

Stereoselective preparations of epoxy-, fluoro- and related derivatives of ricinoleic acid and 13(*S*)-hydroxyoctadeca-9(*Z*),11(*E*)-dienoic acid

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Dedicated to Professor M. Anthony McKervey on his 65th birthday

(received 24 Feb 03; accepted 06 May 03; published on the web 17 May 03)

Abstract

Methyl ricinoleate **4** and methyl 13(*S*)-hydroxyoctadeca-9(*Z*),11(*E*)-dienoate **7** were subjected to epoxidation using mCPBA, or tert-butyl hydroperoxide in the presence of vanadyl acetylacetonate or titanium (IV) isopropoxide with D-(-)- or L-(+)-diisopropyl tartrate. Epoxidations using mCPBA gave equal quantities of the disatereoisomeric epoxides **5/6** and **8/9** from **4** and **7** respectively. Other methods gave preferentially epoxides **5** or **8**, except for treatment of **7** with tert-butyl hydroperoxide in the presence of titanium (IV) isopropoxide and L-(+)-diisopropyl tartrate which gave preferentially epoxide **9**. Hydroxy-derivative **4**, **7**, **5**, **6**, **8** and **9** were converted into the fluoro-derivatives **16** - **21** by trimethylsilylation and treatment with diethylaminosulphur trifluoride. Epoxides **6** and **9** were converted into 2-oxazolines **22** and **23** respectively by reaction with acetamide.

Keywords: Oxygenated fatty acids, fluorinated fatty acids, epoxidation, 2-oxazolines

Introduction

Fatty acids are relatively underused as synthetic starting materials, in spite of their natural abundance. Possible reasons for this include their relative lack of functionality and their general lack of asymmetry. Stereoselective methods of preparing fatty acid derivatives would increase the synthetic utility of these materials. In addition, functionalised fatty acids are of increasing interest in a variety of applications, for example, as defensive agents for plants¹. We have examined the stereoselective epoxidation, fluorination, and certain other transformations, of two chiral fatty acids available in good optical purity: ricinoleic acid **1** (Figure 1), obtainable from

castor oil, and 13(*S*)-hydroxyoctadeca-9(*Z*),11(*E*)-dienoic acid (13(*S*)-HODE) **2**, obtainable by biotransformation of linoleic acid **3**.

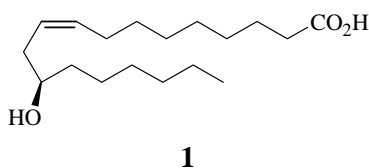


Figure 1

Results and Discussion

The well established oxygenation of linoleic acid **2** using immobilised soybean lipoxygenase² in a DMSO-containing medium³ was used to give preparative quantities of 13(*S*)-HODE **3**. This procedure gave 3.4 to 4.0 g (66-76%) yield of product in excellent optical purity after sodium borohydride reduction of the hydroperoxide product (Figure 2).

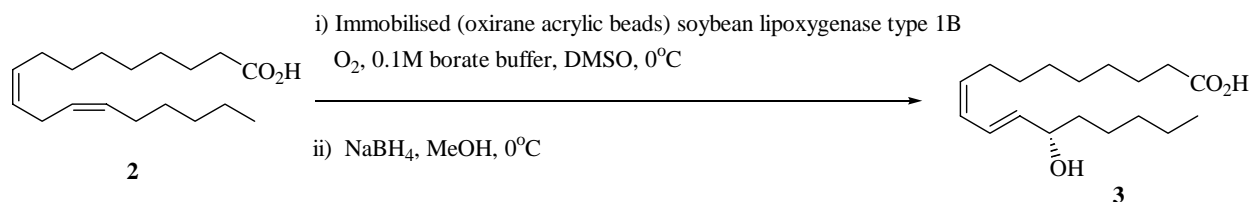


Figure 2

Foglia et al reported diastereoselective epoxidations of methyl ricinoleate **4** in which the product epoxides were obtained as mixtures and the ratios of diastereoisomers determined by GC³. In Table 1, we report the epoxidation of **4** using various methods and give the isolated yields of epoxides **5** and **6**. Equal amounts of **5** and **6** were isolated after epoxidation with mCPBA. Epoxidation using *tert*-butyl hydroperoxide with either vanadyl acetylacetonate or titanium (IV) isopropoxide gave selectively epoxide **5**, previously characterised by Foglia et al³. Addition of D-(-)-diisopropyl tartrate to the *tert*-butyl hydroperoxide/titanium (IV) isopropoxide mixture was found to improve diastereoselectivity. Addition of L-(+)-diisopropyl tartrate had no effect on the diastereoselectivity of *tert*-butyl hydroperoxide/titanium (IV) isopropoxide.

Table 1. Epoxidation of methyl ricinoleate **4**

Reagents	% 5 ^a	% 6 ^a
mCPBA	41	41
TBHP ^b , VO(acac) ₂	77	41
TBHP, Ti(OPr ⁱ) ₄ , D-(-)-DIPT ^c	82	5

^a% isolated yield; ^b*tert*-butyl hydroperoxide; ^cdiisopropyl tartrate.

Piazza et al reported a titanium (IV) isopropoxide-catalysed stereoselective intramolecular epoxidation of the hydroperoxide derivative of compound **3**⁴. In our hands, the intramolecular epoxidation method was low yielding and give large quantities of unreacted starting material. Better yields, with good diastereoselectivities, were obtained using 'external' epoxidising agents on the methyl ester of 13(*S*)-HODE **7** (Table 2). Epoxidation occurred specifically at the 11(*Z*)-alkene closer to the hydroxyl in all cases. Equal amounts of epoxides **8** and **9** were isolated after epoxidation with mCPBA. Epoxidation using *tert*-butyl hydroperoxide and vanadyl acetylacetonate gave selectively epoxide **8**, previously characterised by Piazza et al⁴, as did epoxidation with *tert*-butyl hydroperoxide/titanium (IV) isopropoxide in the presence of D-(-)-diisopropyl tartrate. However, epoxidation of **7** with *tert*-butyl hydroperoxide/titanium (IV) isopropoxide in the presence of L-(+)-diisopropyl tartrate was found to give a reversal in diastereoselectivity, with **9** being obtained in greater quantity.

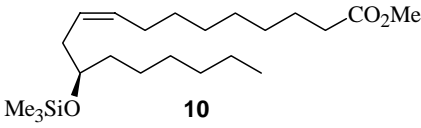
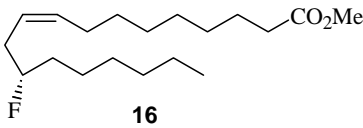
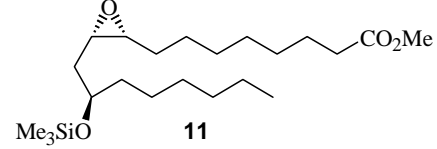
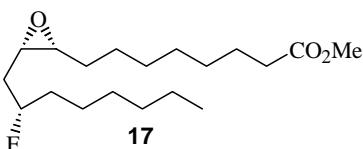
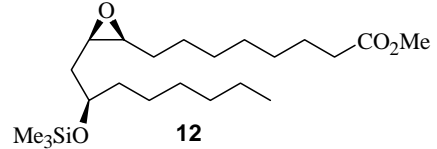
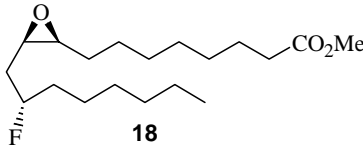
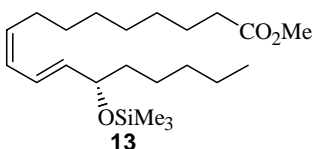
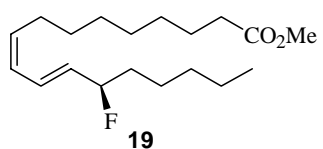
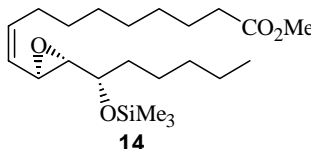
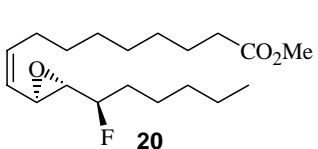
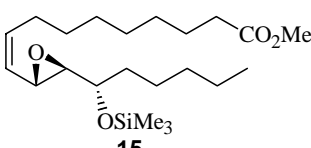
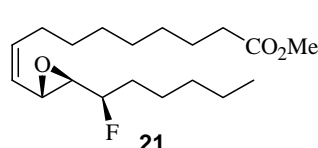
Table 2. Epoxidation of methyl 13(*S*)-HODE **7**

Reagents	% 8 ^a	% 9 ^a
mCPBA	43	43
TBHP ^b , VO(acac) ₂	72	6
TBHP, Ti(OPr ⁱ) ₄ , D-(-)-DIPT ^c	75	11
TBHP, Ti(OPr ⁱ) ₄ , L-(+)-DIPT	6	73

^a% isolated yield; ^b*tert*-butyl hydroperoxide; ^cdiisopropyl tartrate.

Fluorinated analogues of oxygenated fatty acids are of interest due to their potential for displaying modified chemical and biological properties. Shown in Table 3 are results obtained upon treatment of the hydroxy- and epoxyhydroxy-fatty acid esters described above with diethylaminosulphur trifluoride (DAST). We found that much improved yields were obtained by conversion of the substrates into trimethylsilyl ethers by treatment with *N,O*-bis(trimethylsilyl)trifluoroacetamide prior to reaction with DAST. Reaction was found to proceed with inversion of stereochemistry in each case.

Table 3. Reaction of DAST with trimethylsilyl ethers **10 - 15**

Trimethylsilyl ether	Product	% Yield
 <p>10</p>	 <p>16</p>	84
 <p>11</p>	 <p>17</p>	87
 <p>12</p>	 <p>18</p>	86
 <p>13</p>	 <p>19</p>	86
 <p>14</p>	 <p>20</p>	87
 <p>15</p>	 <p>21</p>	89

Heterocyclic derivatives offer well defined stereochemistry with restricted conformational freedom which can influence biological activity. Consequently, we investigated the conversion of epoxides **6** and **9** into 2-oxazoline derivatives by reaction with acetamide in DMF at 100°C⁵. One product only was isolated from both reactions. Coupling constants indicated that these had, respectively, *trans*- and *cis*-stereochemistry at positions 4 and 5 of the oxazoline rings. We therefore believe these to be the oxazolines **22** and **23** (Figure 3).

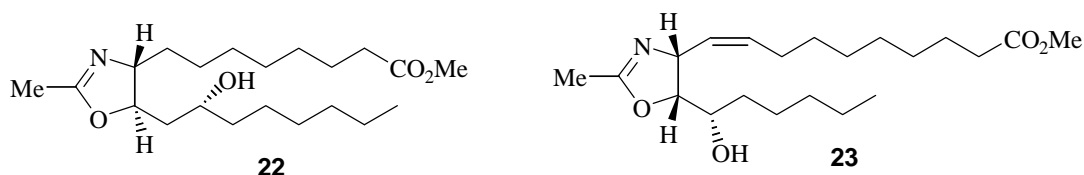


Figure 3

Experimental Section

General Procedures. Infrared spectra (ν_{\max}) were recorded on a Perkin-Elmer 1600 series FTIR spectrometer. ¹H NMR spectra were recorded on a JOEL JNM-FX90Q FT-NMR spectrometer; samples were dissolved in CDCl₃ or *d*₆-DMSO and chemical shifts (δ_{H}) are reported in ppm downfield of tetramethylsilane. Coupling constants (*J*) are quoted in Hz. Optical rotations were recorded on a Bellingham & Stanley ADP220 Polarimeter. Silica gel column chromatography was performed using silica gel G60, 70-230 mesh (Merck Ltd). Methyl esters were prepared by treatment of the carboxylic acids with ethereal solutions of diazomethane. Mass spectrometry was carried out by the EPSRC National Mass Spectrometry Service Centre, University of Swansea, UK. Low resolution mass spectrometry (*m/z*) was carried out on a VG Biotech Quattro II triple quadrupole instrument; accurate mass measurements were carried out on a VG ZAB-E instrument using manual peak matching. Hydroxy-compounds were converted into trimethylsilyl ethers prior to analysis by treatment with *N,O*-bis(trimethylsilyl)trifluoroacetamide at 60°C for 15 minutes.

13(S)-Hydroxyoctadeca-9(Z),11(E)-dienoic acid (13(S)-HODE) (3). Soybean lipoxygenase type 1B (100 mg, Sigma Chemical Co.) was suspended in 1M phosphate buffer (100 mL, pH 7.5). Oxirane acrylic beads (3.0 g Sigma Chemical Co.) were added to the enzyme suspension with magnetic stirring and stored at 4°C for 60 hours. The beads were collected by filtration, washed successively with 0.1M phosphate buffer (100 mL, pH 7.5) and 0.1M borate buffer (100 mL, pH 9.5), and then suspended in 0.1M borate buffer (1L, pH 9.5), cooled to 0°C, stirred mechanically at 1200 rpm and oxygen bubbled through the mixture. An emulsion of linoleic acid (5.0 g, 17.8 mmol) in 0.1M borate buffer (200 mL, pH 9.5) was added portionwise into the enzyme suspension, after which DMSO (100 mL) was added. The mixture was stirred for 2

hours after which the suspension was filtered. The filtrate was acidified to pH 3 by addition of 0.1M aqueous hydrochloric acid and extracted into diethyl ether (3 x 250 mL). The combined extracts were dried over magnesium sulphate, filtered and the diethyl ether evaporated under reduced pressure. The crude hydroperoxide was dissolved in methanol (100 mL) and cooled to 0°C. Sodium borohydride (2.0 g, 0.05 mol) was added and the mixture was stirred at 0°C for 20 minutes and at ambient temperature for a further 40 minutes. The methanolic solution was acidified to pH 3 by addition of 0.1M aqueous hydrochloric acid, dissolved in water (100 mL) and extracted into diethyl ether (3 x 100 mL). The combined extracts were dried over magnesium sulphate and the solvent evaporated under reduced pressure. The residue was subjected to silica gel chromatography using diethyl ether/hexane (30/70) containing 1% glacial acetic acid as eluant to give (13S-HODE) **2** as a colourless oil (3.62 g, 69%), $[\alpha]_D^{25} + 9.6^\circ$ ($c = 0.6 \text{ CHCl}_3$); $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3443, 2997, 2920, 2845, 1707, 896; δ_{H} 0.91 (3H, t, CH_3), 1.26 - 1.68 (18H, m, CH_2), 2.20 (2H, m, 8- CH_2), 2.36 (2H, t, 2- CH_2), 4.10 (1H, m, H-13), 5.41 (1H, t, $J = 10.7$, H-9), 5.70 (1H, m, H-12), 5.80 (2H, s, OH and CO_2H), 5.93 (1H, d, H-10), 6.43 (1H, m, $J = 15.3$, H-11); m/z (Trimethylsilylated methyl ester) (EI) 73 (100%), 74, 173, 225, 293, 311, 367, 382 (M^+).

Epoxidations with mCPBA

A mixture of methyl ester **4** or **7** (100 mg, 0.32 mmol) and mCPBA (120 mg, 0.65 mmol) in dichloromethane (10 mL) was stirred for 1 hour, after which dichloromethane (50 mL) was added and the reaction mixture washed with 10% aqueous ferrous sulphate (3 x 100 mL) and water (50 mL), dried over magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was subjected to silica gel chromatography using diethyl ether/hexane (30/70) containing 1% triethylamine. Epoxidation of methyl ricinoleate **4** gave **5** (43 mg, 41%) and **6** (42 mg, 41%). Epoxidation of methyl 13(S)-HODE **7** gave **8** (45 mg, 43%) and **9** (44 mg, 43%).

Epoxidations with *tert*-butyl hydroperoxide/vanadyl acetylacetonate

Vanadyl acetylacetonate (19 mg, 0.07 mmol) was added to a solution of methyl ester **4** or **7** (100 mg, 0.32 mmol) in dichloromethane (10 mL) at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 10 minutes, after which *tert*-butyl hydroperoxide (0.1 mL, 0.55 mmol, 5.5M in isooctane) was added. The solution was stirred at 0°C for 1 hour, then at ambient temperature for 10 minutes, after which dichloromethane (50 mL) was added and the reaction mixture washed with 10% aqueous ferrous sulphate (3 x 100 mL), dried over magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was subjected to silica gel chromatography using diethyl ether/hexane (30/70) containing 1% triethylamine. Epoxidation of methyl ricinoleate **4** gave **5** (81 mg, 77%) and **6** (3 mg, 2%). Epoxidation of methyl 13(S)-HODE **7** gave **8** (74 mg, 72%) and **9** (6 mg, 6%).

Epoxidations with *tert*-butyl hydroperoxide/titanium (IV) isopropoxide

Titanium (IV) isopropoxide (114 mg, 0.40 mmol) and D-(-)- or L-(+)-diisopropyl tartrate (105 mg, 0.45 mmol) were added to a solution of methyl ester **4** or **7** (100 mg, 0.32 mmol) in dichloromethane (10 mL) at - 20°C under a nitrogen atmosphere. The reaction mixture was stirred for 10 minutes, after which *tert*-butyl hydroperoxide (0.1 mL, 0.55 mmol, 5.5M in isooctane) was added. The solution was stirred at - 20°C for 3 hours, then at ambient temperature for 1 hour, after which dichloromethane (50 mL) was added and the reaction mixture washed with 10% aqueous ferrous sulphate (3 x 100 mL), dried over magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was subjected to silica gel chromatography using diethyl ether/hexane (30/70) containing 1% triethylamine as eluant. Epoxidation of methyl ricinoleate **4** in the presence of D-(-)-diisopropyltartrate gave **5** (88 mg, 82%) and **6** (5 mg, 5%). Epoxidation of methyl 13(*S*)-HODE **7** in the presence of D-(-)-diisopropyltartrate gave **8** (78 mg, 75%) and **9** (11mg, 11%). Epoxidation of methyl 13(*S*)-HODE **7** in the presence of L-(+)-diisopropyltartrate gave **8** (7 mg, 6%) and **9** (76mg, 73%).

Methyl 9(*R*),10(*S*)-epoxy-12(*R*)-hydroxyoctadecanoate (5). $[\alpha]_{\text{D}}^{25} + 5.2^{\circ}$ ($c = 1.0 \text{ CHCl}_3$); $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3446, 2927, 2855, 1740, 1247, 842; δ_{H} 0.91 (3H, t, CH_3), 1.20 - 1.50 (24H, m, CH_2), 2.24 (2H, t, 2- CH_2), 2.75 (1H, brs, OH), 2.81 (2H, m, H-9, H-10), 3.05 (1H, m, H-12), 3.67 (3H, s, OCH_3); m/z (trimethylsilyl ether) (EI) 73 (100%), 187, 55, 75, 129, 155, 199, 259, 271, 297, 316, 385. $[M + H]$ 401.3087 (calc); observed (CI) 401.3086.

Methyl 9(*S*),10(*R*)-epoxy-12(*R*)-hydroxyoctadecanoate (6). $[\alpha]_{\text{D}}^{25} + 3.5^{\circ}$ ($c = 1.0 \text{ CHCl}_3$); $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3461, 2930, 2856, 1742, 1250, 842; δ_{H} 0.91 (3H, t, CH_3), 1.20 - 1.50 (24H, m, CH_2), 2.24 (2H, t, 2- CH_2), 2.75 (1H, brs, OH), 2.81 (2H, m, H-9, H-10), 3.05 (1H, m, H-12), 3.67 (3H, s, OCH_3). m/z (trimethylsilyl ether) (EI) 73 (100%), 187, 55, 75, 129, 155, 199, 259, 271, 297, 316, 385. $[M + H]$ 401.3087 (calc); observed (CI) 401.3086.

Methyl 11(*S*),12(*R*)-epoxy-13(*S*)-hydroxy-9(*Z*)-octadecenoate (8). $[\alpha]_{\text{D}}^{25} + 2.1^{\circ}$ ($c = 1.0 \text{ CHCl}_3$); $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3445, 2997, 2921, 2856, 1743, 849; δ_{H} 0.91 (3H, t, CH_3), 1.21 - 1.62 (18H, m, CH_2), 2.23 - 2.38 (4H, m, H-2, H-8), 2.93 (1H, dd, $J_{11-12} = 2$, $J_{12-13} = 5$, H-12), 3.62 (1H, m, H-13), 3.74 (3H, s, OCH_3), 3.81 (1H, dd, $J_{10-11} = 8$, $J_{11-12} = 2$, H-11), 5.39 (1H, dd, $J_{9-10} = 11$, $J_{10-11} = 8$, H-10), 5.82 (1H, dt, $J_{8-9} = 7$, $J_{9-10} = 11$, H-9); m/z (trimethylsilyl ether) (EI) 41, 55, 67, 73, 74, 75, 81, 95, 155, 173, 187, 199, 270, 327, 367, 383. $[M + H]$ 399.3088 (calc); observed (CI) 399.3086.

Methyl 11(*R*),12(*S*)-epoxy-13(*S*)-hydroxy-9(*Z*)-octadecenoate (9). $[\alpha]_{\text{D}}^{25} + 4.5^{\circ}$ ($c = 1.0 \text{ CHCl}_3$); $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3468, 2997, 2930, 2857, 1741, 893; δ_{H} 0.91 (3H, t, CH_3), 1.21 - 1.62 (18H, m, CH_2), 2.23 - 2.38 (4H, m, H-2, H-8), 2.90 (1H, dd, $J_{11-12} = 2$, $J_{12-13} = 3$, H-12), 3.74 (3H, s, OCH_3), 3.79 (1H, dd, $J_{10-11} = 6$, $J_{11-12} = 2$, H-11), 4.01 (1H, m, H-13), 5.30 (1H, dd, $J_{9-10} = 11$, $J_{10-11} = 9$, H-10), 5.86 (1H, dt, $J_{8-9} = 8$, $J_{9-10} = 11$, H-9); m/z (trimethylsilyl ether) (EI) 41, 55, 67, 73, 74, 75, 81, 95, 155, 173, 187, 199, 270, 327, 367, 383. $[M + H]$ 399.3088 (calc); observed (CI) 399.3086.

Diethylaminosulphur trifluoride fluorinations

Substrate (100 mg) was dissolved in *N,O*-bis(trimethylsilyl)trifluoroacetamide (0.5 mL) and heated at 90°C for 30 minutes, after which the excess *N,O*-bis(trimethylsilyl)trifluoroacetamide was evaporated *in vacuo*. The residue was dissolved in dichloromethane (10 mL) and cooled to -78°C. A solution of diethylaminosulphur trifluoride (0.1 mL, 0.5 mmol) in dichloromethane (1 mL) was added, and the reaction mixture was stirred at -78°C for 1 hour and at ambient temperature for 30 minutes, after which water (100 mL) was added and the mixture washed with aqueous sodium bicarbonate (0.1M, 3 x 50 mL), dried over magnesium sulphate, filtered and the solvent evaporated under a stream of nitrogen. The residue was subjected to silica gel chromatography using diethyl ether/hexane (15/85) containing 1% triethylamine as eluant.

Methyl 12(S)-fluoro-9(Z)-octadecenoate (16). Methyl ricinoleate **4** (0.32 mmol) gave 85 mg (84%); $[\alpha]_D^{25} - 7.5^\circ$ ($c = 1.0$ CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ (film) 2997, 2931, 2857, 1740, 1021, 786; δ_{H} 0.92 (3H, t, CH₃), 1.20 - 1.50 (20H, m, CH₂), 2.02 (2H, m, CH₂), 2.33 (2H, t, CH₂), 2.42 (2H, m, $J = 8, J = 5, \text{CH}_2$), 3.67 (3H, s, OCH₃), 4.49 (1H, m, $J_{\text{HF}} = 48, J = 8, J = 4, \text{H-12}$), 5.65 (2H, m, $J = 11, \text{H-9, H-10}$); m/z (EI) 67 (100%), 74, 220, 262, 294, 295, 314 (M⁺). $[\text{M} + \text{NH}_4]$ 332.2964 (calc); observed (CI) 332.2966.

Methyl 9(R),10(S)-epoxy-12(S)-fluorooctadecanoate (17). Methyl 9(R),10(S)-epoxy-12(R)-hydroxyoctadecanoate **5** (0.32 mmol) gave 87 mg (87%); $[\alpha]_D^{25} - 20.2^\circ$ ($c = 1.0$ CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ (film) 2930, 2856, 1738, 1250, 1175 785; δ_{H} 0.91 (3H, t, CH₃), 1.30 - 1.60 (22H, m, CH₂), 2.02 (2H, t, H-2), 2.34 (2H, m, $J = 8, J = 5, \text{H-11}$), 2.81 (1H, m, H-9), 3.04 (1H, m, $J = 5, \text{H-10}$), 3.67 (3H, s, OCH₃), 4.75 (1H, m, $J_{\text{HF}} = 48, J = 5, \text{H-12}$); m/z (EI) 755 (100%), 74 155, 173, 199, 279, 310, 311. $[\text{M} + \text{NH}_4]$ 348.2909 (calc); observed (CI) 348.2903.

Methyl 9(S),10(R)-epoxy-12(S)-fluorooctadecanoate (18). Methyl 9(S),10(R)-epoxy-12(R)-hydroxyoctadecanoate **6** (0.32 mmol) gave 87 mg (86%); $[\alpha]_D^{25} - 12.1^\circ$ ($c = 1.0$ CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ (film) 2931, 2856, 1739, 1248, 1172 786; δ_{H} 0.91 (3H, t, CH₃), 1.30 - 1.60 (22H, m, CH₂), 2.02 (2H, t, H-2), 2.31 (2H, m, $J = 8, J = 3, \text{H-11}$), 2.81 (1H, m, H-9), 3.05 (1H, m, $J = 5, \text{H-10}$), 3.67 (3H, s, OCH₃), 4.72 (1H, m, $J_{\text{HF}} = 46, J = 5, \text{H-12}$); m/z (EI) 55 (100%), 74 155, 199, 279, 310, 311. $[\text{M} + \text{NH}_4]$ 348.2904 (calc); observed (CI) 348.2901.

Methyl 13(R)-fluorooctadeca-9(Z),11(E)-dienoate (19). Methyl 13(S)-HODE **7** (0.32 mmol) gave 86 mg (86%); $[\alpha]_D^{25} + 4.5^\circ$ ($c = 1.0$ CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ (film) 2997, 1735, 984, 783; δ_{H} 0.91 (3H, t, CH₃), 1.29 - 1.42 (16H, m, CH₂), 1.84 (2H, m, H-14), 2.17 (2H, m, H-8), 2.30 (2H, t, $J = 7, \text{H-2}$), 3.65 (3H, s, OCH₃), 4.82 (1H, m, $J_{\text{HF}} = 48, J_{\text{H12,H13}} = 7, \text{H-13}$), 5.54 (1H, m, $J_{\text{H9,H10}} = 10, \text{H-9}$), 5.75 (1H, dd, $J_{\text{H11,H12}} = 15, J_{\text{H12,H13}} = 7, \text{H-12}$), 6.05 (1H, dd, $J_{\text{H10,H11}} = 11, J_{\text{H9,H10}} = 10, \text{H-10}$), 6.50 (1H, dd, $J_{\text{H11,H12}} = 15, J_{\text{H10,H11}} = 11, \text{H-11}$); m/z (EI) 55 (100%), 74, 218, 260, 292, 293, 312 (M⁺).

Methyl 11(S),12(R)-epoxy-13(R)-fluoro-9(Z)-octadecenoate (20). Methyl 11(S),12(R)-epoxy-13(S)-hydroxy-9(Z)-octadecenoate **8** (0.32 mmol) gave 88 mg (87%) $[\alpha]_D^{25} - 13.5^\circ$ ($c = 0.8$ CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ (film) 3004, 2921, 2856, 1740, 849, 784; δ_{H} 0.91 (3H, t, CH₃), 1.21 - 1.62 (20H, m, CH₂), 2.38 (2H, t, H-2), 2.96 (1H, dd, $J_{\text{H12,H13}} = 9, J_{\text{H11,H12}} = 2, \text{H-12}$), 3.74 (3H, s, OCH₃), 3.79 (1H, dd, $J_{\text{H10,H11}} = 6, J_{\text{H11,H12}} = 2, \text{H-11}$), 4.76 (1H, m, $J_{\text{HF}} = 47, J = 2, \text{H-13}$), 5.30

(1H, dd, $J_{H9,H10} = 11$, $J_{H10,H11} = 6$, H-10), 5.63 (1H, dt, $J_{H9,H10} = 11$, $J_{H8,H9} = 8$, H-9); m/z (EI) 41, 55 (100%), 67, 73, 74, 75, 81, 95, 135, 155, 173, 187, 199, 225, 251, 277, 291, 308, 309, 328 (M^+). $[M + NH_4]$ 346.2901 (calc); observed (CI) 3346.2905.

Methyl 11(R),12(S)-epoxy-13(R)-fluoro-9(Z)-octadecenoate (21). Methyl 11(R),12(S)-epoxy-13(S)-hydroxy-9(Z)-octadecenoate **9** (0.31 mmol) gave 90 mg (89%) $[\alpha]_D^{25} - 9.8^\circ$ ($c = 0.8$ $CHCl_3$); ν_{max}/cm^{-1} (film) 3005, 2931, 2858, 1740, 843, 789; δ_H 0.91 (3H, t, CH_3), 1.21 - 1.62 (20H, m, CH_2), 2.38 (2H, t, H-2), 2.97 (1H, dd, $J = 2$, $J = 2$, H-12), 3.74 (3H, s, OCH_3), 3.79 (1H, dd, $J = 6$, $J = 2$, H-11), 4.78 (1H, dt, $J_{HF} = 49$, $J = 2$, H-13), 5.30 (1H, dd, $J = 11$, $J = 8$, H-10), 5.65 (1H, dt, $J = 11$, $J = 8$, H-9); m/z (EI) 41, 55 (100%), 67, 73, 74, 75, 81, 95, 135, 155, 173, 199, 225, 251, 277, 291, 308, 309, 328 (M^+). $[M + NH_4]$ 346.2906 (calc); observed (CI) 346.2903.

Preparation of 2-oxazolines

A solution of epoxide (50 mg, 0.15 mmol) and acetamide (9 mg, 0.15 mmol) in DMF (20 mL) was heated to 100°C for 24 hours, after which the solvent was removed *in vacuo* and the residue subjected to silica gel chromatography using diethyl ether/ hexane (10/90) as eluant.

4(R)-(7-carboxymethylheptyl)-5(R)-(2(R)-hydroxyoctyl)-2-methyl-2-oxazoline (22). Methyl 9(S),10(R)-epoxy-12(R)-hydroxyoctadecanoate **6** gave 38 mg (69%) $[\alpha]_D^{25} + 10.3^\circ$ ($c = 1.0$ $CHCl_3$); ν_{max}/cm^{-1} (film) 3412, 1734, 1659, 1392; δ_H 0.91 (3H, t, CH_3), 1.18 - 1.87 (27H, m, CH_3 , CH_2), 2.69 (2H, m, $J = 14$, $J = 4$, $J = 3$, CH_2), 3.64 (3H, s, OCH_3), 3.75 (1H, m, $J = 7$, H-5), 3.93 (1H, s, OH), 4.15 (1H, m, $J = 7$, H-4); m/z 73 (100%), 74, 75, 187, 199, 356, 409, 423, 426, 442 $[M + H]^+$. $[M + H]^+$ 442.2356 (calc); observed (CI) 442.2353.

4(R)-(9-carboxymethyl-1-nonenyl)-5(R)-(1(R)-hydroxyhexyl)-2-methyl-2-oxazoline (23).

Methyl 11(R),12(S)-epoxy-13(S)-hydroxy-9(Z)-octadecenoate **9** gave 38 mg (73%) $[\alpha]_D^{25} + 7.2^\circ$ ($c = 1.0$ $CHCl_3$); ν_{max}/cm^{-1} (film) 3454, 1735, 1655, 1372, 722; δ_H 0.91 (3H, t, CH_3), 1.25 - 1.90 (25H, m, CH_3 , CH_2), 3.85 (1H, m, $J = 9$, $CHOH$), 3.62 (3H, s, OCH_3), 3.75 (1H, m, $J = 9$, H-5), 4.01 (1H, s, OH), 4.75 (1H, m, $J = 9$, H-4) 5.30 (2H, m, $J = 11$, $J = 9$, $CH=CH$); m/z 73 (100%), 74, 75, 173, 198, 368, 408, 421, 424, 440 $[M + H]^+$. $[M + H]^+$ 440.2356 (calc); observed (CI) 440.2353.

Acknowledgements

The authors are grateful for the financial support of the Palm Oil Research Institute of Malaysia (PORIM) and for the assistance of the EPSRC National Mass Spectrometry Service Centre, Swansea, UK.

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