VERSATILE SYNTHESIS OF 2-ARYLOXYALKYL-OXIRANE-2-CARBOXYLATE: SYNTHESES OF ETHYL 2-[6-(3-ALKOXYPHENOXY)-HEXYL]OXIRANE-2-CARBOXYLATES

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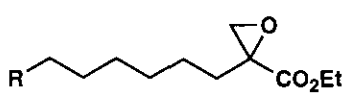
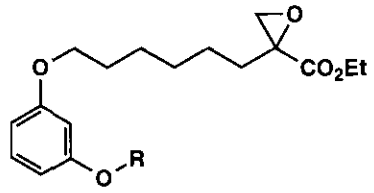
Abstract - A versatile synthetic route to 2-aryloxyalkyl-oxirane-2-carboxylates as potential hypoglycemic agent has been developed *via* combination of dioxirane epoxidation of inactive olefin and facile aryl alkyl ether formation of the labile epoxy alcohol by Mitsunobu reaction.

The esters of 2-alkyl-oxirane-2-carboxylic acid, represented by palmoxirate (**1a**), clomoxir (**1b**) and etomoxir (**1c**), have been found to be a new class of potent hypoglycemic agents.[1] This activity is known to be associated with specific inactivation of carnitine palmitoyltransferase I which is the key enzyme in the transport of long chain acyl-CoA into the mitochondria.[2] In conjunction with investigation of the conformational effects of aryloxyalkyl residue of the 2-substituted oxirane-2-carboxylate on hypoglycemic effects, we have recently been working on syntheses of a series of ethyl 2-(alkoxyaryloxy)alkyloxirane-2-carboxylates (**2a-2h**). Particularly, the bent conformation of these compounds was designed on the basis of the reported fatty acid-binding proteins.[3] We herein report a versatile synthetic route that provides an easy access to a variety of 2-(alkoxyaryloxy)alkyloxirane carboxylates.



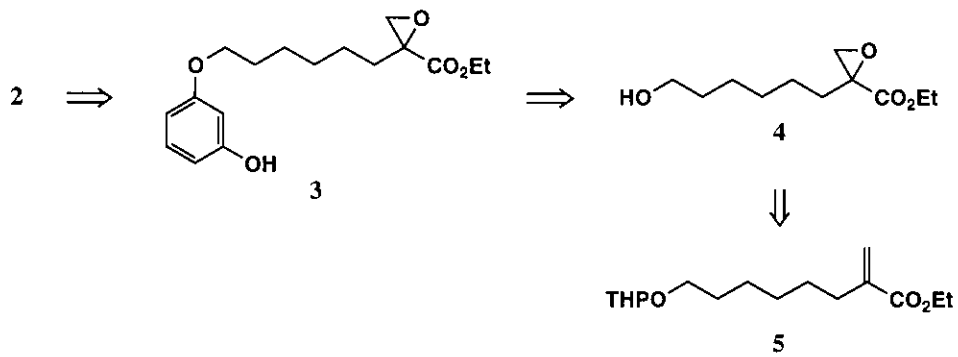
1a: R = C_6H_{13}
1b: R = 4-chlorophenyl
1c: R = 4-chlorophenoxy



2a: R = Bn 2b: R = MOM 2c: R = H 2d: R = methyl
2e: R = allyl 2f: R = acetyl 2g: R = octyloxymethyl
2h: R = MEM

Our synthetic approach shown in Scheme 1 envisages an efficient construction of epoxide from electron deficient olefin (**5**) and introduction of diverse 2-alkoxyaryl moiety *via* facile double aryl alkyl ether formations of the phenolic alcohols in the presence of labile epoxide.

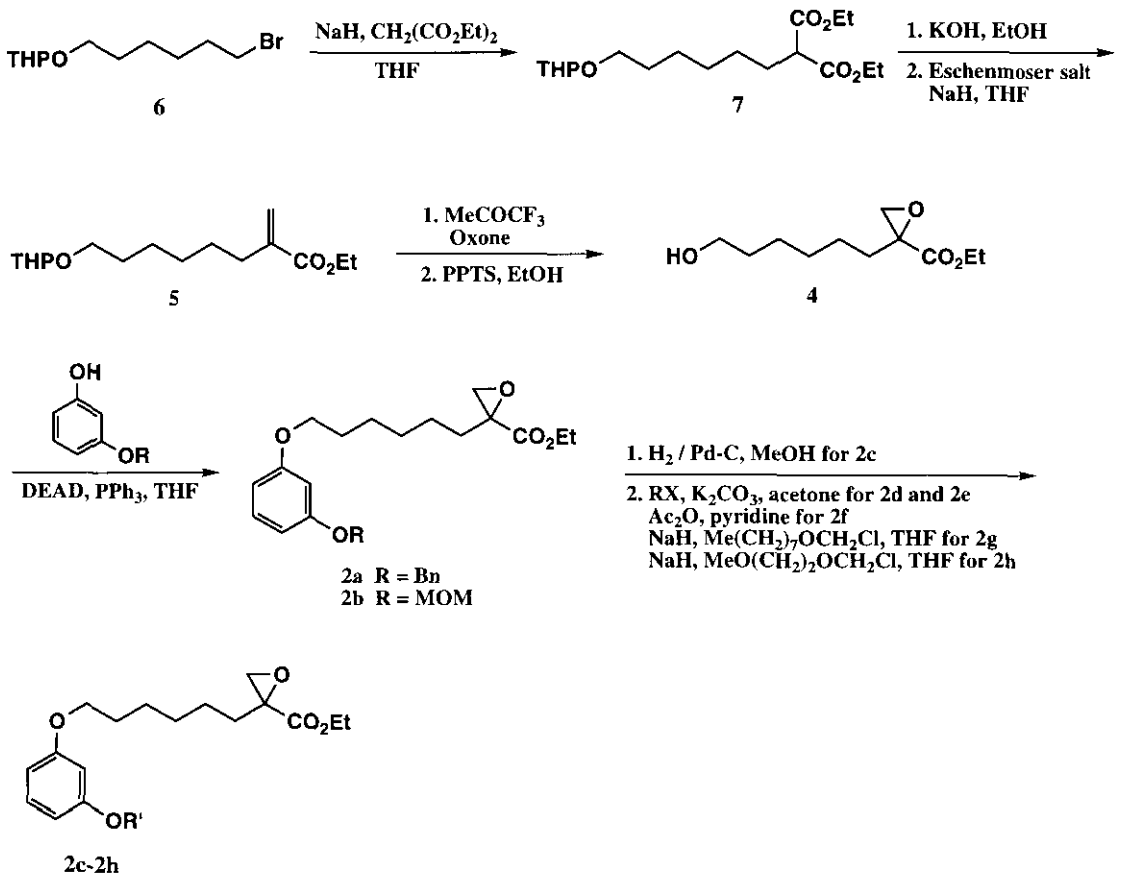
Scheme 1



Our synthesis outlined in Scheme 2 was commenced by preparation of α,β-unsaturated ester (**5**) as an epoxide precursor. The 2-substituted acrylate (**5**) was conveniently derived from the protected bromohexyl alcohol (**6**) in 76 % overall yield by analogy with the reported procedure.[4] The initial epoxidations of the inactive olefin (**5**) under various reaction conditions were not successful. Mostly, the preexistent ether bond was cleaved rather than epoxidation or the starting ester (**5**) remained intact. However, the desired epoxidation could be achieved by employing dioxirane[5] (CH_3COCF_3, Oxone, 72.3 %) as an epoxidizing agent. The formation of aryl alkyl ether linkage of **2** by the initial 3-alkoxyphenoxide displacement resulted in failure due to facile epoxide ring opening. However, the requisite aryl alkyl ethers (**2a**) and (**2b**) were obtained in good yields by Mitsunobu reaction[6] of alcohol (**4**) with resorcinol monoether. The labile epoxide survived only under Mitsunobu conditions. It is also noteworthy that etomoxir (**1c**), one of the most potent hypoglycemic agents, was concisely synthesized from the readily available ethyl 2-alkylacrylate (**5**) in 45 % overall yield by only three step sequence including facile coupling reaction of alcohol (**4**) with 4-chlorophenol in the presence of epoxide. Finally, a variety of terminal side chains of **2c-2h** could be introduced at the last stage by debenzylation of **2a** followed by *O*-alkylations or acylations of the resulting phenol with the corresponding alkyl halides or acid anhydride.

In summary, a versatile synthetic route to 2-(alkoxyaryloxy)alkyloxirane-2-carboxylates as potential hypoglycemic agent has been developed *via* combination of dioxirane epoxidation of an inactive olefin and facile aryl alkyl ether formations of the labile epoxy alcohol by Mitsunobu reaction as well as the subsequent *O*-alkylations of the phenolic hydroxy group.

Scheme 2



EXPERIMENTAL

Unless noted otherwise, all reactions were performed under an argon atmosphere. Column chromatography was performed using silica gel 60 (230-400 mesh, Merck) with indicated solvents. IR spectra were recorded on a Perkin-Elmer 1710 FT-IR spectrometer. ^{1}H and ^{13}C-NMR spectra were recorded on either a JEOL JNM-GCX 400 or JEOL JNM-LA 300 spectrophotometer as solutions in deuteriochloroform ($CDCl_3$). Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the deuterated chloroform ($CHCl_3$). MS spectra were obtained on VG Trio-2 GC-MS instrument. High resolution MS spectra were obtained on HP 5890 Series II.

Diethyl 2-[6-(tetrahydro-2*H*-pyranyloxy)hexyl]malonate (7) To a suspension of NaH (60 %, 1.08 g, 27 mmol, washed with *n*-hexane to remove oil) in THF (50 mL) at 0°C was added a solution of diethyl malonate (4.14 g, 26 mmol) in THF (15 mL). The mixture was warmed to rt and stirred for 10 min. To the

reaction mixture was slowly added a solution of 6-(tetrahydro-2*H*-pyranyloxy)hexyl bromide (6.24 g, 24 mmol) in THF (8 mL) and the mixture was stirred at 70°C for 10 h. After dilution of the reaction mixture with ethyl acetate, the ethyl acetate solution was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel with *n*-hexane-EtOAc (5:1) to afford 8.06 g (99.4 %) of **7** as a colorless oil. IR(neat) 1764, 1034 cm^{-1}; ^{1}H-NMR 4.49 (1H, t, J=4.4 Hz), 4.13 (4H, q, J=7.2 Hz), 3.79 (1H, dt, J=4, 3.2 Hz), 3.65 (1H, dq, J=6.8, 3.0 Hz), 3.45-3.40 (1H, m), 3.30 (1H, dq, J=6.8, 2.4 Hz), 3.24 (1H, t, J=7.6 Hz), 1.84-1.22 (16H, m), 1.21 (6H, t, J=7.2 Hz); ^{13}C-NMR 169.5, 98.8, 67.4, 62.2, 61.1, 52.0, 30.7, 29.5, 29.0, 28.6, 27.2, 25.9, 25.4, 19.6, 14.0; MS (*m/z*) 315 (M^+-C_2H_5); HRMS: Found 315.1808; Calcd for $C_{16}H_{27}O_6$ (M^+-C_2H_5) 315.1808.

Ethyl 2-[6-(tetrahydro-2H-pyranyloxy)hexyl]acrylate (5) A mixture **7** (8.06 g, 23 mmol) and 85% KOH (2.40 g, 35 mmol) in EtOH (70 mL) was stirred at rt for 30 h. After removal of EtOH *in vacuo,* the residue was dissolved in water, acidified to pH 4 with 1N-HCl, and then extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford 7.4 g (99.4 %) of monoacid as a colorless oil which was directly used for the next step. IR(neat) 3100, 1735, 1023 cm^{-1}; ^{1}H-NMR 4.51 (1H, t, J=3.4 Hz), 4.15 (2H, q, J=6.8 Hz), 3.80 (1H, dt, J=9.4, 3.2 Hz), 3.65 (1H, dq, J=6.8, 3.2 Hz), 3.47-3.41 (1H, m), 3.35-3.28 (2H, m), 1.90-1.17 (16H, m) 1.23 (3H, t, J=6.8 Hz).

To a suspension of NaH (60 %, 1.08 g, 27 mmol, washed with *n*-hexane to remove oil) in THF (50 mL) was slowly added a solution of above monoacid (7.40 g, 23 mmol) in THF (12 mL) at 0°C. The mixture was warmed to rt and stirred for 30 min. After addition of Eschenmoser's salt (5.60 g, 30 mmol), the reaction mixture was stirred at 70°C for 24 h and concentrated *in vacuo*. The residue was diluted with ethyl acetate (250 ml) and the organic solution was washed with water, saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford 5.3 g (80.2 %) of **5** as a colorless oil. IR(neat) 1718, 1034 cm^{-1}; ^{1}H-NMR 6.50 (1H, d, J=1.2 Hz), 5.43 (1H, d, J=1.2 Hz), 4.50 (1H, t, J=3.2 Hz), 4.13 (2H, q, J=7.2 Hz), 3.80 (1H, dt, J=9.6, 3.2 Hz), 3.66 (1H, dq, J=6.8, 2.4 Hz), 3.46-3.40 (1H, m), 3.31 (1H, dq, J=6.6, 3.0 Hz), 2.22 (2H, t, J=7.6 Hz), 1.79-1.21 (14H, m), 1.26 (3H, t, J=7.2 Hz); ^{13}C-NMR 167.3, 141.0, 124.1, 98.8, 67.5, 62.3, 60.5, 31.7, 30.7, 29.6, 29.0, 28.3, 26.0, 25.5, 19.6, 14.1; MS (*m/z*) 284 (M^+), 255(M^+-C_2H_5); HRMS: Found 284.1985; Calcd for $C_{16}H_{28}O_4$ (M^+) 284.1988.

Ethyl 2-(6-hydroxyhexyl)-2-oxiranecarboxylate (4) To a solution of **5** (223 mg, 0.78 mmol) in acetonitrile (8 mL) was added Na_2EDTA (4×10^{-4} M, 5 mL). The reaction mixture was cooled to 0°C and

trifluoroacetone (5 mL), $NaHCO_3$ (262 mg, 3.12 mmol) and then Oxone (1.44 g, 2 mmol) were slowly added for 30 min. The reaction mixture was diluted with ethyl acetate, washed with water and brine, and dried over $MgSO_4$. The organic solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel with *n*-hexane-EtOAc (10:1) to afford 170.2 mg (72.3 %) of epoxide as a colorless oil. IR(neat) 1766, 1034 cm^{-1}; ^{1}H-NMR 4.50 (1H, t, J=4.0 Hz), 4.14 (2H, q, J=7.0 Hz), 3.79 (1H, dt, J=8.6, 3.2 Hz), 3.65 (1H, dq, J=6.8, 2.6 Hz), 3.44-3.40 (1H, m), 3.30 (1H, dq, J=6.6, 2.6 Hz), 2.95 (1H, d, J=6.0 Hz), 2.70 (1H, d, J=6.0 Hz), 2.06-1.33 (16H, m), 1.24 (3H, t, J=7.1 Hz); ^{13}C-NMR 170.4, 98.8, 67.4, 62.3, 61.5, 57.0, 51.7, 31.1, 30.7, 29.5, 29.3, 26.0, 25.4, 24.7, 19.6, 14.0; MS (*m/z*) 301 (M^++H); HRMS: Found, 301.2011; Calcd for $C_{16}H_{29}O_5$ (M^++H) 301.2015. Anal. Calcd for $C_{16}H_{28}O_5$: C, 63.97; H, 9.40. Found: C, 63.82; H, 9.48.

A mixture of above epoxide (211 mg, 0.7 mmol) and a catalytic amount of PPTS (pyridinium *p*-toluenesulfonate) in ethanol (10 mL) was stirred at 55°C for 3 h and the reaction mixture was concentrated *in vacuo*. The residue was diluted with ethyl acetate, washed with water and brine, and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel with *n*-hexane-EtOAc (3:1) to afford 116.2 mg (76.6 %) of **4** as a colorless oil. IR (neat) 3368, 1733 cm^{-1}, ^{1}H-NMR 4.22-4.11 (2H, m), 3.57 (2H, t, J=6.4 Hz), 2.96 (1H, d, J=5.9 Hz), 2.71 (1H, d, J=5.9 Hz), 2.09-1.30 (10H, m), 1.24 (3H, t, J=7.1 Hz); ^{13}C-NMR 170.4, 62.7, 61.5, 57.0, 51.7, 32.5, 31.1, 29.2, 25.4, 24.6, 14.1; MS (*m/z*) 217 (M^++H), 199 (M^+-OH) ; HRMS: Found, 217.1442; Calcd for $C_{11}H_{21}O_4$ (M^++H) 217.1440. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.95; H, 9.37.

Ethyl 2-{6-[3-(benzyloxyl)phenoxy]hexyl}-2-oxiranecarboxylate (2a) To a mixture of **4** (33 mg, 0.15 mmol), benzylresorcinol (30.6 mg, 0.15 mmol) and triphenylphosphine (47.2 mg, 0.18 mmol) in THF (5 mL) was added DEAD (26 µL, 0.17 mmol). The reaction mixture was stirred at rt for 2 h and diluted with ethyl acetate. The ethyl acetate solution was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel with *n*-hexane-EtOAc (10:1) to afford 43.7 mg (72 %) of **2a** as a colorless oil. IR(neat) 1732, 1592, 1181, 1152, 1028 cm^{-1}; ^{1}H-NMR 7.42-7.28 (5H, m), 7.16-7.12 (1H, m), 6.56-6.47 (3H, m), 5.02 (2H, s), 4.24-4.15 (2H, m), 3.90 (2H, t, J=6.2 Hz), 3.01 (1H, d, J=6.0 Hz), 2.76 (1H, d, J=6.0 Hz), 2.19-1.34 (10H, m), 1.27 (3H, t, J=7.3 Hz); ^{13}C-NMR 170.4, 160.3, 160.0, 137.0, 129.8, 128.8, 128.5, 128.4, 127.9, 127.4, 107.1, 106.8, 101.7, 69.9, 67.8, 61.5, 56.9, 51.8, 31.1, 29.2, 29.0, 25.8, 24.7, 14.1; MS (*m/z*) 398 (M^+); HRMS: Found 398.2101; Calcd for $C_{24}H_{30}O_5$ (M^+) 398.2093. Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.43; H, 7.51. Found: C, 72.36; H, 7.61.

Ethyl 2-{6-[3-(methoxymethoxy)phenoxy]hexyl}-2-oxiranecarboxylate (2b) The oxiranecarboxylate (**2b**) was prepared from **4** (45.6 mg, 0.21 mmol) and 3-methoxymethyloxyphenol (32.4 mg, 0.21 mmol) by the same procedure described for **2a** and purified by flash column chromatography on silica gel with *n*-hexane-EtOAc (7:1) to afford **2b** (46.1 mg, 62 %) as a colorless oil. IR(neat) 1733, 1593, 1494, 1146 cm^{-1}; ^{1}H-NMR 7.16-7.12 (1H, m), 6.61-6.51 (3H, m), 5.14 (2H, s), 4.24-4.16 (2H, m), 3.91 (2H, t, J=6.4 Hz), 3.46 (3H, s), 3.01 (1H, d, J=5.8 Hz), 2.76 (1H, d, J=5.8 Hz), 2.06-1.32 (10H, m), 1.27 (3H, t, J=7.1 Hz); ^{13}C-NMR 170.4, 160.3, 158.4, 129.8, 108.3, 108.0, 103.1, 94.4, 67.8, 61.6, 61.4, 57.0, 56.0, 51.8, 31.2, 29.2, 25.8, 24.7, 14.1; MS (*m/z*) 352 (M^+), 321(M^+-OCH_3); HRMS: Found 352.1888; Calcd for $C_{19}H_{28}O_6$ (M^+) 352.1881. Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.88; H, 8.03.

Ethyl 2-[6-(3-hydroxyphenoxy)hexyl]-2-oxiranecarboxylate (2c) A solution of **2a** (252.8 mg, 0.63 mmol) in methanol (6 mL) was stirred in the presence of a catalytic amount of palladium (10 % on active carbon) under hydrogen at rt for 2 h. After filtration of the catalyst, the organic layer was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel with *n*-hexane-EtOAc (5:1) to afford 159.6 mg (81.6 %) of **2c** as a colorless oil. IR(neat) 3436, 1733, 1597, 1495, 1471, 1289, 1181, 1149 cm^{-1}; ^{1}H-NMR 7.11-7.06 (1H, m), 6.46-6.38 (3H, m), 5.12-5.08 (1H, m), 4.24-4.16 (2H, m), 3.90 (2H, t, J=6.6 Hz), 3.01 (1H, d, J=5.8 Hz), 2.76 (1H, d, J=5.8 Hz), 2.08-1.34 (10H, m), 1.27 (3H, t, J=7.0 Hz); ^{13}C-NMR 170.6, 160.4, 156.9, 130.0, 107.6, 106.9, 102.0, 67.8, 61.7,57.1, 51.9, 31.1, 29.1, 28.9, 25.7, 24.6, 14.1; MS (*m/z*) 308 (M^+); HRMS: Found 308.1624; Calcd for $C_{17}H_{24}O_5$ (M^+) 308.1619. Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.40; H, 7.87.

Ethyl 2-[6-(3-methoxyphenoxy)hexyl]-2-oxiranecarboxylate (2d) A mixture of **2c** (69.5 mg, 0.23 mmol), K_2CO_3 (100 mg, 0.72 mmol) and methyl iodide (21 μL, 0.34 mmol) in acetone (2 mL) was stirred rt for 2 h and the reaction mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and brine, and dried over $MgSO_4$. After concentration of the organic layer, the residue was purified by flash column chromatography on silica gel with *n*-hexane-EtOAc (10:1) to afford 43.7 mg (72 %) of **2d** as a colorless oil. IR(neat) 1731, 1602, 1495, 1288, 1153, 1045 cm^{-1}; ^{1}H-NMR 7.11-7.07 (1H, m), 6.43-6.36 (3H, m), 4.19-4.11 (2H, m), 3.86 (2H, t, J=6.4 Hz), 3.72 (3H, s), 2.96 (1H, d, J=5.9 Hz), 2.71 (1H, d, J=5.9 Hz), 2.06-1.26 (10H, m), 1.22 (3H, t, J=7.1 Hz); ^{13}C-NMR 170.3, 160.7, 160.3, 129.7, 106.6, 106.0, 100.9, 67.7, 61.5, 56.9, 55.2, 51.7, 31.1, 29.2, 29.0, 25.8, 24.6, 14.0; MS (m/z) 322 (M^+); HRMS: Found 322.1777; Calcd for $C_{18}H_{26}O_5$ (M^+) 322.1780. Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.25; H, 8.09.

Ethyl 2-{6-[3-(allyloxy)phenoxy]hexyl}-2-oxiranecarboxylate (2e) The oxiranecarboxylate (**2e**) was prepared from **2c** (59 mg, 0.19 mmol) and allyl bromide (19.4 μL, 0.23 mmol) by the same procedure described for **2d** and purified by flash column chromatography on silica gel with *n*-hexane- EtOAc (10:1) to afford 53.7 mg (80.5 %) of **2e** as a colorless oil. IR(neat) 1723, 1592, 1494, 1289, 1182 cm^{-1}; ^{1}H-NMR 7.11-7.06 (1H, m), 6.44-6.40 (3H, m), 5.99 (1H, ddt, J=17.2, 10.6, 5.3 Hz), 5.34 (1H, dd, J=17.2, 1.5 Hz), 5.21 (1H, dd, J=10.6, 1.5 Hz), 4.44 (2H, dd, J=5.3, 1.4 Hz), 4.20-4.09 (2H, m), 3.85 (2H, t, J=6.5 Hz), 2.96 (1H, d, J=5.9 Hz), 2.70 (1H, d, J=5.9 Hz), 2.02-1.36 (10H, m), 1.22 (3H, t, J=7.2 Hz); ^{13}C-NMR 170.4, 160.3, 159.8, 133.3, 129.7, 117.5, 106.9, 106.8, 101.6, 68.7, 67.8, 61.5, 56.9, 51.8, 31.1, 29.2, 29.0, 25.8, 24.7, 14.1; MS (*m/z*) 348 (M^+); HRMS: Found 348.1935; Calcd for $C_{20}H_{28}O_5$ (M^+) 348.1937. Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.79; H, 8.06.

Ethyl 2-{6-[3-(acetoxy)phenoxy]hexyl}-2-oxiranecarboxylate (2f) A solution of **2c** (63.7 mg, 0.21 mmol), acetic anhydride (23.8 μL, 0.25 mmol) in pyridine (2 mL) was stirred at rt for 2 h. The reaction mixture was concentrated *in vacuo,* diluted with ethyl acetate, and then washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel with *n*-hexane-EtOAc (10:1) to afford 68.5 mg (94.6 %) of **2f** as a colorless oil. IR(neat) 1768, 1735, 1592, 1211, 1138 cm^{-1}; ^{1}H-NMR 7.25-7.23 (1H, m), 6.75-6.59 (3H, m), 4.25-4.14 (2H, m), 3.90 (2H, t, J=6.4 Hz), 3.01 (1H, d, J=5.8 Hz), 2.76 (1H, d, J=5.8 Hz), 2.26 (3H, s), 2.13-1.34 (10H, m), 1.27 (3H, t, J=7.0 Hz); ^{13}C-NMR 170.3, 169.3, 159.9, 151.5, 129.6, 113.5, 112.1, 108.0, 67.9, 61.5, 56.9, 51.7, 31.1, 29.1, 28.9, 25.7, 24.6, 21.0, 14.0; MS (m/z) 350 (M^+); HRMS: Found 350.1733; Calcd for $C_{19}H_{26}O_6$ (M^+) 350.1729. Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 65.18; H, 7.41.

Ethyl 2-(6-{3-[(octyloxy)methoxy]phenoxy}hexyl)-2-oxiranecarboxylate (2g) To a suspension of NaH (60 %, 7.9 mg, 0.2 mmol) in THF (3 mL) at 0°C was slowly added **2c** (50.7 mg, 0.16 mmol) and a solution of chloromethyl octyl ether (37 μL, 0.2 mmol) in THF (1 mL). The mixture was warmed to rt and stirred for 30 min. The reaction mixture was concentrated *in vacuo* and the resulting residue was diluted with ethyl acetate. The ethyl acetate solution was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel with *n*-hexane-EtOAc (10:1) to afford 59.4 mg (80.2 %) of **2g** as a colorless oil. IR(neat) 1733, 1593, 1494, 1285, 1181, 1153, 1095, 1021 cm^{-1}; ^{1}H-NMR 7.16-7.11 (1H, m), 6.62-6.50 (3H, m), 5.17 (2H, s), 4.25-4.14 (2H, m), 3.90 (2H, t, J=6.5 Hz), 3.63 (2H, t, J=6.7 Hz), 3.00 (1H, d, J=5.9 Hz), 2.76 (1H, d, J=5.9

Hz), 2.11-1.22 (22H, m), 1.27 (3H, t, J=7.1 Hz), 0.85 (3H, t, J=6.7 Hz); ^{13}C-NMR 170.4, 160.2, 158.6, 129.7, 108.2, 107.9, 103.0, 93.3, 68.8, 67.8, 61.5, 57.0, 51.8, 31.7, 31.1, 29.5, 29.2, 29.2, 29.2, 29.1, 26.0, 25.8, 24.7, 22.6, 14.1, 14.0; MS (*m/z*) 450 (M^+); HRMS: Found 450.2984; Calcd for $C_{26}H_{42}O_6$ (M^+) 450.2981. Anal. Calcd for $C_{26}H_{42}O_6$: C, 69.30; H, 9.40. Found: C, 69.42; H, 9.38.

Ethyl 2-(6-{3-[(2-methoxyethoxy)methoxy]phenoxy}hexyl)-2-oxiranecarboxylate (2h) The oxiranecarboxylate (**2h**) was prepared from **2c** (47 mg, 0.15 mmol) , MEMCl (21 μL, 0.18 mmol) and NaH (60%, 7.3 mg, 0.18 mmol) by the same procedure described for **2g** and purified by flash column chromatography on silica gel with *n*-hexane- EtOAc (10:1) to afford 44.2 mg (73.2 %) of **2h** as a colorless oil. IR(neat) 1733, 1605, 1494, 1285, 1182, 1023 cm^{-1}; ^{1}H-NMR 7.15-7.10 (1H, m), 6.62-6.49 (3H, m), 5.22 (2H, s), 4.24-4.13 (2H, m), 3.89 (2H, t, J=6.5 Hz), 3.81-3.78 (2H, m), 3.55-3.52 (2H, m), 3.35 (3H, s), 3.00 (1H, d, J=6.0 Hz), 2.75 (1H, d, J=6.0 Hz), 2.07-1.29 (10H, m), 1.26 (3H, t, J=7.2 Hz); ^{13}C-NMR 170.4, 160.2, 158.4, 129.8, 108.2, 108.0, 103.0, 93.4, 71.6, 67.8, 67.6, 61.5, 59.0, 57.0, 51.8, 31.1, 29.2, 29.0, 25.8, 24.7, 14.1; MS (*m/z*) 396 (M^+); HRMS: Found 396.2147; Calcd for $C_{21}H_{32}O_7$ (M^+) 396.2148. Anal. Calcd for $C_{21}H_{32}O_7$: C, 63.62; H, 8.14. Found: C, 63.79; H, 8.16.

Etomoxir (1c) Etomoxir was prepared from **4** (59.9 mg, 0.28 mmol) and 4-chlorophenol (42.7 mg, 0.34 mmol) by the same procedure described for **2a** and purified by flash column chromatography on silica gel with *n*-hexane-EtOAc (20:1) to afford 72.8 mg (80.4 %) of etomoxir as a colorless oil. IR(neat) 1733, 1598, 1245 cm^{-1}; ^{1}H-NMR 7.15 (2H, m), 6.75 (2H, m), 4.21-4.10 (2H, m), 3.85 (2H, t, J=6.5 Hz), 2.97 (1H, d, J=5.9 Hz), 2.72 (1H, d, J=5.9 Hz), 2.07-1.28 (10H, m), 1.23 (3H, t, J=7.1 Hz); ^{13}C-NMR 170.4, 157.6, 129.2, 125.2, 115.7, 68.1, 61.5, 56.9, 51.8, 31.1, 29.1, 29.0, 25.7, 24.6, 14.0; MS (*m/z*) 326 (M^+); HRMS: Found 326.1292; Calcd for $C_{17}H_{23}O_4Cl$ (M^+) 326.1285. Anal. Calcd for $C_{17}H_{23}O_4Cl$: C, 62.47; H, 7.09. Found: C, 62.37; H, 7.16.

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