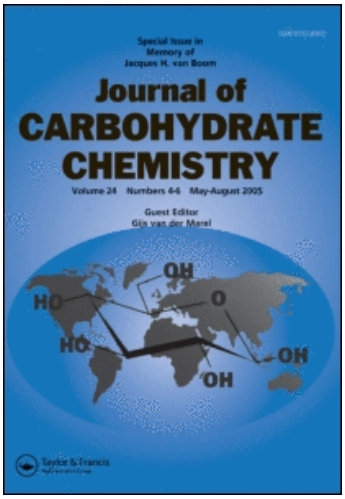

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SYNTHETIC STUDIES ON SIALOGLYCOCONJUGATES 14: SYNTHESIS OF GANGLIOSIDE GM_3 ANALOGS CONTAINING THE CARBON 7 AND 8 SIALIC ACIDS

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ABSTRACT

Ganglioside GM_3 analogs, containing 5-acetamido-3,5-dideoxy-L-arabino-heptulosonic acid and 5-acetamido-3,5-dideoxy-D-galacto-octulosonic acid have been synthesiyed. Glycosylation of 2-(trimethylsilyl)ethyl O-(6-O-benzoyl-β-D-galactopyranosyl)-(1→4)-2,6-di-O-benzoyl-β-D-glucopyranoside (5), with methyl (methyl 5-acetamido-4,7-di-O-acetyl-3,5-dideoxy-2-thio-β-L-arabino-2-heptulopyranosid)onate (2) or with methyl (methyl 5-acetamido-4,7,8-tri-O-acetyl-3,5-dideoxy-2-thio-α-D-galacto-2-octulopyranosid)onate (4), which were respectively prepared from the corresponding 2-S-acetyl derivatives (1 and 3) by selective 2-S-deacetylation and subsequent S-methylation, using dimethyl(methylthio)sulfonium triflate as a glycosyl promoter, gave 2-(trimethylsilyl)ethyl O-(methyl 5-acetamido-4,7-di-O-acetyl-3,5-dideoxy-β-L-arabino-2-heptulopyranosylonate)-(2→3)-O-(6-O-benzoyl-β-D-galactopyranosyl)-(1→4)-2,6-di-O-benzoyl-β-D-glucopyranoside (6) and 2-(trimethylsilyl)ethyl O-(methyl 5-acetamido-4,7,8-tri-O-acetyl-3,5-dideoxy-α-D-galacto-2-octulopyranosylonate)-(2→3)-O-(6-O-benzoyl-β-D-galactopyranosyl)-(1-4)-2,6-di-O-benzoyl-β-D-glucopyranoside (10), respectively. Compounds 6 and 10 were converted, via O-acetylation, selective removal of the 2-(trimethylsilyl)ethyl group, and subsequent imidate formation, into the corresponding trichloroacetimidates 9 and 13, respectively.

Glycosylation of (2S,3R,4E)-2-azido-3-O-benzoyl-4-octadecen-1,3-diol (14) with 9 or 13 afforded the β-glycosides (15 and 18), which were converted, via selective reduction of the azide group, coupling with octadecanoic acid, O-deacylation, and deesterification, into the title compounds, respectively.

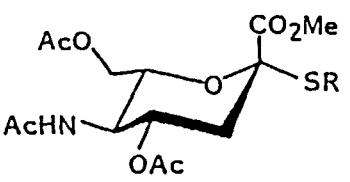
INTRODUCTION

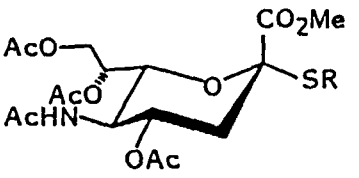
Sialic acids are well known as important constituents of cell-surface glycoproteins and glycolipids, and are involved in their biological functions. Recently, various types of biological behavior of sialoglycoconjugates, such as gangliosides and sialyl-glycopeptides, have been reported by many groups.[1-9] In view of these facts, there has been a great deal of activity in recent years in the syntheses[10-17] of the derivatives and analogs of N-acetyl-neuraminic acid. It is of interest to investigate the relationship between the structures of the sialic acid and the functions of gangliosides.

Previously,[18-21] we have achieved a regio- and α-stereo-selective glycosidation of Neu5Ac, which led to the facile synthesis of a variety of gangliosides. As a part of our research on the synthesis of gangliosides and the study of their biological activity, we describe here the synthesis of ganglioside GM_3 analogs, containing shorter carbon-chain analogs (7 and 8 carbons) of N-acetyl-neuraminic acid.

RESULTS AND DISCUSSION

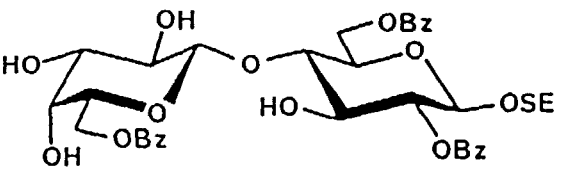
For the synthesis of the desired ganglioside GM_3 analogs, containing shorter carbon-chain sialic acids, we set out to prepare 2-(trimethylsilyl)ethyl O-(6-O-benzoyl-β-D-galactopyranosyl)-(1→4)-2,6-di-O-benzoyl-β-D-glucopyranoside[18,22] (5) as a suitablyprotected glycosyl acceptor and methyl α-2-thioglycosides (2 and 4) of N-acetylneuraminic acid analogs[17] as the glycosyl donors. The acceptor 5 can then be coupled with the donors using dimethyl-(methylthio) sulfonium triflate[18,20,23,24] (DMTST) as a glycosyl





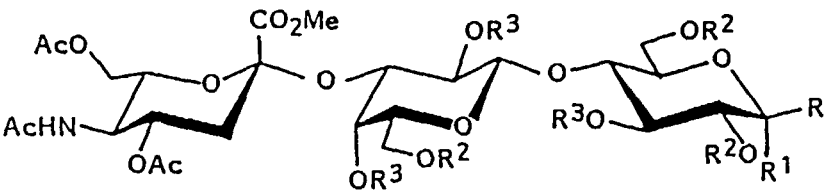
1 R = Ac
2 R = Me

3 R = Ac
4 R = Me



5

Bz = benzoyl
SE = $Me_3SiCH_2CH_2$-



6 R = OSE, R^1 = H, R^2 = Bz, R^3 = H
7 R = OSE, R^1 = H, R^2 = Bz, R^3 = Ac
8 R, R^1 = H, OH, R^2 = Bz, R^3= Ac
9 R = H, R^1 = $OC(=NH)CCl_3$, R^2 = Bz, R^3 = Ac

promotor. The intermediates can be converted, by introduction of a ceramide moiety, into the end products.

Selective 2-S-deacetylation of methyl 5-acetamido-4,7-di-O-acetyl-2-S-acetyl-3,5-dideoxy-2-thio-β-L-*arabino*-2-heptulopyranosonate[17a] (1), with an amount of sodium methoxide calculated to be less than equivalent (95%) to 1 in dry methanol at -40 °C, followed by S-methylation with methyl iodide, gave methyl (methyl 5-acetamido-4,7-di-O-acetyl-3,5-dideoxy-2-thio-β-L-*arabino*-2-heptulopyranosid)onate (2) in 87% yield. In the same way, 2-S-deacetylation of 3[17b] and subsequent S-methylation afforded the methyl α-thioglycoside 4 of 5-acetamido-3,5-dideoxy-D-*galacto*-2-octulosonic acid in 82% yield. Significant signals in the ^{1}H NMR spectra of compounds 2 and 4 were a one-proton doublet of doublets at δ 2.74 ($J_{3a,3e}$ = 12.6 Hz, $J_{3e,4}$ = 4.6 Hz, H-3e) for 2 and at δ 2.75 ($J_{3a,3e}$ = 12.8 Hz, $J_{3e,4}$ = 4.6 Hz, H-3e) for 4, and a one-proton multiplet at δ 4.88 ($J_{3a,4}$ = 11.5 Hz, $J_{4,5}$ = 10.4 Hz, H-4) for 2 and at δ 4.87 ($J_{3a,4}$ = 11.5 Hz, $J_{4,5}$ = 10.4 Hz, H-4) for 4, indicating the anomeric configurations[18,25] assigned. Other ^{1}H NMR data are given in the Experimental Section and are consistent with the structures assigned.

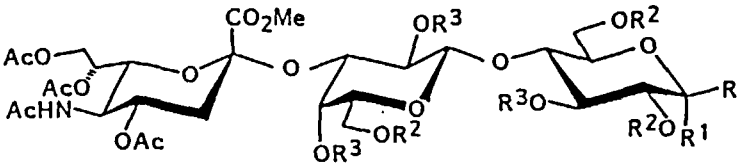
The glycosylation of 5 with the glycosyl donor 2 (2.0 equiv to the acceptor) in acetonitrile for 24 h at -15 °C in the presence of DMTST (4.0 equiv to 2) and 3A molecular sieves, according to a procedure described[18] previously by us, exclusively gave the expected β-glycoside 6 in 48% yield. The unreacted glycosyl acceptor 5 (43%) was recovered from this reaction. In the same way, reaction of methyl (methyl 5-acetamido-4,7,8-tri-O-acetyl-3,5-dideoxy-2-thio-α-D-*galacto*-2-octulopyranosid)onate (4) with 5 yielded the expected α-glycoside, 2-(trimethylsilyl)ethyl O-(methyl 5-acetamido-4,7,8-tri-O-acetyl-3,5-dideoxy-α-D-*galacto*-2-octulopyranosylonate)-(2→3)-O-(6-O-galactopyranosyl)-(1→4)-2,6-di-O-benzoyl-β-D-glucopyranoside (10) in 47 % yield, together with 45% of the unreacted glycosyl acceptor 5. It is noteworthy that neither the unexpected β-glycoside of the sialic acid analogs nor the positional isomer was isolated from either glycosylation reaction, as we observed

previously.[18,20-22] Acetylation of 6 or 10 with acetic anhydride in pyridine gave the acetates 7 and 11 in almost quantitative yields, respectively.

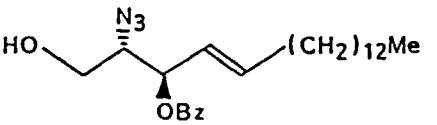
The structures of 7 and 11 were unambiguously proved by 270 MHz ^{1}H NMR spectroscopy. The observed chemical shifts and coupling constants of the sialic acid units for H-3e (δ 2.63, $J_{3a,3e}$ = 12.5 Hz, $J_{3e,4}$ = 4.6 Hz for 7 ; δ 2.55, $J_{3a,3e}$ = 12.5 Hz, $J_{3e,4}$ = 4.6 Hz for 11) and for H-4 (δ 4.96, $J_{3a,4}$ = 12.5 Hz for 7; δ 4.93 ; $J_{3a,4}$ = 12.5 Hz for 11), are characteristic of the anomeric configurations of the α-glycosidic linkages[18,20,27-29] of sialic acid analogs. Other ^{1}H NMR data were consistent with the structures assigned. Selective removal of the 2-(trimethylsilyl)ethyl group in 7 was performed by treatment[18,21,30] of 7 with boron trifluoride etherate in dichloromethane for 10 h at 0-5 °C, to give 8 in quantitative yield. By essentially the same procedure described for 8, compound 11 afforded O-[methyl (5-acetamido-4,7,8-tri-O-acetyl-3,5-dideoxy-α-D-galacto-2-octulopyranosyl)onate]-(2→3)-O-(2,4-di-O-acetyl-6-O-benzoyl-β-D-galactopyranosyl)-(1→4)-3-O-acetyl-2,6-di-O-benzoyl-D-glucopyranose (12) in 87% yield.

Treatment of 8 or 12 with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for 4 h at 0 °C, gave the corresponding α-anomers of trichloroacetimidates 9 and 13 in good yields, respectively. The glycosylation of (2S,3R,4E)-2-azido-3-O-benzoyl-4-octadecen-1,3-diol[31] (14) with 9 or 13 thus obtained, in dichloromethane for 4 h at 0 °C, in the presence of boron trifluoride etherate[18,20,31b] and molecular sieves 4A, gave only the expected β-glycosides (15 and 18) in 78 and 81% yields, respectively. Significant signals in the ^{1}H NMR spectra of 15 and 18 were a one-proton doublet at δ 4.58 ($J_{1,2}$ = 8.2 Hz, H-1, lactose unit of 15) and a one proton doublet at δ 4.69 ($J_{1,2}$ = 7.5 Hz, H-1, lactose unit of 18), showing the newly formed β-glycosidic linkages.

Selective reduction[18,32] of the azide group in compound 15 or 18 with hydrogen sulfide in 5:1 pyridine-water gave the corresponding amines, which, on condensation with octadecanoic acid using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC) in



10 R = OSE, R^1 = H, R^2 = Bz, R^3 = H
11 R = OSE, R^1 = H, R^2 = Bz, R^3 = Ac
12 R, R^1 = H, OH, R^2 = Bz, R^3 = Ac
13 R = H, R^1 = $OC(=NH)CCl_3$, R^2 = Bz, R^3 = Ac



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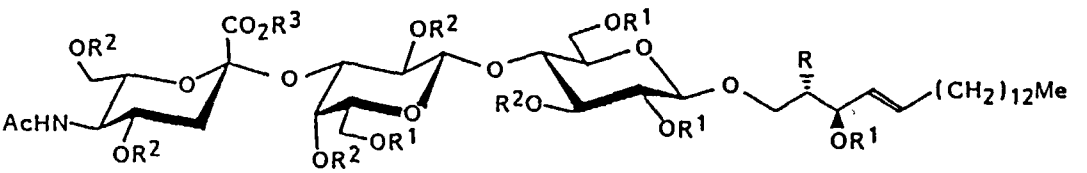
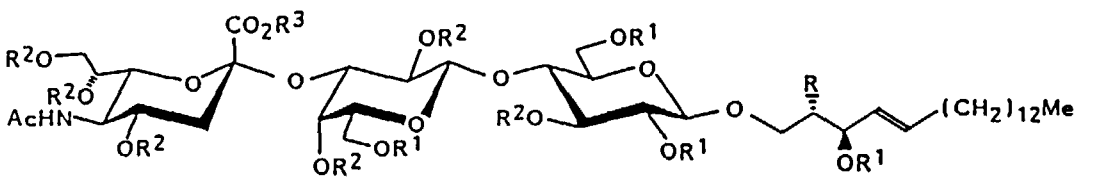


15 R = N_3, R^1 = Bz, R^2 = Ac, R^3 = Me
16 R = $NHCO(CH_2)_{16}Me$, R^1 = Bz, R^2 = Ac, R^3 = Me
17 R = $NHCO(CH_2)_{16}Me$, R^1 = R^2 = R^3 = H



18 R = N_3, R^1 = Bz, R^2 = Ac, R^3 = Me
19 R = $NHCO(CH_2)_{16}Me$, R^1 = Bz, R^2 = Ac, R^3 = Me
20 R = $NHCO(CH_2)_{16}Me$, R^1 = R^2 = R^3 = H

dichloromethane, respectively, gave the corresponding sialyllactosyl ceramide derivatives (16 and 19) in 87 and 93% yields.

Finally, O-deacylation of 16 and 19 with sodium methoxide in methanol, and subsequent saponification of the methyl ester group yielded the title ganglioside GM_3 analogs (17 and 20), containing the shorter carbon-chain sialic acids, in almost quantitative yields.

EXPERIMENTAL

General Procedures. Melting points were determined with a Yanagimoto micro melting-point apparatus and are uncorrected. Specific rotations were determined with a Union PM-201 polarimeter at 25 °C, and IR spectra were recorded with Jasco IRA-100 spectrophotometer. ^1H NMR spectra were recorded with a Jeol JNM-GX270 (270 MHz) spectrometer, and the NMR data were confirmed by use of decoupling techniques. Preparative chromatography was performed on silica gel (Wako Co., 200 mesh) with the solvent systems specified. Concentrations and evaporations were conducted in vacuo.

Methyl (Methyl 5-Acetamido-4,7-di-O-acetyl-3,5-dideoxy-2-thio-β-L-arabino-2-heptulopyranosid)onate (2). To a stirred solution of methyl 5-acetamido-4,7-di-O-acetyl-2-S-acetyl-3,5-dideoxy-2-thio-β-L-arabino-2-heptulopyranosonate[17a] (1, 4.21 g, 10.4 mmol) in dry methanol (100 mL), cooled to -40 °C, was added a solution of sodium metal (218 mg, 9.5 mmol) in dry methanol (5 mL). The mixture was stirred for 5 min at -40 °C, and concentrated at 0 °C to an amorphous mass, which was dissolved in dry N,N-dimethylformamide (DMF, 44 mL). To the stirred solution was added methyl iodide (1.0 mL), and the mixture was stirred for 3 h at room temperature; the course of the reaction being monitored by TLC. Pyridine (8 mL) and acetic anhydride (5.5 mL) were added to the solution. The mixture was stirred for 24 h at room temperature, and concentrated, the residue extracted with dichloromethane, and the extract successively washed with 2M hydrochloric acid and water, dried (sodium sulfate), and the solvent was evaporated to leave a syrup. The residue was chromatographed on a column of silica gel (300 g) with 5:1 ethyl acetate-

hexane, to give 2 (3.43 g, 87.3 %) as a syrup: $[\alpha]_D$ -12.4° (c 1.05, chloroform) ; ^{1}H NMR ($CDCl_3$) δ 1.92 (s, 3H, AcN), 2.06, 2.10, 2.17 (3s, 9H, 2AcO, MeS), 2.74 (dd, 1H, $J_{3a,3e}$ = 12.6 Hz, $J_{3e,4}$ = 4.6 Hz, H-3e), 3.64 (m, 1H, $J_{5,6}$ = 10.6 Hz, $J_{6,7}$ = 3.1 Hz, H-6), 3.82 (s, 3H, MeO), 4.05 (q, 1H, $J_{4,5}$ = 10.6 Hz), 4.25 (m, 2H, H-7,7'), 4.88 (ddd, 1H, H-4), and 5.72 (d, 1H, NH).

Anal. Calcd for $C_{16}H_{23}NO_7S$ (377.4): C, 50.92; H, 6.14; N, 3.71. Found: C, 50.83; H, 6.20; N, 3.73.

Methyl (Methyl 5-Acetamido-4,7,8-tri-O-acetyl-3,5-dideoxy-2-thio-α-D-galacto-2-octulopyranosid)onate (4). To a stirred solution of methyl 5-acetamido-4,7,8-tri-O-acetyl-2-S-acetyl-3,5-dideoxy-2-thio-α-D-galacto-2-octulopyranosonate[17b] (3, 980 mg, 2.05 mmol) in dry methanol (45 mL), cooled to -40 °C, was added a solution of sodium metal (46 mg, 2 mmol) in dry methanol (5 mL). The mixture was worked up in the same manner as described for 2, to give the salt. The sodium salt was treated with methyl iodide (1.0 mL) in dry DMF (15 mL) for 3 h at room temperature. The product was purified by column chromatography on silica gel (150 g) with 5:4 ethyl acetate-hexane, to give 4 (730 mg, 82%) as a syrup: $[\alpha]_D$ +29.7° (c 0.92, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.87-2.15 (5s, 15H, AcN, 3AcO, MeS), 2.75 (dd, 1H, $J_{3a,3e}$ = 12.8 Hz, $J_{3e,4}$ = 4.6 Hz), 3.69 (dd, 1H, $J_{5,6}$ = 10.4 Hz, $J_{6,7}$ = 2.4 Hz, H-6), 3.83 (s, 3H, MeO), 4.10 (dd, 1H, $J_{8,8'}$ = 11.5 Hz, $J_{7,8'}$ = 7.3 Hz, H-8), 4.20 (q, 1H, $J_{4,5} = J_{5,6} = J_{5,NH}$ = 10.4 Hz, H-5), 4.55 (dd, 1H, $J_{7,8}$ = 5.0 Hz, H-8'), 4.87 (ddd, 1H, $J_{3a,4}$ = 11.5 Hz, H-4), 5.29 (ddd, 1H, $J_{6,7}$ = 2.4 Hz, H-7), and 5.52 (dd, 1H, NH).

Anal. Calcd for $C_{18}H_{27}NO_9S$ (449.5): C, 48.10; H, 6.06; N, 3.12 %. Found: C, 48.02; H, 6.24; N, 3.15.

2-(Trimethylsilyl)ethyl O-(Methyl 5-Acetamido-4,7-di-O-acetyl-3,5-dideoxy-β-D-arabino-2-heptulopyranosylonate)-(2→3)-O-(6-O-benzoyl-β-D-galactopyranosyl)-(1→4)-2,6-di-O-benzoyl-β-D-glucopyranoside (6). To a solution of 2-(trimethylsilyl)ethyl O-(6-O-benzoyl-β-D-galactopyranosyl)-(1-4)-2,6-di-O-benzoyl-β-D-glucopyranoside[20,22] (5, 2.11 g, 2.8 mmol) and 2 (2.08 g, 5.5 mmol) in dry acetonitrile (30 mL) was added molecular sieves 3A (MS-3A; 4.27 g). The mixture

was stirred overnight at room temperature and then cooled to -20 °C. To the cooled mixture was added, with stirring, a mixture (7.35 g, 77% DMTST by weight) of dimethyl(methylthio)sulfonium triflate[33] (DMTST) and MS-3A, and the stirring was continued for 24 h at -15 °C; the course of the reaction was monitored by TLC. The precipitates were filtered off, and washed with dichloromethane. The filtrate and washings were combined, and the solution was successively washed with M sodium carbonate and water, dried (sodium sulfate), and then concentrated to leave a syrup, which was chromatographed on a column of silica gel (300 g) with 2 : 1 ethyl acetate-hexane, to give compound 6 (1.45 g, 48%) and starting glycosyl acceptor 5 (910 mg, 43 %).

Crystallization of 6 from ethyl acetate-hexane gave needles: mp 194-196 °C; $[\alpha]_D$ -10.6° (c 0.83, chloroform) ; IR (KBr) 3700-3200 (OH, NH), 1730 and 1270 (ester), 1670 and 1530 (amide), 850 and 840 (TMS), and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) lactose unit δ 0.86 (m, 2H, $Me_3Si\underline{CH_2}CH_2O$), 3.56 (m, 1H, $Me_3SiCH_2\underline{CH_2}O$), 4.40 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), 4.57 (dd, 1H, $J_{5,6}$ = 5.4 Hz, $J_{6,6'}$ = 12.0 Hz, H-6) 4.63 (d, 1H, $J_{1',2'}$ = 8.4 Hz, H-1'), 4.74 (dd, 1H, H-6), 5.24 (dd, 1H, $J_{2,3}$ = 9.0 Hz), and 7.27-8.08 (m, 15H, 3Ph); sialic acid unit δ 2.65 (dd, 1H, $J_{3a,3e}$ = 13.2 Hz, $J_{3e,4}$ = 4.9 Hz, H-3e), 3.80 (s, 3H, MeO), 5.03 (m, 1H, H-4), and 5.70 (d, 1H, $J_{5,NH}$ = 9.3 Hz, NH).

Anal. Calcd for $C_{52}H_{63}NO_{22}Si$ (1084.2): C, 57.61; H, 6.04; N, 1.29. Found: C, 57.58; H, 6.10; N, 1.25.

2-(Trimethylsilyl)ethyl O-(Methyl 5-Acetamido-4,7-di-O-acetyl-3,5-dideoxy-β-L-arabino-2-heptulopyranosylonate)-(2→3)-O-(2,4-di-O-acetyl-6-O-benzoyl-β-D-galactopyranosyl)-(1→4)-3-O-acetyl-2,6-di-O-benzoyl-β-D-glucopyranoside (7). Compound 6 (500 mg, 0.46 mmol) was acetylated with acetic anhydride (5 mL) in pyridine (10 mL) overnight at 30 °C. The product was purified by chromatography on silica gel (150 g) with 5:4 ethyl acetate-hexane, to give 7 (557 mg, 98%) as an amorphous mass: $[\alpha]_D$ -29.2° (c 0.89, chloroform); ^1H NMR (1:1 $CDCl_3$-CD_3OD) lactose unit δ 0.85 (m, 2H, $Me_3Si\underline{CH_2}CH_2O$), 3.53 (m, 1H, $Me_3SiCH_2\underline{CH_2}O$), 4.58 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1), 4.65 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1'), 5.00 (dd, 1H, $J_{2',3'}$ =10.1 Hz, H-2'),

5.18 (near d, 1H, H-4'), 5.20 (dd, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 5.46 (t, 1H, $J_{2,3} = J_{3,4}$ = 9.5 Hz H-3), and 7.28 - 8.04 (m, 15H, 3Ph); sialic acid unit δ 1.68 (t, 1H, $J_{3a,3e} = J_{3a,4}$ = 12.5 Hz, H-3a), 1.88 (s, 3H, AcN), 2.63 (dd, 1H, $J_{3e,4}$ = 4.8 Hz, H-3e), 3.86 (s, 3H, MeO), and 4.96 (m, 1H, H-4); O-acetyl group δ 1.99, 2.01, 2.03, 2.11 and 2.16 (5s, 15H, 5 AcO).

Anal. Calcd for $C_{58}H_{71}NO_{25}S$: (1210.3): C, 57.56; H, 5.91; N, 1.16. Found: C, 57.49; H, 5.98; N, 1.12.

O-(Methyl 5-Acetamido-4,7-di-O-acetyl-3,5-dideoxy-β-L-arabino-2-heptulopyranosylonate)-(2→3)-O-(2,4-di-O-acetyl-6-O-benzoyl-β-D-galactopyranosyl)-(1→4)-3-O-acetyl-2,6-di-O-benzoyl-D-glucopyranose (8). To a solution of 7 (520 mg, 0.43 mmol) in dichloromethane (10 mL), cooled to 0 °C, was added boron trifluoride etherate (320 mg). The mixture was stirred at 0-5 °C; after 10 h, the reaction was complete, and dichloromethane (30 mL) was added to the mixture. The solution was successively washed with M sodium carbonate and water dried (sodium sulfate), and concentrated. The residue was chromatographed on a column of silica gel (100 g) with chloroform and 50:1 chloroform-methanol. The latter eluant gave 8 (470 mg, 98.5%) as an amorphous mass: $[\alpha]_D$ +26.9° (c, 0.62, chloroform); IR (KBr) 3700-3150 (OH, NH), 1750 and 1230 (ester), 1670 and 1540 (amide), and 720 cm^{-1} (Ph).

Anal. Calcd for $C_{53}H_{59}NO_{25}$ (1110.0): C, 57.35; H, 5.36; N, 1.26. Found: C, 57.31; H, 5.55; N, 1.29.

O-(Methyl 5-Acetamido-4,7-di-O-acetyl-3,5-dideoxy-β-L-arabino-2-heptulopyranosylonate)-(2→3)-O-(2,4-di-O-acetyl-6-O-benzoyl-β-D-galactopyranosyl)-(1→4)-3-O-acetyl-2,6-di-O-benzoyl-α-D-glucopyranosyl trichloroacetimidate (9). To a stirred solution of 8 (440 mg, 0.4 mmol) in dichloromethane (3 mL), cooled to -5 °C, were added trichloroacetonitrile (0.8 mL) and DBU (31 mg). The mixture was stirred for 3 h at 0 °C and concentrated to a syrup which was chromatographed on a column of silica gel (50 g) with 70:1 dichloromethane-methanol to give 9 (400 mg, 80.6 %) as an amorphous mass: $[\alpha]_D$ +37.8° (c 0.69, chloroform); ^1H NMR ($CDCl_3$) lactose unit δ 4.64 (d, 1H, $J_{1',2'}$ = 7.9 Hz, H-1'), 5.04 (near t, 1H, H-2'), 5.20 (near

d, J = 3.1 Hz, H-4'), 5.26 (dd, 1H, $J_{1,2}$ = 3.9 Hz, $J_{2,3}$ = 10.2 Hz, H-2), 5.84 (near t, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 6.66 (d, 1H, $J_{1,2}$ = 3.9 Hz, H-1), 7.39-8.04 (m, 15H, 3Ph), and 8.56 (s, 1H, C=NH); sialic acid unit δ 1.70 (t, 1H, $J_{3a,3e} = J_{3a,4}$ = 12.6 Hz, H-3a,) 1.89 (s, 3H, AcN), 2.53 (dd, 1H, $J_{3e,4}$ = 4.7 Hz, H-3e), 3.75 (s, 3H, MeO), 3.93 (q, 1H, $J_{4,5} = J_{5,NH} = J_{5,6}$ = 10.1 Hz, H-5), 4.96 (m, 1H, H-4), and 5.42 (d, 1H, NH); O-acetyl groups δ 2.00, 2.03, 2.04, 2.13, and 2.17 (5s, 15H, 5AcO).

Anal. Calcd for $C_{55}H_{59}N_2O_{25}Cl_3$ (1254.4): C, 52.66; H, 4.74; N, 2.23. Found: C, 52.58; H, 4.86; N, 2.20.

2-(Trimethylsilyl)ethyl O-(Methyl 5-Acetamido-4,7,8-tri-O-acetyl-3,5-dideoxy-α-D-galacto-2-octulopyranosylonate)-(2→3)-O-(6-O-benzoyl-β-D-galactopyranosyl)-(1→4)-2,6-di-O-benzoyl-β-D-glucopyranoside (10). To a solution of 5 (576 mg, 0.76 mmol) and 4 (690 mg, 1.5 mmol), was added MS-3A (1.5 g) in dry acetonitrile (7 mL), and the mixture was stirred overnight at room temperature, and then cooled to -15 °C. A mixture (2.0 g, 77% of DMTST by weight) of DMTST and MS-3A was added to the mixture, and the stirring was continued for 24 h at -15 °C. A similar workup as described for 6 gave compound 10 (415 mg, 47%) as an amorphous mass. Unreacted acceptor 5 (260 mg, 45%) was recovered. $[\alpha]_D$ -1° (c 0.6, chloroform); ^{1}H NMR ($CDCl_3$) lactose unit δ 0.88 (m, 2H, $Me_3Si\underline{CH_2}CH_2O$), 3.57 (m, 1H, $Me_3SiCH_2\underline{CH_2}O$), 4.51 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), 4.64 (d, 1H, $J_{1',2'}$ = 7.9 Hz, H-1'), 5.26 (dd, 1H, $J_{2,3}$ = 8.9 Hz, H-2), and 7.27-8.09 (m, 15H, 3Ph); sialic acid unit δ 1.89 (s, 3H, AcN), 1.98, 2.05, 2.16 (3s, 9H, 3AcO), 2.67 (dd, 1H, $J_{3a,3e}$ = 12.9 Hz, $J_{3e,4}$ = 4.8 Hz, H-3e), 3.59 (m, 1H, H-6), 3.79 (s, 3H, MeO), 4.39 (m, 1H, H-5), 4.98 (m, 1H, H-4), 5.10 (m, 1H, H-7), and 5.35 (d, 1H, $J_{5,NH}$ = 9.5 Hz, NH).

Anal. Calcd for $C_{55}H_{69}NO_{24}Si$ (1156.2): C, 57.13; H, 6.02; N, 1.21. Found: C 57.09; H, 6.20; N, 1.35.

2-(Trimethylsilyl)ethyl O-(Methyl 5-Acetamido-4,7,8-tri-O-acetyl-3,5-dideoxy-α-D-galacto-2-octulopyranosylonate)-(2→3)-O-(2,4,-di-O-acetyl-6-O-benzoyl-β-D-galactopyranosyl)-(1→4)-3-O-acetyl-2,6-di-O-benzoyl-β-D-glucopyranoside (11). Compound 10 (200 mg, 0.17

mmol) was acetylated with acetic anhydride (4 mL)-pyridine (8 mL) overnight at 30 °C; the product was purified by silica gel (50 g) column chromatography using 5:4 ethyl acetate-hexane as the eluent, to give 11 (200 mg, 90%) as an amorphous mass: $[\alpha]_D$+4.2° (c 1.2, chloroform); ^{1}H NMR (1:1 $CDCl_3$-CD_3OD) lactose unit δ 0.85 (m, 2H, $Me_3Si\underline{CH_2}CH_2O$), 3.56 (m, 1H, $Me_3SiCH_2\underline{CH_2}O$), 4.67 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), 4.75 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1'), 5.03 (m, 2H, H-2',4'), 5.22 (dd, $J_{2,3}$ = 9.4 Hz, H-2), 5.47 (t, $J_{3,4}$ = 9.4 Hz, H-3), 7.39-8.09 (m, 15H, 3Ph); sialic acid unit δ 1.66 (t, 1H, $J_{3a,3e}$ = $J_{3a,4}$ = 12.5 Hz, H-3a), 2.55 (dd, 1H, $J_{3e,4}$ = 4.6 Hz, H-3e), 3.47 (dd, 1H, $J_{5,6}$ = 10.6 Hz, $J_{6,7}$ = 2.6 Hz, H-6), 4.93 (m, 1H, H-4), and 5.50 (m, 1H, H-7); O-acetyl groups δ 1.92, 2.00, 2.01, 2.02, 2.12, and 2.22 (6s, 18H, 6AcO).

Anal. Calcd for $C_{61}H_{75}NO_{27}Si$: (1282.3): C, 57.13; H, 5.90; N, 1.09. Found: C, 57.25; H, 5.96; N, 1.20.

O-(Methyl 5-Acetamido-4,7,8-tri-O-acetyl-3,5-dideoxy-α-D-galacto-2-octulopyranosylonate)-(2→3)-O-(2,4-di-O-acetyl-6-O-benzoyl-β-D-galactopyranosyl)-(1→4)-3-O-acetyl-2,6-di-O-benzoyl-D-gluco-pyranose (12). Selective removal of the 2-(trimethylsilyl)ethyl group in 11 (240 mg, 0.19 mmol) was performed as described for the preparation of 8, to give 12 (190 mg, 87%) as an amorphous mass: $[\alpha]_D$ +44.3° (c 0.9, chloroform); IR (KBr) 3500-3100 (OH, NH), 1740 and 1220 (ester), 1660 and 1540 (amide) and 710 cm^{-1} (Ph).

Anal. Calcd for $C_{56}H_{63}NO_{27}$ (1182.1): C, 56.90; H, 5.37; N, 1.18. Found: C, 56.81; H, 5.45; N, 1.24.

O-(Methyl 5-Acetamido-4,7,8-tri-O-acetyl-3,5-dideoxy-α-D-galacto-2-octulopyranosylonate)-(2→3)-O-(2,4-di-O-acetyl-6-O-benzoyl-β-D-galactopyranosyl)-(1→4)-3-O-acetyl-2,6-di-O-benzoyl-α-D-glucopyranosyl trichloroacetimidate (13). To a stirred solution of 12 (180 mg, 0.15 mmol) in dichloromethane (1 mL), cooled to -5 °C, were added trichloroacetonitrile (0.24 mL) and DBU (9.3 mg), and the mixture was stirred for 5 h at 0 °C, and then concentrated to a syrup. The product was purified on a column of silica gel (30 g) with 70:1 dichloromethane-methanol to give 13 (175 mg, 85%) as an amorphous mass: $[\alpha]_D$ +41.5° (c, 0.84, chloroform); ^{1}H NMR lactose

unit δ 4.82 (d, 1H, $J_{1',2'}$ = 7.9 Hz, H-1'), 5.07 (dd, 1H, $J_{2',3'}$ = 9.8 Hz, H-2'), 5.29 (dd, 1H, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 10.2 Hz, H-2), 5.85 (t, 1H, H-3), 6.67 (d, 1H, H-1), 7.27-8.09 (m, 15H, 3Ph), and 8.57 (s, 1H, C = NH); sialic acid unit δ 1.69 (t, 1H, $J_{3a,3e}$ = $J_{3a,4}$ = 12.5 Hz, H-3a), 1.84 (s, 3H, AcN), 2.56 (dd, 1H, $J_{3e,4}$ = 4.4 Hz, H-3e), 3.46 (dd, 1H, $J_{5,6}$ = 10.2 Hz, $J_{6,7}$ = 2.3 Hz, H-6), 3.72 (s, 3H, MeO), 4.85 (m, 1H, H-4), and 5.19 (d, 1H, $J_{NH,5}$ = 10.1 Hz, NH); O-acetyl groups δ 1.89, 2.01, 2.02, 2.04, 2.13, and 2.23 (6s, 18H, 6AcO).

Anal. Calcd for $C_{58}H_{63}N_2O_{27}Cl_3$ (1326.6): C, 57.10, H, 5.20; N, 2.30. Found: C, 57.01; H, 5.41; N, 2.29.

O-(Methyl 5-Acetamido-4,6-di-O-acetyl-3,5-dideoxy-β-L-arabino-2-heptulopyranosylonate)-(2→3)-O-(2,4-di-O-acetyl-6-O-benzoyl-β-D-galactopyranosyl)-(1→4)-O-(3-O-acetyl-2,6-di-O-benzoyl-β-D-gluco-pyranosyl)-(1→1)-(2S,3R,4E)-2-azido-3-O-benzoyl-4-octadecene-1,3-diol (15). To a solution of 9 (360 mg, 0.29 mmol) and (2S,3R,4E)-2-azido-3-O-benzoyl-4-octadecen-1,3-diol[31] (14, 244 mg, 0.58 mmol) in dichloromethane (8 mL) was added MS-4A (5 g), and the mixture was stirred for 30 min at room temperature, and cooled to 0 °C. Boron trifluoride etherate (82 mg) was added to the cooled mixture, and this was stirred for 4 h at 0 °C. The precipitates were filtered off and washed with dichloromethane. The filtrate and washings were combined, and the solution was successively washed with M sodium carbonate and water, dried (sodium sulfate), and concentrated. The residue was chromatographed on a column of silica gel (50 g) with 3:1 ethyl acetate-hexane to give 15 (340 mg, 78%) as an amorphous mass: $[\alpha]_D$ -11.3° (c 0.76, chroloform); IR (KBr) 3350 (NH), 2940 and 2850 (Me, methylene), 2100 (N_3), 1740 and 1230 (ester), 1670 and 1540 (amide), and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) lactose unit δ 4.58 (d, 1H, $J_{1,2}$ = 8.2 Hz, H-1), 4.67 (d, 1H, $J_{1',2'}$ = 7.9 Hz, H-1'), 5.00 (dd, 1H, $J_{2',3'}$ = 10.1 Hz, H-2'), 5.17 (broad d, 1H, H-4'), and 5.25 (dd, 1H, $J_{2,3}$ = 9.4 Hz, H-2); sialic acid unit δ 1.89 (s, 3H, AcN), 2.52 (dd, 1H, $J_{3a,3e}$ = 12.6 Hz, $J_{3e,4}$ = 4.9 Hz, H-3e), 3.74 (s, 3H, MeO), and 4.97 (m, 1H, H-4); sphingosine unit δ 0.88 (t, 3H, $MeCH_2$), 1.24 (m, 24H, $Me(CH_2)_{12}$) and 5.69 (dt, 1H, $J_{4,5}$ = 14.4 Hz,

$J_{5,6} = J_{5,6'} = 7.1$ Hz, H-5); O-acyl groups δ 2.00, 2.01, 2.03, 2.11, and 2.15 (5s, 15H, 5AcO), and 7.26-8.05 (m, 20H, 4Ph).

Anal. Calcd for $C_{78}H_{96}N_4O_{27}$ (1521.6): C, 61.57; H, 6.36; N, 3.68. Found: C, 61.49; H, 6.52; N, 3.61.

O-(Methyl 5-Acetamido-4,7-di-O-acetyl-3,5-dideoxy-β-L-arabino-2-heptulopyranosylonate)-(2→3)-O-(2,4-di-O-acetyl-6-O-benzoyl-β-D-galactopyranosyl)-(1→4)-O-(3-O-acetyl-2,6-di-O-benzoyl-β-D-gluco-pyranosyl)-(1→1)-(2S,3R,4E)-3-O-benzoyl-2-octadecanamido-4-octa-decen-1,3-diol (16). Hydrogen sulfide was bubbled through a solution of 15 (120 mg, 78.9 umol) in pyridine (10 mL) and water (2 mL) for 24 h while the solution was stirred at room temperature; the course of the reaction was monitored by TLC. The mixture was concentrated to a syrup which was dissolved in dry dichloromethane (6 mL). Octadecanoic acid (45 mg, 0.16 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC; 36 mg) were added to the solution, and the mixture was stirred overnight at room temperature. Dichloromethane (40 mL) was added, and the solution was washed with water, dried (sodium sulfate), and concentrated. The residue was chromatographed on a column of silica gel (30 g) with 60:1 dichloromethane-methanol, to give 16 (120 mg, 87%) as an amorphous mass: $[\alpha]_D$ +3.9° (c 0.6, chloroform); IR (KBr) 3350 (NH), 2940 and 2860 (Me, methylene), 1740 and 1230 (ester), 1680, 1660 and 1540 (amide), and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) lactose unit δ 4.57 (2d, 2H, $J_{1,2} = J_{1',2'} = 7.9$ Hz, H-1,1'), 4.99 (dd, 1H, H-2'), and 5.18 (m, 2H, H-2,4'); sialic acid unit δ 1.68 (t, 1H, $J_{3a,3e} = J_{3a,4} = 12.4$ Hz, H-3a), 1.89 (s, 3H, AcN), 2.53 (dd, 1H, $J_{3e,4} = 4.6$ Hz, H-3e), 3.72 (s, 3H, MeO), 4.95 (m, 1H, H-4), and 5.66 (d, 1H, $J_{5,NH} = 9.2$ Hz, NH); cer unit δ 0.88 (t, 6H, 2MeCH_2) and 5.79 (dt, 1H, $J_{4,5} = 14.4$ Hz, $J_{5,6} = J_{5,6'} = 7.1$ Hz, H-5); O-acyl groups δ 1.99, 2.02, 2.03, 2.10, and 2.14 (5s, 15H, 5AcO), and 7.30-8.05 (m, 20H, 4Ph).

Anal. Cacld for $C_{96}H_{132}N_2O_{28}$ (1762.1): C, 65.44; H, 7.55; N, 1.59. Found: C, 65.25; H, 7.82; N, 1.64.

O-(5-Acetamido-3,5-dideoxy-β-L-arabino-2-heptulopyranosylonic acid)-(2→3)-O-(β-D-galactopyranosyl)-(1→4)-O-(β-D-glucopyranosyl)-(1→1)-(2S,3R,4E)-2-octadecanamido-4-octadecen-1,3-diol (17). To a solution of 16 (110 mg, 62.4 umol) in methanol (5 mL) was added sodium methoxide (10 mg), and the mixture was stirred for 8 h at room temperature; the course of the reaction being monitored by TLC. Water (0.5 mL) was added to the mixture at 0 °C, and the solution was stirred for 4 h, and then treated with Amberlite IR-120 (H^+) resin to remove the base. The solution was concentrated to a syrup which was chromatographed on a column of Sephadex LH-20 (50 g) with 1:1 methanol-chloroform, to give 17 (quantitative) as an amorphous mass: $[\alpha]_D$ +0.46° (c 0.85, 1:1 methanol-chloroform); IR (KBr) 3700-3100 (OH, NH), 2940 and 2860 (Me, methylene), 1700 (C=O), and 1640 and 1560 cm^{-1} (amide); ^1H NMR (98:2 $(CD_3)_2SO$-D_2O) lactose unit δ 4.17 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1), 4.25 (d, 1H, $J_{1',2'}$ = 8.0 Hz, H-1'); sialic acid unit δ 1.85 (s, 3H, AcN), 3.04 (dd, 1H, H-3e); Cer unit δ 0.85 (t, 6H, 2$\underline{Me}CH_2$), 5.34 (dd, 1H, $J_{3,4}$ = 7.0 Hz, $J_{4,5}$ = 15.4 Hz, H-4), and 5.52 (dt, 1H, $J_{5,6} = J_{5',6'}$ = 7.1 Hz, H-5).

Anal. Calcd for $C_{57}H_{104}N_2O_{19}$ (1121.5): C, 61.05; H, 9.35; N, 2.50. Found: C, 60.89; H, 9.62; N, 2.51.

O-(Methyl 5-Acetamido-4,7,8-tri-O-acetyl-3,5-dideoxy-α-D-galacto-2-octulopyranosylonate)-(2→3)-O-(2,4-di-O-acetyl-6-O-benzoyl-β-D-galactopyranosyl)-(1→4)-O-(3-O-acetyl-2,6-di-O-benzoyl-β-D-gluco-pyranosyl)-(1→1)-(2S,3R,4E)-2-azido-3-O-benzoyl-4-octadecen-1,3-diol (18). Condensation of 13 (170 mg, 0.12 mmol) with 14 (107 mg, 0.25 mmol), as described for 15, gave compound 18 (165 mg, 81%) as an amorphous mass: $[\alpha]_D$ -1.82° (c 1.3, chloroform); IR (KBr) 3350 (NH), 2940 and 2850 (Me, methylene), 2100 (N_3), 1740 and 1220 (ester), 1680, 1660, and 1530 (amide), and 710 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) lactose unit δ 4.69 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1), 4.75 (d, 1H, $J_{1',2'}$ = 8.1 Hz, H-1') and 5.03 (dd, 1H, H-2'); sialic acid unit δ 1.68 (t, 1H, $J_{3a,3e} = J_{3a,e}$ = 12.3 Hz, H-3a), 1.83 (s, 3H, AcN), 2.55 (dd, 1H, $J_{3e,4}$ = 4.7 Hz, H-3e), 3.71 (s, 3H, MeO), and 4.84 (m, 1H, H-4); Cer unit δ 0.87 (t, 3H, $\underline{Me}CH_2$), 1.24 (s, 24H, $Me(\underline{CH_2})_{12}$), and 5.66 (td, 1H, $J_{4,5}$ = 14.4 Hz, $J_{5,6} = J_{5,6'}$ = 7.2 Hz, H-5); O-acyl groups

δ 1.89, 2.00(3), 2.10, and 2.21 (6s, 18H, 6AcO), and 7.28-8.19 (m, 20H, 4Ph).

Anal. Calcd for $C_{81}H_{100}N_4O_{29}$ (1593.7): C, 61.05; H, 6.32; N, 3.52. Found; C, 61.15; H, 6.30; N, 3.48.

O-(Methyl 5-Acetamido-4,7,8-tri-O-acetyl-3,5-dideoxy-α-D-galacto-2-octulopyranosylonate)-(2→3)-O-(2,4-di-O-acetyl-6-O-benzoyl-β-D-galactopyranosyl)-(1→4)-O-(3-O-acetyl-2,6-di-O-benzoyl-β-D-gluco-pyranosyl)-(1→1)-(2S,3R,4E)-3-O-benzoyl-2-octadecanamido-4-octa-decen-1,3-diol (19). *Selective reduction of the azide group in* 18 (120 mg, 75.3 μmol) with hydrogen sulfide, and subsequent condensation with octadecanoic acid (43 mg, 150 umol using WSC (40 mg), as described for 16, yielded compound 19 (128 mg, 93%) as an amorphous mass: $[\alpha]_D$ +11.0° (c 0.56, chloroform); IR (KBr) 3350 (NH), 2940 and 2860 (Me, methylene), 1740 and 1230 (ester), 1680, 1660, and 1535 (amide), and 710 cm^{-1} (Ph); ^1H NMR (CD_3Cl_3) lactose unit δ 4.60 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1); sialic acid unit δ 1.85 (s, 3H, AcN), 2.56 (dd, 1H, $J_{3a,3e}$ = 11.9 Hz, $J_{3e,4}$ = 4.8 Hz, H-3e), 3.46 (dd, 1H, $J_{5,6}$ = 10.4 Hz, $J_{6,7}$ = 2.6 Hz, H-6), 3.72 (s, 3H, AcN), 4.85 (m, 1H, H-4), and 5.64 (d, 1H, $J_{5,NH}$ = 9.3 Hz, NH); cer unit δ 0.88 (t, 6H, 2MeCH$_2$), and 5.77 (dt, 1H, $J_{4,5}$ = 15.6 Hz, $J_{5,6}$ = $J_{5,6'}$ = 7.8 Hz, H-5); O-acyl groups δ 1.94, 2.01 (2), 2.02, 2.11, and 2.19 (6s, 18H, 6AcO), and 7.27-8.05 (m, 20H, 4Ph).

Anal. Calcd for $C_{99}H_{136}N_2O_{30}$ (1834.2): C, 64.83; H, 7.47; N, 1.53. Found: C, 64.79; H, 7.54; N, 1.53.

O-(5-Acetamido-3,5-dideoxy-α-D-galacto-2-octulopyranosylonic acid)-(2→3)-O-(β-D-galactopyranosyl)-(1→4)-O-(β-D-glucopyranosyl)-(1→1)-(2S,3R,4E)-2-octadecanamido-4-octadecen-1,3-diol (20). O-Deacetylation and subsequent saponification of the methyl ester group of 19 (99 mg, 54 μmol), as described for 17, gave 20 (62 mg, quantitative) as an amorphous mass: $[\alpha]_D$ -2.65° (c 0.6, 1:1 chloroform-methanol); IR (KBr) 3700-3200 (OH, NH), 2940 and 2860 (Me, methylene), 1710 (C=O), and 1630 and 1550 cm^{-1} (amide); ^1H NMR (98:2 $(CD_3)_2SO$-D_2O) lactose unit δ 4.15 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1) and 4.22 (d, 1H, $J_{1',2'}$ = 8.2 Hz, H-1'); sialic acid unit δ 1.90 (s, 3H, AcN) and 2.74 (broad dd, 1H, H-3e); cer unit δ 0.85 (t, 6H,

2MeCH$_2$), 5.37 (dd, 1H, $J_{3,4}$ = 7.5 Hz, $J_{4,5}$ = 15.8 Hz, H-4), and 5.51 (dt, 1H, $J_{5,6}$ = $J_{5,6'}$ = 7.5 Hz, H-5).

Anal. Calcd for $C_{58}H_{106}N_2O_{20}$ (1151.5): C, 60.50; H, 9.28; N, 3.43. Found: C, 60.26; H, 9.41; N, 3.42.

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