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. 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. 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. We herein report a versatile synthetic route that provides an easy access to a variety of 2-(alkoxyaryloxy)alkyloxirane carboxylates.
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

\[
\begin{align*}
2 & \quad \Rightarrow \\
\text{THPO} & \quad \Rightarrow \\
\text{O} & \quad \Rightarrow \\
\text{CO}_2\text{Et} & \quad \Rightarrow \\
\text{HO} & \quad \Rightarrow \\
\text{CO}_2\text{Et} & \quad \Rightarrow \\
\text{3} & \quad \Rightarrow \\
\text{4} & \quad \Rightarrow \\
\end{align*}
\]

Our synthesis outlined in Scheme 2 was commenced by preparation of \(\alpha,\beta\)-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\(_3\)COCF\(_3\), 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 epoxyp alcohol by Mitsunobu reaction as well as the subsequent \(O\)-alkylations of the phenolic hydroxy group.
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, $\delta$) 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-2H-pyran-2-yl)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-2H-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 MgSO₄ 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; ^1H-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); ^13C-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⁺-C₂H₅); HRMS: Found 315.1808; Calcd for C₁₅H₂₇O₆ (M⁺-C₂H₅) 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 MgSO₄ 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; ^1H-NMR 4.51 (1H, t, J=3.4 Hz), 4.15 (2H, q, J=6.8 Hz), 3.80 (1H, dt, J=9.6, 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 NaHCO₃ and brine, and dried over MgSO₄. 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; ^1H-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); ^13C-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⁺-C₂H₅); HRMS: Found 284.1985; Calcd for C₁₆H₂₈O₄ (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 Na₂EDTA (4×10⁻⁴ M, 5 mL). The reaction mixture was cooled to 0°C and
trifluoroacetone (5 mL), NaHCO₃ (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 MgSO₄. 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) \nu 1766, 1034 cm⁻¹; \textsuperscript{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), 3.20 (1H, d, J=6.0 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); \textsuperscript{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 C₁₆H₂₈O₅ (M⁺+H) 301.2015. Anal. Calcd for C₁₆H₂₈O₅: 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 MgSO₄. 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) \nu 3368, 1733 cm⁻¹, \textsuperscript{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); \textsuperscript{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 C₁₁H₂₀O₄ (M⁺+H) 217.1440. Anal. Calcd for C₁₁H₂₀O₄: 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 MgSO₄ 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, 1152, 1028 cm⁻¹; \textsuperscript{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); \textsuperscript{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 C₂₄H₃₀O₅ (M⁺) 398.2093. Anal. Calcd for C₂₄H₃₀O₅: 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; ¹H-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); ¹³C-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⁺-OCH₃); HRMS: Found 352.1888; Calcd for C₁₉H₂₈O₆ (M⁺) 352.1881. Anal. Calcd for C₁₉H₂₈O₆: 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; ¹H-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); ¹³C-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 C₁₇H₂₄O₅ (M⁺) 308.1619. Anal. Calcd for C₁₇H₂₄O₅: 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), K₂CO₃ (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 MgSO₄. 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; ¹H-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); ¹³C-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 C₁₈H₂₆O₅ (M⁺) 322.1780. Anal. Calcd for C₁₈H₂₆O₅: 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; ¹H-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); ¹³C-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 C₂₀H₂₈O₄ (M⁺) 348.1937. Anal. Calcd for C₂₀H₂₈O₄: 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 MgSO₄ 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; ¹H-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); ¹³C-NMR 170.4, 169.3, 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 C₁₅H₂₈O₆ (M⁺) 350.1729. Anal. Calcd for C₁₅H₂₈O₆: 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 MgSO₄ 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; ¹H-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).
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, 29.1, 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 (1e)** 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$_4$Cl (M$^+$) 326.1285. Anal. Calcd for C$_{17}$H$_{23}$O$_4$Cl: C, 62.47; H, 7.09. Found: C, 62.37; H, 7.16.

ACKNOWLEDGEMENT

The present studies were partly supported by the Basic Science Research Institute Program, Ministry of education (BSRI-97-3417), and partly by the Korea Science and Engineering Foundation (KOSEF) through the Research Center for New Drug Development at Seoul National University.

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Received, 26th February, 1998