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Asymmetric synthesis of (*R*)-(+)-etomoxir

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Abstract: An asymmetric synthesis of etomoxir **1**, involving bromolactonization by using (*S*)-(−)-proline as a chiral auxiliary, is reported. © 1997 Elsevier Science Ltd

Introduction

During the last 20 years, substituted oxirane-2-carboxylates such as palmoxirate[1], clomoxir[2], and etomoxir[3] have been recognized as powerful hypoglycemic agents in animals including humans (Figure 1). Mechanistic investigations have shown that the hypoglycemic effect associated with the inhibition of carnitine palmitoyl transferase I (CPT I), which is essential for the transportation of palmitoyl CoA into the mitochondria matrix side for its β-oxidation[4].

The mode of the inhibition process was proved to involve the irreversible inactivation by covalent bond formation of CPT I with CoA esters of (*R*)-enantiomers[4c]. The enantioselective inhibition implies that there is stereochemical complementarity existed between CPT I and CoA esters of oxirane-2-carboxylic acids. Asymmetric syntheses of (*R*)-(+)-etomoxir have been reported using enzymatic resolution[5] and the Sharpless epoxidation[6] as key steps. Although these methods showed high enantioselectivity (92% ee and >98% ee, respectively), the chemical yields were relatively low (45% and 49%, respectively) in each key step. In this paper, we present a new enantioselective synthesis of (*R*)-(+)-etomoxir via bromolactonization[7] by using (*S*)-(−)-proline as a chiral auxiliary (Scheme 1).

Results and discussion

The synthesis of (*R*)-(+)-etomoxir was accomplished in 10 steps starting from the alcohol **6** (Scheme 2). The alcohol **6** was protected with benzylbromide in the presence of NaH to give the bromide **7**. The Horner–Wadsworth–Emmons reaction of triethylphosphonoacetate with the bromide **7** in the presence of formaldehyde under basic conditions gave the α,β-unsaturated ester **8**[8]. Hydrolysis of **8** gave the corresponding acid **9** and the coupling with (*S*)-(−)-ethyl prolinate[9] as a chiral auxiliary in the presence of diethyl phosphorocyanidate (DEPC) gave the amide **10**. After the hydrolysis of **10**, the diastereoselective bromolactonization was carried out with *N*-bromosuccinimide (NBS) in *N*,*N*-dimethylformamide (DMF) to give **12**. Subsequent hydrolysis in 6N aqueous HCl solution and the esterification with diazomethane gave the α-hydroxy ester **13**. The conversion of **13** to epoxide **14** was accomplished in almost quantitative yield by treatment with K_2CO_3 in ethanol. Subsequent Mitsunobu[10] coupling of **14** and 4-chlorophenol gave etomoxir **1** in 45% overall yield over 10 steps from **6**. The absolute configuration of the bromolactone **12** was assigned as 3*S* by chemical correlation

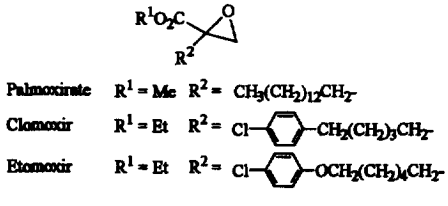

Figure 1.

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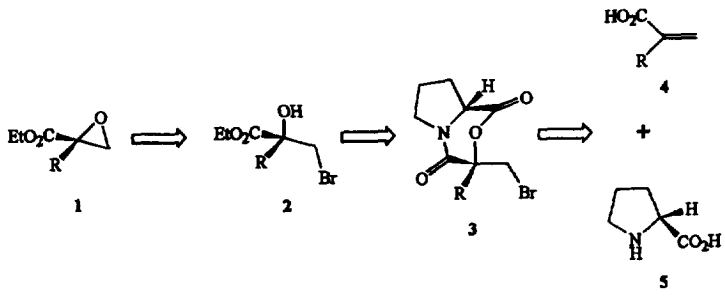
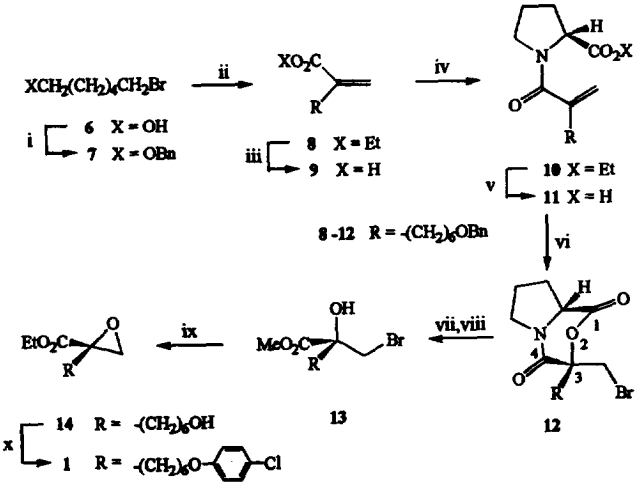


Scheme 1.

to the final product etomoxir **1**, $[\alpha]_D$ +8.55 (c 0.70, $CHCl_3$), 98% ee (lit[6]. +8.56, >98% ee, c 1, $CHCl_3$). The high enantiomeric purity and chemical yield should make this method more practical than other procedures[5,6]. Also the Mitsunobu coupling of **14** with various nucleophiles should allow us to investigate the structure–activity relationship (SAR) of oxirane carboxylate derivatives. The SAR study is currently being investigated.



Reagents and conditions : i. benzylbromide, NaH, THF, rt, 24 h, 93%; ii. triethylphosphonoacetate, NaH, $(CH_2O)_n$, DME, reflux, 12 h, 75%; iii. KOH, abs. EtOH, rt, quant.; iv. (*S*)-(-)-ethyl prolinate, DEPC, Et_3N, DMF, 0 °C, 2 h, 83%; v. KOH, MeOH, water, 90 °C, 10 h, quant.; vi. NBS, DMF, 0 °C to rt, 26 h, 87%; vii. 6N-aq. HCl sol'n, reflux, 12 h; viii. CH_2N_2, ether, 0 °C, 10 min, 90% (2 steps from 12); ix. anhydrous K_2CO_3, abs. EtOH, rt, 6 h, 98%; x. 4-chlorophenol, PPh_3, DEAD, THF, rt, 2 h, 94%.

Scheme 2.

Experimental

General

Optical rotations were measured with a JASCO DIP-1000 digital polarimeter. Infrared spectra were taken on a Perkin–Elmer 1710 FT–IR spectrometer. Mass spectra were obtained on a VG Trio-2 GC-MS instrument; high resolution mass spectra were obtained on a HP 5890 Series II. ^1H and ^{13}C NMR spectra were measured with a JEOL JNM-LA 300, a JEOL JNM-GCX 400, or a Bruker AMX-500 spectrometer using TMS as the internal standard. All reactions were carried out under argon atmosphere, using anhydrous solvents except for those involving hydrolysis. Most

reagents were obtained from commercial suppliers and used without further purification unless noted. Tetrahydrofuran was distilled from Na° and benzophenone.

1-Benzyloxy-6-bromo-hexane 7

To a tetrahydrofuran suspension (20 mL) of 60% NaH (883 mg, 22.08 mmol) was added a tetrahydrofuran solution (40 mL) of 6-bromo-1-hexanol **6** (4 g, 22.08 mmol) and benzylbromide (3.78 g, 22.08 mmol) at 0°C. The reaction mixture was stirred at room temperature (24 h). The excess solvent was removed *in vacuo* and the residue was extracted with ethyl acetate (3×200 mL). The combined ethyl acetate solution was washed with water (2×20 mL) and brine (2×20 mL), then dried over anhydrous $MgSO_4$. The excess solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, 20% ethyl acetate in *n*-hexane) to give **7** as a colorless oil (5.6 g, 93% yield). IR (neat) 3300, 3040, 2950, 2880, 1460, 1100 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.24 (m, 5 H), 4.50 (s, 2 H), 3.47 (t, *J* =6.4 Hz, 2 H), 3.39 (t, *J* =3.6 Hz, 2 H), 1.88–1.82 (m, 2 H), 1.64–1.59 (m, 2 H), 1.47–1.38 (m, 4 H). ^{13}C NMR ($CDCl_3$, 125 MHz) (138.63, 128.32, 127.58, 127.47, 72.89, 70.18, 33.75, 32.73, 29.55, 27.97, 25.39. MS (EI) m/e 270 [M^+]. HRMS (EI) calcd for $C_{13}H_{19}O^{79}Br$ 270.0619, found 270.0623.

Ethyl 2-(6-benzyloxy)hexyl-2-en-propionate 8

To a 1,2-dimethoxyethane suspension (20 mL) of 60% NaH (738 mg, 18.44 mmol) was added a 1,2-dimethoxyethane solution (10 mL) of triethylphosphonoacetate (3.66 mL, 18.44 mmol) at room temperature. The reaction mixture was stirred (1 h) and then 7 (5 g, 18.44 mmol) was added to the reaction. The reaction mixture was refluxed (10 h). After the reaction mixture was cooled down to room temperature, 60% NaH (738 mg, 18.44 mmol) was added at 0°C. The reaction mixture was warmed to room temperature and stirred (1 h). The 1,2-dimethoxyethane solution (10 mL) of 95% paraformaldehyde (618 mg) was added at room temperature. Then the reaction mixture was stirred (1 h). The excess solvent was removed *in vacuo* and the residue was diluted with ethyl acetate (300 mL). The ethyl acetate solution was washed with water (2×10 mL) and brine (2×10 mL) and dried over anhydrous $MgSO_4$, then the residue was purified by column chromatography (SiO_2, 10% ethyl acetate in *n*-hexane) to give **8** as a colorless oil (4.01 g, 75% yield). IR (neat) 2950, 2880, 1720, 1200, 1160, 1100 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.26 (m, 5 H), 6.12 (s, 1 H), 5.50 (s, 1 H), 4.49 (s, 2 H), 4.19 (q, *J* =7.2 Hz, 2 H), 3.46 (t, *J* =6.8 Hz, 2 H), 2.28 (t, *J* =7.4 Hz, 2 H), 1.64–1.57 (m, 2 H), 1.50–1.42 (m, 2 H), 1.40–1.31 (m, 4 H), 1.28 (t, J =7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.29, 141.08, 138.70, 128.27, 127.53, 127.39, 124.04, 72.81, 70.38, 60.43, 31.75, 29.64, 28.97, 28.32, 25.95, 14.15. MS (EI) m/e 290 [M^+]. HRMS (EI) calcd for $C_{18}H_{26}O_3$ 290.1882, found 290.1881.

2-(6-Benzyloxy)hexyl-2-en-propionic acid 9

A mixture of methanol–water (1: 1, 20 mL), **8** (2 g, 6.88 mmol) and 85% potassium hydroxide (681 mg, 10.32 mmol) were refluxed (5 h). The excess methanol was removed *in vacuo* and the water mixture was acidified with 7% aqueous HCl solution (20 mL). The solution was extracted with ethyl acetate (3×100 mL). The combined ethyl acetate solution was washed with brine (2×20 mL), then dried over anhydrous $MgSO_4$. The excess solvent was removed *in vacuo* to give crude **9** as a colorless oil (1.8 g, 100% yield). IR (neat) 3000, 2950, 2880, 1700, 1640, 1460, 1100 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.24 (m, 5 H), 6.27 (s, 1 H), 5.63 (s, 1 H), 4.50 (s, 2 H), 3.46 (t, *J* =6.6 Hz, 2 H), 2.29 (t, *J* =7.35 Hz, 2 H), 1.64–1.57 (m, 2 H), 1.54–1.44 (m, 2 H) 1.37–1.28 (m, 4 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.46, 140.23, 138.66, 128.31, 127.61, 127.45, 126.72, 72.83, 70.37, 31.40, 29.62, 28.97, 28.29, 25.94. MS (EI) m/e 262 [M^+]. HRMS (EI) calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1573.

(S)-(−)-Ethyl prolinate

To an absolute ethanol solution (50 mL) of (*S*)-(−)-proline (5 g, 43.43 mmol) was added thionyl chloride (7.75 g, 65.15 mmol) at 0°C. The mixture was stirred at room temperature (30 min) and refluxed (3 h). The excess solvent was removed *in vacuo* and the residue was dissolved in chloroform (30 mL). The chloroform solution was made basic with excess ammonia saturated in chloroform. The solution was filtered and evaporated *in vacuo*. The residue was purified by distillation *in vacuo* to give pure (*S*)-(−)-ethyl prolinate (5.15 g, 85%). $[\alpha]_D$ −44.8 (c 1, EtOH), (lit.[9], $[\alpha]_D$ −45.0 (c 1.78, EtOH)) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.14 (dq, *J* =7.05, 1.95 Hz, 2 H), 3.72–3.67 (m, 1 H), 3.06–3.01 (m, 1 H), 2.90–2.84 (m, 1 H), 2.12–2.05 (m, 2 H), 1.83–1.68 (m, 3 H), 1.23 (dt, *J* =7.08, 1.95 Hz, 3 H).

(S)-(−)-Ethyl N-(6-benzyloxy)hexyl acryloyl prolinate ***10***

To an *N,N*-dimethylformamide solution (50 mL) of **9** (1.62 g, 6.15 mmol) and (*S*)-(−)-ethyl prolinate (0.969 g, 6.77 mmol) were added diethyl phosphorocyanidate (1.1 mL, 6.77 mmol) and triethylamine (0.94 mL, 6.77 mmol) at 0°C. The reaction mixture was stirred at 0°C (2 h). The reaction solution was diluted with ethyl acetate (300 mL) and the ethyl acetate solution was washed with 5% aqueous HCl solution (2×10 mL), saturated aqueous $NaHCO_3$ solution (2×10 mL), water (5×10 mL) and brine (2×10 mL), then dried over anhydrous $MgSO_4$. The excess solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, 50% ethyl acetate in *n*-hexane) to give **10** as a colorless oil (1.98 g, 83% yield). $[\alpha]_D$ −35.66 (c 0.54, $CHCl_3$). IR (neat) 2960, 1740, 1660, 1640, 1450, 1200, 1100 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30–7.21 (m, 5 H), 5.19 (s, 1 H), 5.16 (s, 1 H), 4.43 (s, 2 H), 4.45–4.41 (m, 1 H), 4.13 (q, *J* =7.1 Hz, 2 H), 3.59–3.50 (m, 2 H), 3.39 (t, *J* =6.8 Hz, 2 H), 2.25 (t, *J* =7.8 Hz, 2 H), 1.98–1.79 (m, 4 H), 1.58–1.50 (m, 2 H), 1.44–1.37 (m, 2 H), 1.21 (t, *J* =7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.20, 170.50, 138.61, 132.79, 128.31, 127.60, 127.45, 115.29, 72.83, 70.38, 61.00, 58.60, 49.14, 33.69, 29.65, 29.33, 29.11, 27.44, 25.96, 25.05, 14.13. MS (EI) m/e 387 [M$^+$]. HRMS calcd for $C_{23}H_{33}NO_4$ 387.2410, found 387.2406.

(S)-(−)-N-(6-Benzyloxy)hexyl acryloyl proline ***11***

A mixture of methanol–water (1: 1, 50 mL), **10** (1.78 g, 4.58 mmol) and 85% potassium hydroxide (0.435 g, 6.87 mmol) was refluxed (10 h). The reaction was cooled down to room temperature and the excess methanol was removed *in vacuo*. The water mixture was acidified with 7% aqueous HCl solution (20 mL) and extracted with ethyl acetate (3×100 mL). The combined ethyl acetate solution was washed with water (2×10 mL) and brine (2×10 mL), then dried over anhydrous $MgSO_4$. The excess solvent was removed *in vacuo* to give crude **11** as a colorless oil (1.65 g, 100% yield). $[\alpha]_D$ −75.50 (c 1.34, $CHCl_3$). IR (neat) 3300, 2950, 1740, 1720, 1600, 1460, 1280, 1180 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.21 (m, 5 H), 5.31 (s, 1 H), 5.24 (s, 1 H), 4.61–4.58 (m, 1 H), 4.50 (s, 2 H), 3.64–3.56 (m, 2 H), 3.46 (t, *J* =6.6 Hz, 2 H), 2.31 (t, *J* =7.4 Hz, 2 H), 2.09–1.88 (m, 4 H), 1.64–1.57 (m, 2 H), 1.49–1.42 (m, 2 H), 1.40–1.34 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.14, 172.40, 144.62, 138.53, 128.33, 127.64, 127.50, 116.48, 72.86, 70.32, 59.70, 49.89, 33.62, 29.57, 28.99, 27.67, 27.44, 25.90, 24.90. MS (EI) m/e 360 [M$^+$ +1]. HRMS (EI) calcd for $C_{21}H_{30}NO_4$ [M$^+$ +1] 360.2175, found 360.2175.

Bromolactone ***12***

To an *N,N*-dimethylformamide solution (20 mL) of **11** (1.6 g, 4.45 mmol) was added an *N,N*-dimethylformamide solution (20 mL) of NBS (1.58 g, 8.9 mmol) at 0°C. The reaction mixture was stirred at 0°C (2 h) and room temperature (24 h). The reaction mixture was diluted with ethyl acetate (300 mL) and the ethyl acetate solution was washed with saturated aqueous $NaHCO_3$ solution (2×15 mL), water (5×10 mL), and brine (2×15 mL). The ethyl acetate solution was dried over anhydrous $MgSO_4$ and the excess ethyl acetate was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, 30% ethyl acetate in *n*-hexane) to give the bromolactone **12** as a colorless oil (1.7 g, 87% yield). $[\alpha]_D$ −66.91 (c 0.97, EtOH). IR (neat) 2950, 1760, 1680, 1460, 1360 cm^{-1}. ^{1}H

NMR ($CDCl_3$, 400 MHz) δ 7.29–7.21 (m, 5 H), 4.45–4.43 (m, 1 H), 4.41 (s, 2 H), 3.80 (d, *J* =11.2 Hz, 1 H), 3.67–3.62 (m, 2 H), 3.53 (d, *J* =11.2 Hz, 1 H), 3.37 (t, *J* =6.4 Hz, 2 H), 2.43–2.40 (m, 2 H), 2.11–1.86 (m, 4 H), 1.72–1.64 (m, 2 H), 1.54–1.48 (m, 2 H), 1.32–1.21 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.50, 163.65, 138.56, 128.33, 127.61, 127.48, 88.75, 72.86, 70.24, 57.99, 45.00, 38.07, 37.84, 29.94, 29.57, 29.06, 25.89, 23.73, 21.53. MS (EI) m/e 437 [M^+]. HRMS (EI) calcd for $C_{21}H_{28}NO_4{}^{79}Br$ 437.1202, found 437.1212.

(S)-(−)-Methyl 2-hydroxy-2-(6-hydroxy)hexyl-3-bromo-propionate ***13***

A 6N aqueous HCl solution (14 mL) of the bromolactone **12** (0.238 g, 0.543 mmol) was refluxed (12 h). The reaction mixture was extracted with ethyl acetate (2×50 mL). The combined ethyl acetate solution was washed with brine (2×5 mL) and dried over anhydrous $MgSO_4$. The excess solvent was removed *in vacuo* to give the crude acid as a pale yellowish oil (132 mg) which was not purified further. To an ether solution (5 mL) of the crude acid was added the ether solution of diazomethane at 0°C. The excess solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, 30% ethyl acetate in *n*-hexane) to give **13** as a colorless oil (138 mg, 90% yield). $[\alpha]_D$ −3.12 (c 1.12, $CHCl_3$). IR (neat) 3450, 2950, 1740, 1440, 1200 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.83 (s, 3 H), 3.66 (d, *J* =10.23 Hz, 1 H), 3.63 (t, *J* =6.33 Hz, 2 H), 3.47 (d, *J* =10.23 Hz, 1 H), 1.87–1.64 (m, 2 H), 1.57–1.51 (m, 4 H), 1.37–1.13 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.98, 77.24, 62.81, 53.19, 39.65, 37.27, 32.48, 29.21, 25.40, 23.84. MS (EI) m/e 283 [M^+ +1]. HRMS (EI) calcd for $C_{10}H_{20}O_4{}^{79}Br$ [M^+ +1] 283.0545, found 283.0543.

(R)-(+)-Ethyl 2-(6-hydroxy)hexyl-oxirane-2-carboxylate ***14***

An anhydrous ethanol solution (5 mL) of **13** (130 mg, 0.459 mmol) and anhydrous K_2CO_3 (63.4 mg, 0.459 mmol) was stirred at room temperature (6 h). The excess solvent was removed *in vacuo* and the residue was extracted with ethyl acetate (2×25 mL) and the combined ethyl acetate solution was washed with brine (2×5 mL) and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, 50% ethyl acetate in *n*-hexane) to give **14** as a colorless oil (97 mg, 98% yield). $[\alpha]_D$ +10.60 (c 0.52, $CHCl_3$). IR (neat) 3450, 2950, 1740 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.23 (dq, *J* =4.14, 2.94 Hz, 2 H), 3.64 (t, *J* =6.33 Hz, 2 H), 3.02 (d, *J* =5.85 Hz, 1 H), 2.77 (d, *J* =5.85 Hz, 1 H), 2.13–2.08 (m, 1H), 1.70–1.36 (m, 9 H), 1.29 (t, *J* =7.06 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.41, 62.82, 61.56, 56.99, 51.81, 32.52, 31.10, 29.20, 25.44, 24.68, 14.08. MS (EI) m/e 217 [M^+ +1]. HRMS (EI) calcd for $C_{11}H_{21}O_4$ [M^+ +1] 217.1440, found 217.1445.

(R)-(+)-Ethyl 2-[6-(4-chlorophenoxy)hexyl]-oxirane-2-carboxylate, (R)-(+)-Etomoxir ***1***

To a tetrahydrofuran (2 mL) solution of **14** (23 mg, 0.106 mmol) and 4-chlorophenol (13.6 mg, 0.106 mmol) was added a tetrahydrofuran solution (1 mL) of triphenylphosphine (41.7 mg, 0.159 mmol) and diethylazodicarboxylate (0.017 mL, 0.159 mmol). The reaction mixture was stirred (2 h) at room temperature. The excess solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2, 3% ethyl acetate in *n*-hexane) to give (*R*)-(+)-etomoxir (**1**) as a colorless oil (32.6 mg, 94% yield). $[\alpha]_D$ +8.55 (c 0.70, $CHCl_3$). IR (neat) 2960, 1740, 1500, 1250 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.21 (d, *J* =8.8 Hz, 2 H), 6.80 (d, *J* =8.8 Hz, 2 H), 4.21 (dq, *J* =7.2, 3.6 Hz, 2 H), 3.89 (t, *J* =6.8 Hz, 2 H), 3.02 (d, *J* =5.86 Hz, 1 H), 2.78 (d, *J* =5.86 Hz, 1 H), 2.13–2.04 (m, 1 H), 1.78–1.73 (m, 2 H), 1.69–1.62 (m, 1H), 1.54–1.33 (m, 6 H), 1.28 (t, *J* =7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.46, 157.67, 129.25, 125.29, 115.71, 68.13, 61.44, 57.02, 51.88, 31.16, 29.21, 29.01, 25.80, 24.70, 14.11. MS (EI) m/e 326 [M^+]. HRMS (EI) calcd for $C_{17}H_{23}O_4{}^{35}Cl$ [M^+] 326.1285, found 326.1282.

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