Improved synthesis of enantiomerically pure Etomoxir and its 2,4-dinitrophenyl analogue

Richard Scott and Bernard T. Golding*

School of Natural Sciences - Chemistry, Bedson Building, University of Newcastle upon Tyne, Newcastle upon Tyne, NE1 7RU, UK. Fax: 0191-222-6929; Tel: 0191-222-6647
E-mail: b.t.golding@ncl.ac.uk

Dedicated to Professor Rodney W. Rickards on the occasion of his 70th birthday

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Abstract

A generally applicable synthesis has been developed for 2-substituted oxirane-2-carboxylic esters, which have attracted interest as inhibitors of carnitine palmitoyltransferase-1 (CPT-1) for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). The route involves alkylation of the dianion of 2-methyl-2-propen-1-ol (methallyl alcohol) followed by Sharpless epoxidation. The utility of the method has been demonstrated by the synthesis of (*R*)-Etomoxir, the best known member of this class of compounds, and ethyl (*R*)-2-[6-(2,4-dinitrophenoxy)hexyl]oxirane-carboxylate, previously synthesised only as a racemate. The high enantiomeric purity of the compounds has been demonstrated by formation of Mosher esters of the products of Sharpless epoxidation and analysis by ^{1}H NMR spectroscopy.

Keywords: Etomoxir, carnitine palmitoyltransferase-1, NIDDM, oxirane-2-carboxylates

Introduction

The enzyme carnitine palmitoyltransferase-1 (CPT-1) catalyses the conversion of long-chain fatty-acid CoA esters, principally the CoA ester **1** of palmitic acid, to carnitine esters such as **2**. The latter can enter the mitochondria, where they are converted back to CoA esters by another carnitine palmitoyltransferase, CPT-2 (Figure 1).[1]

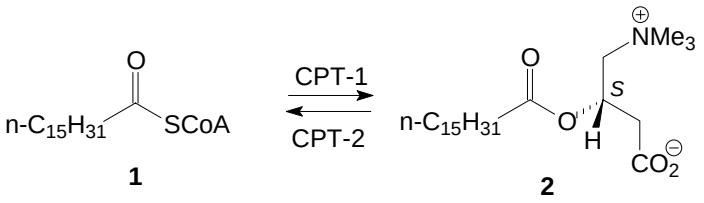


Figure 1. Interconversion of CoA and carnitine esters.

Inside the mitochondria, CoA esters are metabolised by iterative β-oxidations to acetyl CoA, which enters the citric acid cycle, ultimately being degraded to CO_2 with the production of ATP.

By blocking entry of fatty-acid CoA esters into the mitochondria, production of acetyl CoA, ATP and NADH are reduced, thus attenuating gluconeogenesis and hepatic glucose production.[2] Further, the body is forced to rely on glycolysis for the production of acetyl CoA.[3] Therefore, CPT-1 inhibitors have hypoglycaemic (blood-sugar-lowering) effects and have attracted attention as potential treatments for type-2, or non-insulin-dependent diabetes mellitus (NIDDM).[4]

One class of CPT inhibitors is the substituted oxirane carboxylates, of which the best known is probably Etomoxir **3a** (Figure 2).[5] These compounds, of which only the (*R*) enantiomer is active, are converted to CoA esters in the body, mimicking fatty-acid CoA esters. They bind to CPT-1, whereupon the enzyme is covalently alkylated by the epoxide, probably at a histidine residue.[6] Hence, these compounds are irreversible inhibitors. Etomoxir was never brought to market however, due to the very large doses needed for efficacy,[7] as well as side-effects such as cardiac hypertrophy.[8] These side effects are due in part to the lack of selectivity (of Etomoxir **3a** and other similar compounds) for the liver isoform of CPT-1 (L-CPT-1) over the skeletal muscle isoform (M-CPT-1).

M-CPT-1 is the major isoform in the heart, and unwanted inhibition of this isoform is a major factor in the side-effects. To overcome this, the L-CPT-1-selective inhibitor ethyl 2-[6-(2,4-dinitro-phenoxy)-hexyl]oxiranecarboxylic **4** (Figure 2) was developed, although only as a racemate.[9,10] (The free acid form, prepared via a silyl ester rather than the ethyl ester, was used for biological testing).

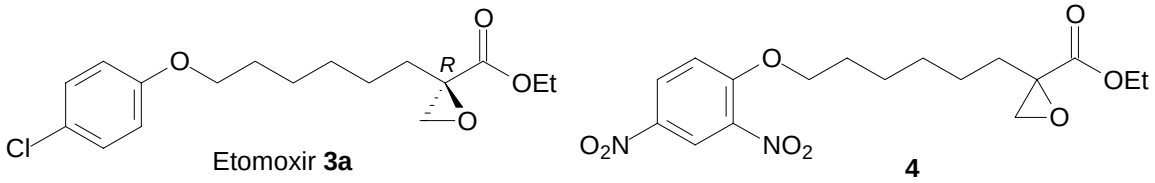
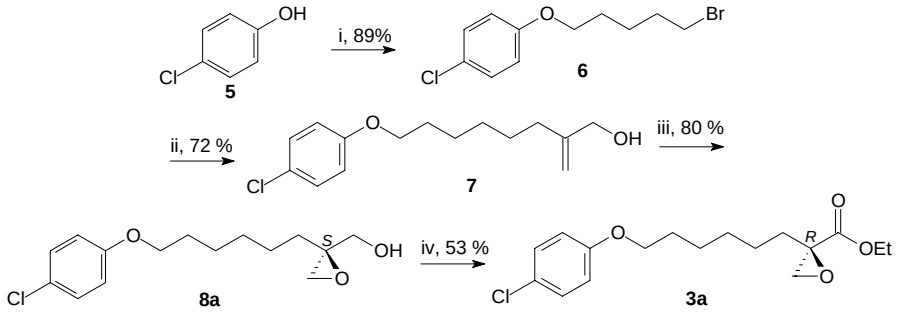


Figure 2. 2-Substituted oxirane-2-carboxylates as CPT-1 inhibitors.

Although Etomoxir **3a** has not been accepted for use treating NIDDM, it has more recently shown potential as a treatment for chronic heart failure.[11] Combined with the demonstration with compound **4** that the side-effects of substituted oxirane-2-carboxylates can be overcome, it seems likely that these compounds and analogues will continue to attract attention. Hence, we have developed a new synthetic methodology for substituted oxirane-2-carboxylates, exemplified by syntheses of **3a** and monochiral **4** [(*R*)-enantiomer **4a**].

Results and Discussion

The key transformations in our method are (i) alkylation of the dianion of methallyl alcohol (2-methyl-2-propen-1-ol) with a bromide corresponding to the desired side-chain of the target, (ii) Sharpless epoxidation[12] of the resulting allyl alcohol, and (iii) oxidation and esterification of the Sharpless product. Various other published syntheses introduce the chirality by enzymatic resolution[13,14] and via a chiral auxiliary.[15] Sharpless epoxidation has been reported before in the synthesis of Etomoxir **3a**, but the synthesis of the necessary precursor **7** was long and inconvenient.[16] Our synthesis of precursor **7** is just two steps, and the complete synthesis of Etomoxir **3a** just four steps. (Scheme 1.)

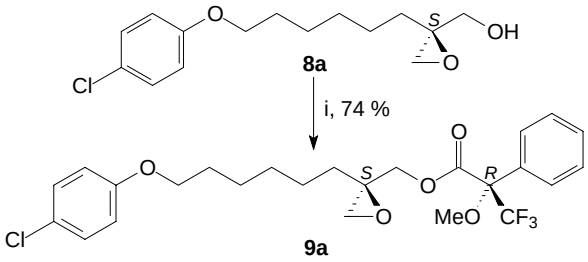


Scheme 1. Reagents and conditions: i, Br-$(CH_2)_5$-Br, NaOH, $Bu_4N.HSO_4$, H_2O, 100 °C, 18 h; ii, Methallyl alcohol, n-BuLi, TMEDA, diethyl ether, petrol, -78 → 25 °C, N_2, 16 h, then add **6**, -78→ 25 °C, N_2, 1 h; iii, L-(+)-diethyl tartrate, $Ti(OiPr)_4$, *t*-BuOOH, powdered 4Å molecular sieves, CH_2Cl_2, -5 → -20 °C, N_2, 3 h; iv, $RuCl_3$, $NaIO_4$, H_2O, CH_3CN, CCl_4, 25 °C, 6 h then EtI, $KHCO_3$, DMF, 25 °C, overnight.

4-Chlorophenol **5** was alkylated with an excess of 1,5-dibromopentane, sodium hydroxide and a phase-transfer catalyst to give the bromide **6** in a slightly modified literature procedure.[17] This was used to alkylate methallyl alcohol, doubly deprotonated with butyl lithium in the presence of TMEDA. We found that this reaction can be facilitated by using 2.5 M butyl lithium diluted to 1.6 M with diethyl ether, and also by allowing the reaction mixture to warm from -78 °C to room temperature over one hour after addition of the bromide. The resulting allyl alcohol **7** was epoxidised under modified Sharpless conditions using L-(+)-diethyl tartrate as the ligand to give compound **8a**, or using D-(-)-diethyl tartrate to give the (*R*)-enantiomer **8b** (not pictured). These stereochemical outcomes are based on the accepted model.[18] Alternatively, epoxidation with mCPBA gave the corresponding racemate (compound **8c**, not pictured). The final step in the synthesis was ruthenium-catalysed periodate oxidation of **8a** and esterification of the resulting crude acid. We initially used diethyl sulfate but found that ethyl iodide was superior, being less toxic and easier to remove. The product (*R*)-Etomoxir **3a** (or (*S*)-Etomoxir **3b**, not pictured, from (*R*) epoxy alcohol **8b**) was easily purified by chromatography on silica. Finally, (*R*)-Etomoxir **3a**

could if desired be hydrolysed using sodium hydroxide to give (*R*)-Etomoxir, sodium salt **10a** (not pictured), and likewise (*S*)-Etomoxir **3b** gave (*S*)-Etomoxir sodium salt **10b** (not pictured).

The high enantiomeric purity of the Etomoxir **3a** was proved by formation of an ester **9a** of its precursor epoxy alcohol **8a** with (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid (Mosher's acid),[19] using diisopropylcarbodiimide as the coupling reagent and DMAP as catalyst (Scheme 2).



Scheme 2. Reagents and conditions: i, (*R*)-Mosher's acid, diisopropyl-carbodiimide, DMAP, DMF, 0 °C, N_2, 18 h.

Both **8a** and its enantiomer **8b** were converted to (*R*)-Mosher esters for comparison (compounds **9a** and **9b** respectively). The crude samples were analysed by ^{1}H NMR before purification, and the peaks of the *AB* system corresponding to the diastereotopic CH_2 group indicated in Figure 3 were carefully integrated. In both cases, a diastereoisomeric ratio of 98 : 2, corresponding to an e.e. of at least 96 % for **8a** and **8b**, was observed. The ^{1}H NMR spectra for these CH_2 groups are shown in Figure 3.

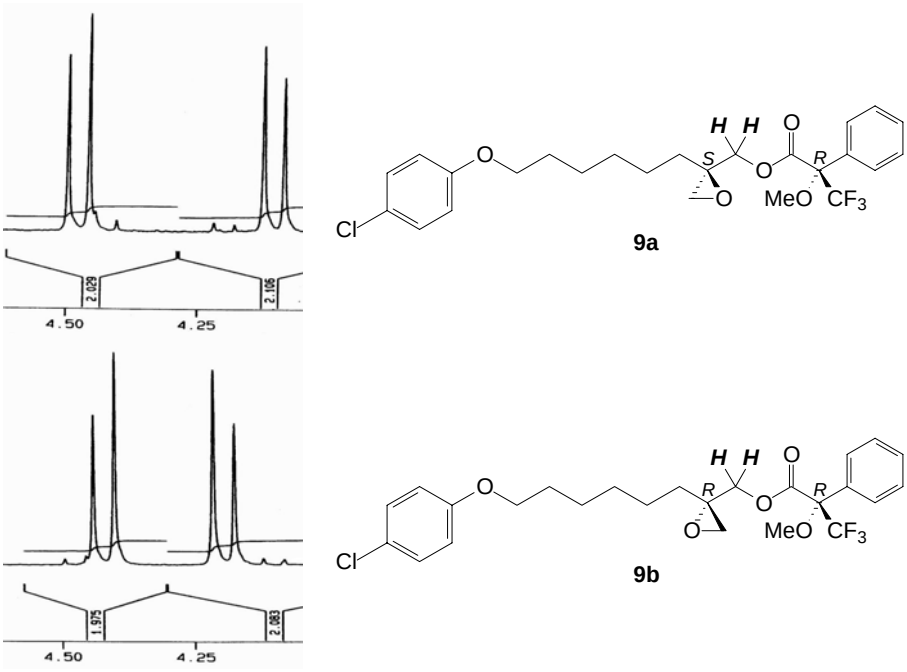
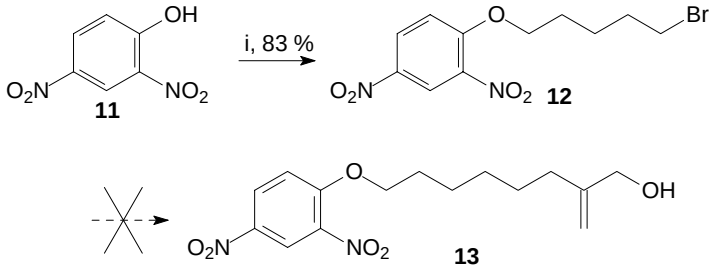


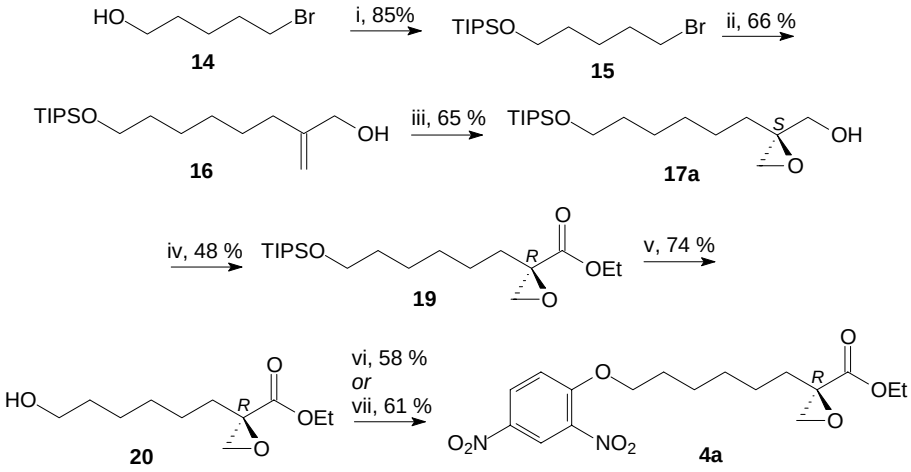
Figure 3. ^{1}H NMR of the diastereotopic CH_2 groups of **9a** and **9b**.

The synthesis of ethyl (*R*)-2-[6-(2,4-dinitrophenoxy)-hexyl]-oxiranecarboxylate **4a** required a partly different strategy. We began by attempting an exactly analogous synthesis to that described for (*R*)-Etomoxir, and accordingly alkylated 2,4-dinitrophenol **11** with an excess of 1,5-dibromopentane in the presence of sodium hydroxide and a phase-transfer catalyst to give the bromide **12** in good yield (Scheme 3). Unfortunately, trying to use **12** to alkylate doubly deprotonated methallyl alcohol resulted only in the formation of a black tar containing none of the desired product **13**.



Scheme 3. Reagents and conditions: i, Br-$(CH_2)_5$-Br, NaOH, $Bu_4N.HSO_4$, H_2O, 100 °C, 18 h.

It was decided to defer coupling of the dinitrophenoxy group until after the methallyl alcohol alkylation, substituting the triisopropylsilyl (TIPS) group as a protecting group in the meantime (Scheme 4). [Mass spectra of compounds containing the TIPS group always gave signals showing fragmentative loss of one isopropyl group (C_3H_7, mass = 43) and no M^+ ion].



Scheme 4. Reagents and conditions: i, TIPS-Cl, imidazole, DMF, 25 °C, 3 h; ii, Methallyl alcohol, $_n$-BuLi, TMEDA, diethyl ether, petrol, -78 → 25 °C, N_2, 16 h, then add **15**, -78 → 25 °C, N_2, 1 h; iii, L-(+)-diethyl tartrate, $Ti(OiPr)_4$, *t*-BuOOH, powdered 4Å molecular sieves, CH_2Cl_2, -5 → -20 °C, N_2, 3 h; iv, $RuCl_3$, $NaIO_4$, H_2O, CH_3CN, CCl_4, 25 °C, 6h then EtI, $KHCO_3$, DMF, 25 °C, overnight; v, TBAF, THF, 25 °C, 1 h; vi, 2,4-dinitrofluorobenzene, DABCO, DMF, 25 °C, 48 h; vii, 2,4-dinitrophenol, DEAD, PPh_3, THF, 0 → 25 °C, 18 h.

5-Bromo-1-pentanol **14** was prepared according to a literature procedure,[20] and protected using triisopropylsilyl chloride and imidazole in DMF to give bromide **15**. This underwent coupling with deprotonated methallyl alcohol satisfactorily in the presence of TMEDA to give allyl alcohol **16**. This was epoxidised under modified Sharpless conditions using L-(+)-diethyl tartrate as the ligand to give compound **17a**, D-(-)-diethyl tartrate to give the (*R*) enantiomer **17b** (not pictured), or mCPBA to give racemate **17c** (not pictured). Enantiomeric purity (e.e. ≥96 %) was again proved by the formation of (*R*)-Mosher esters as above (not pictured, compounds **18a** and **18b** for the (*S*) and (*R*) enantiomers respectively in the experimental section).

Epoxy alcohol **17a** was oxidised and esterified under the same conditions which yielded Etomoxir **3a** to give ester **19**, and the protecting group was removed using tetrabutylammonium fluoride (TBAF) in THF to give alcohol **20**. This alcohol should be used promptly as it appears to go off on standing.

The final step was the coupling of **20** with a source of the 2,4-dinitrophenoxy group to yield the target compound **4a**. To achieve this, two approaches were examined: nucleophilic aromatic substitution with 2,4-dinitrofluorobenzene, and Mitsunobu reaction[21] with 2,4-dinitrophenol. The Mitsunobu reaction, which has been used in the synthesis of 2-substituted-oxirane-2-carboxylates previously,[15,22] was the better of the two, 2,4-dinitrofluorobenzene giving difficult-to-reproduce results and sometimes yielding compound **4a** contaminated with an unidentified impurity difficult to remove by chromatography.

Overall, this route is slightly longer than the route which yielded Etomoxir **3a**, but has the advantage that the use of the Mitsunobu reaction allows for the dereferal of the coupling of the aromatic group until after the formation of the oxirane-carboxylate portion of the molecule. This opens up the possibility of the synthesis of a wide variety of chemically sensitive or non-phenolic analogues.

Conclusions

In conclusion, we have developed a versatile and efficient route to 2-substituted oxirane-2-carboxylates, which should allow the synthesis of a broad range of analogues in enantiomerically pure form. In doing so, we have developed the shortest synthesis yet published of Etomoxir.

Experimental Section

General Procedures. Anhydrous solvents were purchased from Fluka, and *n*-butyllithium from Sigma-Aldrich. TMEDA and methallyl alcohol were distilled immediately before use. *tert*-Butyl hydrogen peroxide in anhydrous toluene was prepared according to the method of Sharpless.[23] All other reagents were used as received. Column chromatography on silica refers to medium

pressure chromatography using Davisil 40 - 63μ silica gel, Fluorochem, Derbyshire, UK. Optical rotations were recorded at 589 nm.

1-Bromo-5-(4-chlorophenoxy)-pentane (6). To NaOH (4.6 g, 115 mmol) in water (120 mL) was added 4-chlorophenol (6.48 g, 50.9 mmol) portionwise with stirring. Tetrabutylammonium hydrogensulfate (116 mg, 0.34 mmol) was added followed by 1,5-dibromopentane (28 mL, 47.5 g, 197 mmol), and the mixture was heated at reflux overnight. The mixture was allowed to cool and extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to an oil which was heated *in vacuo* (10 mmHg, 140 °C) to remove excess 1,5-dibromopentane. The residual oil was purified by column chromatography on silica (eluting with diethyl ether-petrol, 5 : 95) to yield the title compound as a colourless oil, 12.56 g (89%); R_f 0.77 (ethyl acetate-petrol, 1 : 4); ν_{max}/cm^{-1} 2942, 2867, 1492, 1472, 1286, 1244, 824; δ_H (300 MHz, $CDCl_3$) 7.15 (d, *J* = 8.7 Hz, 2H, 2 × ArH), 6.74 (d, *J* = 8.8 Hz, 2H, 2 × ArH), 3.87 (t, *J* = 6.3 Hz, 2H, CH_2OAr), 3.37 (t, *J* = 6.7 Hz, 2H, CH_2Br), 1.84 (quintet, *J* = 7.5 Hz, 2H, CH_2), 1.73 (quintet, *J* = 6.9 Hz, 2H, CH_2), 1.56 (quintet, *J* = 6.9 Hz, 2H, CH_2); δ_C (75.45 MHz, $CDCl_3$) 157.7, 129.4, 125.6, 115.8, 68.0, 33.6, 32.5, 28.5, 24.9; *m/z* 280 (M^+, 7%), 278 (25%), 276 (21), 151 (19), 149 (16), 130 (17), 128 (54), 69 (100); HRMS: calcd for $C_{11}H_{14}{}^{79}Br\,{}^{35}ClO$ 275.9917, found 275.9903.

8-(4-Chlorophenoxy)-2-methylene-octan-1-ol (7). To anhydrous diethyl ether (15 mL) was added *n*-butyllithium (44 mL of a 2.5 M solution in hexane, 110 mmol) under N_2, and the resulting solution was cooled to –78 °C. Freshly distilled tetramethylethylenediamine (16.7 mL, 12.9 g, 111 mmol) was added dropwise and the mixture was allowed to stand for 10 min. Methallyl alcohol (4.6 mL, 4.0 g, 55 mmol) was added dropwise, and the mixture was stirred overnight and allowed to warm to room temperature. After recooling to –78 °C, 1-bromo-5-(4-chlorophenoxy)-pentane **6** (6.39 g, 23.0 mmol) in THF (15 mL) was added dropwise. The mixture was stirred for 1 h, warming to room temperature. Aqueous HCl (0.5 M, 50 mL) was added cautiously. The mixture was partitioned between water and diethyl ether, the layers separated and the aqueous layer re-extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to a residue which was purified by column chromatography on silica (eluting with ethyl acetate-petrol, 10 : 90). The title compound was obtained as a colourless oil, 4.46 g (72%); R_f 0.60 (ethyl acetate-petrol, 2 : 3); ν_{max}/cm^{-1} 3343 (br), 2933, 2858, 1492, 1245, 824; δ_H (300 MHz, $CDCl_3$) 7.14 (d, *J* = 8.9 Hz, 2H, 2 × ArH), 6.73 (d, *J* = 8.9 Hz, 2H, 2 × ArH), 4.95 (s, 1H, =CH), 4.80 (s, 1H, =CH), 4.01 (s, 2H, CH_2OH), 3.84 (t, *J* = 6.5 Hz, 2H, CH_2OAr), 2.01 (t, *J* = 7.3 Hz, 2H, CH_2C=C), 1.70 (quintet, *J* = 6.9 Hz, 2H, CH_2), 1.50 – 1.25 (m, 6H, 3 × CH_2); δ_C (75.45 MHz, $CDCl_3$) 157.8, 149.1, 129.3, 125.4, 115.8, 109.3, 68.3, 66.0, 32.9, 29.2, 27.6, 25.9; *m/z* 270 (M^+, 30%), 268 (100), 130 (26), 128 (93), 81 (95); HRMS: calcd for $C_{15}H_{21}{}^{35}ClO_2$ 268.1230, found 268.1226.

(*S*)-{2-[6-(4-Chloro-phenoxy)-hexyl]-oxiranyl}-methanol (8a). To a slurry of powdered 4Å molecular sieves (0.56 g) in anhydrous dichloromethane (15 ml) under N_2 at –5 °C were added L-(+)-diethyl tartrate (1.2 mL, 1.48 g, 7.17 mmol followed by titanium (IV) isopropoxide (1.4 mL, 1.35 g, 4.75 mmol). The mixture was cooled to –20 °C and *tert*-butyl hydroperoxide

(4.0 mL of a 3.6 M solution in anhydrous toluene, 14.5 mmol) was added. The mixture was allowed to stand for 10 min, and 8-(4-chloro-phenoxy)-2-methylene-octan-1-ol **7** (2.5 g, 9.31 mmol) in anhydrous dichloromethane (6 mL) was added dropwise. The mixture was stirred at –15 °C for 3 h, quenched with water (25 mL), allowed to warm to room temperature and stirred for 1 h. A solution of NaCl (0.25 g) and NaOH (0.75 g) in water (2 mL) was added and the mixture was stirred overnight, then filtered through Celite, and extracted with dichloromethane (2 × 25 mL). The combined dichloromethane layers were dried ($MgSO_4$) and concentrated to a residue which was purified by column chromatography on silica (eluting with diethyl ether-petrol, 30 : 70 → 50 : 50) to yield the title compound as a white solid, 2.11 g (80%); R_f 0.36 (ethyl acetate-petrol, 2 : 3); mp 44 – 45 °C (from petrol-diethyl ether); $[\alpha]_D$ -1.7 (c = 0.01 g mL^{-1} in MeOH); ν_{max}/cm^{-1} 3434 (br), 2861, 2937, 1493, 1245, 825; δ_H (300 MHz, $CDCl_3$) 7.14 (d, *J* = 8.9 Hz, 2H, 2 × ArH), 6.73 (d, *J* = 8.9 Hz, 2H, 2 × ArH), 3.81 (t, *J* = 6.4 Hz, 2H, CH_2OAr), 3.71 + 3.57 (*AB* system, *J* = 12.2 Hz, 2H, CH_2OH), 2.81 + 2.60 (*AB* system, *J* = 4.6 Hz, 2H, epoxide CH_2), 1.69 (t, *J* = 7.3 Hz, 2H, CH_2), 1.6 – 1.5 (m, 4H, 2 × CH_2), 1.5 – 1.2 (m, 4H, 2 × CH_2); δ_C (75.45 MHz, $CDCl_3$) 157.7, 129.4, 125.4, 115.8, 68.2, 62.9, 59.8, 49.9, 31.9, 29.5, 29.1, 26.0, 24.6; *m/z* 286 (M^+, 33%), 284 (94), 196 (11), 141 (17), 130 (95), 128 (100); HRMS: calcd for $C_{15}H_{21}{}^{35}ClO_3$ 284.1181, found 284.1177.

(*R*)-{2-[6-(4-Chloro-phenoxy)-hexyl]-oxiranyl}-methanol (8b). Treatment of 8-(4-Chloro-phenoxy)-2-methylene-octan-1-ol **7** (2.5 g, 9.3 mmol) as described above but employing D-(-)-diethyl tartrate yielded the title compound as a white solid, 1.85 g (70%), which showed identical analytical data as the *(S)* enantiomer **8a**, except $[\alpha]_D$ +1.8 (c = 0.01 g mL^{-1} in MeOH)

***Rac*-{2-[6-(4-Chloro-phenoxy)-hexyl]-oxiranyl}-methanol (8c).** To an ice-cold solution of 8-(4-chlorophenoxy)-2-methylene-octan-1-ol **7** (1.5 g, 5.59 mmol) in dichloromethane (50 mL) was added *m*-chloroperbenzoic acid (c. 90% pure, 1.28 g, 6.7 mmol) in dichloromethane (50 mL) dropwise. The mixture was allowed to warm to room temperature and stirred overnight. After this period, analysis by TLC (ethyl acetate-petrol, 2 : 3) showed starting material remaining, so *m*-chloro-perbenzoic acid (0.20 g, 1.05 mmol) was added and the solution was heated at 40 °C for 1 h. The solution was allowed to cool and washed with aqueous Na_2SO_3 (2 × 50 mL), aqueous $NaHCO_3$ (2 × 50 mL), and water (50 mL), then dried ($MgSO_4$) and concentrated to yield the title compound as a colourless oil, 1.60 g (99%), which gave essentially identical analytical data as the *(S)* enantiomer **8a**. R_f 0.36 (ethyl acetate-petrol, 2 : 3); HRMS: calcd for $C_{15}H_{21}{}^{35}ClO_3$ 284.1181, found 284.1179.

(*R*)-Mosher's ester of (*S*)-{2-[6-(4-chlorophenoxy)-hexyl]-oxiranyl}-methanol (9a). To a solution of (*S*)-{2-[6-(4-chlorophenoxy)-hexyl]-oxiranyl}-methanol **8a** (150 mg, 0.53 mmol) in DMF (5 mL) was added (*R*)-(+)- α-methoxy-α-trifluoromethylphenylacetic acid (Mosher's acid, 500 mg, 2.06 mmol), DMAP (10 mg, 82 *μ*mol) and powdered 4Å molecular sieves (50 mg), and the mixture was cooled to 0 °C under N_2. Diisopropyl carbodiimide (0.3 mL, 243 mg, 1.93 mmol) was added dropwise, and the whole was allowed to warm to room temperature and stirred overnight. The mixture was poured into water and extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed with water (2 × 20 mL), saturated aqueous $NaHCO_3$ (20

mL), 2 M HCl (20 mL) and brine (20 mL), then dried ($MgSO_4$), and concentrated to an oil. ^{1}H NMR analysis showed that the crude sample was a 98 : 2 mixture of diastereoisomers. Purification by column chromatography on silica (eluting with CH_2Cl_2-petrol, 60 : 40 → 100 : 0) yielded the title compound as a colourless oil, 190 mg (74%); R_f 0.35 (diethyl ether-petrol, 3 : 1); ν_{max}/cm^{-1} 2942, 2861, 1753, 1492, 1245, 1170, 1026; δ_H (300 MHz, $CDCl_3$) 7.50 (m, 2H, 2 × ArH), 7.40 (m, 3H, 3 × ArH), 7.15 (d, *J* = 8.9 Hz, 2H, 2 × ArH), 6.74 (d, *J* = 8.9 Hz, 2H, 2 × ArH), 4.48 + 4.11 (*AB* system, *J* = 11.9 Hz, 2H, $CH_2O.C{=}O$), 3.83 (t, *J* = 6.4 Hz, 2H, CH_2OAr), 3.48 (s, 3H, CH_3O), 2.63 + 2.59 (*AB* system, *J* = 4.5 Hz, 2H, epoxide CH_2), 1.7 -1.6 (m, 2H, CH_2), 1.6 – 1.5 (m, 2H, CH_2), 1.4 – 1.1 (m, 6H, 3 × CH_2), δ_C (75.45 MHz, $CDCl_3$) 167.5, 158.1, 130.1, 129.7, 129.2, 128.9, 127.7, 127.2, 116.1, 68.5, 67.8, 57.1, 50.9, 48.9, 43.4, 31.9, 29.6, 29.4, 26.2, 24.7, 22.3; *m/z* 502 (M^+, 12%), 500 (35), 203 (7), 189 (100), 128 (50); HRMS: calcd for $C_{25}H_{28}{}^{35}ClF_3O_5$ 500.1597, found 500.1577.

(*R*)-Mosher's ester of (*R*)-{2-[6-(4-chlorophenoxy)-hexyl]-oxiranyl}-methanol (9b). (*R*)-{2-[6-(4-chlorophenoxy)-hexyl]-oxiranyl}-methanol **8b** (150 mg, 0.53 mmol) was treated with (*R*)-Mosher's acid as above. ^{1}H NMR analysis showed that the crude sample was a 98 : 2 mixture of diasteroisomers. Column chromatography on silica (eluting with CH_2Cl_2-petrol, 60 : 40 → 100 : 0) yielded the title compound as a colourless oil, 154 mg (60%); R_f 0.35 (diethyl ether-petrol, 3 : 1); ν_{max}/cm^{-1} 2942, 2861, 1753, 1492, 1245, 1170, 1026; δ_H (300 MHz, $CDCl_3$) 7.50 (m, 2H, 2 × ArH), 7.40 (m, 3H, 3 × ArH), 7.15 (d, *J* = 8.9 Hz, 2H, 2 x ArH), 6.74 (d, *J* = 8.9 Hz, 2H, 2 × ArH), 4.42 + 4.21 (AB system, *J* = 12.0 Hz, 2H, $CH_2O.C{=}O$), 3.83 (t, *J* = 6.4 Hz, 2H, CH_2OAr), 3.48 (s, 3H, CH_3O), 2.67 + 2.59 (*AB* system, *J* = 4.8 Hz, 2H, epoxide CH_2), 1.7 -1.6 (m, 2H, CH_2), 1.6 – 1.5 (m, 2H, CH_2), 1.4 – 1.1 (m, 6H, 3 × CH_2), δ_C (75.45 MHz, $CDCl_3$) 167.7, 157.9, 130.1, 129.7, 129.2, 128.9, 127.2, 125.6, 116.1, 68.5, 67.1, 57.1, 50.7, 48.9, 43.4, 32.2, 29.7, 29.4, 26.2, 24.7, 22.4; *m/z* 502 (M^+, 20%), 500 (56), 203 (7), 189 (100), 128 (41); HRMS: calcd for $C_{25}H_{28}{}^{35}ClF_3O_5$ 500.1597, found 500.1585.

(*R*)-Etomoxir (3a). To a vigorously stirred solution of (*S*)-{2-[6-(4-chlorophenoxy)-hexyl]-oxiranyl}-methanol **8a** (1.6 g, 5.62 mmol) in tetrachloromethane (11 mL) and acetonitrile (11 mL) at room temperature was added sodium periodate (3.59 g, 16.87 mmol) in water (17 mL) followed by ruthenium trichloride trihydrate (32 mg, 0.12 mmol). After 6 h, the mixture was extracted with dichloromethane (2 × 40 mL), and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated to a black residue. This was dissolved in anhydrous DMF (12 mL) and treated with ethyl iodide (0.80 mL, 1.56 g, 10.0 mmol) followed by portionwise addition of $KHCO_3$ (0.68 g, 6.7 mmol). The mixture was stirred overnight, poured into water and extracted with hexane (3 × 40 mL). The combined hexane layers were dried ($MgSO_4$) and concentrated to a residue which was purified by column chromatography on silica (eluting with diethyl ether-petrol, 20 : 80) to yield the product as a colourless oil, 0.98 g (53%); R_f 0.36 (diethyl ether-petrol, 1 : 3); ν_{max}/cm^{-1} 2938, 2863, 1734, 1493, 1399, 1388, 1245, 1196, 1005, 922, 827; δ_H (300 MHz, $CDCl_3$) 7.23 (d, *J* = 8.9 Hz, 2H, 2 × ArH), 6.83 (d, *J* = 8.9 Hz, 2H, 2 × ArH), 4.26 (m, 2H, CH_2CH_3), 3.93 (t, *J* = 6.5 Hz, 2H, CH_2OAr), 3.05 + 2.79 (*AB* system, *J* = 5.9 Hz, 2H, epoxide CH_2), 1.8 -1.7 (m, 2H, CH_2), 1.7 – 1.6 (m, 2H, CH_2), 1.5 – 1.40

(m, 6H, 3 × CH_2), 1.31 (t, *J* = 7.1 Hz, 3H, CH_3); δ_C (75.45 MHz, $CDCl_3$) 170.4, 157.7, 129.2, 125.3, 115.7, 68.1, 61.6, 57.0, 51.8, 31.1, 29.2, 29.0, 25.8, 24.7, 14.6; *m/z* 328 (M^+, 15%), 326 (46), 153 (6), 141 (10), 130 (32), 128 (100), 107 (20); HRMS: calcd for $C_{17}H_{23}{}^{35}ClO_4$ 326.1285, found 326.1283.

(*S*)-Etomoxir (3b). Treatment of (*R*)-{2-[6-(4-Chloro-phenoxy)-hexyl]-oxiranyl}-methanol **8b** (0.70 g, 2.45 mmol) as described above yielded the title compound as a colourless oil, 0.50 g (63%), which showed identical analytical data as the (*R*) enantiomer **3a**.

(*R*)-Etomoxir, sodium salt (10a). (*R*)-Etomoxir **3a** (0.77 g, 2.36 mmol) was dissolved in THF and treated with 1.036 M volumetric standard aqueous NaOH solution (2.27 mL, 2.35 mmol) dropwise. The mixture was stirred overnight, then concentrated to a slurry of white crystals, which were dissolved in the minimum volume of boiling acetone, cooled and treated with diethyl ether dropwise to induce crystallization. After storage overnight in a freezer, the crystals were collected by suction filtration, washed with ether and dried under vacuum (0.05 mmHg, 40 °C) to afford the product as a dihydrate, 0.37 g (44%); (Found: C, 50.65; H, 6.1. Calc. for $C_{15}H_{18}O_4NaCl.2H_2O$: C, 50.5; H, 6.2 %); $[\alpha]_D$ +17.6 (c = 0.01 g mL^{-1} in MeOH)†; ν_{max}/cm^{-1} 3404 (br), 2930, 1600, 1493, 1244, 820; δ_H (300 MHz, DMSO-d_6) 7.34 (d, *J* = 9.0 Hz, 2H, 2 × ArH), 6.98 (d, *J* = 9.0 Hz, 2H, 2 × ArH), 3.97 (t, *J* = 6.6 Hz, 2H, CH_2OAr), 3.40 (s, 4H, water), 2.68 + 2.48 (*AB* system, *J* = 6.4 Hz, 2H, epoxide CH_2), 2.00 – 1.90 (m, 1H, 0.5 × CH_2), 1.72 (quintet, *J* = 7.0 Hz, 2H, CH_2) 1.50 – 1.30 (m, 7H, 3.5 × CH_2); δ_C (75.45 MHz, DMSO-d_6) 172.0, 157.5, 129.2, 123.9, 116.2, 67.8, 58.9, 50.5, 32.9, 29.1, 28.5, 25.5, 25.2.

(*S*)-Etomoxir, sodium salt (10b). Treatment of (*S*)-Etomoxir **3b** (0.50 g, 1.53 mmol) as described above yielded the title compound as white crystals, 0.33 g (55%) which showed identical analytical data as the (*R*) enantiomer **3a**, except $[\alpha]_D$ -16.4 (c = 0.01 g mL^{-1} in MeOH).†

1-Bromo-5-(2,4-dinitrophenoxy)-pentane (12). To NaOH (0.40 g, 10.0 mmol) in water (10 mL) was added 2,4-dinitrophenol (0.81 g, 4.4 mmol) portionwise with stirring. Tetrabutylammonium hydrogensulfate (10 mg, 2.9 μmol) was added followed by 1,5-dibromopentane (2.4 mL, 4.1 g, 17.0 mmol), and the mixture was heated at reflux overnight. The mixture was allowed to cool and partitioned between water and diethyl ether. The layers were separated and the aqueous layer was re-extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to an oil which was purified by column chromatography on silica (eluting with ethyl acetate-petrol, 10 : 90 → 30 : 70). The title compound was obtained as a pale yellow solid, 1.21 g (83%); R_f 0.55 (ethyl acetate-petrol, 1 : 3); (Found: C, 39.7; H, 3.8; N, 8.35. Calc. for $C_{11}H_{13}BrN_2O_5$: C, 39.65; H, 3.9; N, 8.4 %); ν_{max}/cm^{-1} 2947, 1608, 1521, 1343, 1280; δ_H (300 MHz, $CDCl_3$) 8.69 (d, *J* = 2.8 Hz, 1H, ArH), 8.36 (dd, *J* = 2.8, 9.3 Hz, 1H, ArH), 7.13 (d, *J* = 9.3 Hz, 1H, ArH), 4.18 (d, *J* = 6.2 Hz, 2H, CH_2OAr), 3.39 (t, *J* = 6.6 Hz, 2H, CH_2Br), 1.94 – 1.82 (m, 4H, 2 × CH_2), 1.67 – 1.57 (m, 2H, CH_2); δ_C (75.45 MHz, $CDCl_3$) 157.1, 140.4, 139.3, 129.4, 125.6, 122.3, 114.5, 70.7, 33.6, 32.5, 28.3, 24.9; *m/z* 334 (M^+, 15%), 332 (17), 151 (65), 149 (61), 41 (100); HRMS: calcd for $C_{11}H_{13}{}^{79}BrN_2O_5$ 332.0003, found 332.0008.

1-Bromo-5-(triisopropyl-silyloxy)-pentane (15). To a solution of 1-bromopentan-5-ol **14** (9.38 g, 56.0 mmol) in anhydrous DMF (200 mL) under N_2 at 5 °C was added imidazole (8.04 g, 120.0 mmol) followed by triisopropylsilyl chloride (12.8 mL, 11.55 g, 60.0 mmol) dropwise over 30 min. The mixture was stirred 3 h, then poured into water and extracted with diethyl ether (2 × 100 mL). The combined organic layers were washed with 1 M HCl (50 mL) and water (5 × 50 mL), swirled with solid $NaHCO_3$, dried ($MgSO_4$) and concentrated to an oil. Column chromatography on silica (eluting with diethyl ether-petrol, 2 : 98 → 5 : 95) yielded the product as a colourless oil, 15.4 g (85%); R_f 0.40 (petrol); ν_{max}/cm^{-1} 2942, 2865, 1463, 1109, 882; δ_H (300 MHz, $CDCl_3$) 3.62 (t, *J* = 6.1 Hz, 2H, CH_2OSi), 3.35 (t, *J* = 6.9 Hz, 2H, CH_2Br), 1.82 (quintet, *J* = 7.0 Hz, 2H, CH_2), 1.52 – 1.41 (m, 4H, 2 × CH_2), 1.00 – 0.97 (m, 21H, 3 × ^{i}Pr); δ_C (75.45 MHz, $CDCl_3$) 63.5, 34.3, 33.1, 32.5, 25.0, 18.4, 12.4; *m/z* 281 ($M^+ - C_3H_7$, 29%), 279 (29), 195 (25), 197 (25), 183 (98), 181 (100), 167 (35), 165 (36); HRMS: calcd for $C_{11}H_{24}{}^{79}BrOSi$ (i.e. $M^+ - C_3H_7$) 279.0768, found 279.0779.

8-(Triisopropyl-silyloxy)-2-methylene-octan-1-ol (16). To anhydrous diethyl ether (20 mL) was added *n*-butyllithium (40 mL of a 2.5 M solution in hexane, 100 mmol) under N_2, and the resulting solution was cooled to –78 °C. Freshly distilled tetramethylethylenediamine (15.0 mL, 11.5 g, 100 mmol) was added dropwise and the mixture was allowed to stand for 10 min. Methallyl alcohol (4.18 mL, 3.58 g, 49.7 mmol) was added dropwise, and the mixture was stirred overnight and allowed to warm to room temperature. After recooling to –78 °C, 1-bromo-5-(triisopropyl-silyloxy)-pentane **15** (10.0 g, 31.0 mmol) in THF (15 mL) was added dropwise. The mixture was stirred for 1 h with warming to room temperature, and aqueous HCl (0.5 M, 50 mL) was added cautiously. The mixture was partitioned between water and diethyl ether, and the aqueous layer was re-extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), and concentrated to a residue which was purified by column chromatography on silica (eluting with ethyl acetate-petrol, 5 : 95 → 10 : 90). The title compound was obtained as a colourless oil, 6.40 g (66%); R_f 0.57 (ethyl acetate-petrol, 1 : 4); ν_{max}/cm^{-1} 2939, 2865, 1464, 1109, 883; δ_H (300 MHz, $CDCl_3$) 4.94 (s, 1H, =CH), 4.80 (s, 1H, =CH), 4.01 (s, 2H, CH_2OH), 3.60 (t, *J* = 6.5 Hz, 2H, CH_2OSi), 1.99 (t, *J* = 7.5 Hz, 2H, CH_2.C=C), 1.5 – 1.3 (m, 4H, 2 × CH_2), 1.3 - 1.2 (m, 4H, 2 × CH_2), 0.99 – 0.97 (m, 21H, 3 × ^{i}Pr); δ_C (75.45 MHz, $CDCl_3$) 149.6, 109.3, 66.3, 63.8, 33.3, 33.3, 29.6, 28.1, 26.1, 18.4, 12.4; *m/z* 271 ($M^+ - C_3H_7$, 29%), 131 (96), 123 (85), 119 (100); HRMS: calcd for $C_{15}H_{31}O_2Si$ (i.e. $M^+ - C_3H_7$) 271.2093, found 271.2091.

(*S*)-{2-[6-(Triisopropyl-silyloxy)-hexyl]-oxiranyl}-methanol (17a). To a slurry of powdered 4Å molecular sieves (1.0 g) in anhydrous dichloromethane (30 ml) under N_2 at –5 °C were added L-(+)-diethyl tartrate (2.6 mL, 3.21 g, 15.4 mmol) followed by titanium (IV) isopropoxide (3.0 mL, 2.90 g, 10.2 mmol). The mixture was cooled to –20 °C and *tert*-butyl hydroperoxide (8.6 mL of a 3.6 M solution in anhydrous toluene, 30.0 mmol) was added. The mixture was allowed to stand for 10 min, and 8-(triisopropyl-silyloxy)-2-methylene-octan-1-ol **16** (6.28 g, 20.0 mmol) in anhydrous dichloromethane (15 mL) was added dropwise. The mixture was stirred at –15 °C for 3 h, quenched with water (40 mL), allowed to warm to room temperature and stirred for 1 h.

A solution of NaCl (0.50 g) and NaOH (1.50 g) in water (5 mL) was added and the mixture was stirred overnight.

The mixture was filtered through Celite, extracted with dichloromethane (2 × 50 mL) and ethyl acetate (2 × 50 mL) and the combined organic layers dried ($MgSO_4$) and concentrated to a residue. Purification by column chromatography on silica (eluting with diethyl ether-petrol, 30 : 70 → 50 : 50) yielded the title compound as a colourless oil, 4.28 g (65%); R_f 0.43 (ethyl acetate-petrol, 1 : 4); ν_{max}/cm^{-1} 2940, 2866, 1463, 1105; δ_H (300 MHz, $CDCl_3$) 3.71 + 3.60 (*AB* system, *J* = 12.2 Hz, 2H, CH_2OH), 3.59 (t, *J* = 6.5 Hz, 2H, CH_2OSi), 2.82 + 2.60 (*AB* system, *J* = 4.6 Hz, 2H, epoxide CH_2), 1.5 – 1.4 (m, 4H, 2 × CH_2), 1.3 – 1.2 (m, 6H, 3 × CH_2), 1.00 – 0.98 (m, 21H, 3 × ^iPr); δ_C (75.45 MHz, $CDCl_3$) 63.7, 63.1, 60.1, 50.2, 33.3, 32.4, 30.0, 26.1, 25.0, 18.4, 12.4; *m/z* 287 ($M^+ - C_3H_7$, 18%), 269 (20), 257 (10), 131 (100); HRMS: calcd for $C_{15}H_{31}O_3Si$ (i.e. $M^+ - C_3H_7$) 287.2042, found 287.2044.

(*R*)-{2-[6-(Triisopropyl-silyloxy)-hexyl]-oxiranyl}-methanol (17b). Treatment of 8-(triisopropyl-silyloxy)-2-methylene-octan-1-ol **16** (1.0 g, 3.18 mmol) as described above but employing D-(-)-diethyl tartrate yielded the title compound as a colourless oil, 0.63 g (60%) which showed identical spectroscopic data to the (*S*) enantiomer **17a**.

***Rac*-{2-[6-(Triisopropyl-silyloxy)-hexyl]-oxiranyl}-methanol (17c).** To an ice-cold solution of 8-(triisopropyl-silyloxy)-2-methylene-octan-1-ol **16** (810 mg, 2.58 mmol) in dichloromethane (40 mL) was added *m*-chloroperbenzoic acid (c. 90% pure, 518 mg, 3.0 mmol) portionwise. The solution was allowed to warm to room temperature and stirred overnight, then washed with aqueous Na_2SO_3 (2 × 20 mL) aqueous $NaHCO_3$ (2 × 20 mL), and water (20 mL). The solution was dried ($MgSO_4$), and concentrated to yield the title compound as a colourless oil, 820 mg (96%), which showed essentially identical spectroscopic data to the (*S*) enantiomer **17a**. R_f 0.43 (ethyl acetate-petrol, 1 : 4); HRMS: calcd for $C_{15}H_{31}O_3Si$ (i.e. $M^+ - C_3H_7$) 287.2042, found 287.2047.

(*R*)-Mosher's ester of (*S*)-{2-[6-(triisopropyl-silyloxy)-hexyl]-oxiranyl}-methanol (18a). To a solution of (*S*)-{2-[6-(triisopropyl-silyloxy)-hexyl]-oxiranyl}-methanol **17a** (200 mg, 0.6 mmol) in DMF (5 mL) was added (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (Mosher's acid, 280 mg, 1.20 mmol), DMAP (10 mg, 82 μmol) and powdered 4Å molecular sieves (50 mg), and the mixture was cooled to 0 °C under N_2. Diisopropyl carbodiimide (171 μL, 139 mg, 1.10 mmol) was added dropwise, and the whole was allowed to warm to room temperature and stirred overnight. The mixture was poured into water and extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed with water (2 × 20 mL), saturated aqueous $NaHCO_3$ (20 mL), 2 M HCl (20 mL) and brine (20 mL), then dried ($MgSO_4$), and concentrated to an oil. ^1H NMR analysis showed that the crude sample was a 98 : 2 mixture of diastereoisomers. Purification by column chromatography on silica (eluting with diethyl ether-petrol, 5 : 95 → 20 : 80) yielded the product as a colourless oil, 152 mg (50%); R_f 0.67 (diethyl ether-petrol, 1 : 4); ν_{max}/cm^{-1} 2942, 2865, 1755, 1171, 1027; δ_H (300 MHz, $CDCl_3$) 7.47 – 7.45 (m, 2H, 2 × ArH), 7.37 – 7.32 (m, 3H, 3 × ArH), 4.47 + 4.10 (*AB* system, *J* = 11.9 Hz, 2H, $CH_2OC{=}O$), 3.58 (t, *J* = 6.5 Hz, 2H, CH_2OSi), 3.49 (s, 3H, CH_3O), 2.62 + 2.59 (*AB* system, *J* = 4.6 Hz, 2H, epoxide

CH_2), 1.7 – 1.3 (m, 4H, 2 × CH_2), 1.3 - 1.2 (m, 6H, 3 × CH_2), 1.00 – 0.98 (m, 21H, 3 × ^{i}Pr); δ_C (75.45 MHz, $CDCl_3$) 166.6, 132.4, 130.1, 128.8, 127.7, 126.0, 122.0, 67.8, 63.7, 57.5, 55.9, 50.9, 33.2, 32.0, 29.8, 26.1, 24.9, 18.4, 12.4; *m/z* 503 ($M^+ - C_3H_7$, 24%), 347 (12), 269 (100), 189 (75); HRMS: calcd for $C_{25}H_{38}F_3O_5Si$ (i.e. $M^+ - C_3H_7$) 503.2441, found 503.2438.

(*R*)-Mosher's ester of (*R*)-{2-[6-(triisopropyl-silyloxy)-hexyl]-oxiranyl}-methanol (18b). (*R*)-2-[6-(triisopropyl-silyloxy)-hexyl]-oxiranyl}-methanol **17b** was treated with (*R*)-Mosher's acid as above. ^{1}H NMR analysis before chromatography showed that the crude sample was a 98 : 2 mixture of diasteroisomers. Column chromatography on silica (eluting with diethyl ether-petrol, 5 : 95 → 20 : 80) yielded the title compound as a colourless oil, 137 mg (45%); R_f 0.67 (diethyl ether-petrol, 1 : 4); ν_{max}/cm^{-1} 2942, 2865, 1755, 1171, 1027; δ_H (300 MHz, $CDCl_3$) 7.47 - 7.44 (m, 2H, 2 × ArH), 7.37 – 7.32 (m, 3H, 3 × ArH), 4.42 + 4.20 (*AB* system, *J* = 12.0 Hz, 2H, $CH_2O.C{=}O$), 3.59 (t, *J* = 6.5 Hz, 2H, CH_2OSi), 3.48 (s, 3H, CH_3O), 2.67 + 2.59 (*AB* system, *J* = 4.7 Hz, 2H, epoxide CH_2), 1.7 – 1.3 (m, 4H, 2 × CH_2), 1.3 - 1.2 (m, 6H, 3 × CH_2), 1.00 – 0.98 (m, 21H, 3 × ^{i}Pr); δ_C (75.45 MHz, $CDCl_3$) 166.6, 132.4, 130.1, 128.9, 127.7, 125.5, 121.7, 67.1, 63.7, 57.3, 55.8, 50.7, 33.3, 32.3, 29.9, 26.1, 24.8, 18.4, 12.3; *m/z* 503 ($M^+ - C_3H_7$, 11%), 347 (10), 269 (100), 189 (80); HRMS: calcd for $C_{25}H_{38}F_3O_5Si$ (i.e. $M^+ - C_3H_7$) 503.2441, found 503.2438.

Ethyl (*R*)-(2-oxiranyl)-(8-triisopropyl-silyloxy)-octanoate (19). To a vigorously stirred solution of (*S*)-{2-[6-(triisopropyl-silyloxy)-hexyl]-oxiranyl}-methanol **17a** (3.85 g, 11.7 mmol) in tetrachloromethane (25 mL) and acetonitrile (25 mL) at room temperature was added sodium periodate (7.44 g, 34.8 mmol) in water (40 mL) followed by ruthenium trichloride trihydrate (50 mg, 0.19 mmol). After 6 h, the mixture was extracted with dichloromethane (2 × 50 mL), and the combined dichloromethane extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated to a black residue. This was dissolved in anhydrous DMF (20 mL) and treated with ethyl iodide (1.7 mL, 3.02 g, 19.2 mmol) followed by portionwise addition of $KHCO_3$ (1.92 g, 19.2 mmol). The mixture was stirred overnight, then poured into water and extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to a residue which was purified by column chromatography on silica (eluting with diethyl ether-petrol, 5 : 95 → 10 : 90) to yield the product as a colourless oil, 2.08 g (48%); R_f 0.60 (diethyl ether-petrol, 1 : 4); ν_{max}/cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.23 (m, 2H, CH_2CH_3), 3.68 (t, *J* = 6.5 Hz, 2H, CH_2OSi), 3.04 + 2.80 (*AB* system, *J* = 5.9 Hz, 2H, epoxide CH_2), 2.15 – 2.00 (m, 1H, 0.5 × CH_2), 1.8 – 1.7 (m, 1H, 0.5 × CH_2), 1.7 – 1.5 (m, 4H, 2 × CH_2), 1.5 – 1.3 (m, 4H, 2 × CH_2), 1.31 (t, *J* = 7.1 Hz, 3H, CH_3), 1.02 – 1.00 (m, 21H, 3 × ^{i}Pr); δ_C (75.45 MHz, $CDCl_3$) 170.8, 63.8, 61.9, 57.5, 52.2, 33.3, 31.6, 29.8, 26.0, 25.2, 18.4, 14.5, 12.4; *m/z* 329 ($M^+ - C_3H_7$, 7 %), 265 (15), 241 (100), 157 (49); HRMS: calcd for $C_{17}H_{33}O_4Si$ (i.e. $M^+ - C_3H_7$) 329.2148, found 329.2150.

Ethyl (*R*)-(2-oxiranyl)-(8-hydroxy)-octanoate (20). To a solution of ethyl (*R*)-(2-oxiranyl)-(8-triisopropyl-silyloxy)-octanoate **19** (2.00 g, 5.4 mmol) in anhydrous THF (60 mL) was added TBAF (5.7 mL of a 1.0 M solution in THF, 5.7 mmol) dropwise. The mixture was stirred 1 h, then diluted with ethyl acetate (100 mL), washed with saturated aqueous $NaHCO_3$ (50 mL), and

filtered through a short pad of silica with further ethyl acetate. The solution was concentrated and the residue was purified by column chromatography on silica (eluting with ethyl acetate-petrol, 40 : 60) to yield the product as a colourless oil, 890 mg (74%); R_f 0.41 (ethyl acetate-petrol, 1 : 1); ν_{max}/cm^{-1} 2984, 1742, 1374, 1242, 1048; δ_H (300 MHz, $CDCl_3$) 4.15 (m, 2H, C*H*$_2$CH$_3$), 3.57 (t, *J* = 6.5 Hz, 2H, CH_2OH), 2.96 + 2.71 (*AB* system, *J* = 5.9 Hz, 2H, epoxide CH_2), 2.1 – 1.9 (m, 1H, 0.5 × CH_2), 1.6 – 1.5 (m, 1H, 0.5 × CH_2), 1.50 – 1.25 (m, 8H, 4 × CH_2), 1.22 (t, *J* = 7.1 Hz, 3H, CH_3); δ_C (75.45 MHz, $CDCl_3$) 170.8, 63.3, 62.0, 57.4, 52.2, 33.0, 31.5, 29.6, 25.9, 25.1, 14.6; *m/z* 217 (MH^+, 23%), 199 (14), 171 (45), 153 (100), 135 (24); HRMS: calcd for $C_{11}H_{21}O_4$ (i.e. MH^+) 217.1440, found 217.1438.

Ethyl (*R*)-2-[6-(2,4-dinitrophenoxy)hexyl]oxiranecarboxylate (4a). (Method A) To a solution of ethyl (*R*)-(2-oxiranyl)-(8-hydroxy)-octanoate **20** (98 mg, 0.45 mmol) in anhydrous DMF (4 mL) under N_2 was added DABCO (250 mg, 2.25 mmol) followed by 1-fluoro-2,4-dinitrobenzene (63 μL, 93 mg, 0.49 mmol). The mixture was stirred for 24 h, then poured into water and extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification by column chromatography on silica (eluting with ethyl acetate-petrol, 10 : 90 → 50 : 50) yielded the product as a bright yellow oil, 100 mg (58%); R_f 0.59 (ethyl acetate-petrol, 2 : 3); ν_{max}/cm^{-1} 1609, 1539, 1344, 909, 733 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.68 (d, *J* = 2.8 Hz, 1H, ArH), 8.36 (dd, *J* = 9.3 Hz, 2.8 Hz, 1H, ArH), 7.12 (d, *J* = 9.3 Hz, 1H, ArH), 4.15 (m, 2H, C*H*$_2$CH$_3$), 4.07 (t, *J* = 7.2 Hz, 2H, CH_2OAr), 2.96 + 2.72 (*AB* system, *J* = 5.9 Hz, 2H, epoxide CH_2), 2.1 – 2.0 (m, 1H, 0.5 × CH_2), 1.81 (quartet, *J* = 6.9 Hz, 2H, CH_2), 1.6 – 1.5 (m, 1H, 0.5 × CH_2), 1.50 – 1.25 (m, 8H, 4 × CH_2), 1.22 (t, *J* = 7.1 Hz, 3H, CH_3); δ_C (75.45 MHz, $CDCl_3$) 170.9, 157.4, 140.3, 139.0, 129.4, 122.2, 114.6, 71.1, 62.0, 57.3, 52.3, 31.5, 29.3, 28.9, 25.9, 25.0, 14.5; *m/z* 382 (M^+, 7%), 369 (16), 345 (21), 295 (42), 107 (53), 55 (100); HRMS: calcd for $C_{17}H_{22}N_2O_8$ 382.1376, found 382.1388.

Ethyl (*R*)-2-[6-(2,4-dinitrophenoxy)hexyl]oxiranecarboxylate (4a). (Method B) To a solution of 2,4-dinitrophenol (423 mg, 2.30 mmol) and triphenylphosphine (0.60 g, 2.3 mmol) in anhydrous THF (5 mL) under N_2 at 0 °C was added diethyl azodicarboxylate (362 μL, 400 mg, 2.30 mmol) dropwise, then, after 10 min, ethyl (*R*)-(2-oxiranyl)-(8-hydroxy)-octanoate **20** (250 mg, 1.16 mmol) in THF (2 × 5 mL). The mixture was stirred for 18 h, then poured into dilute brine and extracted with ethyl acetate (2 × 50 mL). The organic extracts were combined, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated. Purification by column chromatography on silica (eluting with ethyl acetate-petrol, 25 : 75) yielded the product as a pale yellow oil, 270 mg (61%), which showed analytical data identical to material produced by method **A**.

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References

† Reference 24 gives optical rotations of +195° and -190° for (*R*)-Etomoxir, sodium salt **3a** and (*S*)-Etomoxir, sodium salt **3b** respectively (c = 0.01 g mL^{-1} in MeOH at 589 nm), but we believe these exceptionally high values to be erroneous.

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