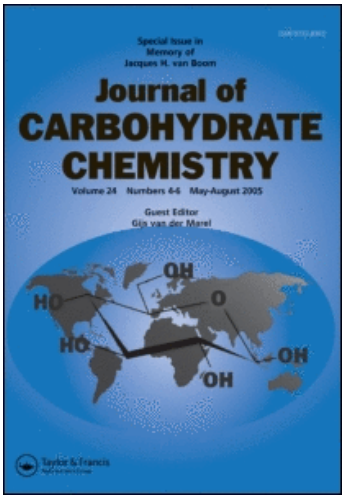

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Synthetic Studies on Sialoglycoconjugates. 4: Synthesis of 5-Acetamido-3,5-Dideoxy-d-Galacto-2-Octulosonic Acid Derivatives and Analogs

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SYNTHETIC STUDIES ON SIALOGLYCOCONJUGATES 4: SYNTHESIS OF 5-ACETAMIDO-3,5-DIDEOXY-D-GALACTO-2-OCTULOSONIC ACID DERIVATIVES AND ANALOGS

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ABSTRACT

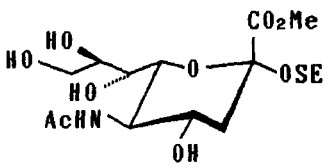
5-Acetamido-3,5-dideoxy-D-galacto-2-octulosonic acid derivatives and the α-2-thioanalog (14) were synthesized. Methyl [2-(trimethylsilyl)ethyl 5-acetamido-3,5-dideoxy-α-D-galacto-2-octulopyranosid]onate (8), prepared from methyl [2-(trimethylsilyl)ethyl 5-acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosid]onate (1) via 8,9-O-isopropylidenation, O-acetylation, O-deisopropylidenation, metaperiodate oxidation, and sodium borohydride reduction, was converted , by selective bromination, into the 8-bromo derivatives (9). Compound 12, derived from 8 via O-acetylation and boron trifluoride etherate treatment, was converted to the 2-chloro derivative (13), which underwent displacement with potassium thioacetate, to yield methyl 5-acetamido-4,7,8-tri-O-acetyl-2-S-acetyl-2-thio-α-D-galacto-2-octulopyranosonate (14).

INTRODUCTION

Sialic acids are well known as important components of glycoproteins and glycolipids, and involved in their biological functions such as masking of cell-surface antigens,[1] mitogenic-receptors acting to some lectins,[2] cell-to-cell recognition,[1] and other behavior.[1,3-6] In view of these facts, it is of interest to investigate the relationship between the structures of the sialic acids and the functions of the sialoglycoconjugates. We now describe a synthesis of some 5-acetamido-3,5-dideoxy-D-galacto-2-octulosonic acid derivatives and an α-2-thioanalog.

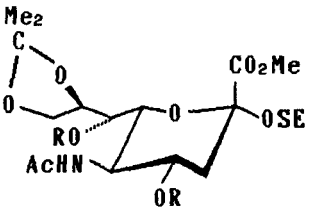
RESULTS AND DISCUSSION

Treatment of methyl [2-(trimethylsilyl)ethyl 5-acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosid]onate[7] (1) with 2,2-dimethoxypropane in N,N-dimethylformamide containing a trace of p-toluenesulfonic acid monohydrate at room temperature gave a mixture from which methyl [2-(trimethylsilyl)ethyl 5-acetamido-3,5-dideoxy-8,9-O-isopropylidene-D-glycero-α-D-galacto-2-nonulopyranosid]onate (2; 79%) and the 7,9-O-isopropylidene derivative (4; 18%) were isolated. Acetylation of 2 or 4 gave the corresponding di-O-acetyl derivatives (3 and 5), respectively. Significant signals in the ^{1}H NMR spectrum of 3 were two three-proton singlets at δ 1.32 and 1.34 (Me_2C), a three-proton singlet at δ 1.86 (N-acetyl), two three-proton singlets at δ 2.02 and 2.12 (2 O-acetyl), a three-proton singlet at δ 3.82 (COOMe), a one-proton doublet of doublets at δ 2.59 ($J_{3a,3e}$ = 12.7 Hz, $J_{3e,4}$ = 4.9 Hz, H-3e), a one-proton multiplet at δ 4.32 (H-8), and a one-proton doublet of doublets at δ 5.33 ($J_{6,7}$= 2.2 Hz, $J_{7,8}$ = 3.7 Hz, H-7), indicating the structure 3. The structure 5 was unambiguously proved by ^{1}H NMR spectroscopy; H-8 appeared at δ 5.15 as multiplet, and H-4 at δ 4.83 (ddd, $J_{3a,4}$ = 12.1 Hz, $J_{3e,4}$ = 4.8 Hz, $J_{4,5}$ = 10.3 Hz). Other NMR data are given in the Experimental Section and are consistent with structure 5. Removal of the isopropylidene group from 3 with 70% aqueous acetic acid at 45 °C gave a crystalline diol 6 in 97% yield; significant signals in ^{1}H NMR spectrum were a one-proton doublet of doublets at δ 5.07 ($J_{6,7}$ = 1.0 Hz, $J_{7,8}$ = 8.1 Hz, H-7) and at δ 4.81 (ddd, $J_{3a,4}$ = 11.7 Hz, $J_{3e,4}$ = 4.9 Hz, $J_{4,5}$ = 10.5 Hz, H-4). Treatment of 6 with sodium metaperiodate in methanol followed by reduction using sodium borohydride, and subsequent acetylation afforded methyl (trimethylsilylethyl 5-acetamido-4,7,8-tri-O-acetyl-3,5-dideoxy-α-D-galacto-2-octulopyranosid)onate (7) as crystals in 87% yield. The ^{1}H NMR spectrum of 7 exhibited five sharp singlets, each integrating for three protons, at δ 1.86, 2.01, 2.04, 2.11, and 3.79, which demonstrated the presence of one N-acetyl, three O-acetyl, and one methyl ester group; H-3a appeared at δ 1.94 ($J_{3a,3e}$ = 12.2 Hz, $J_{3a,4}$ = 12.1 Hz) as a doublet of doublets, H-3e at δ 2.59 (dd, $J_{3e,4}$ = 4.8 Hz), and H-4 at δ 4.84 (ddd, $J_{4,5}$ = 10.3 Hz), indicating structure 7. The observed chemical shifts and coupling constants for H-3e and H-4 are similar to those of the α-glycosides[8] of N-acetylneuraminic acid, and could be applied for determination of the anomeric configuration of the glycosides of N-acetyloctulosonic acid. Treatment of compound 8, derived from 7 by O-deacetylation with sodium methoxide in methanol, with N-bromosuccinimide for 1.5 h at 50 °C



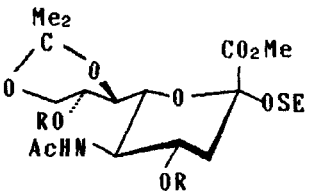
1

SE=$Me_3SiCH_2CH_2$-



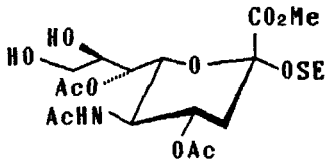
2 R=H

3 R=Ac

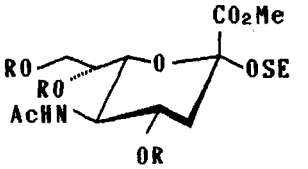


4 R=H

5 R=Ac

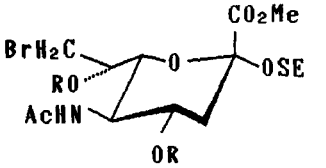


6



7 R=Ac

8 R=H

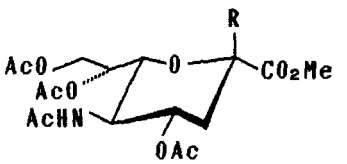


9 R=H

10 R=Ac

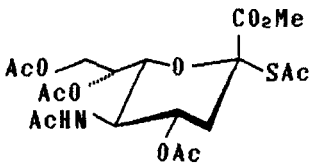
11 R=SEM

SEM=$Me_3SiCH_2CH_2OCH_2$-



12 R=OH

13 R=Cl



14

in the presence of triphenylphosphine in N,N-dimethylformamide afforded 9 as a syrup, which was acetylated to give methyl [2-(trimethylsilyl)ethyl 5-acetamido-4,7-di-O-acetyl-8-bromo-3,5,8-trideoxy-α-D-galacto-2-octulopyranosid)onate (10) in 85% yield. There are six significant signals in ^{1}H NMR spectrum of 10, four three-proton singlet at δ 1.90 (N-acetyl), 2.04, 2.14 (2s, O-acetyl), and 3.84 (COOMe), a one-proton doublet of doublets at δ 2.63 ($J_{3a,3e}$ = 12.5 Hz, $J_{3e,4}$ = 4.8 Hz, H-3e), and at δ 4.94 (ddd, $J_{3a,4}$ = 12.1 Hz, $J_{4,5}$ = 9.9 Hz, H-4). Other ^{1}H NMR data are consistent with structure 10. O-2-(Trimethylsilyl)ethoxymethylation of 9 was performed in the presence of N,N-diisopropylethylamine in dry dichloromethane, to obtain methyl [2-(trimethylsilyl)ethyl 5-acetamido-8-bromo-3,5,8-trideoxy-4,7-di-O-trimethylsilylethoxymethyl-α-D-galacto-2-octulopyranosid]onate (11) in 82% yield. On the other hand, treatment[9] of compound 10 with boron trifluoride etherate in acetonitrile gave crystalline methyl 5-acetamido-4,7,8-tri-O-acetyl-3,5-dideoxy-ß-D-galacto-2-octulopyranosonate (12) in quantitative yield. The latter compound was converted into the corresponding 2β-chloro derivative (13) on treatment[7] with hydrogen chloride in dry dichloromethane for 24 h at room temperature. When treated with potassium thioacetate in dichloromethane-acetone, compound 13 yielded methyl 5-acetamido-4,7,8-tri-O-acetyl-2-S-acetyl-3,5-dideoxy-2-thio-α-D-galacto-2-octulopyranosonate (14) in 83% yield. ^{1}H NMR spectrum of 14 showed signals characteristic[10] of the β-S-acetyl derivative of N-acetylneuraminic acid at δ 2.74 (dd, $J_{3a,3e}$ = 12.8 Hz, $J_{3e,4}$ = 4.8 Hz, H-3e) and at δ 4.96 (ddd, $J_{3a,4}$ = 11.4 Hz, $J_{4,5}$ = 10.6 Hz, H-4). Other significant signals were at δ 1.94 (N-acetyl), 2.05, 2.09, and 2.10 (3 O-acetyl), 2.30 (S-acetyl), and 3.82 (COOMe). Compounds 7-14, obtained herein, could be used not only for the analog synthesis of sialoglycoconjugates but also as the substrates or inhibitors for sialidases.

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 the IR spectra were recorded with a JASCO IR-I spectrophotometer. ^{1}H NMR spectra were recorded with a JEOL JNM-GX 270 spectrometer. Prparative chromatography was performed on silica gel (Waco Co., 200 mesh) with the solvent systems specified. Evaporations were conducted in vacuo.

Methyl [2-(Trimethylsilyl)ethyl 5-Acetamido-3,5-dideoxy-8,9-O-isopropylidene-D-glycero-α-D-galacto-2-nonulopyranosid]onate (2) and Methyl [2-(Tri-

methylsilyl)ethyl 5-Acetamido-3,5-dideoxy-7,9-O-isopropylidene-D-glycero-α-D-galacto-2-nonulopyranosid]onate (4). To a stirred solution of methyl (trimethylsilylethyl 5-acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosid)onate[7] (1; 1.47 g, 3.47 mmol) in N,N-dimethylformamide (DMF; 30 mL) were added 2,2-dimethoxypropane (4 mL) and p-toluenesulfonic acid monohydrate (30 mg) at room temperature; stirring was continued for 1.5 h. The mixture was deacidified with Amberlite IR-45 (OH^-) resin, and filtered, and then washed with methanol. The filtrate and washings were combined, and concentrated to a syrup which was chromatographed on a column of silica gel (150 g) with (a) dichloromethane, (b) 100:1, and (c) 50:1 dichloromethane-methanol. Eluant (b) gave compound 2 (1.16 g, 78.9%) after recrystallization from ether-hexane as needles: mp 92-93 °C, $[\alpha]_D$ - 9.5° (c 0.2, chloroform); IR (KBr) 3400 (OH), 3280 (NH), 1740 and 1250 (ester), 1640 and 1550 (amide), and 860 and 840 cm^{-1} (TMS, Me_2C); ^1H NMR ($CDCl_3$) δ 0.87 (t. 2H, $J_{gem} = J_{SiCH,OCH} = 8.2$ Hz, $Me_3Si\underline{CH_2}CH_2O$), 1.35, 1.39 (2s, 6H, Me_2C), 1.76 (dd, 1H, $J_{3a,3e} = 12.8$ Hz, $J_{3a,4} = 12.5$ Hz, H-3a), 2.02 (s, 3H, AcN), 2.67 (dd, 1H, $J_{3e,4} = 4.4$ Hz, H-3e), 3.44 (dd, 1H, $J_{5,6} = 10.4$ Hz, $J_{6,7} = 2.0$ Hz, H-6), 3.45 (q, 1H, $J_{gem} = J_{SiCH_2,OCH} = 8.2$ Hz, Me_3Si $CH_2\underline{CH_2}O$), 3.60-4.28 (m, 7H, H-4,5,7,8,9,9', $Me_3CH_2\underline{CH_2}O$), 3.78 (s, 3H, MeO), and 6.50 (d, 1H, $J_{NH,5} = 7.8$ Hz, NH).

Eluant (c) gave compound 4 (290 mg, 18%) as an amorphous mass; $[\alpha]_D$ - 95.0° (c 0.5, Chloroform); IR (KBr) 3400 (OH), 3300 (NH), 1740 and 1250 (ester), 1660 and 1550 (amide), and 860 and 840 cm^{-1} (TMS, Me_2C); ^1H NMR δ 0.88 (m, 2H, $Me_3Si\underline{CH_2}CH_2O$), 1.38 (s, 6H, Me_2C), 1.83 (t, 1H, $J_{gem} = J_{3a,4} = 13.0$ Hz, H-3a), 1.99 (s, 3H, AcN), 2.68 (dd, 1H, $J_{3a,3e} = 13.0$ Hz, $J_{3e,4} = 4.6$ Hz, H-3e), 3.80 (s, 3H, MeO), and 6.34 (d, 1H, $J_{NH,5} = 7.2$ Hz, NH).

Anal. Calcd for $C_{20}H_{37}NO_9Si$: C, 51.81; H, 8.04; N, 3.02. Found for 2: C, 51.73; H, 8.11; N, 3.15; for 3: 51.95; H,8.21; N, 3.05.

Methyl [2-(Trimethylsilyl)ethyl 5-Acetamido-4,7-di-O-acetyl-8,9-O-isopropylidene-D-glycero-α-D-galacto-2-nonulopyranosid]onate (3). A sample of 2 (1.4 g, 3.0 mmol) was acetylated with acetic anhydride (4 mL)-pyridine (8 mL) for 4 h at 50 °C. The product was purified by chromatography on a column of silica gel (100 g) with dichloromethane, and then with 200:1 dichloromethane-methanol. The latter eluant gave compound 3 (1.43 g, 86%). Recrystallization from ether-hexane gave needles: mp 124-125 °C, $[\alpha]_D$ -17° (c 0.2, chloroform); IR (KBr) 3280 (NH), 1750 and 1240 (ester), 1660 and 1560 (amide), and 850 cm^{-1} (TMS, Me_2C); ^1H NMR ($CDCl_3$) δ 0.89 (t, 2H, $J_{gem} = J_{SCH,OCH} = 7.1$ Hz, $Me_3Si\underline{CH_2}CH_2O$), 1.32 1.34 (2s, 6H,

Me_2C), 1.86 (s, 3H, AcN), 1.89 (dd, 1H, $J_{3a,3e}$ = 12.7 Hz, $J_{3a,4}$ = 12.0 Hz, H-3a), 2.02, 2.12 (2s, 6H, 2AcO), 2.59 (dd, 1H, $J_{3e,4}$ = 4.9 Hz, H-3e), 3.42, 3.82 (2q, 2H, J_{gem} = $J_{SiCH,OCH}$ = 7.1 Hz, $Me_3SiCH_2\underline{CH_2}O$), 3.82 (s,3H, MeO), 3.84 (dd, 1H, $J_{5,6}$ = 2.2 Hz, H-6), 3.96 (dd, 1H, $J_{9,9'}$ = 8.3 Hz, $J_{8,9'}$ = 2.7 Hz, H-9'), 3.97 (q, 1H, $J_{4,5}$ = $J_{5,6}$ = $J_{5,NH}$ = 10.0 Hz, H-5), 4.01 (dd, $J_{8,9}$ = 2.7 Hz, $J_{9,9'}$ = 8.3 Hz, H-9), 4.32 (ddd, 1H, $J_{7,8}$ = 3.7 Hz, H-8), 4.88 (ddd, 1H, $J_{3a,4}$ = 12.0 Hz, $J_{3e,4}$ = 4.9 Hz, $J_{4,5}$ = 10.0 Hz, H-4), 5.33 (dd, 1H, $J_{6,7}$ = 2.2 Hz, $J_{7,8}$ = 3.7 Hz, H-7), and 5.39 (d, 1H, $J_{NH,5}$ = 10.0 Hz, NH).

Anal. Calcd for $C_{24}H_{41}NO_{11}Si$: C, 52.63; H, 7.54; N, 2.56. Found: C, 52.89; H, 7.55; N, 2.53.

Methyl [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 (5). A sample of 4 (2.3 g, 5.0 mmol) was acetylated with acetic anhydride (5 mL)-pyridine (10 mL) for 4 h at 60 °C. The product was purified by chromatography on a column of silica gel (100 g) with 100:1 dichloromethane-methanol, to give compound 5 in quantitative yield as an amorphous mass: $[\alpha]_D$ -58.0° (c 0.88, chloroform); IR (KBr) 3280 (NH), 1740 and 1210 (ester), 1660 and 1550 (amide), and 860 and 840 cm^{-1} (TMS, Me_2C); ^1H NMR ($CDCl_3$) δ 0.89 (m, 2H, $Me_3Si\underline{CH_2}CH_2O$), 1.35, 1.41 (2s, 6H, Me_2C), 1.93 (s, 3H, AcN), 2.07, 2.08 (2s, 6H, 2AcO), 2.52 (dd, 1H, $J_{3a,3e}$ = 12.8 Hz, $J_{3e,4}$ = 4.8 Hz, H-3e), 3.59 (dd, 1H, $J_{8,9'}$ = 7.3 Hz, $J_{9,9'}$ = 11.7 Hz, H-9'), 3.77 (s, 3H, MeO), 3.75-3.86 (m, 2H, H-6,7), 3.40, 3.91 (2q, 2H, J_{gem} = $J_{SiCH,OCH}$ = 8.4 Hz, $Me_3SiCH_2\underline{CH_2}O$), 4.00 (dd, 1H, $J_{8,9}$ = 5.1 Hz, $J_{9,9'}$ = 11.7 Hz, H-9), 4.27 (q, 1H, $J_{4,5}$ = $J_{5,NH}$ = 10.3 Hz, H-5), 4.83 (ddd, 1H, $J_{3a,4}$ = 12.1 Hz, $J_{3e,4}$ = 4.8 Hz, $J_{4,5}$ = 10.3 Hz, H-4), 5.15 (m, 1H, H-8), and 5.79 (d, 1H, NH).

Anal. Calcd for $C_{24}H_{41}NO_{11}Si$: C, 52.63; H, 7.54; N, 2.56. Found: C, 52.59; H, 7.63; N, 2.61.

Methyl [2-(Trimethylsilyl)ethyl 5-Acetamido-4,7-di-O-acetyl-3,5-dideoxy-2-nonulopyranosid]onate (6). A solution of 3 (1.0 g, 1.83 mmol) in 70 % aqueous acetic acid (10 mL) was heated for 5 h at 40 °C, and the solvent was evaporated to give a syrup. Crystallization from ether-hexane gave 6 (900 mg, 97%) as needles: mp 139-141 °C, $[\alpha]_D$ -22° (c 0.2, chloroform); IR (KBr) 3470 (OH), 3350 (NH), 1730 and 1250 (ester), 1690 and 1530 (amide), and 860 and 840 cm^{-1} (TMS); ^1H NMR ($CDCl_3$) δ 0.87 (t, 2H, J_{gem} = $J_{SiCH,OCH}$ = 7.3 Hz, $Me_3Si\underline{CH_2}CH_2O$), 1.90 (s, 3H, AcN), 2.03, 2.14 (2s, 6H, 2AcO). 2.66 (dd, 1H, $J_{3a,3e}$ = 12.9 Hz, $J_{3e,4}$ = 4.9 Hz, H-3e), 3.40 (q, 1H, $Me_3SiCH_2\underline{CH_2}O$), 3.61-3.95 (m, 5H, H-6,8,9,9', $Me_3SiCH_2\underline{CH_2}O$), 4.17 (q, 1H, $J_{4,5}$ =

$J_{5,6} = J_{5,NH} = 10.5$ Hz, H-5), 4.81 (ddd, 1H, $J_{3a,4} = 11.7$ Hz, $J_{3e,4} = 4.9$ Hz, $J_{4,5} = 10.5$ Hz, H-4), 5.07 (dd, 1H, $J_{6,7} = 1.0$ Hz, $J_{7,8} = 8.1$ Hz, H-7), and 6.36 (d, 1H, NH).

Anal. Calcd for $C_{21}H_{37}NO_{11}Si$: C, 49.68; H, 7.34; N, 2.76. Found: C, 49.75; H, 7.34; N, 2.89.

Methyl [2-(Trimethylsilyl)ethyl 5-Acetamido-4,7,8-tri-O-acetyl-3,5-dideoxy-α-D-galacto-2-octulopyranosid]onate (7). To a stirred solution of 6 (507 mg, 1.0 mmol) in dry methanol (6 mL) was added sodium metaperiodate (278 mg), and the mixture was stirred for 2 h at room temperature. The precipitates were filtered off, and washed with methanol (3 mL). To the combined solution of the filtrate and washings was added, with stirring, sodium borohydride (50 mg) at 0 °C, and the mixture was stirred for 10 min at 0 °C; after completion of the reaction, acetic acid (0.2 mL) was added to the solution to decompose the reagent and the solution was concentrated. The residue was treated with acetic anhydride (2 mL)-pyridine (5 mL) overnight at room temperature. The mixture was concentrated, and extracted with dichloromethane, and the extract successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and the solvent was evaporated to leave a syrup, which was chromatographed on a column of silica gel (50 g) with dichloromethane and 100:1 dichloromethane-methanol. The latter eluant gave compound 7 (450 mg, 87%) as needles (from ether-hexane): mp 71-72 °C, $[\alpha]_D$ -15.5° (c 0.34, chloroform), IR (KBr) 3370 (NH), 1750 and 1230 (ester), 1660 and 1550 (amide), and 860 and 840 cm^{-1} (TMS): ^1H NMR ($CDCl_3$) δ 0.88 (m, 2H, Me_3SiCH_2), 1.86 (s, 3H, AcN), 1.94 (dd, 1H, $J_{3a,3e} = 12.2$ Hz, $J_{3a,4} = 12.1$ Hz, H-3a), 2.01, 2.04, 2.11 (3s, 9H, 3AcO), 2.59 (dd, 1H, $J_{3e,4} = 4.8$ Hz, H-3e), 3.79 (3H, MeO), 3.41, 3.82 (2ddd, 2H, $J_{gem} = 7.0$ Hz, $J_{SiCH,OCH} = 8.8$ Hz, $Me_3SiCH_2\underline{CH_2}O$), 3.89 (dd, 1H, $J_{5,6} = 10.3$ Hz, $J_{6,7} = 2.2$ Hz, H-6), 4.07 (dd, 1H, $J_{8,8'} = 11.7$ Hz, $J_{7,8'} = 7.7$ Hz, H-8'), 4.15 (q, 1H, $J_{4,5} = J_{5,6} = J_{5,NH} = 10.3$ Hz, H-5), 4.51 (dd, 1H, $J_{7,8} = 5.1$ Hz, H-8), 4.84 (ddd, 1H, $J_{3a,4} = 12.1$ Hz, $J_{3e,4} = 4.8$ Hz, H-4), 5.26 (ddd, 1H, H-7), and 5.41 (d, 1H, NH).

Anal. Calcd for $C_{22}H_{37}NO_{11}Si$: C, 50.85; H, 7.17; N, 2.70. Found: C, 50.63; H, 7.25; N, 2.70.

Methyl [2-(Trimethylsilyl)ethyl 5-Acetamido-3,5-dideoxy-α-D-galacto-2-octulopyranosid]onate (8). To a solution of 7 (600 mg, 1.2 mmol) in dry methanol (20 mL) was added sodium methoxide (30 mg), and the mixture was stirred for 1 h at room temperature, and then treated with Amberlite IR-120 (H^+) resin to remove the base. The solvent was evaporated to give compound 8 in quantitative yield. Recrystallization from ether-hexane

gave needles: mp 202-203 °C, $[\alpha]_D$ -12.5° (c 0.21, chloroform); IR (KBr) 3430 (OH), 3300 (NH), 1750 and 1230 (ester), 1630 and 1590 (amide), and 870 and 840 cm^{-1} (TMS); ^1H NMR (1:1 $CDCl_3$-CD_3OD) δ 0.85 (t, $J_{gem} = J_{SiCH, OCH} = 8.1$ Hz, $Me_3SiCH_2CH_2O$), 1.69 (dd, 1H, $J_{3a,3e} = 12.8$ Hz, $J_{3a,4} = 12.1$ Hz, H-3a), 1.99 (s, 3H, AcN), 3.37 (dd, $J_{3a,3e} = 12.8$ Hz, $J_{3e,4} = 4.8$ Hz, H-3e), 3.40, 3.86 (2q, 2H, $J_{gem} = J_{SiCH,OCH} = 8.1$ Hz, $Me_3SiCH_2CH_2O$), 3.55 (ddd, 1H, $J_{4,5} = 10.3$ Hz, H-4), 3.64 (ddd, 1H, $J_{6,7} = 1.5$ Hz, $J_{7,8} = J_{7,8'} = 4.8$ Hz, H-7), 3.70 (m, 2H, H-8,8'), 3.71 (t, 1H, $J_{4,5} = J_{5,6} = 10.3$ Hz, H-5), and 3.79 (s, 3H, MeO).

Anal. Calcd for $C_{16}H_{31}NO_8Si$: C, 48.83; H, 7.94; N, 3.56. Found: C, 48.92; H, 7.95; N, 3.54.

Methyl [2-(Trimethylsilyl)ethyl 5-Acetamido-4,7-di-O-acetyl-8-bromo-3,5,8-trideoxy-α-D-galacto-2-octulopyranosid]onate (10). To a solution of 8 (130 mg, 0.3 mmol) in N,N-dimethylformamide (2 mL) were added, with stirring N-bromosuccinimide (89 mg) and triphenylphosphine (132 mg) at 0 °C, and the mixture was stirred for 1.5 h at 50 °C. Methanol (1 mL) was added to the mixture, and the mixture was then concentrated. The residue was chromatographed on a column of silica gel (20 g) with (a) dichloromethane, (b) 150:1, and (c) 50:1 dichloromethane-methanol. Eluant (c) gave 9 as a syrup, which was acetylated with acetic anhydride (0.2 mL)-pyridine (1 mL) overnight at room temperature. The product was purified by chromatography on a column of silica gel (20 g) with 150:1 dichloromethane-methanol to give compound 10 (152 mg, 85%) as a syrup: $[\alpha]_D$ -16.5° (c 0.2, chloroform): IR (film) 3300 (NH), 1750 and 1230 (ester), 1660 and 1550 (amide), and 860 and 840 cm^{-1} (TMS); ^1H NMR ($CDCl_3$) δ 0.87 (m, 2H, $Me_3SiCH_2CH_2O$), 1.90 (s, 3H, AcN), 2.04, 2.14 (2s, 6H, 2AcO), 2.63 (dd, 1H, $J_{3a,3e} = 12.5$ Hz, $J_{3e,4} = 4.8$ Hz, H-3e), 3.84 (s, 3H, MeO), 4.01 (dd, 1H, $J_{5,6} = 9.9$ Hz, $J_{6,7} = 1.8$ Hz, H-6), 4.12 (q, 1H, $J_{4,5} = J_{5,6} = J_{5,NH} = 9.9$ Hz, H-5), 4.94 (ddd, 1H, $J_{3a,4} = 12.1$ Hz, H-4), 5.05 (ddd, 1H, $J_{6,7} = 1.8$ Hz, $J_{7,8} = 7.3$ Hz, $J_{7,8'} = 8.8$ Hz, H-7), 5.34 (d, 1H, NH).

Anal. Calcd for $C_{20}H_{34}NO_9BrSi$: C, 44.44; H, 6.34; N, 2.59. Found: C, 44.51; H, 6.49; N, 2.48.

Methyl [2-(Trimethylsilyl)ethyl 5-Acetamido-8-bromo-3,5,8-trideoxy-4,7-di-O-2-(trimethylsilyl)ethoxymethyl-α-D-galacto-2-octulopyranosid]onate (11). To a stirred solution of 9 (70 mg, 0.15 mmol) in dry dichloromethane were added 2-(trimethylsilyl)ethoxymethyl chloride (0.3 mL) and N,N-diisopropylethylamine (0.6 mL), and the mixture was heated, with stirring, overnight at 45 °C under a nitrogen atmosphere; the course of the reaction being monitored by TLC. Methanol (0.5 mL) was added to the solution, and the

mixture was heated for 30 min at 45 °C, and concentrated to a syrup which was extracted with dichloromethane. The extract was successively washed with 2M hydrochloric acid, M. sodium carbonate, and water, dried (sodium sulfate), and concentrated to a syrup, which was chromatographed on a column of silica gel (10 g) using dichloromethane and then 100:1 dichloromethane-methanol as the eluants. The latter eluant gave compound 11 (90 mg, 82%) as a syrup: $[\alpha]_D$ +10.0° (c 0.9, chloroform); IR (film) 3280 (NH), 1750 and 1230 (ester), 1650 and 1550 (amide), and 860 and 840 cm^{-1} (TMS); ^1H NMR ($CDCl_3$) δ 0.81-0.95 (m, 6H, $3Me_3Si\underline{CH_2}CH_2O$), 1.69 (dd, 1H, $J_{3a,3e}$ = 12.5 Hz, $J_{3a,4}$ = 12.8 Hz, H-3a), 1.93 (s, 3H, AcN), 2.69 (dd, 1H, $J_{3e,4}$ = 4.4 Hz, H-3e), 2.87-3.43 (m, 11H, H-4,5,7,8,8', $3Me_3SiCH_2\underline{CH_2}O$), 4.02 (d, 1H, $J_{5,6}$ = 10.3 Hz, H-6), 4.60, 4.66, 4.73, 4.79 (4d, 4H, $2OCH_2O$), 5.69 (d, 1H, $J_{NH,5}$ = 8.1 Hz, NH).

Anal. Calcd for $C_{28}H_{52}NO_9BrSi$: C, 46.91; H, 8.15; N, 1.95. Found: C, 46.99; H, 8.30; N, 1.85.

Methyl 5-Acetamido-4,7,8-tri-O-acetyl-3,5-dideoxy-ß-D-galacto-2-octulopyranosonate (12). To a solution of 7 (400 mg, 0.77 mmol) in acetonitrile (7 mL) was added boron trifluoride etherate (0.2 mL), and the mixture was stirred for 1.5 h at room temperature, and then dichloromethane (50 mL) was added. The solution was washed with water, dried (sodium sulfate), and concentrated to leave a solid. Recrystallization from ether gave compound 12 in quantitative yield: mp 165-167 °C, $[\alpha]_D$ -0.1° (c 0.5, chloroform, equil); IR (KBr)3370 (OH), 3280 (NH), 1750 and 1230 (ester), and 1670 and 1550 cm^{-1} (amide); ^1H NMR ($CDCl_3$) δ 1.91 (s, 3H, AcN), 2.03, 2.04, 2.14 (3s, 9H, 3AcO), 3.87 (s, 3H, MeO), 4.08 (dd, 1H, $J_{7,8'}$ = 7.6 Hz, $J_{8,8'}$ = 11.7 Hz, H-8'), 4.15 (dd, 1H, $J_{5,6}$ = 10.5 Hz, $J_{6,7}$ = 1.5 Hz, H-6), 4.25 (q, 1H, $J_{4,5} = J_{5,6} = J_{5,NH}$ = 10.5 Hz, H-5), 4.34 (dd, 1H, $J_{7,8}$ = 4.4 Hz, H-8), 5.25 (ddd, 1H, $J_{3a,4}$ = 11.7 Hz, $J_{3e,4}$ = 5.1 Hz, $J_{4,5}$ = 10.5 Hz, H-4), 5.30 (ddd, 1H, H-7), and 5.83 (d, 1H, NH).

Anal. Calcd for $C_{17}H_{25}NO_{11}$: C, 48.68; H, 6.00; N, 3.34. Found: C, 48.73; H, 6.05; N, 3.33.

Methyl 5-Acetamido-4,7,8-tri-O-acetyl-2-S-acetyl-3,5-dideoxy-2-thio-α-D-galacto-2-octulopyranosonate (14). Compound 12 (290 mg, 0.69 mmol) was dissolved in dry dichloromethane (5 mL), and hydrogen chloride was bubbled through for 10 min at -20 °C, and the solution was kept for 24 h at room temperature. The mixture was concentrated to leave a syrup of compound 13, which was dissolved in dichloromethane (3 mL) and acetone (2 mL). Potassium thioacetate (300 mg) and Drierite (500 mg) were added to the solution, and the mixture was stirred for 4 h at room temperature;

the course of the reaction being monitored by TLC. The mixture was filtered on celite 545 pad and washed with dichloromethane. The filtrate and vashings were combined, and concentrated. The residue was chromatographed on a column of silica gel (30 g) with 2:1 and 1:1 hexane-ethyl acetate. The latter eluant gave compound 14 (275 mg, 83%) as a syrup: $[\alpha]_D$ +50.5° (c 2.7, chloroform); IR (film) 3300 (NH), 1740 and 1240 (ester), 1690 (S-acetyl), and 1660 and 1550 cm^{-1} (amide); ^1H NMR ($CDCl_3$) δ 1.94 (s, 3H, AcN), 2.05, 2.09, 2.10 (3s, 9H, 3AcO), 2.30 (s, 3H, AcS), 2.74 (dd, 1H, $J_{3a,3e}$ = 12.8 Hz, $J_{3e,4}$ = 4.8 Hz, H-3e), 3.82 (s, 3H, MeO), 4.10 (dd, $J_{7,8'}$ = 8.3 Hz, $J_{8,8'}$ = 11.7 Hz, H-8'), 4.25 (q, 1H, $J_{4,5}$ = $J_{5,6}$ = $J_{5,NH}$ = 10.6 Hz, H-5), 4.39 (dd, 1H, $J_{6,7}$ = 2.2 Hz, H-6), 4.47 (dd, $J_{7,8}$ = 4.2 Hz, H-8), 4.96 (ddd, 1H, $J_{3a,4}$ = 11.4 Hz, H-4), 5.32 (m, 1H, H-7), and 6.07 (d, 1H, NH).

Anal. Calcd for $C_{19}H_{27}NO_{11}S$: C, 47.79; H, 5.69; N, 2.93. Found: C, 47.90; H, 5.73; N, 2.89.

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