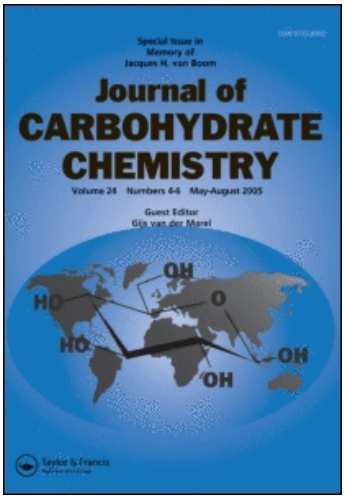

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Synthetic Studies on Sialoglycoconjugates 37: Synthesis of Sialyl-α(2⟶6)-D-glucopyranosyl, 2-Acetamido-2-deoxyhexopyranosyl, and Sialyl-α(2⟶3)-2-acetamido-2-deoxy-D-glucopyranosyl Ceramide or the Analogs at the Lipophilic Part

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SYNTHETIC STUDIES ON SIALOGLYCOCONJUGATES 37: SYNTHESIS OF SIALYL-α(2→6)-D-GLUCOPYRANOSYL, 2-ACETAMIDO-2-DEOXYHEXOPYRANOSYL, AND SIALYL-α(2→3)-2-ACETAMIDO-2-DEOXY-D-GLUCOPYRANOSYL CERAMIDE OR THE ANALOGS AT THE LIPOPHILIC PART

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ABSTRACT

Sialyl-α(2→3)- or sialyl-α(2→6)-β-D-glucopyranosyl- and 2-acetamido-2-deoxy-β-D-hexopyranosyl ceramides or the analogs at the lipophilic residue were synthesized. 2-(Trimethylsilyl)ethyl sialyl-α(2→6)-β-D-gluco-, 2-acetamido-2-deoxy-β-D-gluco-, 2-acetamido-2-deoxy-β-D-galacto- and sialyl-α(2→3)-2-acetamido-2-deoxy-β-D-glucopyranoside derivatives (**1-4**) were converted into the corresponding α-trichloroacetimidate **8** or oxazolines **14**, **15** and **23** which, on coupling with (2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol (**5**) or 2-azidoethanol, gave the corresponding β-glycosides **9**, **16**, **19** and **24**, respectively. Finally, the β-glycosides **9**, **16**, **19** and **24** were transformed, *via* selective reduction of the azide group, condensation with octadecanoic acid or 2-tetradecylhexadecanoic acid (**6**), *O*-deacylation and hydrolysis of the methyl ester group, into the title compounds.

INTRODUCTION

Recently, among the sialoglycoconjugates, various types of biological functions[1-5] of gangliosides have been revealed. In view of these facts, the synthesis of a variety of gangliosides and analogs is critically important in order to investigate their functions at the molecular level. We have reported the total synthesis of several gangliosides and

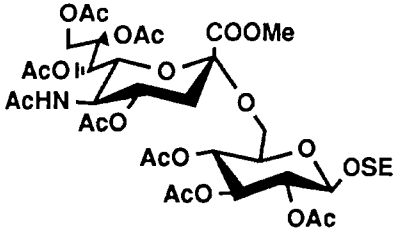
their analogs[6,7] keeping in line with our objective of elucidating the functions of sialoglycoconjugates by using our newly developed method[8-10] for ganglioside synthesis. We describe here the synthesis of sialyl-α(2→6)-β-D-glucopyranosyl ceramide which was isolated[11] from the gamete of sea urchin, and of sialyl-α(2→3)- and sialyl-α(2→6)-2-acetamido-2-deoxy-β-D-galactopyranoses, and of sialyl α(2→6)-2-acetamido-2-deoxy-β-D-glucopyranose lipophilic derivatives.

RESULTS AND DISCUSSION

The key intermediates **1-4**, required for the synthesis of the desired sialoglycolipids, are prepared according to our reported methods,[12,13] are converted into the trichloroacetimidate or oxazoline as the glycosyl donor. The products obtained by coupling of the donors with 2-azidoethanol or (2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol (**5**)[14] could then, by introduction of the lipophilic moiety, be transformed into the end products.

Selective removal of the 2-(trimethylsilyl)ethyl group[15] in **1** was performed by treatment of **1** with BF_3·OEt_2 in dichloromethane for 4 h at 0 °C to give **7** in 95% yield. When treated with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) for 3 h at 0°,[16] compound **7** afforded the trichloroacetimidate **8** in 93% yield after column chromatography. The glycosylation of **5** by **8** in the presence of BF_3·OEt_2 for 4 h at 0 °C, yielded only the expected β-glycoside **9** in 71% yield. Selective reduction[14b,17] of the azide group in **9** with hydrogen sulfide in 5:1 pyridine-water gave the amine, which, on condensation with octadecanoic acid, using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC) in dichloromethane, gave the protected ganglioside **10** in 72% yield. Finally, *O*-deacylation with sodium methoxide in methanol and subsequent saponification of the methyl ester group yielded *O*-(5-acetamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*O*-β-D-glucopyranosyl-(1→1)-ceramide (**11**) in 87% yield.

Treatment of the 2-(trimethylsilyl)ethyl glycosides **2**, **3** or **4** with BF_3·OEt_2 in dichloromethane as described above, and subsequent *O*-acetylation gave the corresponding 1-*O*-acetyl derivatives **12**, **13** and **22** in high yields. Treatment of **12**, **13** or **22** with trimethylsilyl trifluoromethanesulfonate (TMS-triflate) in dichloromethane gave the corresponding oxazolines **14**, **15** and **23** in 90, 74 and 72% yields, respectivery. Coupling of **14** and **15** with 2-azidoethanol and **23** with **5** each in dichloromethane and in the presence of trifluoroacetic acid, followed by chromatography afforded the corresponding β-glycosides **16**, **19** and **24** in good yields, respectively.



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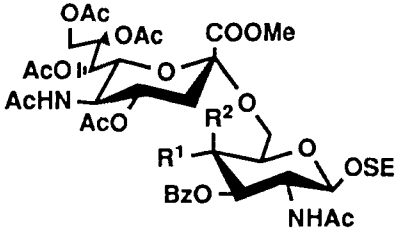
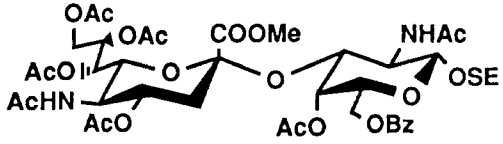


2 R^1 = OAc, R^2 = H
3 R^1 = H, R^2 = OAc



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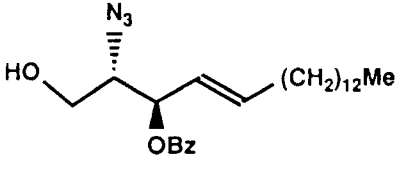
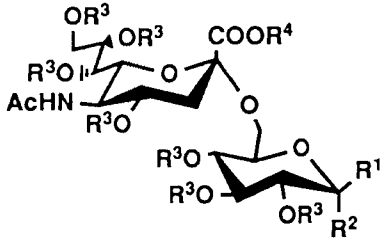
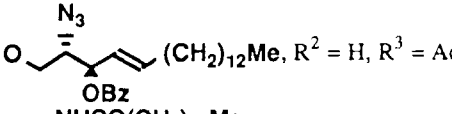


5

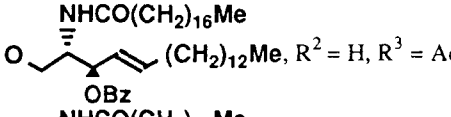
6



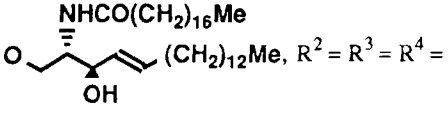
7 R^1, R^2 = OH, H, R^3 = Ac, R^4 = Me
8 R^1 = H, R^2 = OC(=NH)CCl_3, R^3 = Ac, R^4 = Me

9 R^1 = 

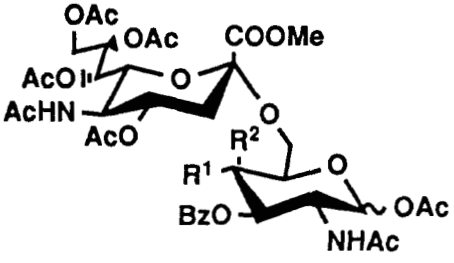
, R^2 = H, R^3 = Ac, R^4 = Me

10 R^1 = 

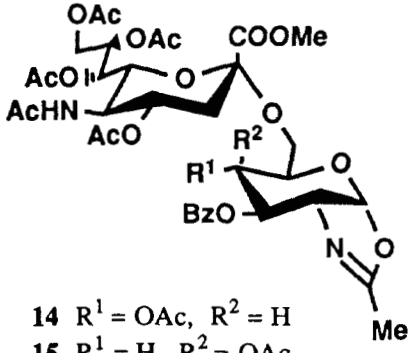
, R^2 = H, R^3 = Ac, R^4 = Me

11 R^1 = 

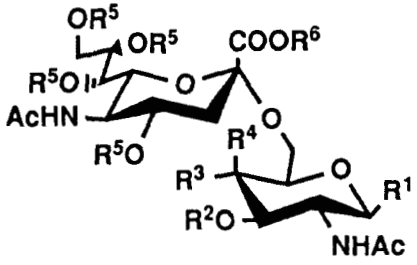
, R^2 = R^3 = R^4 = H

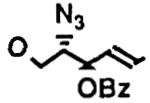


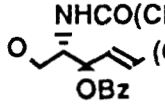
12 R^1 = OAc, R^2 = H
13 R^1 = H, R^2 = OAc

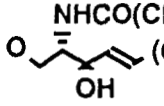


14 R^1 = OAc, R^2 = H
15 R^1 = H, R^2 = OAc



16 R^1 =  R^2 = Bz, R^3 = OAc, R^4 = H, R^5 = Ac, R^6 = Me

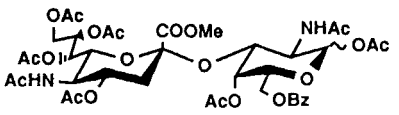
17 R^1 =  R^2 = Bz, R^3 = OAc, R^4 = H, R^5 = Ac, R^6 = Me

18 R^1 =  R^2 = R^4 = R^5 = R^6 = H, R^3 = OH

19 R^1 = $OCH_2CH_2N_3$, R^2 = Bz, R^3 = H, R^4 = OAc, R^5 = Ac, R^6 = Me

20 R^1 = $OCH_2CH_2NHCOCH[(CH_2)_{13}Me]_2$
R^2 = Bz, R^3 = H, R^4 = OAc, R^5 = Ac, R^6 = Me

21 R^1 = $OCH_2CH_2NHCOCH[(CH_2)_{13}Me]_2$
R^2 = R^3 = R^5 = R^6 =H, R^4 = OH



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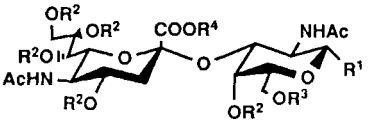
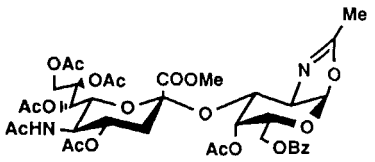


24 $R^1 = OCH_2CH_2N_3$, R^2 = Ac, R^3 = Bz, R^4 = Me
25 $R^1 = OCH_2CH_2NHCOCH[(CH_2)_{13}Me]_2$
R^2 = Ac, R^3 = Bz, R^4 = Me
26 $R^1 = OCH_2CH_2NHCOCH[(CH_2)_{13}Me]_2$
$R^2 = R^3 = R^4 = H$



23

Selective reduction of the azide group in **16** with hydrogen sulfide, and subsequent condensation with octadecanoic acid as described for **10**, gave the per-*O*-acylated sialyl-α(2→6)-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→1)-ceramide (**17**) in 69% yield.

On the other hand, selective reduction of the azide group in **19** or **24** with hydrogen sulfide, and subsequent coupling with 2-tetradecylhexadecanoic acid using WSC in dichloromethane, gave the per-*O*-acylated sialyl-α(2→6)-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→1)-2-(2-tetradecylhexadecanamido)ethanol (**20**) and sialyl-α(2→3)-*O*-(2-acetamido-2-deoxy-β-D-galactopyranosyl)-(1→1)-2-(2-tetradecylhexadecanamido) ethanol (**25**), respectively.

Finally, *O*-deacylation of **17**, **20** or **25** with sodium methoxide and subsequent saponification of the methyl ester group yielded the corresponding three kinds of ganglioside GM4 analogs **18, 21** and **26**.

EXPERIMENTAL

General Procedures. Specific rotations were determined with a Union PM-201 polarimeter at 25 °C, and IR spectra were recorded with a Jasco A-100 spectrophotometer. ^{1}H NMR spectra were recorded with a JEOL JNM-GX 270 spectrometer. Preparative chromatography was performed on silica gel (Wako Chemical Co., 200 mesh) with the solvent systems specified. Concentrations were conducted *in vacuo*.

***O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→6)-2,3,4-tri-*O*-acetyl-**

D-glucopyranose (7). To a stirred solution of 2-(trimethylsilyl)ethyl *O*-(methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→6)-2,3,4-tri-*O*-acetyl-β-D-glucopyranoside[12] (**1**; 840 mg, 0.95 mmol) in dichloromethane (10 mL) cooled to 0 °C, was added dropwise BF_3·OEt_2 (1 mL) and the mixture was stirred for 4 h at 0 °C. The reaction was monitored by TLC and when complete dichloromethane (50 mL) was added. The solution was successively washed with M Na_2CO_3 and water, dried (Na_2SO_4) and concentrated. Column chromatography (50:1 dichloromethene-methanol) of the residue on silica gel (150 g) gave **7** (700 mg, 95%) as an amorphous mass: IR (KBr) 3700-3200 (OH, NH), 1750 and 1220 (ester), and 1660 and 1550 cm^{-1} (amide).

Anal. Calcd for $C_{32}H_{45}NO_{21}$ (779.7): C, 49.29; H, 5.82; N, 1.80. Found: C, 49.08; H, 5.99; N, 1.73.

***O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→6)-2,3,4-tri-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate (8).** To a stirred solution of **7** (300 mg, 0.39 mmol) in dry dichloromethane (5 mL) cooled to 0 °C was added trichloroacetonitrile (0.8 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 0.1 ml), and the mixture was stirred for 3 h at 0 °C and then concentrated. Column chromatography (70:1 dichloromethane-methanol) of the residue on silica gel (50 g) gave **8** (330 mg, 93%) as an amorphous mass: $[\alpha]_D$ +31.0° (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) Neu5Ac unit δ 1.87 (s, 3H, AcN), 2.61 (dd, 1H, $J_{3a,3e}$ = 12.5 Hz, $J_{3e,4}$ = 4.4 Hz, H-3e), 3.80 (s, 3H, MeO), and 4.86 (m, 1H, H-4); Glc unit δ 4.83 (t, 1H, $J_{3,4} = J_{4,5}$ = 9.9 Hz, H-4), 5.11 (dd, 1H, $J_{1,2}$ = 3.3 Hz, $J_{2,3}$ = 10.3 Hz, H-2), 6.54 (d, 1H, $J_{1,2}$ = 3.3 Hz, H-1), and 8.65 (s, 1H C=NH); *O*-acetyl groups δ 2.00, 2.03 (2), 2.09, 2.10, 2.14, 2.15 (7s, 21H, 7AcO).

Anal. Calcd for $C_{34}H_{45}N_2O_{21}Cl_3$ (924.1): C, 44.19; H, 4.91; N, 3.03. Found: C, 44.03; H, 4.98; N, 2.96.

***O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→6)-*O*-(2,3,4-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→1)-(2S,3R,4E)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol (9).** To a solution of **8** (330 mg, 0.357 mmol) and **5** (310 mg, 0.72 mmol) in dichloromethane (5 mL) were added molecular sieves 4Å (AW-300, 2 g), and the mixture was stirred for 1 h at room temperature, then cooled to 0 °C. Boron trifluoride etherate (0.09 mL) was added, and the mixture was stirred for 4 h at 0 °C and then filtered. The insoluble material was washed with dichloromethane, and the combined filtrate and washings were washed with M Na_2CO_3 and water, dried (Na_2SO_4), and concentrated. Column chromatography (2:1 ethyl acetate-hexane) of the residue on

silica gel (50 g) gave **9** (300 mg, 71%) as an amorphous mass: $[\alpha]_D$ -17.0° (*c* 1.4, $CHCl_3$); IR (KBr) 3400 (NH), 2100 (N_3), 1750 and 1220 (ester), 1690 and 1530 (amide), and 710 cm^{-1} (Ph).

Anal. Calcd for $C_{57}H_{82}N_4O_{23}$ (1191.3): C, 57.46; H, 6.94; N, 4.70. Found: C, 57.41; H, 6.90; N, 4.83.

***O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→6)-*O*-(2,3,4-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→1)-(2S,3R,4E)-2-azido-3-*O*-benzoyl-2-octadecanamido-4-octadecene-1,3-diol (10).** Hydrogen sulfide was bubbled through a stirred solution of **9** (123 mg, 0.1 mmol) in aqueous 83% pyridine (12 mL) for 48 h at room temperature wth the reaction being monitored by TLC. The mixture was concentrated, and the residue was stirred with octadecanoic acid (60 mg, 0.2 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC; 60 mg) in dichloromethane (5 mL) overnight at room temperature. Dichloromethane (50 mL) was added, and the mixture was washed with water, dried (Na_2SO_4) and concentrated. Column chromatography (80:1 dichloromethane-methanol) of the residue on silica gel (40 g) gave **10** (106 mg, 72%) as an amorphous mass: $[\alpha]_D$ +1.7° (*c* 0.6, $CHCl_3$); IR (KBr) 3400 (NH), 1750 and 1220 (ester), 1660 and 1550 (amide), and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) Neu5Ac unit δ 2.55 (dd, 1H, $J_{3a,3e}$ = 12.8 Hz, $J_{3e,4}$ = 4.4 Hz, H-3e), 3.72 (s, 3H, MeO), 4.90 (m, 1H, H-4); Glc unit δ 4.45 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1); Cer unit δ 0.88 (t, 6H, J_{Me,CH_2} = 6.6 Hz, *Me*CH_2), 1.26 (s, 52H, 26CH_2) and 7.43-8.04 (m, 5H, Ph).

Anal. Calcd for $C_{75}H_{118}N_2O_{24}$ (1431.8): C, 62.91; H, 8.31; N, 1.96. Found: C, 62.70; H, 8.35; N, 1.94.

***O*-(5-Acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonic acid)-(2→6)-*O*-β-D-glucopyranosyl-(1→1)-(2S,3R,4E)-2-octadecanamido-4-octadecene-1,3-diol (11).** To a solution of **10** (88 mg, 0.62 mmol) in methanol (5 mL) was added sodium methoxide (20 mg), the mixture was stirred for 4 h at room temperature and water (0.5 mL) was added. The solution was stirred for 12 h at room temperature, neutralized with Amberlite IR-120 (H^+) resin and filtered. The resin was washed with methanol and the combined filtrate and washings were concentrated. Column chromatography (methanol) of the residue on Sephadex LH-20 (40 g) gave **11** (54 mg, 87%) as an amorphous mass: $[\alpha]_D$ -11,1° (*c* 0.92, 1:1 MeOH-$CHCl_3$); ^1H NMR [1:1 $(CD_3)_2SO$-CD_3OD] δ 0.87 (t, 6H, J_{Me,CH_2} = 5.1 Hz, 2*Me*CH_2), 1.28 (s, 52H, 26CH_2), 1.94 (s, 3H, AcN), 2.08 (t, 2H, J_{CH_2,CH_2} = 6.6 Hz, CO*CH*$_2$$CH_2$), 2.70 (dd, 1H, $J_{3a,3e}$ = 12.1 Hz, $J_{3e,4}$ = 5.1 Hz, H-3e for Neu5Ac), 4.12 (d, 1H, $J_{1,2}$ = 6.6 Hz, H-1 for Glc), and 5.35-5.57 (m, 2H, H-4,5 for Cer).

Anal. Calcd for $C_{53}H_{98}N_2O_{16}$ (1019.4): C, 62.44; H, 9.69; N, 2.75. Found: C, 62.14; H, 9.84; N, 2.71.

***O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→6)-2-acetamido-1,4-di-*O*-acetyl-3-*O*-benzoyl-2-deoxy-D-glucopyranose (12).** To a cooled solution of **2**[12] (600 mg, 0.64 mmol) in dichloromethane (10 mL) was added BF_3·OEt_2 (0.78 mL), and the mixture was stirred for 3 h at 0 °C and then worked-up, as described for **7** giving the 1-hydroxyl compound (490 mg, 93%) as an amorphous mass. The 1-hydroxyl compound (690 mg, 0.82 mmol) thus obtained was acetylated with acetic anhydride (3 mL)-pyridine (5 mL) overnight at room temperature. The product was purified by column chromatograpy (50:1 dichloromethane-methanol) on silica gel (100 g), to give **12** (723 mg, quantitative) as an amorphous mass. The anomeric ratio (α:β) was estimated at 10:1 from the integration ratio of H-1α and H-1β; ^1H NMR ($CDCl_3$) Neu5Ac unit δ 2.66 (dd, 1H, $J_{3a,3e}$ = 12.8 Hz, $J_{3e,4}$ = 4.8 Hz, H-3e), 3.72 (s, 3H, MeO), 4.88 (ddd, 1H, $J_{3a,4}$ = 12.1 Hz, $J_{4,5}$ = 9.5 Hz, H-4), and 5.32 (m, 2H, H-7,8); GlcNAc unit δ 4.59 (ddd, 1H, $J_{1,2}$ = 3.3 Hz, $J_{2,3}$ = 11.0 Hz, H-2), 5.45 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 5.58 (dd, 1H, $J_{4,5}$ = 9.9 Hz, H-4), 6.22 (d, 1H, H-1), and 7.42-8.03 (m, 5H, Ph); other groups δ 1.84, 1.85 (2s, 6H, 2AcN), and 2.01, 2.03, 2.04, 2.12, 2.15, 2.22 (6s, 18H, 6AcO).

Anal. Calcd for $C_{39}H_{50}N_2O_{21}$ (882.8): C, 53.06; H, 5.71; N, 3.17. Found: C, 53.09; H, 5.64; N, 3.14.

***O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→6)-2-acetamido-1,4-di-*O*-acetyl-3-*O*-benzoyl-2-deoxy-D-galactopyranose (13).** Selective removal of the 2-(trimethylsilyl)ethyl group in **3**[12] (242 mg, 0.26 mmol) with BF_3·OEt_2 (0.3 mL) in dichloromethane (5 mL) and subsequent acetylation with acetic anhydride (2 mL)-pyridine (3 mL), as described for **12**, afforded **13** (216 mg, 98%) as an amorphous mass. The anomeric ratio (α:β) was estimated at 10:1 from the integration ratio of H-1α and H-1β; ^1H NMR ($CDCl_3$) δ 1.85, 1.87 (2S, 6H, 2AcO), 2.53 (dd, 1H, $J_{3a,3e}$ = 12.8 Hz, $J_{3e,4}$ = 4.6 Hz, H-3e for Neu5Ac), 3.78 (s, 3H, MeO), 4.88 (m, 1H, H-4 for Neu5Ac), and 5.48 (dd, 1H, $J_{6,7}$ = 3.5 Hz, $J_{7,8}$ = 10.6 Hz, H-7), 5.65 (broad d, 1H, H-4 for GalNAc), and 6.28 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1).

Anal. Calcd for $C_{39}H_{50}N_2O_{21}$ (882.8): C, 53.06; H, 5.71; N, 3.17. Found: C, 53.15; H, 5.80; N, 3.22.

2-Methyl-[*O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→6)-(4-*O*-acetyl-3-*O*-benzoyl-1,2-deoxy-D-glucopyrano)]-[2,1-d]-2-oxazoline (14).

To a solution of **12** (150 mg, 0.17 mmol) in dichloromethane (10 mL) cooled to 0 °C was added trimethylsilyl trifluoromethanesulfonate (TMS·OTf; 0.05 mL), and the mixture was stirred for 4 h under reflux. Dichloromethane (50 mL) was added, and the mixture was successively washed with M Na_2CO_3 and water, dried (Na_2SO_4), and concentrated. Column chromatography (60:1 dichloromethane-methanol) of the residue on silica gel (40 g) gave **14** (125 mg, 90%) as an amoprhous mass: $[\alpha]_D$ -24.0° (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.60 (dd, 1H, $J_{3a,3e}$ = 12.8 Hz, $J_{3e,4}$ = 4.8 Hz, H-3e for Neu5Ac), 4.88 (ddd, 1H, $J_{3a,4}$ = 11.5 Hz, $J_{4,5}$ = 9.9 Hz, H-4 for Neu5Ac), and 6.04 (d, 1H, $J_{1,2}$ = 7.3 Hz, H-1 for GlcNAc).

Anal. Calcd for $C_{37}H_{46}N_2O_{19}$ (822.8): C, 54.01; H, 5.64; N, 3.40. Found: C, 54.13; H, 5.79; N, 3.45.

2-Methyl-[*O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→6)-(4-*O*-acetyl-3-*O*-benzoyl-1,2-deoxy-D-galactopyrano)]-[2,1-d]-2-oxazoline (15). To a solution of **13** (160 mg, 0.18 mmol) in dichloromethane (5 mL), cooled to 0 °C was added TMS·OTf (0.06 mL), and the mixture was stirred for 2 h under reflux, and then worked-up, as described for **14**, giving **15** (110 mg, 74%) as an amorphous mass: $[\alpha]_D$ -14.0° (*c* 0.5, $CHCl_3$); δ 1.87 (s, 3H, AcN), 2.02, 2.07, 2.09, 2.11, 2.15 (5s, 15H, 5AcO), 2.56 (dd, 1H, $J_{3a,3e}$ = 12.7 Hz, $J_{3e,4}$ = 4.4 Hz, H-3e), 3.34 (dd, 1H, $J_{1,2}$ = 6.8 Hz, $J_{2,3}$ = 10.3 Hz, H-2 for GalNAc), 3.77 (s, 3H, MeO), 4.86 (m, 1H, H-4 for Neu5Ac), 5.30 (dd, 1H, $J_{3,4}$ = 1.5 Hz, H-3 for GalNAc), 5.59 (t, 1H, $J_{4,5}$ =3.1 Hz, H-4 for GalNAc), and 7.38-8.02 (m, 5H, Ph).

Anal. Calcd for $C_{37}H_{46}N_2O_{19}$ (822.8): C, 54.01; H, 5.64; N, 3.40. Found: C, 54.13; H, 5.70; N, 3.48.

***O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→6)-*O*-(2-acetamido-4-*O*-acetyl-3-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl-(1→1)-(2S,3R,4E)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol (16).** To a solution of **14** (50 mg, 61 μmol) and **5** (65 mg, 0.15 mmol) was added Drierite (1 g) and the mixture was stirred for 2 h at room temperature. Trifluoroacetic acid (0.05 mL) was added, and the mixture was stirred for 7 days at room temperature. The reaction was monitored by TLC and, when complete, the precipitate was filtered and washed with dichloromethane. The combined filtrate and washings were washed with M Na_2CO_3 and water, dried (Na_2SO_4) and concentrated. Column chromatography (80:1 dichloromethane-methanol) of the residue on silica gel (30 g) gave **16** (40 mg, 51%) as an amoprhous mass: $[\alpha]_D$ -28.6° (*c* 0.7 $CHCl_3$); IR (KBr) 3400 (NH), 2100 (N_3), 1750 and 1220 (ester), 1660 and 1550 (amide), and 710 cm^{-1} (Ph).

Anal. Calcd for $C_{62}H_{85}N_5O_{22}$ (1252.4): C, 59.46; H, 6.84; N, 5.59. Found: C, 59.38; H, 6.69; N, 5.71.

***O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→6)-*O*-(2-acetamido-4-*O*-acetyl-3-*O*-benzoyl-2-deoxy-β-D-glucopyranosyl-(1→1)-(2S,3R,4E)-3-*O*-benzoyl-2-octadecanamido-4-octadecene-1,3-diol (17).** Selective reduction of the azide group in **16** (70 mg, 60 μmol) and subsequent coupling with octadecanoic acid (32 mg, 0.11 mmol) as described for **10**, afforded **17** (57 mg, 69%) as an amorphous mass: $[\alpha]_D$ -15.7° (*c* 1.1 $CHCl_3$); IR (KBr) 3400 (NH), 2940 and 2840 (methyl, methylene), 1750 and 1220 (ester), 1660 and 1550 (amide), and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.82 (t, 6H, J_{Me,CH_2} = 6.2 Hz, $2MeCH_2$), 1.25 (s, 52H, $26CH_2$), 2.57 (dd, 1H, $J_{3a,3e}$ = 12.5 Hz, $J_{3e,4}$ = 4.8 Hz, H-3e), 4.30 (dd, 1H, $J_{8,9'}$ = 1.5 Hz, $J_{9,9'}$ = 11.7 Hz, H-9'), 4.74 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), 4.84 (m, 1H, H-4 for Neu5Ac), and 5.55-5.85 (m, 2H, H-4,5 for Cer).

Anal. Calcd for $C_{80}H_{121}N_3O_{23}$ (1492.9): C, 64.36; H, 8.17; N, 2.81. Found: C, 64.23; H, 8.25; N, 2.77.

***O*-(5-Acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonic acid)-(2→6)-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→1)-(2S,3R,4E)-2-octadecanamido-4-octadecene-1,3-diol (18).** Deacylation and saponification of **17** (50 mg, 33.5 μmol), as described for **11**, yielded **18** (35 mg, quantitative) as an amorphous mass: $[\alpha]_D$ -38.8° (*c* 0.32, 1:1 MeOH-$CHCl_3$); IR (KBr) 3500-3300 (OH, NH), 2940 and 2840 (methyl, methylene), 1710 (COOH), and 1660 and 1550 cm^{-1} (amide); ^1H NMR (1:1 CD_3OD-$CDCl_3$) δ 0.89 (t, 6H, J_{Me,CH_2} = 6.5 Hz, $2MeCH_2$), 1.25 (~s, 50H, $25CH_2$), 1.46 (2H, $COCH_2CH_2$), 1.98, 2.02 (2s, 6H, AcN), 2.75 (dd, 1H, H-3e), and 5.50-5.85 (m, 2H, H-4,5 for Cer).

Anal. Calcd for $C_{55}H_{101}N_3O_{16}$ (1060.4): C, 62.29; H, 9.60; N, 3.96. Found: C, 62.03; H, 9.88; N, 3.91.

2-Azidoethyl (Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→6)-2-acetamido-4-*O*-acetyl-3-*O*-benzoyl-2-deoxy-β-D-galactopyranoside (19). To a solution of **15** (110 mg, 0.133 mmol) and 2-azidoethanol (0.21 mL, 0.27 mmol) in dichloromethane (5 mL) was added Drierite (2 g) and the mixture was stirred for 2 h at room temperature. Trifluoroacetic acid was added to the mixture until pH 4 was reached, and the mixture was stirred for 3 days at room temperature. The precipitate was collected and washed with dichloromethane, and the combined filtrate and washings were concentrated and then extracted with dichloromethane. The extract was successively washed

with M Na_2CO_3 and water, dried (Na_2SO_4) and concentrated. Column chromatography (60:1 dichloromethene-methanol) of the residue on silica gel (30 g) gave **19** (89 mg, 73%) as an amorphous mass: $[\alpha]_D$ -27.0° (*c* 1.8, $CHCl_3$); IR (KBr) 3250 (NH), 2100 (N_3), 1740 and 1230 (ester), 1650 and 1540 (amide), and 700 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 1.87, 1.89 (2s, 6H, 2AcN), 2.01, 2.06, 2.14, 2.18, 2.24 (5s, 15H, 5AcO), 2.53 (dd, 1H, $J_{3a,3e}$ = 12.8 Hz, $J_{3e,4}$ = 4.3 Hz, H-3e), 3.25-3.44 (m, 4H, $CH_2CH_2N_3$), 3.81 (s, 3H, MeO), 4.61 (dd, 1H, $J_{8,9'}$ = 2.1 Hz, $J_{9,9'}$ = 11.9 Hz, H-9), 4.74 (d, 1H, $J_{1,2}$ = 8.4 Hz, H-1), 4.82 (m, 1H, $J_{3a,4}$ = 12.1 Hz, $J_{4,5}$ = 10.1 Hz, H-4 for Neu5Ac), 5.16 (dd, 1H, $J_{6,7}$ = 1.5 Hz, $J_{7,8}$ = 9.9 Hz, H-7), 8.48 (m, 1H, H-8), 5.51 (dd, 1H, $J_{2,3}$ = 11.2 Hz, $J_{3,4}$ = 3.4 Hz, H-3 for GalNAc), 5.69 (broad d, 1H, H-4 for GalNAc), 7.38-7.95 (m, 5H, Ph).

Anal. Calcd for $C_{39}H_{51}N_5O_{20}$ (909.9): C, 51.48; H, 5.65; N, 7.70. Found: C, 51.43; H, 5.71; N, 7.62.

***O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→6)-*O*-(2-acetamido-4-*O*-acetyl-3-*O*-benzoyl-2-deoxy-β-D-galactopyranosyl)-(1→1)-2-(2-tetradecylhexadecanamido)ethanol (20).** Selective reduction of the azide group in **19** (129 mg, 0.14 mmol) and subsequent coupling with 2-tetradecylhexadecanoic acid (**6**, 125 mg, 0.28 mmol), as described for **10**, gave **20** (127 mg, 68%) as an amorphous mass: $[\alpha]_D$ -20.5° (*c* 0.4, $CHCl_3$); IR (KBr) 3300 (NH), 2940 and 2850 (methyl, methylene), 1750 and 1230 (ester), 1660 and 1550 (amide), and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.87 (t, 6H, J_{Me,CH_2} = 6.2 Hz, 2*Me*CH_2), 1.24 (s, 52H, 26CH_2), 1.88 (2) (2s, 6H, 2AcN), 2.00, 2.01, 2.14, 2.19, 2.23 (5s, 15H, 5AcO), 2.53 (dd, 1H, $J_{3a,3e}$ = 13.0 Hz, $J_{3e,4}$ = 4.2 Hz, H-3e), 3.81 (s, 3H, MeO), 4.61 (d, 1H, $J_{1,2}$ = 8.6 Hz, H-1 for GalNAc), 4.81 (m, 1H, H-4 for Neu5Ac), 5.13 (dd, 1H, $J_{6,7}$ = 2.0 Hz, $J_{7,8}$ = 10.0 Hz, H-7), 5.44 (m, 1H, H-8), 5.50 (dd, 1H, $J_{2,3}$ = 10.8 Hz, $J_{3,4}$ = 3.5 Hz, H-3 for GalNAc), 5.71 (broad d, 1H, H-4 for GalNAc), and 7.29-7.94 (m, 5H, Ph).

Anal. Calcd for $C_{69}H_{111}N_3O_{21}$ (1318.7): C, 62.84; H, 8.48; N, 3.19. Found: C, 62.73; H, 8.62; N, 3.15.

***O*-(5-Acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonic acid)-(2→6)-*O*-(2-acetamido-2-deoxy-β-D-galactopyranosyl)-(1→1)-2-(2-tetradecylhexadecanamido)ethanol (21).** Deacylation and saponification of **20** (105 mg, 80 μmol), as described for **11**, yielded **21** (67 mg, 85%) as an amorphous mass: $[\alpha]_D$ -7.9° (*c* 0.6, 1:1 MeOH-$CHCl_3$); IR (KBr) 3600-3300 (OH, NH), 2940 and 2850 (methyl, methylene), 1700 (COOH), and 1620 and 1540 cm^{-1} (amide); ^1H NMR (1:1 CD_3OD-$CDCl_3$) δ 0.87 (t, 6H, J_{Me,CH_2} =

6.5 Hz, 2*Me*CH_2), 1.24 (s, 52H, 26CH_2), 2.00, 2.03 (2s, 6H, 2AcN), and 2.75 (dd, 1H, $J_{3a,3e}$ = 12.0 Hz, $J_{3e,4}$ = 4.2 Hz, H-3e).

Anal. Calcd for $C_{51}H_{95}N_3O_{15}$ (1004.3): C, 60.99; H, 9.53; N, 4.18. Found: C, 60.70; H, 9.72; N, 4.13.

***O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→3)-2-acetamido-1,4-di-*O*-acetyl-6-*O*-benzoyl-2-deoxy-D-galactopyranose (22).** Selective removal of the 2-(trimethylsilyl)ethyl group in **4**[13] (140 mg, 0.15 mmol) with BF_3·OEt_2 (0.5 mL) in dichloromethane (5 mL), and subsequent acetylation with acetic anhydride (2 mL)-pyridine (3 mL), as described for **12**, gave **22** (130 mg, quantitative) as an amorphous mass. The anomeric ratio (α:β) was estimated at 8:1 from the integration ratio of H-1α and H-1β; ^{1}H NMR ($CDCl_3$) δ 1.84, 2.00 (2S, 6H, 2AcO), 2.64 (dd, 1H, $J_{3a,3e}$ = 13.0 Hz, $J_{3e,4}$ = 4.8Hz, H-3e), 3.75 (s, 3H, MeO), 4.94 (m, 1H, $J_{4,5}$ = 10.3 Hz, H-4 for Neu5Ac), 5.65 (dd, 1H, $J_{6,7}$ = 2.1 Hz, $J_{7,8}$ = 8.5 Hz, H-7), 5.67 (m, 1H, H-8), 5.83 (d, $J_{1a,2}$ = 7.1 Hz, H-1a), 6.35 (d, $J_{1e,2}$ = 3.5 Hz, H-1e), and 7.35-8.03 (m, 5H, Ph).

Anal. Calcd for $C_{39}H_{50}N_2O_{21}$ (882.8): C, 53.06; H, 5.71; N, 3.17. Found: C, 53.15; H, 5.70; N, 3.14.

2-Methyl-[*O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→3)-(4-*O*-acetyl-6-*O*-benzoyl-2-deoxy-D-galactopyrano)]-[2,1-d]-2-oxazoline (23). To a solution of **22** (131 mg, 0.15 mmol) in dichloromethane (3 mL), cooled to 0 °C was added TMS·OTf (0.043 mL), and the mixture was stirred for 2h, and then worked-up, as described for **14**, giving **23** (88 mg, 72%) as an amorphous mass: $[\alpha]_D$ +13.5° (*c* 0.72, $CHCl_3$); ^{1}H NMR δ 1.86 (s, 3H, AcN), 2.01, 2.03, 2.09, 2.11, 2.17 (5s, 15H, 5AcO), 2.66 (dd, 1H, $J_{3a,3e}$ = 12.8 Hz, $J_{3e,4}$ = 4.8 Hz, H-3e), 3.76 (s, 3H, MeO), 4.94 (m, 1H, $J_{3a,4}$ = 11.8 Hz, $J_{4,5}$ = 10.3 Hz, H-4 for Neu5Ac), 5.10 (d, 1H, $J_{3,4}$ = 2.7 Hz, H-4 for GalNAc), 5.14 (d, 1H, $J_{7,8}$ = 9.9 Hz, H-7), 5.38 (dd, 1H, $J_{2,3}$ = 9.5 Hz, H-3 for GalNAc), 5.51 (m, 1H, H-8), 6.01 (d, 1H, $J_{1,2}$ = 7.0 Hz), and 7.40-8.07 (m, 5H, Ph).

Anal. Calcd for $C_{37}H_{46}N_2O_{19}$ (822.8): C, 54.04; H, 5.64; N, 3.40. Found: C, 54.14; H, 6.53; N, 3.41.

2-Azidoethyl *O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→3)-2-acetamido-4-*O*-acetyl-6-*O*-benzoyl-2-deoxy-β-D-galactopyranoside (24). To a solution of **23** (145 mg, 0.18 mmol) and 2-azidoethanol (0.28 mL, 3.6 mmol) in dichloromethane (5 mL) was added Drierite (2.5 g), and the mixture was stirred for 2 h at

room temperature. Trifluoroacetic acid was added to the mixture until pH 4 was reached, and the mixture was stirred for 2 days at room temperature, and then worked-up, as described for **19**, affording **24** (135 mg, 84%) as an amorphous mass: $[\alpha]_D$ -41.5° (*c* 0.15, $CHCl_3$); IR (KBr) 3300 (NH), 2100 (N_3), 1740 and 1230 (ester), 1660 and 1540 (amide), and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 1.86, 1.99 (2s, 6H, 2AcN), 2.06, 2.13 (2), 2.15, 2.16 (5s, 15H, 5AcO), 2.60 (dd, 1H, $J_{3a,3e}$ = 12.5 Hz, $J_{3e,4}$ = 4.6 Hz, H-3e), 3.28-4.00 (m, 4H, $CH_2CH_2N_3$), 3.76 (s, 3H, MeO), 4.60 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1 for GalNAc), 4.88 (m, 1H, $J_{3a,4}$ = 11.9 Hz, $J_{4,5}$ = 10.5 Hz, H-4 for Neu5Ac), 4.99 (d, 1H, $J_{3,4}$ = 2.2 Hz, H-4 for GalNAc), 5.22 (dd, 1H, $J_{6,7}$ = 1.3 Hz, $J_{7,8}$ = 10.0 Hz, H-7), 5.28 (dd, 1H, $J_{2,3}$ = 10.1 Hz, H-3 for GalNAc), 5.63 (m, 1H, H-8), and 7.41-8.04 (m, 5H, Ph).

Anal. Calcd for $C_{39}H_{51}N_5O_{20}$ (909.9): C, 51.48; H, 5.65; N, 7.70. Found: C, 51.34; H, 5.82; N, 7.69.

***O*-(Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→3)-*O*-(2-acetamido-4-*O*-acetyl-6-*O*-benzoyl-2-deoxy-β-D-galactopyranosyl)-(1→1)-2-(2-tetradecylhexadecanamido)ethanol (25).** Selective reduction of the azide group in **24** (134 mg, 0.15 mmol) and subsequent coupling with **6** (130 mg, 0.3 mmol), as described for **10**, gave **25** (108 mg, 56%) as an amorphous mass: $[\alpha]_D$ -10.0° (*c* 0.2, $CHCl_3$); IR (KBr) 3300 (NH), 2940 and 2850 (methyl, methylene), 1740 and 1230 (ester), 1660 and 1540 (amide), and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.87 (t, 6H, J_{Me,CH_2} = 6.5 Hz, $2MeCH_2$), 1.23 (m, 52H, $26CH_2$), 1.85, 1.88 (2s, 6H, 2AcN), 2.02, 2.12, 2.13, 2.15, 2.16 (5s, 15H, 5AcO), 2.61 (dd, 1H, $J_{3a,3e}$ = 12.5 Hz, $J_{3e,4}$ = 4.5 Hz, H-3e), 3.75 (s, 3H, MeO), 4.47 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1), 4.87 (m, 1H, $J_{3a,4}$ = 12.0 Hz, $J_{4,5}$ = 10.4 Hz, H-4 for Neu5Ac), 4.97 (broad d, 1H, H-4 for GalNAc), 5.19 (d, 1H, $J_{7,8}$ = 10.0 Hz, H-7), 5.28 (dd, $J_{2,3}$ = 10.1 Hz, H-3 for GalNAc), 5.63 (m, 1H, H-8), and 7.40-8.03 (m, 5H, Ph).

Anal. Calcd for $C_{69}H_{111}N_3O_{21}$ (1318.7): C, 62.84; H, 8.48; N, 3.19. Found: C, 62.73; H, 8.61; N, 3.18.

***O*-(5-Acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonic acid)-(2→3)-*O*-(2-acetamido-2-deoxy-β-D-galactopyranosyl)-(1→1)-2-(2-tetradecylhexadecanamido)ethanol (26).** Deacylation and subsequent saponification of **25** (97mg, 73 μmol), as described for **11**, yielded **26** (72 mg, quantitative) as an amorphous mass: $[\alpha]_D$ -22° (*c* 0.7, 1:1 MeOH-$CHCl_3$); IR (KBr) 3700-3300 (OH, NH), 2940 and 2850 (methyl, methylene), 1700 (COOH), and 1620 and 1540 cm^{-1} (amide); ^1H NMR (1:1 CD_3OD-$CDCl_3$) δ 0.87 (t, 6H, J_{Me,CH_2} = 6.6 Hz, $2MeCH_2$), 1.25 (s, 52H, $26CH_2$), 2.04 (2) (2s, 6H, 2AcN), and 2.76 (dd, 1H, $J_{3a,3e}$ = 12.5 Hz, $J_{3e,4}$ = 4.2 Hz, H-3e).

Anal. Calcd for $C_{51}H_{95}N_3O_{15}$ (1004.3): C, 60.99; H, 9.53; N, 4.18. Found: C, 60.81; H, 9.70; N, 4.03.

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