Russian Journal of Bioorganic Chemistry, Vol. 30, No. 5, 2004, pp. 454–458. Translated from Bioorganicheskaya Khimiya, Vol. 30, No. 5, 2004, pp. 507–511.

Synthesis of Alkyl Glycerolipids with Functional Groups in Their Polar Heads

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Received June 23, 2003; in final form, November 24, 2003

Abstract—A number of alkyl glycerolipids with short-chain substituents at the C2 atom of glycerol and functional groups (carboxy and amino) in the polar head were synthesized. Cationic alkyl glycerolipids with a hydroxyl function in the hydrophilic moiety were also obtained.

Key words: *alkyl glycerolipids, cationic lipids*

INTRODUCTION

Currently, the direction of synthesis of various analogues of natural lipids and their modified forms with unnatural structures is intensively being developed. The lipids of alkyl type (neutral or those with a positively charged group, i.e., cationic lipids) can be assigned to unnatural [1, 2]. An interest in the compounds of this class is due to a wide spectrum of their biological activities. Effective antagonists of platelet activation factor (PAF), a highly active lipid bioregulator, and compounds with antibacterial, antitumor, and anti-HIV-1 activities were found among the cationic glycerolipids with ether bond [3, 4]. Moreover, the possibility of their use as mediators of transfection of various cells with biologically active substances (polynucleotides, peptides, hormones, etc.) [1, 5, 6] and as liposome components [7] was shown.

It has been established up to date that the lipids with ether bond (e.g., the known lipid preparation 1-octadecyl-2-methyl-*sn*-glycero-3-phosphocholine, ET-18-OMe, and its phosphorless analogues) exert an inhibiting action on metastasis and growth of various tumor cell lines due to their effect on the activity of membrane-bound protein kinase C and diacyl glycerol kinase [9, 10].

Numerous studies of lipids with ether bond allowed the experimental revelation of some requirements to their structures that determine with a great probability their type of biological activity. It turned out that, in the majority of cases, the alkyl lipids with a long-chain oxyalkyl substituent (C_{10}–C_{20}) in position C1 of glycerol backbone and a short-chain (C_1–C_4) in position C2 could exhibit antitumor properties. The presence of a substituted phosphate or a cationic head of ammonium or sulfonium type attached to the 1,2-dialkylglycerol directly or through a spacer group is necessary at C3 of glycerol [3, 11].

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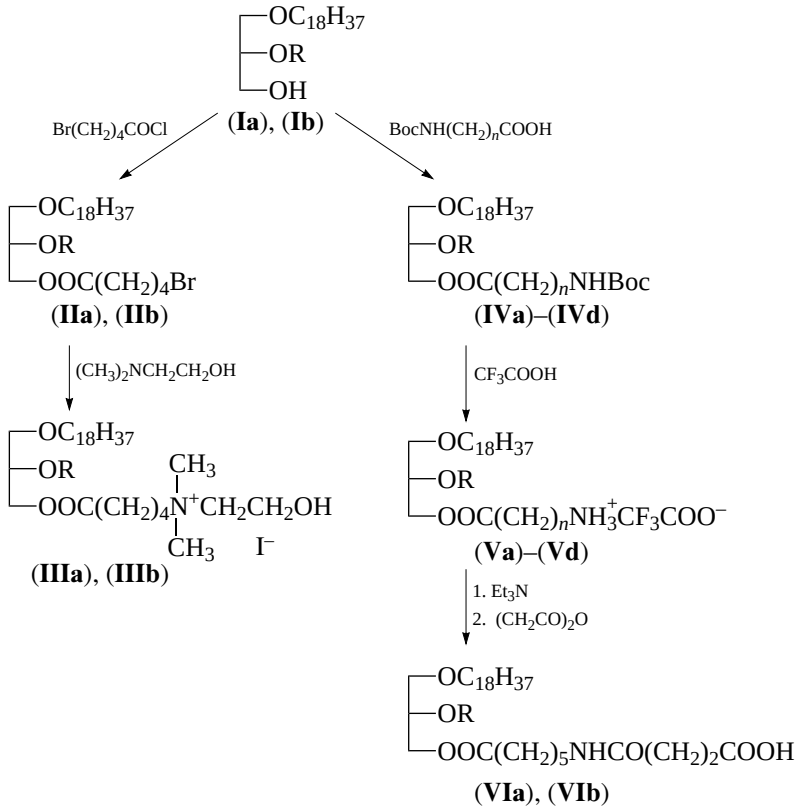
The synthesis of such compounds with various functional groups appears to be topical owing to diverse and high biological activities of alkyl glycerolipids. This offers great opportunities in the creation of conjugates of such lipids with other biologically active substances and in the introduction of fluorescent and spin labels for accomplishing biochemical and biophysical studies [12, 13].

RESULTS AND DISCUSSION

We synthesized glycerolipids with ether bond that not only met the requirements mentioned above but also contained various functional groups in polar parts of their molecules.

rac-1-Octadecyl-2-ethylglycerol (**Ia**) and *rac*-1-octadecyl-2-allylglycerol (**Ib**) [4] were used as starting compounds. They were reacted with 5-bromopentanoic acid chloride to get lipids with hydroxy group in polar moiety. After a chromatographic purification, *rac*-1-octadecyl-2-ethyl/allyl-3-(5bromopentanoyl)glycerols (**IIa**) and (**IIb**) were obtained in yield of 64–69%. The subsequent reaction of the bromoderivatives with *N*,*N*-dimethylaminoethanol was carried in DMSO in the presence of NaI. The substitution of more reactive iodine for bromine under the reaction conditions allowed us to carry out the process more easily and to obtain *rac*-*N*-{4-[(2-ethoxy/allyloxy-3-octadecyloxy)prop-1-yloxycarbonyl]butyl}-*N*,*N*-dimethyl-*N*-(2-hydroxyethyl)ammonium iodides (**IIIa**) and (**IIIb**) in 57–59% yields.

The synthesis of cationic lipids with N^+H_3 group in polar head (**Va**)–(**Vd**) was achieved by the acylation of dialkylglycerols (**Ia**) and (**Ib**) with Boc-aminoundecanoic or Boc-aminocaproic acids in pyridine in the presence of DCC (see scheme). The yields of (**IVa**)–(**IVd**) were 55–68%. The subsequent removal of Boc protective group with trifluoroacetic acid in chloroform resulted in *rac*-1-octadecyl-2-ethyl/allyl-3-(6-ammoni-



(**I**), (**II**), (**III**), (**VI**): R = C_2H_5 (**a**), R = $CH_2CH{=}CH_2$ (**b**),

(**IV**), (**V**): n = 10, R = C_2H_5 (**a**), R = $CH_2CH{=}CH_2$ (**b**);

n = 5, R = C_2H_5 (**c**), R = $CH_2CH{=}CH_2$ (**d**).

oundecanoyl)glycerol trifluoroacetates (**Va**) and (**Vb**) and *rac*-1-octadecyl-2-ethyl/allyl-3-(6-ammoniohexanoyl)glycerol trifluoroacetates (**Vc**) and (**Vd**) in 78–87% yields.

Carboxyl function was introduced in glycerolipid molecule by the successive treatment of ammonium salts (**Vc**) and (**Vd**) with triethylamine and succinic anhydride in the presence of catalytic quantity of *N*,*N*-dimethylaminopyridine in DMSO. *rac*-1-Octadecyl-2-ethyl/allyl-3-(6-succinylamidohexanoyl)glycerols (**VIa**) and (**VIb**) were obtained in 68 and 65% yields, respectively.

The homogeneity and structure of all the compounds synthesized were confirmed by ^{1}H NMR spectroscopy and mass spectrometry.

Thus, we synthesized a number of alkyl glycerolipids with various functional groups (hydroxy, carboxy, and amino) in hydrophilic moiety.

EXPERIMENTAL

We used distilled solvents and the following reagents: DMSO, *N*,*N*-dimethylaminoethanol, and succinic anhydride (Reakhim, Russia); 5-bromovaleric acid (Fluka, Switzerland); 6-aminocaproic acid (Sigma, United States); 11-aminoundecanoic acid, and sodium iodide (Merck, Germany); and triethylamine (Vekton, Russia). ^{1}H NMR spectra (δ, ppm, spin coupling constants *J*, Hz) were registered on a pulse Fourier-transform Bruker MSL-200 spectrometer (200 MHz) in deuterochloroform with tetramethylsilane as an internal standard. Mass spectra were obtained on a time-of-flight Finnigan MAT 900XL-TRAP mass spectrometer (San Jose, CA, United States) with electrospray ionization (ESI). Silufol UV-254 (Chemapol, Czech Republic) was used for TLC; detection was made with phosphomolybdic acid. The following solvent systems were used for TLC: (A) 2 : 1 petroleum ether–ether, (B) 3 : 1 chloroform–methanol, (C) 20 : 1 chloroform–methanol, (D) 7 : 1 chloroform–methanol, and (E) 10 : 1 chloroform–methanol. Silica gel L 40/100 μm (Chemapol, Czech Republic) was used for column chromatography.

***rac*-1-Octadecyl-2-ethyl-3-(5-bromopentanoyl)glycerol (IIa).** Pyridine (0.5 ml) and then dropwise a solution of 5-bromopentanoyl chloride (0.4 g, 2 mmol) in anhydrous chloroform (2 ml) were added to a cooled to 0°C solution of *rac*-1-octadecyl-2-ethylglycerol (**Ia**) (0.75 g, 2 mmol) in anhydrous chloroform (3 ml). The mixture was stirred for 14 h at 20°C; diluted with chloroform (20 ml); washed with 1% HCl (3 × 20 ml) and

water (2 × 20 ml); dried with Na_2SO_4; and evaporated. The residue was chromatographed on a silica gel column eluted with chloroform to get target (**IIa**); yield 0.68 g (64%); R_f 0.6 (A); ^{1}H NMR: 0.86 [3 H, t, *J* 6.8,$(CH_2)_{15}C\underline{H}_3$), 1.17 (3 H, t, *J* 7.1, $OCH_2C\underline{H}_3$), 1.23 [30 H, br s, $(C\underline{H}_2)_{15}CH_3$], 1.47–1.59 (2 H, m, $OCH_2C\underline{H}_2$), 1.71–1.91 [4 H, m, $(C\underline{H}_2)_2CH_2Br$], 2.35 (2 H, t, *J* 7.0, $OCOCH_2$), 3.35–3.46 (7 H, m, $C\underline{H}_2OC\underline{H}_2CH_2$, CHOEt, and CH_2Br), 3.60 (2 H, q, *J* 7.1, $OC\underline{H}_2CH_3$), 4.07 (1 H, dd, *J* 5.8 and 10.6, $CH\underline{H}_aOCO$), and 4.25 1 H, dd, *J* 3.9 and 10.6, $CH\underline{H}_bOCO$).

***rac*-1-Octadecyl-2-allyl-3-(5-bromopentanoyl)glycerol (IIb).** According to the previous procedure, from *rac*-1-octadecyl-2-allylglycerol (**Ib**) (0.51 g, 1.3 mmol) pyridine (0.5 ml) and 5-bromopentanoyl chloride (0.26 g, 1.3 mmol), (**IIb**) was obtained; yield 0.5 g (69%); R_f 0.6 (A); ^{1}H NMR: 0.82 [3 H, t, *J* 6.2, $(CH_2)_{15}C\underline{H}_3$], 1.22 [30 H, br s, $(C\underline{H}_2)_{15}CH_3$], 1.46–1.55 (2 H, m, $OCH_2C\underline{H}_2$), 1.71–1.91 [4H, m, $(C\underline{H}_2)_2CH_2Br$], 2.32 (2 H, t, *J* 6.1, $OCOCH_2$), 3.35–3.46 (6 H, m, $C\underline{H}_2OC\underline{H}_2CH_2$ and $C\underline{H}_2Br$), 3.60–3.71 (1 H, m, CHO-Allyl), 4.02–4.11 (3 H, m, $CH\underline{H}_aOCO$ and $OC\underline{H}_2CH{=}CH_2$), 4.22 (1 H, dd, *J* 4.7 and 12.4, $CH\underline{H}_bOCO$), 5.09–5.29 (2 H, m, $OCH_2CH{=}C\underline{H}_2$), and 5.75–5.95 (1 H, m, $OCH_2C\underline{H} = CH_2$).

***rac*-*N*-{4-[(2-Ethoxy-3-octadecyloxy)prop-1-yloxycarbonyl]butyl}-*N*,*N*-dimethyl-*N*-(2-hydroxyethyl)ammonium iodide (IIIa).** Sodium iodide (0.37 g) and *N*,*N*-dimethylethanol (0.1 ml, 1 mmol) were added to a solution of (**IIa**) (0.45 g, 0.84 mmol) in DMSO (2 ml). The mixture was kept for 5 h at 70°C, diluted with chloroform (20 ml), washed with water (4 × 15 ml), and dried with Na_2SO_4. The residue after the solvent removal was chromatographed on a silica gel column eluted with 3 : 1 chloroform–methanol mixture. Yield of (**IIIa**) was 0.33 g (58.9%); R_f 0.5 (B); MS, *m*/*z*: 544.7 $[M]^+$; ^{1}H NMR: 0.88 [3 H, t, *J* 6.9, $(CH_2)_{15}C\underline{H}_3$], 1.19 (3 H, t, *J* 7.3, $OCH_2C\underline{H}_3$), 1.23 [30 H, br s, $(C\underline{H}_2)_{15}CH_3$], 1.50–1.61 (2 H, m, $OCH_2C\underline{H}_2$), 1.69–1.95 [4 H, m, $(C\underline{H}_2)_2CH_2N^+$], 2.48 (2 H, t, *J* 6.1, $OCOCH_2$), 3.38 [6 H, s, $N^+(CH_3)_2$], 3.43–3.50 (4 H, m, $C\underline{H}_2OC\underline{H}_2CH_2$), 3.58–3.69 (5 H, m, $C\underline{H}OC\underline{H}_2CH_3$ and $N^+CH_2C\underline{H}_2OH$), 3.75–3.81 [2H, m, $(CH_2)_3C\underline{H}_2N^+$], 4.09 (1 H, dd, *J* 5.9 and 11.8, $CH\underline{H}_aOCO$), 4.13–4.22 (2 H, m, $N^+C\underline{H}_2CH_2OH$), and 4.26 (1 H, dd, *J* 4.2 and 11.8, $CH\underline{H}_bOCO$).

***rac*-*N*-{4-[(2-Allyloxy-3-octadecyloxy)prop-1-yloxycarbonyl]butyl}-*N*,*N*-dimethyl-*N*-(2-hydroxyethyl)ammonium iodide (IIIb)** was obtained as described for (**IIIa**) from triester (**IIb**) (0.36 g, 0.67 mmol), NaI (0.29 g) and *N*,*N*-dimethylethanol (0.08 ml, 0.8 mmol); yield 0.26 g (57.1%); R_f 0.5 (B); MS, *m*/*z*: 556.2 $[M]^+$; ^{1}H NMR: 0.86 [3 H, t, *J* 6.8, $(CH_2)_{15}C\underline{H}_3$], 1.24 [30 H, br s, $(C\underline{H}_2)_{15}CH_3$], 1.47–1.59 (2 H, m, $OCH_2C\underline{H}_2$), 1.65–1.77 (2 H, m, $OCOCH_2C\underline{H}_2$), 1.81–1.93 (2 H, m, $C\underline{H}_2CH_2N^+$), 2.46 (2 H, т, *J* 7.0, $OCOCH_2$), 3.34 [6 H, s, $N^+(CH_3)_2$], 3.42 (2 H, t, *J* 6.7, $OC\underline{H}_2CH_2$), 3.44–3.50 (2 H, m, $CH_2OC_{18}H_{37}$), 3.57–3.77 (5 H, m, CHOAll, $N^+CH_2C\underline{H}_2OH$, $CH_2C\underline{H}_2N^+$), 4.05–4.17 (5 H, m, $CH\underline{H}_aOCO$, $OC\underline{H}_2CH{=}CH_2$, and $N^+C\underline{H}_2CH_2OH$), 4.25 (1 H, dd, *J* 6.9 and 11.6, $CH\underline{H}_bOCO$), 5.16 (1 H, ddt, *J* 1.3, 1.7, and 10.3, $OCH_2CH{=}CH\underline{H}_a$), and 5.27 (1 H, ddt, *J* 5.7, 10.3, and 17.2, $OCH_2C\underline{H}{=}CH_2$).

***rac*-1-Octadecyl-2-ethyl-3-[11-(*N*-*tert*-butoxycarbonyl)aminoundecanoyl]glycerol (IVa).** DCC (0.19 g, 0.96 mmol) and then *rac*-1-octadecyl-2-ethylglycerol (0.2 g, 0.54 mmol) were added to a solution of 11-Boc-aminoundecanoic acid (0.24 g, 0.8 mmol) in anhydrous pyridine (1.2 ml). The mixture was kept for 1.5 h at 25°C and evaporated. The residue was dissolved in chloroform (8 ml), and dicyclohexylurea that was not dissolved was filtered off. This operation was repeated 3 times, and the resulting substance was purified by chromatography on a silica gel column eluted with 20 : 1 chloroform–methanol mixture to give (**IVa**); yield 0.24 g (68%); R_f 0.45 (C); MS, *m*/*z*: 556.8 $[M - Boc]^+$, 678.9 $[M + Na]^+$; ^{1}H NMR: 0.86 [3 H, t, *J* 6.6, $(CH_2)_{15}C\underline{H}_3$)], 1.17 (3 H, t, *J* 6.7, $OCH_2C\underline{H}_3$), 1.23–1.31 [42 H, m, $(C\underline{H}_2)_{15}CH_3$ and $(CH_2)_6$], 1.42 [9 H, s, $C(CH_3)_3$], 1.45–1.65 (6 H, m, $OCH_2C\underline{H}_2$, $OCOCH_2C\underline{H}_2$, and $C\underline{H}_2CH_2N$), 2.30 (2 H, t, *J* 7.3, $OCOCH_2$), 3.00–3.13 (2 H, m, CH_2N), 3.35–3.49 (4 H, m, $C\underline{H}_2OC\underline{H}_2CH_2$), 3.61 (2 H, q, *J* 6.7, $OC\underline{H}_2CH_3$), 3.57–3.65 (1 H, m CHOEt, overlapped with q at 3.61), 4.07 (1 H, dd, *J* 5.6 and 11.8, $CH\underline{H}_aOCO$), 4.22 (1 H, dd, *J* 4.2 and 11.8, $CH\underline{H}_bOCO$), and 4.39–4.56 (1 H, m, NH).

***rac*-1-Octadecyl-2-allyl-3-[11-(*N*-*tert*-butoxycarbonyl)aminoundecanoyl]glycerol (IVb)** was obtained as described for (**IVa**) from 11-Boc-aminoundecanoic acid (0.32 g, 1.05 mmol), DCC (0.26 g, 1.26 mmol), and *rac*-1-octadecyl-2-allylglycerol (**Ib**) (0.27 g, 0.7 mmol); yield 0.36 g (64%); R_f 0.45 (C); MS, *m*/*z*: 668.1 $[M]^+$, 690.1 $[M + Na]^+$; ^{1}H NMR: 0.86 [3 H, t, *J* 7.0, $(CH_2)_{15}C\underline{H}_3$], 1.21–1.33 [42 H, m, $(C\underline{H}_2)_{15}CH_3$ and $(CH_2)_6$], 1.41 [9 H, s, $C(CH_3)_3$], 1.45–1.65 (6 H, m, $OCH_2C\underline{H}_2$, $OCOCH_2C\underline{H}_2$, and $C\underline{H}_2CH_2N$), 2.30 (2 H, t, *J* 7.7, $OCOCH_2$), 3.01–3.15 (2 H, m, CH_2N), 3.41 (2 H, t, *J* 6.7, $OC\underline{H}_2CH_2$), 3.45–3.50 (2 H, m, $CH_2OC_{18}H_{37}$), 3.64–3.72 (1 H, m, CHOAllyl), 4.08 (1 H, dd, *J* 5.7 and 11.6, $CH\underline{H}_aOCO$), 4.10 (2 H, ddt, *J* 1.3, 1.7, and 5.7, $OC\underline{H}_2CH{=}CH_2$), 4.22 (1 H, dd, *J* 4.2 and 11.6, $CH\underline{H}_bOCO$), 4.42–4.52 (1 H, m, NH), 5.15 (1 H, ddt, *J* 1.3, 1.7, and 10.3, $OCH_2CH{=}CH\underline{H}_a$), 5.25 (1 H, ddt, *J* 1.7, 1.7, and 17.2, $OCH_2CH{=}CH\underline{H}_b$), and 5.86 (1 H, ddt, *J* 5.7, 10.3, and 17.2, $OCH_2C\underline{H}{=}CH_2$).

***rac*-1-Octadecyl-2-ethyl-3-[6-(*N*-*tert*-butoxycarbonyl)aminohexanoyl]glycerol (IVc)** was obtained as described for (**IVa**) from *rac*-1-octadecyl-2-ethylglyc-

erol (**Ia**) (0.18 g, 0.48 mmol), 6-Boc-aminohexanoic acid (0.15 g, 0.63 mmol), and DCC (0.15 g, 0.75 mmol); yield 0.18 g (63%), R_f 0.53 (C); MS, *m/z*: 587.1 $[M - H]^+$; ^{1}H NMR: 0.85 [3 H, t, *J* 6.4, $(CH_2)_{15}C\underline{H}_3$], 1.16 (3 H, t, *J* 7.3, $OCH_2C\underline{H}_3$), 1.20–1.29 [32 H, m, $(C\underline{H}_2)_{15}CH_3$ and $OCO(CH_2)_2C\underline{H}_2$], 1.41 [9 H, s, $C(C\underline{H}_3)_3$], 1.47–1.65 (6 H, m, $OCH_2C\underline{H}_2$, $OCOCH_2C\underline{H}_2$, and $C\underline{H}_2CH_2N$), 2.31 (2 H, t, *J* 7.3, $OCOC\underline{H}_2CH_2$), 3.02–3.12 (2 H, m, $C\underline{H}_2N$), 3.41 (2 H, t, *J* 6.8, $OC\underline{H}_2CH_2$), 3.42–3.47 (2 H, m, $C\underline{H}_2OC_{18}H_{37}$), 3.60 (2 H, q, *J* 7.3, $OC\underline{H}_2CH_3$), 3.54–3.66 (1 H, m CHOEt, overlapped with q at 3.61), 4.06 (1 H, dd, *J* 5.6 and 11.5, $CH\underline{H}_aOCO$), 4.22 (1 H, dd, *J* 4.3 and 11.9, $CH\underline{H}_bOCO$), and 4.46–4.57 (1 H, m, NH).

***rac*-1-Octadecyl-2-allyl-3-[6-(*N*-*tert*-butoxycarbonyl)aminohexanoyl]glycerol (IVd)** was obtained as described for (**IVa**) from *rac*-1-octadecyl-2-allylglycerol (**Ib**) (0.15 g, 0.4 mmol), 6-Boc-aminohexanoic acid (0.14 g, 0.6 mmol), and DCC (0.15 g, 0.75 mmol); yield 0.13 g (55%), R_f 0.53 (C); MS, *m/z*: 697.3 $[M]^+$, 620.1 $[M + Na]^+$; ^{1}H NMR: 0.86 [3 H, t, *J* 6.8, $(CH_2)_{15}C\underline{H}_3$], 1.19–1.31 [32 H, m, $(C\underline{H}_2)_{15}CH_3$ and $OCO(CH_2)_2C\underline{H}_2$], 1.42 [9 H, s, $C(CH_3)_3$], 1.46–1.75 (6 H, m, $OCH_2C\underline{H}_2$, $OCOCH_2C\underline{H}_2$, and $C\underline{H}_2CH_2N$), 2.31 (2 H, t, *J* 7.3, $OCOC\underline{H}_2CH_2$), 3.02–3.14 (2 H, m, CH_2N), 3.36–3.75 (5 H, m, $C\underline{H}_2OC\underline{H}_2CH_2$ and CHOAllyl), 4.02–4.15 (3 H, m, $CH\underline{H}_aOCO$ and $OC\underline{H}_2CH{=}CH_2$), 4.23 (1 H, dd, *J* 4.3 and 11.9, $CH\underline{H}_bOCO$), 4.46–4.54 (1 H, m, NH), 5.11–5.32 (2 H, m, $OCH_2CH{=}C\underline{H}_2$), and 5.78–6.01 (1 H, m, $OCH_2C\underline{H}{=}CH_2$).

***rac*-1-Octadecyl-2-ethyl-3-[11-ammonioundecanoyl)glycerol trifluoroacetate (Va).** Trifluoroacetic acid (0.2 ml) was added to a solution of (**IVa**) (0.19 g, 0.29 mmol) in chloroform (1 ml). The mixture was stirred for 1.5 h at 40°C and evaporated. The residue was chromatographed on a silica gel column eluted with 7 : 1 chloroform–methanol mixture to give (**Va**); yield 0.17 g (87%); R_f 0.42 (D); MS, *m/z*: 556.2 $[M]^+$; ^{1}H NMR: 0.85 [3 H, t, *J* 6.5, $(CH_2)_{15}C\underline{H}_3$], 1.17 (3 H, t, *J* 7.0, $OCH_2C\underline{H}_3$), 1.21–1.36 [42 H, m, $(C\underline{H}_2)_{15}CH_3$ and $(CH_2)_6$], 1.48–1.69 (6 H, m, $OCH_2C\underline{H}_2$, $OCOCH_2C\underline{H}_2$, and $C\underline{H}_2CH_2NH_3^+$), 2.30 (2 H, t, *J* 7.3, $OCOC\underline{H}_2CH_2$), 2.82–2.95 (2 H, m, $C\underline{H}_2NH_3^+$), 3.41 (2 H, t, *J* 6.8, $OC\underline{H}_2CH_2$), 3.43–3.48 (2 H, m, $CH_2OC_{18}H_{37}$), 3.61 (2 H, q, *J* 7.0, $OC\underline{H}_2CH_3$), 3.58–3.65 (1 H, m CHOEt, overlapped with q at 3.61), 4.07 (1 H, dd, *J* 5.8 and 11.6, $CH\underline{H}_aOCO$), 4.23 (1 H, dd, *J* 4.2 and 11.6, $CH\underline{H}_bOCO$), and 7.84 (3 H, br s, NH_3^+).

***rac*-1-Octadecyl-2-allyl-3-[11-ammonioundecanoyl)glycerol trifluoroacetate (Vb)** was obtained as described for (**Va**) from (**IVb**) (0.35 g, 1.01 mmol) and trifluoroacetic acid (0.2 ml); yield 0.21 g (81%), R_f 0.42 (D); MS, *m/z*: 568 $[M - H]^+$, 569.1 $[M]^+$; ^{1}H NMR: 0.86 [3 H, t, *J* 7.0, $(CH_2)_{15}C\underline{H}_3$], 1.21–1.34 [42 H, m, $(C\underline{H}_2)_{15}CH_3$ and $(CH_2)_6$], 1.54–1.68 (6 H, m, $OCH_2C\underline{H}_2$, $OCOCH_2C\underline{H}_2$, and $C\underline{H}_2CH_2NH_3^+$), 2.30 (2 H, t, *J* 7.7, $OCOC\underline{H}_2CH_2$), 2.83–2.96 $C\underline{H}_2NH_3^+$), 3.41 (2 H, t, *J* 6.8, $OC\underline{H}_2CH_2$), 3.45–3.50 (2 H, m, $CH_2OC_{18}H_{37}$), 3.64–3.72 (1 H, m CHOAllyl), 4.08 (1 H, dd, *J* 5.7 and 11.6, $CH\underline{H}_aOCO$), 4.10 (2 H, ddt, 1.3, 1.7, and 5.7, $OC\underline{H}_2CH{=}CH_2$), 4.22 (1 H, dd, *J* 4.2 and 11.6, $CH\underline{H}_bOCO$), 5.86 (1 H, ddt, *J* 5.7, 10.3, and 17.2, $OCH_2C\underline{H}{=}CH_2$), and 7.84 (3 H, br s, NH_3^+).

***rac*-1-Octadecyl-2-ethyl-3-[6-ammoniohexanoyl)-glycerol trifluoroacetate (Vc)** was obtained as described for (**Va**) from (**IVc**) (0.14 g, 0.24 mmol) and trifluoroacetic acid (0.15 ml). The substance was chromatographed on silica gel eluting with 10 : 1 chloroform–methanol; yield 0.12 g (80%); R_f 0.2 (E); MS, *m/z*: 556.2 $[M]^+$, 557.3 $[M + H]^+$; ^{1}H NMR: 0.86 [3 H, t, *J* 6.8, $(CH_2)_{15}C\underline{H}_3$], 1.17 (3 H, t, *J* 7.0, $OCH_2C\underline{H}_3$), 1.20–1.30 [32 H, m, $(C\underline{H}_2)_{15}CH_3$ and $OCO(CH_2)_2C\underline{H}_2$], 1.48–1.75 (6 H, m, $OCH_2C\underline{H}_2$, $OCOCH_2C\underline{H}_2$, and $C\underline{H}_2CH_2N$), 2.29 (2 H, t, *J* 7.3, $OCOC\underline{H}_2CH_2$), 2.82–2.95 (2 H, m, $C\underline{H}_2NH_3^+$), 3.41 (2 H, t, *J* 6.4, $OC\underline{H}_2CH_2$), 3.42–3.50 (2 H, m, $C\underline{H}_2OC_{18}H_{37}$), 3.60 (2 H, q, *J* 7.0, $OC\underline{H}_2CH_3$), 3.56–3.66 (1 H, m, CHOEt, overlapped with q at 3.60), 4.05 (1 H, dd, *J* 5.6 and 11.5, $CH\underline{H}_aOCO$), 4.20 (1 H, dd, *J* 3.8 and 11.5, $CH\underline{H}_bOCO$), and 8.1 (3 H, br s, NH_3^+).

***rac*-1-Octadecyl-2-ethyl-3-[6-ammoniohexanoyl)-glycerol trifluoroacetate (Vd)** was obtained as described for (**Va**) from (**IVd**) (0.1 g, 0.16 mmol) and trifluoroacetic acid (0.1 ml). The substance was chromatographed on silica gel eluting with 10 : 1 chloroform–methanol; yield 0.08 g (78%); R_f 0.2 (E); MS, *m/z*: 568 $[M - H]^+$, 569.1 $[M]^+$; ^{1}H NMR: 0.85 [3 H, t, *J* 6.8, $(CH_2)_{15}C\underline{H}_3$], 1.19–1.31 [32 H, m, $(C\underline{H}_2)_{15}CH_3$ and $OCO(CH_2)_2C\underline{H}_2$], 1.47–1.77 (6 H, m, $OCH_2C\underline{H}_2$, $OCOCH_2C\underline{H}_2$, and $C\underline{H}_2CH_2N$), 2.32 (2 H, t, *J* 6.8, $OCOC\underline{H}_2CH_2$), 2.86–2.97 (2 H, m, $C\underline{H}_2NH_3^+$), 3.40 (2 H, t, *J* 6.8, $OC\underline{H}_2CH_2$), 3.42–3.50 (2 H, m, $CH_2OC_{18}H_{37}$), 3.58–3.71 (1 H, m CHOAllyl), 4.03–4.13 (3 H, m, $CH\underline{H}_aOCO$ and $OC\underline{H}_2CH{=}CH_2$), 4.21 (1 H, dd, *J* 4.3 and 11.5, $CH\underline{H}_bOCO$), 5.15 (1 H, ddt, *J* 1.3, 1.7, and 10.2, $OCH_2CH{=}CH\underline{H}_a$), 5.26 (1 H, ddt, *J* 1.3, 1.7, and 10.2, $OCH_2CH{=}CH\underline{H}_b$), 5.87 (1 H, ddt, *J* 5.6, 10.2, and 17.5, $OCH_2C\underline{H}{=}CH_2$), and 6.25 (3 H, br s, NH_3^+).

***rac*-1-Octadecyl-2-ethyl-3-[6-succinylamidohexanoyl)glycerol (VIa).** Triethylamine (0.14 ml, 9.9 mmol) was added to a solution of (**Vc**) (0.11 g, 0.19 mmol) in anhydrous chloroform (0.4 ml). The mixture was stirred for 20 min at 0°C and 1 h at 20°C and evaporated. The residue was dissolved in chloro-

form (0.2 ml), and succinic anhydride (0.04 g, 0.39 mmol), DMSO (0.3 ml), and a catalytic amount of DMAP were added. The reaction mixture was kept for 5 h at 80°C, diluted with chloroform (25 ml), washed with water (4 × 15 ml), dried with Na_2SO_4, and evaporated. The residue was chromatographed on a silica gel column eluted with 20 : 1 chloroform–methanol to get (**VIa**); yield 0.08 g (67.8%); R_f 0.7 (D); MS, *m/z*: 608.1 $[M + Na]^+$; ^{1}H NMR: 0.85 [3 H, t, *J* 6.8, $(CH_2)_{15}C\underline{H}_3$], 1.16 (3 H, t, *J* 7.3, $OCH_2C\underline{H}_3$), 1.19–1.33 [32 H, m, $(C\underline{H}_2)_{15}CH_3$ and $OCO(CH_2)_2C\underline{H}_2$], 1.40–1.68 (6 H, m, $OCH_2C\underline{H}_2$, $OCOCH_2C\underline{H}_2$, and $C\underline{H}_2CH_2N$), 2.32 (2 H, t, *J* 7.3, $OCOC\underline{H}_2CH_2$), 2.42–2.51 (2 H, m, $NCOC\underline{H}_2$), 2.61–2.70 (2 H, m, $C\underline{H}_2COOH$), 3.18–3.29 (2 H, m, CH_2N), 3.38–3.48 (4H, m, $C\underline{H}_2OC\underline{H}_2CH_2$), 3.56–3.68 (3 H, m, $OC\underline{H}_2CH_3$ and CHOEt), 4.07 (1 H, dd, *J* 5.6 and 11.9, $CH\underline{H}_aOCO$), 4.23 (1 H, dd, *J* 4.3 and 11.5, $CH\underline{H}_bOCO$), and 6.05 (1 H, m, NH).

***rac*-1-Octadecyl-2-allyl-3-[6-succinylamidohexanoyl)glycerol (VIb)** was obtained as described for (**VIa**) from (**Vd**) (0.08 g, 0.13 mmol), triethylamine (0.1 ml), and succinic anhydride (0.026 g, 0.26 mmol); yield 0.05 g (65.4%); R_f 0.7 (D); ^{1}H NMR: 0.86 [3 H, t, *J* 6.8, $(CH_2)_{15}C\underline{H}_3$], 1.18–1.31 [32 H, m, $(C\underline{H}_2)_{15}CH_3$ and $OCO(CH_2)_2C\underline{H}_2$], 1.45–1.70 (6 H, m, $OCH_2C\underline{H}_2$, $OCOCH_2C\underline{H}_2$, and $C\underline{H}_2CH_2N$), 2.32 (2 H, t, *J* 7.2, $OCOC\underline{H}_2CH_2$), 2.44–2.52 (2 H, m, $NCOC\underline{H}_2$), 2.62–2.71 $C\underline{H}_2COOH$), 3.19–3.30 (2 H, m, CH_2N), 3.42 (2 H, t, *J* 6.8, $OC\underline{H}_2CH_2$), 3.44–3.50 (2 H, m, $CH_2OC_{18}H_{37}$), 3.62–3.74 (1 H, m, CHOAllyl), 4.04–4.14 (3 H, m, $CH\underline{H}_aOCO$ and $OC\underline{H}_2CH{=}CH_2$), 4.24 (1 H, dd, *J* 3.8 and 11.5, $CH\underline{H}_bOCO$), 5.16 (1 H, ddt, *J* 1.3, 1.7, and 10.3, $OCH_2CH{=}CH\underline{H}_a$), 5.26 (1 H, ddt, *J* 1.3, 1.7, and 17.1, $OCH_2CH{=}CH\underline{H}_b$), 5.88 (1 H, ddt, ddt, *J* 5.6, 10.2, and 17.5, $OCH_2C\underline{H}{=}CH_2$), and 5.99–6.10 (1 H, m, NH).

ACKNOWLEDGMENTS

This work was supported by the Russian Foundation for Basic Research, project nos. 01-03-33234, 00-15-866, and 03-03-32482, and the grants: Scientific Research of High Schools on the Priority Directions of Science and Technology, subsection Medicinal and Biologically Active Substances no. 203.05.04.005, Carrying out the Collective Basic Studies on the Basis of Educational Scientific Center on Physiologically Active Substances no. I0563, and the President's Grant for the Support of Leading Scientific Schools of Russia no. NSh-2013.2003.3.

REFERENCES

1. Fuhrhop, J.H. and Tank, H., *Chem. Phys. Lipids*, 1987, vol. 43, pp. 193–199.
2. Grumpton, S.G., Goz, B., and Ishaq, K.S., *Anticancer Res.*, 1988, vol. 8, pp. 1361–1365.
3. Konstantinova, I.D. and Serebrennikova, G.A., *Usp. Khim.*, 1996, vol. 65, pp. 581–598.
4. Konstantinova, I.D., Zaitseva, N.M., Ushakova, I.P., and Serebrennikova, G.A., *Izv. Ross. Acad. Nauk, Ser. Khim.*, 1994, no. 10, pp. 1826–1829.
5. Ballas, N., Zakai, N., Sela, I., and Loyter, A., *Biochim. Biophys. Acta*, 1988, vol. 939, pp. 8–18.
6. Innes, C.L., Smith, P.B., Lanqenbach, R., Tindall, K.R., and Boone, L.R., *J. Virol.*, 1990, vol. 64, pp. 957–964.
7. Duzgunes, N., Goldstein, J.A., Friend, D.S., and Felgner, P.L., *Biochemistry*, 1989, vol. 28, pp. 9179–9184.
8. Sablina, M.A., Ushakova, I.P., and Serebrennikova, G.A., *Khim.–Farm. Zh.*, 1993, vol. 27, pp. 3–13.
9. Marasco, C.J., Piantadosi, C., Meyer, K.L., Morris-Natschke, S., Ishaq, K.S., Small, G.W., and Daniel, L.W., *J. Med. Chem.*, 1990, vol. 33, pp. 985–992.
10. Goddat, J., Coste, H., Vilgrain, I., Chambaz, E., and Driguez, H., *Lipids*, 1992, vol. 27, pp. 331–336.
11. Maslov, M.A., Sycheva, E.V., Morozova, N.G., and Serebrennikova, G.A., *Izv. Ross. Acad. Nauk, Ser. Khim.*, 2000, no. 3, pp. 485–500.
12. Kertscher, P., Ruger, H.-J., Gawrisch, K., and Nuhn, P., *Pharmazie*, 1980, vol. 35, no. 1, pp. 10–14.
13. Heyes, J.A., Niculescu-Duvaz, D., Cooper, R.G., and Springer, C.J., *J. Med. Chem.*, 2002, vol. 45, pp. 105–114.