Synthesis of (10*R*)-Hepoxilin B_3 Methyl Ester and (10*R*)-Trioxilin B_3 Methyl Ester

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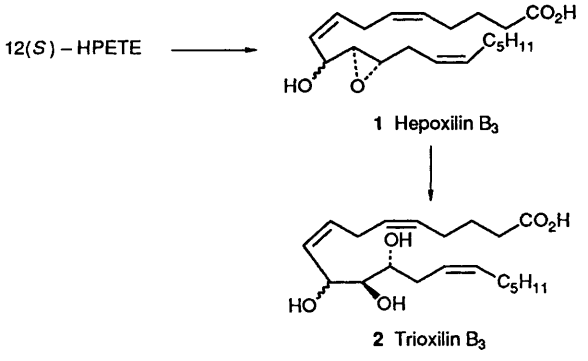
A stereoselective synthesis of methyl (5*Z*,8*Z*,14*Z*; 10*R*,11*R*,12*R*)-trihydroxyeicosa-5,8,14-trienoate and methyl (5*Z*,8*Z*,14*Z*; 10*R*,11*S*,12*S*)-10-hydroxy-11,12-epoxyeicosa-5,8,14-trienoate starting from (−)-D-tartaric acid is described.

As part of an effort to elucidate the biological role of oxygenated metabolites of unsaturated fatty acids, we have recently described the total synthesis of two constituents of substances which are active against rice blast disease.[1] This success prompted us to synthesize other metabolites with analogous structures.

Hepoxilin B_3 **1**, which arises from (12*S*)-12-hydroperoxyeicosatetraenoic acid [12(*S*)-HPETE], is regiospecifically hydrated at C(12) to yield the corresponding triols, namely trioxilin B_3 **2**, by an epoxide hydratase enzyme present in rat lung homogenate; both hepoxilin B_3 and trioxilin B_3 consist of two C(10)-diastereoisomers[2] (Scheme 1).

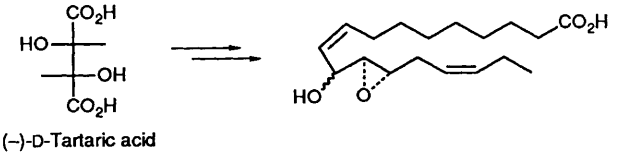


Scheme 1

Metabolites of the hepoxilin/trioxilin pathways are of current interest as presynaptic messengers in Aplysia sensory cells[3] and as pancreatic insulin secretagogues.[4] Because of the limited availability of natural material, further progress in defining the physiological roles of these metabolites and in clarifying their structural assignments is critically dependent on the production of synthetic standards of known configuration.

To our knowledge, the total syntheses of trioxilin B_3 and hepoxilin B_3 have been achieved in only a few laboratories.[2,5,6] We report herein another stereoselective synthesis of the (10*R*)-hepoxilin B_3 and (10*R*)-trioxilin B_3 diastereoisomers. Based on our strategy leading to the preparation of unsaturated fatty acids bearing both chiral allylic and homoallylic alcohol subunits, such as (11*R*,12*S*,13*S*)-11-hydroxy-12,13-epoxyoctadecadienoic acid,[1] the structurally and stereochemically similar compound (10*R*)-hepoxilin B_3 can also be synthesized from (−)-D-tartaric acid (Scheme 2).

On the other hand, as described above, trioxilin B_3 is derived from hepoxilin B_3 with stereochemical inversion at C(12), since the epoxide of hepoxilin B_3 can be constructed from the trihydroxy precursor, *via* intramolecular rear attack of a hydroxy group to an adjacent tosylate, hence (10*R*)-trioxilin B_3 can also be obtained from (−)-D-tartaric acid.



Scheme 2

The synthetic approach is outlined in Scheme 3.

The 4-*O*-benzyl-2,3-*o*-isopropylidene-D-threose **3**, readily available from (−)-D-tartaric acid by the method of Mukaiyama *et al.*,[7] was treated with prop-2-ynyl bromide in the presence of zinc dust to afford the *erythro*-product **4** after column chromatography, HPLC analysis showed that the ratio of *erythro* to *threo* isomer was *ca.* 30:1.[1] Silylation of the free hydroxy group of **4** with TBDMSCl (*tert*-butyldimethylsilyl chloride) gave compound **5**. Alkylation of the terminal alkyne with $C_5H_{11}Br$, followed by partial hydrogenation of the triple bond over Lindlar catalyst afforded the (*Z*)-alkene **7**. Compound **7** was converted into the key intermediate **10** by a four-step sequence {Li–liq. NH_3, Swern oxidation,[8] Wittig reaction under *cis*-olefination conditions with (3*Z*)-7-methoxycarbonylhepta-3-en-1-ylidenetriphenylphosphorane[9] to give the (*Z*)-olefin **9** [the (8*E*)-isomer was not detected] and tetrabutylammonium fluoride}. This key intermediate **10** could be transformed into both (10*R*)-hepoxilin B_3 and (10*R*)-trioxilin B_3.

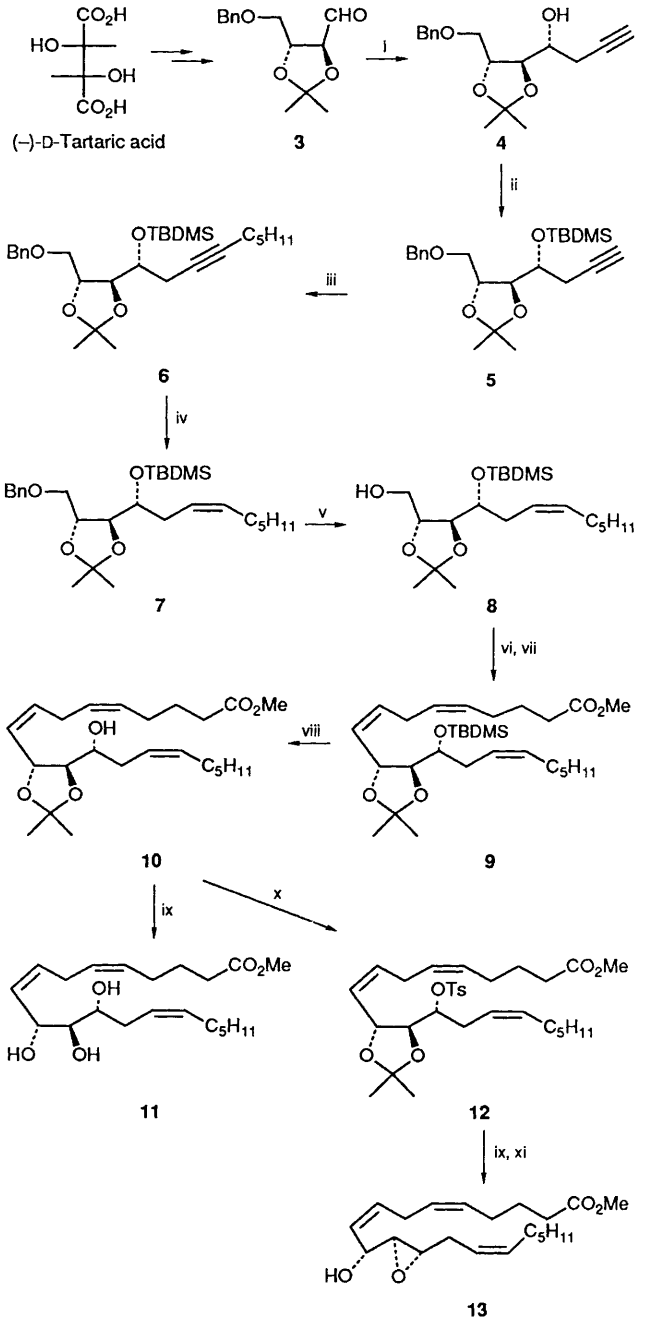
Hydrolysis of compound **10** with toluene-*p*-sulfonic acid (PTSA) in methanol afforded the known triol trienoate **11**, $[\alpha]_D = -16.1°$ (*c* 3.2 in acetone) [lit.[2] $[\alpha]_D = -16.4°$ (*c* 3.5, acetone)]. The ^1H NMR spectroscopic data for compound **11** are identical with those reported.[2] Compound **11** was first converted into its tosylate; after removal of the acetonide moiety and subsequent treatment with potassium carbonate in methanol the (10*R*)-hepoxilin B_3 methyl ester **13**, was obtained, $[\alpha]_D = -68.2°$ (*c* 0.5, in acetone).

In conclusion, we report here a new route to (10*R*)-hepoxilin B_3 methyl ester and (10*R*)-trioxilin B_3 methyl ester from (−)-D-tartaric acid.† The total synthesis of (10*S*)-hepoxilin B_3 and (10*S*)-trioxilin B_3 diastereoisomers is under investigation in this laboratory and will be reported elsewhere.

Experimental

IR spectra were run on a Shimadzu 440 spectrometer. ^1H NMR spectra were recorded with TMS (tetramethylsilane) as an internal standard at 200 MHz on a Varian XL-200 spectrometer or at 600 MHz on an AMX-600 spectrometer, *J* values are given in Hz. Mass spectra (EI) were obtained on a Finnigan

† While this manuscript was prepared, a new synthesis of the (10*S*)-diastereoisomer of trioxilin B_3 was reported.[10]



Scheme 3 *Reagents and conditions:* i, Zn, $BrCH_2C{\equiv}CH$, DMF–Et_2O (1:1), 91%; ii, TBDMSCl, imidazole, DMF, 93%; iii, BuLi, THF–HMPA (8:1), BrC_5H_{11}, 89%; iv, H_2, Pd–Pb–$CaCO_3$, quinoline, 99%; v, Li, liq. NH_3, 95%; vi, Swern oxidation; vii, $Br^-{}^+PPh_3(CH_2)_2$-$CH{=}CH(CH_2)_3CO_2Me$, $KN(SiMe_3)_2$, THF, 78% (vi, vii overall); viii, Bu_4NF, 92%; ix, PTSA, MeOH; x, TsCl, Py; xi, K_2CO_3, MeOH

4201 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 Autopol polarimeter, $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Flash column chromatography was performed on silica gel H(10–40 μ), and with a light petroleum–ethyl acetate system as eluent.

(2R,3R,4R)-1-*Benzyloxy*-2,3-O-*isopropylidenehept*-6-*yne*-2,3,4-*triol* **4**.—Into a stirred mixture of the aldehyde **3** (16.9 g, 65 mmol) and prop-2-ynyl bromide (100 mmol) in dimethylformamide (DMF)–Et_2O (1:1, 120 cm^3) was added zinc dust (8.5 g, 130 mmol) slowly. An exothermic reaction started within a few minutes and the reflux was allowed to continue until most of compound **3** had been consumed (1 h). Then, the reaction mixture was poured into a saturated aqueous NH_4Cl (200 cm^3), extracted with ether (100 cm^3 × 3), and the combined organic phases were dried (Na_2SO_4). After work-up, the product **4** was purified by flash chromatography (silica, EtOAc–light petroleum, 1:9); yield 17.1 g (91%); R_f 0.40, R_f for (4*S*)-diastereoisomer *ca.* 0.45 (EtOAc–hexane, 1:6) (Found: M^+, 290.1526. $C_{17}H_{22}O_4$ requires *M*, 290.1518); $[\alpha]_D^{20}$ +2.7 (*c* 0.8, $CHCl_3$); γ_{max}(film)/cm^{-1} 3450, 3300, 2100w, 1500, 1380 and 1370; δ_H(200 MHz; $CDCl_3$) 1.39 (6 H, s), 2.06 (1 H, t, *J* 2), 2.2–2.50 (2 H, m), 3.6–3.80 (4 H, m), 4.10 (1 H, m), 4.61 (2 H, s) and 7.34 (5 H, m); *m/z* 291 (M^+ + 1, 7%), 275 (M^+ − Me, 15), 273 (M^+ − H_2O) and 91 (100).

(2R,3S,4R)-1-*Benzyloxy*-4-tert-*butyldimethylsilyloxy*-2,3-O-*isopropylidenehept*-6-*yne*-2,3-*diol* **5**.—A mixture of compound **4** (16.0 g, 55 mmol), *tert*-butyldimethylsilyl chloride (10.8 g, 71.5 mmol) and imidazole (15 g, 220 mmol) in DMF (100 cm^3) was stirred at room temp. overnight. The mixture was diluted with Et_2O (200 cm^3) and water (100 cm^3), and the aqueous layer was separated. The organic layer was washed with 5% aq. $NaHCO_3$ (30 cm^3) and brine (30 cm^3) and dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, the residue was purified by chromatography using a mixture of ethyl acetate–light petroleum (1:50) as eluent to give the *title compound* **5** as a colourless oil (20.8 g, 93%) (Found: C, 68.0; H, 9.1. $C_{23}H_{36}O_4Si$ requires C, 68.27; H, 8.97%); $[\alpha]_D^{20}$ − 17.8 (*c* 0.8, $CHCl_3$); γ_{max}(film)/cm^{-1} 3300, 2100w, 1500, 1380 and 1370; δ_H(200 MHz; $CDCl_3$) 0.06 (6 H, s), 0.86 (9 H, s), 1.39 (3 H, s), 1.41 (3 H, s), 1.97 (1 H, t, *J* 2.2), 2.50 (2 H, m), 3.50–3.90 (4 H, m), 4.20 (1 H, m), 4.60 (2 H, s) and 7.32 (5 H, m); *m/z* 403 (M^+ − 1), 389 (M^+ − Me, 1%), 289 (M^+ − $SiMe_2Bu^t$) and 91 (100).

(2R,3S,4R)-1-*Benzyloxy*-4-tert-*butyldimethylsilyloxy*-2,3-O-*isopropylidenedodec*-6-*yne*-2,3-*diol* **6**.—To a stirred solution of compound **5** (7.3 g, 18 mmol) in dry THF (tetrahydrofuran) (90 cm^3) was added BuLi (2.5 mol dm^{-3} in hexane; 21.6 mmol) dropwise at −40 °C. After 20 min, a solution of BrC_5H_{11} (4.1 g, 27 mmol) in HMPA (hexamethylphosphoramidite) (25 cm^3) was added. Stirring was continued for 1 h at the same temperature and overnight at 15 °C. The reaction mixture was diluted with Et_2O (300 cm^3) and saturated aqueous NH_4Cl (150 cm^3). The organic layer was separated, washed with brine (80 cm^3) and dried (Na_2SO_4). Concentration and chromatography (EtOAc–light petroleum, 1:100) of the residue gave pure *title compound* **6** (7.64 g, 89%) (Found: C, 70.8; H, 9.9. $C_{28}H_{46}O_4Si$ requires C, 70.84; H, 9.77%); $[\alpha]_D^{20}$ −19.5 (*c* 0.5 in $CHCl_3$); γ_{max}(film)/cm^{-1} 3010, 2920, 2860, 2160w, 1500, 1380 and 1370; δ_H(200 MHz; $CDCl_3$) 0.1 (6 H, s), 0.87 (9 H, s), 0.90 (3 H, t, *J* 7.2), 1.2–1.60 (6 H, m), 1.41 (6 H, s), 2.15 (2 H, m), 2.45 (2 H, m), 3.6–4.0 (4 H, m), 4.25 (1 H, m), 4.60 (2 H, s) and 7.35 (5 H, m); *m/z* 475 (M^+ + 1, 1%), 459 (M^+ − CH_3, 4), 359 (M^+ − $SiMe_2Bu^t$, 10) and 91 ($C_6H_5CH_2$, 100).

(2R,3S,4R)-1-*Benzyloxy*-4-tert-*butyldimethylsilyloxy*-2,3-O-*isopropylidenedodec*-6-*ene*-2,3-*diol* **7**.—The acetylene **6** (5.8 g, 12.2 mmol) was hydrogenated under atmospheric pressure using Lindlar catalyst (1.0 g) in hexane (80 cm^3) in the presence of quinoline (0.4 g). After uptake of the theoretical amount of hydrogen, the mixture was filtered, and the filtrate was washed with 2 mol dm^{-3} HCl (30 cm^3) and aqueous $NaHCO_3$ (30 cm^3), and dried (Na_2SO_4). Evaporation and chromatography produced the corresponding *alkene* **6** (5.8 g, 99%) (Found: C, 70.6; H, 10.3. $C_{28}H_{48}O_4Si$ requires C, 70.54; H, 10.15%); $[\alpha]_D^{20}$ −25.9 (*c* 0.6, $CHCl_3$); γ_{max}(film)/cm^{-1} 3010, 2920, 2860, 1660w, 1380 and 1370; δ_H(200 MHz; $CDCl_3$) 0.05 (6 H, s), 0.85 (9 H, s), 0.88 (3 H, t, *J* 7.2), 1.2–1.6 (6 H, m), 1.38 (3 H, s), 1.40 (3 H, s), 2.0–2.5 (4 H, m), 3.52 (1 H, m), 3.64–3.84 (3 H, m), 4.16 (1 H, m), 4.59 (2 H, s), 5.45 (2 H, 2 × td, $J_{6,7}$ 10.8, Z) and 7.35 (5 H, m); *m/z* 477

($M^+ + 1$), 461 ($M^+ - CH_3$, 3%), 361 ($M^+ - SiMe_2Bu^t$, 3) and 91 ($C_6H_5CH_2$, 100).

(2R,3S,4R)-4-tert-*Butyldimethylsilyloxy*-2,3-O-*isopropylidenedodec*-6-*ene*-1,2,3-*triol* **8**.—Lithium (0.7 g, 100 g atom) was dissolved in liq. NH_3 (100 cm^3), to which was added a solution of compound **7** (5.5 g, 11.6 mmol) in Et_2O (20 cm^3), and the mixture was stirred for 20 min at −40 °C. Methanol (10 cm^3) was added to the mixture and NH_3 was allowed to evaporate at room temp. After addition of saturated aqueous NH_4Cl (150 cm^3 the mixture was extracted with ether (100 cm^3 × 3). Purification by chromatography (EtOAc–light petroleum, 1:10) gave the *title compound* **8** (4.25 g, 95%) (Found: C, 64.9; H, 11.1. $C_{21}H_{42}O_4Si$ requires C, 65.24; H, 10.99%); $[\alpha]_D^{20}$ −35.8 (*c* 0.75, $CHCl_3$); γ_{max}(film)/cm^{-1} 3450, 1660w, 1380 and 1370; δ_H(200 MHz; $CDCl_3$) 0.10 (6 H, s), 0.90 (9 H, s), 0.91 (3 H, t, *J* 7.2), 1.3–1.60 (6 H, m), 1.39 (3 H, s), 1.40 (3 H, s), 2.0–2.5 (4 H, m), 3.6–3.90 (4 H, m), 4.05 (1 H, m) and 5.45 (2 H, 2 × td, olefinic); *m*/*z* 387 ($M^+ + 1$, 7%), 371 ($M^+ - CH_3$, 11), 329 (20), 311 (20), 271 ($M^+ - SiMe_2Bu^t$, 21) and 131 (100).

(5Z,8Z,14Z; 10R,11S,12R)-*Methyl* 12-tert-*Butyldimethylsilyloxy*-10,11-*isopropylidenedioxyeicosa*-5,8,14-*trienoate* **9**.—To a cooled (−60 °C) solution of $(COCl)_2$ (1.0 g, 7.7 mmol) in CH_2Cl_2 (20 cm^3) was added DMSO (dimethyl sulfoxide) (1.15 g, 14.7 mmol) in CH_2Cl_2 (10 cm^3) and the mixture was stirred for 10 min, after which compound **8** (2.4 g, 6.2 mmol) in CH_2Cl_2 (5 cm^3) was added to it. After stirring for 2 h at −60 °C, Et_3N (3.4 g) in CH_2Cl_2 (5 cm^3) was added and the temperature was gradually raised to 0 °C over 2 h. The mixture was poured into cold phosphate buffer and the products were extracted with Et_2O. The organic layer was washed with water and brine, and concentrated to give the crude aldehyde (2.2 g).

To a suspension of [(3*Z*)-7-methoxycarbonylhept-3-enyl]-triphenylphosphonium bromide (4.5 g, 9 mmol) in THF (60 cm^3) was added dropwise potassium bis(trimethylsilyl)amide [$KN(SiMe_3)_2$] (1 mol dm^{-3}, 9 mmol) at 0 °C. A red solution was obtained after stirring for an additional 1 h at 0 °C and was then cooled to −70 °C. A solution of the above aldehyde in THF (5 cm^3) was added dropwise. The reaction mixture was stirred at −70 to 0 °C over 2 h, and at 0 °C for an additional 1 h. After addition of saturated aqueous NH_4Cl (100 cm^3) the mixture was extracted with ether–light petroleum (1:1, 100 cm^3 × 2). The combined extracts were washed with brine (50 cm^3), dried (Na_2SO_4), concentrated under reduced pressure and chromatographed (EtOAc–light petroleum, 1:100) to give pure (*Z*)-olefin **9** (2.54 g, 78%), R_f 0.82 (EtOAc–hexane 1:20) (Found: C, 69.0; H, 10.35. $C_{30}H_{54}O_5Si$ requires C, 68.92; H, 10.41%); $[\alpha]_D^{20}$ 15.2 (*c* 0.35, $CHCl_3$); γ_{max}(film)/cm^{-1} 3010, 2920, 2860, 1735, 1660w, 1380 and 1370; δ_H(200 MHz; $CDCl_3$) 0.07 (6 H, s), 0.91 (9 H, s), 1.39 (3 H, s), 1.42 (3 H, s), 1.2–1.65 (6 H, m), 1.95–2.40 (8 H, m), 2.90 (2 H, m), 3.66 (3 H, s), 3.70 (1 H, dd, 11-H), 3.94 (1 H, td, 12-H), 4.86 (1 H, dd, *J* 8.2 and 8, 10-H and 5.35–5.65 (6 H, complex, olefinic); *m*/*z* 522 (M^+, 1%), 447 (2), 407 ($M^+ - SiMe_2Bu^t$, 8), 267 (42) and 74 (100).

(5Z,8Z,14Z; 10R,11R,12R)-*Methyl* 12-*Hydroxy*-10,11-*isopropylidenedioxyeicosa*-5,8,14-*trienoate* **10**.—Tetrabutylammonium fluoride in THF (1 mol dm^{-3}; 12 cm^3, 12 mmol) was added to a solution of compound **9** (3.1 g, 5.93 mmol) in dry THF (20 cm^3). After being stirred overnight at room temp., the mixture was hydrolysed (50 cm^3 of water) and extracted with Et_2O (50 cm^3 × 3). After evaporation, the crude product was purified by flash chromatography (EtOAc–light petroleum, 1:15) to give the title compound **10** (2.24 g, 92%) (Found: C, 70.65; H, 10.2. $C_{24}H_{40}O_5$ requires C, 70.55; H, 9.88%; $[\alpha]_D^{20}$ −7.8 (*c* 0.48, $CHCl_3$); γ_{max}(film)/cm^{-1} 3450, 3010, 2920, 2860, 1735, 1660, 1380 and 1370; δ_H(200 MHz; $CDCl_3$) 0.88 (3 H, t, *J* 7.2), 1.43 (3 H, s), 1.44 (3 H, s), 1.25–1.60 (6 H, m), 2.0–2.4 (8 H, m), 2.95 (2 H, m, 7-H), 3.68 (3 H, s), 3.65–3.80 (2 H, m, 11-H, 12-H), 4.85 (1 H, dd, *J* 8.2, 8, 10-H and 5.35–5.65 (6 H, m); *m*/*z* 408 (M^+, 3%), 391 ($M^+ + 1 - H_2O$, 1) and 334 (100).

(5Z,8Z,14Z; 10R,11R,12R)-*Methyl* 10,11,12-*Trihydroxyeicosa*-5,8,14-*trienoate* **11**.—To a stirred solution of **10** (0.9 g, 2.2 mmol) in methanol (15 cm^3) was added toluene-*p*-sulfonic acid (0.2 g). After being stirred for 24 h at room temp., the mixture was worked up as usual. Purification by flash chromatography (EtOAc–light petroleum, 2:3 to 1:1) gave unchanged starting material **10** (0.21 g) and the title compound **11** (0.55 g, 68%) R_f 0.28 (EtOAc–hexane, 1:1); $[\alpha]_D^{20}$ −16.1 (*c* 3.2 in $CHCl_3$); γ_{max}(film)/cm^{-1} 3400br, 1730 and 1660; δ_H(600 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 6.8), 1.2–1.7 (8 H, m), 2.0–2.5 (8 H, m), 2.82–2.96 (2 H, m), 3.48 (1 H, dd, *J* 6 and 6.2), 3.67 (3 H, s), 3.74 (1 H, dt, *J* 4 and 6), 4.72 (1 H, dd, *J* 4 and 10), 5.41 (3 H, m) and 5.60 (3 H, m); *m*/*z* 368 (M^+, 2%), 353 ($M^+ - CH_3$), 351 ($M^+ + 1 - H_2O$, 1), 333 ($M^+ + 1 - 2H_2O$, 12), 315 ($M^+ + 1 - 3H_2O$, 10) and 55 (100).

(5Z,8Z,14Z; 10R,11S,12S)-*Methyl* 10-*Hydroxy*-11,12-*epoxyeicosa*-5,8,14-*trienoate* **13**.—To a solution of compound **10** (0.1 g, 0.25 mmol) in dry CH_2Cl_2 (2 cm^3) was added *p*-TsCl (0.15 g) and pyridine (0.1 cm^3). The mixture was stirred at 0–5 °C for 24 h. Work-up furnished crude **12**. To a stirred solution of tosylate **12** in methanol (5 cm^3) was added toluene-*p*-sulfonic acid (0.1 g). After the mixture had been stirred for 24 h at room temp., K_2CO_3 (0.4 g) was added and stirring was continued for an additional 30 min; the mixture was then diluted with Et_2O (40 cm^3). The organic layer was concentrated under reduced pressure and chromatographed (EtOAc–light petroleum, 1:8) to give the title compound **13** (54 mg, 63%); R_f 0.40 (EtOAc–hexane, 1:4); $[\alpha]_D$ −68.2 (*c* 0.5 in acetone); γ_{max}(film)/cm^{-1} 3450, 1730 and 1660; δ_H(600 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 6), 1.27–1.70 (8 H, m), 2.0–2.2 (4 H, m), 2.30 (2 H, t, *J* 7.5), 2.41 (2 H, m), 2.83 (1 H, dd, *J* 5.3, 2.3, 11-H), 2.90 (2 H, m, 7-H), 2.97 (1 H, dt, *J* 2.2, 5.5, 12-H), 3.67 (3 H, s), 4.33 (1 H, dd, *J* 8.7, 5.3), 5.32–5.4 (3 H, m) and 5.52–5.6 (3 H, m); *m*/*z* 281 (2%), 267, 253, 221, 99 and 55.

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