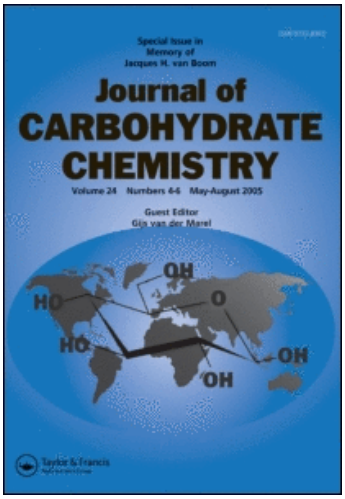

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SYNTHETIC STUDIES ON SIALOGLYCOCONJUGATES 17: SYNTHESIS OF 4-O-, 9-O-, and 4,9-DI-O-ACETYL-N-ACETYLNEURAMINIC ACIDS AND THEIR DERIVATIVES

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ABSTRACT

4-O-, 9-O-, and 4,9-Di-O-acetyl derivatives 9, 13, and 23 of N-acetylneuraminic acid were synthesized from methyl (methyl 5-acetamido-3,5-dideoxy-2-thio-D-glycero-α-D-galacto-2-nonulopyranosid)onate (1) or methyl [2-(trimethylsilyl)ethyl 5-acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosid]onate (14). In addition, the suitably protected derivatives 7 and 11 of the 4-O- and 9-O-acetyl derivatives, which could be used as the glycosyl donors for the synthesis of gangliosides containing the O-acetyl group at C-4 or C-9 in N-acetylneuraminic acid moiety, were synthesized.

INTRODUCTION

N-Acetylneuraminic acid, N-glycolylneuraminic acid, and their various types of derivatives such as acetate, phosphate, and sulfate are widely spread as the terminal units of the carbohydrate chain of cell-surface sialoglycoconjugates, and are involved in a variety of biological functions.[1-3] It is also known that the sialoglycoconjugates contain sialic acids in α-glycosidic linkage. Therefore, synthesis of the sialic acid derivatives, as well as a facile regio- and α-selective glycoside synthesis of sialic acid is critically important, in order to investigate the func-

tions of sialoglycoconjugates at the molecular level. Recently,[4-8] we have achieved a facile α-stereo-selective glycosidation of sialic acids by using the methyl α-2-thioglycoside[4,6] of sialic acids as the glycosyl donors, with dimethyl(methylthio)sulfonium triflate[4,9] (DMTST) in acetonitrile under kinetically controlled conditions, and synthesized a variety of gangliosides and analogs. In this connection we describe here the synthesis of partially acetylated sialic acids such as their 4-O-, 9-O-, and 4,9-di-O-acetyl-Neu5Ac analogs, and their suitably protected derivatives, for use in the synthesis of sialoglycoconjugates. This work is directed to clarifying the structural requirements of the sialic acid moiety in the biological functions of sialo compounds.

RESULTS AND DISCUSSION

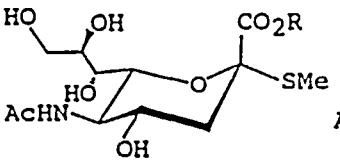
For the synthesis of partially acetylated N-acetylneuraminic acids, and their derivatives protected suitably for use as the glycosyl donors, we set out to prepare benzyl (methyl 5-acetamido-3,5-dideoxy-2-thio-D-glycero-α-D-galacto-2-nonulopyranosid)onate (2) and benzyl [2-(trimethylsilyl)ethyl 5-acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosid]onate (15), and then introduce isopropylidene, acetyl, or chloroacetyl groups, selectively, and convert the appropriate intermediates, by selective removal of the protecting groups, into the end products.

Treatment of methyl (methyl 5-acetamido-3,5-dideoxy-2-thio-D-glycero-α-D-galacto-2-nonulopyranosid)onate[6] (1) with 0.2M aqueous potassium hydroxide, and subsequent benzyl esterification of the carboxyl group gave 2 in 75% yield. In a similar way saponification of the methyl ester in methyl [2-(trimethylsilyl)ethyl 5-acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosid]onate[10] (14), and subsequent benzylation afforded compound 15 in 98% yield. Significant signals in ^{1}H NMR spectra of 2 and 15 were a one-proton doublet of doublets at δ 2.79 ($J_{3a,3e}$ = 12.9 Hz, $J_{3e,4}$ = 4.5 Hz, H-3e, for 2; $J_{3a,3e}$ = 12.8 Hz, $J_{3e,4}$ = 4.6 Hz, for 15), and a one proton-doublet of doublets at δ 3.47 ($J_{6,7}$ = 1.7 Hz, $J_{7,8}$ = 8.8 Hz, H-7) for 2, and a one-proton doublet of doublets at δ 3.64 ($J_{6,7}$ = 1.6 Hz, $J_{7,8}$ = 9.2 Hz) for 15, indicating[4,6,7,11,12] that no anomeric configuration changed during the reactions. Isopropylidenation of 2 with 2,2-dimethoxypropane in N,N-dimethylformamide containing a trace of p-toluenesulfonic acid monohydrate at room temperature gave a mixture,

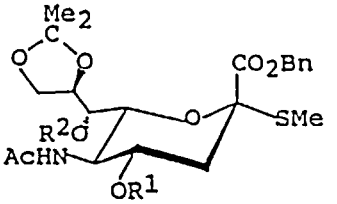
from which benzyl (methyl 5-acetamido-3,5-dideoxy-8,9-O-isopropylidene-2-thio-D-glycero-α-D-galacto-2-nonulopyranosid)onate (3, 79%) and the 7,9-O-isopropylidene derivative (5, 19%) were isolated. In a similar way, acetonation of 15 afforded the 8,9-O-isopropylidene derivative 16 (72%) and the 7,9-O-isopropylidene derivative (18, 20%), respectively. Selective 4-O-acetylation of 3 or 16 with acetyl chloride at -40 °C gave the corresponding 4-O-acetyl derivatives (4 and 17) in 86 and 95% yields, respectively. The structures of 4 and 17 were unambiguously proved by ^{1}H NMR spectroscopy; H-4 of 4 appeared at δ 4.99 ($J_{3a,4} = J_{4,5} = 10.4$ Hz, $J_{3e,4} = 4.9$ Hz) and that of 17 at δ 5.04 ($J_{3a,4} = J_{4,5} = 10.6$ Hz, $J_{3e,4} = 4.9$ Hz), indicating the corresponding position of the O-acetyl group. Other NMR data are given in the Experimental Section and are consistent with structures 4 and 17, respectively.

Removal of the isopropylidene group from 4 with 80% aqueous acetic acid for 8 h at room temperature gave compound 6 in almost quantitative yield; a significant signal in ^{1}H NMR spectrum was a one-proton multiplet at δ 4.99 ($J_{3a,4} = J_{4,5} = 10.4$ Hz, $J_{3e,4} = 4.8$ Hz, H-4), showing that no acetyl migration occurred during hydrolysis. When treated with 80% aqueous acetic acid overnight at 40 °C, compound 17 gave 20 in 97% yield. Direct 9-O-acetylation of 2 with acetyl chloride at -40 °C afforded 10 in 84% yield. Treatment of 6 or 10 with chloroacetic anhydride in pyridine-dichloromethane gave the corresponding mono-O-acetyl-tri-O-chloroacetyl derivatives 7 and 11 in almost quantitative yields, respectively, which could be used as the glycosyl donors for the synthesis of gangliosides containing the O-acetyl group at C-4 or C-9 of N-acetylneuraminic acid.

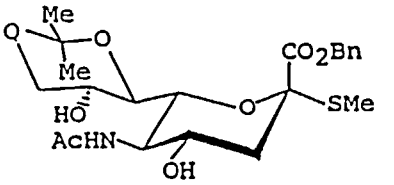
To get 4-O-acetyl-N-acetylneuraminic acid from compound 6, conversion of the methylthio group into a hydroxyl group, and hydrogenolytic removal of the benzyl group were performed stepwise with great care. Treatment of 6 with dimethyl(methylthio)sulfonium triflate[9b] (DMTST) in acetonitrile-1,4-dioxane at -40 °C gave 8 in 68% yield, after column chromatography. The ^{1}H NMR spectrum of 8 exhibited two three-proton singlets at δ 1.94 (N-acetyl) and 2.01 (O-acetyl); H_{3e} appeared at δ 2.32 ($J_{3a,3e} = 12.7$ Hz, $J_{3e,4} = 5.0$ Hz) as a doublet of doublets, indicating the structure assigned. Finally, hydrogenolysis of 8 in methanol in the presence of 10% Pd-C catalyst gave 4-O-acetyl-N-acetylneuraminic acid (9) in quantitative yield. In the same way, hydrolysis of the methylthio group



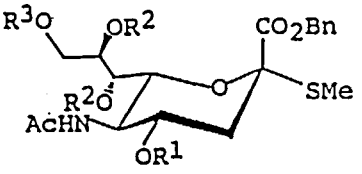
1 R=Me
2 R=Bn
Bn=benzyl



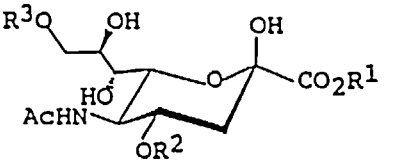
3 $R^1=R^2=H$
4 $R^1=Ac, R^2=H$



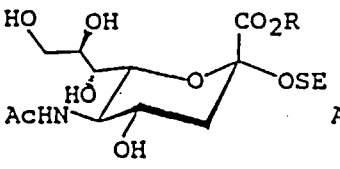
5



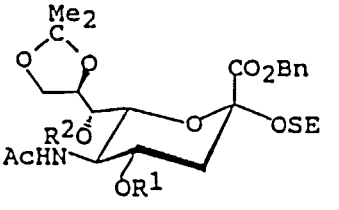
6 $R^1=Ac, R^2=R^3=H$
7 $R^1=Ac, R^2=R^3=CA$
10 $R^1=R^2=H, R^3=Ac$
11 $R^1=R^2=CA, R^3=Ac$
CA=$ClCH_2CO$-



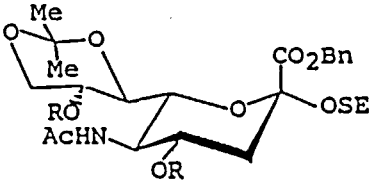
8 $R^1=Bn, R^2=Ac, R^3=H$
9 $R^1=R^3=H, R^2=Ac$
12 $R^1=Bn, R^2=H, R^3=Ac$
13 $R^1=R^2=H, R^3=Ac$



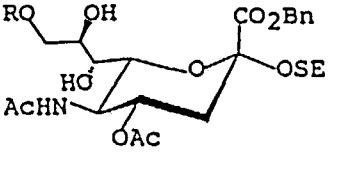
14 R=Me
15 R=Bn
SE=$Me_3SiCH_2CH_2$-



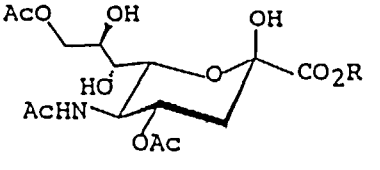
16 $R^1=R^2=H$
17 $R^1=Ac, R^2=H$



18 R=H
19 R=Ac



20 R=H
21 R=Ac



22 R=Bn
23 R=H

in 10 gave compound 12 in 73% yield, which was converted by hydrogenolysis, into 9-O-acetyl-N-acetylneuraminic acid (13) in quantitative yield.

Selective 9-O-acetylation of 20 with acetyl chloride in pyridine-dichloromethane at -40 °C gave the 4,9-di-O-acetyl derivative 21 in 87% yield, which was converted, via selective removal[6,7,12,13] of the 2-(trimethylsilyl)ethyl group with boron trifluoride etherate in dichloromethane and subsequent hydrogenolysis of the benzyl ester group, into 4,9-di-O-acetyl-N-acetylneuraminic acid (23).

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 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 Co., 200 mesh) with the solvent systems specified. Concentrations were conducted in vacuo.

Benzyl (Methyl 5-Acetamido-3,5-dideoxy-2-thio-D-glycero-α-D-galacto-2-nonulopyranosid)onate (2). A solution of methyl (methyl 5-acetamido-3,5-dideoxy-2-thio-D-glycero-α-D-galacto-2-nonulopyranosid)onate (1; 500 mg, 1.48 mmol), derived from the peracetate[6] by de-O-acetylation, in 0.2M potassium hydroxide (7 mL) was stirred for 1.5 h at room temperature, and treated with Amberlite IR-120 (H^+) resin to remove the base. The solution was concentrated to dryness, and the residue dissolved in N,N-dimethylformamide (DMF; 12 mL). To the solution were added, with stirring, Drierite (700 mg), potassium carbonate (130 mg) and benzyl bromide (0.58 mL), and the mixture was stirred overnight at room temperature; the progress of the reaction was monitored by TLC. The mixture was concentrated, and the residue was chromatographed on a column of silica gel (150 g) with 35:1 dichloromethane-methanol, to give 2 (408 mg, 75%). Crystallization from ethanol gave needles: mp 176-178 °C, $[\alpha]_D$ +35.8° (c 0.5, 1:1 chloroform-methanol); ^{1}H NMR (CD_3OD) δ 1.80 (dd, 1H, $J_{3a,3e}$ = 12.9 Hz, $J_{3a,4}$ = 11.2 Hz, H-3a), 1.98 (s, 3H, AcN), 2.03 (s, 3H, MeS), 2.78 (dd, 1H, $J_{3e,4}$ = 4.5 Hz, H-3e), 3.55 (dd, 1H, $J_{5,6}$ = 10.3 Hz, $J_{6,7}$ = 1.7 Hz, H-6), 3.46 (dd, 1H, $J_{7,8}$ = 8.8 Hz, H-7), 3.56-3.65 (m, 2H, H-4,9), 3.71 (t, 1H, $J_{4,5}$ = 10.3 Hz, H-5), 3.72-3.82 (m, 2H, H-8,9'), 5.27 (s, 2H, $PhCH_2$), and 7.32-7.45 (m, 5H, Ph).

Anal. Calcd for $C_{19}H_{27}NO_8S$ (429.5): C, 53.13; H, 6.34; N, 3.26. Found: C, 53.08; H, 6.25; N, 3.24.

Benzyl (Methyl 5-Acetamido-3,5-dideoxy-8,9-O-isopropylidene-2-thio-D-glycero-α-D-galacto-2-nonulopyranosid)onate (3) and Benzyl (Methyl 5-Acetamido-3,5-dideoxy-7,9-O-isopropylidene-2-thio-D-glycero-α-D-galacto-2-nonulopyranosid)onate (5). To a solution of 2 (700 mg, 1.63 mmol) in dry DMF (7 mL) were added 2,2-dimethoxypropane (1.0 mL) and p-toluenesulfonic acid monohydrate (15 mg). The mixture was stirred at room temperature; after 1 h, the starting material was no longer detectable on TLC. The solution was neutralized with sodium hydrogen carbonate, and the precipitates were filtered off, and washed with dichloromethane. The filtrate and washings were combined, and concentrated to a syrup, which was chromatographed on a column of silica gel (100 g) using (a) 4:1 ethyl acetate-hexane and (b) 6:1 ethyl acetate-acetone as the eluants. Eluant (a) gave compound 3 (600 mg, 79%) and eluant (b) afforded 5 (145 mg, 19%).

Compound 3 had $[\alpha]_D$ +14.3° (c 0.35, 1:1 chloroform-methanol); IR (KBr) 3700-3150 (OH, NH), 1740 and 1240 (ester), 1650 and 1550 (amide), 850 (Me_2C), and 700 cm^{-1} (Ph); ^1H NMR (1:1 $CDCl_3$-CD_3OD) δ 1.19, 1.26 (2s, 6H, Me_2C), 1.67 (t, 1H, $J_{3a,3e} = J_{3a,4} = 12.6$ Hz, H-3a), 1.87 (s, 3H, AcN), 1.94 (s, 3H, MeS), 2.70 (dd, 1H, $J_{3e,4} = 4.6$ Hz, H-3e), 3.18 (dd, 1H, $J_{5,6} = 10.4$ Hz, $J_{6,7} = 1.7$ Hz, H-6), 3.63 (t, 1H, $J_{4,5} = 10.4$ Hz, H-5), 3.92 (m, 2H, H-9,9'), 4.08 (q, 1H, $J_{7,8} = J_{8,9} = J_{8,9'} = 6.0$ Hz, H-8), 5.06, 5.15 (2d, 2H, $J_{gem} = 12.2$ Hz, $PhCH_2$), and 7.22-7.28 (m, 5H, Ph).

Anal. Calcd for $C_{22}H_{31}NO_8S$ (469.6): C, 56.28; H, 6.65; N, 2.98. Found: C, 56.19; H, 6.81; N, 2.90.

Compound 5 had $[\alpha]_D$ -27.5° (c 0.55, chloroform); IR (KBr) 3700-3150 (OH, NH), 1730 and 1230 (ester), 1660 and 1570 (amide), 850 (Me_2C), and 730 cm^{-1} (Ph); ^1H NMR (1:1 $CDCl_3$-CD_3OD) δ 1.39 (2s, 6H, Me_2C), 1.87 (t, 1H, $J_{3a,3e} = J_{3a,4} = 12.3$ Hz, H-3a), 1.96 (s, 3H, AcN), 2.04 (s, 3H, MeS), 2.83 (dd, 1H, $J_{3e,4} = 4.6$ Hz, H-3e), 5.20, 5.27 (2d, 2H, $J_{gem} = 12.3$ Hz, $PhCH_2$), and 7.37 (s, 5H, Ph).

Found: C, 56.42; H, 6.59; N, 2.75.

Benzyl (Methyl 5-Acetamido-4-O-acetyl-3,5-dideoxy-8,9-O-isopropylidene-2-thio-D-glycero-α-D-galacto-2-nonulopyranosid)onate (4). To a solution of 3 (200 mg, 0.43 mmol) in pyridine (3 mL)-dichloromethane

(2 mL), cooled to -40 °C, was added dropwise a solution of acetyl chloride (0.05 mL) in dichloromethane (1 mL), and the mixture was stirred for 1 h at -40 °C. Methanol (1 mL) was added to the mixture, and the mixture was concentrated to a syrup which was chromatographed on a column of silica gel (30 g) with 80:1 dichloromethane-methanol, to give 4 (187 mg, 86%) as a syrup: $[\alpha]_D$ -14.3° (c 0.57, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.31, 1.39 (2s, 6H, Me_2C), 1.96 (s, 3H, AcN), 2.08 (2s, 6H, AcO, MeS), 2.79 (dd, 1H, $J_{3a,3e}$ = 12.7 Hz, $J_{3e,4}$ = 4.9 Hz, H-3e), 3.30 (dd, 1H, $J_{5,6}$ = 10.4 Hz, $J_{6,7}$ = 1.7 Hz, H-6), 4.99 (dt, 1H, $J_{3a,4}$ = $J_{4,5}$ = 10.4 Hz, H-4), 5.17, 5.34 (2d, 2H, J_{gem} = 12.2 Hz, PhC$\underline{H}_2$), 6.04 (d, 1H, $J_{NH,5}$ = 8.1 Hz, NH), and 7.28-7.40 (m, 5H, Ph).

Anal. Calcd for $C_{24}H_{33}NO_9S$ (511.6): C, 56.35; H, 6.50; N, 2.74. Found: C, 56.29; H, 6.48; N, 2.72.

Benzyl (Methyl 5-Acetamido-4-O-acetyl-3,5-dideoxy-2-thio-D-glycero-α-D-galacto-2-nonulopyranosid)onate (6). A solution of 4 (180 mg, 0.35 mmol) in 80% aqueous acetic acid (10 mL) was stirred for 8 h at room temperature, and concentrated to give 6 (164 mg, quantitative) as an amorphous mass: $[\alpha]_D$ +4.6° (c 0.6, 1:1 chloroform-methanol); IR (KBr) 3600-3150 (OH, NH), 1750 and 1220 (ester), 1650 and 1560 (amide), and 700 cm^{-1} (Ph); ^{1}H NMR (1:1 $CDCl_3$-CD_3OD) δ 1.95 (s, 3H, AcN), 2.04, 2.06 (2s, 6H, AcO, MeS), 2.93 (dd, 1H, $J_{3a,3e}$ = 12.7 Hz, $J_{3e,4}$ = 4.8 Hz, H-3e), 3.67 (dd, 1H, $J_{8,9}$ = 5.9 Hz, $J_{9,9'}$ = 11.9 Hz, H-9), 4.09 (t, 1H, $J_{4,5}$ = $J_{5,6}$ = 10.4 Hz, H-5), 5.31 (s, 2H, PhC$\underline{H}_2$), and 7.33-7.47 (m, 5H, Ph).

Anal. Calcd for $C_{21}H_{26}NO_9S$ (468.5): C, 53.84; H, 5.59; N, 2.99. Found: C, 53.79; H, 5.65; N, 2.83.

Benzyl (Methyl 5-Acetamido-4-O-acetyl-7,8,9-tri-O-chloroacetyl-3,5-dideoxy-2-thio-D-glycero-α-D-galacto-2-nonulopyranosid)onate (7). To a solution of 6 (50 mg, 0.11 mmol) in pyridine (1 mL)-dichloromethane (1 mL), cooled to 0 °C, was added chloroacetic anhydride (0.07 mL), and the mixture was stirred for 1 h at 0 °C, and then extracted with dichloromethane. The extract was successively washed with 2M hydrochloric acid, water, dried (sodium sulfate), and concentrated to a syrup, which was chromatographed on a column of silica gel (10 g) with 150:1 dichloromethane-methanol, to give 7 (72 mg, 97%) as a syrup: $[\alpha]_D$ +9.3° (c 0.43, chloroform); IR (film) 3360 (NH), 1740 and 1230 (ester), 1660 and 1530 (amide), and 690 cm^{-1} (Ph); ^{1}H NMR ($CDCl_3$) δ 1.87 (s, 3H, AcN), 1.95 (s, 3H, AcO), 2.03 (s, 3H, MeS), 2.80 (dd, 1H, $J_{3a,3e}$ = 12.9 Hz, $J_{3e,4}$ = 4.6 Hz, H-3e),

3.76 (dd, 1H, $J_{5,6}$ = 10.7 Hz, $J_{6,7}$ = 2.3 Hz, H-6), 4.07-4.36 (m, 8H, 3ClCH$_2$CO, H-5,9), 4.51 (dd, 1H, $J_{8,9'}$ = 2.6 Hz, $J_{9,9'}$ = 12.6 Hz, H-9'), 4.84 (dt, 1H, $J_{3e,4}$ = 4.6 Hz, $J_{3a,4}$ = $J_{4,5}$ = 11.7 Hz, H-4), 5.18, 5.27 (2d, 2H, J_{gem} = 12.1 Hz, PhCH$_2$), 5.28 (d, 1H, $J_{NH,5}$ = 10.1 Hz, NH), 5.36 (dd, 1H, $J_{7,8}$ = 8.8 Hz, H-7), 5.55 (m, 1H, H-8), and 7.38 (s, 5H, Ph).

Anal. Calcd for $C_{27}H_{32}NO_{12}Cl_3S$ (701.0): C, 46.26; H, 4.60; N, 2.00. Found: C, 46.30; H, 4.71; N, 1.93.

Benzyl 5-Acetamido-4-O-acetyl-3,5-dideoxy-D-glycero-β-D-galacto-2-nonulopyranosonate (8). To a solution of 6 (110 mg, 0.235 mmol) in acetonitrile (2 mL) and 1,4-dioxane (2 mL), cooled to -40 °C, was added DMTST (100 mg), and after 3 min, one drop of water was added to the mixture, and this was stirred for 10 min at -20 °C while the progress of the reaction was monitored by TLC. The mixture was directly chromatographed on a column of silica gel (30 g) with 5:1 ethyl acetate-acetone to give 8 (70 mg, 68%) as an amorphous mass: $[\alpha]_D$ -3.2° (c 0.6, 3:1 methanol-water); IR (KBr) 3600-3300 (OH, NH), 1740 and 1230 (ester), 1660 and 1550 (amide), and 700 cm^{-1} (Ph); ^{1}H NMR (CD$_3$OD) δ 1.94 (s, 3H, AcN), 2.01 (s, 3H, AcO), 2.32 (dd, 1H, $J_{3a,3e}$ = 12.7 Hz, $J_{3e,4}$ = 5.0 Hz, H-3e), 3.50 (dd, 1H, $J_{5,6}$ = 9.2 Hz, $J_{6,7}$ = 2.1 Hz, H-6), 4.13 (m, 2H, H-5,7), 5.19, 5.26 (2d, 2H, J_{gem} = 12.4 Hz, PhCH$_2$), 5.30 (m, 1H, H-4), and 7.31-7.87 (m, 5H, Ph).

Anal. Calcd for $C_{20}H_{27}NO_{11}$ (441.4): C, 54.42; H, 6.17; N, 3.14. Found: C, 54.20; H, 6.39; N, 3.15.

5-Acetamido-4-O-acetyl-3,5-dideoxy-D-glycero-β-D-galacto-2-nonulopyranosonic acid (9). Compound 8 (35 mg, 79 μmol) was dissolved in methanol (5 mL), 10% Pd-C catalyst (30 mg) was added, and hydrogen was bubbled through while the mixture was stirred for 1 h at room temperature. The catalyst was removed by filtration, and the filtrate was concentrated below 30 °C, to give a hygroscopic amorphous mass (28 mg, quantitative), which showed a single spot on TLC: $[\alpha]_D$ -38.5° (c 0.6, 2:1 methanol-water); IR (KBr) 3700-3200 (OH, NH), 1740 and 1250 (ester), 1710 (C=O), and 1660 and 1550 cm^{-1} (amide); ^{1}H NMR (1:1 CDCl$_3$-CD$_3$OD) δ 1.96 (s, 3H, AcN), 2.04 (s, 3H, AcO), 2.26 (dd, 1H, $J_{3a,3e}$ = 12.2 Hz, $J_{3e,4}$ = 4.6 Hz, H-3e), 3.51 (d, 1H, H-7), 3.63 (dd, 1H, $J_{8,9}$ = 5.5 Hz, $J_{9,9'}$ = 11.0 Hz, H-9), 3.82 (dd, 1H, $J_{8,9'}$ = 4.8 Hz, H-9'), and 5.33 (m, 1H, H-4).

Anal. Calcd for $C_{13}H_{21}NO_{10}$ (351.3): C, 44.45; H, 6.03; N, 3.99. Found: C, 44.63; H, 6.25; N, 3.82.

Benzyl (Methyl 5-Acetamido-9-O-acetyl-3,5-dideoxy-2-thio-D-glycero-α-D-galacto-2-nonulopyranosid)onate (10). To a solution of 2 (2.4 g, 5.6 mmol) in pyridine (20 mL) and dichloromethane (40 mL), cooled to -40 °C, was gradually added, with stirring, a solution of acetyl chloride (0.5 mL) in dry dichloromethane (20 mL), and the mixture was stirred for 30 min at -40 °C; at that time, no starting material was detectable on TLC. Methanol (1 mL) was added to the mixture, and concentrated. The residue was chromatographed on a column of silica gel (200 g) with 30:1 dichloromethane-methanol to give 10 (2.2 g, 84%): $[\alpha]_D$ +35.8° (c 0.8, 1:1 chloroform-methanol): ^{1}H NMR ($CDCl_3$): δ 1.93 (s, 3H, AcN), 2.03, 2.09 (2s, 6H, AcO, MeS), 2.89 (dd, 1H, $J_{3a,3e}$ = 12.9 Hz, $J_{3e,4}$ = 4.7 Hz, H-3e), 4.18 (dd, 1H, $J_{8,9}$ = 6.9 Hz, $J_{9,9'}$ = 11.5 Hz, H-9), 4.20 (m, 1H, H-9'), 5.21, 5.31 (2d, 2H, $PhCH_2$), 6.45 (d, 1H, $J_{NH,5}$ = 7.9 Hz, NH), and 7.36 (s, 5H, Ph).

Anal. Calcd for $C_{21}H_{29}NO_9S$ (471.5): C, 53.49; H, 6.20; N, 2.97. Found: C, 53.46; H, 6.29; N, 2.74.

Benzyl (Methyl 5-Acetamido-9-O-acetyl-4,7,8-tri-O-chloroacetyl-3,5-dideoxy-2-thio-D-glycero-α-D-galacto-2-nonulopyranosid)onate (11). To a solution of 10 (700 mg, 1.49 mmol) in pyridine (2 mL) and dichloromethane (3 mL), cooled to -5 °C, was added dropwise chloroacetic anhydride (1.0 g), and the mixture was stirred for 1 h at 0 °C. Processing as described for 7, gave 11 (1.0 g, 96%) as a syrup: $[\alpha]_D$ +7.2° (c 0.67, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3H, AcN), 1.96, 2.04 (2s, 6H, AcO, MeS), 2.85 (dd, 1H, $J_{3a,3e}$ = 12.8 Hz, $J_{3e,4}$ = 4.6 Hz, H-3e), 3.80 (dd, 1H, $J_{5,6}$ = 10.8 Hz, $J_{6,7}$ = 2.2 Hz, H-6), 4.08 (dd, 1H, $J_{8,9}$ = 4.8 Hz, $J_{9,9'}$ = 12.8 Hz, H-9), 4.01-4.34 (m, 7H, $3ClCH_2CO$, H-5), 4.37 (dd, 1H, $J_{8,9'}$ = 2.6 Hz, H-9'), 4.92 (td, 1H, $J_{4,5}$ = $J_{3a,4}$ = 11.5 Hz, H-4), 5.20, 5.27 (2d, 2H, J_{gem} = 12.1 Hz, $PhCH_2$), 5.24 (d, 1H, $J_{NH,5}$ = 10.1 Hz, NH), 5.38 (dd, 1H, H-8), and 7.39 (s, 5H, Ph).

Anal. Calcd for $C_{27}H_{32}NO_{12}Cl_3S$ (701.0): C, 46.26; H, 4.60; N, 2.00. Found: C, 46.29; H, 4.62; N, 1.94.

Benzyl 5-Acetamido-9-O-acetyl-3,5-dideoxy-D-glycero-β-D-galacto-2-nonulopyranosonate (12). Selective hydrolysis of the methylthio group in 10 (250 mg, 0.53 mmol), as described for the preparation of 8, gave 12 (170 mg, 72.6%) as an amorphous mass: $[\alpha]_D$ -20.5° (c 0.6, 1:1 chloroform-

methanol); ^{1}H NMR (1:1 $CDCl_3$-CD_3OD) δ 2.03 (s, 3H, AcN), 2.09 (s, 3H, AcO), 2.30 (dd, 1H, $J_{3a,3e}$ = 13.0 Hz, $J_{3e,4}$ = 4.8 Hz, H-3e), 4.19 (dd, 1H, $J_{8,9}$ = 6.2 Hz, $J_{9,9'}$ = 11.5 Hz, H-9), 4.40 (dd, 1H, $J_{8,9'}$ = 2.4 Hz, H-9'), 5.18, 5.26 (2d, 2H, J_{gem} = 12.8 Hz, PhCH$_2$), and 7.36 (s, 5H, Ph).

Anal. Calcd for $C_{20}H_{27}NO_{10}$ (441.4): C, 54.42; H, 6.17; N, 3.17. Found: C, 54.42; H, 6.24; N, 3.09.

5-Acetamido-9-O-acetyl-3,5-dideoxy-D-glycero-β-D-galacto-2-nonulopyranosonic acid (13). Hydrogenation of 12 (30 mg, 68 μmol) as described for 9, gave 13 (24 mg, quantitative) as an amorphous mass: $[\alpha]_D$ -14.1° (c 0.44, methanol); IR (KBr) 3700-3200 (OH, NH), 1740 and 1220 (ester), 1710 (C=O), and 1650 and 1540 cm^{-1} (amide); ^{1}H NMR (1:1 $CDCl_3$-CD_3OD) δ 1.80 (t, 1H, $J_{3a,3e}$ = 12.1 Hz, H-3a), 2.02 (s, 3H, AcN), 2.08 (s, 3H, AcO), 2.20 (dd, 1H, $J_{3e,4}$ = 4.6 Hz, H-3e), 4.13 (dd, 1H, $J_{8,9}$ = 5.7 Hz, $J_{9,9'}$ = 11.5 Hz, H-9), and 4.31 (dd, 1H, $J_{8,9'}$ = 4.6 Hz, H-9').

Anal. Calcd for $C_{13}H_{21}NO_{10}$ (351.3): C, 44.45; H, 6.03; N, 3.99. Found: C, 44.38; H, 6.14; N, 3.80.

Benzyl [2-(Trimethylsilyl)ethyl 5-Acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosid]onate (15). Conversion of the methyl ester group in 14[10] (1.5 g, 3.54 mmol) into the benzyl ester was performed, according to the method described in the preparation of 2, to give 15 (1.7 g, 98%) as an amorphous mass: $[\alpha]_D$ -15.3° (c 0.7, methanol); IR (KBr) 3700-3200 (OH, NH), 1740 and 1240 (ester), 1650 and 1550 (amide), and 700 cm^{-1} (Ph); ^{1}H NMR (CD_3OD) δ 0.85 (m, 2H, $Me_3SiCH_2CH_2$), 1.80 (t, 1H, $J_{3a,3e}$ = $J_{3a,4}$ = 12.4 Hz, H-3a), 2.05 (s, 1H, AcN), 2.78 (dd, 1H, $J_{3e,4}$ = 4.6 Hz, H-3e), 3.64 (dd, 1H, $J_{6,7}$ = 1.8 Hz, $J_{7,8}$ = 8.5 Hz, H-7), 3.67 (m, 1H, H-4), 3.81 (t, 1H, $J_{4,5}$ = $J_{5,6}$ = 10.1 Hz, H-5), 5.34 (s, 2H, PhCH$_2$), and 7.41-7.47 (m, 5H, Ph).

Anal. Calcd for $C_{23}H_{37}NO_9Si$ (499.6): C, 55.29; H, 7.46; N, 2.80. Found: C, 55.18; H, 7.46; N, 2.73.

Benzyl [2-(Trimethylsilyl)ethyl 5-Acetamido-3,5-dideoxy-8,9-O-isopropylidene-D-glycero-α-D-galacto-2-nonulopyranosid]onate (16) and Benzyl [2-(Trimethylsilyl)ethyl 5-Acetamido-3,5-dideoxy-7,9-O-isopropylidene-D-glycero-α-D-galacto-2-nonulopyranosid]onate (18). Acetonation of 15 (310 mg, 0.62 mmol) with 2,2-dimethoxypropane (0.45 mL) as described for the preparation of 3 and 5, gave the 8,9-O-isopropylidene derivative 16 (245 mg, 74.2%) and 7,9-O-isopropylidene derivative 18 (68 mg, 20%).

Compound 16 had $[\alpha]_D$ -15.0° (c 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 0.79 (m, 2H, $Me_3Si\underline{CH_2}CH_2$), 1.30, 1.39 (2s, 6H, Me_2C), 1.79 (t, 1H, $J_{3a,3e} = J_{3a,4} = 12.2$ Hz, H-3a), 2.02 (s, 3H, AcN), 2.73 (dd, 1H, $J_{3e,4} = 4.6$ Hz, H-3e), 3.36, 3.80 (2m, 2H, $Me_3SiCH_2\underline{CH_2}$), 5.19, 5.24 (2d, 2H, $J_{gem} = 12.1$ Hz, $Ph\underline{CH_2}$), 6.12 (d, 1H, $J_{NH,5} = 8.1$ Hz, NH), and 7.35 (s, 5H, Ph).

Anal. Calcd for $C_{26}H_{41}NO_9Si$ (539.7): C, 57.86; H, 7.66; N, 2.60. Found: C, 57.69; H, 7.64; N, 2.58.

Compound 18 had $[\alpha]_D$ -50.7° (c 2.4, chloroform); ^{1}H NMR ($CDCl_3$) δ 0.79 (m, 2H, $Me_3Si\underline{CH_2}CH_2$), 1.21, 1.37 (2s, 6H, Me_2C), 1.85 (t, 1H, $J_{3a,3e} = J_{3a,4} = 13.0$ Hz, H-3a), 1.97 (s, 3H, AcN), 2.74 (dd, 1H, $J_{3e,4} = 4.8$ Hz, H-3e), 3.28 (m, 1H, one proton in $Me_3SiCH_2\underline{CH_2}$), 5.15, 5.26 (2d, 2H, $J_{gem} = 12.1$ Hz, $Ph\underline{CH_2}$), 6.28 (d, 1H, $J_{NH,5} = 7.6$ Hz, NH), and 7.35 (s, 5H, Ph).

Found: C, 57.70; H, 7.86; N, 2.54.

Benzyl [2-(Trimethylsilyl)ethyl 5-Acetamido-4-O-acetyl-3,5-dideoxy-8,9-O-isopropylidene-D-glycero-α-D-galacto-2-nonulopyranosid]onate (17). Selective 4-O-acetylation of 16 (200 mg, 0.37 mmol) as described for 4 gave 17 (205 mg, 95%) as an amorphous mass: $[\alpha]_D$ -24° (c 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 2H, $Me_3Si\underline{CH_2}CH_2$), 1.38, 1.46 (2s, 6H, Me_2C), 2.03 (s, 3H, AcN), 2.15 (s, 3H, AcO), 2.73 (dd, 1H, $J_{3a,3e} = 12.7$ Hz, $J_{3e,4} = 4.8$ Hz, H-3e), 3.55 (m, 2H, H-6, one proton in $Me_3SiCH_2\underline{CH_2}$), 3.90 (m, 1H, one proton in $Me_3SiCH_2\underline{CH_2}$), 4.04 (td, 1H, $J_{4,5} = J_{5,6} = 10.6$ Hz, $J_{5,NH} = 8.1$ Hz, H-5), 4.07 (dd, 1H, $J_{8,9} = 8.2$ Hz, $J_{9,9'} = 14.0$ Hz, H-9), 4.15 (dd, 1H, $J_{8,9'} = 7.6$ Hz, H-9'), 4.29 (q, 1H, H-8), 5.04 (td, 1H, $J_{3a,4} = 10.6$ Hz, H-4), 5.23, 5.36 (2d, 2H, $J_{gem} = 12.0$ Hz, $Ph\underline{CH_2}$), 6.05 (d, 1H, NH), and 7.44 (s, 5H, Ph).

Anal. Calcd for $C_{28}H_{43}NO_{10}Si$ (581.7): C, 57.81; H, 7.45; N, 2.41. Found: C, 57.79; H, 7.65; N, 2.36.

Benzyl [2-(Trimethylsilyl)ethyl 5-Acetamido-4,8-di-O-acetyl-3,5-dideoxy-7,9-O-isopropylidene-D-glycero-α-D-galacto-2-nonulopyranosid]onate (19). Acetylation of 18 (100 mg, 0.19 mmol) with acetic anhydride (1 mL)-pyridine (2 mL) overnight at room temperature gave 19 (113 mg, quantitative) as an amorphous mass: $[\alpha]_D$ -51.5° (c 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 0.84 (m, 2H, $Me_3Si\underline{CH_2}CH_2$), 1.37, 1.41 (2s, 6H, Me_2C), 1.93 (s, 3H, AcN), 2.05, 2.11 (2s, 6H, 2AcO), 2.61 (dd, 1H, $J_{3a,3e} = 12.7$ Hz, $J_{3e,4} = 4.8$ Hz, H-3e), 3.35 (m, 1H, one proton in $Me_3SiCH_2\underline{CH_2}$), 3.64 (dd,

1H, $J_{8,9}$ = 7.2 Hz, $J_{9,9'}$ = 11.5 Hz, H-9), 4.04 (dd, 1H, $J_{8,9'}$ = 5.1 Hz, H-9'), 4.31 (q, 1H, $J_{4,5} = J_{5,6} = J_{5,NH}$ = 10.3 Hz, H-5), 4.86 (ddd, 1H, H-4), 5.11 (d, 1H, NH), 5.22 (m, 1H, H-8), 5.24 (s, 2H, Ph$\underline{CH_2}$), and 7.38 (s, 5H, Ph).

Anal. Calcd for $C_{30}H_{45}NO_{11}Si$ (623.8): C, 57.77; H, 7.27; N, 2.25. Found: C, 57.69; H, 7.34; N, 2.24.

Benzyl [2-(Trimethylsilyl)ethyl 5-Acetamido-4-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosid]onate (20). A solution of 17 (320 mg, 0.55 mmol) in 80% aqueous acetic acid (10 mL) was stirred overnight at 40 °C, and concentrated to a syrup, which was chromatographed on a column of silica gel (50 g) with 40:1 dichloromethane-methanol to give 20 (290 mg, 97%) as an amorphous mass: $[\alpha]_D$ -13.0° (c 1.4, chloroform); IR (KBr) 3600-3200 (OH, NH), 1750 and 1230 (ester), 1640 and 1570 (amide), 860 and 840 (TMS), and 700 cm^{-1} (Ph); ^1H NMR ($CDCl_3$) δ 0.85 (m, 2H, $Me_3Si\underline{CH_2}CH_2$), 2.04 (s, 3H, AcN), 2.16 (s, 3H, AcO), 2.79 (dd, 1H, $J_{3a,3e}$ = 12.8 Hz, $J_{3e,4}$ = 4.9 Hz, H-3e), 3.34 (m, 1H, one proton in $Me_3SiCH_2\underline{CH_2}$), 3.50 (dd, 1H, $J_{5,6}$ = 10.4 Hz, $J_{6,7}$ = 1.6 Hz, H-6), 4.97 (ddd, 1H, H-4), 5.22, 5.30 (2d, 2H, J_{gem} = 11.9 Hz, Ph$\underline{CH_2}$), 6.22 (d, 1H, $J_{NH,5}$ = 7.5 Hz, NH), and 7.45 (s, 5H, Ph).

Anal. Calcd for $C_{25}H_{39}NO_{10}Si$ (541.7): C, 55.44; H, 7.26; N, 2.59. Found: C, 55.30; H, 7.34; N, 2.43.

Benzyl [2-(Trimethylsilyl)ethyl 5-Acetamido-4,9-di-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosid]onate (21). To a solution of 20 (290 mg, 0.54 mmol) in pyridine (3 mL) and dichloromethane (3 mL), cooled to -40 °C, was added dropwise a solution of acetyl chloride (0.55 mL) in dichloromethane (2 mL), and the mixture was stirred for 30 min while the progress of the reaction was monitored by TLC. The mixture, to which methanol (1 mL) was added, was concentrated to a syrup and chromatographed on a column of silica gel (30 g) with 70:1 dichloromethane-methanol, to afford 21 (275 mg, 87%) as an amorphous mass: $[\alpha]_D$ -19.0° (c 1.1, chloroform); ^1H NMR ($CDCl_3$) δ 0.85 (m, 2H, $Me_3Si\underline{CH_2}CH_2$), 2.04 (s, 3H, AcN), 2.15, 2.16 (2s, 6H, 2AcO), 2.79 (dd, 1H, $J_{3a,3e}$ = 12.9 Hz, $J_{3e,4}$ = 4.9 Hz, H-3e), 3.32 (m, 1H, one proton in $Me_3SiCH_2\underline{CH_2}$), 3.54 (dd, 1H, $J_{5,6}$ = 10.1 Hz, $J_{6,7}$ = 1.2 Hz, H-6), 3.85-3.94 (m, 2H, H-7, one of proton in $Me_3SiCH_2\underline{CH_2}$), 4.02 (td, 1H, H-5), 4.15 (m, 1H, H-8), 4.26 (dd, 1H, $J_{8,9}$ = 6.4 Hz, $J_{9,9'}$ = 11.4 Hz, H-9), 4.52 (broad d, 1H, H-9'), 4.94 (ddd, 1H, H-4), 5.29, 5.36 (2d, 2H, J_{gem} = 12.1 Hz, Ph$\underline{CH_2}$), and 7.44 (s, 5H, Ph).

Anal. Calcd for $C_{27}H_{41}NO_{11}Si$ (583.7): C, 55.56; H, 7.08; N, 2.40. Found: C, 55.45; H, 7.13; N, 2.39.

Benzyl 5-Acetamido-4,9-di-O-acetyl-3,5-dideoxy-D-glycero-β-D-galacto-2-nonulopyranosonate (22). To a solution of 21 (246 mg, 0.42 mmol) in dichloromethane (3.5 mL), cooled to 0 °C, was added dropwise a solution of boron trifluoride etherate (127 mg) in dichloromethane (1 mL), and the mixture was stirred for 9 h at 0 °C. Water (0.1 mL) was added to the solution, and this was treated with Amberlite IR-410 (OH^-) resin. The solution was concentrated to a syrup, which was chromatographed on a column of silica gel (30 g) with 4:1 ethyl acetate-hexane, to give 22 (140 mg, 68%) as an amorphous mass: $[\alpha]_D$ -28.5° (c 2.3, chloroform); IR (KBr) 3700-3150 (OH, NH), 1740 and 1240 (ester), 1660 and 1550 (amide), and 700 cm^{-1} (Ph); ^1H NMR (1:1 $CDCl_3$-CD_3OD) δ 1.99 (s, 3H, AcN), 2.05, 2.10 (2s, 6H, 2AcO), 2.33 (dd, 1H, $J_{3a,3e}$ = 12.8 Hz, $J_{3e,4}$ = 5.1 Hz, H-3e), 3.97 (m, 1H, H-8), 4.21 (dd, 1H, $J_{8,9}$ = 6.1 Hz, $J_{9,9'}$ = 11.5 Hz, H-9), 4.41 (dd, 1H, $J_{8,9'}$ = 2.4 Hz, H-9'), 5.17, 5.26 (2d, 2H, J_{gem} = 12.4 Hz, $PhCH_2$), 5.32 (m, 1H, H-4), and 7.36 (s, 5H, Ph).

Anal. Calcd for $C_{22}H_{29}NO_{11}$ (483.5): C, 54.66; H, 6.05; N, 2.90. Found: C, 54.40; H, 6.11; N, 2.86.

5-Acetamido-4,9-di-O-acetyl-3,5-dideoxy-D-glycero-β-D-galacto-2-nonulopyranosonic acid (23). Hydrogenolytic removal of the benzyl group in 22 (115 mg, 0.24 mmol) as described for 9, gave 23 (90 mg, 96%) as an amorphous mass: $[\alpha]_D$ -36.5° (c 1.8, methanol); IR (KBr) 3500-3300 (OH, NH), 1730 and 1250 (ester), 1710 (C=O), and 1660 and 1540 cm^{-1} (amide); ^1H NMR (1:1 CD_3OD-D_2O) δ 1.95 (t, 1H, $J_{3a,3e}$ = $J_{3a,4}$ = 12.6 Hz, H-3a), 1.99 (s, 3H, AcN), 2.06, 2.11 (2s, 6H, 2AcO), 2.31 (dd, 1H, $J_{3e,4}$ = 4.9 Hz, H-3e), 3.57 (d, 1H, $J_{5,6}$ = 9.5 Hz, H-6), 3.94 (m, 1H, H-8), 4.16 (dd, 1H, $J_{8,9}$ = 6.6 Hz, $J_{9,9'}$ = 12.7 Hz, H-9), 4.20 (t, 1H, H-5), 4.38 (dd, 1H, $J_{8,9'}$ = 2.3 Hz, H-9'), and 5.33 (td, 1H, H-4).

Anal. Calcd for $C_{15}H_{23}NO_{11}$ (393.4): C, 45.80; H, 5.89; N, 3.56. Found: C, 45.69; H, 5.86; N, 3.40.

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