Synthesis of (*R,S*)-(5*Z*,8*E*,10*E*)-12-Hydroxyheptadeca-5,8,10-trienoic Acid and of (*R,S*) and (*S*)-(5*Z*,8*Z*,10*E*,14*Z*)-12-Hydroxyeicosa-5,8,10,14-tetraenoic Acid and their Racemic 5,6,8,9-Tetradeuterioisomers

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(5*Z*,8*Z*,10*E*,14*E*)-12-Hydroxyeicosa-5,8,10,14-tetraenoic acid [(S) and (*R,S*)-enantiomers], (*R,S*)-(5*Z*,8*Z*,10*E*,-14*Z*)-12-hydroxy-5,6,8,9-tetradeuterio-5,8,10,14-tetraenoic acid, (*R,S*)-(5*Z*,8*E*,10*E*)-12-hydroxyheptadeca-5,8,10-trienoic acid, and (*R,S*)-(5*Z*,8*E*,10*E*)-12-hydroxy-5,6,8,9-tetradeuterioheptadeca-5,8,10-trienoic acid have been prepared by total synthesis. Deuterium was introduced at selected sites by partial reduction. All the acids were prepared from the common intermediate ethyl 10,10-diethoxydeca-5,8-dienoate. The c.d. spectrum of (*S*)-(7h) confirmed its identity with the natural product.

The mechanism of the reaction of heptynyl-lithium with (*S*)-1-chloro-2,3-epoxypropane has been shown to be by attack on the epoxide group, with subsequent recyclisation of the chloroalkoxide to give (*S*)-1,2-epoxydec-4-yne.

DURING aggregation, blood platelets release (*S*)-(5*Z*,8*E*,10*E*)-12-hydroxyheptadeca-5,8,10-trienoic acid [(HHT) (*S*)-(13h)] and (*S*)-(5*Z*,8*Z*,10*E*,14Z)-12-hydroxyeicosa-5,8,10,14-tetraenoic acid [(HETE)] (*S*)-(7h) both of which are derived from arachidonic acid.[1,2] In our laboratory, because of interest in blood platelet behaviour, either g.l.c.–m.s. or h.p.l.c. have been applied to the determination of nanogram quantities of these hydroxy-acids. Although they can be prepared in submilligram quantities by biosynthesis from arachidonic acid, for the development of more reliable assays and as a check on the procedures involved, larger amounts (20—50 mg) were required. We thus undertook the syntheses of HHT and HETE in which either hydrogen or deuterium atoms were incorporated at selected sites.

METHODS AND RESULTS

The structural differences between HHT and HETE lie on either side of the C(10)–C(11) bond so it seemed most logical to build up the two different sides separately then join them, as Corey had done, with a Wittig reaction.[3]

Corey's elegant synthesis of (*S*)-HETE[3] made use of more than one Wittig reaction but in our experience these are seldom more than 85% stereoselective. We thus looked for a route in which catalytic hydrogenation could be employed to introduce the double bonds. Not only did we have considerable experience with this reaction but we could be sure the stereospecificity was >95%. These considerations, coupled with the request from our biologists to prepare not only racemic HETE and HHT but also the same compounds containing four deuterium atoms between C(3) and C(10) of the molecules, led us to a scheme by which the C(1) to C(10) fragment of all the compounds could be prepared from the same intermediate by hydrogenation or deuteriation (Scheme 1).

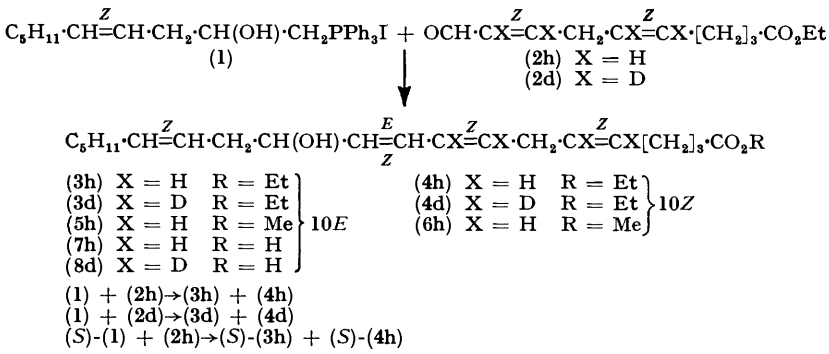
The Wittig Salts.—The preparation of the unsaturated epoxide (17) by reaction of hept-1-yne (14), diethylmagnesium, and 1-chloro-2,3-epoxypropane (15) followed by base extraction of hydrogen chloride from the intermediate chloro-compound (16) has been reported earlier.[4] In the meantime, it was discovered that in liquid ammonia heptynyl-lithium reacted with 1-chloro-2,3-epoxypropane to give the same epoxide (17) directly. This is in complete contrast to the reaction of sodium alkynes with chloro-epoxyalkanes which furnish alkyl-2-en-4-yn-1-ols.[5]

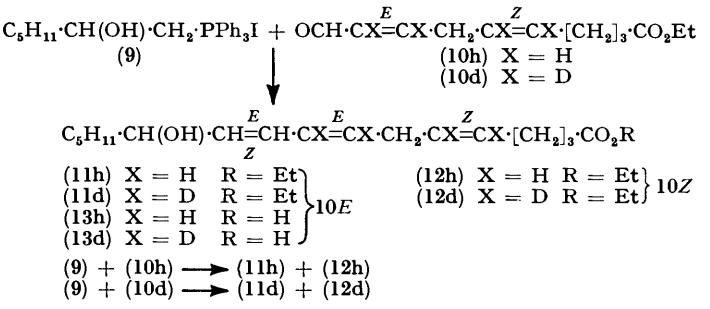
Although we were uncertain of the mechanism we felt intuitively that it followed the same pathway as the diethylmagnesium reaction, the heptynyl-lithium attacking the epoxide with subsequent elimination of lithium chloride from the intermediate lithium alcoholate. Our first priority, however, was to determine whether this route would give the desired racemic Wittig salt (1). Since the idea of reducing an acetylenic Wittig salt was unattractive we reduced the acetylenic epoxide (17) directly to the *Z*-olefinic epoxide (18) which was converted into the iodo-hydroxyalkene (19) by means of sodium iodide in acetic and propionic acids.[6] Reaction of this with triphenylphosphine in benzene at 45 °C [3] afforded the desired racemic phosphonium salt (1) as an oil which on trituration with ether followed by evacuation became solid and melted without decomposition at 111—112 °C.

We then turned our attention to the synthesis of the chiral Wittig salt (*S*)-(1), corresponding to (*S*)-HETE. For this route, chiral 1-chloro-2,3-epoxypropane was required and if our contention that attack occurred on the epoxide group was correct then we needed the (*S*)-form. This we prepared by the route of Baldwin *et al.*[7] which is shown in Scheme 2.

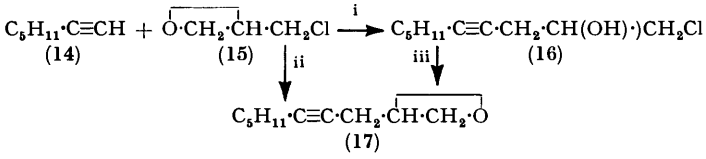
Starting from D-mannitol (20) the diacetonide (21) was made by the method of Baer [8] with improvements by Bird and Chadha.[9] The conversion of this into (*S*)-1-chloro-2,3-epoxypropane (*S*)-(15) is a cumbersome although reliable synthesis. Our first attempt gave us material with an optical purity of only 10%, probably due to racemization during subsequent distillation.[10] On a second run the optical purity was 88% although the published procedure was followed carefully.[7]

The absolute configuration of the reaction product of (*S*)-1-chloro-2,3-epoxypropane with heptynyl-lithium was determined by reducing it with hydrogen over P2

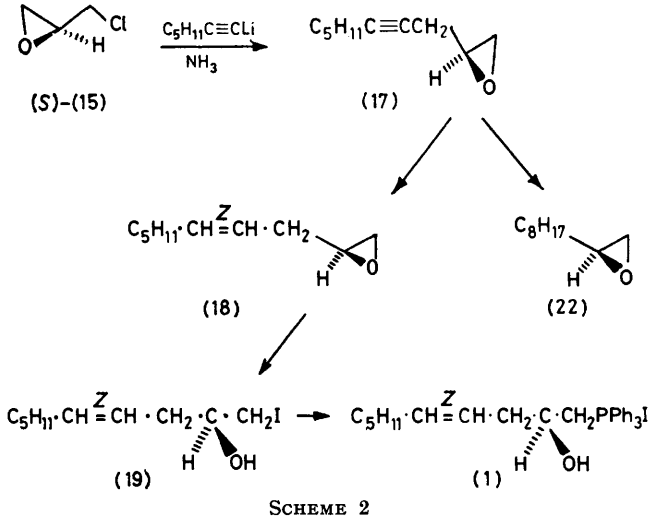




SCHEME 1

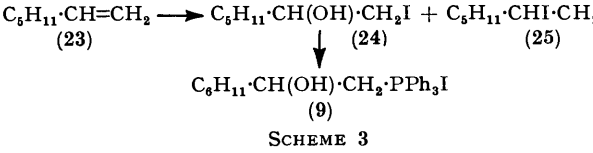


nickel boride [11] to give 1,2-epoxydecane (22) which had a negative optical rotation. Although the compound itself has not been reported, the (*S*) antipodes of both 1,2-epoxytridecane and 1,2-epoxybutane have been shown to have negative rotations,[12] thus substantiating our premise that attack occurs at the epoxide carbon atom as shown in Scheme 2. Although McClure *et al.* have studied the reaction of chiral 1-chloro-2,3-epoxypropane with nucleophiles [13] this type of reaction was not directly deducible from his results although it follows the general trend. The product we obtained had an optical purity of 76% showing the reaction to be only 94% stereospecific. The compound was converted into the optically active Wittig salt (*S*)-(1) analogously to the racemic compound. The salt exhibited twice the expected number of aromatic protons in the ^{1}H n.m.r. spectrum although the preparation had not differed in any obvious way from that of the racemic compound (1). We suppose that the triphenylphosphine had extracted the elements of hydrogen iodide from the iodo-hydroxyalkane giving an almost exactly equimolar mixture of Wittig salt and triphenylphosphine hydrogen iodide.



SCHEME 2

The Wittig salt (9) for the preparation of racemic HHT (13 h) and its tetradeuterio-analogue (13d) was prepared as shown in Scheme 3.



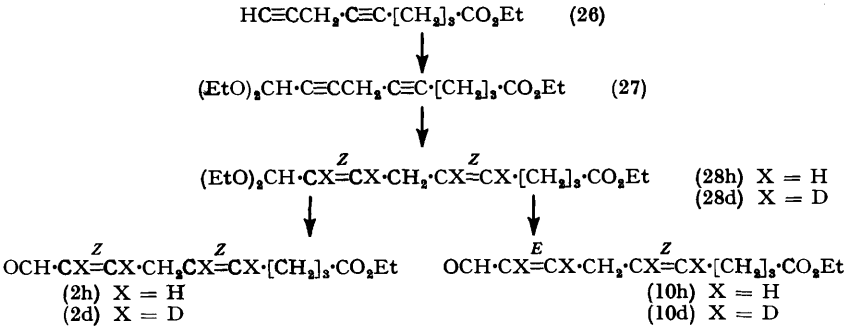
SCHEME 3

Hept-1-ene (23) was treated with mercuric oxide and iodine in moist ether to give a mixture of 1-iodoheptan-2-ol

(24) and 2-iodoheptan-1-ol (25) in which the desired one (24) predominated. Separation was effected on a column of silica, although there were considerable losses due to the instability of the product. Our success with the conversion of epoxide into iodohydroxyalkane indicates this to be the method of choice. Conversion into the Wittig salt (9) also gave a salt with twice as many protons in the aromatic region as predicted.

To determine what sort of mixture it could be, a known weight was titrated with methyl-lithium in THF following the same principle as for the analysis of organolithium reagents.[14] Since the end-point was not visible an excess of methyl-lithium was added and the end point found by back titration with butan-2-ol in xylene. This gave a value which was in agreement with our suggestion of an equimolar mixture of salt and triphenylphosphine hydrogen iodide.

Aldo Ester End-group. Starting from ethyl nona-5,8-dynoate (26) [15] the aldehydes required for the Wittig coupling were prepared as outlined in Scheme 4.



SCHEME 4

Reaction of the terminal acetylene with triethyl orthoformate and zinc iodide as catalyst gave the diacetal (27) in poor yield. This can be attributed to the skipped diyne system as the same reaction with ethyl nona-8-ynoate had previously afforded the acetal in >80% yield.[16] Reduction with hydrogen and deuterium separately over Lindlar's catalyst gave the corresponding di-*Z*-acetal esters (28 h) and (28 d). Mild hydrolysis (aqueous oxalic acid in acetone, 0 °C, 10 min) gave the di-*Z*-aldo-esters necessary for the HETE series whilst under more forcing conditions (aqueous oxalic acid in acetone, 20 °C, 2 days) the 8*Z* bond was isomerized to the 8*E* isomer and gave the *Z*–*E* aldo-esters (10h) and (10d) necessary for the HHT series. Thus from the same starting material (27) we were able to prepare all the aldehydes necessary for all the Wittig coupling reactions.

We also explored the method used by Corey; [3] manganese dioxide oxidation of the corresponding alcohol: $HOCH_2{\cdot}CH{=}CH{\cdot}CH_2{\cdot}CH{=}CH[CH_2]_3{\cdot}CO_2Me$ (29). In our hands it was an impractical reaction; the manganese dioxide is extremely voluminous and large losses due to absorption occur. This is particularly difficult when a fast reaction is required (thus a large excess of oxidant) and the product must be removed quickly from the reaction to avoid *Z*–*E* isomerisation. For this reason we switched to the hydrolysis of the acetal which is both controllable and easy to follow on t.l.c., the *E* compound being more polar than the *Z*.

Wittig Coupling.—This reaction was carried out five times in the way Corey described.[3] The Wittig salt was treated with two equivalents of methyl-lithium in THF (or three equivalents in those cases where ^1H n.m.r. had indicated twice the expected number of aromatic protons) and the oxido-ylide formed treated with the corresponding aldehyde. The elimination of triphenylphosphine oxide was accelerated by addition of hexamethylphosphoric amide, and the products subjected to careful column chromatography. In all cases the products with the newly formed bond were *Z*–*E* mixtures. Whilst in the HETE series they were difficultly separable, in the HHT series they were still closer in polarity, and samples of the desired compounds (11h) and (11d) were contaminated with the 10*Z*-isomers (12h) and (12d) respectively. Although the ^1H n.m.r. spectra of the ethyl ester of both racemic and (*S*)-HETE (3h) agreed reasonably with that of Corey's methyl ester,[3] the u.v. spectra gave extinction coefficients considerably lower. Seven different compounds had values all of which lay between 19 400 and 26 000 (lit.,[3] 32 800).

A more fundamental discrepancy was noted in the optical rotation of the (*S*)-HETE methyl ester, (*S*)-(5h). We initially measured that of the ethyl ester (*S*)-(3h) and were unable to find a measurable value (although ^1H n.m.r. had shown it to be 76% optically pure). We then converted it into the methyl ester (*S*)-(5h), thus having the identical compound to that of Corey.[3] We now found a small but negative rotation $[\alpha]_D^{23}$ −0.5° (*c* 5.0, $CHCl_3$). This suggested we were in the (*R*), series as Corey had reported [3] $[\alpha]_D^{25}$ + 1.50° (*c* 0.2, $CHCl_3$)*. However, we had c.d. data on natural (S)-HETE methyl ester, (*S*)-(5h).[17] Comparison of the spectra run in EPA † at −185 °C showed that both had strong negative Δε values indicating our material must have the same absolute configuration as the natural (*S*)

* The concentration at which this was measured seems a little low; on our instrument this would represent a deflection of *ca.* 0.001° which is beyond its capabilities.

† EPA is a mixture of isopentane, diethyl ether, and ethanol (5:5:2, v/v/v) which remains liquid at low temperatures. In the values reported account has been taken of the shrinkage of solvent with temperature.[17]

enantiomer. If the 10*Z*-isomer was present (from which our material had been rigorously separated) it could be causing a change in the sign of rotation. We therefore purified our sample of (*S*)-10*Z*-HETE ethyl ester (*S*)-(14h) and converted it into the corresponding methyl ester (*S*)-(6h). This material had an even stronger negative rotation $[\alpha]_D^{23}$ − 2.06° (*c* 5.4, $CHCl_3$) which excludes the possibility of it being a contaminant in Corey's sample.

In all cases the hydrolyses of the ethyl esters gave the acids in almost quantitative yields with no tendency for double bond migration.

EXPERIMENTAL

I.r. spectra were run on a Perkin-Elmer 580 spectrophotometer as liquid films between KBr plates. U.v. spectra were obtained from solutions in ethanol on a Unicam SP 1 800 U.V. spectrophotometer. Specific rotations were measured on a Carl Zeiss LEP A2 polarimeter with cells of length 5 cm. C.d. values were obtained on a Jobin Yvon Dichrographe III. ^{1}H N.m.r. spectra were recorded on a Varian EM 360 (60 MHz), Bruker WP 200 (200 MHz) or a Varian SC 300 (300 MHz), the optical purities (defined as [*S*-enantiomer] − [*R*-enantiomer]/[*S*-enantiomer] + [R-enantiomer]) were measured after the addition of the optically active shift reagent tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III). Mass spectra were measured on an AEI MS 902 mass spectrometer at 70 eV and a source temperature of 200 °C.

(S)-1-*Chloro*-2,3-*epoxypropane*, (*S*)-(15).—(*R*)-3-Tosyloxypropane-1,2-diol, m.p. 49—57 °C, $[\alpha]_D^{23}$ − 9.06° (*c* 6.34, MeOH) {lit.,[7] m.p. 54—59 °C, $[\alpha]_D^{D}$ − 9.3° (*c* 4.99, MeOH)} (49.2 g) was added all at once to a solution of triphenylphosphine (52.8 g) in CCl_4 (80 ml) and DMF (200 ml), both of these solvents having been dried by passage through a short column of alumina. After the addition the temperature was raised to 50 °C over 15 min. The mixture was then stirred for 3 h after which the DMF was distilled off at 50 °C/< 100 Pa and the residue taken up in water and extracted with CH_2Cl_2. The extracts were washed with saturated NaCl solution, dried (Na_2SO_4), evaporated, and then evacuated (18 h at 70 Pa) to leave 104.95 g of brown oil containing triphenylphosphine oxide and (*S*)-1-chloro-3-tosyloxypropan-2-ol.

Sodium 2-hydroxyethoxide was prepared from sodium (6.1 g, very small pieces) and ethylene glycol (180 ml, dry). The above brown oil was dissolved in ethylene glycol (180 ml, dry) and added to the sodium 2-hydroxyethoxide solution. After being stirred for 5 min the mixture was evacuated at < 100 Pa and everything distilling at room temperature was trapped in a CO_2–acetone bath. On warming the contents of the trap to *ca.* −30 °C a clear liquid was obtained with white floating ' blobs ' in it. The liquid was pipetted off (10.3 g) to leave *ca.* 400 mg of mainly ethyleneglycol (i.r.). I.r. of the main distillate indicated it to be 1-chloro-2,3-epoxypropane with a trace of CH_2Cl_2 and water; $[\alpha]_D^{23}$ + 24.62° (pure) {lit.,[8] $[\alpha]_D^{20}$ 28.1° (*c* 2.47, CH_3OH)}; δ (60 MHz, $CDCl_3$) 2.71 (1 H, dd, *J* 5.0 Hz, *J* 2.5 Hz, 1-H), 2.92 (1 H, t, *J ca.* 4.5 Hz, 1-H), 3.28 (1 H, c, 2-H), and 3.61 (2 H, c, 2-H); optical purity was 88%.

1,2-*Epoxydec*-4-*yne* (17).—Lithium metal (2.4 g 0.34 g-atom) was added to distilled ammonia (350 ml) and a trace of ferric nitrate. When the reaction was complete hept-1-yne (35 g, 0.36 mol) was added during 2 min. After the mixture had been stirred for 15 min 1-chloro-2,3-epoxypropane (50 g, 0.54 mol) was added quickly and stirring was continued for 3.5 h. Ether (200 ml) was added and the mixture allowed to evaporate overnight. Ice and water were then added and the mixture made acid by addition of NH_4Cl. The mixture was filtered through Hyflo and the layers separated.

The aqueous phase was extracted twice with ether and the combined organic phases washed with $NaHCO_3$ solution and saturated NaCl solution and then dried (Na_2SO_4) and evaporated to leave an orange oil (47.2 g) which was distilled to give the acetylenic epoxide (34.2 g, 66%) as a colourless oil, b.p. 93—99 °C/1.2 kPa. A centre fraction had $n_D^{23.5}$ 1.4541. The i.r. and ^{1}H n.m.r. spectra were in agreement with those reported previously;[4] *m/e* 152,151 (*P* and *P* − 1), 137 (*P* − 15), 109 (*P* − 43), 96, 95, 81, 79, 67, and 53.

Similarly (*S*)-1,2-epoxydec-4-yne, (*S*)-(17), was prepared from lithium (0.35 g), hept-1-yne (5.75 g), and (*S*)-1-chloro-2,3-epoxypropane (4.7 g, optical purity 94%). The crude product obtained (5.4 g) was chromatographed on silica using a gradient elution of 0 to 15% ether in light petroleum. This gave the epoxide (4.0 g) as a pale yellow oil. A small sample (600 mg) was distilled, b.p. (oil-bath) 80—87 °C/500 Pa $[\alpha]_D^{23}$ + 30.2° [*c* 4.37, hexane] + 31.1° [*c* 1.56 hexane]. G.l.c. indicated it to be only one compound; δ (200 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 6.8 Hz, 10-H), 1.1—1.4 (4 H, c, 8-, 9-H), 1.48br (2 H, quintet, *J ca.* 6.5 Hz, 7-H), 2.14 (2 H, tt, *J* 6.8 Hz, *J* 2 Hz, 6-H), 2.40 (1 H, ddt, *J* 17.0 Hz, *J* 5.0 Hz, *J* 2.3 Hz, 3-H), 2.58 (1 H, ddt, *J* 17.0 Hz, *J* 4.3 Hz, *J* 2.0 Hz, 3-H), 2.63 (1 H, dd, *J* 4.8 Hz, *J* 2.5 Hz, 1-H), 2.75br (1 H, t, *J ca.* 4.5 Hz, 1-H), and 3.05 (1 H, c, 2-H). The optical purity was 76%.

Z-1,2-*Epoxydec*-4-*ene* (18).—1,2-Epoxydec-4-yne (10.0 g) was hydrogenated over Lindlar's catalyst (1.0 g) in light petroleum (b.p. 40—60 °C) in the presence of quinoline (0.3 g) at atmospheric pressure. After uptake of one equivalent of hydrogen the reaction ceased and the mixture was filtered through silica gel to remove catalyst. Evaporation of the residue left a colourless oil (9.4 g). G.l.c. indicated a purity of >95%. A small sample was bulb-to-bulb distilled and had b.p. (oil-bath) 90—95 °C/1.6 kPa, n_D^{24} 1.4438; $\nu_{max.}$ 3 058 and 840 cm^{-1} (epoxy); 3 010, 1 660, and 720 cm^{-1} (*Z*-unsaturation); *m/e* 154 (*P*), 136 (*P* − 18), 123 (*P* − 31) 110 (*P* − 44) (200 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 6.5 Hz, 10-H), 1.1—1.5 (6 H, c, 7-, 8-, 9-H), 2.25 (1 H, dt, *J* 15.0 Hz, *J ca.* 6 Hz, 3-H), 2.40 (1 H, dt, *J* 15.0 Hz, *J ca.* 6 Hz, 3-H), 2.50 (1 H, dd, *J* 5.0 Hz, *J* 2.8 Hz, 1-H), 2.72br (1 H, t, *J ca.* 4 Hz, 1-H), 2.92 (1 H, c, 2-H), 5.38 (1 H, dt, *J* 10.5 Hz, *J* 7.0 Hz, 5-H, tentative assignment), and 5.52 (1 H, dt, *J* 10.5 Hz, *J* 7.0 Hz, 4-H tentative assignment).

Similarly (*S*)-*Z*-1,2-epoxydec-4-ene, (S)-(18), was prepared from (*S*)-1,2-epoxydec-4-yne (3.5 g), Lindlar's catalyst (400 mg), and quinoline (2 drops) by hydrogenation in light petroleum (15 ml). The product obtained (2.5 g) was slightly yellow and a small sample (550 mg) was distilled, b.p. 75—80 °C (oil-bath)/500 Pa as a colourless oil. G.l.c. indicated only one peak; $[\alpha]_D^{23}$ + 3.50° [*c* 1.88, hexane]. Optical purity was 76%.

(S)-1,2-*Epoxydecane* (22).—P2 Nickel was prepared by adding 5 ml from a filtered solution of $NaBH_4$ (4 g), aqueous NaOH (5 ml; 2 mol/l), and ethanol (95 ml) to nickel acetate tetrahydrate (1.25 g) dissolved in 95% methanol (50 ml). (*S*)-1,2-Epoxy-4-decyne [58% (+) and 42% (−)] (1.5 g, 0.01 mol) was added and hydrogenation carried out at

atmospheric pressure. The reaction stopped after two molar equivalents had been taken up. After filtration the filtrate was taken up in water and extracted with pentane and the extracts dried (Na_2SO_4) and evaporated to leave an almost colourless (oil 950 mg). This was distilled to give the (*S*)-1,2-epoxydecane as a colourless oil, b.p. 95—100 °C (oil bath) 1.3 kPa, n_D^{22} 1.4305, $[\alpha]_D^{23}$ — 2.09° [*c* 13.866, hexane]; δ (200 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 6.5 Hz, 10-H), 1.1—1.7 (14 H, c, 3-, 4-, 5-, 6-, 7-, 8-, 9-H), 2.44 (1 H, dd, *J* 4.8 Hz, *J* 2.8 Hz, 1-H), 2.72 (1 H, t, *J* 4.5 Hz, 1-H), and 2.89 (1 H, c, 2-H). Optical purity *ca.* 6%.

Z-1-*Iododec*-4-*en*-2-*ol* (19).—*Z*-1,2-Epoxydec-4-ene (9.0 g) was added to a stirred suspension of dry sodium iodide (17.0 g), dry sodium acetate (1.2 g), acetic acid (15 ml), and propionic acid (38 ml) at —30 °C. After 45 min at —20 to —30 °C it was stirred in an ice-bath for a further 45 min and then poured into a mixture of $NaHCO_3$, water, and ether. After the reaction had subsided the organic layer was separated and the aqueous layer extracted twice with ether. The combined ether layers were washed with water, a small quantity of $NaHSO_3$ solution (this immediately almost decolourized the pale yellow solution), water, saturated NaCl solution, and then dried (Na_2SO_4) and evaporated to leave 15.5 g of pale yellow oil. Since this showed a peak at 1 700 cm^{-1} in the i.r. spectrum it was filtered through a column of silica gel (containing 15% by weight of water) using ether–light petroleum (1/1, v/v) as solvent. Evaporation gave a pale yellow oil (14.7 g) which no longer exhibited the 1 700 cm^{-1} absorption in the i.r. region; $\nu_{max.}$ 3 600—3 200 (in CCl_4 3 620 and 3 576), 1 470, 1 270, and 1 220 cm^{-1} (alcohol); 3 010, 1 650, and 720 cm^{-1} (*Z*-unsaturation); 1 180 and 590 cm^{-1} (CH_2I); *m/e* 282 (*P*), 184 (*P*—98), 181, 171, 155 (*P*—I), 137 (*P*—18-I), 112, 70, and 69; δ (200 MHz, $CDCl_3$) 0.89 (3 H, t, *J* 6.8 Hz, 10-H), 1.1—1.6 (6 H, c, 7-, 8-, 9-H), 2.06br (2 H, q, *J ca.* 6.8 Hz, 6-H), 2.35 (2 H, t, *J* 6.8 Hz, 3-H), 3.25 (1 H, dd, *J* 10.0 Hz, *J* 6.3 Hz, 1-H), 3.39 (1 H, dd, *J* 10.0 Hz, *J* 3.8 Hz, 1-H), 3.56 (1 H, c, 2-H), 5.36 (1 H, dt, *J* 10.5 Hz, *J* 7.0 Hz, 5-H tentative assignment), and 5.58 (1 H, dt, *J* 10.5 Hz, *J* 7.0 Hz, 4H tentative assignment).

Similarly (*S*)-*Z*-1-iododec-4-en-2-ol, (*S*)-(19), was prepared from (*S*)-*Z*-1,2-epoxydec-4-ene (2.2 g), dry sodium iodide (4.2 g), dry sodium acetate (0.3 g), acetic acid (3.6 ml), and propionic acid (9.2 ml). The product was evacuated but not distilled and gave 3.5 g of pale yellow oil $[\alpha]_D^{23}$ + 8.2° (*c* 1.84, benzene). ^1H N.m.r. indicated an optical purity of *ca.* 76%.

Z-2-*Hydroxydec*-4-*enyltriphenylphosphonium Iodide* (1).—Triphenylphosphine (31 g) was dissolved in benzene (20 ml) and filtered through a small quantity of silica gel (containing 15% water) to give a colourless, clear solution. *Z*-1-Iododec-4-en-2-ol (14.2 g) was filtered through the same silica gel and the silica washed with a small quantity of benzene. After 3 days at 45 °C in the dark t.l.c. indicated no reaction so a small quantity of dry silica gel was added and after being stirred the mixture was filtered to give a very pale yellow solution. After 21 days a sample (1.0 ml) was stirred with dry ether and after the ether had been decanted the remaining white oil was evacuated at 15 Pa. The foam obtained was shown to be the phosphonium salt by ^1H n.m.r. After a further 21 days a large crystalline precipitate had formed. The supernatant yellow solution was decanted and the precipitate triturated with ether. The ether was decanted and this was repeated. The remaining solid was evacuated to leave the phosphonium salt as a white powder, m.p. 111—112 °C δ (200 MHz, $CDCl_3$) 0.84 (3 H, t, *J* 6.5 Hz, 10-H), 1.1—1.5 (6 H, c, 7-, 8-, 9-H), 2.03 (2 H, br q, *J ca.* 6.5 Hz, 6-H), 2.67br (2 H, t, *J* 6.3 Hz, 3-H), 3.38br (1 H, t, *J ca.* 14.5 Hz, 1-H), 3.79 (1 H, tt, *J* 15.0 Hz, *J* 10.5 Hz, 1-H), 4.14 (1 H, c, 2-H), 5.38 (1 H, dt, *J* 10.5 Hz, *J* 7.0 Hz, 5-H tentative assignment), 5.56 (1 H, dt, *J* 10.5 Hz, *J* 7.0 Hz, 4-H tentative assignment), and 7.6—8.0 (15 H, c, arom.).

Similarly (*S*)-*Z*-2-hydroxydec-4-enyltriphenylphosphonium iodide, (*S*)-(1), was prepared from (*S*)-*Z*-1-iododec-4-en-2-ol (3.4 g), triphenylphosphine (6.5 g), and benzene (10 ml). After 16 days at 45 °C the supernatant liquid was decanted and the white precipitate which had formed was washed with a small quantity of benzene. The crystals were washed with ether then dried to leave a pale yellow solid. It began to melt at 108—112 °C but did not melt properly till 170 °C (decomp.).

1-*Iodoheptan*-2-*ol* (24).—Hept-1-ene (24.5 g) was dissolved in ether (130 ml) and water (7 ml) and yellow mercuric oxide (30 g) was added. Iodine (63 g) was then added in small portions with vigorous stirring during 30 min, the temperature being between 10 and 20 °C. After a further 1 h of stirring the iodine colour had not gone and more mercuric oxide (10 g) was added; stirring was continued until the colour had gone. The mixture was filtered and washed with a solution of $NaHSO_3$ and KI in water. This gave a colourless organic layer and a yellow aqueous phase. The organic phase was separated and washed with saturated NaCl solution, dried (Na_2SO_4), and left overnight at 5 °C. The now dark red solution was evaporated to leave a red oil (58 g). Since t.l.c. indicated a large non-polar component the mixture was separated on a column of silica (on which it was clearly unstable) and gave 22.4 g of 1-iodoheptan-2-ol (200 MHz, $CDCl_3$) 0.89 (3 H, t, *J* 6.8 Hz, 7-H), 1.1—1.5 (6 H, c, 4-, 5-, 6-H), 1.54 (2 H, c, 3-H), 3.24 (1 H, dd, *J* 10.3 Hz, *J* 6.8 Hz, 1-H), 3.39 (1 H, dd, *J* 10.3 Hz, *J* 3.5 Hz, 1-H), and 3.52 (1 H, c, 2-H).

2-*Hydroxyheptyltriphenylphosphonium Iodide* (9).—Triphenylphosphine (40 g) and 1-iodoheptan-2-ol (15 g) were dissolved in benzene (20 ml) and filtered through a small plug of silica gel. The mixture was kept at 45 °C and after 10 days a second layer appeared with crystals in it. After it had been shaken and left for a further 24 h at 45 °C the lower layer was almost totally solid. It was left a further 21 days after which time it was poured into dry ether and the ether-insoluble material triturated with ether, benzene, and THF to leave a hard toffee-like product which would not solidify. Evacuation in a desiccator over P_2O_5 gave a dry foam (19.5 g) which remained dry and was easily powdered, δ (200 MHz, $CDCl_3$) 0.80 (3 H, t, *J* 6.5 Hz, 7-H), 1.0—1.5 (6 H, c, 4-, 5-, 6-H), 1.79 (1 H, c, 3-H), 1.96 (1 H, c, 3-H), 3.32br (1 H, t, *J ca.* 14.5 Hz, 1-H), 3.92 (1 H, dt, *J* 14.5 Hz, *J* 10.2 Hz, 1-H), 4.06 (1 H, c, 2-H), and 7.5–8.0 (15 H, c, arom.).

Ethyl 10,10-*Diethoxydeca*-5,8-*diynoate* (27).—Ethyl nona-5,8-diynoate (26) (15.0 g), triethyl orthoformate (30 g) 2,2,4-trimethylpentane (100 ml), and zinc iodide (0.6 g) were refluxed under a Soxhlet containing calcium chloride. The catalyst quickly became black and t.l.c. indicated no further reaction, even on addition of a new batch of catalyst. The mixture was cooled and filtered through a small plug of Florisil to give a pale orange solution. Fresh zinc iodide (0.9 g) was added and the mixture again refluxed under the Soxhlet until reaction ceased. After filtration through a short plug of Florisil the filtrate was evaporated initially at water vacuum-pump pressure and finally under oil-pump

pressure to remove the last triethyl orthoformate. The remaining orange oil (18.4 g) was chromatographed on silica gel (+ 15% water) using a gradient elution of 5 to 15% ether in light petroleum. Combination of the fractions gave the diyne acetal (9.45 g, 38.6%) as a colourless oil, *m/e* 280, 279 (*P* and *P*−1), 235 (*P*−45), 161, 133, 103, and 45; $\nu_{max.}$ 1 738, 1 250, and 1 180 cm^{-1} (ethyl ester); 2 990, 1 480, 1 160, 1 082, 1 055 and 1 018 cm^{-1} (ethyl acetal); 1 450 and 1 330 ($CH_2C{\equiv}C$); 1 420 and 1 320 cm^{-1} (skipped methylene); (200 MHz, $CDCl_3$) 1.21 (6 H, t, *J* 7.3 Hz, CH_3CH_2OC), 1.79 (2 H, quint, *J* 7.3 Hz, 3-H), 2.21 (2 H, tt, *J* 7.3 Hz, 4-H), 2.39 (2 H, t, *J* 7.3 Hz, 2-H), 3.18br (2 H, q, *J ca.* 2 Hz, 7-H), 3.56 (2 H, dq, *J* 9.8 Hz, *J* 7.3 Hz, CH_3CH_2OC), 3.72 (2 H, dq, *J* 9.8 Hz, *J* 7.3 Hz, CH_3CH_2OC), 4.10 (2 H, q, *J* 7.5 Hz, CH_3CH_2OOC), and 5.22br (1 H, t, *J ca.* 1.8 Hz, 10-H).

Ethyl (5*Z*,8*Z*)-10,10-*Diethoxydeca*-5,8-*dienoate* (28 h) and *Ethyl* (5Z,8Z)-10,10-*Diethoxy*-5,6,8,9-*tetradeuteriodeca*-5,8-*dienoate* (28d).—Ethyl 10,10-diethoxydeca-5,8-diynoate (4.3 g) was dissolved in light petroleum (20 ml) and hydrogenated in the presence of Lindlar's catalyst (1.5 g) and quinoline (3 drops). The reaction stopped three times; each time the mixture was filtered through a small column of Florisil, washed through with light petroleum ether, and new catalyst added. The last filtrate was evaporated to give the diene-acetal (28 h) as a pale yellow oil (3.15 g, 72%) which was not purified further; *m/e* 284, 283 (*P* and *P*−1), 239 (*P*−45), 238, 199, 193, 186, 142, 129, 103, and 88; δ (300 MHz, $CDCl_3$) 1.22 (6 H, t, *J* 7.0 Hz, CH_3CH_2OC), 1.25 (3 H, t, *J* 7.0 Hz, CH_3CH_2OOC), 1.69 (2 H, quint, *J* 7.3 Hz, 3-H), 2.10br (2H, q, *J ca.* 6 Hz, 4-H), 2.30 (2 H, t, *J* 7.5 Hz, 2-H), 2.90 (2 H, c, 7-H), 3.52 (2 H, dq, *J* 9.5 Hz, *J* 7.0 Hz, CH_3CH_2OC), 3.65 (2 H, dq, *J* 9.5 Hz, *J* 7.0 Hz, CH_3CH_2OC), 4.13 (2 H, q, *J* 7.0 Hz, CH_3CH_2OOC), 5.24 (1 H, d, *J* 6.3 Hz, 10-H), 5.40 (2 H, c, 5-H and 6-H), 5.49 (1 H, dd, *J* 11.0 Hz, *J* 6.3 Hz, 9-H), and 5.58 (1 H, dt, *J* 11.0 Hz, *J* 7.0 Hz, 8-H).

In the same way reduction of the diynoate (4.3 g) with deuterium gave the tetradeuteriodiene acetal (28d) (3.3 g, 75%) as a pale yellow oil which was not purified further, *m/e* 288, 287 (*P* and *P*−1), 247 (*P*−45), 243, 242, 197, 188, 174, 103, and 88; $\nu_{max.}$ 1 738 and 1 372 cm^{-1} (ethyl ester); 2 980, 1 480, 1 160, and 1 055 cm^{-1} (diethyl acetal); 1 632 cm^{-1} (*Z* unsaturation shifted *ca.* 30 cm^{-1} which indicates the hydrogens are replaced by deuterium atoms), 2 100 and 2 250 cm^{-1} (C–D); δ (300 MHz, $CDCl_3$) 1.21 (6 H, t, *J* 7.0 Hz, CH_3CH_2OC), 1.25 (3 H, t, *J* 7.0 Hz, CH_3CH_2OOC), 1.70 (2 H, quint, *J* 7.3 Hz, 3-H), 2.10br (2 H, t, *J ca.* 7.5 Hz, 4-H), 2.30 (2 H, t, *J* 7.5 Hz, 2-H), 2.90br (2 H, s, 7-H), 3.53 (2 H, dq, *J* 9.5 Hz, *J* 7.0 Hz, CH_3CH_2OC), 3.66 (2 H, dq, *J* 9.5 Hz, *J* 7.0 Hz, CH_3CH_2OC), 4.14 (2 H, q, *J* 7.0 Hz, CH_3CH_2OOC), and 5.24br (1 H, s, 10-H).

Ethyl (5Z,8Z)-9-*Formylnona*-5,8-*dienoate* (2h) and *Ethyl* (5Z,8Z),5,6,8,9-*Tetradeuterio*-9-*formylnona*-5,8-*dienoate* (2d).—The diene acetal (28h) (0.95 g) was dissolved in acetone (2 ml) and cooled to 0 °C. A cooled solution of 4% oxalic acid in acetone (15 ml) was added followed immediately by water (10 ml). After 12 min, t.l.c. indicated only a trace of starting material. After 20 min the mixture was poured into $NaHCO_3$ solution and extracted twice with pentane. The pentane extracts were washed twice with saturated NaCl solution, dried (Na_2SO_4, $NaHCO_3$), and evaporated to leave an almost colourless oil (0.65 g) which t.l.c. showed to contain only a trace of starting material and only a trace of the 8-*E*-aldehyde (more polar). The material was azeotroped with benzene to ensure dryness, taken up in toluene (20 ml), and used immediately. In exactly the same way the tetradeuterio-dienal (2d) was prepared from the corresponding acetal (28d) and used immediately.

Ethyl (5Z,8E)-9-*Formylnona*-5,8-*dienoate* (10h) *Ethyl* (5Z,8E)-9-*Formyl*-5,6,8,9-*tetradeuterionona*-5,8-*dienoate* (10d).—(*a*) The diene acetal (28h) (1.0 g) was dissolved in THF (25 ml) and aqueous H_2SO_4 (0.125 mol/l, 20 ml) was added. After 16 h, t.l.c. indicated it to be totally isomerized from 8*Z* to 8*E*. It was poured into $NaHCO_3$ solution and extracted with pentane. The extracts were washed twice with saturated NaCl solution, dried (Na_2SO_4), and evaporated to leave 0.7 g of aldehyde. This was taken up in pentane and filtered through a 2-cm long column of silica gel (containing 15% by weight water) which left a yellow band on the top. The filtrate was evaporated and azeotroped twice with benzene to leave a yellow oil, 0.7 g.

(*b*) The diene acetal (28h) was dissolved in acetone (2 ml) and 4% oxalic acid in acetone (15 ml) and water (10 ml) were added. After 16 h t.l.c. indicated it to be *ca.* 90% 8*E* and 10% 8*Z*. It was poured into $NaHCO_3$ solution and extracted with pentane to give a pale yellow oil (550 mg). Further extraction with ether gave more material but less pure. These more-polar impurities are not soluble in pentane. The pentane-soluble fraction was kept for 24 h then co-distilled twice with toluene and taken up in toluene; δ (300 MHz, $CDCl_3$) 1.25 (3 H, t, *J* 7.0 Hz, CH_3CH_2OOC), 1.71 (2 H, quint, *J* 7.3 Hz, 3-H), 2.10br (2 H, q, *J ca.* 7 Hz, 4-H), 2.30 (2 H, t, *J* 7.3 Hz, 2-H), 3.08 (2 H, c, 7-H), 4.13 (2 H, q, *J* 7.0 Hz, CH_3CH_2OOC), 5.47 (1 H, dt, *J* 10.8 Hz, *J* 7.0 Hz, 5-H tentative assignment), 5.58 (1 H, dt, *J* 10.8 Hz, *J* 7.0 Hz, 6-H tentative assignment), 6.15 (1 H, ddt, *J* 15.8 Hz, *J* 7.8 Hz, *J* 1.8 Hz, 9-H), 6.83 (1 H, dt, *J* 15.8 Hz, *J* 6.3 Hz, 8-H), and 9.56 (1 H, d, *J* 7.8 Hz, 10-H); *m/e* 210 (*P*), 192 (*P*-H_2O), 166 (*P*−42), 147, 136, 122, and 88. In exactly the same way the tetradeuterio-compound (10d) was prepared by hydrolysis and isomerization of the corresponding *Z*,*Z* acetal (28d); *m/e* 214 (*P*) 196 (*P*−H_2O), 185 (*P*−29), 169 (*P*−45), 150, 140, 126, and 88.

Ethyl (5Z,8E,10E)-12-*Hydroxyheptadeca*-5,8,10-*trienoate* (11h) [(*R*,*S*)-*HHT Ethyl Ester*] and *Ethyl* (5Z,8E,10Z)-12-*Hydroxyheptadeca*-5,8,10-*trienoate*.—2-Hydroxyheptyltriphenylphosphonium iodide (2.55 g, 2.86 mmol) was dissolved in THF and at −78 °C a solution of MeLi in THF (7.73 ml; 1.11M) was added. The temperature was allowed to rise to −30 °C. The mixture was cooled to −75 °C and toluene (50 ml) was added followed by the *E*-aldehyde (0.65 g) dissolved in toluene (15 ml). After a further 30 min at −78 °C the mixture was warmed to −30 °C and HMPTA (2.1 ml) was added. It was stirred for 2 h during which the temperature was allowed to rise from −30 to −10 °C. Then it was poured onto ice and aqueous NH_4Cl and extracted with ether. The extracts were washed with $NaHCO_3$ solution and saturated aqueous NaCl, dried (Na_2SO_4), and then filtered through a short column of silica gel (containing 15% by weight water). The filtrate was evaporated to leave the product (515 mg) which was chromatographed on a 40-cm long column of silica gel using a gradient of 0 to 40% ether in n-hexane (600 ml of each) as eluant. Due to the very close mobility of the compounds separation was not perfect. The collected fractions were A, best 162.2 mg; B, 85.3 mg contained a little slightly more-polar component; C, 97.9 mg contained a little slightly more-polar and less polar components. Fraction A had $\lambda_{max.}$ 232 nm ε 19 450 (EtOH) *m/e* 308 (*P*), 290 (*P*−H_2O), 263 (*P*−45), 194, 153 129, 99, and 88; $\nu_{max.}$ 1 740, 1 375, 1 250, 1 160, and 1 030 cm^{-1} (ethyl ester); 3 010, 1 660, and 730 cm^{-1} (isolated *Z*

bond); 990 cm^{-1} (*E-E*-conjugated bonds); 3 620 (in CCl_4) and 1 050 cm^{-1} (sec. alcohol); δ (300 MHz, $CDCl_3$) *ca.* 55 : 45 mixture of 10*E* and 10*Z* isomers respectively; 10*E* 0.88 (3 H, t, *J* 6.8 Hz, 17-H), 1.25 (3 H, t, *J* 7.0 Hz, CH_3CH_2OOC) 1.2—1.7 (8 H, c, 13-, 14-, 15-, 16-H), 1.69 (2 H, quintet, *J* 7.3 Hz, 3-H), 2.09 (2 H, br q, *J* 7 Hz, 4-H), 2.30 (2 H, t, *J* 7.5 Hz, 2-H), 2.82 or 2.85 (2 H, c, 7-H), 4.13 (2 H, q, *J* 7.0 Hz, CH_3CH_2OOC and 1 H, overlapped by CH_3CH_2OOC, 12-H), 5.45 (2 H, c, 5-, 6-H), 5.61 (1 H, dd, *J* 15.0 Hz, *J* 7.0 Hz, 11-H), 5.72 (1 H, dt, *J* 15.0 Hz, *J* 7.0 Hz, 8-H), 6.06 or 6.37 (1 H, dd, *J* 15.0 Hz, *J* 10.5 Hz, 9-H), 6.18 (1 H, dd, *J* 15.0 Hz, *J* 10.5 Hz, 10-H), 10*Z* 0.88 (3 H, t, *J* 6.8 Hz, 17-H), 1.25 (3 H, t, *J* 7.0 Hz, CH_3CH_2OOC), 1.2—1.7 (8 H, c, 13-, 14-, 15-, 16-H), 1.69 (2 H, quint, *J* 7.3 Hz, 3-H), 2.09br (2 H, q, *J ca.* 7 Hz, 4-H), 2.30 (2 H, t, *J* 7.5 Hz, 2-H), 2.85 or 2.82 (2 H, c, 7-H), 4.13 (2 H, q, *J* 7.0 Hz, CH_3CH_2 OOC), 4.57br (1 H, q, *J ca.* 8 Hz, 12-H), 5.32br (1 H, t, *J ca.* 9.5 Hz, 11-H), 5.45 (2 H, c, 5-, 6-H), 5.72 (1 H, dt, *J* 15.0 Hz, *J* 7.0 Hz, 8-H), 6.03br (1 H, t, *J ca.* 10.5 Hz, 10-H), and 6.37 or 6.06 (1 H, dd, *J* 15.0 Hz, *J* 11.0 Hz, 9-H).

Ethyl (5Z,8E,10E)-5,6,8,9-*Tetradeuterio*-12-*hydroxyheptadeca*-5,8,10-*trienoate* (11d) and *Ethyl* (5Z,8E,10Z)-5,6,8,9-*Tetradeuterio*-12-*hydroxyheptadeca*-5,8,10-*trienoate* (12d).—This compound was prepared analogously to (*R,S*)-HHT ethyl ester using Wittig salt (2.55 g), MeLi in THF (7.9 ml of 1.11 mol), tetradeuterioaldehyde (10d) (400 mg), and HMPTA (1.8 ml). Chromatography gave: fraction A 112 mg, purest; B 93.4 mg, slightly less pure. Fraction A had $\lambda_{max.}$ 232 nm (ε 21 270) (EtOH); *m/e* 312 (*P*), 294 (*P*−18), 267, 241, 197, 155, 99, and 88; $\nu_{max.}$ 1 738, 1 375, 1 250—1 160, and 1 030 cm^{-1} (ethyl ester); 2 225, 1 630, and 600 cm^{-1} (isolated *Z* bond [2D]); 970 cm^{-1} (*E* CH=CH; conjugated with CD=CD does not shift it); 725 cm^{-1} [conjugated *E* (2D)], 3 600—3 200 (3 620 in CCl_4) and 1 050 cm^{-1} (sec. alcohol); δ (200 MHz, $CDCl_3$) *ca.* 55/45 mixture of 10*E* and 10*Z* isomers respectively; 10*E* 0.89 (3 H, t, *J* 6.8 Hz, 17-H), 1.24 (3 H, t, *J* 7.0 Hz, CH_3CH_2OOC), 1.1—1.8 (8 H, c, 13-, 14-, 15-, 16-H), 1.68 (3 H, quintet, *J* 7.3 Hz, 3-H), 2.08br (2 H, t, *J ca* 7.5 Hz, 4-H), 2.30 (2 H, t, *J* 7.3 Hz, 2-H), 2.80 or 2.82br (2 H, s, 7-H), 4.11 (2 H, q, *J* 7.0 Hz, CH_3CH_2OOC and 1 H, overlapped by CH_3CH_2OOC, 12-H), 5.58 (1 H, dt, *J* 15.0 Hz, *J* 7.0 Hz, 11-H), 6.16br (1 H, d, *J ca.* 15 Hz, 10H); 10*Z* 0.89 (3 H, t, *J* 6.8 Hz, 17-H), 1.24 (3 H, t, *J* 7.0 Hz, CH_3CH_2OOC), 1.1—1.8 (8 H, c, 13-, 14-, 15-, 16-H), 1.68 (2 H, quint, *J* 7.3 Hz, 3-H), 2.08br (2 H, t, *J ca.* 7.5 Hz, 4-H), 2.30 (2 H, t, *J* 7.3 Hz, 2-H), 2.82 or 2.80br (2 H, s, 7-H), 4.11 (2 H, q, *J* 7.0 Hz, CH_3CH_2OOC), 4.55br (1 H, q, *J ca.* 7.5 Hz, 12-H), 5.30br (1 H, t, *J ca.* 9.5 Hz, 11-H), and 6.00br (1 H, d, *J ca.* 11 Hz, 10-H).

Ethyl (5Z,8Z,10E,14Z)-12-*Hydroxyeicosa*-5,8,10,14-tetra*enoate* (3h) [(R,S)-*HETE Ethyl Ether*].—The phosphonium salt (1.8 g) was suspended in freshly distilled THF (15 ml) and a solution of methyl-lithium in THF (5.9 ml of 1.10 mol/l) was added at −78 °C. The solution became yellow and on warming to −30 °C became bright red and clear. It was re-cooled to −78 °C and toluene (20 ml) was added. It was kept for 90 min at −78 °C whilst the aldehyde (0.56 g) was prepared (*vide supra*) and then dissolved in toluene (20 ml) and added at −78 °C. It was kept at this temperature for 30 min and then allowed to warm to −30 °C. HMPTA (2.3 g) was added and the temperature kept between −30 and −10 °C for 2 h; after this the mixture was poured into ice–water and NH_4Cl solution, separated, and the aqueous solution extracted twice with ether. The combined organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated to give a cloudy oil (2.7 g). This was separated on a column of silica gel (50 g containing 15% by weight water) using a gradient 0—40% ether in light petroleum (400 ml of each solvent) then finally 200 ml of 40% ether in light petroleum. Combining fractions gave 298 mg of HETE ethyl ester which was only one spot on t.l.c. and a less-pure fraction (240 mg) containing traces of impurities. The purest fraction had $\lambda_{max.}$ 236 nm ε 23 100 (EtOH); *m/e* 348 (*P*), 330 (*P*−18), 303 (*P*−45), 237, 219, 191, 173, 163, 131, 107, and 88; $\nu_{max.}$ 1 738, 1 375, and 1 160 cm^{-1} (ethyl ester); 3 010, 1 655, and 720br (*Z*-unsaturation); 1 400 cm^{-1} (skipped CH_2); 3 450 and 1 095 cm^{-1} (sec. alcohol); 985 and 952 cm^{-1} (*Z-E* conjugated system); δ (200 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 6.8 Hz, 20-H), 1.25 (3 H, t, *J* 7.3 Hz, CH_3CH_2OOC), 1.1—1.5 (6 H, c, 17-, 18-, 19-H), 1.69 (2 H, quint, *J* 7.3 Hz, 3-H), 2.05 (2 H, q, *J* 6.8 Hz, 16-H), 2.12 (2 H, q, *J* 6.8 Hz, 4-H), 2.30 (2 H, t, *J* 7.3 Hz, 2-H and 2 H, overlapped by 2-H, 13-H), 2.92 (2 H, c, 7-H), 4.12 (2 H, q, *J* 7.3 Hz, CH_3CH_2OOC), 4.22br (1 H, q, *J ca.* 6.5 Hz, 12-H), 5.3—5.5 (4 H, c, 5-, 6-, 8-, and 15-H tentative assignment), 5.57 (1 H, dt, *J* 10.5 Hz, *J* 7.0 Hz, 14-H tentative assignment), 5.72 (1 H, dd, *J* 15.0 Hz, *J* 6.3 Hz, 11-H), 5.99 (1 H, t, *J* 10.8 Hz, 9-H), and 6.55 (1 H, dd, *J* 15.0 Hz, *J* 11.0 Hz, 10-H); optical purity *ca.* 76%.

Ethyl (5Z,8Z,10E,14Z)-5,6,8,9-*Tetradeuterio*-12-*hydroxyeicosa*-5,8,10,14-*tetraenoate* (3d) and *Ethyl* (5Z,8Z,10Z,14Z)-5,6,8,9-*Tetradeuterio*-12-*hydroxyeicosa*-5,8,10,14-*tetraenoate* (4d).—These compounds were prepared analogously to (*R,S*)-HETE ethyl ester using Wittig salt (1.8 g), methyl-lithium in THF (6.1 ml of 1.11 mol/l), tetradeuterioaldehyde (0.6 g), and HMPTA (2.3 ml). Careful chromatography separated the 10*E*-(less-polar) from the 10*Z*-isomer (more-polar). Fraction A [less-polar, 10*E* isomer (3d)] 225.9 mg; B [more-polar, 10*Z*-isomer (4d)], 125.3 mg; C (mixed fractions) 75.8 mg. Fraction A had $\lambda_{max.}$ 236 nm (ε 23 700) (EtOH); *m/e* 352 (*P*), 334 (*P*−18) 307 (*P*−45), 311, 241 (*P*−111), 223, 222, 195 (241-46), 176 P^{2+}-, 167, 88 (ethyl ester); i.r. 1 738, 1 380, 1 250, 1 160, and 1 032 cm^{-1} (ethyl ester); 3 010, 1 655, and 725br cm^{-1} (isolated *Z* bond); 2 240, 1 630, and 600br cm^{-1} (isolated deuteriated *Z* bond); 3 600-3200 (3 618 in CCl_4) cm^{-1} (sec. alcohol); 968 cm^{-1} [2 D (*Z*) in the conjugated system]; δ (200 MHz, $CDCl_3$) 0.89 (3 H, t, *J* 6.8 Hz, 20-H), 1.25 (3 H, t, *J* 7.0 Hz, CH_3CH_2 OOC), 1.1—1.5 (6 H, c, 17-, 18-, 19-H), 1.69 (2 H, quint, *J* 7.3 Hz, 3-H), 2.05br (2 H, q, *J ca.* 7 Hz, 16-H), 2.11br (2 H, t, *J ca.* 7.5 Hz, 4-H), 2.30 (2 H, t, *J* 7.3 Hz, 2-H and 2 H, overlapped by 2-H, 13-H), 2.90br (2 H, s, 7-H), 4.11 (2 H, q, *J* 7.0 Hz, CH_3CH_2OOC), 4.20br (1 H, q, *J ca.* 6.5 Hz, 12-H), 5.36 (1 H, dt, *J* 10.8 Hz, 15-H tentative assignment), 5.54 (1 H, dt, *J* 10.8 Hz, 14-H tentative assignment), 5.71 (1 H, dd, *J* 15.3 Hz, *J* 6.5 Hz, 11-H), and 6.54 (1 H, d, *J* 15.3 Hz, 10-H). Fraction B and $\lambda_{max.}$ 236 nm (ε 21 100); *m/e* 352 (*P*). The spectrum was almost identical with that of fraction A; $\nu_{max.}$ 1 738, 1 380, 1 250, 1 160, and 1 035 cm^{-1} (ethyl ester); 3 020, 1 670, and 725br cm^{-1} (isolated *Z* bond); 2 240, 1 630, and 600br cm^{-1} (isolated deuteriated *Z* bond); 3 600—3 200 (3 618 in CCl_4) cm^{-1} (sec. alcohol); δ (200 MHz, $CDCl_3$) 0.89 (3 H, t, *J* 6.8 Hz, 20-H), 1.25 (3 H, t, *J* 7.0 Hz, CH_3CH_2OOC), 1.1—1.5 (6 H, c, 17-, 18-, 19-H), 1.70 (2 H, quint, *J* 7.3 Hz, 3-H), 2.06br (2 H, q, *J ca.* 6.5 Hz, 16-H), 2.11br (2 H, t, *J ca.* 7 Hz, 4-H), 2.31 (2 H, t, *J* 7.3 Hz, 2-H and 2 H, overlapped by 2-H, 13-H), 2.91br (2 H, s, 7-H), 4.11 (2 H, q, *J* 7.0 Hz, CH_3CH_2OOC), 4.60br (1 H, q, *J ca.* 7.5 Hz, 12-H), 5.36 (1 H, dt, *J* 10.8 Hz, *J* 7.3 Hz, 15-H tentative assignment), 5.47 (1 H, dd, *J* 11.0 Hz, *J* 7.5 Hz, 11-H), 5.55

(1 H, dt, *J* 10.8 Hz, *J* 7.3 Hz, 14-H tentative assignment), and 6.34 (1 H, d, *J* 11.0 Hz, 10-H).

(S)-*Ethyl* (5*Z*,8*Z*,10*E*,14*Z*)-12-*Hydroxyeicosa*-5,8,10,14-*tetraenoate* (S)-(3h) [(S)-*HETE Ethyl Ester*] and (S)-*Ethyl* (5*Z*,8*Z*,10*Z*,14*Z*)-12-*Hydroxyeisosa*-5,8,10,14-*tetraenoate* (S)-(4h) [10*Z*-*HETE Ethyl Ester*].—These compounds were prepared analogously to (*R*,*S*)-HETE ethyl ester from (*S*)-*Z*-2-hydroxy-4-decenyltriphenylphosphonium iodide (2.8 g), methyl-lithium in THF (8.3 ml of 1.11 mol), the aldehyde (2h) (0.9 g), and HMPTA (2.2 ml). Chromatography gave the 10*E*-isomer as a pure compound and the 10*Z*-isomer as a mixture with the 10*E*-isomer. Fraction A 148.6 mg (10*E*); fraction B 205.8 mg (10*E*,10*Z* mixture); fraction C 129.2 mg (10*Z* and more-polar fraction). Fraction A gave no measurable optical rotation even using the whole sample in 3 ml EtOH, ^{1}H n.m.r. indicated an optical purity of 76%; $\lambda_{max.}$ (EtOH) 236 nm (ε 22 500); CD $\Delta\varepsilon_{232}$ (23 °C) + 0.348 (hexane). The i.r. and ^{1}H n.m.r. spectra were identical with those of (*R*,*S*)-HETE ethyl ester. Fraction B (205.8 mg) was separated on a long column of silica gel using 0—35% ether in light petroleum as eluant to give the 10*Z*-isomer (91.2 mg); $[\alpha]_D^{21}$ −1.87° (*c*, 6.1 $CHCl_3$).

(S)-*Methyl* (5*Z*,8*Z*,10*E*,14*Z*)-12-*Hydroxyeicosa*-5,8,10,14-*tetraenoate* (S)-(5h) [(S)-HETE *Methyl Ester*].—(*S*)-HETE ethyl ester (100 mg) was dissolved in anhydrous potassium carbonate in methanol (5 ml, 0.1 mol/l). After 1 h it was poured into aqueous NH_4Cl (25 ml, 0.1 mol/l) and extracted with ether. The extracts were washed with saturated NaCl, dried (Na_2SO_4), and evaporated to leave the methyl ester (102.8 mg) as a yellow oil; $\lambda_{max.}$ (EtOH) 236 nm (ε 23 000); $[\alpha]_D^{23}$ − 0.5° (*c* 5.0, $CHCl_3$); $\nu_{max.}$ 1 740, 1 438, 1 250, 1 200, and 1 160 cm^{-1} (methyl ester); 3 010, 1 655, and 725br cm^{-1} (*Z* unsaturation); 3 450br and 1 090 cm^{-1} (sec. alcohol); 985 and 950 cm^{-1} (*Z*–*E* conjugation); *m/e* 334 (*P*), 316 (*P*-H_2O), 305, 303, 223, 205, 193, 191, 179, 173, 163, 145, and 74; c.d. $\Delta\varepsilon_{230}$ + 0.97 (ethanol) $\Delta\varepsilon_{234}$ (+25 °C) − 0.85 (EPA) $\Delta\varepsilon_{230}$ (−185 °C) − 2.65 (EPA) $\Delta\varepsilon_{238}$ + 0.85 (ethanol) $\Delta\varepsilon_{247}$ (+25 °C) + 1.02 (EPA) $\Delta\varepsilon_{247}$ (−185 °C) − 0.93 (EPA); δ(200 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 6.8 Hz, 20-H), 1.1—1.5 (6 H, c, 17-, 18-, 19-H), 1.70 (2 H, quint, *J* 7.3 Hz, 3-H), 2.05 (2 H, q, *J* 6.8 Hz, 16-H), 2.12 (2 H, q, *J* 6.8 Hz, 4-H), 2.33 (2 H, t, *J* 7.3 Hz, 2-H and 2 H, overlapped by 2-H, 13-H), 2.92 (2 H, c, 7-H), 3.67 (3 H, s, CH_3OOC), 4.23 (1 H, q, *J* 6.5 Hz, 12-H), 5.3—5.5 (4 H, c, 5-, 6-, 8-H and 15-H tentative assignment), 5.59 (1 H, dt, *J* 10.0 Hz, *J* 7.0 Hz, 14-H tentative assignment, 5.74 (1 H, dd, *J* 15.0 Hz, *J* 6.3 Hz, 11-H), 6.00 (1 H, t, *J* 10.8 Hz, 9-H), and 6.56 (1 H, dd, *J* 15.0 Hz, *J* 10.8 Hz, 10-H); optical purity 76%.

(S)-*Methyl* (5*Z*,8*Z*,10*Z*,14*Z*)-12-*Hydroxyeicosa*-5,8,10,14-*tetraenoate* (S)-(6h) [10*Z*-(S)-*HETE Methyl Ester*].—10*Z*-(S)-HETE ethyl ester (91.2 mg) was treated for 2 h with anhydrous potassium carbonate in methanol (0.1 mol/l). Work-up as for the 10*E*-isomer gave the methyl ester (81.5 mg) as a pale yellow oil $\lambda_{max.}$ (EtOH) 236 nm (ε 26 000); $[\alpha]_D^{23}$ − 2.06° (*c* 5.4, $CHCl_3$); c.d. (EPA) $\Delta\varepsilon_{232}$ (−185 °C) + 4.14, $\Delta\varepsilon_{248}$ (−185 °C) + 3.53, and $\Delta\varepsilon_{236}$ (+25 °C) + 2.13; δ (200 MHz, $CDCl_3$) 0.89 (3 H, t, *J* 6.8 Hz, 20-H), 1.1—1.5 (6 H, c, 17-, 18-, 19-H), 1.70 (2 H, quint, *J* 7.3 Hz, 3-H), 2.06br (2 H, q, *J ca.* 7 Hz, 16-H), 2.12br (2 H, q, *J ca.* 7 Hz, 4-H), 2.32 (2 H, t, *J* 7.5 Hz, 2-H and 2H, overlapped by 2-H, 13-H), 2.92 (2 H, c, 7-H), 3.67 (3 H, s, CH_3OOC), 4.62br (1 H, q, *J ca.* 7.5 Hz, 12-H), 5.2—5.7 (6 H, c, 5-, 6-, 8-, 11-, 14-, 15-H), and 6.1—6.5 (2 H, c, 9-, 10-H); $\nu_{max.}$ 1 740, 1 440, 1 250, 1 200, 1 160, and 1 040 cm^{-1}; 5*Z*-methyl ester, 3 020, 1 660, and 740 (isolated *Z*-unsaturation); 1 040 cm^{-1} (α unsaturated sec. OH); 3 620 cm^{-1} (in CCl_4) (sec. OH); *m/e* 334 (*P*), 316, 305, 303, 223, 205, 193, 191, 179, 173, 163, 145, and 74.

Hydrolysis of the Esters to the Corresponding Acids.—A standard solution was prepared from sodium hydroxide (1.0 g), water (12.5 ml), and ethanol (87.5 ml). The ester was taken up in *ca.* 3 equiv. of this basic solution and warmed at 55 °C in an oil-bath. T.l.c. was used to follow the reaction. When the reaction was complete (*ca.* 1—3 h) it was poured into dilute aqueous oxalic acid, extracted with ether, and the extracts dried (Na_2SO_4) and evaporated to leave the acid as a waxy oil. U.v. of these oils indicated no rearrangements of the chromophore.

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