CHEMISTRY AND TECHNOLOGY OF MEDICINAL COMPOUNDS AND BIOLOGICALLY ACTIVE SUBSTANCES

ХИМИЯ И ТЕХНОЛОГИЯ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ И БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ

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RESEARCH ARTICLE

Amination of epoxides as a convenient approach for the synthesis of lipophilic polyamines

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Abstract

Objectives. *Alkylated derivatives of polyamines are able to block the growth of cancer cells due to their embedding into the polyamine biosynthesis mechanisms. The study aimed to synthesize lipophilic derivatives of norspermine or triethylenetetramine based on the formation of a C–N bond during the opening of the oxirane ring by primary amines to expand a number of synthetic polyamine derivatives with antitumor activity.*

Methods. *The starting compounds—glycidol alcoholate or epichlorohydrin—were reacted with hexadecyl bromide or sodium hexadecanolate to give glycidyl hexadecyl ether. The key reaction for the preparation of lipophilic polyamines was the amination of lipophilic epoxides with polyamines in the presence of calcium triflate. Acylation of the hydroxyl group formed during the opening of oxirane was carried out by the action of 4-dimethylaminopyridine and acetic anhydride. The introduction of an alkyl substituent in the presence of sodium hydride led to intramolecular cyclization with the formation of an oxoazolidine cycle. The regioselectivity of the oxirane ring opening reaction at the C(1) position of glycerol was confirmed by two-dimensional heteronuclear {^{1}H,^{13}C} nuclear magnetic resonance spectroscopy.*

Results. *An approach to the synthesis of novel lipophilic polyamines based on the catalytic amination of epoxides was developed and tested. Compounds based on norspermine and triethylentetramine containing a hydroxyl group at the C(2) atom of the glycerin backbone were obtained. For norspermine derivatives, the hydroxyl group was modified: an acetyl substituent was introduced and a derivative containing an oxoazolidine cycle was obtained.*
Conclusions. *The obtained lipophilic polyamines can be considered as potential antitumor agents, for which cytotoxicity against various cancer cells will be evaluated in the future.*

Keywords: *lipophilic polyamines, lipids, alkyl glycerolipids, oxiranes*

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НАУЧНАЯ СТАТЬЯ

Аминирование эпоксидов как удобный способ синтеза липофильных полиаминов

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Аннотация

Цели. *Алкилированные производные полиаминов способны блокировать рост раковых клеток за счет встраивания в механизмы биосинтеза полиаминов. Цель исследования – синтезировать новые липофильные производные норспермина или триэтилентетрамина, основанные на формировании связи C–N при раскрытии оксиранового кольца первичными аминами, для расширения ряда синтетических производных полиаминов, обладающих противоопухолевой активностью.*
Методы. *Исходные соединения – алкоголят глицидола или эпихлоргидрин – вводили во взаимодействие с гексадецилбромидом или гексадецилатом натрия, получая гексадецилглицидиловый эфир. Ключевой реакцией получения липофильных полиаминов являлось аминирование липофильных эпоксидов полиаминами в присутствии трифлата кальция. Ацилирование гидроксильной группы, образовавшейся в ходе раскрытия оксирана, проводили действием 4-диметиламинопиридина и уксусного ангидрида. Введение алкилильного заместителя в присутствии гидрида натрия приводило к внутримолекулярной циклизации с образованием оксоазолидинового цикла. Региоселективность реакции раскрытия оксиранового цикла по C(1) положению глицерина подтверждали двумерной гетероядерной {^{1}H,^{13}C} спектроскопией ядерного магнитного резонанса.*

Результаты. *Разработан и апробирован подход к синтезу новых липофильных полиаминов, основанный на каталитическом аминирование эпоксидов. Получены соединения на основе норспермина и триэтилентетрамина, содержащие гидроксильную группу при C(2) атоме глицеринового остова. Для производных норспермина проведена модификация гидроксильной группы: введен ацетильный заместитель и получено производное, содержащее оксоазолидиновый цикл.*

Выводы. *Полученные липофильные полиамины можно рассматривать как потенциальные противоопухолевые агенты, для которых в дальнейшем будет проведена оценка цитотоксичности против различных раковых клеток.*

Ключевые слова: *липофильные полиамины, липиды, алкильные глицеролипиды, оксираны*

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INTRODUCTION

Natural polyamines (NPs) such as spermine, spermidine, and putrescine play an important role in homeostasis and proliferation of eukaryotic cells; moreover, their level in tumor cells is higher than in normal cells [1]. Alkylated derivatives of natural and synthetic NPs can reduce the intracellular content of natural NPs and block the growth of cancer cells due to incorporation into the mechanisms of NP biosynthesis [1–4]. Conjugation of NPs with antitumor agents leads to an increase in both the therapeutic effect and the selectivity of the latter; this is due to the activation of the NP transport system in cancer cells, which require NP for rapid proliferation [5–9].

Positively charged derivatives of alkyl glycerolipids are promising antitumor agents, which are capable to inhibit the growth of cancer cells depending on the structure of the cationic domain [10, 11]. Earlier in order to find potential antitumor agents, we carried out the synthesis of unsymmetrical conjugates of NPs and alkyl glycerolipids (Fig. 1) based on the interaction of bromo derivatives of diglycerides with regioselectively protected 2-nitrobenzenesulfonylamide derivatives of NPs, followed by ethylation and removal of protective groups [12]. Dialkylated lipophilic NPs based on norspermine and triethylenetetramine had the highest antitumor activity, while the length of the alkyl substituent at the C(1) atom of glycerol was found to have no significant effect on the ability of the compounds to induce cancer cell death.

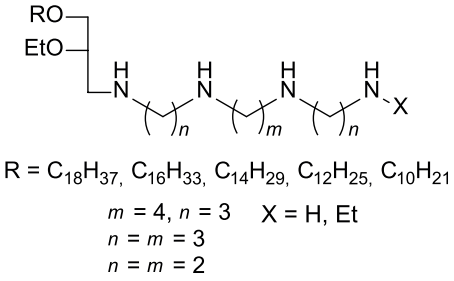


Fig. 1. Structure of asymmetric lipophilic polyamines.

In order to expand the range of synthetic NP derivatives offering antitumor activity, we developed the synthesis of new conjugates of norspermine or triethylenetetramine with glycerolipids, based on the opening of oxiranes by primary amines. The resulting hydroxy-containing NP derivatives can additionally be subjected to acylation or intramolecular cyclization, which leads to new lipophilic NP derivatives.

MATERIALS AND METHODS

We used commercial solvents and reagents (*Chimmed*, Russia; *Component-Reaktiv*, Russia; *Sigma-Aldrich*, USA; *Acros-Organics*, USA). Prior to the reaction, dichloromethane (DCM) was boiled over CaH_2; methanol was boiled over magnesium shavings; tetrahydrofuran (THF) was kept over KOH, boiled over Na in the presence of benzophenone and distilled; dimethylformamide (DMF) was kept over calcined 4 Å molecular sieves.

The reaction progress was monitored by thin layer chromatography on Silica gel 60 F_{254} plates (*Merck*, Germany). Spots were visualized under ultraviolet light (254 nm) or phosphomolybdic acid-$Ce(SO_4)_2$ reagent followed by heating. Column chromatography was performed on silica gel 0.040–0.063 mm Kieselgel 60 (*Merc*k, Germany).

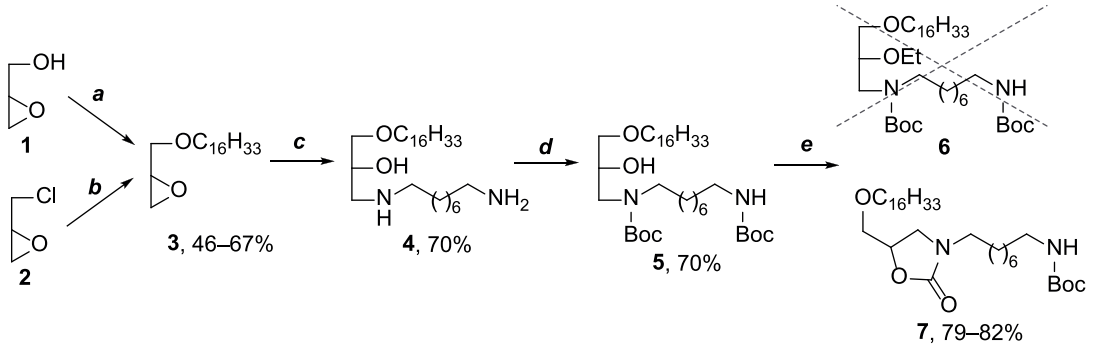
^1H, ^{13}C nuclear magnetic resonance (NMR), $^1H,^1H$ correlation spectroscopy (COSY), $^1H,^{13}C$ heteronuclear single quantum coherence (HSQC), and $^1H,^{13}C$ heteronuclear multiple bond correlation (HMBC) spectra were recorded on DPX-300 and Avance II 600 pulsed Fourier transform spectrometers (*Bruker*, Germany) in $CDCl_3$, CD_3OD, or D_2O. Chemical shifts (δ) are given in parts per million with respect to the peak of the residual proton of the solvent, spin-spin coupling constants (*J*) are given in Hz. Mass spectra were recorded on an Apex Ultra 7T Fourier-transform ion cyclotron resonance (FT-ICR) mass spectrometer (*Bruker*, Germany).

RESULTS AND DISCUSSION

The synthetic approach to the preparation of lipophilic NPs includes several key steps: synthesis of an alkyl glycidyl ether, opening of the oxirane ring with amines, and modification of the hydroxyl group at the C(2) atom of glycerol. In order to evaluate this approach, its stepwise optimization was initially carried out using *N*,*N*′-diaminooctane, a structural analogue of the synthetic NP triethylenetetramine (Scheme 1).

The synthesis of glycidyl hexadecyl ether (**3**) was carried out in several ways, starting from *rac*-glycidol (**1**) or *rac*-epichlorohydrin (**2**). Thus, *rac*-glycidol (**1**) was treated with sodium hydride and then reacted with hexadecyl bromide to give compound **3** in 46% yield (Table 1).

In order to increase the yield of compound **3**, its synthesis was optimized using *rac*-epichlorohydrin (**2**) as the starting compound (see Table). Hexadecanol was converted to



Scheme 1. Synthetic approach to obtaining lipophilic polyamines.
Reagents and conditions: ***a*** – NaH, $C_{16}H_{33}Br$, DMF, 24°C; ***b*** – $C_{16}H_{33}OH$, NaOH or NaH, hexane, 60°C; ***c*** – $NH_2(CH_2)_8NH_2$, $Ca(OTf)_2$, MeCN, 24°C, ***d*** – Boc_2O, Et_3N, CH_2Cl_2 24°C or Boc_2O, K_2CO_3, MeOH, 24°C; ***e*** – EtBr, Na/dimethyl sulfoxide (DMSO), benzene, 24°C or EtBr, NaH, THF, 65°C.

Table. Synthesis parameters of hexadecylglycidyl ether

Terms	Reagents	Conditions	Yield, %
a	*rac*-glycidol (**1**), $C_{16}H_{33}Br$	NaH, DMF, 24°C	46
b	*rac*-epichlorohydrin (**2**), $C_{16}H_{33}OH$	NaH, hexane, 60°C	52
		NaOH, hexane, 60°C	67
		NaOH, DMF, 60°C	7
		NaOH, 60°C	59

alcoholate by the action of sodium hydroxide or hydride, which was then treated with *rac*-epichlorohydrin (**2**). The highest yield of compound **3** (67%) was achieved when the reaction was carried out in hexane using sodium hydroxide; the replacement of the solvent with DMF led to a decrease in the yield to 7%. The condensation of *rac*-epichlorohydrin (**2**) and hexadecanol in the absence of a solvent yielded 59%. Replacing sodium hydroxide with hydride in hexane gave compound **3** in 52% yield.

The noncatalytic opening of oxiranes by amines with the formation of β-amino alcohols is characterized by a low reaction rate and modest regioselectivity [13]. An universal approach to the aminolysis of epoxides is the use of metal salts as catalysts, which increase the electrophilicity of epoxides due to coordination with metal atoms [13]. The use of cheap and easy-to-prepare calcium trifluoromethanesulfonate (triflate) allows regioselective opening of epoxides [14]. The oxirane ring of compound **3** was opened by the action of *N*,*N*′-diaminooctane in the presence of calcium triflate (0.5 equiv.) in acetonitrile, which led to the formation of amino alcohol **4** in 70% yield. The regioselectivity of the reaction (opening of the oxirane ring at the C(1) position of glycerol) was confirmed by the data of two-dimensional heteronuclear {^{1}H,^{13}C} NMR spectroscopy (Fig. 2a) by the presence of cross peaks corresponding to the simultaneous interaction of protons of the CH_2O and CH groups of glycerol (A and B) and methylene protons (C) of the $NHCH_2$-group of the diamine with the carbon of the CH_2NH-group of the glycerol skeleton.

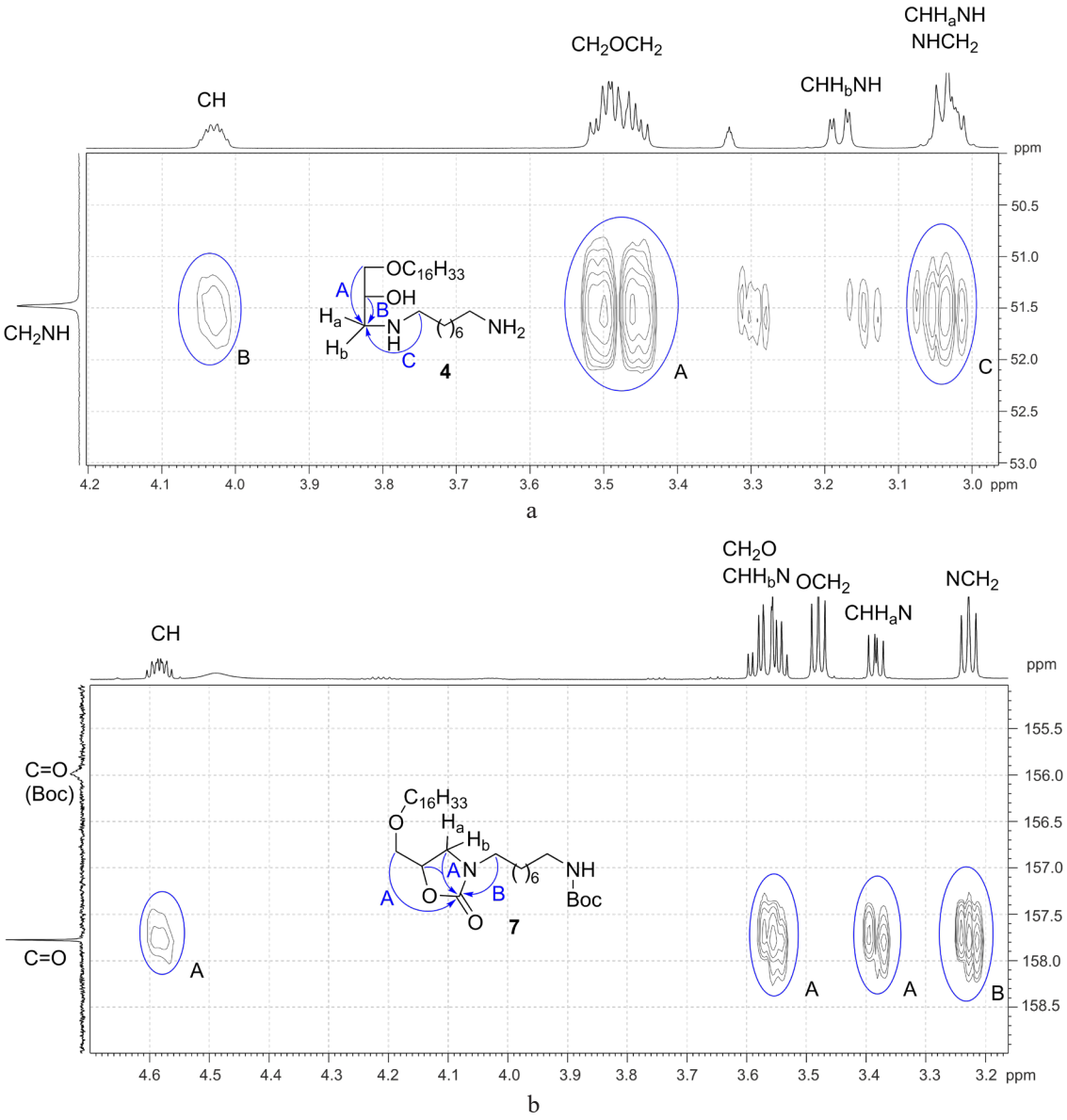


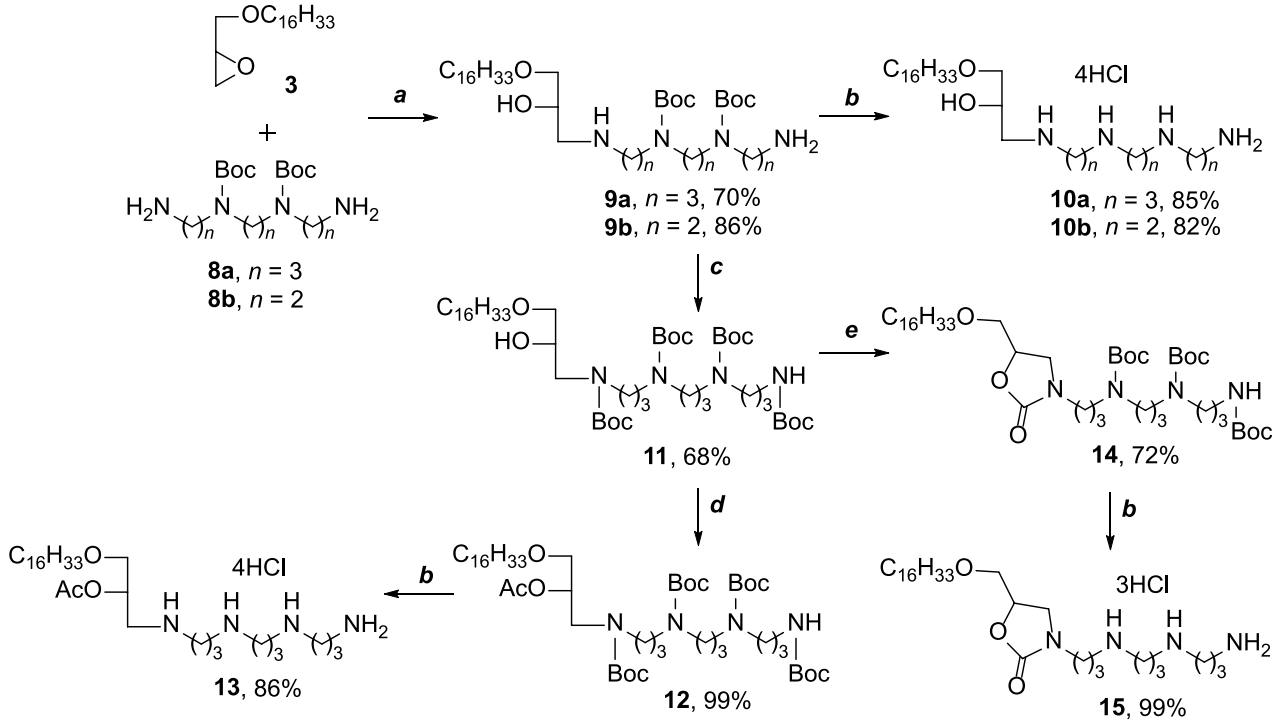
Fig. 2. (a) Fragment of the ^{1}H,^{13}C HMBC spectrum of compound **4**, (b) fragment of the ^{1}H,^{13}C HMBC spectrum of compound **7**.

For the further introduction of an alkyl substituent at the OH group at the C(2) atom of the glycerol backbone, the amino groups were protected. To this end, compound **4** was treated with di-*tert*-butyl dicarbonate in the presence of triethylamine or calcium carbonate to give compound **5** in 78% yield. To ethylate the hydroxyl group at the C(2) atom of glycerol, compound **5** was converted into an alcoholate by the action of sodium hydride and treated with ethyl bromide, with the expectation of obtaining compound **6**. However, following isolation of the reaction product, no signals of the ethyl group protons were detected in the ^{1}H NMR spectrum; the proton signal at C(2) glycerol atom shifted downfield (δ 4.55–4.62 ppm). In addition to the signal of the carbonyl carbon of the Boc group, an additional signal appeared in the ^{13}C NMR spectrum in the low field with a chemical shift of 157.67 ppm. Analysis of the heteronuclear correlation spectra {^{1}H,^{13}C}-HMBC (Fig. 2b) indicated the presence of cross peaks characterizing the interaction of this carbonyl carbon atom both with all protons of the glycerol backbone (A) and with protons of the CH_2N group of the diamine (B); however, no correlations with the Boc protection carbonyl carbon were detected.

Based on NMR spectroscopy data collection, we hypothesized that compound **5** in the presence of the strong base undergoes intramolecular cyclization via the transesterification mechanism to form compound **7** containing an oxazolidine ring, which was subsequently confirmed by literature data [15] and high-resolution mass spectrometry data.

Based on model synthesis, we implemented an approach to the synthesis of lipophilic NPs containing free hydroxyl groups (**10a** and **10b**) or an acyl substituent (**13**) at the C(2) atom of glycerol, as well as a derivative (**15**) with an oxazoline ring (Scheme 2). Epoxide **3** was opened using a 3-fold excess of previously obtained Boc-protected derivatives of norspermine **8a** and triethylene-tetramine **8b** [16]. The reaction was carried out in the presence of calcium triflate in acetonitrile at 85°C. Compounds **9a** and **9b** were isolated by column chromatography in 70% and 86% yields, respectively. Removal of the Boc-protected groups of compound **9a** and **9b** by the action of a 4N HCl solution in dioxane led to the formation of lipophilic NPs **10a** and **10b** with a free hydroxyl group at the C(2) atom of the glycerol backbone.

To modify the hydrophobic domain of the lipophilic norspermine **9a**, the primary and secondary amino groups of NPs were blocked with



Scheme 2. Synthetic approach to obtaining lipophilic polyamines.
Reagents and conditions: ***a*** – $Ca(OTf)_2$, MeCN, 85°C; ***b*** – HCl·dioxane, CH_2Cl_2, 24°C;
c – Boc_2O, K_2CO_3, MeOH, 24°C; ***d*** – Ac_2O, 4-dimethylaminopyridine (DMAP), CH_2Cl_2, 24°C; ***e*** – NaH, THF, 65°C.

Boc-protection group under basic conditions to obtain compound **11** in 68% yield. Further introduction of the acetyl group was achieved by treating compound **11** with a mixture of 4-dimethylaminopyridine and acetic anhydride in quantitative yield, and subsequent deprotection of the amino groups of compound **12** led to lipophilic NPs **13**. Treatment of norspermine derivative **11** with sodium hydride in tetrahydrofuran gave compound **14** in 72% yield; removing of Boc groups allowed NPs **15** with an oxazolidine ring to be obtained.

CONCLUSIONS

The developed approach to the synthesis of new lipophilic derivatives of norspermine and triethylenetetramine based on the opening of oxiranes by polyamines is presented. In the course of a model interaction with *N*,*N*′-diaminooctane, it was shown that the opening of the oxirane ring occurs regioselectively at the C(1) atom of the glycerol backbone. Lipophilic NPs containing a hydroxyl or acetyl group at the C(2) atom of glycerol, as well as a derivative with an oxoazolidine ring, were obtained, for which antitumor activity will be studied in the future.

EXPERIMENTAL

Obtaining the compounds

rac-Hexadecylglycidyl ether (3)

A) 73 mg (1.843 mmol) of NaH (60% dispersion in mineral oil) was added in portions to a solution of *rac*-glycidol (**1**) (0.112 mL, 1.675 mmol) cooled to 4°C in 10 mL of anhydrous DMF and stirred for 20 min. Then $C_{16}H_{33}Br$ (0.665 mL, 2.178 mmol) and a catalytic amount of TBAI were added and stirred for 20 h. The reaction mixture was diluted with water (20 mL), extracted with Et_2O (4 × 15 mL), the organic layer was washed with saturated aqueous NaCl solution (4 × 10 mL), dried with Na_2SO_4, filtered, and evaporated. The residue was chromatographed on a silica gel column eluting with a petroleum ether–EtOAc (25:1) system. The yield of compound **3** was 160 mg (46%).

B) Anhydrous NaOH (174 mg, 4.355 mmol) and TBAI (112 mg g, 0.350 mmol) were added to a solution of $C_{16}H_{33}OH$ (849 mg, 3.500 mmol) in 15 mL of hexane with vigorous stirring, and the mixture was stirred for 15 min at 4°C. Then a solution of *rac*-epichlorohydrin (**2**) (0.341 mL, 4.355 mmol) in 5 mL of hexane was added dropwise. The reaction mixture was stirred for 16 h at 60°C. The precipitate was filtered off; the organic solvent was removed in vacuo. The residue was chromatographed on a silica gel column eluting with a petroleum ether–EtOAc (25:1) system. The yield of compound **3** was 673 mg (67%).

C) To a solution of $C_{16}H_{33}OH$ (0.406 g, 1.675 mmol) cooled to 4°C in 10 mL of hexane, 80 mg (2.010 mmol) of NaH (60% dispersion in mineral oil) was added in portions with active stirring and stirred for 15 min. Then, with vigorous stirring, a catalytic amount of TBAI and a solution of *rac*-epichlorohydrin (**2**) (0.196 mL 2.513 mmol) in 5 mL of hexane were added. The reaction mixture was stirred for 16 h at 60°C, cooled, diluted with water (25 mL), extracted with DCM (4 × 20 mL), the organic layer was washed with water (4 × 20 mL), dried with Na_2SO_4, filtered, and evaporated. The residue was chromatographed on a silica gel column eluting with a petroleum ether–EtOAc (25:1) system. The yield of compound **3** was 260 mg (52%).

D) A catalytic amount of TBABr was added to $C_{16}H_{33}OH$ (3.0 g, 12.37 mmol) melted at 55°C, the reaction mixture was heated to 70°C, NaOH (742 mg, 18.56 mmol) was added, and the mixture was stirred for 20 min. Then, *rac*-epichlorohydrin (**2**) (1.9 mL, 24.75 mmol) was added to the reaction mixture and stirred for 12 h at 70°C. The reaction mixture was cooled, diluted with water (25 mL), extracted with DCM (4 × 30 mL), the organic layer was washed with water (4 × 25 mL), dried with Na_2SO_4, filtered, and evaporated. The residue was chromatographed on a silica gel column eluting with a petroleum ether–EtOAc (25:1) system. The yield of compound **3** was 2.17 g (59%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.7 Hz, 3 H, CH_3), 1.24 (br. s., 26 H, $(C\underline{H}_2)13CH_3$), 1.27–1.65 (m, 2 H, $OCH_2C\underline{H}_2$), 2.54–2.80 (m, 2 H, $C\underline{H}_2OCH$), 3.04–3.17 (m, 1 H, CH), 3.29–3.70 (m, 4 H, CH_2OCH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.26, 22.83, 29.50, 29.61, 29.73, 29.74, 29.80, 29.83, 32.06, 44.47, 51.04, 71.58, 71.86.

N-(*rac*-3-hexadecyloxy-2-hydroxyprop-1-yl)-1,8-diaminooctane (4)

N,*N*′-diaminooctane (218 mg, 1.520 mmol) and $Ca(OTf)_2$ (142 mg, 0.2529 mmol) were added to a solution of compound **3** (150 mg, 0.5059 mmol) in 5 mL of MeCN and stirred for 2 h at 24°C. The solvents were removed in vacuo, the residue was chromatographed on a silica gel column, eluting with a DCM–MeOH–25% aq. NH_3 (3:1:0.1) system. The yield of compound **4** was 156 mg (70%).

^{1}H NMR (600 MHz, CD_3OD) δ 0.90 (т, J = 7.0 Hz, 3 H CH_3), 1.28 (br. s, 26 H, $(C\underline{H}_2)_{13}CH_3$), 1.39 (br. s, 8 H, $(CH_2)_4$), 1.53–1.61 (m, 2 H, $NH_2CH_2C\underline{H}_2$), 1.62–1.73 (m, 4 H, $OCH_2C\underline{H}_2$, $NHCH_2C\underline{H}_2$), 2.89–2.93 (m, 2 H, $NH_2C\underline{H}_2$), 2.98–3.20 (m, 4 H, $C\underline{H}_2NHC\underline{H}_2$), 3.41–3.51 (m, 4 H, $C\underline{H}_2OC\underline{H}_2$), 3.98–4.04 (m, 1 H, CH). ^{13}C NMR (151 MHz, MeOH-d_4) δ 14.61, 23.80, 26.87, 27.14, 27.18, 27.29, 28.34, 29.81, 30.59, 30.64, 30.69, 30.86, 30.90, 33.13, 40.63, 48.97, 51.48, 66.87, 72.64, 73.74. FT-ICR mass spectrum, *m*/*z*: 443.457 $[M+H]^+$, calculated for $C_{27}H_{58}N_2O_2$ 442.458.

N^1-(*rac*-3-hexadecyloxy-2-hydroxyprop-1-yl)-*N*^{1,8}-bis(*tert*-butyloxycarbonyl)-1,8-diaminooctane (5)

A solution of Boc_2O (53 mg, 0.244 mmol) in 1 mL of MeOH was added in drops to a solution of compound 4 (36 mg, 0.0813 mmol) and K_2CO_3 (45 mg, 0.325 mmol) cooled to 4°C in 4 mL of MeOH and stirred for 10 h at 20°C. The precipitate was filtered off; the organic solvent was removed in vacuo. The residue was chromatographed on a silica gel column, eluting with a toluene–methylethylketone (MEK) (7:1) system. The yield of compound **5** was 36 mg (70%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3 H, CH_3), 1.26 (br. s., 26 H, $(C\underline{H}_2)_{13}CH_3$), 1.30 (br. s., 8 H, $(CH_2)4$), 1.44–1.47 (m, 20 H, $2C(CH_3)_3$, $NHCH_2C\underline{H}_2$), 1.49–1.54 (m, 2 H, $NCH_2C\underline{H}_2$), 1.54–1.59 (m, 2 H, $OCH_2C\underline{H}_2$), 3.06–3.13 (m, 2 H, $NHC\underline{H}_2$), 3.17–3.33 (m, 4 H, $C\underline{H}_2NC\underline{H}_2$), 3.33–3.47 (m, 4 H, CH_2OCH_2), 3.88–3.93 (m, 1 H, CH). ^{13}C NMR (151 MHz, $CDCl_3$) 14.18, 22.81, 26.32, 26.90, 26.91, 28.61, 29.40, 29.44, 29.76, 29.77, 29.79, 29.81, 29.82, 29.83, 29.84, 30.26, 70.78, 71.82, 72.81, 79.15, 80.01, 156.15.

rac-*N*-[(8-*tert*-butyloxycarbonylamino)octyl]-5-(hexadecyloxymethyl)-oxoazolidin-2-one (7)

NaH (3 mg, 0.0762 mmol, 60% dispersion in mineral oil) was added to a solution of compound **5** (25 mg, 0.0381 mmol) cooled to 4°C in 10 mL of anhydrous THF and stirred for 7 h, gradually heating the mixture to 65°C. After 5 h the organic solvent was removed in vacuo. The residue was chromatographed on a silica gel column, eluting with a toluene–MEK (7:1) system. The yield of compound **7** was 18 mg (82%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, J = 7.1 Hz, 3 H, CH_3), 1.22–1.33 (m, 34 H, $(CH_2)_{13}CH_3$, $(CH_2)_4$), 1.40–1.48 (m, 11 H, $C(C\underline{H}_3)$, $NHCH_2C\underline{H}_2$), 1.50–1.58 (m, 4 H, $OCH_2C\underline{H}_2$, $NCH_2C\underline{H}_2$), 3.06–3.12 (m, 2 H, $NHC\underline{H}_2$), 3.21–3.40 (m, 4 H, CH_2NCH_2), 3.46–3.60 (m, 4 H, CH_2OCH_2), 4.55–4.62 (m, 1 H, CH). ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.07, 22.65, 26.01, 26.45, 26.67, 27.22, 28.41, 29.09, 29.13, 29.33, 29.43, 29.59, 29.67, 31.89, 40.55, 44.00, 46.61, 71.09, 71.68, 72.12, 78.97, 155.86, 157.67. FT-ICR mass spectrum, *m*/*z*: 569.488 $[M+H]^+$, calculated for $C_{33}H_{64}N_2O_5$ 569.489.

General procedure for obtaining compounds 9a and 9b

Compound **8a** or **8b** (0.5019 mmol) and $Ca(OTf)_2$ (0.0836 mmol) were added to a solution of compound **3** (0.1673 mmol) in 5 mL of MeCN, and the mixture was stirred for 7 h at 85°C. The precipitate was filtered off; the organic solvent was removed in vacuo. The residue was chromatographed on a silica gel column, eluting with a DCM–MeOH–25% aq. NH_3 (5:1:0.1) system.

N^4,*N*^{8}-bis(*tert*-butyloxycarbonyl)-1-[*N*-(*rac*-3-hexadecyloxy-2-hydroxyprop-1-yl)amino]-11-amino-4,8-diazoundecane (9a)

The yield was 80 mg (70%). ^{1}H NMR (300 MHz, $CDCl_3$–CD_3OD (3:1)) δ 0.84 (t, J = 6.6 Hz, 3 H, CH_3), 1.22 (br. s., 26 H, $(C\underline{H}_2)_{13}CH_3$), 1.41 (br. s., 18 H, 2 $C(CH_3)_3$), 1.47–1.57 (m, 2 H, $OCH_2C\underline{H}_2$), 1.58–1.79 (m, 6 H, 3 $NCH_2C\underline{H}_2CH_2N$), 2.58–2.75 (m, 6 H, CH_2NHCH_2, $C\underline{H}_2NH_2$), 3.15 (m, 8 H, 2 $CH_2NBocCH_2$), 3.19–3.30 (m, 4 H, CH_2OCH_2), 3.77–3.91 (m, 1 H, CH). ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD (3:1)) δ 14.06, 22.63, 26.06, 28.42, 28.97–30.22, 31.87, 39.15, 44.81, 46.77, 52.21, 68.64, 71.66, 73.43, 79.43, 155.59. FT-ICR mass spectrum, *m*/*z*: 687.606 $[M+H]^+$, 721.599 $[M+Cl]^-$, calculated for $C_{38}H_{79}N_4O_6$ 687.6060, calculated for $C_{38}H_{79}ClN_4O_6$ 721.561.

N^3,*N*^{6}-bis(*tert*-butyloxycarbonyl)-1-[*N*-(*rac*-3-hexadecyloxy-2-hydroxyprop-1-yl)amino]-8-amino-3,6-diazaoctane (9b)

The yield was 93 mg (86%). ^{1}H NMR (300 MHz, $CDCl_3$–CD_3OD (3:1)) δ 0.86 (t, J = 6.6 Hz, 3 H, CH_3), 1.23 (br. s, 26 H, $(C\underline{H}_2)_{13}CH_3$), 1.44 (br. s, 18 H, 2 $C(CH_3)_3$), 1.43–1.49 (m, 2 H, $OCH_2C\underline{H}_2$), 2.56–2.89 (m, 6 H, CH_2NHCH_2, $C\underline{H}_2NH_2$), 3.18–3.36 (m, 8 H, 2 $C\underline{H}_2NBocCH_2$), 3.36–3.48 (m, 4 H, CH_2OCH_2), 3.76–3.89 (m, 1 H, CH). ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD (3:1)) δ 14.13, 22.69, 26.10, 28.47, 29.23–29.96, 31.93, 40.72,

45.81, 48.09, 51.96, 68.83, 71.72, 73.32, 79.86, 155.70. FT-ICR mass spectrum, *m*/*z*: 645.560 $[M+H]^+$, calculated for $C_{35}H_{73}N_4O_6$ 645.553.

N^4,N^8-bis(*tert*-butyloxycarbonyl)-1-[*N*-(*rac*-3-hexadecyloxy-2-hydroxyprop-1-yl)-*N*-(*tert*-butoxycarbonyl)amino]-11-(*tert*-butoxycarbonyl)-amino-4,8-diazaundecane (11)

A solution of Boc_2O (42 mg, 0.1908 mmol) in 1 mL of MeOH was added in drops to a solution of compound 7a (44 mg, 0.0636 mmol) and K_2CO_3 (35 mg, 0.254 mmol) cooled to 4°C in 4 mL of MeOH and stirred for 10 h at 20°C. The organic solvent was removed in vacuo, the residue was chromatographed on a silica gel column, eluting with a toluene–MEK (5:1) system. The yield of compound **11** was 24 mg (68%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.23 (br. s, 26 H, $(CH_2)_{13}CH_3$), 1.36–1.48 (m, 36 H, 4 $C(C\underline{H}_3)_3$), 1.48–1.49 (m, 2 H, $OCH_2C\underline{H}_2$), 1.58–1.69 (m, 2 H, $NHCH_2C\underline{H}_2$), 1.69–1.82 (m, 4 H, $NCH_2C\underline{H}_2$), 3.00–3.19 (m, 8 H, 3 $NC\underline{H}_2$, $C\underline{H}_2NH$), 3.19–3.38 (m, 10 H, 3 $NC\underline{H}_2$, CH_2OCH_2), 3.83–3.97 (m, 1 H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.13, 22.69, 26.11, 28.44, 28.97–30.32, 31.91, 37.34, 44.78, 46.91, 51.02, 70.46, 71.64, 72.60, 79.69, 155.36, 156.03.

N^4,N^8-di(*tert*-butyloxycarbonyl)-1-[*N*-(*rac*-3-hexadecyloxy-2-acetoxyprop-1-yl)-*N*-(*tert*-butoxycarbonyl)amino]-11-(*tert*-butoxycarbonyl)-amino-4,8-diazaundecane (12)

Ac_2O (7.3 μL, 0.0777 mmol) was added to a solution of DMAP (6.3 mg, 0.0518 mmol) in 1 mL of DCM and stirred for 5 min. The resulting mixture was added to a solution of compound **9** (23 mg, 0.0259 mmol) in 2 mL of DCM and stirred for 20 h. The organic solvent was removed in vacuo, the residue was chromatographed on a silica gel column, eluting with a toluene–EtOAc (5:1) system. The yield of compound **12** was 24 mg (99%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.25 (br. s., 26 H, $(C\underline{H}_2)_{13}CH_3$), 1.40–1.48 (m, 36 H, 4 $C(CH_3)_3$), 1.50–1.57 (m, 2 H, $OCH_2C\underline{H}_2$), 1.61–1.77 (m, 4 H, $NCH_2C\underline{H}_2$), 2.05 (s, 3 H, $C(O)CH_3$), 3.05–3.11 (m, 2 H, $C\underline{H}_2NH$), 3.11–3.54 (m, 18 H, 7 CH_2N, CH_2OCH_2), 5.15–5.19 (m, 1H, CH). ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.25, 21.30, 22.82, 26.18, 28.56, 28.60, 29.49, 29.61, 29.69, 29.79, 29.83, 32.06, 44.99, 45.93, 70.15, 71.60, 71.85, 79.73, 155.49, 156.19, 170.56.

rac-*N*-[(N^4,N^8-bis(*tert*-butyloxycarbonyl)-11-(*tert*-butoxycarbonyl)amino]-4,8-diazaundecanyl)-5-(hexadecyloxymethyl)-oxoazolidin-2-one (14)

NaH (1.2 mg, 0.0311 mmol, 60% dispersion in mineral oil) was added to a solution of compound **11** (15 mg, 0.0169 mmol) cooled to 4°C in 5 mL of anhydrous THF and stirred for 20 h, gradually heating to 65°C. The organic solvent was removed in vacuo, the residue was chromatographed on a silica gel column, eluting with a toluene–MEK (5:1) system. The yield of compound **14** was 10 mg (72%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.26 (br. s., 26 H, $(CH_2)_{13}CH_3$), 1.40–1.50 (m, 27 H, 3 $C(CH_3)_3$), 1.50–1.60 (m, 2 H, $OCH_2C\underline{H}_2$), 1.60–1.70 (m, 2 H, $NHCH_2C\underline{H}_2$), 1.70–1.85 (m, 4 H, $NCH_2C\underline{H}_2$), 3.04–3.66 (m, 18 H, 6 NCH_2, CH_2OCH_2), 4.51–4.57 (m, 1 H, CH). ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.25, 22.82, 26.15, 28.58, 28.60, 28.62, 29.49, 29.60, 29.72, 29.73, 29.77, 29.79, 29.81, 29.82, 29.83, 32.06, 42.12, 44.87, 46.86, 71.19, 72.00, 72.27, 79.78, 79.85, 155.47, 157.91.

General procedure for removing tert-butoxycarbonyl protecting groups

4N HCl in dioxane (1 mL) was added to a solution of compounds **9a**, **9b**, **12**, **14** (0.0291 mmol) in 2 mL DCM and stirred for 1 h at 24°C. The organic solvent was removed in vacuo.

1-[*N*-(*rac*-3-hexadecyloxy-2-hydroxyprop-1-yl)amino]-11-amino-4,8-diazaundecane tetrahydrochloride (10a)

The yield was 16 mg (85%). ^{1}H NMR (300 MHz, D_2O–CD_3OD (1:1)) δ 0.97 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.36 (br. s., 26 H, $(C\underline{H}_2)_{13}CH_3$), 1.59–1.75 (m, 2 H, $OCH_2C\underline{H}_2$), 2.12–2.38 (m, 6 H, $NHCH_2C\underline{H}_2$), 3.11–3.38 (m, 14 H, 6 $C\underline{H}_2NH$, $C\underline{H}_2NH_2$), 3.51–3.68 (m, 4 H, CH_2OCH_2), 4.11–4.29 (m, 1 H, CH). ^{13}C NMR (75 MHz, D_2O–CD_3OD (1:1)) δ 14.11, 22.70, 26.00, 28.47, 29.37, 29.46, 29.54–29.90, 31.94, 37.51, 41.97, 44.74, 46.74, 71.07, 71.86, 72.14, 79.70. FT-ICR mass spectrum, *m*/*z*: 487.495 $[M+H]^+$, calculated for $C_{28}H_{63}N_4O_2$ 487.492.

1-[*N*-(*rac*-3-hexadecyloxy-2-hydroxyprop-1-yl)amino]-8-amino-3,6-diazaoctane tetrahydrochloride (10b)

The yield was 23 mg (82%). ^{1}H NMR (300 MHz, D_2O–CD_3OD (1:1)) δ 0.88 (t, *J* = 6.9 Hz, 3 H, $C\underline{H}_3$),

1.23 (br. s., 26 H, $(C\underline{H}_2)_{13}CH_3$), 1.52–1.67 (m, 2 H, $OCH_2C\underline{H}_2$), 3.10–3.73 (m, 14 H, 6 CH_2NH, $C\underline{H}_2NH_2$), 3.36–3.48 (m, 4 H, CH_2OCH_2), 3.76–3.89 (m, 1 H, CH). ^{13}C (75 MHz, D_2O–CD_3OD (1:1)). ^{13}C NMR (75 MHz, D_2O–CD_3OD (1:1)) δ 14.11, 22.70, 26.00, 28.47, 29.37, 29.46, 29.54–29.90, 31.94, 37.51, 41.97, 44.74, 46.74, 71.07, 71.86, 72.14, 79.70. FT-ICR mass spectrum, *m*/*z*: 445.448 $[M+H]^+$, calculated for $C_{25}H_{57}N_4O_2$ 445.447.

1-[*N*-(*rac*-3-hexadecyloxy-2-acetoxyprop-1-yl)amino]-11-amino-4,8-diazaundecane tetrahydrochloride (13).

The yield was 15 mg (86%). ^{1}H NMR (600 MHz, D_2O–CD_3OD (1:1)) δ 0.88 (t, *J* = 6.9 Hz, 3 H, $C\underline{H}_3$), 1.26 (br. s., 26 H, $(C\underline{H}_2)_{13}CH_3$), 1.53–1.59 (m, 2H, $OCH_2C\underline{H}_2$), 2.10–2.22 (m, 9 H, $C(O)CH_3$, $NHCH_2C\underline{H}_2$, $NCH_2C\underline{H}_2$), 3.09–3.42 (m, 14 H, 6 $C\underline{H}_2NH$, $C\underline{H}_2NH_2$), 3.46–3.67 (m, 4 H, CH_2OCH_2), 5.25–5.29 (m, 1 H, CH). ^{13}C NMR (151 MHz, D_2O–CD_3OD (1:1)) δ 14.58, 23.49, 23.82, 24.81, 24.89, 26.74, 30.21, 30.30, 30.38, 30.52, 30.77, 32.78, 37.63, 41.97, 45.70, 45.72, 45.80, 46.29, 47.18, 72.03, 72.82, 74.58, 160.59. FT-ICR mass spectrum, *m*/*z*: 529.506 $[M+H]^+$, calculated for $C_{30}H_{65}N_4O_3$ 529.505.

rac-*N*-[11-(11-amino-4,8-diazaundecanyl)]-5-(hexadecyloxymethyl)oxoazolidin-2-one trihydrochloride (15)

The yield was 8 mg (99%). ^{1}H NMR (600 MHz, D_2O–CD_3OD (1:1)) δ 0.88 (t, *J* = 6.7 Hz, 3 H, CH_3), 1.27 (br. s., 26 H, $(C\underline{H}_2)_{13}CH_3$), 1.53–1.60 (m, 2 H, $OCH_2C\underline{H}_2$), 1.97–2.03 (m, 2 H, $NH_2CH_2C\underline{H}_2$), 2.09–2.21 (m, 4 H, $NCH_2C\underline{H}_2$), 3.07–3.72 (m, 18 H, 6 $C\underline{H}_2NH$, $C\underline{H}_2NH_2$, CH_2OCH_2), 3.78–3.85 (m, 1 H, CH). ^{13}C NMR (151 MHz, D_2O–CD_3OD (1:1)) δ 14.58, 23.49, 23.82, 24.81, 24.89, 26.74, 30.21, 30.30, 30.38, 30.52, 30.77, 32.78, 37.63, 41.97, 45.70, 45.72, 45.80, 46.29, 47.18, 72.03, 72.82, 74.58, 160.59. FT-ICR mass spectrum, *m*/*z*: 529.515 $[M-H+H_2O]^-$, calculated for $C_{29}H_{61}N_4O_4$ 529.469.

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K.A. Perevoshchikova – design of experiments, writing the text of the article, carrying out the synthesis;

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