Synthesis of lipid mediators based on 1,2-dialkylglycerol and cholesterol for targeted delivery of oligo- and polynucleotides into hepatocytes

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The synthesis of cationic glycolipids containing galactose or lactose residue as hepatocyte-targeted markers is described.

Key words: cationic lipids, cholesterol, dialkylglycerol, galactose, lactose, lipofection, hepatocytes.

Among the methods of delivery of genetic material into eukaryoic cells, considerable place belongs to lipofection, *i.e.*, transfer by means of cationic amphiphiles or liposomes.[1] The positively charged liposomes form electrostatic complexes with nucleic acid molecules that have been called lipoplexes. In these complexes, nucleic acids are protected from degradation under the action of cell enzymes, they penetrate into the cell by the endocytosis mechanism. The gene delivery *in vitro* by lipid transfer agents is a routine procedure; however, the use of this method *in vivo* is restricted by low efficiency of the transfer, which is due to the presence of various types of biological barriers (for example, to the interaction of DNA—lipid complexes with blood plasma proteins and their capture by the reticuloendothelial system, and to low specificity of targeting organs and tissues).[2] For increasing the efficiency of the delivery of genetic material, special elements that help overcoming the biological barriers are introduced in the structure of cationic amphiphiles.[3] For example, for addressing specific cells, the molecule of a cationic lipid is modified by targeting peptide or carbohydrate ligands.[4]

Cationic lipids comprise an extensive range of compounds with common structural features such as the presence of positively charged and hydrophobic domains connected by a spacer.[5—7] The hydrophilic positively charged domain is needed for binding nucleic acid and the hydrophobic domain is needed for its encapsulation. In recent years, carbohydrate residues have been incorporated more and more often in cationic amphiphile structures; they acts as targeting markers for the delivery of nucleic acids to hepatocytes,[8—11] macrophages,[12,13] and the nucleus of the HeLa cells.[14] It is known that on the surface of hepatocytes, glycoprotein receptors are exposed, by means of which cell selectively recognize, bind, and internalize galactose-containing molecular assemblies. This feature can be used for targeted delivery of medical drugs by means of liposomes incorporating synthetic galactolipids. In addition, the carbohydrate residue can serve as the basis for construction of one or more cationic groups.[15—18] Amphiphiles containing carbohydrate residues are able to change the supramolecular structure of lipoplexes, inducing a pH-dependent transition of lipids from the lamellar to micellar phase and thus increasing the efficiency of the delivery of genetic material.[19,20] In addition, carbohydrate fragments increase the colloid stability of lipoplexes in blood serum[21,22] and decrease their toxicity.[23]

Here we report the synthesis of monocationic galactolipids, which are potential transfer agents of poly- and oligonucleotides into eukaryotic cells. We assume that synthesized glycolipids would be able to specifically interact with hepatocyte receptors owing to the presence of targeting carbohydrate residues.

As the hydrophobic domain needed for incorporation into a lipid bilayer, we used cholesterol and 1,2-di-*O*-tetradecyl-*rac*-glycerol residues. In the series of glycerol derivatives with saturated long-chain hydrocarbon residues, lipids containing tetradecyl substituents favor the best penetration of lipoplexes into the cells.[5,24] The binding of hydrophobic, hydrophilic, and targeting domains was performed by a spacer based on 6-aminohexanol, which is a suitable bifunctional molecule for the assembly of domains into a common structure of cationic glycolipid. The amino group in the 6-aminohexanol molecule can serve for the formation of a positively charged ammonium group, while the hydroxyl group can serve as the acceptor for the introduction of carbohydrate residues. In the designed glycolipid molecules, the cationic head is

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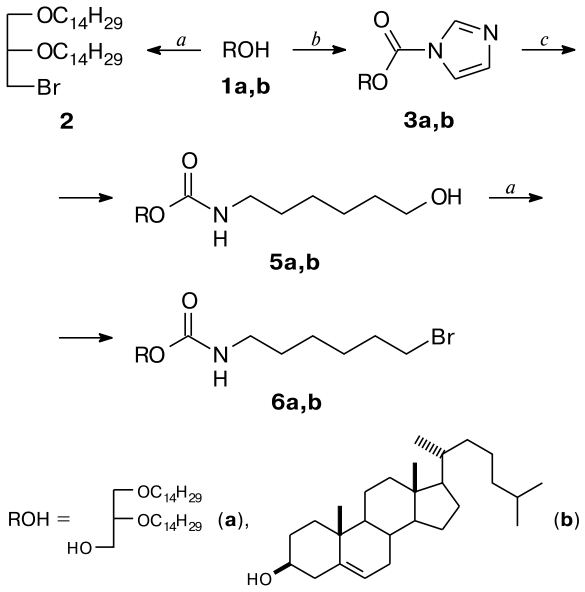
attached to the hydrophobic fragment either directly or through a hexamethylene spacer. In the latter case, the spacer was linked to the hydrophobic domain by an urethane bond.

According to the developed synthetic route, first, we prepared bromo derivatives of 1,2-di-*O*-tetradecyl-*rac*-glycerol and cholesterol (Scheme 1). The starting 1,2-di-*O*-tetradecylglycerol (**1a**) was made to react with CBr_4 in the presence of Ph_3P to give bromide **2** in 90% yield. For the synthesis of cationic lipids where the positively charged group is remote from the hydrophobic residue, 1,2-di-*O*-tetradecylglycerol (**1a**) and cholesterol (**1b**) were treated, in the first step, with an excess of carbonyldiimidazole (CDI) in the presence of Et_3N to give stable imidazolides **3a,b**. The second step was addition of the spacer group to the activated hydrophobic component. The optimal yields of diglyceride **5a** (80%) and cholesterol **5b** (96%) derivatives were attained using a 1.5-fold excess of 6-aminohexanol (**4**). Then the hydroxyl group was replaced by bromine under the same conditions as for compound **2**. For both the diglyceride and the cholesterol derivatives, the bromination proceeded smoothly and rapidly, resulting in compounds **6a** and **6b** in 96 and 83% yields, respectively.

Scheme 1



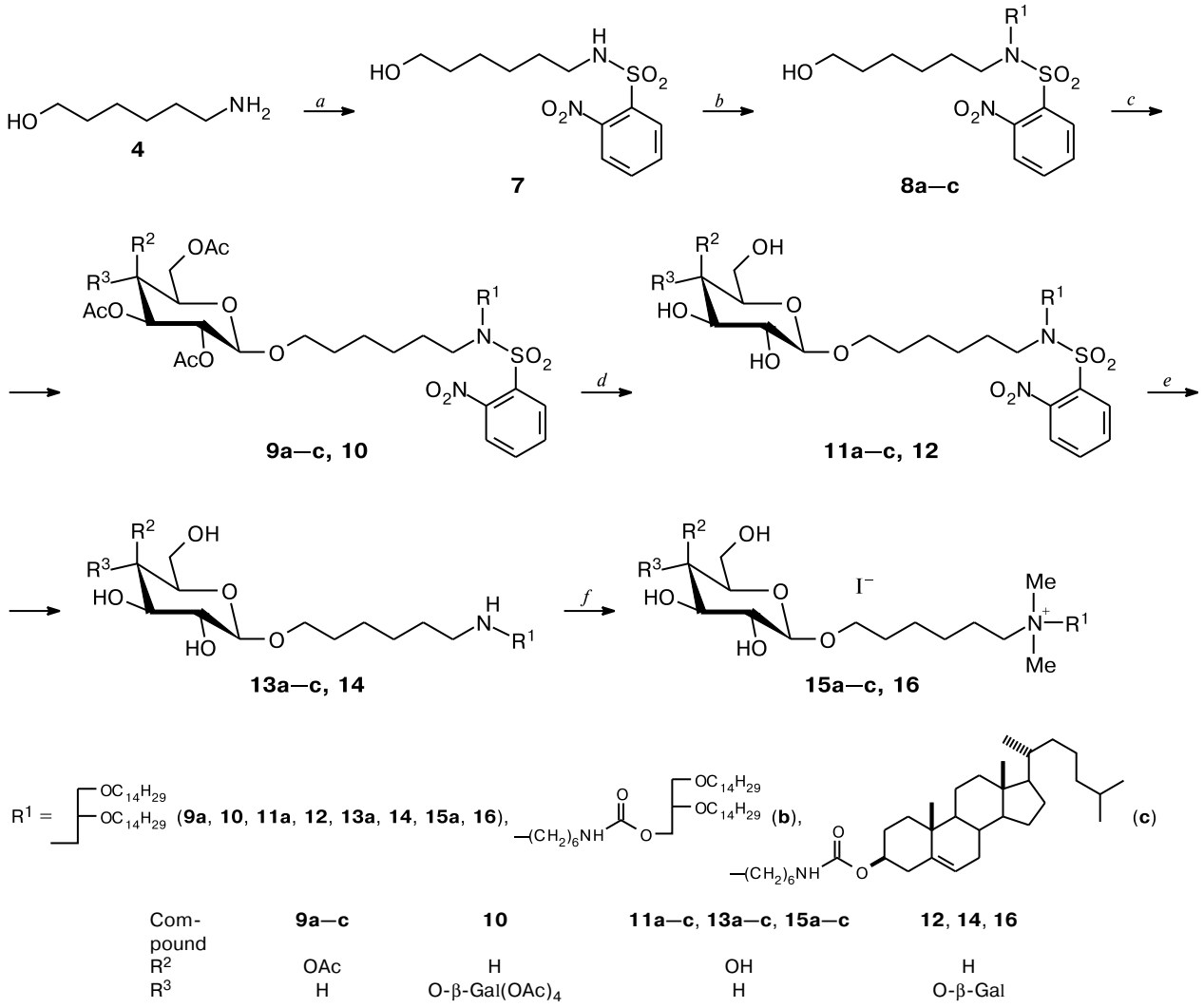
Reagents and conditions: (*a*) CBr_4, Ph_3P, 24 °C; (*b*) CDI, Et_3N, 40 °C; (*c*) $HO(CH_2)_6NH_2$ (**4**), 40 °C.

For the formation of the "procationic" center, the reaction of nitrobenzenesulfonamides with alkyl halides in the presence of cesium carbonate was used. The introduction of 2-nitrobenzenesulfonyl protection provides control over the degree of the N-alkylation. This reaction (the Fukuyama reaction[25—27]) is widely used for the synthesis of secondary amines, because the nitrobenzenesulfonyl group is easily removed under the action of benzenethiol or thioglycolic acid. This approach was implemented as the reaction between 6-aminohexanol (**4**) and 2-nitrobenzenesulfonyl chloride in the presence of Et_3N. This gave sulfonamide **7** (Scheme 2), which was alkylated with bromo derivatives **2**, **6a**, and **6b** in the presence of Cs_2CO_3 in DMF at 80 °C to give amides **8a—c** in 64—86% yields. Note that in the case of bromides **6a**,**b** with a spacer group, the reaction time was 3 h, whereas alkylation with bromide **2** required 48 h, apparently, due to steric hindrance.

The next important stage of the synthesis was the introduction of the carbohydrate markers by the formation of a glycosidic bond. Glycosylation of compounds **8a—c** with 2,3,4,6-tetra-*O*-acetyl-α-D-galactosyl and 2,2′,3,3′,4′,6,6′-hepta-*O*-acetyl-α-lactosyl bromides was carried out by one of the variants of the Königs—Knorr method in a Soxhlet apparatus using $CdCO_3$ as the promoter (see Ref. 28). The yields of the β-glycosylation products **9a—c** and **10** were 45% (for lactose) and 69% (for galactose). The ^1H NMR spectra of these compounds showed doublet signals for protons at the anomeric centers with spin-spin coupling constants $J_{1,2}$ = 7.8—8.0 Hz, indicating the β-configuration of the anomeric center. In the ^{13}C NMR spectra, the signals for anomeric carbon atoms occur at δ 101.20—101.53, thus supporting the β-configuration of the anomeric center. The concomitant α-anomers were isolated in 3 to 8% yields. The acetyl derivative of alcohol **8a** was formed as a glycosylation by-product (yield 10%). Glycosylation of alcohols is rather often accompanied by the formation of their acetyl derivatives.[29]

The subsequent stages of the synthesis were to be N-desulfonylation and deacetylation of compounds **9a—c** and **10** and completion of the cationic head. Two sequences of deprotection reactions were tested. In the first of them, 2-nitrobenzenesulfonyl group was the first to be removed (treatment with benzenethiol in the presence of K_2CO_3). The secondary amines thus formed were isolated in low yields, which was caused by the difficulty of their preparative purification. In addition, we observed partial deacetylation of the carbohydrate component, probably, due to the basicity of the secondary amino group. The second approach according to which compounds **9a—c** and **10** were first deacetylated and then the 2-nitrobenzenesulfonyl group was removed was free from these drawbacks. In addition, in this case, the useful UV-detectable label was longer retained in the lipid molecule. To remove the acetyl protection, compounds **9a—c** and **10** were treated with a freshly prepared methanolic sodium methoxide. After neutralization of the reaction mixture with an ion-exchange resin, products **11a—c**, **12** were isolated by column chromatography on silica gel in 61—98% yields. The removal of the 2-nitrobenzenesulfonyl protection in compounds **11a—c** and **12** was carried out by treatment with a tenfold excess of benzenethiol and potassium

Scheme 2



Compound	9a—c	10	11a—c, 13a—c, 15a—c	12, 14, 16
R^2	OAc	H	OH	H
R^3	H	O-β-Gal(OAc)$_4$	H	O-β-Gal

Reagents and conditions: (*a*) 2-$NO_2C_6H_4SO_2Cl$, Et_3N, 24 °C; (*b*) **2** or **6a**,**b**, Cs_2CO_3, DMF, 80 °C; (*c*) Gal(OAc)$_4$Br or Lac(OAc)$_7$Br, $CdCO_3$, C_6H_6, 80 °C; (*d*) MeONa/MeOH, 24 °C; (*e*) PhSH, K_2CO_3, 24 °C; (*f*) MeI, K_2CO_3, MeCOEt, 50 °C.

carbonate in DMF. Due to the high polarity of secondary amines **13a—c**, **14**, they were isolated by reversed phase chromatography on silica gel LiChroprep® RP-18.

The synthesis of monocationic lipids was completed by quaternization of secondary amines **13a—c**, **14**, which was performed by treatment with an excess of MeI. After reversed phase chromatography, compounds **15a—c**, **16** were isolated in 69—87% yields and their structures were confirmed by NMR spectroscopy and mass spectrometry.

Thus, we developed an approach to the preparation of monocationic lipids with a marker group based on galactose and lactose. The obtained glycolipids are meant for targeted delivery of the genetic material to hepatocytes.

Experimental

Distilled solvents, Russian (Khimmed, Reachim) and foreign (Merck, Fluka, Aldrich, Acros) commercial reagents were used. Benzene was refluxed with Na metal and distilled immediately prior to the reaction; CH_2Cl_2 and Et_3N were refluxed with CaH_2 and distilled; DMF (Merck) was kept over calcined molecular sieves 4 Å.

Thin-layer chromatography was carried out on Kieselgel 60 F_{254} and Kieselgel RP-18 F_{254S} plates (Merck). The spots were visualized by the Dragendorff reagent,[30] phosphomolybdic acid—cerium(IV) sulfate system followed by heating,[31] or under UV light (254 nm). Column chromatography was carried out on silica gel Kieselgel 60 (40—63 μm, Merck) and LiChroprep® RP-18 (40—63 μm, Merck). The ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 pulse Fourier transform spec-

trometer in $CDCl_3$ unless otherwise stated (internal $SiMe_4$). Mass spectra were run on Bruker Ultraflex time-of-flight mass spectrometer (Germany) with laser desorption ionization using 2,5-dihydroxybenzoic acid as the matrix. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer (Japan). Optical rotation was measured on a Digytor Jasco DIP 360 photoelectrical spectropolarimeter (Japan). The melting points were determined on a Boetius hot stage (Germany).

***rac*-1-Bromo-1-deoxy-2,3-di-*O*-tetradecylglycerol (2).** A solution of CBr_4 (8.257 g, 24.90 mmol) in CH_2Cl_2 (10 mL) was added with stirring to a cooled (4 °C) solution of 1,2-di-*O*-tetradecyl-*rac*-glycerol (**1a**)[32] (6.036 g, 12.45 mmol) and Ph_3P (6.531 g, 24.90 mmol) in anhydrous CH_2Cl_2 (30 mL). After 50 min, MeOH (20 mL) was added, the mixture was stirred for 10 min, and the solvents were removed *in vacuo*. The solid residue was chromatographed on a column with silica gel using the petroleum ether—EtOAc mixture (50 : 1) as the eluent to give 6.571 g (96%) of compound **2**. Found (%): C, 67.97; H 11.65. $C_{31}H_{63}BrO_2$. Calculated (%): C, 67.98; H, 11.59. ^{1}H NMR, δ: 0.85 (t, 6 H, 2 $CH_2\underline{Me}$, J = 6.4 Hz); 1.24 (br.s, 44 H, 2 $(CH_2)_{11}$); 1.49—1.62 (m, 4 H, 2 $OCH_2C\underline{H}_2$); 3.43 (t, 2 H, CH_2Br, J = 6.1 Hz); 3.46—3.63 (m, 7 H, $OC\underline{H}_2C\underline{H}CH_2$, 2 $OC\underline{H}_2CH_2$).

[*rac*-2,3-Bis(tetradecyloxy)propyl]imidazole-1-carboxylate (3a). *N*,*N*′-Carbonyldiimidazole (0.7 g, 4.32 mmol) and Et_3N (0.43 mL, 3.1 mmol) were added to a solution of 1,2-di-*O*-tetradecyl-*rac*-glycerol (**1a**) (1.0 g, 2.06 mmol) in anhydrous CH_2Cl_2 (17 mL). The reaction mixture was refluxed for 2 h, cooled, washed with 3% HCl (3×5 mL) and water (2×5 mL), and dried with Na_2SO_4, and the solvent was evaporated to give 1.19 g of product **3a**, which was used without further purification.

(Cholest-5-en-3β-yl) imidazole-1-carboxylate (3b) was prepared in the same way as compound **3a** from cholesterol (**1b**) (1.0 g, 2.59 mmol) and CDI (0.81 g, 4.99 mmol) in the presence of Et_3N (0.52 mL, 3.74 mmol). This gave 1.17 g of compound **3b**, which was used without further purification.

[*rac*-2,3-Bis(tetradecyloxy)propyl] *N*-(6-hydroxyhexyl)-carbamate (5a). 6-Aminohexanol (**4**) (0.75 g, 6.40 mmol) was added to a solution of compound **3a** (2.47 g, 4.27 mmol) in anhydrous CH_2Cl_2 (10 mL), and the mixture was stirred under reflux for 2.5 h. The reaction mixture was washed with 3% HCl (5 mL) and water (2×5 mL), and dried with Na_2SO_4, and the solvent was evaporated. The residue was chromatographed on a column with silica gel, the target compound being eluted with a petroleum ether—EtOAc mixture (2 : 1) to give 2.14 g (80%) of compound **5a**, m.p. 54—56 °C. Found (%): C, 72.60; H, 12.17; N, 2.13. $C_{38}H_{77}NO_5$. Calculated (%): C, 72.67; H, 12.36; N, 2.23. ^{1}H NMR, δ: 0.85 (t, 6 H, 2 $CH_2\underline{Me}$, J = 6.6 Hz); 1.20—1.40 (m, 48 H, 2 $(CH_2)_{11}$, $N(CH_2)_2(C\underline{H}_2)_2(CH_2)_2OH$); 1.42—1.58 (m, 8 H, 3 $OCH_2C\underline{H}_2$, $NHCH_2C\underline{H}_2$); 3.15 (dt, 2 H, $NHC\underline{H}_2$, J = 6.3 Hz, J = 6.7 Hz); 3.37—3.64 (m, 9 H, $OC\underline{H}_2C\underline{H}CH_2$, 2 $OC\underline{H}_2CH_2$, $C\underline{H}_2OH$); 4.06 (dd, 1 H, $CH_2OC(O)$, J = 5.4 Hz, J = 11.5 Hz); 4.17 (dd, 1 H, $CH_2OC(O)$, J = 4.0 Hz, J = 11.5 Hz); 4.62—4.77 (m, 1 H, NH). ^{13}C (δ: 14.49, 23.07, 25.69, 26.42, 26.48, 26.78, 29.75, 29.88, 30.03, 30.08, 30.35, 30.39, 32.30, 32.96, 41.24, 63.12, 64.58, 70.79, 70.97, 72.16, 77.24, 156.84.

Cholest-5-en-3β-yl-*N*-(6-hydroxyhexyl)carbamate (5b). 6-Aminohexanol (**4**) (0.47 g, 4.01 mmol) was added to a solution of compound **3b** (1.29 g, 2.68 mmol) in anhydrous CH_2Cl_2 (10 mL), and the mixture was stirred under reflux for 2.5 h. The reaction mixture was washed with 3% HCl (5 mL) and water (2×5 mL), dried with Na_2SO_4, and the solvent was evaporated. The residue was chromatographed on a column with silica gel using the $CHCl_3$—MeOH mixture (40 : 1) as the eluent to give 1.39 g (96%) of compound **5b**, m.p. 186—188 °C, $[\alpha]_D^{20}$ −12 (*c* 0.5, $CHCl_3$). Found (%): C, 76.96; H, 11.22; N, 2.57. $C_{34}H_{59}NO_3$. Calculated (%): C, 77.07; H, 11.22; N, 2.64. ^{1}H NMR, δ: 0.61 (s, 3 H, C(13)Me); 0.79 (d, 3 H, C(25)Me, J = 6.5 Hz); 0.80 (d, 3 H, C(25)Me, J = 6.5 Hz); 0.85 (d, 3 H, C(20)Me, J = 6.5 Hz); 0.94 (s, 3 H, C(10)Me); 0.98—1.57 (m, 29 H, Chol, $NHCH_2(C\underline{H}_2)_4$); 1.68—2.00 (m, 5 H, Chol); 2.13—2.35 (m, 2 H, $H_2C(4)$); 3.03—3.16 (m, 2 H, $C\underline{H}_2NH$); 3.57 (t, 2 H, $C\underline{H}_2OH$, J = 6.4 Hz); 4.34—4.49 (m, 1 H, H(3)); 4.50—4.61 (m, 1 H, NH); 5.27—5.34 (m, 1 H, H(6)). ^{13}C NMR, δ: 12.03, 18.89, 19.51, 21.21, 22.73, 22.99, 24.00, 24.46, 25.48, 26.57, 28.19, 28.35, 28.41, 30.19 , 32.06, 35.97, 36.36, 36.73, 37.17, 38.76, 39.69, 39.91, 40.87, 42.49, 50.18, 56.30, 56.86, 62.90, 74.39, 122.64, 140.03, 156.40.

[*rac*-2,3-Bis(tetradecyloxy)propyl] *N*-(6-bromohexyl)carbamate (6a). Triphenylphosphine (1.34 g, 5.12 mmol) was added to a cooled (0 °C) solution of compound **5a** (2.14 g, 3.41 mmol) in anhydrous CH_2Cl_2 (10 mL). Then CBr_4 (1.69 g, 5.12 mmol) was added in portions, and the mixture was stirred for 1 h at 25 °C. Methanol (5 mL) was added and after 10 min, the solvents were removed *in vacuo*. The residue was chromatographed on a column with silica gel using a petroleum ether—EtOAc mixture (10 : 1) as the eluent to give 2.25 g (96%) of compound **6a**, m.p. 32—34 °C. Found (%): C, 65.95; H, 11.14; N, 1.91. $C_{38}H_{76}BrNO_4$. Calculated (%): C, 66.06; H, 11.09; N, 2.03. ^{1}H NMR, δ: 0.85 (t, 6 H, 2 $CH_2\underline{Me}$, J = 6.9 Hz); 1.15—1.58 (m, 54 H, 2 $(CH_2)_{11}$, 2 $OCH_2C\underline{H}_2$, $NHCH_2(C\underline{H}_2)_3(CH_2)_2Br$); 1.78—1.88 (m, 2 H, $C\underline{H}_2CH_2Br$); 3.14 (dt, 2 H, $NHC\underline{H}_2$, J = 6.2 Hz, J = 6.9 Hz); 3.36 (t, 2 H, CH_2Br, J = 6.8 Hz); 3.38—3.63 (m, 7 H, $OC\underline{H}_2C\underline{H}CH_2$, 2 $OC\underline{H}_2CH_2$); 4.06 (dd, 1 H, $CH_2OC(O)$, J = 5.3 Hz, J = 11.4 Hz); 4.18 (dd, 1 H, $CH_2OC(O)$, J = 3.8 Hz, J = 11.4 Hz); 4.64—4.73 (m, 1 H, NH). ^{13}C NMR, δ: 14.50, 23.07, 26.26, 26.42, 26.47, 28.17, 29.75, 29.87, 30.03, 30.07, 30.20, 30.39, 32.30, 32.99, 34.06, 41.26, 64.57, 70.75, 70.95, 72.15, 77.21, 156.77.

(Cholest-5-en-3β-yl) *N*-(6-bromohexyl)carbamate (6b) was prepared in the same way as compound **6a** from **5b** (1.39 g, 2.57 mmol), Ph_3P (1.35 g, 5.13 mmol), and CBr_4 (1.70 g, 5.13 mmol). The product was isolated by chromatography on silica gel (petroleum ether—EtOAc (15 : 1)) giving 1.29 g (83%) of compound **6b**, m.p. 106—108 °C, $[\alpha]_D^{20}$ −21 (*c* 1, $CHCl_3$). Found (%): C, 69.24; H, 10.15; N, 2.31. $C_{34}H_{58}BrNO_2$. Calculated (%): C, 68.90; H, 9.86; N, 2.36. ^{1}H NMR, δ: 0.61 (s, 3 H, C(13)Me); 0.79 (d, 3 H, C(25)Me, J = 6.5 Hz); 0.80 (d, 3 H, C(25)Me, J = 6.5); 0.85 (d, 3 H, C(20)Me, J = = 6.5 Hz); 0.94 (s, 3 H, C(10)Me); 0.98—1.57 (m, 27 H, Chol, $NHCH_2(C\underline{H}_2)_3(CH_2)_2Br$); 1.68—1.98 (m, 7 H, Chol, $C\underline{H}_2CH_2Br$); 2.12—2.34 (m, 2 H, $H_2C(4)$); 3.03—3.15 (m, 2 H, $NHC\underline{H}_2$); 3.34 (t, 2 H, CH_2Br, J = 6.8 Hz); 4.35—4.48 (m, 1 H, H(3)); 4.48—4.62 (m, 1 H, NH); 5.28—5.33 (m, 1 H, H(6)). ^{13}C NMR, δ: 12.04, 18.90, 19.52, 21.23, 22.74, 23.00, 24.01, 24.47, 26.08, 27.99, 28.19, 28.37, 28.42, 30.08, 32.07 32.81, 33.91, 35.98, 36.37, 36.75, 37.18, 38.76, 39.70, 39.92, 40.94, 42.50, 50.20, 56.32, 56.87, 74.40, 122.66, 140.03, 156.35.

***N*-(6-Hydroxyhexyl)-2-nitrobenzenesulfonamide (7)**. Molecular sieves 4 Å and Et_3N (6 mL) were added with stirring to a cooled (4 °C) solution of 6-aminohexanol (**4**) (2.00 g, 17.07 mmol) in anhydrous CH_2Cl_2 (30 mL). Then a solution of 2-nitrobenze-

nesulfonyl chloride (4.51 g, 20.35 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise. After 24 h, the reaction mixture was filtered through Celite® 545 and washed with CH_2Cl_2, and the solvent was removed *in vacuo*. The residue was chromatographed on a column with silica gel using a $CHCl_3$—MeOH mixture (100 : 1) as the eluent to give 3.97 g (77%) of compound **7**, m.p. 77—78 °C. Found (%): C, 47.77; H, 6.15; N, 9.28. $C_{12}H_{18}N_2O_5S$. Calculated (%): C, 47.67; H, 6.00; N, 9.27. ^{1}H NMR, δ: 1.21—1.59 (m, 8 H, $NCH_2(C\underline{H}_2)_4CH_2OH$); 3.07 (dt, 2 H, $C\underline{H}_2NH$, J = 6.4 Hz); 3.58 (t, 2 H, $C\underline{H}_2OH$, J = 6.4 Hz); 5.23—5.38 (m, 1 H, NH); 7.68—7.78 (m, 2 H, Ar); 7.80—7.88 and 8.06—8.15 (both m, 1 H each, Ar).

***N*-(6-Hydroxyhexyl)-*N*-[*rac*-2,3-bis(tetradecyloxy)propyl]-2-nitrobenzenesulfonamide (8a).** Cesium carbonate (0.63 g, 1.94 mmol) was added to a solution of compound **7** (0.50 g, 1.66 mmol) in anhydrous DMF (10 mL). Then a solution of compound **2** (0.73 g, 1.33 mmol) in anhydrous DMF (3 mL) was added in portions. The reaction mixture was kept for 48 h at 80 °C and cooled to 24 °C, petroleum ether (15 mL) was added, and the mixture was washed with water (3×5 mL). The organic products were extracted from the aqueous phase with petroleum ether (5×10 mL). The combined organic extract was dried with Na_2SO_4 and filtered, and the solvent was removed *in vacuo*. The residue was chromatographed on a column with silica gel using a petroleum ether—EtOAc mixture (2.5 : 1) as the eluent to give 0.66 g (64%) of compound **8a** as a crystallizing oil. Found (%): C, 67.14; H, 10.48; N, 3.73. $C_{43}H_{80}N_2O_7S$. Calculated (%): C, 67.15; H, 10.48; N, 3.64. ^{1}H NMR, δ: 0.81 (t, 6 H, 2 $CH_2\underline{Me}$, J = 6.5 Hz); 1.15—1.29 (m, 48 H, 2 $(CH_2)_{11}$, $N(CH_2)_2(C\underline{H}_2)_2(CH_2)_2OH$); 1.34—1.54 (m, 8 H, 2 $OCH_2C\underline{H}_2$, $NCH_2C\underline{H}_2(CH_2)_2C\underline{H}_2CH_2OH$); 3.21—3.50 (m, 11 H, $OCH_2CHCH_2NCH_2$, 2 $OC\underline{H}_2CH_2$); 3.54 (t, 2 H, CH_2OH, J = 6.5 Hz); 7.52—7.64 (m, 3 H, Ar); 7.93—7.99 (m, 1 H, Ar). ^{13}C NMR, δ: 14.49, 23.06, 25.64, 26.45, 26.48, 26.61, 27.95, 29.74, 29.87, 30.02, 30.08, 30.42, 32.29, 32.93, 49.06, 49.10, 63.08, 70.71, 70.87, 72.12, 78.09, 124.40, 131.35, 131.81, 133.56, 134.36, 148.47.

[*rac*-2,3-Bis(tetradecyloxy)propyl] *N*-[13-hydroxy-7-(2-nitrophenylsulfonyl)-7-azatridecyl]carbamate (8b). Cesium carbonate (0.23 g, 0.70 mmol) and then a solution of compound **6a** (0.36 g, 0.52 mmol) in anhydrous DMF (5 mL) were added with stirring to a solution of compound **7** (0.11 g, 0.364 mmol) in anhydrous DMF (10 mL). The reaction mixture was kept for 3 h at 80 °C, cooled to 24 °C, diluted with $CHCl_3$ (10 mL), and washed with water (10 mL), the aqueous phase was extracted with $CHCl_3$ (3×5 mL), the combined organic extract was washed with water (5 mL), dried with Na_2SO_4, and filtered, and the solvents were removed *in vacuo*. The residue was chromatographed on a column with silica gel using a petroleum ether—EtOAc mixture (1.5 : 1) as the eluent to give 0.285 g (86%) of compound **8b** as a crystallizing oil. Found (%): C, 64.83; H, 10.89; N, 4.49. $C_{50}H_{93}N_3O_9S \cdot H_2O$. Calculated (%): C, 64.55; H, 10.59; N, 4.52. ^{1}H NMR, δ: 0.83 (t, 6 H, 2 $CH_2\underline{Me}$, J = 6.8 Hz); 1.17—1.33 (m, 52 H, 2 $(CH_2)_{11}$, 2 $N(CH_2)_2(C\underline{H}_2)_2$); 1.35—1.55 (m, 12 H, 2 $OCH_2C\underline{H}_2$, 3 $NCH_2C\underline{H}_2$, $C\underline{H}_2CH_2OH$); 3.03—3.13 (m, 2 H, $NHC\underline{H}_2$); 3.18—3.26 (m, 4 H, CH_2NCH_2); 3.35—3.55 (m, 7 H, $OC\underline{H}_2C\underline{H}CH_2$, 2 $OC\underline{H}_2CH_2$); 3.56 (t, 2 H, $C\underline{H}_2OH$, J = 6.4 Hz); 4.03 (dd, 1 H, $CH_2OC(O)$, J = 5.3 Hz, J = 11.3 Hz); 4.14 (dd, 1 H, $CH_2OC(O)$, J = 4.3 Hz, J = 11.3 Hz); 4.67—4.78 (m, 1 H, NH); 7.55—7.69 (m, 3 H, Ar); 7.92—8.05 (m, 1 H, Ar). ^{13}C NMR, δ: 14.29, 22.85, 25.42, 26.27, 26.42, 28.21, 29.53, 29.67, 29.82, 29.86, 30.17, 32.09, 32.66, 41.00, 47.33, 62.80, 64.36, 70.55, 70.76, 71.95, 77.00, 124.27, 130.87, 131.68, 133.47, 133.89, 148.18, 156.59.

(Cholest-5-en-3β-yl) *N*-[13-hydroxy-7-(2-nitrophenylsulfonyl)-7-azatridecyl]carbamate (8c) was prepared in the same way as compound **8b** from **7** (0.13 g, 0.43 mmol) and **6b** (0.26 g, 0.43 mmol) in the presence of Cs_2CO_3 (0.84 g, 2.58 mmol). Compound **8c** was formed (0.301 g, 86%) as a crystallizing oil, $[\alpha]_D^{20}$ −15 (*c* 1, $CHCl_3$). Found (%): C, 68.01; H, 10.21; N, 5.51. $C_{46}H_{75}N_3O_7S$. Calculated (%): C, 67.86; H, 9.28; N, 5.16. ^{1}H NMR, δ: 0.65 (s, 3 H, C(13)Me); 0.73 (d, 3 H, C(25)Me, J = 6.5 Hz); 0.84 (d, 3 H, C(25)Me, J = 6.5 Hz); 0.89 (d, 3 H, C(20)Me, J = 6.5 Hz); 0.98 (s, 3 H, C(10)Me); 0.99—1.57 (m, 37 H, Chol, $NHCH_2(C\underline{H}_2)_4CH_2NCH_2(C\underline{H}_2)_4CH_2OH$); 1.68—1.98 (m, 5 H, Chol); 2.15—2.38 (m, 2 H, $H_2C(4)$); 3.05—3.19 (m, 2 H, $NHC\underline{H}_2$); 3.20—3.28 (m, 4 H, CH_2NCH_2); 3.60 (t, 2 H, $C\underline{H}_2OH$, J = 6.5 Hz); 4.38—4.53 (m, 1 H, H(3)); 4.54—4.64 (m, 1 H, NH); 5.32—5.37 (m, 1 H, H(6)); 7.56—7.68 (m, 3 H, Ar); 7.96—8.00 (m, 1 H, Ar). ^{13}C NMR, δ: 12.24, 19.09, 19.71, 21.42, 22.94, 23.20, 24.21, 24.67, 25.64, 26.55, 26.65, 28.39, 28.44, 28.56, 28.61, 29.74, 29.87, 30.07, 30.19, 30.27, 32.90, 36.17, 36.56, 36.94, 37.38, 38.96, 39.90, 40.12, 41.07, 42.69, 46.03, 47.52, 50.39, 56.51, 57.07, 63.06, 64.72, 122.84, 124.48, 131.11, 131.88, 133.65, 135.22, 140.25, 148.01, 156.53.

***N*-[*rac*-2,3-Bis(tetradecyloxy)propyl]-*N*-[6-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyloxy)hexyl]-2-nitrobenzenesulfonamide (9a).** Calcined $CdCO_3$ (0.230 g, 1.333 mmol) was added to a solution of compound **8a** (0.343 g, 0.446 mmol) in anhydrous benzene (40 mL), and the mixture was stirred under reflux in a Soxhlet apparatus with calcined granulated silica gel. After six cycles, a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide[33] (0.549 g, 1.333 mmol) in anhydrous benzene (2 mL) was added dropwise to the reaction mixture. After 7 h, the precipitate was filtered off and washed with $CHCl_3$, and the solvents were removed *in vacuo*. The residue was chromatographed on a column with silica gel using a toluene—EtOAc mixture (10 : 1 → 2 : 1) as the eluent to give 0.338 g (69%) of compound **9a** as a crystallizing oil, $[\alpha]_D^{20}$ −2 (*c* 1.9, $CHCl_3$). Found (%): C, 62.39; H, 9.17; N, 2.57. $C_{57}H_{98}N_2O_{16}S$. Calculated (%): C, 62.27; H, 8.98; N, 2.55. ^{1}H NMR, δ: 0.81 (t, 6 H, 2 $CH_2\underline{Me}$, J = 6.5 Hz); 1.16—1.25 (m, 48 H, 2 $(CH_2)_{11}$, $N(CH_2)_2(C\underline{H}_2)_2(CH_2)_2O$); 1.31—1.57 (m, 8 H, 2 $C\underline{H}_2CH_2O$, $NCH_2C\underline{H}_2(CH_2)_2C\underline{H}_2CH_2O$); 1.91 (s, 3 H), 1.98 (s, 6 H), 2.08 (s, 3 H) (4 MeCO); 3.16—3.56 (m, 12 H, $OCH_2CHCH_2NCH_2$, 2 $CH_2C\underline{H}_2O$, $CH\underline{H}_aO$); 3.70—3.88 (m, 2 H, $CH\underline{H}_bO$, H(5) Gal); 4.07—4.11 (m, 2 H, H(6) Gal); 4.38 (d, 1 H, H(1) Gal, $J_{1,2}$ = 7.8 Hz); 4.94 (dd, 1 H, H(3) Gal, $J_{3,4}$ = 3.4 Hz, $J_{3,2}$ = = 10.3 Hz); 5.12 (dd, 1 H, H(2) Gal, $J_{2,1}$ = 7.8 Hz, $J_{2,3}$ = 10.3 Hz); 5.30—5.35 (m, 1 H, H(4) Gal); 7.50—7.64 (m, 3 H, Ar); 7.93—8.00 (m, 1 H, Ar). ^{13}C NMR, δ: 14.20, 20.67, 20.76, 20.83, 22.75, 25.45, 26.14, 26.27, 27.65, 29.35, 29.43, 29.56, 29.72, 29.77, 30.11, 32.00, 48.76, 61.31, 67.12, 68.95, 70.08, 70.40, 70.56, 70.64, 71.03, 71.80, 76.98, 101.34, 124.10, 131.06, 131.54, 133.28, 134.05, 148.15, 169.48, 170.27, 170.38, 170.49.

[*rac*-2,3-Bis(tetradecyloxy)propyl]-*N*-[13-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyloxy)-7-(2-nitrophenylsulfonyl)-7-azatridecyl]carbamate (9b). Calcined $CdCO_3$ (0.78 g, 4.52 mmol) was added to a solution of compound **8b** (1.37 g, 1.50 mmol) in anhydrous benzene (20 mL), and the mixture was refluxed with stirring in a Soxhlet apparatus with calcined granulated silica gel. After five cycles, 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyra-

nosyl bromide (0.93 g, 2.26 mmol) was added in portions. The reaction mixture was stirred under reflux for 15 h, the precipitate was filtered off, and the solvents were removed *in vacuo*. The residue was chromatographed on a column using a toluene—EtOAc mixture (4.5 : 1) as the eluent to give 1.13 g (60%) of compound **9b** as a crystallizing oil, $[\alpha]_D^{20}$ +3.5 (*c* 1, $CHCl_3$). Found (%): C, 61.76; H, 9.30; N, 3.36. $C_{64}H_{111}N_3O_{18}S$. Calculated (%): C, 61.86; H, 9.00; N, 3.38. ^{1}H NMR, δ: 0.81 (t, 6 H, 2 $CH_2\underline{Me}$, J = 6.5 Hz); 1.14—1.31 (m, 52 H, 2 $(CH_2)_{11}$, 2 $N(CH_2)_2(C\underline{H}_2)_2$); 1.34—1.56 (m, 12 H, 3 $OCH_2C\underline{H}_2$, 3 $NCH_2C\underline{H}_2$); 1.91 (s, 3 H), 1.98 (s, 6 H), 2.08 (s, 3 H) (4 MeCO); 3.01—3.10 (m, 2 H, $NHC\underline{H}_2$); 3.15—3.24 (m, 4 H, CH_2NCH_2); 3.34—3.58 (m, 8 H, $OC\underline{H}_2C\underline{H}CH_2$, 2 $OC\underline{H}_2CH_2$, $CH\underline{H}_aO$); 3.74—3.87 (m, 2 H, $CH\underline{H}_bO$, H(5) Gal); 3.97—4.17 (m, 4 H, $CH_2OC(O)$, H(6) Gal); 4.38 (d, 1 H, H(1) Gal, $J_{1,2}$ = = 8.0 Hz); 4.62—4.70 (m, 1 H, NH); 4.94 (dd, 1 H, H(3) Gal, $J_{3,4}$ = 3.4 Hz, $J_{3,2}$ = 10.6 Hz); 5.13 (dd, 1 H, H(2) Gal, $J_{2,1}$ = 8.0 Hz, $J_{2,3}$ = 10.6 Hz); 5.31—5.34 (m, 1 H, H(4) Gal); 7.52—7.66 (m, 3 H, Ar); 7.91—8.26 (m, 1 H, Ar). ^{13}C NMR, δ: 14.29, 20.77, 20.86, 20.95, 22.86, 25.55, 26.22, 26.27, 26.42, 28.20, 29.53, 29.67, 29.83, 30.18, 32.10, 41.02, 47.18, 61.42, 64.39, 67.23, 69.08, 70.18, 70.56, 70.76, 71.12, 71.95, 77.03, 101.53, 124.29, 130.90, 131.71, 133.50, 133.95, 148.18, 156.57, 169.60, 170.35, 170.46.

(Cholest-5-en-3β-yl) *N*-[13-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyloxy)-7-(2-nitrophenylsulfonyl)-7-azatridecyl]carbamate (9c) was prepared in the same way as compound **9b** from **8c** (0.98 g, 1.20 mmol), $CdCO_3$ (0.617 g, 3.58 mmol), and 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (0.736 g, 1.79 mmol). Chromatography on silica gel (toluene—EtOAc, 3 : 1) gave 0.882 g (64%) of compound **9c** as a crystallizing oil, $[\alpha]_D^{20}$ −1.5 (*c* 1, $CHCl_3$). Found (%): C, 63.33; H, 8.19; N, 3.22. $C_{60}H_{93}N_3O_{16}S$. Calculated (%): C, 62.97; H, 8.19; N, 3.67. ^{1}H NMR, δ: 0.65 (s, 3 H, C(13)Me); 0.73 (d, 3 H, C(25)Me, J = 6.5 Hz); 0.84 (d, 3 H, C(25)Me, J = 6.5 Hz); 0.89 (d, 3 H, C(20)Me, J = 6.5 Hz); 0.98 (s, 3 H, C(10)Me); 0.99—1.57 (m, 37 H, Chol, $NHCH_2(C\underline{H}_2)_4CH_2NCH_2(C\underline{H}_2)_4CH_2O$); 1.68—1.95 (m, 5 H, Chol); 1.92 (s, 3 H), 1.98 (s, 6 H), 2.08 (s, 3 H) (4 MeCO); 2.16—2.34 (m, 2 H, $H_2C(4)$); 3.00—3.10 (m, 2 H, $NHC\underline{H}_2$); 3.14—3.25 (m, 4 H, CH_2NCH_2); 3.39 (dt, 1 H, $CH\underline{H}_aO$, J = 6.9 Hz, J = 9.5 Hz); 3.75—3.87 (m, 2 H, $CH\underline{H}_bO$, H(5) Gal); 4.01—4.16 (m, 2 H, H(6) Gal); 4.33—4.48 (m, 1 H, H(3)); 4.38 (d, 1 H, H(1) Gal, $J_{1,2}$ = 7.9 Hz); 4.50—4.59 (m, 1 H, NH); 4.95 (dd, 1 H, H(3) Gal, $J_{3,4}$ = 3.5 Hz, $J_{3,2}$ = 10.5 Hz); 5.13 (dd, 1 H, H(2) Gal, $J_{2,1}$ = 7.9 Hz, $J_{2,3}$ = = 10.5 Hz); 5.26—5.33 (m, 2 H, H(6) Chol, H(4) Gal); 7.52—7.65 (m, 3 H, Ar); 7.91—7.96 (m, 1 H, Ar). ^{13}C NMR, δ: 12.01, 18.86, 19.49, 20.79, 20.87, 20.96, 21.19, 22.72, 22.99, 23.97, 24.44, 25.53, 26.36, 26.42, 28.17, 28.33, 28.38, 29.44, 29.85, 30.06, 32.02, 32.06, 35.95, 36.33, 36.71, 37.15, 38.73, 39.67, 39.87, 40.85, 42.45, 47.21, 47.27, 50.15, 56.26, 56.83, 61.40, 67.21, 68.90, 69.05, 70.19, 70.73, 71.10, 71.84, 74.35, 101.50, 122.63, 124.28, 130.87, 131.71, 133.50, 133.89, 140.00, 148.16, 156.34, 169.60, 170.37, 170.47, 170.61.

***N*-[*rac*-2,3-Bis(tetradecyloxy)propyl]-*N*-[6-(2,2′,3,3′,4′,6,6′-hepta-*O*-acetyl-β-lactosyloxy)hexyl]-2-nitrobenzenesulfonamide (10)** was prepared in the same way as compound **9a** from **8** (0.760 g, 0.988 mmol), $CdCO_3$ (0.341 g, 1.978 mmol), and 2,2′,3,3′,4′,6,6′-hepta-*O*-acetyl-α-lactosyl bromide[34] (1.411 g, 2.017 mmol). Chromatography on silica gel (toluene—EtOAc, 12 : 1) gave 0.740 g (54%) of compound **10** as a crystallizing oil, $[\alpha]_D^{23}$ −8.15 (*c* 1, $CHCl_3$). MS, m/z (I_{rel} (%)): 1387.935 $[M + H]^+$ (100). Calculated for $C_{69}H_{114}N_2O_{24}S$: 1386.748 $[M]^+$. ^{1}H NMR, δ: 0.84 (t, 6 H, 2 $CH_2\underline{Me}$, J = 6.8 Hz); 1.20—1.30 (m, 48 H, 2 $(CH_2)_{11}$, $N(CH_2)_2(C\underline{H}_2)_2(CH_2)_2O$); 1.32—1.55 (m, 8 H, 2 $C\underline{H}_2CH_2O$, $NCH_2C\underline{H}_2(CH_2)_2C\underline{H}_2CH_2O$); 1.91, 1.96, 1.98, 1.99, 2.06, 2.08 and 2.10 (all s, 3 H each, 7 COMe); 3.18—3.57 (m, 12 H, $OCH_2CHCH_2NCH_2$, 2 $CH_2C\underline{H}_2O$, $CH\underline{H}_aO$); 3.65—3.75 (m, 2 H, $CH\underline{H}_bO$, H(5) Lac); 3.78—3.86 (m, 1 H, H(5′) Lac); 3.91—4.12 (m, 4 H, H(6), H(6′) Lac); 4.37 (d, 1 H, H(1′) Lac, $J_{1',2'}$ = 7.8 Hz); 4.41 (m, 1 H, H(4) Lac); 4.43 (d, 1 H, H(1) Lac, $J_{1,2}$ = 7.8 Hz); 4.79 (dd, 1 H, H(2) Lac, $J_{2,1}$ = 7.8 Hz, $J_{2,3}$ = 9.4 Hz); 4.89 (dd, 1 H, H(3′) Lac, $J_{3',4'}$ = 3.4 Hz, $J_{3',2'}$ = = 10.3 Hz); 5.03 (dd, 1 H, H(2′) Lac, $J_{2',1'}$ = 7.8 Hz, $J_{2',3'}$ = = 10.3 Hz); 5.12 (t, 1 H, H(3) Lac, $J_{3,2}$ = $J_{3,4}$ = 9.4 Hz); 5.29 (m, 1 H, H(4′) Lac); 7.50—7.62 (m, 3 H, Ar); 7.90—8.03 (m, 1 H, Ar). ^{13}C NMR, δ: 14.19, 20.57, 20.70, 20.92, 22.79, 25.53, 26.22, 26.24, 26.36, 27.75, 29.43, 29.46, 29.62, 29.77, 29.81, 30.21, 32.04, 48.89, 48.96, 61.00, 62.27, 66.86, 69.39, 69.99, 70.64, 70.91, 71.19, 71.90, 71.98, 72.85, 73.09, 76.49, 77.90, 100.75, 101.20, 124.17, 131.16, 131.53, 133.30, 148.15, 169.16, 169.63, 169.83, 170.12, 170.19, 170.42.

***N*-[*rac*-2,3-Bis(tetradecyloxy)propyl]-*N*-[6-(β-D-galactopyranosyloxy)hexyl]-2-nitrobenzenesulfonamide (11a).** A 1 *M* solution of MeONa in MeOH (0.5 mL) was added to a solution of compound **9a** (0.973 g, 0.885 mmol) in a $CHCl_3$: MeOH mixture (1 : 1). After 30 min, the reaction mixture was neutralized with the ion-exchange resin Amberlite IR-120 (H^+). The resin was filtered off and washed with MeOH, the solvents were removed *in vacuo*, and the residue was chromatographed on a column with silica gel using a toluene—acetone mixture (2 : 1 → 1 : 2) as the eluent to give 0.501 g (61%) of compound **11a** as a crystallizing oil, $[\alpha]_D^{20}$ −2.5 (*c* 3, $CHCl_3$). Found (%): C, 63.00; H, 10.07; N, 2.95. $C_{49}H_{90}N_2O_{12}S$. Calculated (%): C, 63.19; H, 9.74; N, 3.01. ^{1}H NMR, δ: 0.82 (t, 6 H, 2 $CH_2\underline{Me}$, J = 6.8 Hz); 1.16—1.28 (m, 48 H, 2 $(CH_2)_{11}$, $N(CH_2)_2(C\underline{H}_2)_2(CH_2)_2O$); 1.32—1.56 (m, 8 H, 2 $C\underline{H}_2CH_2O$, $NCH_2C\underline{H}_2(CH_2)_2C\underline{H}_2CH_2O$); 3.19—3.64 (m, 15 H, $OCH_2CHCH_2NCH_2$, 2 $CH_2C\underline{H}_2O$, $CH\underline{H}_aO$, H(6) Gal, H(3) Gal); 3.72—3.87 (m, 3 H, $CH\underline{H}_bO$, H(5) Gal, H(2) Gal); 3.95—3.99 (m, 1 H, H(4) Gal); 4.17 (d, 1 H, H(1) Gal, $J_{1,2}$ = = 7.4 Hz); 7.53—7.65 (m, 3 H, Ar); 7.94—87.98 (m, 1 H, Ar). ^{13}C NMR, δ: 14.17, 22.75, 25.41, 26.11, 26.16, 27.47, 29.43, 29.56, 29.72, 29.77, 30.09, 31.98, 48.58, 61.85, 69.23, 70.07, 70.55, 71.49, 71.80, 73.67, 74.21, 77.58, 103.27, 124.15, 130.98, 131.68, 133.46, 133.88, 148.09.

[*rac*-2,3-Bis(tetradecyloxy)propyl] *N*-[13-(β-D-galactopyranosyloxy)-7-(2-nitrophenylsulfonyl)-7-azatridecyl]carbamate (11b). A 0.5 *M* solution of MeONa in MeOH (0.2 mL) was added to a solution of compound **9b** (0.13 g, 0.11 mmol) in MeOH (10 mL). After 1 h, the reaction mixture was neutralized with the ion-exchange resin Dowex 50W×8 (H^+). The resin was filtered off and washed with MeOH, and the solvent was removed *in vacuo*. The residue was chromatographed on a column with silica gel using a toluene—acetone mixture (1 : 1) as the eluent to give 0.094 g (84%) of compound **11b** as a crystallizing oil, $[\alpha]_D^{20}$ +4 (*c* 1, $CHCl_3$—MeOH, 1 : 1). MS, m/z (I_{rel} (%)): 1096.576 $[M + Na]^+$ (100), 1112.578 $[M + K]^+$ (100). Calculated for $C_{56}H_{103}N_3O_{14}S$: 1073.716 $[M]^+$. ^{1}H NMR, δ: 0.80 (t, 6 H, 2 CH_2Me, J = 6.5 Hz); 1.18—1.35 (m, 52 H, 2 $(CH_2)_{11}$, 2 $N(CH_2)_2(C\underline{H}_2)_2$); 1.36—1.61 (m, 12 H, 2 $OCH_2C\underline{H}_2$, 3 $NCH_2C\underline{H}_2$, $C\underline{H}_2CH_2O$); 3.04—3.13 (m, 2 H, $NHC\underline{H}_2$);

3.20—3.28 (m, 4 H, CH_2NCH_2); 3.38—3.90 (m, 14 H, $OCH_2CHCH_2OC(O)$, 2 OCH_2CH_2, CH_2O, H(2) Gal, H(3) Gal, H(5) Gal, H(6) Gal); 3.99—4.04 (m, 1 H, H(4) Gal); 4.05 (dd, 1 H, $CH_aOC(O)$, J = 5.3 Hz, J = 11.2 Hz); 4.15 (dd, 1 H, $CH_bOC(O)$, J = 4.1 Hz, J = 11.2 Hz); 4.20—4.25 (m, 1 H, H(1) Gal); 4.76—4.90 (m, 1 H, NH); 7.57—7.72 (m, 3 H, Ar); 7.93—8.00 (m, 1 H, Ar). ^{13}C NMR, δ: 14.29, 22.85, 25.50, 26.20, 26.26, 26.32, 26.41, 28.09, 29.52, 29.67, 29.81, 29.86, 29.98, 30.17, 32.08, 41.03, 47.18, 61.97, 64.39, 69.32, 70.12, 70.58, 70.77, 71.64, 71.96, 73.71, 74.34, 77.01, 103.34, 124.33, 130.76, 131.87, 133.68, 148.13, 156.63.

(Cholest-5-en-3β-yl) *N*-[13-(β-D-galactopyranosyloxy)-7-(2-nitrophenylsulfonyl)-7-azatridecyl]carbamate (11c) was prepared in the same way as compound **11b** from **9c** (0.350 g). This gave 0.26 g (87%) of compound **11c**, m.p. 78—80 °C, $[\alpha]_D^{20}$ −18 (*c* 1, $CHCl_3$—MeOH, 1 : 1). MS, *m/z* (I_{rel} (%)): 998.597 $[M + Na]^+$ (100), 1014.588 $[M + K]^+$ (100). Calculated for $C_{52}H_{85}N_3O_{12}S$: 975.585 $[M]^+$. ^{1}H NMR, δ: 0.60 (s, 3 H, C(13)Me); 0.70 (d, 3 H, C(25)Me, J = 6.5 Hz); 0.80 (d, 3 H, C(25)Me, J = 6.5 Hz); 0.86 (d, 3 H, C(20)Me, J = 6.5 Hz); 0.94 (s, 3 H, C(10)Me); 0.98—1.54 (m, 37 H, Chol, $NHCH_2(CH_2)_4CH_2NCH_2(CH_2)_4CH_2O$); 1.70—1.99 (m, 5 H, Chol); 2.13—2.31 (m, 2 H, $H_2C(4)$); 2.95—3.06 (m, 2 H, $NHCH_2$); 3.13—3.26 (m, 4 H, CH_2NCH_2); 3.35—4.00 (m, 8 H, CH_2O, H(2) Gal, H(3) Gal, H(4) Gal, H(5) Gal, H(6) Gal); 4.13—4.22 (m, 1 H, H(1) Gal, $J_{1,2}$ = 7.9 Hz); 4.34—4.45 (m, 1 H, H(3)); 4.68—4.71 (m, 1 H, NH); 5.26—5.31 (m, 1 H, H(6)); 7.52—7.68 (m, 3 H, Ar); 7.86—7.94 (m, 1 H, Ar). ^{13}C NMR, δ: 12.03, 18.88, 19.51, 21.20, 22.73, 22.99, 24.02, 24.45, 25.48, 26.34, 26.44, 28.17, 28.35, 28.40, 29.49, 30.02, 32.02, 35.97, 36.35, 36.72, 37.15, 38.76, 39.68, 39.90, 40.90, 42.47, 47.25, 50.15, 56.30, 56.84, 61.60, 69.12, 70.17, 71.51, 73.70, 74.36, 103.38, 122.62, 124.34, 130.70, 131.95, 133.66, 133.74, 140.02, 148.12.

***N*-[*rac*-2,3-Bis(tetradecyloxy)propyl]-*N*-[6-(β-lactosyloxy)-hexyl]-2-nitrobenzenesulfonamide (12)** was prepared in the same way as compound **11a** from **10** (0.376 g) and a 0.1 *M* solution of MeONa in MeOH (2 mL). Chromatography on silica gel (toluene—acetone—water, 10 : 50 : 1) gave 0.295 g (98%) of compound **12** as a crystallizing oil, $[\alpha]_D^{23}$ −4 (*c* 1, $CHCl_3$). MS, *m/z* (I_{rel} (%)): 1131.960 $[M + K]^+$ (100). Calculated for $C_{55}H_{100}N_2O_{17}S$: 1092.674 $[M]^+$. ^{1}H NMR, δ: 0.80 (t, 6 H, 2 CH_2Me, J = 6.8 Hz); 1.21—1.31 (m, 48 H, 2 $(CH_2)_{11}$, $N(CH_2)_2(CH_2)_2(CH_2)_2O$); 1.32—1.55 (m, 8 H, 2 CH_2CH_2O, $NCH_2CH_2(CH_2)_2CH_2CH_2O$); 3.05—4.50 (m, 27 H, $OCH_2CHCH_2NCH_2$, 3 CH_2CH_2O, Lac); 7.52—7.67 (m, 3 H, Ar); 7.91—7.98 (m, 1 H, Ar). ^{13}C NMR, δ: 14.27, 22.86, 25.55, 26.26, 26.31, 26.37, 27.60, 28.40, 29.54, 30.26, 32.11, 48.67, 61.89, 70.24, 70.69, 70.90, 71.93, 73.58, 76.88, 77.68, 102.81, 103.70, 124.33, 131.09, 131.89, 133.73, 134.00.

***N*-[*rac*-2,3-Bis(tetradecyloxy)propyl]-*N*-[6-(β-D-galactopyranosyloxy)hexyl]amine (13a).** Potassium carbonate (0.742 g, 5.369 mmol) and PhSH (0.550 mL, 5.369 mmol) were added to a solution of compound **11a** (0.500 g, 0.537 mmol) in anhydrous DMF (5 mL), and the mixture was stirred for 2 h at 24 °C. The reaction mixture was filtered through Celite® 545 and washed with MeOH, and the solvents were removed *in vacuo*. The residue was chromatographed on a column with reversed-phase silica gel LiChroprep RP-18 using a $CHCl_3$—MeOH—25% aq. NH_3 mixture (10 : 100 : 1) as the eluent to give 0.334 g (83%) of compound **13a** as a crystallizing oil, $[\alpha]_D^{20}$ −4 (*c* 1.6, $CHCl_3$). MS, *m/z* (I_{rel} (%)): 746.683 $[M + H]^+$ (100). Calculated for $C_{43}H_{87}NO_8$: 745.643 $[M]^+$. ^{1}H NMR, δ: 0.79 (t, 6 H, 2 CH_2Me, J = 6.8 Hz); 1.13—1.33 (m, 48 H, 2 $(CH_2)_{11}$, $N(CH_2)_2(CH_2)_2(CH_2)_2O$); 1.35—1.60 (m, 8 H, 2 CH_2CH_2O, $NCH_2CH_2(CH_2)_2CH_2CH_2O$); 2.50—2.69 (m, 4 H, CH_2NCH_2); 3.26—3.59 (m, 11 H, OCH_2CHCH_2N, 2 CH_2CH_2O, CH_aO, H(6) Gal, H(3) Gal); 3.72—3.85 (m, 3 H, CH_bO, H(5) Gal, H(2) Gal); 3.91—3.95 (m, 1 H, H(4) Gal); 4.13 (d, 1 H, H(1) Gal, $J_{1,2}$ = 7.4 Hz). ^{13}C NMR, δ: 14.18, 22.78, 25.82, 26.24, 26.75, 29.16, 29.46, 29.62, 29.79, 30.31, 32.03, 49.55, 51.24, 61.97, 69.40, 70.15, 70.51, 71.52, 71.86, 73.75, 74.42, 103.53.

[*rac*-2,3-Bis(tetradecyloxy)propyl] *N*-[13-(β-D-galactopyranosyloxy)-7-azatridecyl]carbamate (13b) was prepared in the same way as compound **13a** from **11b** (0.07 g, 0.06 mmol), K_2CO_3 (0.08 g, 0.5 mmol), and PhSH (0.06 mL, 0.59 mmol). Reversed-phase chromatography ($CHCl_3$—MeOH—25% aq. NH_3 (20 : 100 : 1)) gave 0.05 g (87%) of compound **13b**, m.p. 40—42 °C, $[\alpha]_D^{20}$ −4 (*c* 1, $CHCl_3$—MeOH, 1 : 1). MS, *m/z* (I_{rel} (%)): 889.6 $[M + H]^+$ (100), 911.6 $[M + Na]^+$ (50), 927.6 $[M + K]^+$ (90). Calculated for $C_{50}H_{100}N_2O_{10}$: 888.74 $[M]^+$. ^{1}H NMR (400 MHz, $CDCl_3$—CD_3OD, 3 : 1), δ: 0.80 (t, 6 H, 2 CH_2Me, J = 7.0 Hz); 1.13—1.32 (m, 52 H, 2 $(CH_2)_{11}$, 2 $N(CH_2)_2(CH_2)_2$); 1.36—1.59 (m, 12 H, 2 OCH_2CH_2, 3 NCH_2CH_2, CH_2CH_2O); 2.45 (br.t, 4 H, CH_2NCH_2, J = 7.6 Hz); 3.03 (br.t, 2 H, $NHCH_2$, J = 7.0 Hz); 3.33—3.80 (m, 14 H, $OCH_2CHCH_2OC(O)$, 2 OCH_2CH_2, CH_2O, H(2) Gal, H(3) Gal, H(5) Gal, H(6) Gal); 3.98 (dd, 1 H, $CH_aOC(O)$, J = 5.0 Hz, J = 11.5 Hz); 4.07 (dd, 1 H, $CH_bOC(O)$, J = 4.2 Hz, J = 11.5 Hz); 4.13 (d, 1 H, H(1) Gal, $J_{1,2}$ = 6.9). ^{13}C NMR (100 MHz, $CDCl_3$—CD_3OD, 3 : 1), δ: 13.99, 22.64, 25.70, 25.97, 26.55, 26.92, 29.32, 29.46, 29.61, 29.66, 29.90, 31.89, 49.51, 61.30, 64.01, 68.88, 69.96, 70.31, 70.62, 71.33, 71.82, 73.52, 74.61, 103.39, 156.91.

(Cholest-5-en-3β-yl) *N*-[13-(β-D-galactopyranosyloxy)-7-azatridecyl]carbamate (13c) was prepared in the same way as compound **13b** from **11c** (0.07 g, 0.07 mmol), K_2CO_3 (0.08 g, 0.61 mmol), and PhSH (0.06 mL, 0.61 mmol). This gave 0.05 g (88%) of compound **13c,** m.p. 63—65 °C, $[\alpha]_D^{20}$ −11 (*c* 1, $CHCl_3$—MeOH, 1 : 1). MS, *m/z* (I_{rel} (%)): 791.751 $[M + H]^+$ (100). Calculated for $C_{46}H_{82}N_2O_8$: 790.607 $[M]^+$. ^{1}H NMR (400 MHz, $CDCl_3$—CD_3OD, 5 : 1), δ: 0.61 (s, 3 H, C(13)Me); 0.79 (d, 3 H, C(25)Me, J = 6.5 Hz); 0.80 (d, 3 H, C(25)Me, J = 6.5 Hz); 0.84 (d, 3 H, C(20)Me, J = 6.5 Hz); 0.93 (s, 3 H, C(10)Me); 0.90—1.60 (m, 37 H, Chol, $NHCH_2(CH_2)_4CH_2NCH_2(CH_2)_4CH_2O$); 1.72—1.98 (m, 5 H, Chol); 2.14—2.32 (m, 2 H, $H_2C(4)$); 2.48—2.61 (m, 4 H, CH_2NCH_2); 2.98—3.14 (m, 2 H, $NHCH_2$); 3.40—4.18 (m, 9 H, CH_2O, Gal); 4.35—4.46 (m, 1 H, H(3)); 4.90—4.97 (m, 1 H, NH); 5.24—5.32 (m, 1 H, H(6)). ^{13}C NMR (100 MHz, $CDCl_3$—CD_3OD, 5 : 1), δ: 11.89, 18.75, 19.33, 21.15, 22.54, 22.79, 23.94, 24.34, 28.04, 28.26, 29.72, 31.97, 35.85, 36.27, 36.77, 37.37, 38.62, 39.58, 39.84, 42.40, 56.31, 56.83, 60.62, 60.79, 61.41, 65.19, 69.72, 71.19, 73.46, 75.68, 79.20, 100.29, 122.35, 140.28.

***N*-[*rac*-2,3-Bis(tetradecyloxy)propyl]-*N*-[6-(β-lactosyloxy)-hexyl]amine (14)** was prepared in the same way as compound **13b** from **12** (0.231 g, 0.211 mol), K_2CO_3 (0.301 g, 2.201 mmol), and PhSH (0.21 mL, 2.110 mmol). This gave 0.126 g (66%) of compound **14** as a crystallizing oil, $[\alpha]_D^{23}$ −6.23 (*c* 1, $CHCl_3$—CH_3OH, 4 : 1). MS, *m/z* (I_{rel} (%)): 908.889 $[M + H]^+$ (100), 930.904 $[M + Na]^+$ (25), 946.892 $[M + K]^+$ (50). Calculated for $C_{49}H_{97}NO_{13}$: 907.696 $[M]^+$. ^{1}H NMR (400 MHz, Py-d_5), δ: 0.74 (t, 6 H, 2 CH_2Me, J = 7.0 Hz); 1.03—1.34 (m, 50 H,

2 $(CH_2)_{11}$, $NCH_2(C\underline{H}_2)_3(CH_2)_2O$); 1.42—1.53 (m, 6 H, 3 $C\underline{H}_2CH_2O$); 2.37—2.48 and 2.59—2.71 (both m, 2 H each, CH_2NCH_2); 3.28—4.23 (m, 21 H, $OC\underline{H}_2C\underline{H}CH_2N$, 3 $CH_2C\underline{H}_2O$, Lac); 4.44 (d, 1 H, H(1′) Lac, $J_{1',2'}$ = 7.8 Hz); 4.71 (d, 1 H, H(1) Lac, $J_{1,2}$ = 8.1 Hz). ^{13}C NMR (100 MHz, Py-d_5), δ: 14.78, 23.40, 26.82, 27.04, 27.98, 30.08, 30.27, 30.44, 30.63, 30.99, 31.15, 32.63, 50.88, 52.34, 62.36, 62.80, 70.34, 70.88, 72.20, 72.59, 73.12, 74.87, 75.35, 76.53, 76.83, 77.31, 79.12, 82.57, 104.62, 105.97.

***N*-[*rac*-2,3-Bis(tetradecyloxy)propyl]-*N*-[6-(β-D-galactopyranosyloxy)hexyl]-*N*,*N*-dimethylammonium iodide (15a).** Potassium carbonate (7.4 mg, 0.0533 mmol) and MeI (1 mL, 16.07 mmol) were added successively to a solution of compound **13a** (39.8 mg, 0.0533 mmol) in anhydrous ethyl methyl ketone (1.5 mL). The reaction mixture was stirred for 2.5 h at 80 °C and the solvent was removed *in vacuo*. The residue was chromatographed on a column with silica gel LiChroprep®RP-18 using a MeOH—water mixture (100 : 1 → 100 : 0) as the eluent to give 0.0364 g (76%) of compound **15a** as a crystallizing oil. MS, *m*/*z* (I_{rel} (%)): 774.840 $[M - I]^+$ (100). Calculated for $C_{45}H_{92}NO_8$: 774.682 $[M - I]^+$. ^{1}H NMR (400 MHz, $CDCl_3$—Py-d_5, 2.5 : 1), δ: 0.80 (t, 6 H, 2 $CH_2\underline{Me}$, J = 6.8 Hz); 1.21 (br.s, 48 H, 2 $(CH_2)_{11}$, $N(CH_2)_2(C\underline{H}_2)_2(CH_2)_2O$); 1.48—1.62 (m, 8 H, 2 $C\underline{H}_2CH_2O$, $NCH_2C\underline{H}_2(CH_2)_2C\underline{H}_2CH_2O$); 3.48 and 3.50 (both s, 3 H each, N^+Me_2); 3.39—3.87 (m, 12 H, $OC\underline{H}_2C\underline{H}CH_2N$, 2 $CH_2C\underline{H}_2O$, $CH_2N^+CH_2$, $CH\underline{H}_aO$); 3.96—4.14 (m, 4 H, H(2) Gal, H(3) Gal, H(5) Gal, $CH\underline{H}_bO$); 4.33—4.44 (m, 2 H, H(6) Gal); 4.51—4.54 (m, 1 H, H(4) Gal); 4.67 (d, 1 H, H(1) Gal, $J_{1,2}$ = = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$—CD_3OD, 2 : 1), δ: 14.05, 22.40, 22.70, 25.29, 25.49, 26.10, 26.24, 28.85, 29.39, 29.52, 29.72, 30.11, 31.97, 52.23, 52.50, 61.42, 65.66, 66.49, 68.86, 69.00, 71.45, 72.18, 73.26, 73.70, 74.71, 77.40, 103.48.

***N*-{6-[*rac*-2,3-Bis(tetradecyloxy)propyloxycarbonylamino]-hexyl}-*N*-[6-(β-D-galactopyranosyloxy)hexyl]-*N*,*N*-dimethylammonium iodide (15b).** Methyl iodide (0.01 mL, 0.12 mmol) was added to a solution of compound **13b** (0.03 g, 0.03 mmol) in anhydrous ethyl methyl ketone (1.5 mL). The reaction mixture was stirred for 2.5 h at 80 °C and the solvent was removed *in vacuo*. The residue was chromatographed on a column with silica gel LiChroprep®RP-18 using a MeOH—water mixture (100 : 1) as the eluent to give 0.029 g (81%) of compound **15b** as a crystallizing oil. MS, *m*/*z* (I_{rel} (%)): 917.999 $[M - I]^+$ (100). Calculated for $C_{52}H_{105}N_2O_{10}$: 917.777 $[M - I]^+$. ^{1}H NMR (400 MHz, $CDCl_3$—CD_3OD, 4 : 1): 0.80 (t, 6 H, 2 $CH_2\underline{Me}$, J = 7.0 Hz); 1.13—1.33 (m, 52 H, 2 $(CH_2)_{11}$, 2 $N(CH_2)_2(C\underline{H}_2)_2$), 1.36—1.71 (m, 12 H, 2 $OCH_2C\underline{H}_2$, 3 $NCH_2C\underline{H}_2$, $C\underline{H}_2CH_2O$); 3.00 (s, 6 H, N^+Me_2); 3.02—3.87 (m, 20 H, $NHC\underline{H}_2$, $CH_2N^+CH_2$, $OC\underline{H}_2C\underline{H}CH_2OC(O)$, 2 $OC\underline{H}_2CH_2$, CH_2O, Gal); 3.95—4.06 (m, 2 H, $CH_2OC(O)$); 4.12 (d, 1 H, H(1) Gal, $J_{1,2}$ = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$—CD_3OD, 2 : 1), δ: 14.19, 22.55, 22.77, 22.94, 25.53, 25.85, 26.15, 26.36, 29.16, 29.63, 29.79, 29.97, 30.32, 32.23, 33.75, 40.91, 51.04, 61.76, 64.62, 64.81, 64.96, 69.37, 69.72, 70.83, 71.02, 71.81, 72.23, 74.16, 75.26, 77.39, 77.86, 103.87.

***N*-{6-(Cholest-5-en-3β-yloxycarbonylamino)hexyl]-*N*-[6-(β-D-galactopyranosyloxy)hexyl]-*N*,*N*-dimethylammonium iodide (15c)** was prepared in the same way as compound **15b** from **13c** (0.02 g, 0.025 mmol) and MeI (0.01 mL, 0.12 mmol). This gave 0.021 g (88%) of compound **15c**, m.p. 80—82 °C, $[\alpha]_D^{20}$ −8.8 (*c* 0.5, $CHCl_3$—MeOH, 1 : 1). MS, *m*/*z* (I_{rel} (%)): 819.414 $[M - I]^+$ (100). Calculated for $C_{48}H_{87}N_2O_8$: 819.646 $[M - I]^+$. ^{1}H NMR (400 MHz, $CDCl_3$—CD_3OD, 5 : 1), δ: 0.61 (s, 3 H, C(13)Me); 0.78 (d, 3 H, C(25)Me, J = 6.5 Hz); 0.79 (d, 3 H, C(25)Me, J = 6.5 Hz); 0.84 (d, 3 H, C(20)Me, J = 6.5 Hz); 0.93 (s, 3 H, C(10)Me); 0.90—1.98 (m, 42 H, Chol, $NHCH_2(C\underline{H}_2)_4CH_2NCH_2(C\underline{H}_2)_4CH_2O$); 2.14—2.30 (m, 2 H, $H_2C(4)$); 3.00 and 3.03 (both s, 3 H each, N^+Me_2); 3.40—4.18 (m, 15 H, $NHC\underline{H}_2$, CH_2NCH_2, CH_2O, Gal); 4.31—4.45 (m, 1 H, H(3)); 5.27—5.35 (m, 1 H, H(6)). ^{13}C NMR (100 MHz, $CDCl_3$—CD_3OD, 2 : 1), δ: 11.87, 18.66, 19.24, 21.04, 22.40, 22.53, 22.66, 23.83, 24.24, 25.18, 25.57, 25.76, 26.05, 27.95, 28.17, 28.94, 29.47, 31.91, 35.76, 36.20, 36.58, 37.01, 38.58, 39.50, 39.78, 40.37, 42.34, 50.12, 51.09, 56.23, 56.75, 61.28, 64.56, 64.69, 68.97, 69.56, 71.35, 73.48, 74.62, 103.31, 122.44, 139.90.

***N*-[*rac*-2,3-Bis(tetradecyloxy)propyl]-*N*-[6-(β-lactosyloxy)-hexyl]-*N*,*N*-dimethylammonium iodide (16).** Potassium carbonate (8.5 mg, 0.0616 mmol) and MeI (0.0766 mL, 0.123 mmol) were added with stirring to a solution of amine **14** (0.056 g, 0.0616 mmol) in ethyl methyl ketone (9 mL). The reaction mixture was kept for 3 h at 50 °C, the solvent was removed *in vacuo*, and the residue was chromatographed on a column with the silica gel LiChroprep®RP-18 using a toluene—$CHCl_3$—MeOH—AcOH mixture (2 : 2 : 5 : 0.02 → 1 : 1 : 4 : 0.01) as the eluent to give 0.0458 g (69%) of compound **16** as a crystallizing oil, $[\alpha]_D^{23}$ −3.1 (*c* 1, $CHCl_3$—CH_3OH, 1 : 1). MS, *m*/*z* (I_{rel} (%)): 936.759 $[M - I]^+$ (100). Calculated for $C_{51}H_{102}NO_{13}$: 936.735 $[M - I]^+$. ^{1}H NMR ($CDCl_3$—CD_3OD, 3 : 1), δ: 0.84 (t, 6 H, 2 $CH_2\underline{Me}$, J = 6.8 Hz); 1.21 (br.s, 48 H, 2 $(CH_2)_{11}$, $N(CH_2)_2(C\underline{H}_2)_2(CH_2)_2OH$); 1.45—1.65 (m, 8 H, 2 $C\underline{H}_2CH_2O$, $NCH_2C\underline{H}_2(CH_2)_2C\underline{H}_2CH_2O$); 3.31—4.49 (m, 33 H, $OC\underline{H}_2C\underline{H}CH_2N$, 3 $CH_2C\underline{H}_2O$, $CH_2N^+CH_2$, N^+Me_2, Gal). ^{13}C NMR ($CDCl_3$—Py-d_5, 2 : 1), δ: 13.24, 21.80, 25.25, 25.37, 27.09, 28.49, 28.85, 29.28, 29.46, 31.03, 32.26, 32.67, 34.88, 35.28, 36.13, 37.83, 38.60, 38.82, 49.09, 51.17, 55.74, 60.04, 60.82, 64.16, 65.03, 67.08, 68.28, 70.71, 70.94, 72.45, 72.86, 74.45, 76.56, 102.31, 103.05.

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