A Chemoenzymatic Approach to Hydroperoxyeicosatetraenoic Acids. Total Synthesis of 5(S)-HPETE

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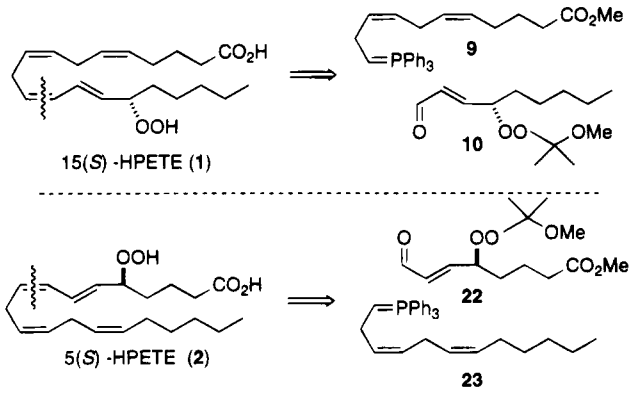
A new synthetic approach to enantiomerically pure hydroperoxyeicosatetraenoic acids (HPETEs) is described in which the tetraene skeleton is assembled through chemoselective olefination of a protected hydroperoxy aldehyde. Soybean lipoxygenase-mediated dioxygenation of both natural and unnatural fats produces hydroperoxy dienes in high enantiomeric excess; the observed regioselectivity supports a revised hypothesis for substrate specificity. Protection of the diene hydroperoxides as peroxy ketals is followed by regioselective ozonolysis to afford enantiomerically pure 4-peroxy 2,3-enals which undergo olefination to produce peroxytetraenoates. Removal of the monoperoxy ketal and the methyl ester affords enantiomerically pure HPETEs. The generality of the strategy is illustrated with the first chemical synthesis of 5(*S*)-HPETE.

The hydroperoxyeicosatetraenoic acids (HPETEs) (Scheme 1) formed upon lipoxygenase-mediated peroxidation of arachidonic acid are unstable natural products which act as intermediates in a number of disease conditions, including anaphylaxis, atherosclerosis, and carcinogenesis.[1–4] For example, 15-HPETE (**1**), derived from the action of 15-lipoxygenase, is believed to influence platelet aggregation, whereas 5(*S*)-HPETE (**2**), produced via 5-lipoxygenase, is a critical intermediate in the biosynthesis of asthma-inducing leukotrienes.[5,6] Despite the biomedical importance of HPETEs and other polyunsaturated hydroperoxides, there has been no method for their chemical synthesis in enantiomerically pure form. We wish to report a general strategy for the synthesis of HPETEs and related materials based on the olefination of chemoenzymatically derived peroxyaldehydes. This approach is illustrated with the total synthesis of 15(*S*)-HPETE (**1**) and 5(*S*)-HPETE (**2**) (Scheme 1).[7]

The known instability of HPETEs, the most obvious challenge in any synthetic scheme, has channeled all previous approaches toward penultimate introduction of the hydroperoxide group. This strategy, while logical, is limited by the methodology available for direct introduction of a hydroperoxide. For example, reaction between singlet oxygen and arachidonic acid proceeds via nonselective attack at each olefinic carbon to produce a mixture of eight racemic HPETE regioisomers.[8] Radical autoxidation produces an even broader array of products.[9–11] Nucleophilic displacement of sulfonates

Scheme 1



derived from enantiomerically pure alcohols was unsuccessful as an approach to enantiomerically pure 5-, 11-, and 15-HPETEs; in each case, only racemic hydroperoxides were isolated.[12–15] Displacement of an enantiomerically pure phosphite by H_2O_2 has been found to produce 12(*S*)-HPETE in 30% ee.[16] Although enantiomerically pure HPETEs have been obtained through chromatographic resolution of diastereomeric peroxyketals, synthesis of the necessary racemic precursors is limited by many of the same drawbacks described above.[17,18]

Whereas the central tenet of all previous strategies for HPETE synthesis has been concern for the stability of the peroxide linkage, our approach, as illustrated in Scheme 1 for 5(*S*)- and 15(*S*)-HPETE, is based upon a complementary strategy in which reversibly protected hydroperoxides are employed as stable synthetic inter-

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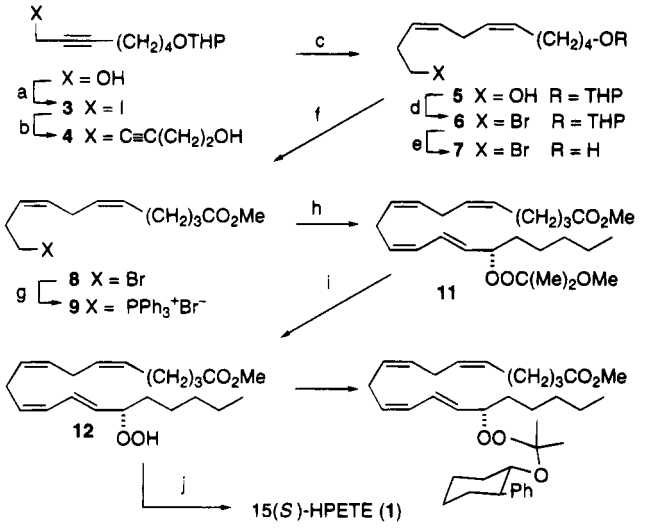
Scheme 2[a]

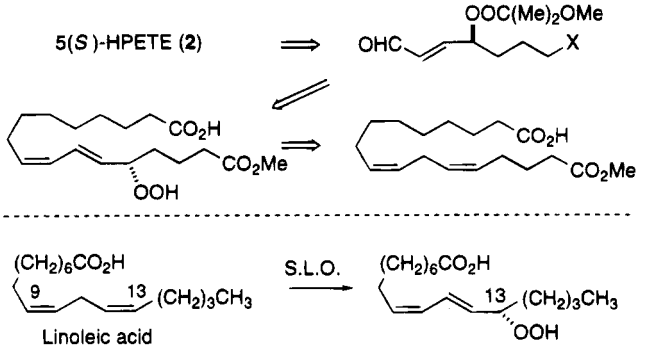


[a] Key: (a) I_2, imidazole, Ph_3P (72%); (b) 3-butynol, EtMgBr, CuBr·Me_2S (86%); (c) $Ni(OAc)_2$, $NaBH_4$, $H_2N(CH_2)_2NH_2$, H_2 (68%); (d) CBr_4, imidazole, Ph_3P (96%); (e) TsOH, MeOH (95%); (f) H_2CrO_4 then CH_2N_2 (93%); (g) Ph_3P; (h) LiN(TMS)$_2$, THF/HMPA, **10** (83%); (i) HOAc/H_2O (95%); (j) (i) LiOH, H_2O_2, THF/H_2O; (ii) cycloheptene (82%, two steps).

mediates. The key bond construction is based upon a reaction developed in our laboratories, the synthesis of diene hydroperoxide subunits through olefination of γ-peroxy-α,β-unsaturated aldehydes.[19] The simplicity of this strategy is illustrated by our synthesis of 15(*S*)-HPETE (**1**) through Wittig olefination of peroxy enal **10** with the ylide derived from phosphonium salt **9**.[7] Synthesis of the phosphonium salt was carried out by a modification of a published route as shown in Scheme 2.[20] Selective C-alkylation of the dianion of 3-butyn-1-ol with propargyl iodide **3** afforded dodecynol **4** in good yield.[21,22] Semihydrogenation with P2 Nickel in the presence of ethylenediamine furnished *Z,Z*-dienol **5** which was converted to the corresponding bromide (**6**).[23] Deprotection of the tetrahydropyranyl group to bromo alcohol **7** was followed by conversion to the methyl ester (**8**) which underwent displacement with triphenylphosphine to form phosphonium salt **9**.[20]

Peroxy enal **10** was available in three steps and 70% overall yield from linoleic acid.[19,24] Addition of **10** to the ylide derived from **9** furnished the peroxy ketal of 15-HPETE methyl ester (**11**) in 83% yield with ≥95% *Z* selectivity at the newly formed 11-olefin. Removal of the peroxy ketal protecting group and semipreparative HPLC purification afforded 15(*S*) HPETE methyl ester (**12**) indistinguishable from enzymatically-derived material.[25] Analysis of the high field ^1H NMR spectra of the diastereomeric peroxyketals formed upon reaction with (−)-2-(phenylcyclohexyl)-2-propenyl ether demonstrated that the product was formed in >95% ee.[18] Unfortunately, attempted saponification of methyl ester **12** with aqueous LiOH led to decomposition.[26] However, saponification in the presence of a slight excess of H_2O_2 led to the rapid disappearance of the ester and the appearance of a peracid.[27,28] The hydroperoxyperacid was not isolated but was concentrated in the presence of excess cycloheptene to afford 15(*S*)-HPETE (**1**) indistinguishable from enzymatically derived material in 12 steps and 15% overall yield from commercially available starting materials.[25]

Scheme 3



Total Synthesis of 5(S)-HPETE. Our retrosynthetic strategy for 5-HPETE (**2**) also relied upon Wittig olefination of an enzymatically-derived peroxy enal (Scheme 3). However, in contrast to the approach to 15-HPETE, the peroxy enal precursor for 5-HPETE must contain a functional group suitable for eventual transformation into the carboxylate "head". Consequently, application of our chemoenzymatic strategy would require regio- and stereoselective dioxygenation of an unnatural fat bearing a latent carboxylate group; this oxidation was anticipated to be the most challenging aspect of the proposed synthesis. The regio- and stereoselectivity of lipoxygenase-mediated dioxygenation has been extensively studied for linoleic acid and other natural ω-6 polyunsaturated fats. However, only limited data are available regarding the compatibility of lipoxygenases with chemically modified substrates.[29-34] The regioselectivity of dioxygenation of a series of unnatural fats was recently reported to be less dependent upon the presence of functional groups than upon the relative hydrophobicity of the proximal and distal diene substituents.[35,36] Stereoselectivity was uniformly high and independent of

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(26) The 15-HPETE methyl ester (**14**) was the only intermediate in which it was possible to preparatively remove the small amount of 11*E* isomer produced during Wittig olefination. Attempted saponification of the hydroperoxyester in the absence of H_2O_2 led to extensive decomposition. This side reaction was unaffected by the presence of an oxygen radical scavenger (BHT) and did not occur during saponification of the peroxyketal methyl ester. Attempted enzyme-mediated hydrolyses proceeded very slowly and were accompanied by extensive decomposition.
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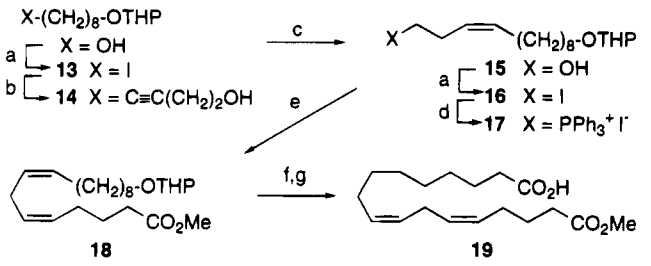
Scheme 4[a]



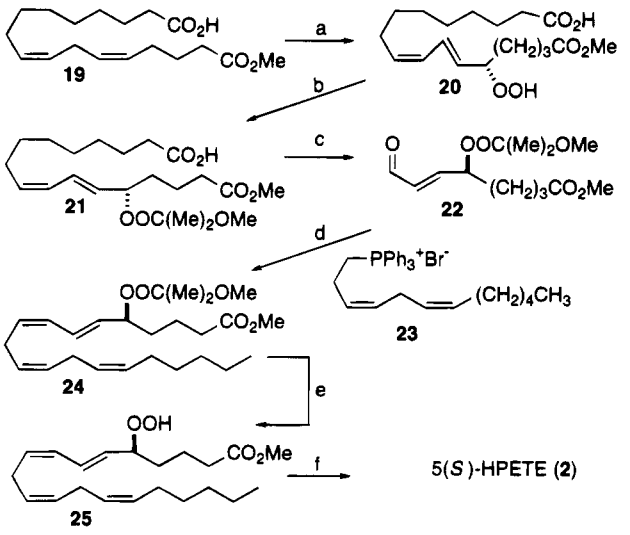
[a] Key: (a) I_2, imidazole, Ph_3P (89–92%); (b) 3-butynol, *n*-BuLi (75%); (c) $Ni(OAc)_2$, $NaBH_4$, $H_2N(CH_2)_2NH_2$, H_2 (94%); (d) Ph_3P, toluene (81%); (e) $LiN(TMS)_2$, THF/HMPA, 4-formyl butyrate (67%); (f) TsOH, MeOH (95%); (g) H_2CrO_4 (90%).

regioselectivity, in agreement with observations made during oxidations of linoleic acid under altered conditions.[30] Our retrosynthesis therefore called for preparation and enzymatic oxidation of a heptadecadienoic acid monomethyl ester (Scheme 3). The terminal carbomethoxy group would provide an excellent precursor for the required carboxylate while introducing only a modest perturbation to the hydrophobicity of the fatty acid tail.

Synthesis of the requisite 9*Z*,12*Z*-heptadecadienoic diacid monomethyl ester was accomplished by a modification of known approaches (Scheme 4). Dodecynol **14** was obtained through selective C-alkylation of the dilithio dianion of butynol with iodide **13**.[20,37,38] Semihydrogenation with P2 Nickel in the presence of several equivalents of ethylenediamine produced homoallylic alcohol **15**.[23] Activation as the homoallyl iodide (**16**) was followed by displacement with triphenylphosphine in toluene/acetonitrile to the phosphonium salt **17**. Curiously, attempted displacement in neat toluene led to deprotection of the tetrahydropyranyl acetal, a phenomenon which has apparently been observed previously.[39] The corresponding ylide was coupled with 4-formyl butyrate, available upon ozonolysis of cyclopentene, to produce heptadecadiene **18**.[40] Removal of the acetal was followed by Jones oxidation to furnish the desired diacid monoester **19** in good overall yield.

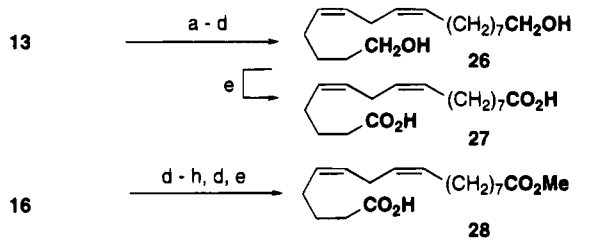
Lipoxygenase-mediated dioxygenation of the unnatural fatty acid **19** and workup with diazomethane provided hydroperoxide **20** in good yield (Scheme 5). The diene hydroperoxide product was formed as a single regioisomer based upon ^{13}C NMR and HPLC analysis. Comparison of the ^1H NMR spectra of the diastereomeric peroxyketals formed upon ketalization of the corresponding dimethyl ester with both (−)- and (±)-2-(phenylcyclohexyl)-2-propenyl ether indicated the hydroperoxide stereocenter had been formed in >95% ee.[18] Protection of the hydroperoxide as the 2-(methoxypropyl)peroxy ketal **21** was followed by selective ozonolysis to furnish the C_1–C_8 synthon **22** in good overall yield. The peroxy enal was coupled with the known phosphonium salt **23**, corresponding to the C_9–C_{20} fragment of 5-HPETE,[41,42] to produce 5(*S*)-HPETE monoperoxy ketal methyl ester **24** with high 9*Z* selectivity. Deprotection of the peroxy

Scheme 5[a]



[a] Key: (a) soybean lipoxygenase, pH 9, O_2 (84%); (b) 2-methoxypropene, PPTS; (c) O_3 then Ph_3P (60%, two steps); (d) $LiN(TMS)_2$, THF/HMPA, **23**, then **22** (88%); (e) HOAc/H_2O (93%); (f) (i) LiOH, H_2O_2, THF/H_2O; (ii) cyclohexene (83%, two steps).

Scheme 6[a]



[a] Key: (a) LiC≡CH, ethylenediamine, DMSO (91%); (b) EtMgBr, CuBr·Me_2S, **3** (92%); (c) $Ni(OAc)_2$, $NaBH_4$, $H_2N(CH_2)_2NH_2$, H_2 (82%); (d) TsOH, MeOH (85–99%); (e) H_2CrO_4 (63–91%); (f) CH_2N_2 (94%); (g) Ph_3P (99%); (h) $LiN(TMS)_2$, THF/HMPA, 5-(2-tetrahydropyranyloxy)pentanal (48%).

ketal afforded 5(*S*)-HPETE methyl ester **25**, which was judged to be >95% ee based upon conversion to the peroxy ketal derived from (−)-2-phenylcyclohexanol.[18] Saponification of the methyl ester with LiOH in THF/aqueous H_2O_2 afforded an intermediate hydroperoxy peracid which was not isolated but reduced *in situ* with cyclohexene to complete the first chemical synthesis of 5(*S*)-HPETE. (**2**) Surprisingly, no optical rotation had been previously reported for either the free acid or methyl ester of 5(*S*)-HPETE. The rotation of the corresponding alcohol, 5-(*S*)-HETE methyl ester, agreed with reported values.[13,15,43]

Lipoxygenase Mediated Dioxygenation of α,ω-Difunctionalized Fats. Several other α,ω-functionalized fats were also investigated as substrates for soybean lipoxygenase; their syntheses are illustrated in Scheme 6. The enzymatic oxygenation of the unnatural acids is compared in Scheme 7. Linoleic acid, a natural substrate, undergoes rapid reaction to produce the 13(*S*)-hydroperoxide as illustrated in entry 1. The 16-carbomethoxyhexadecadienoic acid (**19**) used for the synthesis

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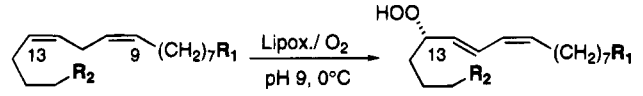
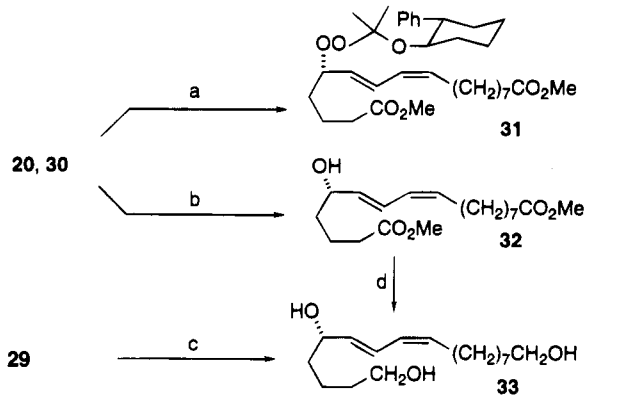
Scheme 7



	R_1	R_2		Yield	Isomer	e.e.	
(1)	CO_2H	CH_2CH_3		80	13*S*	>95%	
(2)	CO_2H	CO_2Me	(19)	80	13*S*	>95%	(20)
(3)	CH_2OH	CH_2OH	(26)	72	13*S*	>95%	(29)
(4)	CO_2H	CO_2H	(27)	0	–	–	
(5)	CO_2Me	CO_2H	(28)	3	13*S*	>80%	(30)

Scheme 8[a]



[a] Key: (a) (i) CH_2N_2; (ii) 2-propenyl ether of (−)-*trans*-2-phenylcyclohexanol (80%, two steps); (b) (i) CH_2N_2; (ii) Ph_3P (90%, two steps); (c) Ph_3P (99%); (d) LAH (86%).

of 5(*S*)-HPETE reacted at least as rapidly as linoleate to selectively produce the 13(*S*)-hydroperoxide (**20**) (entry 2). Our initial selection of **19** as a lead substrate had been largely based on the decision to avoid introduction of highly polar functional groups into the "tail". We were therefore quite surprised to find that the 1,17-heptadecadienol **26** was rapidly converted to one major hydroperoxide regioisomer **29** (entry 3). As seen in entry 4, the presence of a carboxylate group in the tail was less acceptable; α,ω diacid **27** failed to undergo dioxygenation even upon prolonged reaction. The "end-switched" diacid monoester **28** also reacted very slowly to afford a minute yield of hydroperoxide **30**, which was neverthless found to be the 13*S* configuration (entry 5). Our results appear to support the hypothesis that lipoxygenase regioselectivity is primarily influenced by the span of the hydrophobic domains flanking the Z,Z-diene moiety.[35,36,44] The failure of **27** or **28** to undergo significant oxidation can be attributed to the severe reduction in hydrophobicity accompanying the presence of the ionized carboxylate.

The absolute stereochemistry and enantiomeric excess of the hydroperoxides were determined as shown in Scheme 8. Hydroperoxy acids **20** and **30** were directly compared upon esterification and conversion to the (−)-2-phenylcyclohexanol monoperoxy ketals (**31**); the absolute stereochemistry of **20** was previously established through conversion to 5(*S*)-HPETE and 5(*S*)-HETE.[18] The hydroxy methyl ester (**32**) derived from **20** was reduced to a triol (**33**) which could be directly compared with the triol derived upon reduction of hydroperoxy diol **29.** It is notable that all substrates were dioxygenated to the (*S*)-hydroperoxides in good to excellent enantiomeric excess.

In conclusion, we have demonstrated that chemoselective olefination of enzymatically derived and reversibly protected hydroperoxy enals provides a new and versatile approach to the synthesis of HPETEs and related molecules. The ability of soybean lipoxygenase to tolerate synthetically versatile functional groups in close proximity to the active site bodes well for further chemoenzymatic applications.

Experimental Section

All reagents and solvents were used as supplied commercially, except as noted: THF was distilled from Na/Ph_2-CO; HMPA was distilled from CaH_2 and stored over 4 Å sieves; DMF was stored over 4 Å sieves. ^1H and ^{13}C NMR spectra were recorded on 300, 360, or 500 MHz spectrometers in $CDCl_3$; individual peaks are reported as (multiplicity, number of hydrogens, coupling constant). *J* values are given in hertz. Optical rotations were obtained in a 1 dm cell in $CHCl_3$ unless otherwise noted. Elemental analyses were obtained from M-H-W Laboratories, Phoenix, AZ. Semipreparative HPLC was performed with a 2.1 × 25 cm Rainin Dynamax Si column with refractive index detection. All peroxides and hydroperoxides were handled and stored in the presence of approximately 0.1% butylated hydroxytoluene (BHT), added from a 1 M stock solution in CH_2Cl_2. Progress of reactions involving peroxides was monitored by TLC, using an *N,N'*-dimethyl-*p*-phenylenediamine indicator; hydroperoxides immediately yield a pink spot while perketals or peroxides exhibit a pink or green-red color after mild charring.[28]

2-[(7-Iodo-5-heptynyl)oxy]-2*H*-tetrahydropyran (3). To a 0 °C solution containing 7-(tetrahydro-2*H*-pyran-2-yloxy)-3-heptyn-1-ol (6.20 g, 29.2 mmol, 1 equiv), imidazole (2.78 g, 1.4 equiv), and Ph_3P (11.49 g, 1.5 equiv) in 120 mL of CH_2Cl_2 was added I_2 (10.38 g, 1.4 equiv). After 30 min, the solution was brought to room temperature and stirred for 1 h. The dark suspension was washed with 10% Na_2SO_3 (2 × 100 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (10% EA/hex) afforded 6.79 g (72%) of the propargyl iodide as a colorless oil which displayed spectra identical to literature reports based on a different method:[45] R_f = 0.52 in 10% EA/hex; ^1H NMR (500 MHz) δ 4.55 (t, 1H, *J* = 3.4), 3.84 (m, 1H), 3.72 (dt, 1H, *J* = 6.5, 9.7), 3.68 (bs, 2H), 3.49 (m, 1H), 3.39 (dt, 1H, *J* = 6.4, 9.7), 2.19 (m, 2H), 1.72−1.49 (10H); ^{13}C NMR (125 MHz) δ 98.8, 86.4, 66.9, 62.3, 30.7, 28.9, 25.5, 25.2, 19.6, 18.9, −17.0.

11-(Tetrahydro-2*H*-pyran-2-yloxy)undeca-3,6-diyn-1-ol (4). To a room temperature solution of 3-butyn-1-ol (4.41 g, 62.9 mmol) in dry THF (100 mL) under N_2 was added EtMgBr (52.5 mL, 126 mmol, 2.4 M in ether) over a period of 30 min. The gray suspension was stirred for 1 h, and CuBr·Me_2S (647 mg, 3.15 mmol) was added, followed, after 10 min, by a solution of the iodoheptyne (6.45 g, 20 mmol) in THF (10 mL). After 4 h, the reaction was quenched with saturated NH_4Cl and diluted with hexane and 2 N NH_4OH. The organic phase was washed with 2 N NH_4OH and brine, dried (Na_2SO_4), and concentrated. Flash chromatography (20% EA/hex) afforded 4.56 g (86%) of a colorless oil which yellowed upon standing: R_f = 0.15 in 20% EA/hex; ^1H NMR (500 MHz) δ 4.55 (dd, 1H, *J* = 4.0, 2.8), 3.85 (m, 1H), 3.74 (dt, 1H, *J* = 6.4, 9.7), 3.69 (t, 2H, *J* = 6.0), 3.49 (m, 1H), 3.39 (dt, 1H, *J* = 6.4, 9.7), 3.12 (m, 2H), 2.43 (m, 2H), 2.19 (m, 2H), 1.81 (m, 1H, OH), 1.72−1.49 (10H); ^{13}C NMR (125 MHz) 98.7, 76.7, 74.3, 66.9, 62.2, 61.0, 30.6, 28.8, 25.4, 23.0, 19.5, 18.5, 9.7; HRMS calcd for $C_{16}H_{24}O_3Li$ (M + Li) 271.1886, found 271.1876.

11-(Tetrahydro-2*H*-pyran-2-yloxy)-3(*Z*),6(*Z*)-undecadien-1-ol (5). Nickel acetate tetrahydrate (3.81 g, 15 mmol) was dissolved in 200 mL of 95% ethanol and placed under a balloon of H_2. Sodium borohydride (15 mL of a 1 M solution in ethanol) was added at room temperature, followed, after 20 min, by

(44) During the course of these studies, we found some commercial batches of soybean lipoxygenase to be nearly inactive. Typically, 50−100 mg of good quality commercial enzyme will dioxygenate 2 g of linoleic acid within 2 h.

(45) Kunau, W. *Chem. Phys. Lipids* **1970**, *7*, 108−120.

ethylenediamine (4 mL, 60 mmol). The diynol (4.11 g, 15.5 mmol) was added in absolute ethanol (25 mL), and the reaction was monitored by TLC. After 3 h, the reaction was filtered through Celite and diluted with water. The hexane extract was dried (Na_2SO_4) and concentrated. Flash chromatography (30% EA/hex) gave 2.75 g (68%) of the dienol as a colorless oil: R_f = 0.78 in 50% EA/hex; ^{1}H NMR (500 MHz) δ 5.49–5.27 (m, 4H), 4.56 (dd, 1H, J = 4.0, 3.2), 3.84 (m, 1H), 3.71 (dt, 1H, J = 6.9, 9.7), 3.62 (t, 2H, J = 6.7), 3.48 (m, 1H), 3.37 (dt, 1H, J = 6.6, 9.7), 2.80 (t, 2H, J = 7), 2.33 (q, 2H, J = 6.9), 2.07 (q, 2H, J = 7.2), 1.82–1.41 (11H); ^{13}C NMR (125 MHz) δ 131.3, 130.1, 127.8, 125.4, 98.8, 67.4, 62.3, 62.2, 30.9, 30.7, 29.3, 27.0, 26.2, 25.8, 25.5, 19.6.

11-Bromo-1-(tetrahydro-2*H*-pyran-2-yloxy)-5(*Z*),8(*Z*)-undecadiene (6). To a 0 °C solution of the diene alcohol (2.70 g, 10.1 mmol), imidazole (963 mg, 1.4 equiv), and Ph_3P (3.98 g, 1.5 equiv) in CH_2Cl_2 (100 mL) was added CBr_4 (4.69 g, 1.4 equiv). After 5 min, the reaction mixture was brought to room temperature and stirred for 1 h. The reaction was quenched with 10% Na_2SO_3 and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (10% EA/hex) to furnish 3.21 g (96%) of the bromo diene: R_f = 0.76 in 20% EA/hex; ^{1}H NMR (500 MHz) δ 5.49–5.35 (m, 4H), 4.55 (t, 1H, J = 3.4), 3.84 (m, 1H), 3.71 (m, 1H), 3.48–3.38 (m, 2H), 3.35 (t, 2H, J = 7.2) 2.76 (t, 2H, J = 7.2), 2.62 (t, 2H, J = 7.2), 2.07 (q, 2H, J = 7.2), 1.82–1.41 (10H); ^{13}C NMR (125 MHz) δ 131.2, 130.4, 127.4, 126.1, 98.8, 67.4, 62.3, 32.4, 30.8, 30.7, 29.3, 27.1, 26.2, 25.8, 25.5, 19.6; HRMS calcd for $C_{16}H_{27}O_2BrLi$ (M + Li) 337.1355, found 337.1349.

11-Bromo-5(*Z*),8(*Z*)-undecadien-1-ol (7).[20] To a solution of the diene acetal (1.32 g, 3.98 mmol) in MeOH (40 mL) was added $TsOH{\cdot}H_2O$ (166 mg, 0.2 equiv). The reaction was quenched after 2 h by addition of 5% Na_2CO_3 (5 mL) and concentrated. Flash chromatography (20% EA/hex) afforded 935 mg (95%) of a colorless oil: R_f = 0.29 in 20% EA/hex; ^{1}H NMR (500 MHz) δ 5.49–5.35 (m, 4H), 3.60 (t, 2H, J = 6.6), 3.34 (t, 2H, J = 7.3), 2.76 (t, 2H, J = 7.0), 2.61 (q, 2H, J = 7.2), 2.06 (q, 2H, J = 7.2), 1.57 (bs, 1H), 1.53 (m, 2H), 1.40 (m, 2H); ^{13}C NMR (75 MHz) δ 131.0, 130.1, 127.5, 126.1, 62.7, 32.3, 32.3, 30.7, 26.9, 25.7, 25.7; HRMS calcd for $C_{11}H_{19}OBrLi$ (M + Li) 253.0780, found 253.0765.

Methyl 11-Bromo-5(*Z*),8(*Z*)-undecadienoate (8)[20] was prepared by a literature procedure except that the crude acid was filtered through silica gel with hexane/2-propanol/HOAc (225:25:1). Esterification with diazomethane in ether afforded 424 mg (93%) of the ester as a colorless oil: R_f = 0.54 in 10% EA/hex; ^{1}H NMR (500 MHz) δ 5.49–5.35 (m, 4H), 3.66 (s, 3H), 3.36 (t, 2H, J = 7.2), 2.76 (t, 2H, J = 6.0), 2.63 (q, 2H, J = 7.0), 2.31 (t, 2H, J = 7.5), 2.09 (app q, 2H, J = 5.5, 6.5), 1.68 (quintet, 2H, J = 7.5); ^{13}C NMR δ 173.8, 130.8, 129.1, 128.2, 126.151.3, 33.2, 32.2, 30.6, 26.4, 25.6, 24.6.

(10-(Methoxycarbonyl)-3(*Z*),6(*Z*)-decadienyl)triphenylphosphonium bromide (9) was prepared according to a reported procedure except that the crude phosphonium salt was azeotropically dried with toluene and used without further purification:[20] ^{1}H NMR (300 MHz) δ 7.75 (15H), 5.51 (1H), 5.27 (m, 3H), 3.86 (m, 2H), 3.60 (s, 3H), 2.50 (t, 2H, J = 7), 2.40 (m, 2H), 2.21 (t, 2H, J = 7.4), 1.90 (q, 2H), 1.59 (quintet, 2H); HRMS calcd for $C_{30}H_{34}O_2P$ (M^+) 457.2296, found 457.2292.

4(*S*)-[(1-Methoxy-1-methylethyl)dioxy]-2(*E*)-nonenal (10) was prepared according to a reported procedure.[24]

Methyl 15(*S*)-[(1-Methoxy-1-methylethyl)dioxy]-5(*Z*),8(*Z*),11(*Z*),13(*E*)-eicosatetraenoate (11). To a −20 °C solution of phosphonium salt **9** (752 mg, 1.4 mmol) and HMPA (3 mL) in dry THF (14 mL) under N_2 was added dropwise a solution of $LiN(TMS)_2$ (1.25 mmol, 1 M in THF). The red solution was stirred for 20 min and then cooled to −78 °C. A solution of aldehyde **10** (98 mg, 0.4 mmol) and HMPA (1 mL) in THF (14 mL) was added via double-needle, and the resulting solution was stirred for 1 h. The reaction was quenched with water (2 mL) and extracted with hexane. After drying (Na_2SO_4) and concentration, the residue was purified by flash chromatography (10% EA/hex) to give 140 mg (83%) of the perketal as a 95:5 mixture of 11*Z*:11*E* isomers: R_f = 0.53 in 10% EA/hex; ^{1}H NMR (300 MHz) δ 6.50 (dd, 1H, J = 15.3, 10.9), 6.00 (t, 1H, J = 10.7), 5.64 (dd, 1H, J = 15.1, 8.0), 5.37 (m, 5H), 4.40 (q, 1H, J = 7.6), 3.66 (s, 3H), 3.28 (s 3H), 2.95 (bt, 2H, J= 6,), 2.79 (t, 2H, J = 5.5), 2.30 (t, 2H, J = 7.6), 2.10 (qt, 2H, J = 7), 1.69 (quintet, 2H, J = 7.40), 1.46–1.25 (14H), 0.87 (t, 3H, J = 6.5); ^{13}C NMR (75 MHz) δ 174.1, 133.6, 130.1, 129.0, 128.7, 128.6, 128.2, 127.6, 127.5, 104.6, 84.7, 51.5, 49.2, 33.4, 33.0, 31.7, 26.5, 26.1, 25.6, 25.1, 24.7, 23.0, 22.8, 22.5, 14.1; HRMS calcd for $C_{25}H_{42}O_5Li$ (M + Li) 429.3193, found 429.3207.

Methyl 15(*S*)-Hydroperoxy-5(*Z*),8(*Z*),11(*Z*),13(*E*)-eicosatetraenoate (15-HPETE Methyl Ester, 12). The perketal ester (28 mg, 66 mmol, 95:5 11*Z*/11*E*) and a trace of BHT were dissolved in 90:10 acetic acid/H_2O (2 mL). After 90 min, the solution was concentrated to dryness and directly subjected to flash chromatography (20% EA/hex) to afford 22 mg (95%) of hydroperoxy ester. Traces of the 11*E* isomer were removed by HPLC (5% EA/hex): R_f = 0.5 in 20% EA/hex; $[\alpha]_D$ = −2.5 (c = 0.48, MeOH); ^{1}H NMR (500 MHz) δ 8.02 (s, 1H), 6.60 (dd, 1H, J = 15.1, 11.1), 6.02 (t, 1H, J = 11), 5.60 (dd, 1H, J = 15.1, 8.1), 5.45 (dt, 1H, J = 10.7, 7.5), 5.38 (m, 4H), 4.38 (q, 1H), 3.66 (s, 3H), 2.96 (m, 2H), 2.80 (t, 2H, J = 6), 2.32 (t, 2H, J = 7.5), 2.09 (q, 2H, J = 7.5), 1.69 (quintet, 2H, J = 7.5), 1.48–1.24 (8H), 0.87 (t, 3H, J = 6.5); ^{13}C NMR (75 MHz) δ 174.4, 132.1, 131.1, 129.4, 129.0, 128.8, 128.7, 127.7, 127.3, 86.6, 51.6, 33.4, 32.5, 31.7, 26.5, 26.2, 25.6, 25.0, 24.7, 22.5, 14.0; UV λ_{max} 237 nm (ϵ = 27 000, MeOH); HRMS calcd for $C_{21}H_{34}O_4Li$ (M + Li) 357.2618, found 357.2606.

15(*S*)-[[1-Methyl-1(α,*R*)-[(2β-phenylcyclohexyl)oxy]ethyl]dioxy]-5(*Z*),8(*Z*),11(*Z*),13(*E*)-eicosatetraenoate. To a solution of the 15(*S*)-HPETE methyl ester (8 mg, 20 μmol) in CH_2Cl_2 (2 mL) was added the 2-propenyl ether of (−)-*trans*-2-phenylcyclohexanol (10 μL) and a trace amount of pyridinium *p*-toluenesulfonate. After 1 h, the reaction was quenched with water and extracted with hexane. The concentrated organic extracts were directly compared by high-field NMR against the mixture of diastereomers obtained upon reaction of the hydroperoxide with racemic enol ether. Comparison of the methyl singlets at 0.5 ppm indicated that the hydroperoxide was formed in >95% ee.[18]

15(*S*)-Hydroperoxy-5(*Z*),8(*Z*),11(*Z*),13(*E*)-eicosatetraenoic Acid (15-HPETE, 1). To a 0 °C solution of 15-HPETE methyl ester (24 mg, 69 mmol) and a trace of BHT in 3:1 THF/H_2O (1.4 mL) under N_2 was added H_2O_2 (0.03 mL, 4 equiv, 35% solution) and LiOH (6 mg, 2 equiv). After 10 min, the mixture was allowed to warm to room temperature and was stirred for 1 day. The solution was acidified to pH 3 with 10% aqueous HCl and extracted with CH_2Cl_2 (2 × 10 mL). The organic phase was diluted with cycloheptene (5 mL) and concentrated. Flash chromatography of the residue afforded 18 mg (82%) of 15(*S*)-HPETE as a colorless oil: $[\alpha]_D$ = −4.6 (c = 0.4, MeOH); ^{1}H NMR (500 MHz) δ 6.60 (dd, 1H, J = 14.9, 11.3), 6.01 (t, 1H, J = 10.9), 5.59 (dd, 1H, J = 15.3, 8.1), 5.45 (m, 1H), 5.38 (m, 4H), 4.38 (dd, 1H, J = 7.6, 6.7), 2.96 (m, 2H), 2.80 (t, 2H), 2.36 (t, 2H, J = 7.3), 2.09 (q, 2H, J = 7.5), 1.69 (quintet, 2H, J = 7.5), 1.47–1.28 (8H), 0.87 (t, 3H, J = 6.5); ^{13}C NMR (125 MHz) δ 178.0, 131.8, 131.3, 129.6, 128.8, 128.8, 128.7, 127.6, 127.3, 86.7, 33.2, 32.4, 31.7, 26.4, 26.1, 24.9, 24.3, 22.5, 14.0; HRMS calcd for $C_{20}H_{32}O_4Na$ (M + Na) 359.2198, found 359.2192.

An authentic sample of 15(*S*)-HPETE (**1**) generated from soybean lipoxygenase and arachidonic acid by literature procedures was identical in every respect except rotation: $[\alpha]_D$ = −4.4 (c = 0.4, MeOH).[24,25] Treatment of the lipoxygenase-derived material with ethereal diazomethane afforded 15-HPETE methyl ester identical with **12** in every respect except optical rotation: $[\alpha]_D$ = −3.5 (c = 1.45, MeOH). ^{1}H NMR analysis of the chiral peracetals formed upon reaction with *trans*-2-phenylcyclohexyl 2-propenyl ether indicated that the enzymatically derived hydroperoxide was formed in >95% ee.

2-[(8-Iodooctyl)oxy]-2*H*-tetrahydropyran (13) was prepared from 8-(2-tetrahydro-2*H*-pyran-2-yloxy)-1-octanol by a similar procedure as employed for **3** except that ether/CH_3CN (3:1) was used as solvent. Chromatography (10% EA/hex) afforded 14.65 g (92%) of iodooctane as a colorless oil: R_f = 0.45 in 10% EA/Hex; ^{1}H NMR (300 MHz) δ 4.54 (t, 1H), 3.84 (m, 1H), 3.72 (dt, 1H, J = 9.5, 6.9), 3.49 (m, 1H), 3.39 (m, 1H),

3.15 (t, 2H, J = 7.0), 1.80–1.29 (18H); ^{13}C NMR (75 MHz) δ 98.8, 67.5, 62.3, 33.4, 30.7, 30.3, 29.6, 29.2, 28.4, 26.1, 25.4, 19.6, 7.2.

12-(2-Tetrahydro-2*H*-pyran-2-yloxy)-3-dodecyn-1-ol (14).[46] To a −78 °C solution of 3-butyn-1-ol (4.21 g, 60 mmol) and HMPA (21 mL, 120 mmol) in THF (120 mL) under N_2 was added *n*-BuLi (44 mL, 110 mmol, nominally 2.5 M in hexane). The reaction was brought to −30 °C for 45 min after which was added the iodooctane acetal (10.22 g, 30 mmol) in THF (20 mL). The reaction mixture was stirred at room temperature for 6 h and then quenched with water. The EA/hex extract was dried over Na_2SO_4 and concentrated. Purification by flash chromatography on silica gel (30% EA/hex) provided 6.32 g (75%) of the diynol as a colorless oil: R_f =0.25 in 20% EA/hex; ^{1}H NMR (300 MHz) δ 4.53 (t, 1H, J = 3.6), 3.84 (m, 1H), 3.70 (dt, 1H, J = 9.5, 6.7), 3.63 (t, 2H, J = 6.7), 3.47 (m, 1H), 3.35 (m, 1H), 2.57 (t, 1H, J = 6.0), 2.31 (tt, 2H, J = 6.7, 2.4), 2.05 (tt, 2H, J = 6.9, 2.4), 1.79–1.26 (18H); ^{13}C NMR (75 MHz) δ 98.6, 82.0, 76.3, 67.4, 62.4, 62.1, 61.1, 30.5, 29.5, 29.1, 28.8, 28.7, 28.6, 25.9, 25.3, 19.4, 18.5.

12-(2-Tetrahydro-2*H*-pyran-2-yloxy)-3(*Z*)-dodecen-1-ol (15) was prepared from diyne **14** in a similar manner as **5** to furnish 94% of the dodecenol as a colorless oil:[46] R_f = 0.28 in 20% EA/hex; ^{1}H NMR (300 MHz) δ 5.46 (m, 1H, olefinic proton), 5.29 (m, 1H, olefinic proton), 4.53 (t, 1H, J = 3.6), 3.83 (m, 1H), 3.70 (dt, 1H J = 9.5, 6.7), 3.63 (q, 2H, J = 6.3), 3.47 (m, 1H), 3.35 (dt, 1H, J = 9.5, 6.7), 2.27 (q, 2H, J = 6.7), 2.01 (apparent q, 2H, J = 6.9), 1.79–1.26 (18H); ^{13}C NMR (75 MHz) δ 133.2, 125.0, 98.7, 67.6, 62.2, 62.2, 30.7, 30.7, 29.6, 29.6, 29.3, 29.1, 27.2, 26.1, 25.4, 19.6; HRMS (M + H) calcd for $C_{17}H_{32}O_3$ 283.2273, found 283.2274.

(12-Iodo-9(*Z*)-dodecenyloxy)-2*H*-tetrahydropyran (16) was prepared from alcohol **15** in a similar manner to **3** except that 3:1 ether/CH_3CN was employed as a solvent. Chromatography (10% EA/hex) afforded 7.27 g (89%) of the iododecene as a colorless oil: R_f = 0.68 in 20% EA/hex; ^{1}H NMR (300 MHz) δ 5.46 (m, 1H), 5.29 (m, 1H), 4.53 (t, 1H, J = 3.6), 3.83 (m, 1H), 3.70 (dt, 1H, J = 9.5, 6.7), 3.47 (m, 1H), 3.35 (dt, 1H, J = 9.5, 6.9), 3.09 (t, 2H, J = 7.4), 2.59 (apparent q, 2H, J = 7.1), 1.96 (app q, J = 6.7), 1.79–1.26 (10H); ^{13}NMR (75 MHz) δ 132.6, 127.6, 98.7, 67.5, 62.2, 31.4, 30.7, 30.4, 29.4, 29.3, 29.1, 27.3, 26.1, 25.4, 19.6, 5.4. Anal. Calcd: C, 51.78; H, 7.92. Found: C, 51.79; H, 8.04.

[12-(2-Tetrahydro-2*H*-pyran-2-yloxy)-3(*Z*)-dodecen-1-yl]triphenylphosphonium Iodide (17). To a solution of the iododecene (7.27 g, 18.5 mmol) in 3:1 toluene/CH_3CN (50 mL) was added Ph_3P (4.86 g, 1 equiv), and the reaction was maintained at 60 °C for 48 h. After removal of solvents *in vacuo*, the residue was washed with anhydrous ether and dried under high vacuum to give a viscous oil (9.9 g, 81%) which was used without further purification: ^{1}H NMR (300 MHz) δ 7.72 (15H), 5.46 (q, 1H), 5.29 (m, 1H), 4.45 (t, 1H), 3.75 (m, 2H), 3.59 (m, 2H), 3.39 (m, 2H), 3.27 (dt, 1H, J = 9.5, 6.7), 3.24 (m, 2H), 1.71–1.07 (19H).

Methyl 17-(2-Tetrahydro-2*H*-pyran-2-yloxy)-5(*Z*),8(*Z*)-heptadecadienoate (18). To a stirred −20 °C solution of the Wittig salt (7.00 g, 10.7 mmol) and HMPA (5.0 mL, 28.7 mmol) in dry THF (100 mL) under N_2 was added dropwise a solution of $LiN(TMS)_2$ in THF (8.5 mmol, nominally 1 M). The resulting red solution was stirred at 0 °C for 1 h and then cooled to −78 °C. A solution of methyl 4-formylbutyrate (910 mg, 7 mmol) in THF (4 mL) was slowly added, and the resulting mixture was maintained at −78 °C for 90 min before the reaction was quenched with water. The hexane extract was dried and concentrated. The residue was subjected to flash chromatography (10% EA/hex) to furnish 1.79 g (67%) of the dienoate as a colorless oil: R_f = 0.60 in 20% EA/hex; ^{1}H NMR (300 MHz) δ 5.33 (m, 4H), 4.53 (t, 1H), 3.83 (m, 1H), 3.70 (m, 1H), 3.63 (s, 3H), 3.47 (m, 1H), 3.37 (dt, 1H, J = 9.6, 6.7), 2.72 (t, 2H, J = 6.1), 2.28 (t, 2H, J = 7.5), 2.07 (q, 2H, J = 6.7), 2.02 (q, 2H, J = 6.4), 1.69–1.45 (10H), 1.27 (10H); ^{13}C NMR (75 MHz) δ 173.7, 130.1, 129.0, 128.4, 127.4, 98.6, 67.4, 62.0, 51.2, 33.1, 30.6, 29.6, 29.4, 29.3, 29.2, 29.0, 27.0, 26.3, 26.0, 25.4, 25.3, 24.6, 19.5; HRMS calcd for $C_{23}H_{40}O_4Li$ (M + Li) 387.3087, found 387.3087.

Methyl 17-hydroxy-(5*Z*),8(*Z*)-heptadecadienoate was prepared from acetal **18** in a similar manner as for **7**. Workup and chromatography (40% EA/hex) afforded 1.18 g (95%) of the hydroxyheptadecadienoate as a colorless oil: R_f = 0.16 in 20% EA/hex; ^{1}H NMR (500 MHz) δ 5.36 (m, 4H), 3.65 (s, 3H), 3.62 (t, 2H, J = 6.7), 2.74 (t, 2H, J = 6.7), 2.31 (t, 2H, J = 7.7), 2.09 (q, 2H, J = 7.1), 2.03 (q, 2H, J = 6.9), 1.69 (m, 2H), 1.55 (m, 2H), 1.33–1.29 (10H); ^{13}C NMR (125 MHz) δ 174.0, 130.2, 129.1, 128.5, 127.6, 62.8, 51.3, 33.3, 32.7, 29.5, 29.4, 29.3, 29.1, 27.1, 26.4, 25.7, 25.5, 24.7. Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 73.11; H, 10.67.

9(*Z*),12(*Z*)-Heptadecadiendioic Acid, 17-Methyl Ester (19). To a 0 °C solution of methyl-17-hydroxy-5(Z),8(Z)-heptadecadienoate (1.14 g, 3.85 mmol) in acetone (120 mL) was added dropwise excess Jones reagent (10 mmol, 4 mL, 2.5 M) under N_2. After the reaction was judged to be complete by TLC, the precipitate was removed by filtration and the orange solution was diluted with water. The reaction mixture was extracted with 20% EA/hex and washed with brine. The organic layer was concentrated and dried in the presence of a trace of butylated hydroxytoluene to afford the acid (1.07 g) as a pale yellow oil, which was used without further purification: R_f = 0.49 in 1:25:225 HOAc/IPA/hex; ^{1}H (500 MHz) δ 5.36 (4H), 3.66 (s, 3H), 2.75 (t, 2H, J = 6.7), 2.34 (t, 2H, J = 7.5), 2.31 (t, 2H, J = 7.5), 2.09 (q, 2H, J = 7.3), 2.03 (q, 2H, J = 6.9), 1.69 (m, 2H, J = 7.46), 1.63 (m, 2H), 1.31 (8H); ^{13}C NMR (75 MHz) δ 180.0, 174.1, 130.1, 129.1, 128.5, 127.6, 51.4, 34.0, 33.3, 29.4, 29.0, 28.9, 28.9, 27.1, 26.4, 25.5, 24.7, 24.5; HRMS calcd for $C_{18}H_{30}O_4$ (M^+): 310.2144, found 310.2140.

13(*S*)-Hydroperoxy-9(*Z*),12(*Z*)-heptadecadiendioic Acid, 17-Methyl Ester (20). To a 0 °C solution of pH 9 borate buffer (500 mL, 0.2 M) under continuous O_2 aspiration was added soybean type I lipoxygenase (49 mg, Sigma) followed by a solution of methyl-5(Z),8(Z)-heptadecadiendioic acid (1.00 g, 3.22 mmol) in cold 95% EtOH (40 mL). After being stirred for 5 h, the reaction mixture was acidified to pH 3 with aqueous HCl (10%) and stabilized with a trace of butylated hydroxytoluene (BHT). The suspension was extracted with 40% EA/hex and dried. Removal of solvent *in vacuo* afforded the hydroperoxy acid as a colorless oil (931 mg, 84%), which was used without further purification: R_f = 0.44 in HOAc/IPA/Hex (1:25:225); ^{1}H NMR (500 MHz) δ 6.56 (dd, 1H, J = 15.3, 11.2), 5.98 (t, 1H, J = 10.9), 5.56 (dd, 1H, J = 15.3, 8.1), 5.48 (dt, 1H, J = 10.9, 7.8), 4.40 (q, 1H, J = 7.3), 3.66 (s, 3H), 2.33 (4H), 2.17 (q, 2H, J = 7.7), 1.71–1.38 (14H); ^{13}C NMR (75 MHz) δ 179.5, 174.2, 133.7, 130.6, 129.7, 127.5, 85.8, 51.6, 33.9, 33.6, 31.7, 29.2, 28.8, 28.8, 28.7, 27.6, 24.5, 20.4.

13(*S*)-[(1-Methoxy-1-methylethyl)dioxy]-9(*Z*),12(*Z*)-heptadecadiendioic Acid, 17-Methyl Ester (21). To a solution of hydroperoxide **21** (647 mg, approximately 1.89 mmol) in CH_2Cl_2 (10 mL) was added 2-methoxypropene (0.3 mL, 3.13 mmol, 1.7 equiv) and pyridinium *p*-toluenesulfonate (15 mg). After being stirred for 1 h, the reaction was quenched with water and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated to afford 780 mg of the peroxy ketal as a colorless oil which was used without further purification: R_f = 0.64 in 20% EA/hex: ^{1}H NMR (360 MHz) δ 6.56 (dd, 1H, J = 15.2), 5.98 (t, 1H, J = 10.9), 5.59 (dd, 1H, J = 15.1, 8.0), 5.42 (dt, 1H, J = 10.8, 7.6), 4.37 (q, 1H, J = 7.6), 3.65 (s, 3H), 3.28 (s, 3H); 2.33 (4H), 2.16 (q, 2H), 1.7–1.38 (20H).

Methyl 5(*S*)-[(1-Methoxy-1-methylethyl)dioxy]-8-oxo-6(*E*)-octenoate (22). Into a −78 °C solution of the crude perketal methyl ester (780 mg, 1.88 mmol) in 15% MeOH/CH_2Cl_2 (8 mL) was bubbled a gentle stream of O_3/O_2 for 3 min; excess ozone was subsequently purged with a stream of dry N_2. Ph_3P (493 mg, 1 equiv) was added, and the reaction was stirred for 1 h at 0 °C under N_2. The solvent was removed, and the residue was submitted to flash chromatography (20–30% EA/hex) to afford the perketal aldehyde (309 mg, 60% over two steps) as a colorless oil: R_f = 0.20 in 20% EA/hex); $[\alpha]_D$ = −74 (c = 0.5); ^{1}H NMR (300 MHz) δ 9.57 (d, 1H, J = 7.9), 6.77 (dd, 1H, J = 16.0, 6.2), 6.27 (ddd, 1H, J = 16.0, 7.9, 1.2), 4.67 (q, 1H, J = 6.2), 3.65 (s, 3H), 3.26 (s, 3H), 2.35 (t, 2H, J = 6.9), 1.76–1.65 (4H), 1.37 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75

(46) Maurer, B.; Grieder, A. *Helv. Chim. Acta* **1977**, *60*, 1155–1160.

MHz) δ 193.2, 173.3, 155.3, 132.5, 105.1, 82.1, 51.4, 49.2, 33.4, 31.7, 22.8, 22.5, 20.6.

3(Z),6(Z)-Dodecadien-1-yltriphenylphosphonium bromide (23) was prepared according to literature procedures.[41,42]

Methyl 5(S)-[(1-Methoxy-1-methylethyl)dioxy]-6(E),8-(Z),11(Z),14(Z)-eicosatetraenoate (24). To a −20 °C solution of the crude phosphonium salt (969 mg, assumed 1.9 mmol) and HMPA (0.33 mL, 1.9 mmol) in 19 mL of dry THF under N_2 was added dropwise a THF solution of $LiN(TMS)_2$ (1.5 mmol, 1.5 mL, nominally 1 M). The resulting orange-red solution was stirred at −20 °C for 45 min and then cooled to −78 °C prior to slow addition of a solution of the perketal aldehyde **22** (165 mg, 0.6 mmol) in 2 mL of THF. After 1 h, the reaction was quenched with water and extracted with 20% EA/hex. The organic layer was dried and concentrated. The residue was purified by flash chromatography (10% EA/hex) to furnish 222 mg (88%) of 5(S)-HPETE perketal methyl ester as a 95:5 mixture of 8Z:8E stereoisomers: R_f = 0.6 in 20% EA/hex; ^{1}H NMR (300 MHz) δ 6.51 (dd, 1H, J = 15.3, 11.2), 5.98 (t, 1H, J = 10.9), 5.61 (dd, 1H, J = 15.3, 8.0), 5.36 (5H), 4.36 (q, 1H, J = 7.6), 3.64 (s, 3H), 3.26 (s, 3H), 2.94 (t, 2H, J = 6.2), 2.79 (t, 2H, J = 6.0), 2.32 (t, 2H, J = 7.2), 2.03 (q, 2H, J = 6.9), 1.69 (2H), 1.55−1.25 (14H), 0.86 (t, 3H J = 6.8); ^{13}C NMR (75 MHz) δ 173.7, 132.7, 130.6, 130.5, 128.9, 128.0, 127.9, 127.4, 127.3, 104.6, 84.0, 51.4, 49.2, 33.8, 32.5, 31.5, 29.3, 27.2, 26.1, 25.6, 23.0, 22.7, 22.5, 20.9, 14.0; HRMS calcd for $C_{25}H_{42}O_5Li$ (M + Li) 429.3192, found 429.3210.

Methyl 5(S)-Hydroperoxy-6(E),8(Z),11(Z),14(Z)-eicosatetraenoate (5-HPETE Methyl Ester) (25). By a procedure similar to that employed for **12**, perketal **23** (80 mg, 0.19 mmol) was deprotected to afford, after flash chromatography (20% EA/hex), 62 mg (93%) of 5-HPETE methyl ester as a colorless oil. Traces of remaining 8E isomer were removed by HPLC with 7% EA/hex: R_f =0.36 in 20% EA/hex; $[\alpha]_D$ = −6.6 (c = 1.25, MeOH); ^{1}H NMR (300 MHz) δ 7.96 (s, 1H), 6.61 (dd, 1H, J = 15.1, 11.1), 6.01 (t, 1H, J = 10.9), 5.60 (dd, 1H, J = 15.1, 7.5,), 5.39 (m, 5H), 4.42 (q, 1H, J = 7.6), 3.67 (s, 3H), 2.97 (t, 2H, J = 6.7), 2.80 (t, 2H, J = 6.2), 2.35 (t, 2H, J = 6.8), 2.04 (q, 2H, J = 6.8), 1.76−1.28 (10H), 0.88 (t, 3H); ^{13}C NMR(75 MHz) δ 174.0, 131.7, 131.1, 130.6, 129.7, 129.1, 127.6, 127.3, 127.1, 85.9, 51.6, 33.7, 31.7, 31.5, 29.3, 27.2, 26.1, 25.7, 22.6, 20.5, 14.0; UV λ_{max} 236 nm (ε = 23 000, MeOH); HRMS calcd for $C_{21}H_{34}O_4Li$ (M + Li) 357.2617, found 357.2618.

5(S)-[[1-Methyl-1(α,R) -[(2β-phenylcyclohexyl)oxy]ethyl]dioxy]-6(E),8(Z),11(Z),14(Z)-eicosatetraenoate. To a solution of the 5(S)-HPETE methyl ester (5 mg, 14 μmol) in CH_2Cl_2 (1 mL) was added a solution of the 2-propenyl ether of (−)-*trans*-2-phenylcyclohexanol (6 mg, 2 equiv) and a trace amount of pyridinium *p*-toluenesulfonate. After 1 h, the reaction was quenched with water and extracted with hexane. The organic extracts were dried and concentrated whereupon the residue was directly analyzed by HPLC (3% EA/hex, 1 mL/min) to afford 5(S)-HPETE perketal as a single peak (6.5 mg, 80%):[18] R_f = 0.65 in 20% EA/hex; ^{1}H NMR (300 MHz) δ 7.24 (m, 5H), 6.44 (dd, 1H, J = 15.3, 11.2), 5.95 (t, 1H, J = 10.9), 5.51 (dd, 1H, J = 15.3, 8.0), 5.35 (m, 5H, olefinic), 4.30 (q, 1H, J = 7.9), 3.65 (s, 3H), 3.55 (m, 1H), 2.94 (t, 2H, J = 6.2), 2.51 (m, 1H), 2.32 (t, 2H, J = 7.2); 2.03 (q, 2H, J = 6.9), 1.87−1.25 (18H), 1.14 (s, 3H), 0.86 (t, 3H), 0.49 (s, 3H).

5(S)-Hydroperoxy-6(E),8(Z),11(Z),14(Z)-eiscosatetraenoic Acid (5-HPETE, 2). Deprotection of 5-HPETE methyl ester **25** (40 mg, 0.11 mmol) by a procedure similar to that used for the synthesis of **1** but with cyclohexene as the peracid scavenging agent afforded 32 mg (83%) of 5(S)-HPETE as a colorless oil: $[\alpha]_D$ = +6.1 (c = 0.83, MeOH); ^{1}H NMR (300 MHz) δ 6.61 (dd, 1H, J = 15.1, 11.1), 6.01 (t, 1H), 5.60 (dd, 1H, J = 15.1, 7.5), 5.39 (m, 5H, olefinic protons), 4.42 (q, 1H, J = 7.6), 2.97 (t, 2H, J = 6.7), 2.80 (t, 2H, J = 6.2), 2.40 (t, 2H, J = 6.7), 2.04 (q, 2H, J = 6.8), 1.75−1.28 (10H), 0.88 (t, 3H, J = 6.8); ^{13}C NMR (75 MHz) 179.2, 131.7, 131.1, 130.6, 129.8, 129.1, 127.6, 127.3, 127.1, 86.0, 33.6, 31.7, 31.5, 29.3, 27.2, 26.1, 25.6, 22.5, 20.4, 14.0.

Methyl 5(S)-Hydroxy-6(E),8(Z),11(Z),14(Z)-eiscosatetraenoate (5-HETE). To a solution of 5(S)-HPETE methyl ester (5 mg, 14 μmol) in ethyl acetate (0.5 mL) was added Ph_3P (4 mg, 1 equiv). The mixture was stirred at room temperature for 30 min and then directly subjected to chromatography (20% EA/hex) to afford 4 mg (80%) of 5(S)-HETE methyl ester as a colorless oil: R_f = 0.25 in 20% EA/hex; $[\alpha]_D$ = +13.6 (c = 0.11, C_6H_6) (lit.[13,15,43] $[\alpha]_D$ = +14 (c = 2, C_6H_6)); ^{1}H NMR (300 MHz) δ 6.52 (dd, 1H, J = 15.0, 11.0), 5.98 (t, 1H, J = 11.2), 5.68 (dd, 1H, J = 15.3, 6.9), 5.37 (5H), 4.18 (q, 1H, J = 6.3), 3.66 (s, 3H), 2.97 (t, 2H J = 6.7), 2.80 (t, 2H, J = 6.3), 2.35 (t, 2H, J = 7.3), 2.04 (q, 2H, J = 6.4), 1.73−1.28 (10H), 0.88 (t, 3H, J = 6.8).

2-(9-Decynyloxy)-2H-tetrahydropyran was prepared by a variant of a reported procedure:[47] To a 0 °C solution of lithium acetylide ethylenediamine complex (4.16 g, 1.4 equiv) in 1:1 DMSO/pentane (100 mL) was added a solution of 1-(2-tetrahydropyranyloxy)-8-iodooctane (11.0 g, 32.3 mmol) in pentane (30 mL). The reaction was stirred at room temperature for 6 h and quenched with water. The reaction was extracted with hexane, dried (Na_2SO_4), and concentrated to afford 7.01 g (91%) of a colorless oil which was used without further purification: R_f = 0.51 in 10% EA/hex; ^{1}H NMR (300 MHz) δ 4.55 (m, 1H), 3.83 (m, 1H), 3.70 (dt, 1H, J = 9.5, 6.7), 3.47 (m, 1H), 3.35 (dt, 1H, J = 9.5, 6.7), 2.12 (m, 2H), 1.88 (t, 1H, J = 2.6), 1.78−1.28 (18H).

1,17-Bis(Tetrahydro-2H-pyran-2-yloxy)-5,8-heptadecadiyne. A solution of 2-(9-decynyloxy)-2H-tetrahydropyran (5.81 g, 24.37 mmol, 1.4 equiv) in dry THF (50 mL) was coupled with 2-(7-iodo-5-heptyn-1-yl)-2H-tetrahydropyran (**3**) using a similar procedure as employed for compound **4** to afford 92% of the heptadecadiyne as a colorless oil which slowly yellowed upon standing: R_f = 0.48 in 20% EA/hex; ^{1}H NMR (300 MHz) δ 4.53 (t, 2H, J = 3.6), 3.83 (m, 2H), 3.70 (dt, 2H, J = 9.5, 6.7), 3.47 (m, 2H), 3.35 (dt, 2H, J = 9.5, 6.7), 3.09 (quintet, 2H, J = 2.4), 2.15 (m, 4H); ^{13}C NMR (75 MHz) δ 98.2, 98.2, 79.8, 74.4, 74.1, 67.1, 66.5, 61.6, 61.6, 30.3, 30.3, 29.3, 28.9, 28.7, 28.5, 28.4, 28.3, 25.8, 25.1, 19.2, 19.1, 18.3, 18.1, 9.2; HRMS calcd for $C_{27}H_{44}O_4$ (M^+) 432.3240, found 432.3240.

1,17-Bis(Tetrahydro-2H-pyran-2-yloxy)-5(Z),8(Z)-heptadecadiene was produced from the diyne in 82% yield by a similar procedure as employed for **5**: R_f = 0.59 in 20% EA/hex; ^{1}H NMR (300 MHz) δ 5.33 (m, 4H), 4.53 (s, 2H), 3.83 (m, 2H), 3.70 (dt, 2H, J = 9.5, 6.7), 3.47 (m, 2H), 3.35 (dt, 2H, J = 9.5, 6.7), 2.73 (t, 2H, J = 5.7), 2.04 (m, 4H), 1.80−1.26 (28H); ^{13}C NMR (75 MHz) δ 130.1, 129.7, 128.2, 127.8, 98.7, 98.7, 67.5, 67.3, 62.2, 62.1, 30.7, 29.7, 29.5, 29.4, 29.4, 29.3, 29.2, 27.1, 26.9, 26.2, 26.1, 25.5, 25.4, 19.6, 19.5; HRMS calcd for $C_{27}H_{48}O_4$ (M^+) 436.3552, found 436.3558.

5(Z),8(Z)-Heptadecadien-1,17-diol (26) was prepared in 98% yield through deprotection of the bisTHP diene through a similar procedure as employed for **7**: R_f = 0.40 in 5:35:60 MeOH/EA/Hex; ^{1}H NMR (300 MHz) δ 5.35 (4H, olefinic protons), 3.62 (m, 4H), 2.75 (t, 2H, J = 5.7), 2.07−1.98 (4H), 1.96 (2H, s), 1.53 (app. quintet, 4H), 1.28 (12H); ^{13}C NMR (75 MHz) δ 130.2, 129.6, 128.4, 127.8, 62.9, 62.7, 32.7, 32.3, 29.5, 29.4, 29.3, 29.1, 27.1, 26.9, 25.7, 25.7, 25.6; HRMS calcd for $C_{17}H_{33}O_2$ (M + H) 269.2480, found 269.2494.

5(Z),8(Z)-Heptadecadiene-1,17-dioic acid (27) was prepared in 63% yield from the heptadecadienediol by a similar procedure as used for **19** except that the diacid was purified by flash chromatography (225:25:1 hexane/IPA/HOAc): R_f = 0.25 in 225:25:1 hexane/IPA/HOAc; ^{1}H NMR (300 MHz) δ 5.37 (4H), 2.75 (t, 2H, J = 6.1), 2.34 (m, 4H), 2.11 (q, 4H), 1.69 (app quintet, 2H), 1.61 (m, 2H), 1.28 (8H); ^{13}C NMR (75 MHz) δ 180.5, 180.2, 130.2, 129.3, 128.4, 127.6, 34.0, 33.4, 29.4, 29.0, 28.9 (overlapping peaks), 27.1, 26.3, 25.5, 24.5, 24.4; HRMS calcd for $C_{17}H_{29}O_4$ (M + H) 297.2066, found 297.2068.

12-Iodo-9(Z)-dodecen-1-ol was prepared by the deprotection of acetal **16** by a procedure similar to that used for the synthesis of **7**. After purification by flash chromatography (30% EA/hex), the iodododecenol was obtained in 99% yield as a colorless oil: R_f = 0.34 in 20% EA/hex; ^{1}H NMR (300 MHz) δ 5.46 (1H), 5.28 (1H), 3.56 (t, 2H, J = 6.6), 3.11 (t, 2H, J = 7.3), 2.60 (q, 2H, J = 7.2), 2.04 (bs, 1H), 1.96 (apparent q, 2H, J = 6.7), 1.50 (quintet, 2H), 1.26 (10H); ^{13}C NMR (75 MHz) δ

(47) Rossi, R.; Carpita, A.; Gaudenzi, L.; Quirici, M. G. *Gazz. Chim. Ital.* **1980**, *110*, 237−246.

132.5, 127.6, 62.7, 32.6, 31.4, 29.3, 29.2, 29.0, 27.3, 25.6, 5.4. Anal. Calcd for $C_{12}H_{23}OI$: C, 46.46, H, 7.47. Found: C, 46.56, H, 7.26.

12-Iodo-9(Z)-dodecenoic acid was prepared in 91% yield from iodododecenol using a similar procedure as employed for the synthesis of **19**: R_f = 0.1 in 20% EA/hex; ^{1}H NMR (300 MHz) δ 5.52 (m, 1H), 5.48 (m, 1H), 3.08 (t, 2H, J = 7.3), 2.60 (q, 2H, J = 7.3), 2.33 (t, 2H, J = 7.5), 1.99 (q, 2H, J = 6.7), 1.61 (quintet, 2H, J = 7.3), 1.29 (8H); ^{13}C NMR (75 MHz) δ 180.5, 132.5, 127.8, 34.0, 31.4, 29.3, 29.0, 28.9, 28.9, 27.3, 24.5, 5.5; HRMS calcd for $C_{12}H_{21}O_2I$ (M^+) 324.0587, found 324.0570.

Methyl 12-Iodo-9(Z)-dodecenoate. To a 0 °C solution of 12-iodo-9(Z)-dodecenoic acid (2.64 g, 8.46 mmol) in ether (25 mL) was added a distilled solution of diazomethane/ether until the yellow color persisted. The reaction was purged with a stream of dry N_2 to remove excess diazomethane and concentrated *in vacuo*. The residue was purified by flash chromatography (10% EA/hex) to provide 2.59 g (94%) of the methyl dodecenoate as a colorless oil: R_f = 0.73 in 20% EA/hex; ^{1}H NMR (300 MHz) δ 5.46 (m, 1H), 5.28 (m, 1H), 3.61 (s, 3H), 3.11 (t, 2H, J = 7.3), 2.60 (q, 2H, J = 7.2), 2.29 (t, 2H J = 7.5), 1.96 (q, 2H J = 6.7), 1.61 (quintet, 2H), 1.29 (8H); ^{13}C NMR (75 MHz) δ 174.1, 132.4, 127.7, 51.3, 33.9, 31.4, 29.3, 29.0, 28.9, 28.9, 27.3, 24.8, 5.4; HRMS calcd for $C_{13}H_{23}O_2I$ (M^+) 338.0743, found 338.0753.

(11-Carbomethoxy-3(Z)-undecenyl)triphenylphosphonium Iodide. To a solution of methyl 12-iodo-9(Z)-dodecenoate (2.59 g, 7.94 mmol) in CH_3CN (25 mL) was added Ph_3P (2.08 g, 1 equiv). After the solution was stirred for 2 days at 80 °C, the solvent was removed *in vacuo*. The residue was washed with anhydrous ether to give a viscous oil (4.6 g, appx 99%) which was used without further purification: ^{1}H NMR (300 MHz) δ 7.78 (15H), 5.46 (m, 1H), 5.28 (m, 1H), 3.68 (m, 2H), 3.61 (s, 3H), 2.49, (m, 2H), 2.29 (t, 2H, J = 7.5), 1.96 (q, 2H, J = 6.7), 1.61 (quintet, 2H), 1.29 (m, 8H).

5-(Tetrahydro-2*H*-pyran-2-yloxy)pentanal was prepared according to a reported procedure:[48] R_f = 0.28 in 20% EA/hex; ^{1}H NMR (300 MHz) δ 9.73 (t, 1H, J = 1.8), 4.53 (t, 1H, J = 3.4), 3.83 (m, 1H), 3.70 (dt, 1H, J = 9.5, 6.7), 3.47 (m, 1H), 3.35 (dt, 1H J = 9.5, 6.7), 2.43 (td, 2H, J = 5.6, 1.6), 1.71–1.48 (10H).

Methyl 17-(Tetrahydro-2*H*-pyran-2-yloxy)-9(Z),11(Z)-heptadecadienoate. To a stirred −20 °C solution of phosphonium salt (3.84 g, 6.53 mmol) and HMPA (2.3 mL) in THF (65 mL) under N_2 was added dropwise a 1 M THF solution of $LiN(TMS)_2$ (6 mL, 6 mmol). The resulting red solution was brought to 0 °C for 1 h before being recooled to −78 °C. A solution of 5-(tetrahydro-2*H*-pyran-2-yloxy)pentanal (745 mg, 4 mmol) in THF (5 mL) was slowly added, and resulting mixture was stirred for 90 min before being quenched with water. The hexane extract was dried and concentrated. The residue was purified by flash chromatography (10% EA/hex) to give 745 mg (48%) of the diene ester as a colorless oil: R_f = 0.60 in 20% EA/hex; ^{1}H NMR (300 MHz) δ 5.32 (m, 4H, olefinic protons), 4.56 (t, 1H, J = 3.4), 3.83 (m, 1H), 3.70 (m, 1H), 3.63 (s, 3H), 3.47 (m, 1H), 3.37 (dt, 1H, J = 9.7, 6.4), 2.72 (t, 2H, J = 5.6), 2.28 (t, 2H, J = 7.5), 2.07 (m, 4H), 1.78–1.38 (12H), 1.27 (8H); ^{13}C NMR (75 MHz) δ 174.2, 130.0, 129.7, 128.2, 127.9, 98.7, 67.4, 62.2, 51.4, 34.0, 30.7, 29.5, 29.3, 29.1, 29.0, 27.1, 27.0, 26.3, 25.6, 25.5, 24.9, 19.6; HRMS calcd for $C_{23}H_{40}O_4Li$ (M + Li) 387.3087, found 387.3087.

Methyl 17-hydroxy-9(Z),11(Z)-heptadecadienoate was prepared in 85% yield from the acetal by a similar procedure as employed for synthesis of **7** except that flash chromatography required 40% EA/hex: R_f = 0.20 in 20% EA/hex; ^{1}H NMR (300 MHz) δ 5.34 (4H), 3.64 (s, 3H,), 3.63 (t, 2H, J = 6.7), 2.74 (t, 2H, J = 5.6), 2.27 (t, 2H, J = 7.5), 2.05 (m, 4H), 1.60 (m, 4H), 1.44 (m, 2H), 1.29 (8H); ^{13}C NMR (75 MHz) δ 174.3, 130.0, 129.5, 128.2, 127.8, 62.5, 51.3, 33.9, 32.2, 29.3, 29.0, 28.9, 28.9, 27.0, 26.8, 25.7, 25.5, 24.8; HRMS calcd for $C_{18}H_{33}O_3$ (M + H) 297.2430, found 297.2430.

17-Methyl-5(Z),8(Z)-heptadecadiendioic acid (28) was prepared in 80% yield from the alcohol by a similar procedure as employed for synthesis of **19** except that the crude product was subjected to flash chromatography (1:25:225 HOAc:2-propanol:hexane): R_f = 0.49 in 1:25:225 HOAc/IPA/hex; ^{1}H (300 MHz) δ 5.32 (4H), 3.63 (s, 3H), 2.74 (t, 2H, J = 5.6), 2.33 (t, 2H, J = 7.5), 2.27 (t, 2H, J = 7.5), 2.10 (q, 2H, J = 6.4), 2.05 (q, 2H, J = 6.4), 1.68 (quintet, 2H, J = 7.4), 1.58 (m, 2H), 1.27 (8H); ^{13}C NMR (75 MHz) δ 179.6, 174.4, 130.2, 129.3, 128.4, 127.6, 51.4, 34.0, 33.3, 29.5, 29.0, 29.0, 28.9, 27.1, 26.4, 25.5, 24.8, 24.5; HRMS calcd for $C_{18}H_{30}O_4Li$ (M + H) 317.2303, found 317.2310.

5(S)-Hydroperoxy-6(E),8(Z)-heptadecadiene-1,17-diol (29). To a 0 °C solution of pH 9 borate buffer (200 mL, 0.2 M) under continuous O_2 aspiration was added soybean type I lipoxygenase (5 mg) followed by a solution of the heptadecadienediol (**26**) (100 mg, 0.37 mmol) in cold 95% ethanol (2 mL). After being stirred for 5 h, the reaction was acidified to pH 3 with 10% HCl and stabilized with a trace of butylated hydroxytoluene (BHT). The suspension was extracted with 50% EA/hexane, and the organic phase was dried (Na_2SO_4). After removal of solvent, the residue was purified by flash chromatography (5/35/60/MeOH/EA/hexane) to afford 80 mg (72%) of hydroperoxy diol as a colorless oil: R_f = 0.29 in 5/35/60/MeOH/EA/hexane; $[\alpha]_D$ = −5.2 (c = 1.2, MeOH); ^{1}H NMR (300 MHz) δ 8.47 (s, 1H), 6.56 (dd, 1H, J = 15.3, 11.0), 5.99 (t, 1H, J = 11.3), 5.56 (dd, 1H, J = 15.3, 8.1), 5.48 (dt, 1H, J = 11.0, 7.9) 4.37 (app q, 1H, J = 7.9), 3.62 (4H), 2.16 (app q, 2H, J = 6.8), 1.72–1.29 (20H); ^{13}C NMR (75 MHz) δ 133.8, 131.3, 129.6, 127.6, 86.2, 62.9, 62.5, 32.5, 32.3, 32.2, 29.3, 29.2, 29.1, 28.8, 27.5, 25.6, 21.4; UV λ_{max} 235 nm (ϵ = 32 000, MeOH).

17-Methyl-5(S)-hydroperoxy-6(E),8(Z)-heptadecadiendioic acid (30) was prepared by a similar procedure as for the synthesis of hydroperoxide **29**. Purification by flash chromatography (1:25:225 HOAc:2-propanol:hexane) produced 10 mg (3%) of the the hydroperoxy acid as a colorless oil: R_f = 0.44 in 1:25:225 HOAc:2-propanol:hex; ^{1}H NMR (300 MHz) δ 6.54 (dd, 1H, J =15.3, 11.2), 5.96 (t, 1H, J =10.9), 5.56 (dd, 1H, J =15.3, 8.1), 5.48 (dt, 1H, J =10.9, 7.8), 4.40 (q, 1H, J =7.3), 3.64 (s, 3H), 2.33 (4H), 2.17 (q, 2H, J =7.7), 1.71–1.34 (14H).

Dimethyl 5(S)-[[1-Methyl-1(αf,R)-[(2β-phenylcyclohexyl)-oxy]ethyl]dioxy]-6(E),8(Z)-heptadecadiene-1,17-dioate (from 5(S)-Hydroperoxy-6(E),8(Z)-heptadecadiene-1,17-dioate Dimethyl Ester (31). To a 0 °C solution of 13(S)-hydroperoxy-9(Z),12(ZE)-heptadecadienoic acid 17-methyl ester (10 mg, 29 mmol) in ether (1 mL) was added a distilled solution of diazomethane/ether until the yellow color persisted. Excess diazomethane was purged with a stream of dry N_2, and the reaction was concentrated *in vacuo*. To a solution of the crude dimethyl hydroperoxyheptadecadiendioate (10.5 mg, 29 mmol) in CH_2Cl_2 (1mL) was added (−)-*trans*-2-phenylcyclohexyl 2-propen-2-yl ether (12 mg, 2 equiv) and a trace amount of PPTS. After being stirred for 30 min, the reaction was quenched with water and extracted with hexane. The organic extracts were dried and concentrated. The residue was loaded directly onto a normal-phase HPLC column (silica, 7% EA/hex, 1 mL/min) to afford a single chiral perketal derivative of 5(S)-hydroperoxy-6(E),8(Z)-heptadecadiene-1,17-dioate dimethyl ester (14 mg, 80%). ^{1}H NMR and HPLC analysis showed that the perketal was formed in >95% ee: R_f = 0.56 in 20% EA/hexane; ^{1}H NMR (300 MHz) δ 7.24 (m, 5H, Ar), 6.40 (dd, 1H, J = 15.3), 5.91 (t, 1H, J = 10.9), 5.48 (dd, 1H, J = 15.3, 8.1), 5.40 (dt, 1H, J = 10.9, 7.8), 4.28 (q, 1H, J = 7.9), 3.66 (s, 6H), 3.55 (m, 1H), 2.51 (m, 1H), 2.33 (m, 4H), 2.17 (q, 2H), 1.91–1.28 (22H), 1.14 (s, 3H), 0.49 (s, 3H); HRMS calcd for $C_{34}H_{52}O_7Na$ (M + Na) 595.3611, found 595.3613.

1,17-Dimethyl 13(S)-Hydroxy-9(Z),11(E)-heptadecadiendioate (32). To a 0 °C solution of the 17-methyl-13(S)-hydroperoxy-9(Z),11(E)-heptadecadiendioic acid **30** (10 mg, 29 mmol) in ether (1 mL) was added a distilled ethereal solution of diazomethane until the yellow color persisted. The solvent was removed *in vacuo*, and the crude dimethyl ester was redissolved in ethyl acetate (1 mL). Ph_3P (11 mg, 1 equiv) was added, and the reaction was stirred for 30 min. After removal of solvent *in vacuo*, the residue was subjected to flash chromatography (10% EA/hex) to afford spectroscopically pure hydroxybismethyl ester (9 mg, 90%) identical in every respect

(48) Nishitani, K.; Yamakawa, K. *Tetrahedron Lett.* **1977**, *28*, 655–658.

except rotation with the sample derived from **20**: $R_f = 0.16$ in 20% EA/hex; $[\alpha]_D = +9.3$ ($c = 0.45$, MeOH); alcohol **20** $[\alpha]_D = +11.5$ ($c = 0.75$, MeOH); ^{1}H (300 MHz) δ 6.45 (dd, 1H, $J =$ 15.3, 11.0), 5.96 (t, 1H, $J = 11.0$), 5.65 (dd, 1H, $J = 15.3, 6.8$), 5.42 (dt, 1H, $J = 10.7, 6.8$), 4.15 (q, 1H, $J = 6.7$), 3.64 (s, 6H), 2.33 (t, 2H, $J = 7.15$), 2.28 (t, 2H, $J = 7.52$), 2.16 (m, 2H), 1.77–1.28 (14H); ^{13}C NMR (75 MHz) δ 174.3, 174.1, 135.4, 133.1, 127.7, 126.0, 72.1, 51.5, 51.4, 36.6, 34.0, 33.8, 29.4, 29.0, 28.9, 27.7, 24.9, 20.8.

(5*S*)-6(*E*),8(*Z*)-Heptadecadien-1,5,17-triol (33). To a solution of the hydroperoxy diol **29** (17 mg, 0.57 mmol) in ethyl acetate (1.5 mL) was added Ph_3P (18 mg, 1.2 equiv). The mixture was stirred for 1 h and then directly subjected to chromatography with 5/35/60/MeOH/EA/hexane to afford 16 mg (99%) of triol as a colorless oil: $R_f = 0.19$ in 5:35:60 MeOH/EA/hexane; $[\alpha]_D = +18.2$ ($c = 0.18$, MeOH); ^{1}H NMR (300 MHz) δ 6.48 (dd, 1H, $J = 15.3, 11.2$), 5.96 (t, 1H, $J = 10.9$), 5.65 (dd, 1H, $J = 15.3, 6.9$), 5.43 (q, 1H, $J = 10.7$) 4.16 (q, 1H, $J = 6.2$), 3.62 (4H), 2.16 (q, 2H, $J = 6.9$), 2.13–1.29 (21H); ^{13}C NMR (75 MHz) δ 135.6, 133.0, 127.7, 125.9, 72.7, 63.0, 62.7, 36.9, 32.7, 32.5, 29.4, 29.3, 29.2, 28.9, 27.6, 25.6, 21.6; HRMS calcd for $C_{17}H_{32}O_3Li$ (M + Li) 291.25115, found 291.25119.

(5*S*)-6(*E*),8(*Z*)-Heptadecadiene-1,5,17-triol (33, from 32). To a 0 °C solution of 1,17-dimethyl 5(*S*)-hydroxy-6(*E*),8(*Z*)-heptadecadienedioate (10 mg, 29 mmol) in ether (1 mL) was added $LiAlH_4$ (5 mg, 1.5 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was filtered through celite and concentrated. The residue was pufied by flash chromatography (5:35:60 MeOH/EA/hexane) to afford 7.2 mg (86%) of pure triol identical in every respect except rotation with the triol derived from the hydroperoxy diol: $[\alpha]_D = +15.0$ ($c = 0.36$, MeOH).

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Supplementary Material Available: ^{1}H NMR spectra of compounds **1-33** and unnumbered intermediates from Schemes 6 and 8 (44 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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