DESIGN AND SYNTHESES OF 2-OXIRANECARBOXYLATE DERIVATIVES AND THEIR HYPOGLYCEMIC ACTIVITIES†

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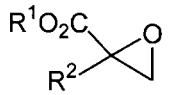
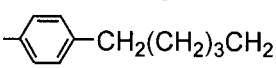
Abstract - A series of 2-oxiranecarboxylate derivatives were prepared as carnitine palmitoyl transferase I (CPT-I) inhibitors for the development of new antidiabetic agents. The syntheses and biological activities were reported. The most promising derivative (**13b**) showed 2.5 times more hypoglycemic activity and 2 times lower acute toxicity compared to Etomoxir (**3**).

2-Oxiranecarboxylate derivatives such as Palmoxirate (**1**),[1] Clomoxir (**2**)[2] and Etomoxir (**3**)[3,4] were reported as potent hypoglycemic agents in fasted animals and humen[5] (Figure 1). These compounds inactivate carnitine palmitoyl transferase I (CPT I), which is a rate limiting enzyme for transport of long chain acyl CoA into the mitochondria matrix for fatty β-oxidation.[6] The mode of inactivation involves the irreversible binding with CPT I through a stable covalent modification.[7] The inactivation of CPT I inhibits fatty acid oxidation, which gradually increases the utilization of glucose and finally the following decrement of gluconeogenesis leads hypoglycemic activity.[8-10]



Palmoxirate (**1**) $R^1 = CH_3$ $R^2 = CH_3(CH_2)_{12}CH_2$

Clomoxir (**2**) $R^1 = C_2H_5$ $R^2 =$ 

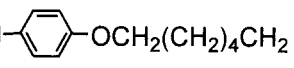
Etomoxir (**3**) $R^1 = C_2H_5$ $R^2 =$ 

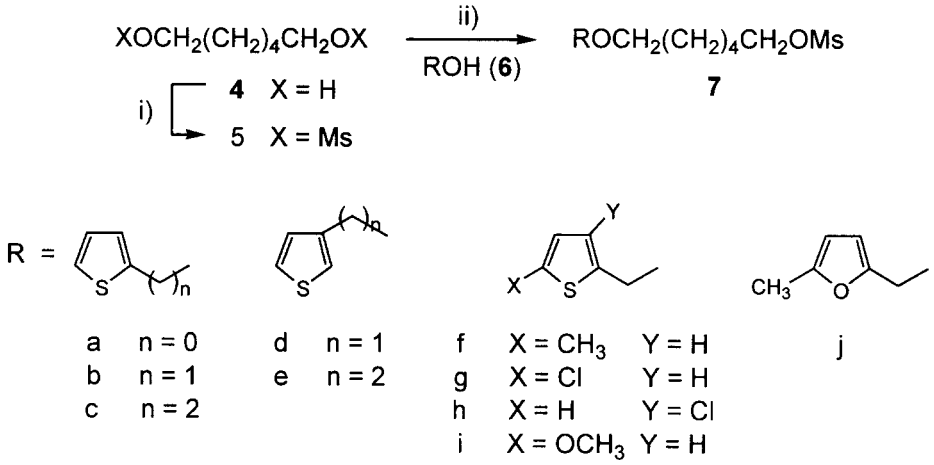
Figure 1

† Dedicated to Prof. Teruaki Mukaiyama for the celebration of his 73rd Birthday

Etomoxir has been most widely studied as a CPT I inhibitor in the series of 2-oxiranecarboxylates.[4,11] It was reported that **3** is 7 and 15 times more effective compared with tolbutamide and buformin, respectively which are currently clinically using as hypoglycemic agents.[4] Although Etomoxir had quite potent hypoglycemic effect, the drug development research was discontinued by its long-term toxicity such as myocardial hypertrophy.[6] As a part of our program directed toward the development of new antidiabetic agents which have more potent activity and lower toxicity, we designed and synthesized a new series of 2-oxiranecarboxylate derivatives as CPT I inhibitors by modification of **3**. The structure-activity relationship studies were carried out by comparison of the hypoglycemic activities of prepared derivatives.

Based on previous studies,[9] the oxirane ring in **3** appeared to be essential for drug action. So we planned to modify the side chain of Etomoxir as a strategy for our SAR study. As shown in Schemes 1 and 2, we designed a new series of 2-oxiranecarboxylate derivatives (**13a-j**) by replacing the phenyl group in **3** with heterocyclic groups such as thiophene and furane. Also the length of the side chain was changed by increasing of the carbon number between heterocycle ring and oxygen.

Scheme 1

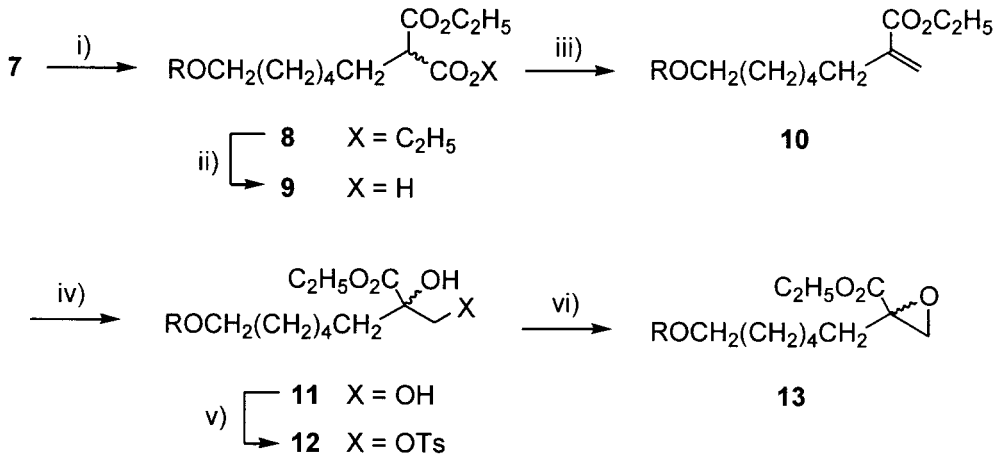


Reagents: i) MsCl(2.2 eq.)/TEA/THF, rt, 1 h, (100%), iv) ROH (**6a-j**) /NaH/THF, rt, 16 h (50-78%)

The syntheses of 2-oxirancarboxylate derivatives (**13a-j**) were accomplished in 6 steps starting from mesylate (**7a-j**) (Scheme 1). 1,6-Hexanediol (**4**) was dimesylated to give **5** and by using **5**, the alcohols (**6a-j**), could be directly converted to **7a-j**, respectively. Diethyl malonate was alkylated with **6a-j**, followed by partial hydrolysis with one equivalent of KOH to give the half esters (**9a-j**).[12] Treatment of half esters with Eschenmoser's salt[13] in the presence of NaH produced ethyl 2-methylenecarboxylates (**10a-j**), which were dihydroxylated with 4-methylmorpholine *N*-oxide (NMO) and OsO_4[14] to afford the 2,3-dihydroxypropionates

(**11a-j**). The following tosylation and cyclization with excess K_2CO_3 furnished the desired ethy oxiranecarboxylates (**13a-j**) (Scheme 2).

Scheme 2



Reagents: i) diethyl malonate/NaH/THF, reflux, 16 h (63-100%), ii) KOH (1.0 eq.)/C_2H_5OH, rt, 1 h (60-89%), iii) Eschenmoser's salt/NaH/THF, reflux, 16 h (70-84%), iv) NMO/OsO_4/Acetone/H_2O/*tert*-C_4H_9OH, rt, 1 h, v) TsCl/Pyr, rt, 3 h, vi) K_2CO_2/C_2H_5OH, rt 5 h (62-85% from **10**)

The oral hypoglycemic activities of the prepared derivatives compared with Etomoxir (**3**) were listed in Table I Generally the replacement of benzene ring in **3** with thiophene showed comparable hypoglycemic activity to **3** Especially **13b** showed the most potent hypoglycemic activity (75.9%) and the activity of **13e-h** (30.7 - 42.2%) was similar to **3** (31.0%).

Table 1. The oral hypoglycemic activity[15,16] of prepared 2-oxiranecarboxylate derivatives (50 mg/kg).

Compd. No.	Hypoglycemic activity (inhibition %)	Compd. No.	Hypoglycemic activity (inhibition %)
3	31.0		
13a	21.4	**13f**	33.7
13b	75.9	**13g**	32.7
13c	5.6	**13h**	30.7
13d	9.3	**13i**	5.9
13e	42.2	**13j**	6.8

Inspection of Table 1 showed that the hypoglycemic activity was dramatically changed by the length of alkyl linker chain between thiophene ring and oxygen (**13a-c**). For example the hypoglycemic activity of **13a**, **13b** and **13c** were 21.4, 75.9 and 5.6% , respectively. Similar result was observed in 3-substituted thiophene derivatives (**13d**, **13e**). **13e** showed 42.2% of hypoglycemic activity, whereas **13d** showed only 9.3% of hypoglycemic activity. It is suggested that there is optimal length of the linker chain to maximize the binding interaction with CPT I. 3- or 5-Substituted derivatives (**13g**, **13h**) with chlorine and methyl (**13f**) in thiophene ring resulted in comparable activities (32.7 - 33.7%) with **3**, whereas substitution with 5-methoxy (**13i**) led loss of activity (5.9%). Replacement of furan mioety with thiophene moiety drastically decreased hypoglycemic activity (**13j** 6.8% ; **13f** 33.7%). Among the synthesized derivatives, **13b** which showed the highest hypoglycemic activity was selected and the LD_{50} was evaluated. The LD_{50} of **13b** was 487 mg/kg and that of etomoxir was 250 mg/kg. The 2.5-fold higher hyperglycemic activity and 2-fold lower acute toxicity of **13b** compared with Etomoxir encouraged us to proceed with preclinical study for a new antidiabatic drug.

In conclusion, a series of 2-oxiranecarboxylate derivatives bearing thiophene or furan moiety were prepared and their hypoglycemic activities were reported. Among this series, **13b** showed the most potent hypoglycemic activity (75.9%) compared with **3** (31%). Also The LD_{50} of **13b** (478 mg/kg) was 2 times lower than **3** (250 mg/kg).

EXPERIMENTAL

General method.

^1H and ^{13}C NMR spectra were measured with a Bruker ARX-300 spectrometer using TMS (Me_4Si) as the internal standard. MS spectra were obtained on a VG Trio-2 GC-MS instrument; high resolution MS spectra were obtained on a HP 5890 Series II. Microanalysis were performed with EA1110 CE INSTRUMENT. All reactions were carried out under argon atmosphere, using anhydrous solvents. Most reagents were obtained from the best commercial suppliers and used without further purification unless noted. Tetrahydrofuran was distilled from Na and benzophenone.

1,6-Hexyl dimesylate (5). To a tetrahydrofuran suspension (70 mL) of 1,6-hexanediol (**4**) (5 g, 42.3 mmol) was added methanesulfonyl chloride (7.2 mL, 93.1 mmol) and triethylamine (14.7 mL, 106.0 mmol) at 0 °C . The reaction mmxture was stirred at rt (1.5 h). The excess solvent was removed *in vacuo* and the residue was extracted with methylene chloride (3 × 200 mL). The combined methylene chloride solution was washed with water (2 × 20 mL), *aq*. 5%-HCl. (2 × 20 mL) and brine (2 × 20 mL), then dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by recrystalization (ethyl acetate and *n*-hexane) to give **5** as a colorless needle (10.7 g, 92%) ; mp 58-59 °C ; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.50 (m, 4 H), 1.81 (m,

4 H), 3.02 (s, 6 H), 4.24 (t, J = 6.38 Hz, 4 H). *Anal.* Calcd for $C_8H_{18}O_6S_2$: C, 35.02; H, 6.61. Found: C, 35.12; H 6.57.

6-(2-Thiophenoxy)hexylmesylate (7a)

To a tetrahydrofuran (100 mL) suspension of 95% NaH (883 mg, 34.95 mmol) was added a tetrahydrofura solution (10 mL) of **6a** (3.50 g, 34.95 mmol) at 0 °C. The reaction mixture was stirred for 10 min and then (11.51 g, 41.94 mmol) was added to the reaction. The reaction mixture was stirred for 16 h at rt. The solven was removed *in vacuo* and the residue was diluted with ethyl acetate (200 mL). The ethyl acetate solution wa washed with water (2 × 50 mL) and brine (2 × 50 mL), then dried over anhydrous $MgSO_4$. The residue wa purified by column chromatography (SiO_2, ethyl acetate : *n*-hexane = 1 : 4) to give **7a** as a pale yellow oil (7.1 g, 73%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (m, 4 H), 1.79 (m, 4 H), 3.01 (s, 3 H), 4.03 (t, J = 6.26 Hz, 2 H) 4.24 (t, J = 6.42 Hz, 2 H), 6.19 (br, 1 H), 6.54 (d, J = 5.60 Hz, 1 H), 6.71 (dd, J = 3.74, 5.60 Hz, 1 H). *Anal* Calcd for $C_{11}H_{18}O_4S_2$: C, 47.46; H, 6.52. Found: C, 47.41; H, 6.47.

6-(2-Thiophenemethoxy)hexylmesylate (7b)

By using the preceding procedure and the utilization of 95% NaH (442 mg, 17.52 mmol) and **6b** (5.80 g, 21.(mmol), **5** (2.0 g, 17.52 mmol) gave **7b** as a pale yellow oil (3.95 g, 77%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 1.58 (m, 4 H), 1.61 (m, 2 H), 1.85 (m, 2 H), 3.40 (t, J = 6.40 Hz, 2 H), 4.22 (t, J = 6.56 Hz, 2 H), 4.65 (s, 2 H) 6.95 (m, 2 H), 7.26 (m, 1 H). *Anal.* Calcd for $C_{12}H_{20}O_4S_2$: C, 49.29; H, 6.89. Found: C, 49.21; H, 6.81.

6-(2-Thiopheneethoxy)hexylmesylate (7c)

By using the preceding procedure and the utilization of 95% NaH (570 mg, 22.58 mmol) and **6c** (2.89 g, 22.5 mmol), **5** (5.0 g, 18.22 mmol) gave **7c** as a pale yellow oil (3.52 g, 51%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (m, 4 H), 1.60 (m, 2 H), 1.76 (m, 2 H), 3.00 (s, 3 H), 3.09 (t, J = 6.60 Hz, 2 H), 3.46 (t, J = 6.40 Hz, 2 H), 3.6 (t, J = 6.60 Hz, 2 H), 4.22 (t, J = 6.52 Hz, 2 H), 6.85 (m, 1 H), 6.93 (dd, J = 3.47, 5.03 Hz, 1 H), 7.14 (dd, J = 1.00, 5.03 Hz, 1 H). *Anal.* Calcd for $C_{13}H_{22}O_4S_2$: C, 50.95; H, 7.24. Found: C, 50.24; H, 7.17.

6-(3-Thiophenemethoxy)hexylmesylate (7d)

By using the preceding procedure and the utilization of 95% NaH (332 mg, 13.14 mmol) and **6d** (1.50 g, 13.1 mmol), **5** (4.33 g, 15.77 mmol) gave **7d** as an oil (2.46 g, 64%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (m, 4 H), 1.61 (m, 2 H), 1.74 (m, 2 H), 2.98 (s, 3 H), 3.45 (t, J = 6.40 Hz, 2 H), 4.21 (t, J = 6.50 Hz, 2 H), 4.49 (s, 2 H), 7.06 (d, J = 4.67 Hz, 1 H), 7.19 (s, 1 H), 7.29 (m, 1 H). *Anal.* Calcd for $C_{12}H_{20}O_4S_2$: C, 49.29; H, 6.89. Found: C 49.11; H, 6.75.

6-(3-Thiopheneethoxy)hexylmesylate (7e)

By using the preceding procedure and the utilization of 95% NaH (570 mg, 22.58 mmol) and **6e** (2.89 g, 22.58 mmol), **5** (5.0 g, 18.22 mmol) gave **7e** as a pale yellow oil (3.93 g, 57%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (m, 4 H), 1.59 (m, 2 H), 1.75 (m, 2 H), 2.91 (t, J = 6.94 Hz, 2 H), 3.00 (s, 3 H), 3.44 (t, J = 6.46 Hz, 2 H), 3.63 (t, J = 7.04 Hz, 2 H), 4.22 (t, J = 6.55 Hz, 2 H), 6.98 (dd, J = 1.25, 4.90 Hz, 2 H), 7.02 (m, 1 H), 7.25 (dd, J = 3.10, 4.90 Hz, 1 H). *Anal.* Calcd for $C_{13}H_{22}O_4S_2$: C, 50.95; H, 7.24. Found: C, 50.73; H, 7.13.

6-(5-Methyl-2-thiophenemethoxy)hexylmesylate (7f)

By using the preceding procedure and the utilization of 95% NaH (138 mg, 5.47 mmol) and **6f** (1.25 g, 5.47 mmol), **5** (1.5 g, 5.47 mmol) gave **7f** as a pale yellow oil (1.60 g, 96%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (m, 4 H), 1.60 (m, 2 H), 1.75 (m, 2 H), 2.30 (s, 3 H), 2.46 (d, J = 0.82 Hz, 3 H), 3.45 (t, J = 6.40 Hz, 2 H), 4.22 (t, J = 6.56 Hz, 2 H), 4.56 (s, 2 H), 6.60 (d, J = 3.36 Hz, 1 H), 6.76 (d, J = 3.36 Hz, 1 H). *Anal.* Calcd for $C_{13}H_{22}O_4S_2$: C, 50.95; H, 7.24. Found: C, 50.84; H, 7.23.

6-(5-Chloro-2-thiophenemethyl)hexylmesylate (7g)

By using the preceding procedure and the utilization of 95% NaH (240 mg, 9.49 mmol) and **6g** (1.41 g, 9.49 mmol), **5** (3.12 g, 11.39 mmol) gave **7g** as a pale yellow oil (1.54 g, 50%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (m, 4 H), 1.60 (m, 2 H), 1.74 (m, 2 H), 3.00 (s, 3 H), 3.46 (t, J = 6.30 Hz, 2 H), 4.22 (t, J = 6.53 Hz, 2 H), 4.54 (s, 2 H), 6.75 (d, J = 3.72 Hz, 1 H), 6.77 (d, J = 3.72 Hz, 1 H). *Anal.* Calcd for $C_{12}H_{19}O_4ClS_2$: C, 44.09; H, 5.86. Found: C, 43.85; H, 5.64.

6-(3-Chloro-2-thiophenemethoxy)hexylmesylate (7h)

By using the preceding procedure and the utilization of 95% NaH (250 mg, 9.11 mmol) and **6h** (1.47 g, 9.89 mmol), **5** (3.26 g, 11.87 mmol) gave **7h** as a colorless oil (1.07 g, 33%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42 (m, 4 H), 1.62 (m, 2 H), 1.76 (m, 2 H), 3.00 (s, 3 H), 3.50 (t, J = 6.37 Hz, 2 H), 4.22 (t, J = 6.50 Hz, 2 H), 4.64 (s, 2 H), 6.90 (d, J = 5.20 Hz, 2 H), 7.27 (d, J = 5.20 Hz, 1 H). *Anal.* Calcd for $C_{12}H_{19}O_4ClS_2$: C, 44.09; H, 5.86. Found: C, 43.95; H, 5.94.

6-(5-Methoxy-2-thiophenemethoxy)hexylmesylate (7i)

By using the preceding procedure, 95% NaH (386 mg, 15.26 mmol) and **6i** (2.0 g, 12.60 mmol), **5** (4.95 g, 18.03 mmol) gave **7i** as an oil (0.67 g, 26%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (m, 4 H), 1.57 (m, 2 H), 1.75 (m, 2 H), 3.00 (s, 3 H), 3.44 (m, 2 H), 3.87 (s, 3 H), 4.22 (m, 2 H), 4.48 (s, 2 H), 6.04 (d, J = 3.80 Hz, 1 H), 6.60 (d, J = 3.80 Hz, 1 H). *Anal.* Calcd for $C_{13}H_{22}O_5S_2$: C, 48.42; H, 6.88. Found: C, 48.39; H, 6.95.

6-(5-Methyl-2-furanemethoxy)hexylmesylate (7j)

By using the preceding procedure and the utilization of 95% NaH (572 mg, 22.65 mmol) and **6j** (2.54 g, 22.65 mmol), **5** (7.46 g, 27.18 mmol) gave **7j** as a pale yellow oil (2.79 g, 43%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (m, 4 H), 1.61 (m, 2 H), 2.29 (d, J = 0.81 Hz, 3 H), 3.00 (s, 3 H), 3.46 (t, J = 6.54 Hz, 2 H), 4.22 (t, J = 6.53 Hz, 2 H), 4.37 (s, 2 H), 5.92 (m, J = 3.01 Hz, 1 H), 6.19 (d, J = 3.01 Hz, 1 H). *Anal.* Calcd for $C_{13}H_{22}O_5S$: C, 53.77; H, 7.64. Found: C, 51.88; H, 7.45.

Diethyl 6-(2-thiophenoxy)hexylmalonate (8a)

To a tetrahydrofuran (5 mL) suspension of 95% NaH (77 mg, 3.06 mmol) and diethyl malonate (490 mg, 3.06 mmol) was added a tetrahydrofuran solution (5 mL) of **7a** (710 mg, 2.55 mmol) at 0 °C. The reaction mixture was refluxed for 16 h. The solvent was removed *in vacuo* and the residue was diluted with ethyl acetate (100 mL). The ethyl acetate solution was washed with water (2 × 10 mL) and brine (2 × 10 mL), then dried over anhydrous $MgSO_4$. The residue was purified by column chromatography (SiO_2, ethyl acetate : *n*-hexane = 1 : 5) to give **8a** as a pale yellow oil (84 mg, 94%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, J = 7.10 Hz, 6 H), 1.35-1.45 (m, 6 H), 1.77 (m, 2 H), 1.89 (m, 2 H), 3.32 (t, J = 7.52 Hz, 1 H), 4.01 (t, J = 6.40 Hz, 2 H), 4.20 (q, J = 7.10 Hz, 4 H), 6.19 (dd, J = 1.28, 3.70 Hz, 1 H), 6.53 (dd, J = 1.28, 5.68 Hz, 1 H), 6.71 (dd, J = 3.70, 5.68 Hz, 1 H). *Anal.* Calcd for $C_{17}H_{26}O_5S$: C, 59.62; H, 7.65. Found: C, 58.34; H, 7.64.

Diethyl 6-(2-thiophenemethoxy)hexylmalonate (8b)

By using the preceding procedure and the utilization of 95% NaH (308 mg, 17.5 mmol) and diethyl malonate (1.85 mL, 12.19 mmol), **7b** (3.24 g, 11.08 mmol) gave **8b** as a pale yellow oil (3.50 g, 89%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, J = 7.10 Hz, 6 H), 1.32 (m, 6 H), 1.60 (m, 2 H), 1.90 (m, 2 H), 3.30 (t, J = 7.56 Hz, 1 H), 3.46 (t, J = 6.50 Hz, 2 H), 4.20 (q, J = 7.10 Hz, 4 H), 4.65 (s, 2 H), 6.96-6.99 (m, 2 H), 7.28 (dd, J = 1.68, 4.77 Hz, 1 H). *Anal.* Calcd for $C_{18}H_{28}O_4S$: C, 60.65; H, 7.92. Found: C, 59.64; H, 7.51.

Diethyl 6-(2-thiopheneethoxy)hexylmalonate (8c)

By using the preceding procedure and the utilization of 95% NaH (319 mg, 12.64 mmol) and diethyl malonate (2.02 g, 12.64 mmol), **7c** (3.52 g, 11.49 mmol) gave **8c** as a pale yellow oil (4.29 g, 100%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, J = 7.16 Hz, 6 H), 1.31 (m, 6 H), 1.58 (m, 2 H), 1.89 (m, 2 H), 3.09 (t, J = 6.80 Hz, 2 H), 3.31 (t, J = 7.58 Hz, 1 H), 3.44 (t, J = 6.56 Hz, 2 H), 3.64 (t, J = 6.80 Hz, 2 H), 4.20 (q, J = 7.16 Hz, 4 H), 6.85 (m, 1 H), 6.93 (dd, J = 3.40, 5.10 Hz, 1 H), 7.14 (dd, J = 1.00, 5.10 Hz, 1 H). *Anal.* Calcd for $C_{19}H_{30}O_5S$: C, 61.59; H, 8.16. Found: C, 59.86; H, 8.04.

Diethyl 6-(3-thiophenemethoxy)hexylmalonate (8d)

By using the preceding procedure and the utilization of 95% NaH (255 mg, 10.09 mmol) and diethyl malonat (1.62 g, 10.09 mmol), **7d** (2.46 g, 8.41 mmol) gave **8d** as a pale yellow oil (2.60 g, 87%). ^{1}H NMR ($CDCl_3$, 30(MHz) δ 1.26 (t, J = 7.04 Hz, 6 H), 1.20-1.40 (m, 6 H), 1.59 (m, 2 H), 1.88 (m, 2 H), 3.31 (t, J = 7.44 Hz, 1 H) 3.44 (t, J = 6.50 Hz, 2 H), 4.19 (q, J = 7.04 Hz, 4 H), 4.50 (s, 2 H), 7.06 (d, J = 4.75 Hz, 1 H), 7.19 (br, 1 H) 7.29 (m, 1 H), *Anal.* Calcd for $C_{18}H_{28}O_4S$: C, 60.65; H, 7.92. Found: C, 59.42; H, 7.68.

Diethyl 6-(3-thiopheneethoxy)hexylmalonate (8e)

By using the preceding procedure and the utilization of 95% NaH (389 mg, 15.39 mmol) and diethyl malonat (2.47 g, 15.39 mmol), **7e** (3.93 g, 12.83 mmol) gave **8e** as a pale yellow oil (4.74 g, 100%).; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, J = 7.14 Hz, 6 H), 1.33 (m, 6 H), 1.56 (m, 2 H), 1.89 (m, 2 H), 2.91 (t, J = 7.00 Hz, 2 H), 3.31 (t, J = 7.56 Hz, 1 H), 3.43 (t, J = 6.59 Hz, 2 H), 3.62 (t, J = 7.00 Hz, 2 H), 4.20 (q, J = 7.14 Hz, 4 H), 6.98 (dd, J = 1.15, 4.89 Hz, 1 H), 7.02 (m, 1 H), 7.25 (dd, J = 3.90, 4.89 Hz, 1 H). *Anal.* Calcd for $C_{19}H_{30}O_5S$: C, 61.59; H, 8.16. Found: C, 60.72; H, 8.20.

Diethyl 6-(5-methyl-2-thiophenemethoxy)hexylmalonate (8f)

By using the preceding procedure and the utilization of 95% NaH (145 mg, 5.74 mmol) and diethyl malonate (0.87 mL, 5.74 mmol), **7f** (1.60 g, 5.22 mmol) gave **8f** as a pale yellow oil (1.26 g, 65%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, J = 7.15 Hz, 6 H), 1.32 (m, 6 H), 1.57 (m, 2 H), 1.87 (m, 2 H), 2.46 (d, J = 0.91 Hz, 3 H), 3.30 (t, J = 7.58 Hz, 1 H), 3.43 (t, J = 6.58 Hz, 2 H), 4.19 (m, 4 H), 4.56 (s, 2 H), 6.60 (d, J = 3.36 Hz, 1 H), 6.76 (d, J = 3.36 Hz, 1 H). *Anal.* Calcd for $C_{19}H_{30}O_5S$: C, 61.59; H, 8.16. Found: C, 60.45; H, 7.98.

Diethyl 6-(5-chloro-2-thiophenemethoxy)hexylmalonate (8g)

By using the preceding procedure and the utilization of 95% NaH (131 mg, 5.18 mmol) and diethyl malonate (0.79 mL, 5.18 mmol), **7g** (1.54 g, 4.71 mmol) give **8g** as a pale yellow oil (1.60 g, 87%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, J = 7.16 Hz, 6 H), 1.33 (m, 6 H), 1.57 (m, 2 H), 1.88 (m, 2 H), 3.30 (t, J = 7.53 Hz, 1 H), 3.44 (t, J = 6.50 Hz, 2 H), 4.19 (q, J = 7.16 Hz, 4 H), 4.53 (s, 2 H), 6.74 (d, J = 3.71 Hz, 1 H), 6.77 (d, J = 3.71 Hz, 1 H). *Anal.* Calcd for $C_{18}H_{27}O_5Cl$ S: C, 55.30; H, 6.96. Found: C, 54.80; H, 6.23.

Diethyl 6-(3-chloro-2-thiophenemethoxy)hexylmalonate (8h)

By using the preceding procedure and the utilization of 95% NaH (91 mg, 3.60 mmol) and diethyl malonate (0.55 mL, 3.60 mmol), **7h** (1.07 g, 3.27 mmol) gave **8h** as a pale yellow oil (1.05 g, 82%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, J = 7.11 Hz, 6 H), 1.33 (m, 6 H), 1.58 (m, 2 H), 1.88 (m, 2 H), 3.30 (t, J = 7.53 Hz, 1 H), 3.48 (t, J = 6.50 Hz, 2 H), 4.19 (q, J = 7.11 Hz, 4 H), 4.63 (s, 2 H), 6.89 (d, J = 5.20 Hz, 1 H), 7.26 (d, J = 5.20 Hz, 1 H). *Anal.* Calcd for $C_{18}H_{27}O_5Cl$ S: C, 55.30; H, 6.96. Found: C, 54.20; H, 6.15.

Diethyl 6-(5-methoxy-2-thiophenemethoxy)hexylmalonate (8i)

By using the preceding procedure and the utilization of 95% NaH (58 mg, 2.29 mmol) and diethyl malonate (0.35 mL, 2.29 mmol), **7i** (0.67 g, 2.08 mmol) gave **8i** as a pale yellow oil (0.34 g, 43%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, J = 7.10 Hz, 6 H), 1.33 (m, 6 H), 1.55 (m, 2 H), 1.89 (m, 2 H), 3.42 (t, J = 6.55 Hz, 2 H), 3.87 (s, 3 H), 4.19 (q, J = 7.10 Hz, 4 H), 4.48 (s, 2 H), 6.03 (d, J = 3.76 Hz, 1 H), 6.60 (d, J = 3.76 Hz, 1 H). *Anal.* Calcd for $C_{19}H_{30}O_6S$: C, 59.04; H, 7.82. Found: C, 58.21; H, 7.76.

Diethyl 6-(5-methyl-2-furanmethoxy)hexylmalonate (8j)

By using the preceding procedure and the utilization of 95% NaH (267 mg, 10.57 mmol) and diethyl malonate (1.69 g, 10.57 mmol), **7j** (2.79 g, 9.61 mmol) gave **8j** as a pale yellow oil (3.66 g, 100%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, J = 7.13 Hz, 6 H), 1.32 (m, 6 H), 1.58 (m, 2 H), 1.88 (m, 2 H), 2.29 (s, 3 H), 3.30 (t, J = 7.58 Hz, 1 H), 3.44 (t, J = 6.68 Hz, 2 H), 4.19 (q, J = 7.13 Hz, 4 H), 4.36 (s, 2 H), 5.91 (d, J = 3.01 Hz, 1 H), 6.18 (d, J = 3.01 Hz, 1 H). *Anal.* Calcd for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53. Found: C, 63.89; H, 8.35.

Ethyl 6-(2-thiophenoxy)hexylmalonate (9a)

To an ethanol solution (30 mL) of **8a** (0.82 g, 2.40 mmol) was added a 85% potasium hydroxide (174 mg, 2.64 mmol) and the reaction mixture was stirred for 6 h at rt. The solvent was removed *in vacuo* and the residue was diluted with water (150 mL). The water solution was washed with ethyl acetate (20 mL x 3) to remove starting material. The "pH" was adjusted to 2.0 with aq. 5%- HCl solution, then extracted with ethyl acetate (3 x 50 mL). The combined ethyl acetate solution was washed with brine (2 x 20 mL), then dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to gave **9a** as a pale yellow oil (0.66 g, 88%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, J = 7.06 Hz, 3 H), 1.40 (m, 6 H), 1.77 (m, 2 H), 1.93 (m, 2 H), 3.38 (t, J = 7.48 Hz, 1 H), 4.01 (t, J = 6.48 Hz, 2 H), 4.24 (q, J = 7.06 Hz, 2 H), 6.19 (dd, J = 1.30, 3.70 Hz, 1 H), 6.53 (dd, J = 1.30, 5.70 Hz, 1 H), 6.71 (dd, J = 3.70, 5.70 Hz, 1 H), 7.55 (br, 1 H). *Anal.* Calcd for $C_{15}H_{22}O_5S$: C, 57.30; H, 7.05. Found: C, 56.83; H, 6.86.

Ethyl 6-(2-thiophenemethoxy)hexylmalonate (9b)

By using the preceding procedure **8b** (3.52 g, 9.82 mmol) gave **9b** as an oil (2.54 g, 79%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, J = 7.15 Hz, 3 H), 1.34 (m, 6 H), 1.60 (m, 2 H), 1.90 (m, 2 H), 3.36 (t, J = 7.43 Hz, 1 H), 3.46 (t, J = 6.50 Hz, 2 H), 4.22 (q, J = 7.15 Hz, 2 H), 4.66 (s, 2 H), 6.95-6.99 (m, 2 H), 7.28 (dd, J = 1.50, 4.85 Hz, 1 H). *Anal.* Calcd for $C_{16}H_{24}O_5S$: C, 58.51; H, 7.37. Found: C, 58.31; H, 7.45.

Ethyl 6-(2-thiopheneethoxy)hexylmalonate (9c)

By using the preceding procedure **8c** (4.29 g, 11.52 mmol) gave **9c** as an oil (2.08 g, 52%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, *J* = 6.96 Hz, 3 H), 1.35 (m, 6 H), 1.58 (m, 2 H), 1.91 (m, 2 H), 3.09 (t, K = 6.70 Hz, 2 H), 3.38 (t, *J* = 7.37 Hz, 1 H), 3.44 (t, *J* = 6.75 Hz, 2 H), 3.65 (t, *J* = 6.70 Hz, 2 H), 4.24 (q, *J* = 6.96 Hz, 2 H), 6.85 (br, 1 H), 6.93 (m, 1 H), 7.14 (br, 1 H), 7.83 (br, 1 H). *Anal.* Calcd for $C_{17}H_{26}O_5S$: C, 59.62; H, 7.65. Found: C, 59.45; H, 7.62.

Ethyl 6-(3-thiophenemethoxy)hexylmalonate (9d)

By using the preceding procedure **8d** (2.60 g, 7.29 mmol) gave **9d** as an oil (2.13 g, 89%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, *J* = 7.15 Hz, 3 H), 1.34 (m, 6 H), 1.59 (m, 2 H), 1.91 (m, 2 H), 3.37 (t, *J* = 7.24 Hz, 1 H), 3.45 (t, *J* = 6.77 Hz, 2 H), 4.23 (q, *J* = 7.15 Hz, 2 H), 4.50 (s, 2 H), 7.07 (br, 1 H), 7.20 (br, 1 H), 7.29 (m, 1 H). *Anal.* Calcd for $C_{16}H_{24}O_5S$: C, 58.51; H, 7.37. Found: C, 58.32; H, 7.21.

Ethyl 3-thiopheneethoxy)hexylmalonate (9e)

By using the preceding procedure **8e** (4.74 g, 12.72 mmol) gave **9e** as an oil (3.26 g, 74%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, *J* = 7.12 Hz, 3 H), 1.34 (m, 6 H), 1.57 (m, 2 H), 1.91 (m, 2 H), 2.91 (t, *J* = 7.08 Hz, 2 H), 3.37 (t, *J* = 7.46 Hz, 1 H), 3.44 (t, *J* = 6.60 Hz, 2 H), 3.64 (t, *J* = 7.08 Hz, 2 H), 4.22 (q, *J* = 7.12 Hz, 2 H), 6.98 (dd, *J* = 1.17, 4.90 Hz, 1 H). 7.02 (dd, *J* = 1.0, 2.96 Hz, 1 H). 7.25 (dd, *J* = 2.96, 4.90 Hz, 1 H). 8.3 (br, 1 H). *Anal.* Calcd for $C_{17}H_{26}O_5S$: C, 59.62; H, 7.65. Found: C, 59.36; H, 7.62.

Ethyl 6-(6-(5-methyl-2-thiophenemethoxy)hexylmalonate (9f)

By using the preceding procedure **8f** (1.26 g, 3.38 mmol) gave **9f** as an oil (0.61 g, 59%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, *J* = 7.10 Hz, 3 H), 1.33 (m, 6 H), 1.55 (m, 2 H), 1.91 (m, 2 H), 2.46 (t, *J* = 0.80 Hz, 3 H), 3.37 (t, *J* = 7.37 Hz, 1 H), 3.44 (t, *J* = 6.55 Hz, 2 H), 4.23 (q, *J* = 7.10 Hz, 2 H), 4.56 (s, 2 H), 6.60 (d, J = 3.36 Hz, 1 H), 6.76 (d, *J* = 3.36 Hz, 1 H). *Anal.* Calcd for $C_{17}H_{26}O_5S$: C, 59.62; H, 7.65. Found: C, 59.47; H, 7.64.

Ethyl 5-chloro-2-thiophenemethoxy)hexylmalonate (9g)

By using the preceding procedure **8g** (1.59 g, 4.07 mmol) gave **9g** as an oil (1.25 g, 85%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, *J* = 7.16 Hz, 3 H), 1.35 (m, 6 H), 1.58 (m, 2 H), 1.91 (m, 2 H), 3.37 (t, *J* = 7.47 Hz, 1 H), 3.45 (t, *J* = 6.38 Hz, 2 H), 4.23 (q, *J* = 7.16 Hz, 2 H), 4.54 (s, 2 H), 6.75 (m, 2 H). *Anal.* Calcd for $C_{16}H_{23}O_5ClS$: C, 52.96; H, 6.39. Found: C, 52.54; H, 6.32.

Ethyl 6-(3-chloro-2-thiophenemethoxy)hexylmalonate (9h)

By using the preceding procedure **8h** (1.05 g, 2.69 mmol) gave **9h** as an oil (0.77 g, 79%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, *J* = 7.07 Hz, 3 H), 1.35 (m, 6 H), 1.58 (m, 2 H), 1.91 (m, 2 H), 3.37 (t, *J* = 7.43 Hz, 1 H),

3.47 (t, J = 6.50 Hz, 2 H), 4.23 (q, J = 7.07 Hz, 2 H), 4.63 (s, 2 H), 6.89 (d, J = 5.16 Hz, 1 H), 7.26 (d, J = 5.16 Hz, 1 H). *Anal.* Calcd for $C_{16}H_{23}O_5ClS$: C, 52.96; H, 6.39. Found: C, 52.74; H, 6.35.

Ethyl 6-(5-methoxy-2-thiophenemethoxy)hexylmalonate (9i)

By using the preceding procedure **8i** (340 mg, 0.88 mmol) gave **9i** as an oil (260 mg, 83%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, J = 7.16 Hz, 3 H), 1.32 (m, 6 H), 1.57 (m, 2 H), 1.95 (m, 2 H), 3.42 (m, 3 H), 3.89 (s, 3 H), 4.24 (q, J = 7.16 Hz, 2 H), 4.48 (s, 2 H), 6.03 (d, J = 3.54 Hz, 1 H), 6.60 (d, J = 3.54 Hz, 1 H). *Anal.* Calcd for $C_{17}H_{26}O_6S$: C, 56.96; H, 7.31. Found: C, 56.83; H, 7.38.

Ethyl 6-(5-methyl-2-furanmethoxy)hexylmalonate (9j)

By using the preceding procedure **8j** (3.66 g, 10.27 mmol) gave **9j** as an oil (1.76 g, 52%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, J = 7.08 Hz, 3 H), 1.34 (m, 6 H), 1.58 (m, 2 H), 1.91 (m, 2 H), 2.29 (s, 3 H), 3.37 (t, J = 7.28 Hz, 1 H), 3.45 (t, J = 6.50 Hz, 2 H), 4.24 (q, J = 7.08 Hz, 2 H), 4.37 (s, 2 H), 5.91 (s, 1 H), 6.18 (d, J = 2.46 Hz, 1 H). *Anal.* Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.46; H, 7.94.

Ethyl 2-[6-(2-thiophenoxy)hexyl]-2-methylidenepropionate (10a)

To a tetrahydrofuran (10 mL) suspension of 95% NaH (94 mg, 3.73 mmol) was added a tetrahydrofuran solution (5 mL) of **9a** (650 mg, 2.07 mmol) at 0 °C. The reaction mixture was stirred for 30 min and then Eschenmosher's salt (459 mg, 2.48 mmol) was added to the reaction. The reaction mixture was refluxed for 16 h. The solvent was removed *in vacuo* and the residue was diluted with ethyl acetate (100 mL). The ethyl acetate solution was washed with water (2 × 10 mL) , 1 N-aq. HCl. (2 × 10 mL), 5% aq.-$NaHCO_3$ (2 × 10 mL) and brine (2 × 10 mL), then dried over anhydrous $MgSO_4$. After the solvent was removed *in vacuo*, the residue was purified by column chromatography (SiO_2, ethyl acetate : *n*-hexane = 1 : 5) to gave **10a** as a pale yellow oil (400 mg, 68%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31 (t, J = 7.14 Hz, 3 H), 1.35-1.55 (m, 6 H), 1.80 (m, 2 H), 2.31 (br, 2 H), 4.02 (t, J = 6.46 Hz, 2 H), 4.21 (q, J = 7.14 Hz, 2 H), 5.52 (m, 1 H), 6.13 (d, J = 1.36 Hz, 1 H), 6.19 (dd, J = 1.47, 3.75 Hz, 1 H), 6.53 (dd, J = 1.47, 5.75 Hz, 1 H), 6.71 (dd, J = 3.75, 5.75 Hz, 1 H). *Anal.* Calcd for $C_{15}H_{22}O_3S$: C, 68.80; H, 7.85. Found: C, 68.78; H, 7.92.

Ethyl 2-[6-(2-thiophenemethoxy)hexyl]-2-methylidenepropionate (10b)

By using the preceding procedure **9b** (2.42 g, 7.37 mmol) gave **10b** as an oil (1.82 g, 83%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, J = 7.14 Hz, 3 H), 1.35 (m, 4 H), 1.45 (m, 2H), 1.60 (m, 2 H), 2.29 (m, 2 H), 3.47 (t, J = 6.52 Hz, 2 H), 4.20 (q, J = 7.13 Hz, 2 H), 4.65 (s, 2H), 5.50 (m, 1 H), 6.12 (m, 1 H), 6.96-6.99 (m, 2 H), 7.28 (dd, J = 1.57, 4.65 Hz, 1 H), *Anal.* Calcd for $C_{16}H_{24}O_3S$: C, 64.83; H, 8.16. Found: C, 64.78; H, 8.09.

Ethyl 2-[6-(2-thiopheneethoxy)hexyl]-2-methylidenepropionate (10c)

By using the preceding procedure **9c** (2.08 g, 6.04 mmol) gave **10c** as an oil (880 mg, 47%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, J = 7.14 Hz, 3 H), 1.35 (m, 4 H), 1.47 (m, 2H), 1.58 (m, 2 H), 2.29 (m, 2 H), 3.10 (t, J = 6.70 Hz, 2 H), 3.45 (t, J = 6.51 Hz, 2 H), 3.65 (t, J = 6.70 Hz, 2 H), 4.21 (q, J = 7.14 Hz, 2H), 5.51 (s, 1 H), 6.13 (s, 1 H), 6.85 (br, 1 H), 6.93 (br, 1 H), 7.14 (m, 1 H). *Anal.* Calcd for $C_{17}H_{26}O_3S$: C, 65.77; H, 8.44. Found: C, 65.53; H, 8.39.

Ethyl 2-[6-(3-thiophenemethoxy)hexyl]-2-methylidenepropionate (10d)

By using the preceding procedure **9c** (2.07 g, 6.30 mmol) gave **10d** as an oil (1.24 g, 66%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, J = 7.07 Hz, 3 H), 1.35 (m, 4 H), 1.47 (m, 2H), 1.60 (m, 2 H), 2.29 (m, 2 H), 3.45 (t, J = 6.48 Hz, 2 H), 4.20 (q, J = 7.07 Hz, 2 H), 4.50 (s, 2 H), 5.50 (s, 1 H), 6.12 (s, 1 H), 7.07 (d, J = 4.38 Hz, 1 H), 7.20 (br, 1 H), 7.20 (br, 1 H), 7.28 (m, 1 H). *Anal.* Calcd for $C_{16}H_{24}O_3S$: C, 64.83; H, 8.16. Found: C, 64.68; H, 8.16.

Ethyl 2-[3-thiopheneethoxy)hexyl]-2-methylidenepropionate (10e)

By using the preceding procedure **9e** (3.26 g, 9.46 mmol) gave **10e** as an oil (2.29 g, 78%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, J = 7.13 Hz, 3 H), 1.34 (m, 4 H), 1.47 (m, 2H), 1.58 (m, 2 H), 2.29 (m, 2 H), 2.91 (t, J = 7.0 Hz, 2 H), 3.44 (t, J = 6.63 Hz, 2 H), 3.63 (t, J = 7.0 Hz, 2 H), 4.21 (q, J = 7.13 Hz, 2 H), 6.99 (dd, J = 1.17, 4.90 Hz, 1 H), 7.02 (m, 1 H), 7.25 (dd, J = 3.0, 4.90 Hz, 1 H). *Anal.* Calcd for $C_{17}H_{26}O_3S$: C, 65.77; H, 8.44. Found: C, 65.53; H, 8.43.

Ethyl 2-[6-(5-methyl-2-thiophenemethoxy)hexyl]-2-methylidenepropionate (10f)

By using the preceding procedure **9f** (610 mg, 1.77 mmol) gave **10f** as an oil (2.54 g, 79%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, J = 7.15 Hz, 3 H), 1.22-1.58 (m, 8 H), 2.29 (br, 2 H), 2.46 (d, J = 0.83 Hz, 3 H), 3.44 (t, J = 6.59 Hz, 2 H), 4.20 (q, J = 7.15 Hz, 2 H), 4.56 (s, 2 H), 5.50 (m, 1 H), 6.12 (d, J = 1.56 Hz, 1 H), 6.60 (m, 1 H), 6.76 (d, J = 3.35 Hz, 1 H). *Anal.* Calcd for $C_{17}H_{26}O_3S$: C, 65.77; H, 8.44. Found: C, 65.46; H, 8.35.

Ethyl 2-[6-(5-chloro-2-thiophenemethoxy)hexyl]-2-methylidenepropionate (10g)

By using the preceding procedure **9g** (1.25 g, 3.44 mmol) gave **10g** as an oil (0.90 g, 79%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, J = 7.13 Hz, 3 H), 1.20-1.80 (m, 8 H), 2.29 (br, 2 H), 3.45 (t, J = 6.53 Hz, 2 H), 4.20 (q, J = 7.13 Hz, 2 H), 4.54 (s, 2 H), 5.51 (m, 1 H), 6.13 (d, J = 1.33 Hz, 1 H), 6.74 (d, J = 3.74 Hz, 1 H), 6.77 (d, J = 3.74 Hz, 1 H), *Anal.* Calcd for $C_{16}H_{23}O_3ClS$: C, 58.08; H, 7.01. Found: C, 57.97; H, 6.95.

Ethyl 2-[6-(3-chloro-2-thiophenemethoxy)hexyl]-2-methylidenepropionate (10h)

By using the preceding procedure **9h** (770 mg, 2.12 mmol) gave **10h** as an oil (540 mg, 77%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, J = 7.07 Hz, 3 H), 1.20-1.80 (m, 6 H), 1.91 (m, 2 H), 3.37 (br, 1H), 3.47 (br, 2 H), 4.23 (q, J = 7.07 Hz, 2 H), 4.63 (s, 2 H), 6.89 (d, J = 5.16 Hz, 1 H), 7.26 (d, J = 5.16 Hz, 1 H), *Anal.* Calcd for $C_{16}H_{23}O_3ClS$: C, 58.08; H, 7.01. Found: C, 58.02; H, 7.14.

Ethyl 2-[6-(5-methoxy-2-thiophenemethoxy)hexyl]-2-methylidenepropionate (10i)

By using the preceding procedure **9i** (260 mg, 0.73 mmol) gave **10i** as an oil (200 mg, 84%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, J = 7.13 Hz, 3 H), 1.28-1.57 (m, 8 H), 2.29 (m, 2 H), 3.43 (t, J = 6.62 Hz, 2 H), 3.87 (s, 3H), 4.20 (q, J = 7.13 Hz, 2 H), 4.48 (s, 2 H), 5.50 (d, J = 1.18 Hz, 1 H), 6.03 (d, J = 3.77 Hz, 1 H), 6.12 (s, 1 H), 6.59 (d, J = 3.77 Hz, 1 H), *Anal.* Calcd for $C_{17}H_{26}O_4S$: C, 62.55; H, 8.03. Found C, 62.39; H, 8.10.

Ethyl 2-[6-(5-methyl-2-furanmethoxy)hexyl]-2-methylidenepropionate (10j)

By using the preceding procedure **9j** (1.76 g, 5.36 mmol) gave **10j** as an oil (720 mg, 45%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, J = 7.14 Hz, 3 H), 1.32-1.50 (m, 8 H), 1.44 (m, 2 H), 1.57 (m, 2 H), 2.29 (s, 3 H), 3.45 (t, J = 6.67 Hz, 2 H), 4.20 (q, J = 7.14 Hz, 2 H), 4.37 (s, 2 H), 5.50 (s, 1 H), 5.91 (br, 1 H), 6.12 (s, 1 H), 6.18 (d, J = 2.55 Hz, 1 H). *Anal.* Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.29; H, 8.81.

Ethyl 2-[6-(2-thiophenoxy)hexyl]oxirane-2-carboxylate (13a)

To the acetone-H_2O (1 : 1) solution (12 mL) of NMO (60%, 0.27 mL, 1.56 mmol) and **10a** (400 mg, 1.41 mmol) was added 2.5% *t*-BuOH solution of OsO_4 (0.71 mL, 0.07 mmol). The reaction mixture was stirred for 1.5 h at rt. The excess NMO was quenched by addition of $Na_2S_2O_4$. The solvent was removed *in vacuo* and the residue was diluted with ethyl acetate (100 mL). The ethyl acetate solution was washed with water (2 × 20 mL) and brine (2 × 20 mL), then dried over anhydrous $MgSO_4$. After the solvent was removed *in vacuo*, almost pure diol (**11a,** 440 mg) was obtained and the following tosylation was proceeded without further purification. To a pyridine solution (5 mL) of **11a** (440 mg, 1.40 mmol) was added *p*-toluenesulfonyl chloride (3.0 g, 16 mmol) at 0 °C. The reaction mixture was stirred for 3 h. The excess solvent was removed *in vacuo* and the residue was diluted with ethyl acetate (150 mL). The ethyl acetate solution was washed with 1 N-aq. HCl soln. (2 × 20 mL), 5% aq.-$NaHCO_3$ (2 × 20 mL), water (2 × 20 mL) and brine (2 × 10 mL), then dried over anhydrous $MgSO_4$. The residure was dissolved in anhydrous ethanol (10 mL) and anhydrous K_2CO_3 (1.0 g) was added to the reaction. The reaction mixture was stirred for 6 h at rt. The excess K_2CO_3 was removed by filtration and the excess ethanol was removed *in vacuo*. The residue was diluted with ethyl acetate (100 mL). The ethyl acetate solution was washed with water (2 × 20 mL) and brine (2 × 20 mL), then dried over anhydrous $MgSO_4$. After the solvent was removed *in vacuo*, the residue was purified by column chromatography (SiO_2, ethyl acetate : *n*-hexane = 1 : 5) to give **13a** as a colorless oil (360 mg, 85 %). ^{1}H NMR

($CDCl_3$, 300 MHz) δ 1.29 (t, J = 7.13 Hz, 3 H), 1.30-1.80 (m, 9 H), 2.11 (m, 1 H), 2.78 (d, J = 5.90 Hz, 1 H) 3.03 (d, J = 5.90 Hz, 1 H), 4.02 (t, J = 6.44 Hz, 2 H), 4.20 (q, J = 7.13 Hz, 2 H), 6.19 (dd, J = 1.45, 3.75 Hz, 1 H), 6.53 (dd, J = 1.45, 5.75 Hz, 1 H), 6.71 (dd, J = 3.75, 5.75 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.10 24.65, 25.65, 28.99, 29.13, 31.12, 51.83, 56.97, 61.58, 73.74, 104.50, 111.67, 124.65, 165.72, 170.39. MS (EI) m/z 298 [M^+]; HRMS (EI) 298.122 72 [M^+] (calcd for $C_{15}H_{22}O_4S$ 298.123 96). *Anal.* Calcd for $C_{15}H_{22}O_4S$: C 60.38; H, 7.43. Found: C, 60.15; H, 7.37.

Ethyl 2-[6-(2-thiophenemethoxy)hexyl]oxirane-2-carboxylate (13b)

By using the preceding procedure **10b** (1.82 g, 6.14 mmol) gave **13b** as an oil (1.65 g, 86%). ^1H NMR ($CDCl_3$ 300 MHz) δ 1.29 (t, J = 7.16 Hz, 3 H), 1.30-1.50 (m, 6 H), 1.54-1.70 (m, 3 H), 2.08 (m, 1 H), 2.78 (d, J = 5.93 Hz, 1 H), 3.02 (d, J = 5.93 Hz, 1 H), 3.46 (t, J = 6.50 Hz, 2 H), 4.22 (q, J = 7.16 Hz, 2 H), 4.65 (s, 2 H), 6.95-6.99 (m, 2 H), 7.28 (dd, J = 1.58, 4.79 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.13, 24.72, 25.93, 29.32, 29.50 31.17, 51.84, 57.04, 61.59, 67.31, 70.00, 125.63, 126.15, 126.58, 141.45, 170.45. MS (EI) m/z 312 [M^+] HRMS (EI) 312.140 21 [M^+] (calcd for $C_{16}H_{24}O_4S$ 312.139 62). *Anal.* Calcd for $C_{16}H_{24}O_4S$: C, 61.51; H, 7.74 Found: C, 61.39; H, 7.68.

Ethyl 2-[6-(2-thiopheneethoxy)hexyl]oxirane-2-carboxylate (13c)

By using the preceding procedure **10c** (880 mg, 7.37 mmol) gave **13c** as an oil (574 mg, 62%). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, J = 7.13 Hz, 3 H), 1.30-1.70 (m, 9 H), 2.08 (m, 1 H), 2.77 (d, J = 5.90 Hz, 1 H), 3.02 (d, J = 5.90 Hz, 1 H), 3.08 (t, J = 6.81 Hz, 2 H), 3.44 (t, J = 6.52 Hz, 2 H), 3.64 (t, J = 6.81 Hz, 2 H), 4.21 (q, J = 7.13 Hz, 2 H), 6.84 (dd, J = 1.04, 3.58 Hz, 1 H), 6.92 (dd, J = 3.58, 5.08 Hz, 1 H), 7.13 (dd, J = 1.04, 5.08 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.01, 24.62, 25.84, 29.21, 29.42, 30.36, 31.06, 51.71, 56.91, 61.45, 70.83, 71.25, 123.46, 124.90, 124.49, 141.29, 170.31. MS (EI) m/z 326 [M^+]; HRMS (EI) 326.154 92 [M^+] (calcd for $C_{17}H_{26}O_4S$ 326.155 28). *Anal.* Calcd for $C_{17}H_{26}O_4S$: C, 62.55; H, 8.03. Found: C, 61.98; H, 8.32.

Ethyl 2-[6-(3-thiophenemethoxy)hexyl]oxirane-2-carboxylate (13d)

By using the preceding procedure **10d** (1.24 g, 4.18 mmol) gave **13d** as an oil (1.01 g, 78%). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, J = 7.13 Hz, 3 H), 1.36 (m, 6 H), 1.60 (m, 3 H), 2.06 (m, 1 H), 2.77 (d, J = 5.90 Hz, 1 H), 3.02 (d, J = 5.90 Hz, 1 H), 3.44 (t, J = 6.55 Hz, 2 H), 4.21 (q, J = 7.13 Hz, 2 H), 4.50 (s, 2 H), 7.07 (br, 1 H), 7.20 (br, 1 H), 7.30 (dd, J = 1.97, 4.82 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.06, 24.66, 25.92, 29.27, 29.51, 31.11, 51.75, 56.96, 61.50, 68.04, 70.19, 122.46, 125.81, 127.24, 139.74, 170.37. MS (EI) m/z 312 [M^+]; HRMS (EI) 312.140 50 [M^+] (calcd for $C_{16}H_{24}O_4S$ 312.139 62). *Anal.* Calcd for $C_{16}H_{24}O_4S$: C, 61.51; H, 7.74. Found: C, 61.35; H, 7.86.

Ethyl 2-[3-thiopheneethoxy)hexyl]oxirane-2-carboxylate (13e)

By using the preceding procedure **10e** (2.29 g, 7.33 mmol) gave **13e** as an oil (1.80 mg, 87%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, J = 7.16 Hz, 3 H), 1.30-1.70 (m, 9 H), 2.10 (m, 1 H), 2.78 (d, J = 5.92 Hz, 1 H), 2.91 (t, J = 7.10 Hz, 2 H), 3.03 (d, J = 5.92 Hz, 1 H), 3.43 (t, J = 6.59 Hz, 2 H), 3.62 (t, J = 7.10 Hz, 2 H), 4.22 (q, J = 7.16 Hz, 2 H), 6.98 (dd, J = 1.34, 4.90 Hz, 1 H), 7.02 (m, 1 H), 7.26 (dd, J = 2.99, 4.90 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.02, 24.62, 25.87, 29.23, 29.45, 30.63, 31.07, 51.73, 56.93, 61.48, 70.80, 70.86, 120.91, 125.04, 128.39, 139.24, 170.34. MS (EI) m/z 326 [M^+]; HRMS (EI) 326.154 10 [M^+] (calcd for $C_{17}H_{26}O_4S$ 326.155 28). *Anal.* Calcd for $C_{17}H_{26}O_4S$: C, 62.55; H, 8.03. Found: C, 62.49; H, 8.02.

Ethyl 2-[6-(5-methyl-2-thiophenemethoxy)hexyl]oxirane-2-carboxylate (13f)

By using the preceding procedure **10f** (196 mg, 0.63 mmol) gave **13f** as an oil (144 mg, 70%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, J = 7.14 Hz, 3 H), 1.30-1.70 (m, 9 H), 2.08 (m, 1 H), 2.46 (s, 3 H), 2.78 (d, J = 5.98 Hz, 1 H), 3.02 (d, J = 5.98 Hz, 1 H), 3.44 (t, J = 6.57 Hz, 2 H), 4.22 (q, J = 7.14 Hz, 2 H), 4.56 (s, 2 H), 6.60 (m, 1 H), 6.76 (d, J = 3.35 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.13, 14.72, 24.72, 25.93, 29.32, 29.50, 31.17, 51.84, 57.04, 61.59, 67.31, 70.00, 125.63, 126.58, 141.45, 142.12, 170.45. MS (EI) m/z 326 [M^+]; HRMS (EI) 326.155 10 [M^+] (calcd for $C_{17}H_{26}O_4S$ 326.155 28). *Anal.* Calcd for $C_{17}H_{26}O_4S$: C, 62.55; H, 8.03. Found: C, 62.39; H, 8.34.

Ethyl 2-[5-chloro-2-thiophenemethoxy)hexyl]oxirane-2-carboxylate (13g)

By using the preceding procedure **10g** (900 mg, 2.72 mmol) gave **13g** as an oil (774 mg, 82%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, J = 7.13 Hz, 3 H), 1.45 (m, 6 H), 1.77 (m, 3 H), 2.11 (m, 1 H), 2.78 (d, J = 5.91 Hz, 1 H), 3.03 (d, J = 5.86 Hz, 1 H), 4.02 (t, J = 6.44 Hz, 2 H), 4.20 (q, J = 7.13 Hz, 2 H), 6.19 (dd, J = 1.44, 3.75 Hz, 1 H), 6.53 (dd, J = 1.45, 5.75 Hz, 1 H), 6.71 (dd, J = 3.76, 5.75 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.10, 24.68, 25.88, 29.27, 29.44, 31.14, 51.79, 56.99, 61.54, 67.53, 70.07, 125.27, 125.52, 129.91, 140.48, 170.40. MS (EI) m/z 346 [M^+]; HRMS (EI) 346.098 72 [M^+] (calcd for $C_{16}H_{23}O_4ClS$ 346.100 69). *Anal.* Calcd for $C_{16}H_{23}O_4ClS$: C, 55.40; H, 6.68. Found: C, 55.32; H, 6.75.

Ethyl 2-[6-(3-chloro-2-thiophenemethoxy)hexyl]oxirane-2-carboxylate (13h)

By using the preceding procedure **10h** (540 mg, 1.63 mmol) gave **13h** as an oil (487 mg, 86%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, J = 7.13 Hz, 3 H), 1.37 (m, 6 H), 1.60 (m, 3 H), 2.08 (m, 1 H), 2.77 (d, J = 5.91 Hz, 1 H), 3.02 (d, J = 5.91 Hz, 1 H), 3.49 (t, J = 6.51 Hz, 2 H), 4.22 (q, J = 7.13 Hz, 2 H), 4.63 (s, 2 H), 6.89 (d, J = 5.30 Hz, 1 H), 7.26 (d, J = 5.30 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.09, 24.68, 25.85, 29.25, 29.41, 31.14, 51.77, 56.99, 61.53, 64.80, 70.34, 123.41, 124.67, 127.46, 134.10, 170.39. MS (EI) m/z 346 [M^+]; HRMS (EI) 346.101 55 [M^+] (calcd for $C_{16}H_{23}O_4ClS$ 346.100 69). *Anal.* Calcd for $C_{16}H_{23}O_4ClS$: C, 55.40; H,

6.68. Found: C, 55.14; H, 6.59.

Ethyl 2-[6-(5-methoxy-2-thiophenemethoxy)hexyl]oxirane-2-carboxylate (13i)

By using the preceding procedure **10i** (200 mg, 0.61 mmol) gave **13i** as an oil (157 mg, 75%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, J = 7.14 Hz, 3 H), 1.30-1.80 (m, 9 H), 2.07 (m, 1 H), 2.77 (d, J = 5.90 Hz, 1 H), 3.02 (d, J = 5.90 Hz, 1 H), 3.42 (t, J = 6.55 Hz, 2 H), 3.87 (s, 3 H), 4.21 (q, J = 7.14 Hz, 2 H), 4.48 (s, 2 H), 6.03 (d, J = 3.75 Hz, 1 H), 6.60 (d, J = 3.75 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.08, 24.68, 25.91, 29.29, 29.46, 31.14, 51.77, 56.99, 61.15, 61.52, 68.01, 69.54, 102.83, 124.09, 127.40, 166.68, 170.40. MS (EI) m/z 342 [M$^+$]; HRMS (EI) 342.148 56 [M$^+$] (calcd for $C_{17}H_{26}O_5S$ 342.150 18). *Anal.* Calcd for $C_{17}H_{26}O_5S$: C, 59.62; H, 7.65. Found: C, 59.37; H, 7.52.

Ethyl 2-[6-(5-methyl-2-furanmethoxy)hexyl]oxirane-2-carboxylate (13j)

By using the preceding procedure **10j** (720 mg, 2.43 mmol) gave **13j** as an oil (547 mg, 72%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, J = 7.13 Hz, 3 H), 1.30-1.70 (m, 9 H), 2.07 (m, 1 H), 2.28 (s, 3 H), 2.77 (d, J = 5.92 Hz, 1 H), 3.02 (d, J = 5.92 Hz, 1 H), 3.44 (t, J = 6.65 Hz, 2 H), 4.21 (q, J = 7.13 Hz, 2 H), 4.36 (s, 2 H), 5.90 (br, 1 H), 6.17 (d, J = 2.96 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.50, 13.98, 24.58, 25.77, 29.18, 29.32, 31.03, 51.63, 56.87, 61.43, 64.68, 69.93, 105.98, 109.90, 150.01, 152.31, 170.28. MS (EI) m/z 310 [M$^+$]; HRMS (EI) 310.178 59 [M$^+$] (calcd for $C_{17}H_{26}O_5$ 310.178 08). *Anal.* Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.57; H, 8.21.

Biological Assay

The hypoglycemic activity test was performed as follows. Male sprague-Dawley rats (200 - 250 g) were housed in stainess-steel cages in a room maintained at 20-24°C with a 12 h light/dark cycle. The rats received food and water ad libitum except for the specified periods. Diabetes was induced using streptozotocin (STZ).[15,16] After a 24 h-fast, rats were injected intravenously with 45 mg/kg STZ (Sigma Chem Co., St. Louis, MO) which was freshly prepared in a cold 0.1 M citrate buffer (pH 4.5). Antidiabetic effects were studied only using the rats showing serum glucose levels of over 350 mg/dl on day 7 after STZ administration. Vehicle or synthetic compounds (50 mg/kg) dissolved in 5% ethanol-saline were administered orally. Blood samples were obtained 2 h after drug administration and serum glucose concentrations determined using an enzymatic kit from Young-Dong Pharm. Corp (Seoul, Korea).

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