Pergamon

Bioorganic & Medicinal Chemistry 6 (1998) 2133–2138

BIOORGANIC & MEDICINAL CHEMISTRY

Synthesis of 2-[6-(2,4-Dinitrophenoxy)hexyl]oxiranecarboxylic Acid: A Selective Carnitine Palmitoyltransferase-1 Inhibitor

Tracy L. Hutchison and Wayne J. Brouillette*

Department of Chemistry, University of Alabama at Birmingham, Birmingham, Alabama 35294, USA

Received 1 May 1998; accepted 14 July 1998

Abstract—Carnitine palmitoyltransferases 1 and 2 (CPT-1 and CPT-2) catalyze the transfer of long chain fatty acids between carnitine and coenzyme A. Unlike CPT-2, CPT-1 exists in at least two isoforms with different physical and kinetic properties. Liver and skeletal muscle each contain a different isoform of CPT-1. Cardiac muscle contains both isoforms, and the minor component is identical to the isoform found in the liver. 2-[6-(2,4-Dinitrophenoxy)hexyl]oxiranecarboxylic acid (**2**) was reported to be a selective inhibitor for the liver isoform of CPT-1. A synthesis of **2** is described here which involves the reaction of diethyl malonate with 1-bromo-6-phenoxyhexane.

Introduction

Carnitine (**1**, 3-hydroxy-4-trimethylammoniobutyrate) serves as a substrate for a class of enzymes, the carnitine acyltransferases, which catalyze the reversible transfer of an acyl group between an acyl-CoA and the β-hydroxy group of carnitine (Fig. 1). Different carnitine acyltransferases are selective for different acyl chain lengths. The most well understood function of carnitine involves its substrate activity for the long chain acyltransferases, which is required for the transfer of long chain fatty acids into the mitochondrial matrix where they undergo β-oxidation (Fig. 2).[1] Long chain acyl-CoA esters are unable to cross the inner mitochondrial matrix. Rather, the long chain fatty acyl-CoA is esterified to carnitine by carnitine palmitoyltransferase-1 (CPT-1) to produce an acylcarnitine and free CoA. The fatty acylcarnitine is then transported across the inner mitochondrial membrane by the carnitine–acylcarnitine translocase, and it is then converted back to carnitine and the fatty acyl-CoA by carnitine palmitoyltransferase-2 (CPT-2). The fatty acyl-CoA can then enter into β-oxidation for energy production.

CPT-2 appears to exist as a single protein ($\approx$70 kDa) in an individual species.[2] Recently, it has been shown that CPT-1 exists in at least two isoforms that have different physical and kinetic properties. Weis and McGarry have shown that liver and skeletal muscle each contain a single isoform of CPT-1, while the heart contains two isoforms.[3] The major component of heart muscle is identical to the skeletal muscle isoform (M-CPT-1), while the minor component is identical to the liver isoform (L-CPT-1).

The inhibition of CPT-1 has shown potential as a clinical approach to the treatment of non-insulin-dependent diabetes mellitus (NIDDM). NIDDM is characterized by elevated levels of glucose (hyperglycemia) and excess fatty acid oxidation. The excess free fatty acid oxidation allows gluconeogenesis to proceed at elevated rates without utilization of glucose.[4,5] By inhibiting CPT-1, the rate determining step in long chain fatty acid oxidation, the rate of acetyl-CoA production is diminished. This in turn lowers the rate of gluconeogenesis, which allows glucose to be used for energy production in glycolysis, thus lowering hyperglycemia.

Prior to the finding that CPT-1 exists in two isoforms, two glycolic acid derivatives were reported to be irreversible inhibitors of CPT-1. These inhibitors include tetradecylglycidic acid (TDGA)[6] and ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylic acid (Etomoxir).[7,8] Both compounds were found to be effective

*Corresponding author. Tel: 205 934 4747; fax: 205 934 2543.

0968-0896/98/$ - see front matter
PII: S0968-0896(98)00175-8

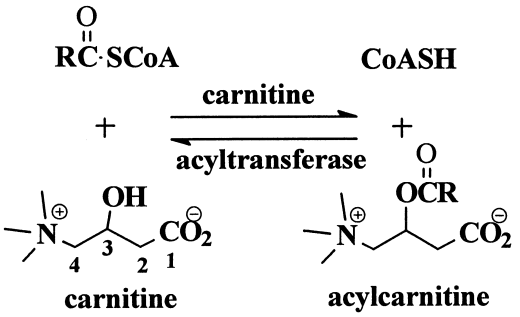


Figure 1. Reaction of carnitine with an acyl-CoA.

hypoglycemic agents in animals. However, neither compound has been developed into a clinical treatment for hyperglycemia, probably because they cause myocardial hypertrophy in animals via the inhibition of M-CPT-1.[9] Recently, two inhibitors selective for the liver isoform of CPT-1 have been identified. One of these, a long chain phosphonate ester of carnitine, was reported to be a reversible, competitive inhibitor of CPT-1 by Anderson et al.[9] The phosphonate did not cause myocardial hypertrophy in vivo and was thus assumed to selectively inhibit L-CPT-1. The other, 2-[6-(2,4-dinitrophenoxy)-hexyl]oxirane-2-carboxylic acid (**2**), was reported to be an irreversible inhibitor selective for L-CPT-1.[3] Previously described glycolic acids (like etomoxir and TDGA) caused myocardial hypertrophy as well as hypoglycemia, and thus were nonselective inhibitors. Here we report a synthesis of **2** from phenol and 1,6-dibromohexane.

Results and Discussion

Chemistry

As shown in Scheme 1, ether **4** was prepared from phenol and excess 1,6-dibromohexane following a procedure used by Diana et al. for the preparation of 1-(2-chloro-4-methoxyphenoxy)-6-bromohexane from 2-chloro-4-methoxyphenol and 1,6-dibromohexane.[10] Simple distillation of the crude reaction mixture provided pure **4**. This intermediate was then converted to **5** by reacting **4** with diethyl malonate and sodium ethoxide following a procedure used by Ho et al. for reacting 1-bromotetradecane with diethyl malonate.[11] Compounds **6** and **7** were also prepared by methods reported by Ho et al. for similar compounds which do not contain the aromatic ring.[11] Hydrolysis of one of the ester groups in **5** with one equivalent of potassium hydroxide in ethanol gave the monoester **6**. The acrylic ester **7** was obtained by reacting **6** with diethylamine and 37% formaldehyde. As a first approach, ester **7** was converted to the ethyl ester analogue of **11** (see Scheme 1), but attempts to hydrolyze the ethyl ester at the end of the synthesis proved to be problematic. Attempted ester hydrolysis under basic conditions displaced the

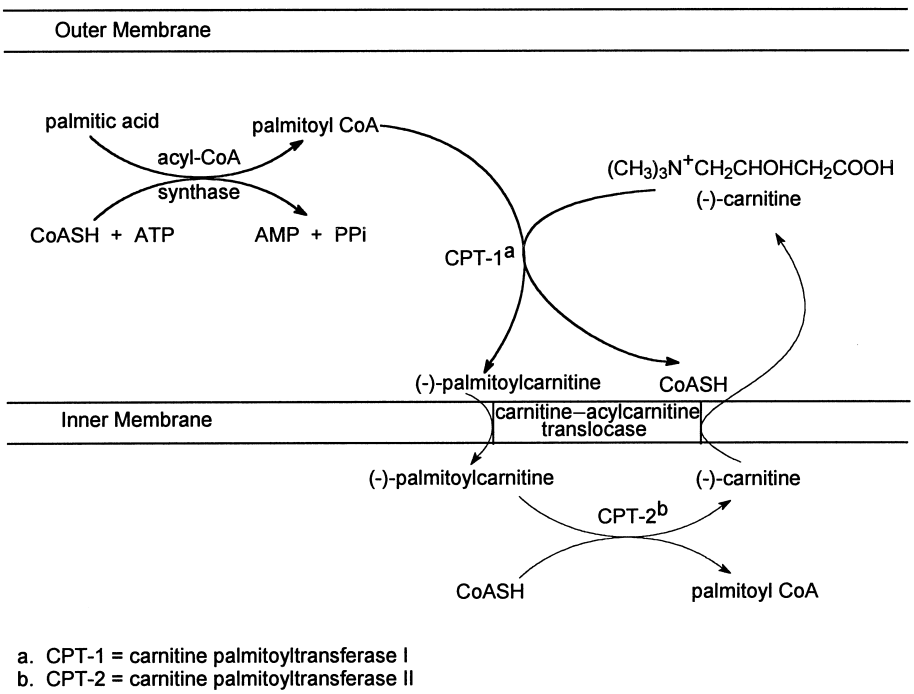
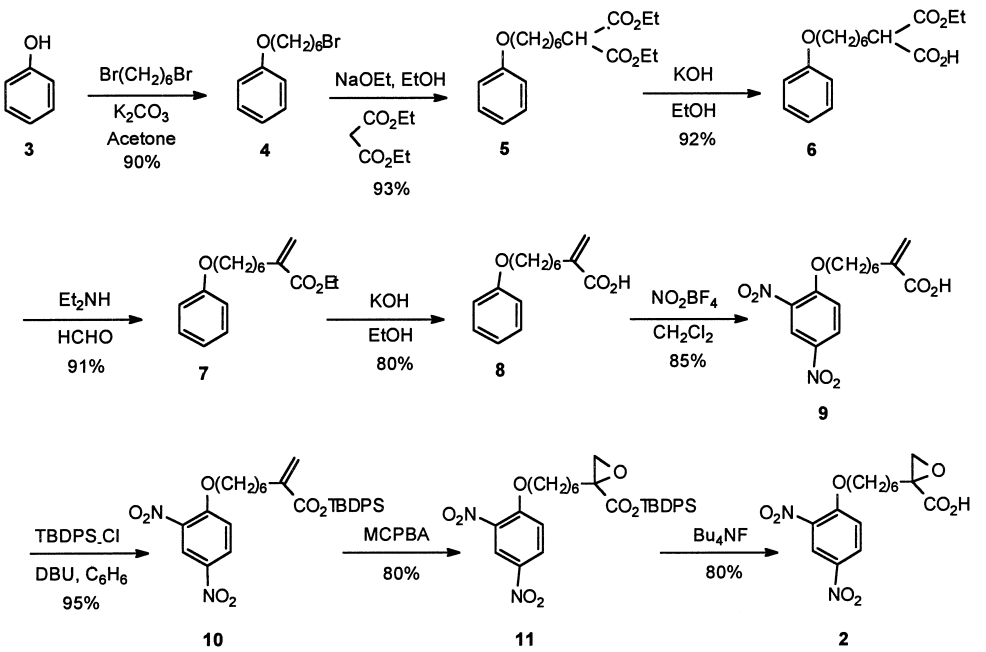


Figure 2. The carnitine pathway.



Scheme 1.

dinitrophenol group, while hydrolysis under acidic conditions opened the epoxide ring. Therefore, ethyl ester **7** was hydrolyzed to provide **8**, which underwent reaction with nitronium tetrafluoroborate[12] to provide **9** as a solid. The *tert*-butyldiphenylsilyl ester, **10**, was then prepared from the corresponding acid and *tert*-butyldiphenylsilyl chloride.[13] This ester was then epoxidized with MCPBA followed by removal of the silyl ester group using tetrabutylammonium fluoride to yield **2**.

Experimental

General

Melting points were determined on an electrothermal melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 or a Bruker ARX-300 spectrometer. Chemical shifts are referenced in ppm downfield from internal TMS for ^{1}H and ^{13}C NMR spectra. IR spectra were obtained on a Bruker Vector 22 FT-IR or a Perkin–Elmer 1310 IR spectrometer. Mass spectra were recorded by electrospray on a Perkin–Elmer Sciex API-III spectrometer. Flash chromatographic separations were on Baker silica gel, 40 μm, and TLC was performed on Whatman brand silica gel plates (250 μm layer, 5×10 cm). HPLC separations were performed using a Rainin Dynamax silica column on a Rainin Rabbit HPLC system. All liquid reagents were distilled prior to use. Ethanol was distilled over magnesium ethoxide, methylene chloride was distilled over phosphorus pentoxide, and tetrahydrofuran was distilled over sodium metal and benzophenone prior to use. Benzene and 1,2-dichloroethane were distilled over calcium hydride. Acetone was dried over potassium permangenate followed by distillation from calcium sulfate. All other solvents were reagent grade, obtained from Fisher Scientific or Aldrich Chemical Company, and were used without further purification. Elemental analyses were performed at Atlantic Microlab of Atlanta, GA.

6-Bromo-1-phenoxyhexane (4). A mixture of phenol (**3**, 22.1 g, 234 mmol), 1,6-dibromohexane (250 mL, 35.1 g, 1.63 mol), anhydrous K_2CO_3 (66.9 g, 400 mmol), and 18-crown-6 (2.00 g, 757 mmol) in acetone (1.00 L) was heated to reflux for 24 h. The reaction mixture was concentrated to dryness and ethyl acetate (200 mL) was added. The ethyl acetate solution was washed with 5% Na_2CO_3 (3×100 mL), saturated NaCl (3×100 mL) and dried (Na_2SO_4). The solvent was removed in vacuo to yield a mixture of **4** and 1,6-dibromohexane (203 g), which was distilled to yield **4** (56.0 g, 90.4%) as an oil: bp 104–106°C/0.2 mm Hg (lit.[14] 126–130 °C/2 mm Hg).

Diethyl 2-(6-phenoxyhexyl)propanedioate (5). Diethyl malonate (6.35 mL, 6.70 g, 41.8 mmol) was added dropwise to a freshly prepared mixture of sodium (0.850 g, 37.0 mmol) in dry ethanol (200 mL) under a nitrogen atmosphere. Compound **4** (7.17 g, 27.9 mmol) was

added rapidly, and the reaction mixture was heated at reflux for 2.5 h. The solvent was removed in vacuo to yield a white residue which was dissolved in H_2O (100 mL) and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with saturated NaCl solution (2×50 mL) and dried (Na_2SO_4). The solvent was removed in vacuo to yield **5** as an oil (7.73 g, 82.4%), which was purified by distillation: bp 173–174 °C/0.4 mm Hg; R_f 0.63 (30% ethyl acetate/70% hexanes); IR (neat) 1732 and 1742 (C=O), 1245 (asymmetric C–O–C), 1033 (symmetric C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, 6H, $CO_2CH_2CH_3$), 1.30–1.50 (m, 6H, $O(CH_2)_2CH_2CH_2CH_2$), 1.70–1.80 (m, 2H, OCH_2CH_2), 1.90–2.00 (m, 2H, $CH_2CH(CO_2Et)_2$), 3.30 (t, 1H, $CH(CO_2Et)_2$), 3.95 (t, 2H, OCH_2), 4.20 (q, 4H, $CO_2CH_2CH_3$), 6.85–6.95 (m, 3H, aromatic), 7.20–7.30 (m, 2H, aromatic); ^{13}C NMR ($CDCl_3$) δ 169.3, 158.9, 129.2, 120.3, 114.3, 67.4, 61.1, 51.8, 28.9, 28.8, 28.5, 27.1, 25.6, 13.9; MS (ES) m/z 337 $(M + H)^+$. Anal. calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.96; H, 8.34.

Ethyl 2-(6-phenoxyhexyl)propanedioate (6). Compound **5** (10.0 g, 29.7 mmol) was suspended in 1 N KOH/ethanol (40.0 mL, 40.0 mmol). The reaction mixture was stirred at 25 °C under a nitrogen atmosphere for 6 h. The solvent was removed in vacuo to yield a white residue which was taken up in H_2O (75 mL) and extracted with ether (3×50 mL). The aq layer was acidified with 5% HCl (pH 2) and extracted with ether (3×50 mL). The combined ether extracts were dried (Na_2SO_4) and the solvent was removed in vacuo to yield **6** as an oil (8.91 g, 97.3%), which was purified by distillation: bp 148–149 °C/0.3 mm Hg; R_f 0.34 (30% ethyl acetate/70% hexanes); IR (neat) 3500–2500 (OH), 1712 and 1737 (C=O), 1245 (asymmetric C–O–C), 1033 (symmetric C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, $CO_2CH_2CH_3$), 1.35–1.40 (m, 4H, $O(CH_2)_3CH_2CH_2$), 1.40–1.50 (m, 2H, $O(CH_2)_2CH_2$), 1.70–1.80 (p, 2H, OCH_2CH_2), 1.90–2.00 (m, 2H, $CHCH_2$), 3.35 (t, 1H, $CH(CO_2Et)(CO_2H)$), 3.95 (t, 2H, OCH_2), 4.20 (q, 2H, OCH_2CH_3), 6.85–6.95 (m, 3H, aromatic), 7.21–7.29 (m, 2H, aromatic); ^{13}C NMR ($CDCl_3$) δ 175.1, 169.5, 159.1, 129.4, 120.5, 114.5, 67.7, 61.7, 51.8, 29.2, 29.0, 28.8, 27.2, 25.8, 14.1; MS (ES) m/z 265 $(M\text{-}CO_2)^+$. Anal. calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.29; H, 7.92.

Ethyl 2-methylene-8-phenoxyoctanoate (7). Compound **6** (6.90 g, 22.4 mmol) was added to a mixture of diethylamine (10.0 mL, 7.07 g, 96.7 mmol) and 37% formaldehyde (18.0 mL, 239 mmol) under a nitrogen atmosphere. The mixture was heated to reflux for 30 min, diluted with H_2O (50 mL), and extracted with ether (3×50 mL). The combined ether layers were washed with 5% HCl (3×50 mL), saturated NaCl (2×50 mL), and dried (Na_2SO_4); then the solvent was removed in vacuo to yield **7** as an oil (5.69 g, 91.9%), which was purified by distillation: bp 132–133 °C/0.2 mm Hg; R_f 0.71 (30% ethyl acetate/70% hexanes); IR (neat) 1710 (C=O), 1620 (C=C), 1240 (asymmetric C–O–C), 1030 (symmetric C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, OCH_2CH_3), 1.50–1.35 (m, 6H, $O(CH_2)_2CH_2CH_2CH_2$) 1.72–1.81 (m, 2H, OCH_2CH_2), 2.31 (t, 2H, $CH_2C(=C)CO_2Et$), 3.95 (t, 2H, OCH_2), 4.20 (q, 2H, $CO_2CH_2CH_3$), 5.51 (dd, 1H, $C=CH_2$), 6.15 (d, 1H, $C=CH_2$), 6.95–6.85 (m, 3H, aromatic), 7.23–7.31 (m, 2H, aromatic); ^{13}C NMR ($CDCl_3$) δ 167.3, 159.1, 141.0, 129.3, 124.1, 120.4, 114.5, 67.7, 60.5, 31.7, 29.2, 28.9, 28.3, 25.8, 14.2; MS (ES) m/z 277 $(M+H)^+$. Anal. calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.98; H, 8.78.

2-Methylene-8-phenoxyoctanoic acid (8). A mixture of 2.0 N KOH/ethanol (10.0 mL, 20.0 mmol) and **7** (1.40 g, 5.07 mmol) was stirred at 25 °C for 8 h. The solvent was removed in vacuo to yield a white residue which was dissolved in H_2O (50 mL) and extracted with ethyl acetate (3×25 mL). The aqueous layer was acidified (pH 3) with 5% HCl and extracted with ethyl acetate (3×25 mL). The combined organic extracts were washed with saturated NaCl (3×25 mL) and dried (Na_2SO_4). The solvent was removed in vacuo to yield **8** as a white solid (1.12 g, 88.9%): mp 53–54 °C (benzene); R_f 0.44 (30% ethyl acetate/70% hexanes); IR (KBr) 3500–2500 (OH), 1693 (C=O), 1625 (C=C), 1250 (asymmetric C–O–C), 1034 (symmetric C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35–1.42 (m, 2H, $O(CH_2)_3CH_2$), 1.42–1.60 (m, 4H, $O(CH_2)_2CH_2$ and $O(CH_2)_4CH_2$), 1.73–1.82 (p, 2H, OCH_2CH_2), 2.32 (t, 2H, $O(CH_2)_5CH_2$), 3.95 (t, 2H, OCH_2), 5.65 (d, 1H, $C=CH_2$), 6.28 (s, 1H, $C=CH_2$), 6.85–6.95 (m, 3H, aromatic), 7.25–7.29 (m, 2H, aromatic); ^{13}C NMR ($CDCl_3$) δ 172.3, 159.1, 140.1, 129.4, 127.0, 120.5, 114.5, 67.8, 31.5, 29.2, 29.0, 28.3, 25.9; MS (ES) m/z 248 $(M+H)^+$. Anal. calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.45; H, 8.15.

2-Methylene-8-(2,4-dinitrophenoxy)octanoic acid (9). Compound **8** (2.00 g, 8.10 mmol) in anhydrous CH_2Cl_2 (200 mL) was cooled under a nitrogen atmosphere in an ice bath for 30 min. NO_2BF_4 (6.81 g, 51.3 mmol) was added to the cooled reaction mixture. After 1 h, the reaction was quenched with cold H_2O (50 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were washed with saturated NaCl (2×50 mL) and dried (Na_2SO_4). The solvent was removed in vacuo to yield **9** as a yellow solid (2.55 g, 93.8%): mp 93–94 °C (ether); R_f 0.45 (90% CH_2Cl_2/9% hexanes/1% HOAc); IR (KBr) 3250–2500 (OH), 1694 (C=O), 1627 (C=C), 1518 (asymmetric N···O), 1349 (symmetric N···O), 1073 (symmetric C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35–1.43 (m, 2H, $O(CH_2)_3CH_2$),

1.49–1.58 (m, 4H, $O(CH_2)_2CH_2$ and $O(CH_2)_4CH_2$), 1.85–1.95 (p, 2H, OCH_2CH_2), 2.32 (t, 2H, $O(CH_2)_5CH_2$), 4.25 (t, 2H, OCH_2), 5.65 (d, 1H, $C=CH_2$), 6.28 (d, 1H, $C=CH_2$), 7.19 (d, 1H, aromatic H-6), 8.45 (dd, 1H, aromatic H-5), 8.75 (d, 1H, aromatic H-3); ^{13}C NMR ($CDCl_3$) δ 171.96, 156.90, 139.99, 139.82, 129.01, 127.19, 121.88, 114.23, 70.82, 31.41, 28.65, 28.59, 28.23, 25.49; MS (ES) *m/z* 338 $(M+H)^+$. Anal. calcd for $C_{15}H_{18}N_2O_7$: C, 53.25; H, 5.36; N, 8.28. Found: C, 53.15; H, 5.18; N, 8.09.

***tert*-Butyldiphenylsilyl 2-methylene-8-(2,4-dinitrophenoxy)octanoate (10).** DBU (0.150 mL, 0.26 g, 1.00 mmol) and *t*-butyldiphenylchlorosilane (0.25 mL, 0.96 mmol) were added to a mixture of **9** (300 mg, 0.890 mmol) in dry benzene (100 mL) under a nitrogen atmosphere. The reaction was stirred at 25 °C for 60 min and quenched with H_2O (80 mL). The organic layer was washed consecutively with 5% HCl (2×50 mL), 5% $NaHCO_3$ (2×50 mL), and saturated NaCl (2×50 mL) and then was dried (Na_2SO_4). The solvent was removed in vacuo to yield **10** (503 mg) as a mixture. The crude mixture was chromatographed on a flash silica gel column (3×34 cm, 30% ethyl acetate/hexanes) to first provide a mixture (95 mg) of **10** and unreacted *t*-butyldiphenylchlorosilane. Further elution gave **10** (380 mg, 74.3%) as a light-yellow solid: mp 87–89 °C; R_f 0.67 (30% ethyl acetate/hexanes); IR (KBr) 1692 (C=O), 1607 (C=C), 1530 (asymmetric N···O), 1345 (symmetric N···O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 9H, $SiC(CH_3)_3$), 1.35–1.42 (m, 2H, $O(CH_2)_3CH_2$), 1.45–1.55 (m, 4H, $O(CH_2)_2CH_2$ and $O(CH_2)_4CH_2$), 1.80–1.90 (p, 2H, OCH_2CH_2), 2.35 (t, 2H, $O(CH_2)_5CH_2$), 4.18 (t, 2H, OCH_2), 5.68 (d, 1H, $C=CH_2$), 6.37 (d, 1H, $C=CH_2$), 7.12 (d, 1H, aromatic), 7.31–7.42 (m, 6H, aromatic), 7.65–7.71 (dd, 4H, aromatic), 8.38 (dd, 1H, aromatic), 8.72 (d, 1H, aromatic); ^{13}C NMR ($CDCl_3$) δ 166.31, 156.87, 141.93, 139.94, 135.30, 131.97, 130.06, 128.97, 127.73, 125.93, 121.83, 114.21, 77.22, 70.79, 31.87, 28.69, 28.54, 28.46, 26.96, 25.41, 19.28; MS (ES) *m/z* 594 $(M+NH_4)^+$; Anal. calcd for $C_{31}H_{36}N_2O_7Si$: C, 64.56; H, 6.31; N, 4.86. Found: C, 64.33; H, 6.18, N, 4.78.

***tert*-Butyldiphenylsilyl 2-[6-(2,4-dinitrophenoxy)hexyl]oxiranecarboxylate (11).** Compound **10** (770 mg, 1.34 mmol) in dry 1,2-dichloroethane (60.0 mL) was combined with MCPBA (1.45 g, 8.40 mmol) and 3-*tert*-butyl-4-hydroxy-5-methyl-phenylsulfide (31.0 mg, 0.0865 mmol) and heated to 60 °C for 14 h. The heating was stopped and the reaction mixture was cooled to room temperature followed by cooling in an ice bath. The cold solution was washed with cold 5% Na_2CO_3 (3×50 mL) and saturated NaCl (2×50 mL) and then dried (Na_2SO_4). The solvent was removed in vacuo to yield **11** (760 mg, 96%) as an oily solid. IR (KBr) 1707 (C=O), 1608 (C=C), 1536 (asymmetric N···O), 1343 (symmetric N···O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 9H, Si-C(CH_3)$_3$, 1.31–1.42 (m, 2H, $O(CH_2)_3CH_2$), 1.43–1.62 (m, 4H, $O(CH_2)_2CH_2$ and $O(CH_2)_4CH_2$), 1.82–1.89 (p, 2H, OCH_2CH_2), 2.34 (t, 2H, $O(CH_2)_5CH_2$), 4.19 (t, 2H, OCH_2), 5.66 (d, 1H, $C=CH_2$), 6.34 (d, 1H, $C=CH_2$), 7.13 (d, 1H, aromatic), 7.34–7.44 (m, 6H, aromatic), 7.67–7.69 (dd, 4H, aromatic), 8.37 (dd, 1H, aromatic), 8.72 (d, 1H, aromatic); ^{13}C NMR ($CDCl_3$) δ 168.06, 157.25, 142.31, 135.68, 132.35, 130.44, 129.35, 128.11, 126.31, 122.22, 114.59, 71.17, 32.25, 29.07, 28.92, 28.84, 27.34, 25.78; MS (ES) *m/z* 592 (M−H). Anal. calcd for $C_{31}H_{36}N_2O_8Si$: C, 62.82; H, 6.13; N, 4.72. Found: C: 63.06; H, 6.21; N, 4.89.

2-[6-(2,4-Dinitrophenoxy)hexyl]oxiranecarboxylic acid (2). Tetrabutylammonium fluoride (0.50 mL, 1.0 M in anhydrous THF, 0.50 mmol) was added to a mixture of **11** (140 mg, 0.24 mmol) in dry THF (2.0 mL). This mixture was stirred at 0 °C for 30 min. The solvent was removed under vacuum, ethyl acetate (20 mL) was added, and the mixture was washed with cold 5% $NaHCO_3$ (3×10 mL). The combined $NaHCO_3$ extracts were cooled in ice and acidified with cold 5% HOAc (pH 4). The acidic solution was extracted with ethyl acetate (3×20 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo to yield **2** (62 mg, 74%) as a solid: mp 101–103 °C (CH_3OH/ether); ^1H NMR (MeOH-d_4) δ 1.41–1.73 (m, 7H, hexyl H-1a, H-2, H-3, H-4), 1.86 (p, 2H, hexyl H-5), 2.10–2.23 (m, 1H, hexyl H-1b), 2.73 (d, 1H, OCH_2), 2.93 (d, 1H, OCH_2), 4.35 (t, 2H, hexyl H-6), 7.41 (d, 1H, aromatic), 8.43 (dd, 1H, aromatic), 8.84 (d, 1H, aromatic); ^{13}C NMR (MeOH-d_4) 174.08, 157.98, 141.36, 130.09, 127.33, 122.30, 116.21, 71.93, 58.08, 52.63, 32.26, 30.05, 29.62, 26.58, 25.84; MS *m/z* 353 (M−H); Anal. calcd. for $C_{15}H_{18}N_2O_8$: C, 50.84; H, 5.13; N, 7.90. Found: C, 51.15; H, 5.28; N, 8.14.

References

1. Bremer, J. *Physiol. Rev.* **1983**, *63*, 1420.
2. Weis, B. C.; Esser, V.; Foster, D. W.; McGarry, J. D. *J. Biol. Chem.* **1994**, *269*, 18712.
3. Weis, B. C.; Cowan, A. T.; Brown, N.; Foster, D. W.; McGarry, J. D. *J. Biol. Chem.* **1994**, *269*, 26443.
4. DeFronzo, R. A. *Diabetes* **1988**, *5*, 271.
5. Golay, A.; Swislocki, A.; Chen, Y.-Di. I.; Reaven, G. M. *Metabolism* **1987**, *36*, 692.
6. Tutwiler, G. F.; Ho, W.; Mohrbacher, R. J. *Methods Enzymol.* **1981**, *72*, 533.
7. Lilly, K.; Chuang, C.; Kerner J.; VanRenterghern R.; Bieber, L. L. *Biochem. Pharmacology* **1992**, *43*, 353.
8. Lopaschuk, G. D.; McNeil, G. F.; McVeigh, J. J., *Mol. Cell. Biochem.* **1989**, *88*, 175.

9. Anderson, R. C.; Balestra, M.; Bell, R. A.; Deems, R. O.; Fillers, W. S.; Foley, J. E.; Fraser, J. D.; Mann, W. R.; Rudin, M.; Villhauer, E. B. *J. Med. Chem.* **1995**, *38*, 3448.

10. Diana, G. D., Salvador, J.; Xalay, E. S.; Carabateas, P. M.; Williams, G. L.; Collins, J. C.; Pancid, F. *J. Med. Chem.* **1977**, *20*, 757.

11. Ho, W.; Tutwiler, G. F.; Cottrell, S. C.; Morgans, D. J.; Tarhan, O.; Mohrbacher, R. J. *J. Med. Chem.* **1986**, *29*, 2184.

12. Prakash, G. K.; Wang, Q.; Li, X.; Olah, G. A. *Helv. Chem. Acta* **1990**, *73*, 1167.

13. Davis, J. T.; Moore, R. N.; Imperiali, B.; Pratt, A. J.; Kobayashi, K.; Masamune, S.; Sinskey, A. J.; Walsh, C. T. *J. Biol. Chem.* **1987**, *262*, 82.

14. Illuminati, G.; Mandolini, L.; Masci, B. *J. Org. Chem.* **1974**, *39*, 2598.