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Synthesis of alkyl-type functionalised glycerolipids from methylthiomethyl ethers

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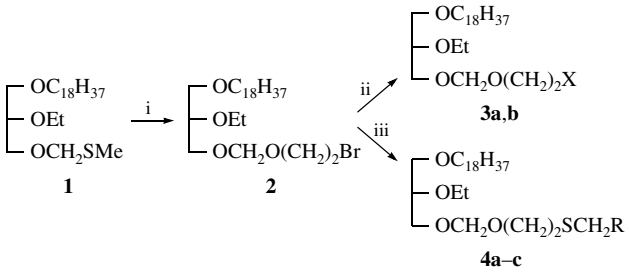
The synthesis of alkyl-type glycerolipids containing functional groups in the polar domain from methylthiomethyl ethers is described.

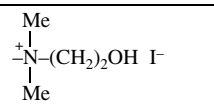
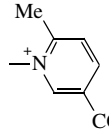
Alkyl-type glycerolipids are of interest owing to the wide spectrum of their biological activity. Compounds with antibacterial, anti-AIDS-1[1,2] and antitumor effects[3] have been found among them. Furthermore, it is promising to use such lipids as components of liposomes in studies of the structures of model membranes,[4] as well as for the delivery of various biologically active compounds (polynucleotides, peptides, hormones, *etc.*)[5–7] and boron-containing compounds[8] into eukaryotic cells.

The creation of conjugates of alkyl-type glycerolipids with other bioactive compounds in order to achieve additive or synergetic effects, as well as the introduction of fragments that facilitate biochemical and biophysical studies (fluorescent labels, spin labels, *etc.*) into molecules of these lipids, is a problem of current interest.[9,10] In view of this, it seems important to create glycerolipids with a simple ether bond containing various functional groups, which can be used to modify the molecule.

Studies on the structure–biological activity relationship create impetus for the modification of glycerolipids and for the convenient and efficient synthesis of these compounds. For example, the modified Pummerer rearrangement, which was previously used in nucleoside chemistry, was recently employed to obtain a new type of alkyl glycerolipids.[11,12] Methylthiomethyl ethers of diglycerides were converted into highly reactive α-bromoethers, which readily reacted with various nucleophiles. The use of tertiary amines as nucleophiles made it possible to incorporate a cationic 'head' into the molecules of an alkyl lipide; this 'head' was separated by an oxymethylene fragment from the glycerol skeleton. Note that the incorporation of a spacer group in a molecule eliminates steric hindrances in the subsequent conjugation. The aim of this work was to obtain alkyl-type functionalised glycerolipids (neutral or positively charged), in which the polar domain containing a functional group is separated by a spacer from the hydrophobic part. A methylthiomethyl ether of a diglyceride as a starting compound in the synthesis allowed us to obtain lipids with a spacer group bound to the glycerol skeleton through an acid-labile acetal bond (Scheme 1). We used *rac*-1-octadecyl-2-ethyl-3-methylthiomethylglycerol **1**, which was obtained by a modified Pummerer rearrangement,[12] as the starting compound.

Key compound **2** was obtained by the treatment of methylthiomethyl ether **1** with bromine (1.1 equiv.) in the presence of an excess (4 equiv.) of 2,6-lutidine. The resulting α-bromoether was treated with 2-bromoethanol (2 equiv.) without isolation. As a result, bromide **2** was obtained in 56% yield after chromatographic purification (petroleum ether–EtOAc, 45:1). The ^{1}H NMR spectrum of this compound contains a characteristic signal of protons of the acetal group, *viz.*, a singlet with a δ 4.73 ppm.



Compound	X	R	Yield (%)
3a		–	52
3b		–	71
4a	–	CH_2OH	77
4b	–	COOH	72
4c	–	CH_2NH_2	60

Scheme 1 *Reagents and conditions*: i, Br_2, 2,6-lutidine, $Br(CH_2)_2OH$, dichloroethane, 24 °C, 20 min; ii, X, NaI, DMSO, 70 °C, 5 h (**3a**) and 100 °C, 3 h (**3b**); iii, $HSCH_2R$, 1 N KOH/EtOH, 24 °C, 4–7 h.

Cationic lipids **3a**,**b** containing functional groups in the hydrophilic domain were obtained by the quaternization of functionalised amines. For this purpose, compound **2** was treated with an appropriate tertiary amine (1.5 equiv.) in DMSO and a threefold excess of NaI. Replacement of bromine under the reaction conditions with iodine, which is more reactive, made it possible to perform the process under mild conditions to give alkyl glycerolipids **3a**,**b** in good yields (52 and 71%, respectively). Potassium 6-methylnicotinate was used as an amine in the synthesis of lipid **3b**, which was obtained as an internal salt. The purification of lipids was performed by flash column chromatography on silica gel using a mixture of $CHCl_3$–MeOH (5:1) for compounds **3a** and (70:1) for **3b**.

Neutral alkyl glycerolipids **4a–c** were synthesised by thioalkylation of mercapto compounds containing functional groups with bromide **2**. The reaction was carried out under argon atmosphere in a 1 N KOH solution in ethanol with a threefold excess of the thio component. Chromatographic purification on silica gel [$CHCl_3$ for **4a**; $CHCl_3$–MeOH (20:1) for **4b**,**c**] gave neutral

alkyl-type glycerolipids **4a–c** with mercaptoethanol, cysteamine or thioglycolic acid residues as hydrophilic domains in good yields (60–77%).

^{1}H NMR spectroscopic and mass-spectrometric data agree with the structures of the compounds obtained.†

† **2**: ^{1}H NMR [Bruker MSL-300, 300 MHz, $CDCl_3$, with $CHCl_3$ as the internal standard (δ 7.24)] δ: 0.85 [t, 3H, $(CH_2)_{15}Me$, J 6.8 Hz], 1.19 (t, 3H, OCH_2Me, J 6.8 Hz), 1.23 [br. s, 30H, $(CH_2)_{15}$Me], 1.47–1.63 (m, 2H, OCH_2CH_2), 3.37–3.72 (m, 11H, CH_2OCH_2, $CHOCH_2$, CH_2OCH_2O, CH_2Br), 3.86 (t, 2H, CH_2CH_2Br, J 6.2 Hz), 4.73 (s, 2H, OCH_2O). MS (Vision 2000 MALDI TOF), m/z: 510 $[M + H]^+$.

3a: ^{1}H NMR, δ: 0.85 [t, 3H, $(CH_2)_{15}Me$, J 6.8 Hz], 1.18 (t, 3H, OCH_2Me, J 6.8 Hz), 1.23 [br. s, 30H, $(CH_2)_{15}$Me], 1.46–1.59 (m, 2H, OCH_2CH_2), 3.36–3.47 (m, 10H, N^+Me_2, $CH_2OCH_2CH_2$), 3.52–3.69 (m, 5H, $CHOCH_2$, CH_2OCH_2O), 3.81–3.95 (m, 4H, $OCH_2CH_2N^+$, CH_2OH), 3.98–4.07 (m, 2H, $OCH_2CH_2N^+$), 4.11–44.21 (m, 2H, $N^+CH_2CH_2OH$), 4.71 (s, 2H, OCH_2O). MS, m/z: 510 $[M + H]^+$.

3b: ^{1}H NMR, δ: 0.85 [s, 3H, $(CH_2)_{15}Me$, J 6.9 Hz], 1.17 (t, 3H, OCH_2Me, J 6.9 Hz), 1.26 [br. s, 30H, $(CH_2)_{15}$Me], 1.46–1.57 (m, 2H, OCH_2CH_2), 2.67 (s, 3H, MeC), 3.40 (t, 2H, OCH_2CH_2, J 6.7 Hz), 3.44–3.48 (m, 2H, $CH_2OC_{18}H_{37}$), 3.54–3.69 (m, 5H, $CHOCH_2$, CH_2OCH_2O), 3.84–3.89 (m, 2H, $OCH_2CH_2N^+$), 4.47–4.51 (m, 2H, $OCH_2CH_2N^+$), 4.74 (s, 2H, OCH_2O), 7.23 (dd, 1H, β-Py, J 8.0 and < 1 Hz), 8.19 (dd, 1H, γ-Py, J 8.0 and 2.2 Hz), 9.10 (dd, 1H, α-Py, J 2.2 and < 1 Hz). MS, m/z: 688.5 $[M + Na]^+$.

4a: ^{1}H NMR, δ: 0.86 [t, 3H, $(CH_2)_{15}Me$, J 6.8 Hz], 1.18 (t, 3H, OCH_2Me, J 6.9 Hz), 1.23 [br. s, 30H, $(CH_2)_{15}$Me], 1.48–1.58 (m, 2H, OCH_2CH_2), 2.74 (t, 2H, J 6.4 Hz) and 2.76 (t, 2H, CH_2SCH_2, J 6.2 Hz), 3.42 (t, 2H, OCH_2CH_2, J 6.6 Hz), 3.45–3.49 (m, 2H, $CH_2OC_{18}H_{37}$), 3.55–3.75 (m, 9H, $CHOCH_2$, CH_2OCH_2O, OCH_2CH_2S, CH_2OH), 4.73 (s, 2H, OCH_2O). MS, m/z: 530.9 $[M + Na]^+$.

4b: ^{1}H NMR, δ: 0.86 [t, 3H, $(CH_2)_{15}Me$, J 6.8 Hz], 1.19 (t, 3H, OCH_2Me, J 7.0 Hz), 1.23 [br. s, 30H, $(CH_2)_{15}$Me], 1.49–1.60 (m, 2H, OCH_2CH_2), 2.87 (t, 2H, OCH_2CH_2S, J 6.2 Hz), 3.29 (s, 2H, SCH_2COOH), 3.44 (t, 2H, OCH_2CH_2, J 6.7 Hz), 3.46–3.51 (m, 2H, $CH_2OC_{18}H_{37}$), 3.57–3.82 (m, 7H, $CHOCH_2$, OCH_2CH_2S, CH_2OCH_2O), 4.70 (s, 2H, OCH_2O). MS, m/z: 555.8 $[M + Na]^+$.

4c: ^{1}H NMR, δ: 0.85 [t, 3H, $(CH_2)_{15}Me$, J 6.8 Hz], 1.18 (t, 3H, OCH_2Me, J 6.9 Hz), 1.23 [br. s, 30H, $(CH_2)_{15}$Me], 1.48–1.59 (m, 2H, OCH_2CH_2), 2.66 (t, 2H, J 6.2 Hz) and 2.71 (t, 2H, J 6.6 Hz, CH_2SCH_2), 2.84–2.92 (m, 2H, CH_2N), 3.41 (t, 2H, OCH_2CH_2, J 6.6 Hz), 3.45–3.49 (m, 2H, $CH_2OC_{18}H_{37}$), 3.53–3.66 (m, 5H, $CHOCH_2$, CH_2OCH_2O), 3.69 (t, 2H, OCH_2CH_2S, J 6.6 Hz), 4.69 (s, 2H, OCH_2O). MS, m/z: 507.6 $[M + H]^+$, 529.5 $[M + Na]^+$.

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References

1 I. D. Konstantinova and G. A. Serebrennikova, *Usp. Khim.*, 1996, **65**, 581 (*Russ. Chem. Rev.*, 1996, **65**, 537).

2 I. D. Konstantinova and G. A. Serebrennikova, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 1826 (*Russ. Chem. Bull.*, 1994, **43**, 1731).

3 F. Civoli and L. W. Daniel, *Cancer Chemother. Pharmacol.*, 1998, **42**, 319.

4 N. Duzgunes, J. A. Goldstein, D. S. Friend and P. L. Felgner, *Biochemistry*, 1989, **28**, 9179.

5 J. H. Fuhrhop and H. Tank, *Chem. Phys. Lipids*, 1987, **43**, 193.

6 N. Ballas, N. Zakai, I. Sela and A. Loyter, *Biochim. Biophys. Acta*, 1988, **939**, 8.

7 C. L. Innes, P. B. Smith, R. Lanqenbach, K. R. Tindall and L. R. Boone, *J. Virol.*, 1990, **64**, 957.

8 A. H. Solowey, W. Tjarks, B. A. Barnum, F.-G. Rong, R. F. Barth, I. M. Codogni and J. G. Wilson, *Chem. Rev.*, 1998, **98**, 1515.

9 J. Goddat, H. Coste, I. Vilgrain, E. Chambaz and H. Driguez, *Lipids*, 1992, **27**, 331.

10 M. A. Maslov, E. V. Siycheva, N. G. Morosova and G. A. Serebrennikova, *Izv. Akad. Nauk, Ser. Khim.*, 2000, 385 (*Russ. Chem. Bull., Int. Ed.*, 2000, **49**, 385).

11 I. D. Konstantinova, S. G. Zavgorodny, A. I. Miroshnikov, I. P. Ushakova and G. A. Serebrennikova, *Bioorg. Khim.*, 1995, **21**, 66 (*Russ. J. Bioorg. Chem.*, 1995, **21**, 58).

12 M. A. Maslov, N. G. Morosova and G. A. Serebrennikova, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 1778 (*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, 1931).

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