Removal of solvent at reduced pressure gave crude product. Purification by flash chromatography (1.5 × 10 cm, 4% ethyl acetate in petroleum ether) yielded the pure aldehyde **4** as an oil: 129 mg (76.8%); $[\alpha]^{20}_D$ −8.92° (*c* 4.4, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 2910, 2840, 1725, 1710, 1100; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 [s, 9 H, $C(CH_3)_3$], 1.17 (t, 6 H, SCH_2CH_3), 2.05–2.64 (m, 6 H, SCH_2CH_3, CH_2CHS), 4.05 (dd, J = 7.14 Hz, J = 9.52 Hz, 1 H, CHOSi), 4.14 (t, 1 H, J = 7.14 Hz, $CHSCH_2$), 7.33 (m, 6 H, *m,p*-Ar-H), 7.60 (m, 4 H, OArH), 9.67 (s, 1 H, CHO); MS [*m/e* (70 eV, %)] 446 ($M^{\bullet+}$, 0.4), 389 ($M^{\bullet+}$ − CMe_3, 9.1), 384 ($M^{\bullet+}$ − C_2H_5SH, 13.3), 327 ($M^{\bullet+}$ − CMe_3 − C_2H_5SH, 100), 135 ($C_2H_5SCH{=}^+SC_2H_5$, 51.5).

4(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-6,6-bis(ethylthio)-hex-2(*E*)-enal (5). A mixture of the aldehyde (300 mg, 0.673 mmol) and (formylmethylidene)triphenylphosphorane (235 mg, 1.15 equiv) in dry benzene (4 mL) was stirred at 70 °C for 6.5 h and cooled to room temperature, and the solvent was removed at reduced pressure. Flash chromatography of the residue (3 × 15 cm, 3% ethyl acetate in petroleum ether, Kieselgel 60 HF_{254} from BDH) yielded the pure α,β-unsaturated aldehyde **5** [225 mg (79%)] plus recovered starting aldehyde [30 mg (10%)]: $[\alpha]^{20}_D$ −16.1° (*c* 2.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 2920, 2860, 1690, 1110, 970; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.07 (s, 9 H, CMe_3), 1.19 (2 t, 6 H, SCH_2CH_3), 1.80–2.43 (m, 6 H, SCH_2CH_3, CH_2CHS), 3.74 (t, CHS), 4.73 (q, 1 H, J = 4.8 Hz, J = 7.1 Hz, HCOSi), 6.01 (dd, 1 H, J = 9.5 Hz, J = 14.3 Hz, CH=C*H*CHO), 6.65 (dd, 1 H, J = 14.3 Hz, J = 7.1 Hz, CH=CHCHO), 7.24–7.72 (m, 10 H, 2 Ph), 9.34 (d, 1 H, J = 9.5 Hz, CHO); MS [*m/e* (70 eV, %)] 472 ($M^{\bullet+}$, 1.2), 415 ($M^{\bullet+}$ − CMe_3, 6.9), 410 ($M^{\bullet+}$ − C_2H_5SH, 4.3), 381 ($M^{\bullet+}$ − 91, C_2H_5SH, C_2H_5, 32.3), 327 ($M^{\bullet+}$ − 145, 100), 135 ($C_2H_5SCH{=}S^+C_2H_5$, 41.8), 353 ($M^{\bullet+}$ − CMe_3 − EtSH, 50.0), 3.23 ($M^{\bullet+}$ − 149, $OHCCH{=}CHCH{=}^+OSiPh_2CMe_3$, 17.8).

1,1-Bis(ethylthio)-3(*S*)-[(*tert*-butyldiphenylsilyl)oxy]-4-(*E*),6(*Z*)-dodecadiene (8). To a solution of hexyltriphenylphosphonium bromide (487 mg, 1.14 mmol) in THF (2 mL) at −78 °C was added *n*-butyllithium (*n*-BuLi; 1.6 M, 0.790 mL) via syringe. The reaction was allowed to warm to room temperature and stirring continued for 30 min; then, the solution of dark red ylide **6** was cooled to −78 °C. A solution of the aldehyde **5** (426 mg, 0.903 mmol) in THF (1.5 mL) was then added dropwise. After 15 min, water (5 mL) was added and the resulting mixture was warmed to room temperature. The solution of ammonium acetate (25%, 25 mL) was added, and the mixture was extracted with ether (2 × 100 mL). The combined ether extracts were then dried over anhydrous magnesium sulfate. Removal of solvent at reduced pressure afforded crude product. Purification by flash chromatography (1.6%, EtOAc in petroleum ether) gave the Wittig adducts **8**: 280 mg (57.4%); $[\alpha]^{22}_D$ −27° (*c* 2.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 2960, 2940, 2860, 1110, 1065, 990; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 [t, 3 H, $(CH_2)_4CH_3$], 1.09 [s, 9 H, $C(CH_3)_3$], 1.12 (t, 3 H, SCH_2CH_3), 1.15 (t, 3 H, SCH_2CH_3), 1.27 [m, 6 H, $CH_2(CH_2)_3CH_3$], 1.68–2.12 (m, 4 H, SCH_2CH_3; 1 H, $CH{=}CHCH_2CH_2$), 2.29 (m, 1 H, $CH{=}CHCH_2CH_2$), 2.51 (m, 2 H, CH_2CHS), 3.79 (t, 1 H, J = 7.6 Hz, HCS), 4.17 (dd, 1 H, J = 13.0, J = 7.2 Hz,

HCOSi), 5.34 (m, 1 H, CH=C*H*CH$_2$), 5.50 (dd, 1 H, J = 13.0 Hz, J = 7.2 Hz, CH=C*H*CHOSi), 5.79 (br t, 1 H, C*H*=CHCH$_2$), 6.09 (dd, 1 H, J = 13.0 Hz, J = 8.7 Hz, C*H*=CHCHOSi), 7.34 (m, 6 H, *p,m*-Ar-H), 7.66 (m, 4 H, OArH); MS [*m/e* (70 eV, %)] 540 ($M^{\bullet+}$, 0.3), 483 ($M^{\bullet+}$ - CMe_3, 12.8), 421 ($M^{\bullet+}$ - CMe_3 - C_2H_5SH, 28.4), 417 [$M^{\bullet+}$ - CH=CHCH=CH(CH$_2$)$_4$CH$_3$, 100], 360 [$M^{\bullet+}$ - CMe_3 - CH=CHCH=CH(CH$_2$)$_4$CH$_3$, 16.7], 199 ($^+$O=SiHPh$_2$, 34.4).

3(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-4(*E*),6(*Z*)-dodecadienal (9). To a stirred solution of silver nitrate (0.293 g, 1.725 mmol) and *N*-chlorosuccinimide (0.215 g, 1.610 mmol) in 3:1 acetonitrile–water (5 mL) at −10 °C was added a solution of the thioacetal **8** (250 mg, 0.463 mmol) in acetonitrile (1.5 mL). The resulting mixture was stirred at −10 °C for 10 min, and dimethyl sulfoxide (Me_2SO, 0.12 mL) was added. After a further 10 min at −10 °C, 15 mL of 25% aqueous ammonium acetate was added. The mixture was allowed to warm to room temperature and filtered through Celite, washing with water (50 mL) and dichloromethane (150 mL). The filtrate was partitioned, and the aqueous phase was extracted with dichloromethane (3 × 100 mL). The combined organic phases were washed with brine and dried over anhydrous sodium sulfate at 0 °C, and the solvent was removed at reduced pressure at 25 °C. Flash chromatography of the residue (25:1 petroleum ether–ethyl acetate) afforded the desired aldehyde **9**: 99 mg (49%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3 H, CH$_2$C*H*$_3$), 1.02 [s, 9 H, C(CH$_3$)$_3$], 1.22 [m, 6 H, CH$_2$(C*H*$_2$)$_3$CH$_3$], 2.00 (m, 2 H, CH=CHC*H*$_2$CH$_2$), 2.51 (m, 2 H, C*H*$_2$CHO), 4.67 (m, 1 H, HCOSi), 5.36 (m, 1 H, CH=C*H*CH$_2$), 5.47 (dd, 1 H, CH=C*H*CHOSi), 5.69 (br t, 1 H, C*H*=CHCH$_2$), 6.22 (dd, 1 H, C*H*=CHCHOSi), 7.30–7.71 (m, 10 H, ArH), 9.71 (t, 1 H, CHO).

Methyl 11(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-5(*Z*),8(*Z*),12(*E*),14(*Z*)-eicosatetraenoate (12). To a well-stirred solution of the phosphonium salt **7** (154 mg, 0.291 mmol) in THF (1 mL) and HMPA (0.25 mL) at 0 °C was added a solution of lithium hexamethyldisilazane (LiHMDS) (0.582 mmol) in THF (1 mL) and HMPA (0.25 mL) over 3 min. The resulting mixture was stirred at 0 °C until a clear orange–red solution was obtained (~1 h); then, the solution was cooled to −78 °C. A solution of the aldehyde **9** (80 mg, 0.194 mmol) in THF (1 mL) was then added dropwise. The resulting mixture was stirred at −78 °C for 60 min and then at room temperature for 60 min and was treated with anhydrous sodium bicarbonate (3 equiv, 49 mg) followed by dimethyl sulfate (80 μL), and stirring was continued for 1 h. It was then diluted with 25% aqueous ammonium acetate (20 mL) and extracted with ether (2 × 100 mL). The combined ether extracts were washed with water (50 mL) and dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure. Flash chromatography of the residue (3 × 15 cm column, 30:1 petroleum ether–ethyl acetate, Kieselgel 60 HF_{254} from BDH) afforded the Wittig adducts **12** [55 mg (52%)] as a mixture of cis and trans isomers (4.5:1 by 200-MHz ^{1}H NMR): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (t, 3 H), 1.03 [s, 9 H, C(CH$_3$)$_3$], 1.23 (m, 6 H, C$_{17,18,19}$-H), 1.66 (sextet, 2 H, C$_3$-H), 2.00 [br q, 4 H, C$_2$, C$_4$-H), 2.22 (m, 4 H, C$_4$-H, C$_{16}$-H), 2.55 (m, 2 H, C$_8$(*Z*)C$_7$-H), 2.90 (m, 2 H, C$_8$(*E*)C$_7$-H), 3.54 (s, 3 H, OCH$_3$), 4.19 (m, 1 H, C$_{11}$-H), 5.17–5.36 (m, 5 H, C$_{5,6,8,9,15}$-H), 5.56 (dd, 1 H, C$_{12}$-H), 5.83 (br t, 1 H, C$_{14}$-H), 6.19 (dd, 1 H, C$_{13}$-H), 7.32 (m, 6 H, *p,m*-Ar-H), 7.63 (m, 4 H, OArH); MS [*m/e* (70 eV, %)] 572 ($M^{\bullet+}$, 0.7), 515 ($M^{\bullet+}$ - CMe_3, 16.4), 391 ($M^{\bullet+}$ - MeO$_2$C(CH$_2$)$_3$CH=CHCH$_2$CH=CHCH$_2$, 100).

Methyl 11(*S*)-Hydroxy-5(*Z*),8(*Z*),12(*E*),14(*Z*)-eicosatetraenoate (13). To a stirred solution of the mixture of cis and trans **12** (55 mg, 0.096 mmol) in THF (1 mL) at room temperatuee was added a solution of tetra-*n*-butylammonium fluoride trihydrate (0.182 mmol) in THF (1 mL). The resulting mixture was heated at 40–45 °C for 4–5 h and after cooling diluted with water (50 mL) and extracted with ether (3 × 50 mL). The combined ether extracts were dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure. Flash chromatography (10:1 petroleum ether–ethyl acetate, Kieselgel 60 HF_{254} from BDH) gave the desired product [22 mg (69%)]. Further purification by standard-phase HPLC (7.8 mm × 30 cm μ-Porasil column, 15% ethyl acetate in hexanes) afforded the methyl ester of 11(*S*)-HETE **13**: 15 mg (47%); $[\alpha]^{22}_D$ −10.3° (*c* 1.2, $CHCl_3$); UV (hexane) λ_{max} 235 nm; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (br t, 3 H, C$_{20}$-H), 1.18–1.38 (m, 6 H, C$_{16,17,18}$-H), 1.69 (sextet, 3 H, C$_3$-H, OH), 2.00–2.19 (m, 4 H, C$_{2,4}$-H), 2.22–2.37 (m, 4 H, C$_{10,16}$-H), 2.80 (br t, 2 H, C$_7$-H), 3.67 (s, 3 H, OCH$_3$), 4.19 (m, 1 H, C$_{11}$-H), 5.29–5.56 (m, 5 H, C$_{5,6,8,9,15}$-H), 5.66 (dd, 1 H, $J_{11,12}$ = 6.4 Hz, $J_{12,13}$ = 14.4 Hz, C$_{12}$-H), 5.97 (br t, 1 H, $J_{13,14}$ = 11.2 Hz, $J_{14,15}$ = 10.2 Hz, $J_{14,16}$ ≃ 1.2 Hz, C$_{14}$-H), 6.50 (dd, 1 H, $J_{13,14}$ = 11.2 Hz, $J_{12,13}$ = 14.4 Hz, $J_{13,11}$ ≤ 1.0 Hz, C$_{13}$-H); MS [*m/e* (70 eV, %)] (trimethylsilyl ether) 391 ($M^{\bullet+}$ - CH$_3$, 0.8), 283 [$M^{\bullet+}$ - CH=CHCH=CH(CH$_2$)$_4$CH$_3$, 8.1], 225 ($M^{\bullet+}$ - MeO$_2$C(CH$_2$)$_3$CH=CHCH$_2$CH=CHCH$_2$, 100).

Methyl 12(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-14,14-bis(ethylthio)-5(*Z*),8(*Z*),10(*E*)-tetradecatrienoate (10). To a well-stirred solution of the ylide **7** generated by treatment of its corresponding triphenylphosphonium iodide (503 mg, 0.949 mmol) in 3 mL of 25% HMPA in THF with LiHMDS (2.8 equiv, 1.898 mmol) in 1 mL of 25% HMPA in THF at 0 °C for 45 min, at −78 °C, was added a solution of the α,β-unsaturated aldehyde **5** (320 mg, 0.678 mmol) in THF (1.5 mL). The mixture was stirred at −78 °C for 1 h and at room temperature for 1 h and then treated with anhydrous sodium bicarbonate (170 mg, 3 equiv) followed by dimethyl sulfate (270 μL). After 30 min the mixture was diluted with 25% aqueous ammonium acetate (20 mL) and extracted with ether (2 × 50 mL). The combined ether extracts were washed with 25% aqueous ammonium acetate (20 mL) and water (20 mL) and dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure. Chromatography of the residue (35:1 (v/v) petroleum ether–ethyl acetate, Kieselgel 60 HF_{254} from BDH) afforded the Wittig adducts **10**: 310 mg (75%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.02 (s, 9 H, CMe_3), 1.12 (t, 3 H, SCH$_2$C*H*$_3$), 1.15 (t, 3 H, SCH$_2$C*H*$_3$), 1.68 (m, 2 H, C$_{13}$-H), 1.88 (m, 1 H, C$_{13}$-H), 2.05 (m, 3 H, C$_{13}$-H, C$_4$-H), 2.29 (m, 4 H, SC*H*$_2$CH$_3$, C$_4$-H), 2.51 (m, 2 H, SC*H*$_2$CH$_3$), 1.71 (br t, 2 H, C$_7$-H), 3.64 (s, 3 H, OC*H*$_3$), 3.81 (t, 1 H, C$_{14}$-H), 4.51 (q, 1 H, C$_{12}$-H), 5.31 (m, 3 H, C$_{5,6,8}$-H), 5.53 (q, 1 H, C$_{11}$-H), 5.78 (br t, 1 H, C$_9$-H), 6.07 (q, 1 H, C$_{10}$-H), 7.36 (m, 6 H, Ar-H), 7.66 (m, 4 H, Ar-H); MS [*m/e* (70 eV, %)] 610 ($M^{\bullet+}$, 2.8), 553 ($M^{\bullet+}$ - CMe_3, 22.6), 549 ($M^{\bullet+}$ - SC_2H_5, 11.3), 491 ($M^{\bullet+}$ - CMe_3 - HSC_2H_5, 22.5), 488 ($M^{\bullet+}$ - SC_2H_5 - SC_2H_5, 41.0), 487 ($M^{\bullet+}$ - HSC_2H_5 - SC_2H_5, 100).

Methyl 12(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-14-oxo-5(*Z*),8(*Z*),10(*E*)-tetradecatrienoate (11). To a well-stirred solution of silver nitrate (0.24 g, 3.1 equiv) and *N*-chlorosuccinimide (0.176 g, 3.1 equiv) in acetonitrile–water (3:1 v/v, 5.5 mL) at −10 °C was added a solution of the thioacetal **10** (250 mg, 0.41 mmol) in acetonitrile (1.2 mL). The resulting mixture was stirred at −10 °C for 10 min, and then Me_2SO (0.1 mL) was added. After a further 10 min at −10 °C, 15 mL of methylene chloride and 15 mL of 25% aqueous ammonium acetate were added. The mixture was filtered through a pad of Celite, washing with methylene chloride (100 mL) and 25% aqueous ammonium acetate (50 mL). The filtrate was partitioned, and the aqueous phase was extracted with methylene chloride (3 × 50 mL). The combined organic phases were washed with brine (50 mL) and dried over anhydrous sodium sulfate at 0 °C for 15 min. Removal of the solvent in vacuo at 25 °C afforded the crude aldehyde. Purification by short-column chromatography (1.5 × 13 cm, 10:1 (v/v) petroleum ether–ethyl acetate) gave the desired aldehyde **11** as a yellow oil: 125 mg (61%); IR ($CHCl_3$, cm^{-1}) 1725 (CH=O); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (s, 9 H, CMe_3), 1.64 (m, 2 H, C$_3$-H), 2.00 (m, 2 H, C$_4$-H), 2.26 (t, 2 H, C$_2$-H), 2.50 (m, 2 H, C$_{13}$-H), 2.72 (br t, 2 H, C$_7$-H), 3.60 (s, 3 H, OCH$_3$), 4.67 (q, 1 H, C$_{12}$-H), 5.30 (m, 3 H, C$_{5,6,8}$-H), 5.60 (q, 1 H, C$_{11}$-H), 5.82 (br t, 1 H, C$_9$-H), 6.22 (q, 1 H, C$_{10}$-H), 7.32 (m, 6 H, Ar-H), 7.62 (m, 4 H, Ar-H), 9.66 (t, 1 H, CHO); MS [*m/e* (70 eV, %)] 504 ($M^{\bullet+}$, 1.0), 473 ($M^{\bullet+}$ - OCH$_3$, 9.3), 447 ($M^{\bullet+}$ - CMe_3, 48.0), 225 ($Ph_2Si^+OCHCH_2$, 63.2), 199 (Ph_2Si^+OH, 100).

Methyl 12(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-5(*Z*),8(*Z*),10(*E*),14(*Z*)-eicosatetraenoate (14). To a solution of 1-hexylidenetriphenylphosphonium bromide (111 mg, 1.5 equiv) in THF (1.5 mL) at room temperature was added *n*-BuLi (1.6 M, 162 μL). After 15 min the red-orange solution was cooled to −78 °C and a solution of the aldehyde **11** in THF (1 mL) was added. After 15 min, the reaction mixture was allowed to warm to room temperature and 25% aqueous ammonium acetate (5 mL) was added. The resulting mixture was diluted with water (10 mL) and extracted with ether (2 × 50 mL). The combined ether extracts were washed with brine (20 mL) and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure. Flash chromatography of the residue (25:1 (v/v) petroleum ether–ethyl acetate) afforded the Wittig adduct **14**: 41 mg (42%,

yield not optimized); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (br t, 3 H, C_{20}-H), 1.03 [s, 9 H, $C(CH_3)_3$], 1.21 (m, 6 H, $C_{17,18,19}$-H), 1.66 and 1.86 (2 m, 4 H, C_3-H, C_{16}-H), 2.05 (m, 2 H, C_2-H), 2.25 (m, 4 H, $C_{4,13}$-H), 2.75 (br t, 2 H, C_7-H), 3.61 (s, 3 H, OCH_3), 4.20 (br q, 1 H, C_{12}-H), 5.18–5.41 (m, 5 H, $C_{5,6,8,14,15}$-H), 5.60 (dd, 1 H, $J_{11,10}$ = 14.3 Hz, $J_{11,12}$ = 7.0 Hz, C_{11}-H), 5.86 (br t, 1 H, $J_{9,8}$ = 10.7 Hz, $J_{9,10}$ = 14.2 Hz, C_9-H), 6.21 (dd, 1 H, $J_{10,11}$ = 14.3 Hz, $J_{10,9}$ = 14.2 Hz, C_{10}-H); MS [*m/e* (70 eV, %)] 572 ($M^{\bullet+}$ 0.2), 515 ($M^{\bullet+}$ – CMe_3, 10.0), 461 [$M^{\bullet+}$ – $CH_2CH{=}CH(CH_2)_4CH_3$, 100].

Methyl 12(*S*)-Hydroxy-5(*Z*),8(*E*),10(*E*),14(*Z*)-eicosatetraenoate (15). The mixture of **14** (40 mg, 0.07 mmol) and tetra-*n*-butylammonium fluoride trihydrate (46.7 mg, 1.9 equiv) in THF (1.5 mL) was heated at 45 °C for 4 h. The reaction mixture was diluted with water (50 mL) and extracted with ether (3 × 50 mL). The combined extracts were dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure. Flash chromatography of the residue (10:1 (v/v) petroleum ether–ethyl acetate) gave the desired product, 20 mg (90%). Further purification by standard-phase HPLC (μ-Porasil column, 7.5% ethyl acetate in hexanes) afforded the optically pure methyl ester of 12(*S*)-HETE **15**: $[\alpha]^{22}_D$ +1.3° (*c* 0.3, $CHCl_3$); UV (MeOH) λ_{max} 234 nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3 H, *J* = 7.0 Hz, C_{20}-H), 1.34 (m, 6 H, $C_{17,18,19}$-H), 1.74 (m, 2 H, C_3-H), 1.95 (br s, OH), 2.13 (m, 4 H, C_{13}-H, C_{16}-H), 2.36 (t, 4 H, C_2-H, C_4-H), 2.97 (t, 2 H, *J* = 7.0 Hz, C_7-H), 3.74 (s, 3 H, CO_2CH_3), 4.27 (m, 1 H, C_{12}-H), 5.37–5.50 (m, 4 H, $C_{5,6,8,15}$-H), 5.61 (m, 1 H, C_{14}-H), 5.77 (dd, 1 H, $J_{10,11}$ = 15 Hz, $J_{11,12}$ = 7.2 Hz, C_{11}-H), 6.02 (t, 1 H, *J* = 12 Hz, C_9-H), 6.59 (dd, 1 H, $J_{10,11}$ = 15 Hz, $J_{9,10}$ = 11.1 Hz, C_9-H); MS [*m/e* (70 eV, %)] 316 ($M^{\bullet+}$ – H_2O, 3.2), 303 ($M^{\bullet+}$ – OCH_3, 2.4), 223 [$M^{\bullet+}$ – $CH_2CH{=}CH(CH_2)_4CH_3$, 44.4], 141 [$M^{\bullet+}$ – 223, loss of $MeO_2C(CH_2)_3CH{=}CHCH_2CH{=}CHCH{=}CH$, 10.0], 191 (223 – CH_4O, 33.2), 107 (191 – 84, 100).

Methyl 9(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-11,11-bis(ethylthio)-5(*Z*),7(*E*)-undecadienoate (18). To a stirred solution of the ylide **17** generated by treatment of (4-carboxybutyl)triphenylphosphonium bromide (1.860 g, 4.30 mmol) with LiHMDS (8.62 mmol) in THF (10 mL) and HMPA (2.5 mL) at 0 °C for 1.5 h, at –78 °C, was added a solution of the aldehyde **5** (1.10 g, 2.33 mmol) in THF (5 mL) over 5 min. After stirring at –78 °C for 5 min, the reaction mixture was allowed to warm to room temperature. After a further 4 h, sodium bicarbonate (387 mg, 3 equiv) was added, followed by dimethyl sulfate (1 mL, 3 equiv). The resulting mixture was stirred at room temperature for 2.5 h and diluted with water (100 mL). It was then extracted with ether (3 × 100 mL), and the combined extracts were dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure. Flash chromatography of the residue (5% ethyl acetate in hexanes) afforded the desired ester **18**: 950 mg (72%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (s, 9 H, CMe_3), 1.13 (t, 3 H, SCH_2CH_3), 1.15 (t, 3 H, SCH_2CH_3), 1.66 (m, 2 H, C_4-H), 1.88 (m, 1 H, C_{13}-H), 2.01 (m, 3 H, C_{13}-H, C_3-H), 2.30 (t, 2 H, C_2-H), 2.51 (2 t, 4 H, SCH_2CH_3), 3.64 (s, 3 H, OCH_3), 3.81 (br t, 1 H, C_{11}-H), 5.26 (br q, 1 H, C_5-H), 5.50 (q, 1 H, C_8-H), 5.85 (br t, 1 H, C_6-H), 6.02 (br q, 1 H, C_7-H).

Methyl 9(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-11-oxo-5(*Z*),7(*E*)-undecadienoate (19). To a stirred solution of silver nitrate (241 mg, 3 equiv) and *N*-chlorosuccinimide (190 mg, 3 equiv) in acetonitrile (7 mL) and water (2 mL) at –10 °C was added a solution of the thioacetal **18** (270 mg, 0.474 mmol) in acetonitrile (2 mL). After stirring at –10 °C for 10 min, the reaction mixture was diluted with 25% aqueous ammonium acetate (50 mL) and methylene chloride (50 mL). The mixture was filtered through Celite, washing with water (25 mL) and methylene chloride (150 mL). The filtrate was partitioned. The organic phase was washed with 25% aqueous ammonium acetate (25 mL) and brine (25 mL) and dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure. Flash chromatography of the residue (15% ethyl acetate in petroleum ether) afforded the desired aldehyde **19**: 160 mg (73%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (s, 9 H, CMe_3), 1.66 (m, 2 H, C_4-H), 2.04 (br q, 2 H, C_3-H), 2.26 (t, 2 H, C_2-H), 2.55 (m, 2 H, C_{10}-H), 3.66 (s, 3 H, OCH_3), 4.70 (m, 1 H, C_9-H), 5.30 (br q, 1 H, C_5-H), 5.64 (q, 1 H, C_8-H), 5.88 (br t, 1 H, C_6-H), 6.23 (br q, 1 H, C_7-H), 7.40 (m, 6 H, Ar-H), 7.66 (m, 4 H, Ar-H), 9.72 (br s, CH=O); MS [*m/e* (70 eV, %)] 464 ($M^{\bullet+}$, 0.1), 225 ($Ph_2Si^+OCHCH_2$, 61.2), 199 (Ph_2Si^+OH, 100).

Methyl 9(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-5(*Z*),7(*E*),11(*Z*),14(*Z*)-eicosatetraenoate (21). To a stirred solution of the phosphorane **20** generated by treatment of (*Z*)-3-non-3-en-1-yltriphenylphosphonium iodide (397 mg, 0.772 mmol) in THF (5 mL) with *n*-BuLi (1.6 M, 404 μL, 2 equiv) at 0 °C for 1 h, at –78 °C, was added a solution of the aldehyde **19** in THF (2 mL). The resulting mixture was stirred at –78 °C for 1 h and then at 0 °C for 15 min. The reaction mixture was diluted with 25% aqueous ammonium acetate (50 mL) and extracted with ether (3 × 150 mL). The combined extracts were dried over anhydrous magnesium sulfate. Removal of solvent and purification by flash chromatography (3% ethyl acetate in petroleum ether) afforded the Wittig adduct **21**: 135 mg (73%, *Z*:*E* at Δ^{11} ~ 98:2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (t, 3 H, C_{20}-H), 1.02 [s, 3 H, $C(CH_3)_3$], 1.26 (m, 6 H, $C_{17,18,19}$-H), 1.66 (m, 2 H, C_3-H), 1.86–2.10 (m, 4 H, $C_{10,16}$-H), 2.24 (t, 4 H, $C_{2,4}$-H), 2.56 (m, 2 H, C_{13}-H), 3.64 (s, 3 H, OCH_3), 4.20 (m, 1 H, C_9-H), 5.20–5.42 (m, 5 H, $C_{5,11,12,14,15}$-H), 5.59 (dd, 1 H, $J_{8,7}$ = 15.6 Hz, $J_{8,9}$ = 6.2 Hz, C_8-H), 5.88 (t, 1 H, $J_{6,7}$ = 10.8 Hz, C_6-H), 6.17 (dd, 1 H, $J_{7,6}$ = 10.8 Hz, $J_{7,8}$ = 15.6 Hz, C_7-H), 7.34 (m, 6 H, *m,p*-Ar-H), 7.64 (m, 4 H, OArH); MS [*m/e* (70 eV, %)] 515 ($M^{\bullet+}$ – $C(CH_3)_3$, 1.5], 421 [$M^{\bullet+}$ – $CH_2CH{=}CHCH_2CH{=}CH(CH_2)_4CH_3$, 21], 199 ($Ph_2Si^+OH$, 100).

Methyl 9(*S*)-Hydroxy-5(*Z*),7(*E*),11(*Z*),14(*Z*)-eicosatetraenoate (22). To a liquid of tetra-*n*-butylammonium fluoride (2.3 equiv) at room temperature was added a solution of the silyl ether **21** (115 mg, 0.201 mmol) in THF (5 mL). The resulting mixture was stirred at 45 °C for 2.5 h. The reaction mixture was filtered through a pad of silica gel (Merck 60F), washing with 20% ethyl acetate in hexanes (~50 mL). The solvents were removed at reduced pressure. After purification by flash chromatography (20% ethyl acetate in petroleum ether) and HPLC (Microporasil column, 20% ethyl acetate in hexanes), the pure 9(*S*)-HETE methyl ester **22** was obtained: 48 mg (72%); $[\alpha]^{22}_D$ –7.1° (*c* 2.05, $CHCl_3$); UV (CH_3OH) λ_{max} 231 nm, 212 (sh); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, 3 H, C_{20}-H), 1.30 (m, 6 H, $C_{17,18,19}$-H), 1.73 (m, 3 H, OH, C_3-H), 2.03 and 2.25 (m, 4 H, C_{10}-H and C_{16}-H), 2.33 (t, 4 H, $C_{2,4}$-H), 2.81 (br q, 2 H, C_{13}-H), 3.68 (s, 3 H, OCH_3), 4.23 (br s, 1 H, C_9-H), 5.35–5.85 (m, 5 H, $C_{5,11,12,14,15}$-H), 5.71 (dd, 1 H, $J_{8,7}$ = 14.3 Hz, $J_{8,9}$ = 6.3 Hz, C_8-H), 6.03 (t, 1 H, $J_{6,7}$ = 11.1 Hz, C_6-H), 6.44 (dd, 1 H, $J_{7,6}$ = 11.1 Hz, $J_{7,8}$ = 14.3 Hz, C_7-H); MS [*m/e* (70 eV, %)] (trimethylsilyl ether) 316 ($M^{\bullet+}$ – $HOSiMe_3$, 2.4), 255 [$M^{\bullet+}$ – $CH_2CH{=}CHCH_2CH{=}CH(CH_2)_4CH_3$, 100]; HRMS (*m/z*) for $C_{21}H_{32}O_2$ (M^+ – H_2O), calcd 316.240, found 316.249.

Methyl 8(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-9,10-(isopropylidenedioxy)-5(*Z*)-decenoate (25). To a stirred solution of (4-carboxybutyl)triphenylphosphonium bromide (3 g, 6.767 mmol) in THF (12 mL) and HMPA (3 mL) at 0 °C was added a solution of LiHMDS generated by treatment of 1,1,1,3,3,3-hexamethyldisilazane (2.712 mL, 12.854 mmol) with *n*-BuLi (1.6 M, 7.62 mL, 12.192 mmol) in THF (8 mL) and HMPA (2 mL) over 5 min. After stirring for 30 min at room temperature the deep red ylide **17** was formed.

To a solution of the aldehyde **16** (1.000 g, 2.425 mmol) in THF (10 mL), obtained by hydrolysis of the thioacetal **2**, at –78 °C, was added the above red solution dropwise until red color existed. Stirring continued at –78 °C for 30 min and another 30 min at room temperature. The reaction mixture was diluted with water (150 mL) and methylene chloride (50 mL). The resulting mixture was acidified with aqueous hydrogen chloride (1 N) to pH 4. The mixture was partioned, and the aqueous phase was extracted with methylene chloride (3 × 75 mL). The combined organic phases were dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure. Flash chromatography of the residue (20% ethyl acetate in petroleum ether) gave the desired acid, 680 mg (57%). It was dissolved in methanol (5 mL) and treated with freshly distilled diazomethane in ether (~15 mL) at room temperature. After about 10 min, a few drops of acetic acid were added and the solvents were removed at reduced pressure. The ester **25** (700 mg) was obtained in quantitative yield: MS [*m/e* (70 eV, %)] 453 [$M^{\bullet+}$ – $C(CH_3)_3$, 1.4], 409 ($M^{\bullet+}$ – $ROCH_2CHOR'$, R′ = R = CMe_2, 1.6), 395 (453 – H_3CCOCH_3, 15.9), 199 (Ph_2Si^+OH, 100).

Methyl 8(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-9,10-dihydroxy-5(*Z*)-decenoate (26). The mixture of ester **25** (250 mg, 0.49 mmol) in 4 mL of trifluoroacetic acid–water–THF (1:1:2, v/v)

was stirred at room temperature for 6 h. The reaction mixture was neutralized with sodium carbonate powder, diluted with water (50 mL), and extracted with ether (3 × 50 mL). The combined ether extracts were washed with brine (30 mL) and dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure. Flash chromatography of the residue (1:4:15 (v/v) *i*-PrOH–ethyl acetate–hexanes) afforded the diol **26**: 150 mg (65%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.01 [s, 9 H, $C(CH_3)_3$], 1.54 (m, 2 H, CH_2CH_2CH=CH), 1.80 (m, 2 H, CH_2CH_2CH=CH), 2.16 (m, 4 H, $MeOOCCH_2$, CH_2CHOSi), 3.62 (s, 3 H, OCH_3), 3.54–3.82 (m, 4 H, $SiOCHCH(OH)CH_2OH$), 4.26 (, 2 H, CH=CH), 7.40 (m, 6 H, *m,p*-Ar-H), 7.68 (m, 4 H, OArH).

Methyl 8(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-9-oxo-5(*Z*)-nonenoate (27) and Methyl 8(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-11-oxo-5(*Z*),9(*E*)-undecadienoate (28). To a solution of sodium periodate (492 mg, 3 equiv) in 30% aqueous acetone (3 mL) at room temperature was added a solution of the diol **26** (360 mg, 0.766 mmol) in THF (3 mL) over 2 min. The resulting mixture was stirred at room temperature for 15 min and then filtered through Celite, washing with water (50 mL) and ether (100 mL). The filtrate was partitioned, and the aqueous phase was extracted with ether (2 × 50 mL). The combined ether extracts were washed with brine (50 mL) and dried over anhydrous magnesium sulfate. Removal of solvent at reduced pressure afforded the crude aldehyde **27** [338 mg (100%)] which was mixed with (formylmethylene)triphenylphosphorane (1.1 equiv, 256 mg) in dry benzene (4 mL). The mixture was heated at 80 °C for 9 h and then filtered through a pad of silica gel, washing with ether (50 mL). Removal of the solvent in vacuo and chromatography of the residue (9% ethyl acetate in petroleum ether, Kieselgel 60 HF_{254} from BDH) afforded the desired α,β-unsaturated aldehyde **28**: 260 mg (73% yield based on the diol **26**); $[\alpha]^{22}_D$ +15.3° (*c* 2.9, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.09 [s, 3 H, $C(CH_3)_3$], 1.60 (m, 2 H, $MeOOCCH_2CH_2$), 1.82 (br t, 2 H, CH_2CH=CH), 2.20 (m, 4 H, $MeOOCCH_2$, CH_2CHOSi), 3.65 (s, 3 H, OCH_3), 4.46 (m, 1 H, CHCOSi), 5.33 (m, 2 H, CH_2CH=CHCH$_2$), 6.20 (dd, 1 H, J = 14 Hz, J' = 6.8 Hz, CH=CHCHO), 6.70 (dd, 1 H, J = 14 Hz, J' = 6.0 Hz, CH=CHCHO), 7.39 (m, 6 H, *m,p*-Ar-H), 7.62 (m, 4 H, OArH), 9.46 (d, 1 H, J = 6.8 Hz, CHO); MS [*m/e* (70 eV, %)] 464 ($M^{\bullet+}$, 0.9), 407 ($M^{\bullet+}$ – $C(CH_3)_3$, 100], 323 [$M^{\bullet+}$ – $MeOOC(CH_2)_3CH$=$CHCH_2$, 41.9].

Methyl 8(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-5(*Z*),9(*E*),11(*Z*),14(*Z*)-eicosatetraenoate (29). (a) To a solution of *n*-pentyl bromide (391 mg, 2.586 mmol) in THF (7 mL) at −78 °C was added *tert*-butyllithium (1.7 M, 3.04 mL, 5.172 mmol). The resulting mixture was stirred at −78 °C for 30 min. The reaction mixture was warmed to −50 °C and copper(I) bromide–dimethyl sulfide (311 mg, 1.509 mmol) was added. After the mixture was stirred 1 h, acetylene (58 mL) was bubbled into the solution. Stirring continued for 30 min. Then vinyltriphenylphosphonium bromide (477 mg, 1.293 mmol) was added followed by HMPA (0.7 mL) and stirring continued at −50 °C overnight (~18 h).

To a solution of the α,β-unsaturated aldehyde **28** (200 mg, 0.431 mmol) in THF (1 mL) at −50 °C was added dropwise the above ylide solution, and the resulting mixture was allowed to warm to −20 °C during 1.5 h and then to 0 °C during 1 h. The mixture was diluted with 10% aqueous ammonium chloride (10 mL) and ether (20 mL) and filtered through Celite, washing with ether (100 mL). The combined filtrate was washed with 10% aqueous ammonium chloride (50 mL). The aqueous phase was extracted with ether (100 mL). The combined ethereal phase was washed with brine (20 mL) and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure. Flash chromatography of the residue (3% ethyl acetate in petroleum ether) gave the desired product [130 mg (53%)], which was contaminated with incorporation of two acetylene units.

(b) To a solution of α,β-unsaturated aldehyde **28** (100 mg, 0.216 mmol) in THF (5 mL), at −78 °C, was slowly added a red solution of the ylide **20** generated by treatment of (*Z*)-non-3-en-1-yltriphenylphosphonium iodide (596 mg, 1.160 mmol) with *n*-BuLi (1.6 M, 0.725 mL) in THF (8 mL) at 0 °C for 30 min, until red color existed. The resulting mixture was stirred for 15 min, and a few drops of water were added. The mixture was diluted with chloroform (100 mL) and washed with brine (30 mL) once. The organic phase was dried over anhydrous sodium sulfate, and solvent was removed under diminished pressure. Flash chromatography of the residue (3% EtOAc in hexanes) gave the desired Wittig adduct: 106 mg (86%); MS [*m/e* (70 eV, %)] 572 ($M^{\bullet+}$, 0.1)e, 515 [$M^{\bullet+}$ – $C(CH_3)_3$, 10.9], 431 [$M^{\bullet+}$ – $MeOOC(CH_2)_3CH$=$CHCH_2$, 100], 409 [$M^{\bullet+}$ – CH=CHCH=$CHCH_2CH$=$CH(CH_2)_4CH_3$, 1.2].

Methyl 8(*S*)-Hydroxy-5(*Z*),9(*E*),11(*E*),14(*Z*)-eicosatetraenoate (30). The mixture of the silyl ether **29** (130 mg, 0.227 mmol) and tetra-*n*-butylammonium fluoride dried from its trihydride (143 mg, 0.455 mmol) in THF (5 mL) was heated at 40–45 °C for 5 h. After workup as usual and flash chromatography (5% *i*-PrOH in hexanes), a yellow oil [69 mg (91%)] was obtained. Further purification by HPLC (Porasil, 0.2% *i*-PrOH in hexanes) gave the pure 8(*S*)-HETE methyl ester **30**: 40 mg (53%); $[\alpha]^{22}_D$ −4.75° (*c* 0.4, $CHCl_3$); UV (hexane) λ_{max} 235 nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3 H, C_{20}-H), 1.32 (m, 6 H, $C_{17,18,19}$-H), 1.56 (br s, 1 H, OH), 1.73 (pentet, 2 H, C_3-H), 2.11 (sextet, 4 H, $C_{2,16}$-H), 2.35 (t, 4 H, $C_{4,7}$-H), 2.95 (t, 2 H, C_{13}-H), 3.71 (s, 3 H, OCH_3), 4.23 (q, 1 H, C_8-H), 5.16–5.59 (m, 5 H, $C_{4,5,12,14,15}$-H), 5.72 (dd, 1 H, $J_{9,8}$ = 7.3 Hz, $J_{9,10}$ = 14.5 Hz, C_9-H), 6.00 (br t, 1 H, $J_{11,10}$ = 11.1 Hz, $J_{11,12}$ = 9.7 Hz, C_{11}-H), 6.56 (dd, 1 H, $J_{10,9}$ = 14.5 Hz, $J_{10,11}$ = 11.1 Hz, C_{10}-H); MS [*m/e* (70 eV, %)] (trimethylsilyl ether) 406 ($M^{\bullet+}$, 0.02), 391 ($M^{\bullet+}$ – CH_3, 0.3), 316 ($M^{\bullet+}$ – Me_3SiOH, 0.3), 265 [$M^{\bullet+}$ – $MeO_2C(CH_2)_3CH$=$CHCH_2$, 100], 243 [$M^{\bullet+}$ – CH=CHCH=$CHCH_2CH$=$CH(CH_2)_4CH_3$, 5.2]; HRMS (*m/z* for $C_{21}H_{32}O_4$ (M^+ – H_2O), calcd 316.240, found 316.244.

Methyl 3-Formyl-2,3-*O*-isopropylidene-D-erythrofuranoside (D-Apiose Aldal) and Derivatives

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A practical synthesis of the known 3-formyl-2,3-*O*-isopropylidene-D-erythrofuranose (D-apiose aldal, **2d**) is described. Several selectively protected derivatives and their transformations which allow preferential manipulation of the diastereotopic hydroxymethylene groups of apiose are reported.

A projected convergent synthesis of tetrodotoxin[1] required a suitably modified and protected form of the branched-chain sugar, D-apiose[2] (**1**). The key compound in this study is dialdehyde **2** in which the *pro-R* CH_2OH

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