Convenient synthesis of cationic glycerolipids *via* methylthiomethyl ethers

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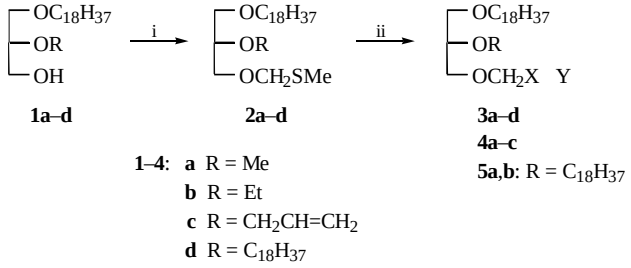
Glycerol ether lipids containing various positively charged groups have been prepared *via* corresponding methylthiomethyl ethers.

The biological activity of positively charged non-phosphorus glycerolipids, which contain both various aliphatic residues in the hydrophobic domain and polar groups, is well known.[1] Cationic lipids exhibit antitumor activity due to the inhibition of protein kinase C and diacylglycerokinase;[1] they inhibit replication of the HIV-1 virus[1] and are effective antagonists of the platelet activating factor.[1,2] In the last decade different cationic lipids have been synthesised for the purpose of gene therapy.[3,4] The genetic modification of somatic cells with cationic lipids is an alternative route to viral-mediated gene therapy and has some advantages such as safety and simplicity. Therefore, the preparation of new types of cationic lipids and the investigation of structure–activity relationships seems to be promising for bioorganic chemistry.

Although several approaches to the introduction of positively charged heads to lipids, which are based on the alkylation of either tertiary amines with 3-bromo-3-deoxy-,[5–7] 3-*O*-methanesulfonyl-[7] and 3-*O*-toluenesulfonyl-substituted[7] 1,2-dialkylglycerols or O-substituted 3-(dimethylamino)-1,2-propanediol with short-chain alkyl halides,[4,8] are widely used, the yields of desirable products are low. This fact can be explained by the elimination of outgoing groups and by steric hindrances. In early reports,[9,10] metylthiomethyl (MTM) ethers have been recommended as protective groups for the hydroxyl function because of their stability and selective cleavage under certain conditions. More recently, MTM ethers were employed in nucleoside[11] and lipid[12] chemistry. To increase the yields, we propose herein a convenient procedure for the preparation of positively charged glycerolipids *via* corresponding MTM ethers (Scheme 1).

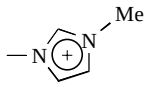
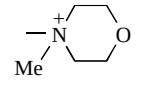
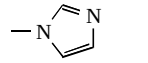
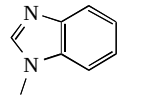


Scheme 1 *Reagents and conditions*: i, DMSO–Ac_2O–AcOH, benzene, 24 °C, 2–5 days; ii, XH or X, dichloroethane, 24 °C, 10–30 min.

In the synthesis of compounds **2**, initial 1,2-dialkylglycerols **1** were treated with a mixture of DMSO, acetic anhydride and acetic acid (the molar ratio 6.5:3.4:1) as described previously,[9,12] and the mixture was kept from two to five days. MTM ethers were purified using chromatography on silica gel. The yields were generally equal to 50–61%. The ^{1}H NMR spectra exhibited characteristic signals of MTM groups, *viz.*, singlets at 2.12–2.15 and 4.64–4.68 ppm for SMe and OCH_2S, respectively.

The treatment of MTM ethers (highly reactive asymmetric O,S-acetals) with bromine gives α-bromo ethers, which can be easily displaced with various nucleophiles. The reaction of MTM derivatives **2** with different secondary (XH) or tertiary (X) heterocyclic amines (Table 1) in the presence of bromine afforded cationic lipids **3**–**5** in 90–98% yields. The limitation of the proposed method was demonstrated with lipid **2c**, whose allylic group can interact with bromine. The yields of compounds **3c** and **4c** were no higher than 45%.

Table 1 Synthesised compounds.

Compound	R	X	Y	Yield (%)
3a	Me		Br$^-$	97
3b	Et			97
3c	$CH_2CH=CH_2$			45
3d	$C_{18}H_{37}$			96
4a	Me		Br$^-$	92
4b	Et			91
4c	$CH_2CH=CH_2$			35
5a	$C_{18}H_{37}$			92
5b				80

In a typical procedure, to a solution of MTM ether **2a**–**d** (0.1 mmol) in 1 ml of anhydrous dichloroethane, a corresponding amine (0.5 mmol) and, after 5 min, an excess of bromine (0.12–0.15 mmol) were added at room temperature. The reaction mixture was stirred for 10–30 min. After the removal of the organic solvent in a vacuum, volatile amine traces were additionally removed at a reduced pressure (0.5 Torr). The resulting lipid was purified by chromatography on silica gel.

^{1}H NMR spectroscopy, mass spectrometry and elemental analysis data for all of the novel compounds are in accordance with the assigned structures.†

† **3a**: ^{1}H NMR (Bruker MSL-200, 200 MHz, $CDCl_3$, $SiMe_4$ as an internal standard) δ: 0.85 [t, 3H, $(CH_2)_{15}CH_3$, *J* 6.8 Hz], 1.22 [br. s, 30H, $(CH_2)_{15}$Me], 1.50 (m, 2H, OCH_2CH_2), 3.35–3.49 (m, 8H, OCH_2CH_2, $CH_2OC_{18}H_{37}$, CHOMe, OMe), 3.68 (dd, 1H, *J* 5.1 and 10.7 Hz) and 3.83 (dd, 1H, CH_2O, *J* 3.0 and 10.7 Hz), 4.10 (s, 3H, N^+Me), 5.81 (dd, 2H, OCH_2N^+, *J* 10.2 and 13.2 Hz), 7.29 and 7.44 (m, 2H, –CH=CH), 10.59 (m, 1H, –CH=N). MS (Vision 2000 time-of-flight mass spectrometer with matrix-assisted laser desortion ionization), *m*/*z*: 452.6, [M – Br]$^+$.

3b: ^{1}H NMR, δ: 0.84 [t, 3H, $(CH_2)_{15}CH_3$, *J* 6.8 Hz], 1.14 (t, 3H, OCH_2CH_3, *J* 7.0 Hz), 1.21 [br. s, 30H, $(CH_2)_{15}$Me], 1.49 (m, 2H, OCH_2CH_2), 3.32–3.43 (m, 4H, OCH_2CH_2, $CH_2OC_{18}H_{37}$), 3.49–3.61 (m, 3H, CHOEt, OCH_2Me), 3.68 (dd, 1H, *J* 5.1 and 10.7 Hz) and 3.83 (dd, 1H, CH_2O, *J* 3.0 and 10.7 Hz), 4.10 (s, 3H, N^+Me), 5.79 (dd, 2H, OCH_2N^+, *J* 10.3 and 12.6 Hz), 7.36 and 7.46 (m, 2H, –CH=CH), 10.49 (m, 1H, –CH=N). MS, *m*/*z*: 466.4 [M – Br]$^+$.

3c: ^{1}H NMR, δ: 0.85 [t, 3H, $(CH_2)_{15}CH_3$, *J* 6.8 Hz], 1.22 [br. s, 30H, $(CH_2)_{15}$Me], 1.50 (m, 2H, OCH_2CH_2), 3.35–3.50 (m, 5H, OCH_2CH_2, $CH_2OC_{18}H_{37}$, CHOAll), 3.63–3.81 (m, 2H, CH_2O), 4.00 (m, 2H, OCH_2–CH=CH_2), 4.08 (s, 3H, N^+Me), 5.19 (m, 2H, OCH_2–CH=CH_2), 5.80 (m, 3H, OCH_2N^+, OCH_2CH=CH_2), 7.26 and 7.44 (m, 2H, –CH=CH), 10.61 (m, 1H, –CH=N). MS, *m*/*z*: 479.6 [M – Br]$^+$.

3d: ^{1}H NMR, δ: 0.85 [t, 6H, $2(CH_2)_{15}CH_3$, *J* 6.4 Hz], 1.23 [br. s, 60H, $2(CH_2)_{15}$Me], 1.50 (m, 4H, $2OCH_2CH_2$), 3.34–3.57 (m, 7H, $2OCH_2CH_2$, $CH_2OC_{18}H_{37}$, $CHOC_{18}H_{37}$), 3.68 (dd, 1H, CH_2O, *J* 5.2 and 10.0 Hz) and 3.79 (dd, 1H, CH_2O, *J* 3.2 and 10.0 Hz), 4.09 (s, 3H, N^+Me), 5.79 (dd, 2H, OCH_2N^+, *J* 10.2 and 14.5 Hz), 7.27 and 7.42 (m, 2H, –CH=CH), 10.69 (m, 1H, –CH=N). MS, *m*/*z*: 693.1 [M – Br]$^+$.

4a: ^{1}H NMR, δ: 0.84 [t, 3H, $(CH_2)_{15}CH_3$, *J* 6.8 Hz], 1.22 [br. s, 30H, $(CH_2)_{15}$Me], 1.51 (m, 2H, OCH_2CH_2), 3.35–3.48 (m, 8H, OCH_2CH_2, $CH_2OC_{18}H_{37}$, CHOMe, OMe), 3.52 (s, 3H, N^+Me), 3.70 (m, 4H, $2NCH_2CH_2O$), 4.00 (m, 5H, $2NCH_2CH_2O$, CH_2O), 4.15 (dd, 1H, CH_2O, *J* 2.6 and 11.1 Hz), 5.35 (dd, 2H, OCH_2N^+, *J* 7.9 and 20.7 Hz). MS, *m*/*z*: 471.8 [M – Br]$^+$.

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4b: ^{1}H NMR, δ: 0.84 [t, 3H, $(CH_2)_{15}CH_3$, J 6.4 Hz], 1.16 (t, 3H, OCH_2CH_3, J 6.8 Hz), 1.22 [br. s, 30H, $(CH_2)_{15}Me$], 1.50 (m, 2H, OCH_2CH_2), 3.34–3.51 (m, 4H, OCH_2CH_2, $CH_2OC_{18}H_{37}$), 3.53 (s, 3H, N^+Me), 3.58 (q, 1H, OCH_2Me, J 6.8 Hz), 3.60 (m, 1H, $CHOEt$), 3.62 (q, 1H, OCH_2Me, J 6.8 Hz), 3.71 (m, 4H, $2NCH_2CH_2O$), 4.00 (m, 5H, $2NCH_2CH_2O$, CH_2O), 4.13 (dd, 1H, CH_2O, J 3.0 and 10.7 Hz), 5.35 (dd, 2H, OCH_2N^+, J 8.1 and 20.9 Hz). MS, m/z: 485.8 $[M - Br]^+$.

4c: ^{1}H NMR, δ: 0.86 [t, 3H, $(CH_2)_{15}CH_3$, J 6.5 Hz], 1.22 [br. s, 30H, $(CH_2)_{15}Me$], 1.50 (m, 2H, OCH_2CH_2), 3.35–3.53 (m, 8H, OCH_2CH_2, $CH_2OC_{18}H_{37}$, $CHOAll$, N^+Me), 3.71 (m, 4H, $2NCH_2CH_2O$), 3.92–4.17 (m, 8H, $2NCH_2CH_2O$, $OCH_2CH=CH_2$, CH_2O), 5.20–5.49 (m, 3H, OCH_2N^+, $OCH_2CH=CH_2$), 5.80 (m, 1H, $OCH_2CH=CH_2$). MS, m/z: 497.8 $[M - Br]^+$.

5a: ^{1}H NMR, δ: 0.85 [t, 6H, $2(CH_2)_{15}CH_3$, J 6.8 Hz], 1.23 [br. s, 60H, $2(CH_2)_{15}Me$], 1.51 (m, 4H, $2OCH_2CH_2$), 3.34–3.56 (m, 9H, $2OCH_2$–CH_2, $CH_2OC_{18}H_{37}$, $CHOC_{18}H_{37}$, CH_2O), 5.34 (br. s, 2H, OCH_2N), 7.06 and 7.11 (m, 2H, –CH=CH), 7.74 (m, 1H, –CH=N). MS, m/z: 678.0 $[M]^+$, 699.8 $[M + Na]^+$.

5b: ^{1}H NMR, δ: 0.86 [t, 6H, $2(CH_2)_{15}CH_3$, J 6.8 Hz], 1.23 [br. s, 60H, $2(CH_2)_{15}Me$], 1.52 (m, 4H, $2OCH_2CH_2$), 3.28 (br. t, 4H, $2OCH_2CH_2$, J 6.8 Hz), 3.35–3.55 (m, 5H, $CH_2OC_{18}H_{37}$, $CHOC_{18}H_{37}$, CH_2O), 5.59 (br. s, 2H, OCH_2N), 7.29 (m, 2H), 7.53 (m, 2H) and 7.99 (m, 1H, benzimidazole). MS, m/z: 726.9 $[M]^+$, 748.9 $[M + Na]^+$.

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