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MODEL MULTIFUNCTIONAL EPOXIDES RELATED TO HEPOXILIN A[1]

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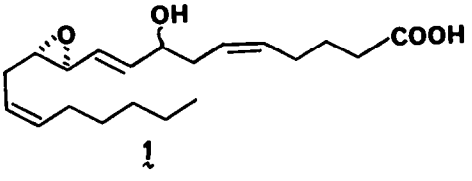
Abstract: An enolic epoxy fatty acid, 8,9-(S,S)-epoxy-5-hydroxy-6-dodecenoic acid, has been synthesized. This compound is a model system for the biologically important compound, hepoxilin A. The model epoxy fatty acid cyclized readily to form an epoxy lactone. Acid-catalyzed ring opening resulted in the formation of isomeric oxadienes which were structurally differentiated by comparison of their 2-D COSY NMR spectra. Thiols cleaved the epoxide ring rapidly and quantitatively.

One of the most abundant polyunsaturated, long chain fatty acids in humans and other mammals is arachidonic acid, a major component of cellular phospholipids. Arachidonic acid is released from membrane stores by calcium-dependent phospholipases and it may then undergo autoxidation[2] or it may be enzymatically oxygenated.[3,4] The 12-lipoxygenase pathway of arachidonic acid oxidation eventually results in the formation of two multifunctional epoxy fatty acids, hepoxilin A(1) and hepoxilin B (2). These compounds have been isolated from rat lung and rat pancreatic islet cells by Pace-Asciak and coworkers and have been shown to potentiate the glucose-dependent release of insulin.[5] It has been suggested that they may also be involved in the mobilization of calcium ions.[6-10]



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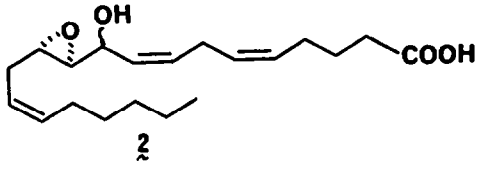

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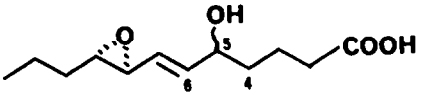

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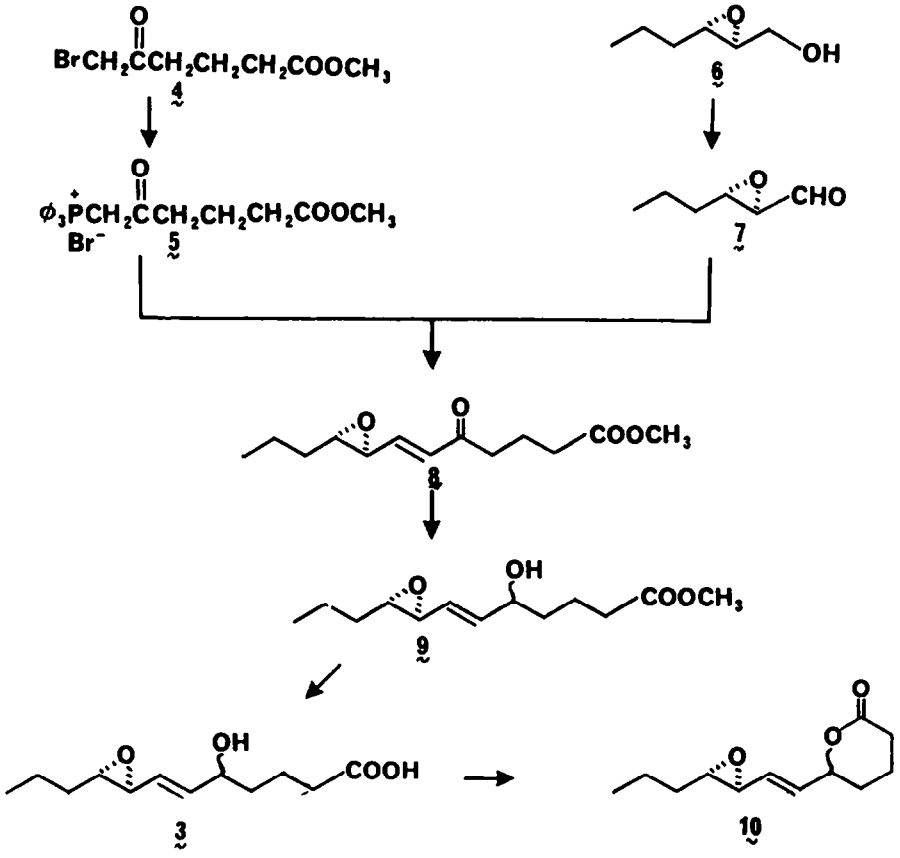
The multifunctional epoxide moieties present in the structures of the hepoxilins have been suggested as playing very important roles in their biological activities. In order to contribute to the understanding of the chemistry of these functionalized unsaturated epoxides of lipid origin, we have been investigating the stereospecific synthesis and reactivity of simpler model systems with the same multifunctional nature and stereochemistry. We wish to present the synthesis and cleavage reactions of a simple analogue of hepoxilin A, 8,9-(S,S)-epoxy-5-hydroxy-6-dodecenoic acid (3).

The starting material for the synthesis was methyl-6-bromo-5-oxohexanoate (4), which was prepared from methyl-4-(chloroformyl)butyrate by reaction with diazomethane followed by gaseous HBr.[11] Reaction of the α-bromoketone with triphenylphosphine in toluene produced the phosphonium salt 5 which was properly constituted to couple as its ylide with an aldehyde. The latter, 2,3-(R,S)-epoxyhexanal (7), was easily prepared in two steps from trans- 2-hexen-1-ol. The first step was a Sharpless asymmetric epoxidation to the 2,3-(S,S)-epoxyhexan-1-ol (6).[12] The second step was an oxidation of the epoxy alcohol 6 with pyridinium dichromate[13] to give 2,3-(R,S)-epoxyhexanal (7) in 76% yield. Carbon elongation of the epoxyaldehyde 7 was achieved in 57% yield by reaction with the ylide of the phosphonium salt 5.[14] The carbon elongated product 8 was optically active and showed a UV absorbance at 234 nm (ε 11500). The ^{13}C NMR spectrum showed an expected single resonance for each of the carbons. Reduction of 8 with $NaBH_4$[15] under carefully controlled conditions resulted in the two diastereoisomers 9. This reaction could be conveniently monitored by the disappearance of the UV absorbance at λ_{max} 234 nm.

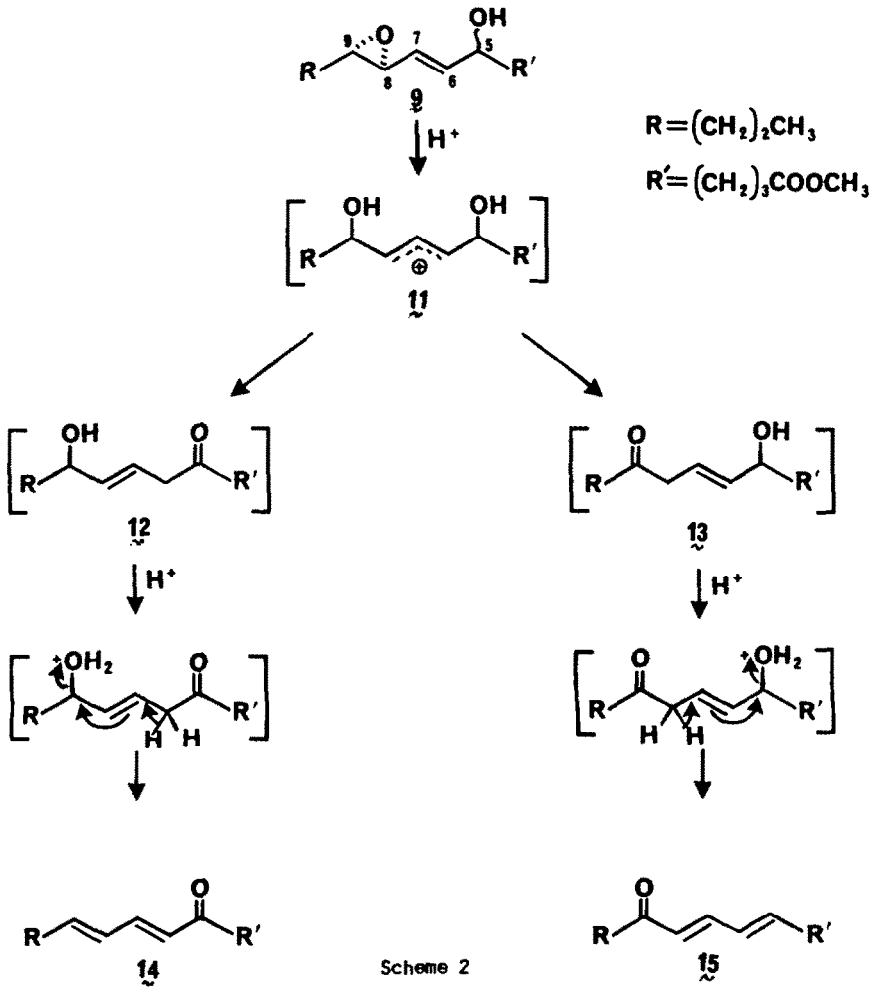
The diastereoisomers of compound 9 could not be separated on silica gel or alumina, due in part to the instability of 9 on these adsorbents. However, evidence for the presence of two stereoisomers in approximately equal amounts was clearly seen in the ^{13}C NMR data. Carbons 4, 5, and 6 in each case exhibited two resonances. The ^1H NMR spectrum showed that the trans epoxide stereochemistry was maintained ($J_{8,9}$ = 2.0 Hz) and that the geometry about the double bond was trans ($J_{6,7}$ = 15.6 Hz).



Scheme 1

Compound 9 is the appropriate model multifunctional epoxy fatty acid for reactivity studies. However, its hydrolysis to the deprotected compound was also examined. Conditions were carefully chosen so that the epoxide moiety would remain intact. This could be achieved by warming 9 with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene[16] followed by an appropriate aqueous work-up. Purification by preparative layer chromatography on silica gel gave a compound whose spectral data were consistent with deprotection but also with a structure 10 containing a lactone rather than a carboxylic acid. The ^{1}H NMR data showed that the epoxide moiety was intact in the final product with a multiplet at δ 2.82 and the doublet of doublets at δ 3.10. Loss of the methyl ester was shown in the ^{1}H NMR data by the disappearance of the sharp singlet at δ 3.67 ppm observed for compound 9. Missing from the ^{1}H NMR data, however, was a peak representing the acid proton. The ^{13}C NMR spectrum showed a carbonyl peak at 171.4 ppm indicative of a lactone rather than a carboxylic acid.

Treatment of the multifunctional epoxide 9 in diethyl ether with aqueous acid resulted in the formation of isomeric oxodienes 14 and 15. A plausible mechanism for the formation of the oxodienes is shown in Scheme 2. The acid-catalyzed cleavage of the epoxide ring would result initially in the formation of a regioequivalent carbocation intermediate 11. Loss of a proton from the 5- or 9-carbon yield dienols which are capable of tautomerizing in each case to the δ-ketol intermediates 12 and 13. Acid-catalyzed dehydration of the latter forms the fully conjugated oxodienes.



Scheme 2

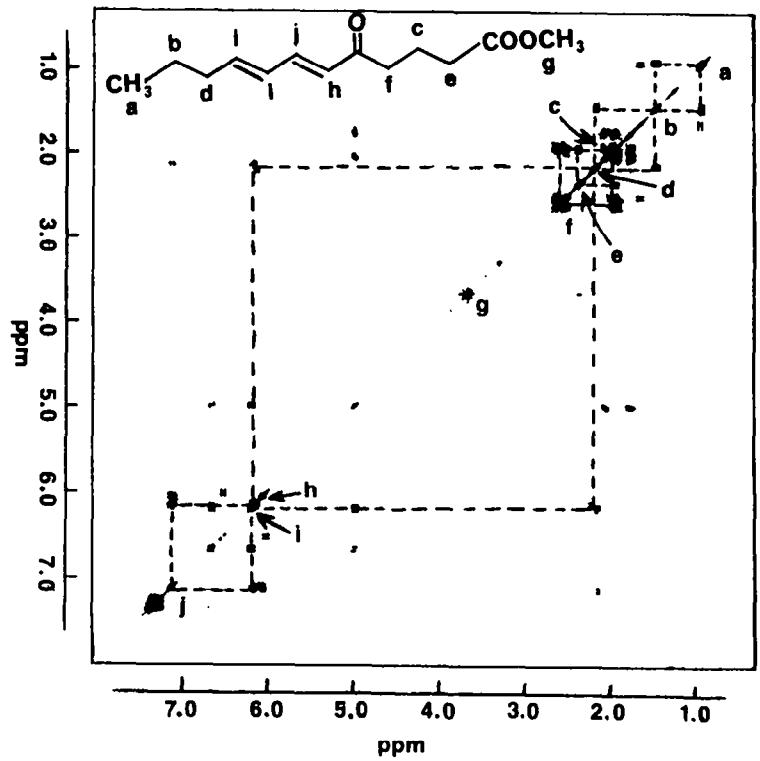


Fig. 1 COSY spectrum of oxodiene 14

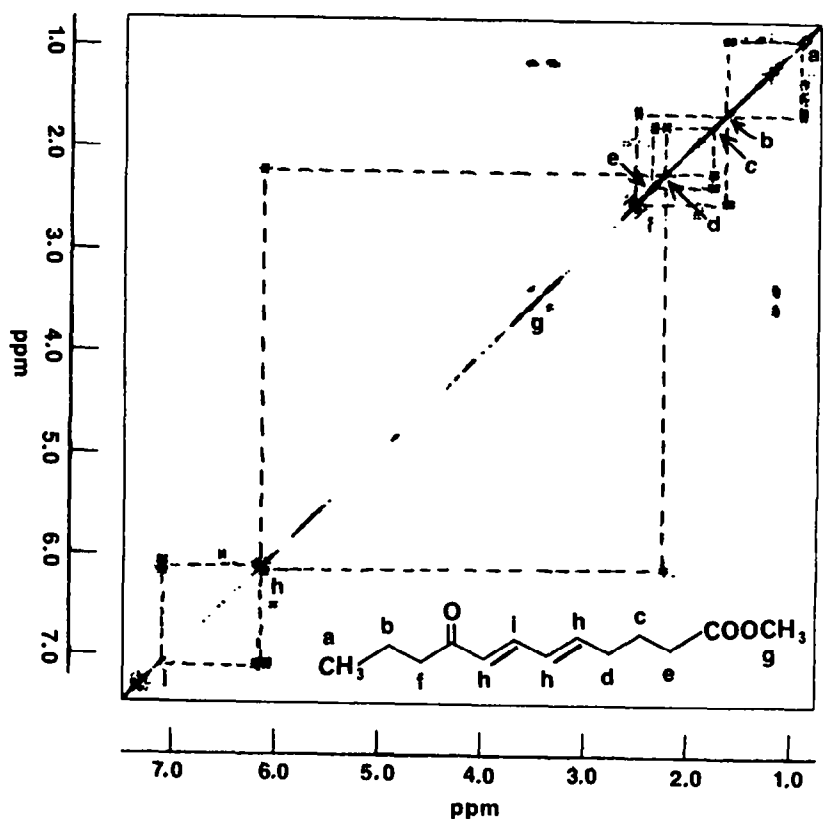
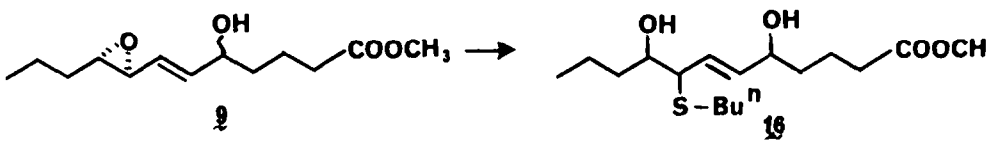


Fig. 2 COSY spectrum of oxodiene 15

The oxodienes 14 and 15 are very similar structurally and spectroscopically. From the spectral data obtained it was obvious that two isomeric oxodienes had been isolated. However, the ^1H NMR and ^{13}C NMR were so similar that it was impossible to differentiate between the two isomers from routine high-field NMR spectra. However, the use of 2-D NMR with correlated spectroscopy (COSY) allowed differentiation between the two structures. The ^1H COSY spectrum for compounds 14 and 15 including assignments are shown in Figures 1 and 2.

Although oxodienes have not been isolated yet from the various lipid peroxidation pathways in mammalian systems, this does not preclude their existence in natural systems as some products isolated from model studies have correlated well with those obtained from mammalian systems.[17,18] Very recently a novel natural eicosanoid, having an ultraviolet absorbance similar to the oxodienes has been isolated.[19] The identification of this compound has not yet been made.

A model reaction of the synthetic multifunctional epoxide 9 with a thiol was also carried out. This reaction was of interest because of the analogy to leukotriene C_4 (LTC_4) which is enzymatically formed from LTA_4 by the addition of glutathione to the epoxide function of LTA_4.[3] The reaction of 9 with n-butanethiol produced, in quantitative yield, the epoxide ring opened product 16 (Scheme 3). This compound was identified by NMR and mass spectral data which showed loss of the epoxide ring and addition of a butane thiol moiety.



Scheme 3

In summary, a model multifunctional epoxide related to hepoxilin A has been synthesized. It is reactive and relatively unstable. The free acid prefers to exist in the corresponding lactone form. Under acid catalyzed conditions, it is readily cleaved to oxodienes in high yields. It is quantitatively converted to its ring opened thiol derivative by reaction with thiols.

EXPERIMENTAL SECTION

The infrared spectra were recorded on a Beckman 20A and IBM Model 98 FTIR. The ^1H NMR, ^{13}C NMR, and COSY spectra were recorded on a Bruker WM-360 pulse Fourier transform NMR spectrometer. The mass spectrometers employed were a Hewlett-Packard 5985 GC/MS system and an AEI MS-30 high resolution instrument. The ultraviolet data were recorded with a Cary Model 219 ultraviolet-visible spectrophotometer. Optical rotations were recorded on a Perkin-Elmer 141 Automated Polarimeter at 25 °C. Toluene and dichloromethane were dried and distilled over CaH_2 prior to use. Methyl-4-(chloroformyl)butyrate (Aldrich) and trans-2-hexen-1-ol (Aldrich) were used without further purification. Triphenylphosphine was recrystallized from hexane and dried in vacuo (50 °C). Preparative layer chromatography employed EM silica gel PF254 plates, activated for 3 h at 135 °C. Column chromatography employed powder silica gel (60-200 mesh).

Methyl 6-bromo-5-oxo-hexanoate 4. Methyl-4-(chloroformyl)butyrate (3.4 g, 25.2 mmol) was added to a solution of diazomethane (121.6 mmol) in diethylether (400 mL) at room temperature. After 2 h,

N_2 was bubbled through the solution to remove excess CH_2N_2. Then gaseous HBr was bubbled through the solution until the yellow color of the diazoketone was dissipated. The solution was washed with sodium bicarbonate solution (2 x 50 mL) and water (2 x 50 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent removed in vacuo to yield 4.5 g (72%) of product. The product is contaminated with approximately 10% of the α-chloroketone analogue. ^1H NMR ($CDCl_3$) δ 1.94 (tt, J = 7.0 Hz, 7.0 Hz, 2H), 2.38 (t, J = 7.0 Hz, 2H), 2.76 (t, J = 7.0 Hz, 2H), 3.67 (s, 3H), 3.90 (s, 2H); mass spectrum m/z (relative intensity) 193 (M^+ - OCH_3, 32.9), 191 (33.6), 165 (M^+ - $COOCH_3$, 27.0), 163 (27.0), 129 (M^+ - CH_2Br, 100.0), 123 (25.2), 121 (23.4), 101 (36.1), 95 (19.9), 93 (20.2), 59 (12.1).

Phosphonium salt 5. Triphenylphosphine (2.6 g, 10 mmol) was added to a stirred solution of methyl-6-bromo-5-oxo-hexanoate 4 (1.89 g, 7.2 mmol) in toluene (50 mL). The mixture was allowed to stir at room temperature with protection from moisture for 28 h. The reaction mixture was filtered and the filtrate was dried in vacuo (50 °C) to yield the phosphonium salt 5 as an off white solid (1.7 g, 50%): ^1H NMR ($CDCl_4$) δ 1.89 (m, 2H), 2.33 (m, 2H), 3.01 (m, 2H), 3.63 (s, 3H), 5.88 (d, J=14.8 Hz, 2H), 7.5 (m, 15H); mass spectrum, m/z(relative intensity) 405 (M^+-Br, 1.2), 404 (M^+-HBr, 4.2), 373 (5.2), 318 (15.8), 303 (100.0), 262 (6.9).

2,3-(S,S)-Epoxyhexan-1-ol 6. This compound was prepared from trans-2-hexen-1-ol (5.9 mL, 50.0 mmol) as previously described[12] to give 3.94 g (68%) of product: bp 65-66 °C/1 torr (lit.[11] bp 31-33 C/0.30-0.40 torr); $[\alpha]_D$ = -44.7 ; ^1H NMR ($CDCl_3$) δ 0.96 (m, 3H), 1.52 (m, 4H), 2.90 (m, 2H), 3.63 (m, 3H).

2,3-(R,S)-Epoxyhexan-1-al 7. 2,3-(S,S)-Epoxyhexan-1-ol 6 (0.4g, 3.4 mmol) and pyridinium dichromate (1.9 g, 5.0 mmol) in dry dichloromethane (50 mL) was stirred at room temperature for 14 h. Then 50 mL Et_2O was added to the reaction mixture and this was filtered and dried over Na_2SO_4. The solvent was removed and the residue was purified by column chromatography (Et_2O) to yield 0.3 g (76%) of 7: ^1H NMR ($CDCl_3$) δ 0.98 (m, 3H), 1.55 (m, 4H), 3.17 (m, 2H), 9.01 (d, J=6.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.7, 19.2, 33.3, 56.6, 59.1, 198.1; IR (neat) 2900 cm^{-1} (C-H), 1725 cm^{-1} (C=O), 1205 cm^{-1}, 920 cm^{-1}, 870 cm^{-1} (epoxide ring); mass spectrum, m/z (relative intensity) 114 (M^+, 0.5), 113 (M^+-H, 3.4), 85 (0.7), 71 (100.0); HRMS (EI) calcd for $C_6H_{10}O_2$ 114.0681, found 114.0670; optical rotation $[\alpha]_D$ +2.55 (c 3.84, $CHCl_3$).

Methyl-8,9-(S,S)-epoxy-5-oxo-6-dodecenoate 8. A solution of the phosphonium ylide 5 (1.5 g, 3.0 mmol) in 50 mL $CHCl_3$ was shaken with 1 N NaOH (20 mL) for 5 minutes. The organic layer was saved and the aqueous layer was extracted with $CHCl_3$ (2 x 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and condensed. The residue, without further purification, was dissolved in toluene (50 mL) and 2,3-(R,S)-epoxyhexanal (0.34 g, 3.0 mmol) was added. The reaction was allowed to stir at room temperature under a N_2 atmosphere for 36 h. The solvent was removed under reduced pressure and then the residue was washed with Et_2O (3 x 50 mL) and filtered. The filtrate was dried over Na_2SO_4, filtered, and condensed to yield 1.4 g of residue. Purification by silica gel column chromatography with ether as the eluent yielded 0.4 g (57%) product as an oil: UV λ_{max} (EtOH) 234 nm (ε 11500); ^1H NMR ($CDCl_3$) δ 0.97 (m, 3H), 1.55 (m, 4H), 1.95 (m, 2H), 2.36 (t, J=7.0 Hz, 2H), 2.63 (t, J=6.8 Hz, 2H), 2.88 (m, 1H), 3.20 (m, 1H), 3.65 (s, 3H), 6.47 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.8, 19.1(2C), 33.0, 33.9, 39.3, 51.4, 56.4, 61.4, 131.1, 142.9, 173.4, 198.3. IR (neat) 2980 cm^{-1} (C-H), 1730 cm^{-1} (C=O), 1675 cm^{-1} (C=C), 1630 cm^{-1}, 1200 cm^{-1}, 970 cm^{-1}, 890 cm^{-1} (epoxide ring); mass spectrum m/z (relative intensity) 240 (M^+, 7.3), 222 (M^+ - H_2O, 10.8), 209 (4.0), 197 (30.3), 181 (M^+ - $COOCH_3$, 1.3), 139 (22.0), 129 (18.8), 101 (13.2), 84 (100.0); HRMS (EI) calcd for $C_{13}H_{20}O_4$ 240.1362, found 240.1360; optical rotation $[\alpha]_D$ -19.3 (c 0.68, $CHCl_3$).

Methyl-8,9-(S,S)-epoxy-5-hydroxy-6-dodecenoate 9. A solution of $NaBH_4$ (0.038 g, 1.0 mmol) in MeOH (5 mL) was added to a solution of methyl-8,9-(S,S)-epoxy-5-oxo-6-dodecenoate 8 (0.34 g, 1.4 mmol) in MeOH (10 mL) which had been cooled to 0 C. The mixture was allowed to stir at 0° C for 30 minutes and then allowed to warm to room temperature for 30 minutes. The reaction mixture was poured into a 20 mL brine solution, which was extracted with Et_2O (4 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and condensed. The residue was purified by preparative layer chromatography on silica gel using 5% MeOH/CH_2Cl_2 as the eluent. The band at R_f 0.3 yielded 0.19 g (80%) of 9: ^1H NMR ($CDCl_3$) δ 0.96 (m, 3H), 1.52 (m, 6H), 2.35 (m, 5H), 2.83 (m, 1H), 3.09 (dd, J=7.5, 2.0 Hz, 1H), 3.67 (s, 3H), 4.15 (m, 1H), 5.42 (dd, J=15.6, 7.5 Hz, 1H), 5.93 (dd, J=15.6, 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 19.2, 20.7, 33.8, 34.0, 36.36, 36.41, 51.5, 57.8, 60.5, 71.40, 71.50, 128.39, 128.45, 137.5, 174.0; IR (neat) 3437 cm^{-1} (O-H), 2909 cm^{-1} (C-H), 1735 cm^{-1} (C=O), 1200 cm^{-1}, 901 cm^{-1} (epoxide ring); mass spectrum m/z (relative intensity) (TMS derivative) 314 (M^+, 5.6), 313 (M^+ -H, 12.0), 299 (M^+ -CH_3, 6.8), 285 (3.3), 225 (5.2), 213 (20.9), 203 (18.2), 145 (42.9), 117 (77.8), 93 (100.0), 73 (68.5); HRMS (EI) calcd for $C_{13}H_{22}O_4$ 242.1518, found 224.1412 (M^+ - H_2O).

Lactone Product 10. Methyl-8,9-(S,S)-epoxy-5-hydroxy-6-dodecenoate 9 (0.25 g, 1.0 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.5 mL, 10 mmol) in toluene (100 mL) were heated to 110°C for 48 h. The solvent was removed and the residue was dissolved in ether (100 mL). This solution was washed with 5% HCl (2 x 50 mL) and $NaHCO_3$ (1 x 20 mL). The organic layer was dried over Na_2SO_4. The solvent was removed and the residue was purified by silica gel preparative layer chromatography using 1:1 ether/ethyl acetate as the eluting agent to give 0.11 g (51%) of 10 as an oil: ^1H NMR

($CDCl_3$) δ 0.96 (m, 3H), 1.53 (m, 4H), 1.95 (m, 4H), 2.51 (m, 2H), 2.82 (m, 1H), 3.10 (dd, J = 2.0, 6.8 Hz, 1H), 4.84 (m, 1H), 5.65 (ddd, J = 1.8, 6.8, 15.8 Hz, 1H), 5.93 (dd, J = 5.1, 15.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.5, 18.7, 18.8, 19.8, 28.7, 30.2, 34.5, 57.93, 57.99, 61.20, 61.30, 74.7, 130.8, 131.5, 132.5, 132.7, 171.4; IR (neat) 2960 cm^{-1} (C-H), 1735 cm^{-1} (C=O), 1240 cm^{-1} (C-O), 1039 cm^{-1}, 969 cm^{-1}; mass spectrum m/z (relative intensity) 210 (M^+, 0.3), 193 (M^+-OH, 1.1), 181 (M^+-C_2H_5, 1.7), 174 (5.5), 167 (1.7), 156 (11.0), 138 (12.6), 111 (28.2), 95 (45.2), 81 (100.0), 43 (15.3); HRMS (EI) calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1258.

Methyl 5-oxo-6(E),8(E)-dodecadienoate 14 and Methyl 9-oxo-5(E),7(E)-dodecadienoate 15. A solution of methyl-8,9-(S,S)-epoxy-5-hydroxy-6-dodecenoate 9 (0.086 g, 0.34 mmol) in diethyl ether (10 mL) was cooled to 0°C with an ice bath and then a 30% $HClO_4$ solution (1 mL) was added. The reaction was allowed to warm to room temperature with vigorous stirring. After 72 h, 5 mL H_2O was added to it. The organic layer was saved and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative layer chromatography on silica gel with 5% MeOH/CH_2Cl_2 as the eluent. Bands at R_f 0.8 and 0.5 yielded 36.0 mg (44%) of 14 and 38.0 mg (46%) of 15, respectively. For the oxodiene 14: UV (EtOH) λ_{max} 268 (ε 10750); ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7.4 Hz, 3H), 1.46 (m, 2H), 1.95 (m, 2H), 2.16 (m, 2H), 2.37 (m, 2H), 2.62 (t, J = 7.2 Hz, 2H), 3.67 (s, 3H), 6.07 (d, J = 15.6 Hz, 1H), 6.20 (m, 2H), 7.15 (dd, J = 6.0, 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6, 19.5, 21.9, 33.2, 35.1, 38.8, 51.5, 127.7, 128.8, 143.2, 145.6, 173.6, 199.8; IR (neat) 2957 cm^{-1} (C-H), 1738 cm^{-1} (C=O, ester), 1653 cm^{-1} (C=O, ketone), 1507 cm^{-1} (C=C), 950 cm^{-1}; mass spectrum m/z (relative intensity) 224 (M^+, 2.4), 193 (M^+ -OCH_3, 16.5), 181 (M^+ -$CH_2CH_2CH_3$, 84.1), 165 (M^+ -$COOCH_3$, 5.1), 123 (100.0), 107 (28.2). For the oxodiene 15: UV (EtOH) λ_{max} 273 (ε 11320); ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7.4 Hz, 3H), 1.63 (q, J = 7.4 Hz, 2H), 1.77 (m, 2H), 2.23 (q, J = 7.0 Hz, 2H), 2.35 (m, 2H), 2.51 (t, J = 7.3 Hz, 2H), 3.29 (s, 3H), 6.13 (m, 3H), 7.10 (dd, J = 9.9, 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 17.8, 23.9, 29.6, 32.2, 35.2, 42.4, 128.3, 129.7, 142.4, 143.4, 174.6, 200.9; IR (neat) 2957 cm^{-1} (C-H), 1735 cm^{-1} (C=O, ester), 1635 cm^{-1} (C=O, ketone), 1550 cm^{-1} (C=C), 950 cm^{-1}; mass spectrum m/z (relative intensity) 225 (M^+ +H, 5.2), 224 (M^+, 0.5), 209 (M^+ -CH_3, 3.7), 193 (M^+ -OCH_3, 10.7), 165 (3.4), 129 (69.8), 115 (60.4), 71 (100.0); HRMS (EI) calcd for $C_{13}H_{20}O_3$ 224.1413, found 224.1414.

Methyl-5,9-dihydroxy-8-butanethiol-6-dodecenoate 16. Methyl-8,9-(S,S)-epoxy-5-hydroxy-6-dodecenoate 9 (0.05 g, 0.21 mmol), triethylamine (0.14 mL, 0.8 mmol), and n-butanethiol (0.09 mL, 0.8 mmol) in MeOH (6 mL) were allowed to stir at room temperature for 45 h. The reaction mixture was streaked on a silica gel preparative layer plate. The plate was eluted with 5% MeOH/$CHCl_3$. The band at R_f = 0.4 was cut out and eluted with 5% MeOH/$CHCl_3$ to give 59.6 mg of (100%) of 16 as an oil: ^1H NMR ($CDCl_3$) δ 0.91 (m, 6H), 1.49 (m, 12H), 2.37 (m, 4H), 3.09 (m, 4H), 3.66 (s, 3H), 4.01 (m, 1H), 5.59 (m, 2H); mass spectrum m/z (relative intensity) 315 (M^+-OH, 1.0), 301 (M^+-OCH_3, 1.6), 283 (0.7), 277 (1.7), 242 (M^+-BuSH, 75.7), 229 (12.9), 211 (1.3), 185 (29.6), 153 (100.0); HRMS (EI) calcd for $C_{17}H_{32}O_4S$ 332.2022, found 332.2012.

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