

Functionalization of 2-Deoxy-2,3-dehydro-*N*-acetylneuraminic Acid Methyl Ester¹⁾

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(Received July 3, 1986)

The acetyl protected 2-deoxy-2,3-dehydroneuraminic acid methyl ester was functionalized by modifying its 2,3-double bond to convert it into new glycosyl donors such as 2,3-dibromo-, 2,3-epoxy-, and 2-halo-3-hydroxyneuraminic acid derivatives.

In the glycosylation of *N*-acetylneuraminic acid (NeuAc), most reactions have so far been carried out by use of 2-chloro derivative of the pentaacetylated neuraminic acid methyl ester **1** first prepared by Kuhn et al.²⁾ The largest problem in these reactions is that the main product is the 2-deoxy-2,3-dehydro-NeuAc derivative **2**³⁾ generated by the competitive elimination of hydrogen chloride when the reactivity of the glycosyl acceptor is low. As it was difficult to prevent the elimination of hydrogen chloride in the 2-chloro derivative **1**, we have tried to utilize **2** having the 2,3-double bond to prepare new and useful glycosyl donors. The paucity of reports on reactivity of the 2,3-dehydro compound **2** prompted us to investigate it. We report here some functionalizations of **2**, which was easily prepared in 81% yield by treatment of **1** with DBU in benzene and by crystallization from hexane-ethyl acetate.

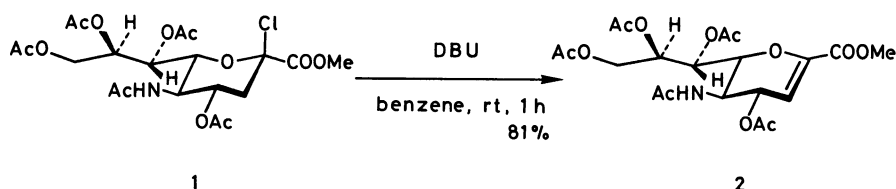
Reactivity of the 2,3-Double Bond of 2. First we carried out bromination of **2** by treatment with bromine in dichloromethane or by electrochemical oxidation of sodium bromide⁴⁾ in acetonitrile–water (Pt–Pt electrodes) to give the 2 β ,3 α -dibromide **3a**⁵⁾ as white crystals in 93 or 98% yield, respectively (Table 1, Entries 1, 2). In ¹H NMR spectrum the $J_{3eq,4}$ coupling constant of **3a** is 3.4 Hz, indicating that the configuration of the bromo groups is trans diaxial. The dibromide **3a** is a useful glycosyl donor for the glycosylation since the 3-axial position is blocked by the bromo group to prevent the elimination reaction.⁵⁾

Treatment of **2** with *N*-bromosuccinimide (NBS) in acetonitrile–water at 20 °C gave in 98% yield two bromohydrins which were separated by silica-gel column chromatography (Entry 3). The more mobile isomer was adduct **4b** having a trans diequatorial bromine

(59% yield), and the slower was trans diaxial adduct **3b** (39% yield), which showed 11.0 and 3.7 Hz of $J_{3,4}$ coupling constant, respectively, in ¹H NMR spectra. Interestingly in this bromohydration, the product ratio was variable according to the reaction temperature. Thus, at a low temperature (–20 °C) the diequatorial adduct **4b** was obtained predominantly (dimethyl sulfoxide was used as the solvent since the reaction was very slow when acetonitrile was used), whereas at a high temperature (60–80 °C) the thermodynamically more stable diaxial isomer **3b** was formed in preference to **4b** (Entries 4, 5, 6). The use of *N*-iodosuccinimide (NIS) instead of NBS gave similar results but no adduct was obtained with *N*-chlorosuccinimide (NCS) (Entries 7, 8, 9).

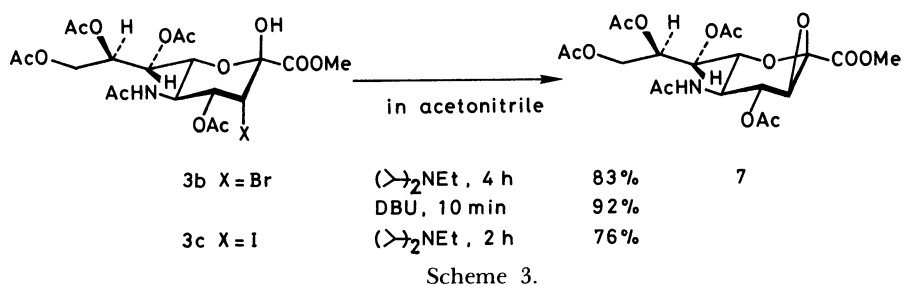
Bromoacetoxylation of **2** was effective with NBS–sodium acetate–acetic acid system to give **3d** (41% yield) and **4d** (41% yield) (Entry 10). Without sodium acetate this reaction required a longer reaction time. Similar result was obtained in iodoacetoxylation of **2** except the ratio of yields of **3e** (80%) and **4e** (11%) (Entry 11). Chloroacetoxylation of **2** did not proceed similarly to the above chlorohydrin reaction (Entry 12). Treatment of **2** with NBS or 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one (TBCD) in methanol gave in quantitative yield a mixture of methyl 3-bromo glycosides **3f** and **4f** (Entries 13, 14), which was separated and the both glycosides were debrominated with tributylstannane to give methyl β -glycoside **5**⁶⁾ (**3**: X=H, Y=OMe) and α -glycoside **6**⁶⁾ (**4**: X=H, Y=OMe) in 96% yield. Iodomethoxylation was failed owing to decomposition of NIS with methanol (Entry 15). Attempts of haloglycosylation of **2** with NXS (X=Br, I)-sugar derivative combinations⁷⁾ were unsuccessful.

Conversion of 3b and 3c to Glycosyl Donors 7 and 8a–c. Since direct epoxidation of **2** with various peroxides was unsuccessful, we have examined conversion of **3b** and **3c** to the epoxide **7**. Treatment of the

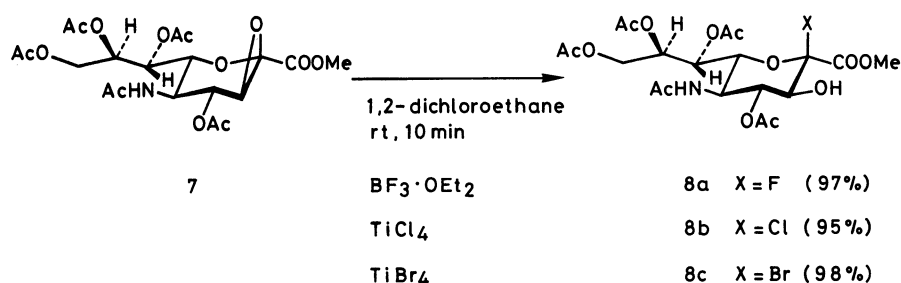


Scheme 1.

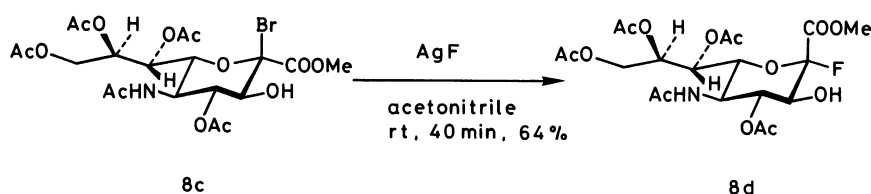
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Scheme 3.



Scheme 4.



Scheme 5.

bromohydrin **3b** with *N,N*-diisopropylethylamine in anhydrous acetonitrile for 4 h gave the β -epoxide **7** as white crystals in 83% yield (Scheme 3). As some decomposition products were detected during the period of the reaction, **3b** was treated with DBU for 10 min to afford **7** in 92% yield. Similarly, the iodohydrin **3c** was converted with *N,N*-diisopropylethylamine to the epoxide **7** in 76% yield. In ^1H NMR spectrum of the epoxide **7**, the $J_{3,4}$ coupling constant was 0 Hz, and in mass (FAB) spectrum of **7**, molecular ion m/z 490 ($\text{M}+1$) was observed. On the other hand the diequatorial bromohydrins **4b** and **4c** were unreactive to the above epoxidation conditions.

We found that the epoxide **7** was very sensitive to the Lewis acids such as boron trifluoride-ether complex, titanium(IV) chloride, and titanium(IV) bromide. When the epoxide **7** was treated with boron trifluoride-ether complex in 1,2-dichloroethane, a single product was obtained. The vicinal coupling constant between H-3_{ax} and fluoro group of the product was 22.6 Hz in ¹H NMR spectrum and the molecular ion *m/z* 510 was observed in mass (FAB) spectrum. From these data structure of the product was deduced as the fluorohydrin **8a** shown in Scheme 4. The treatment of **7** with titanium(IV) chloride or titanium(IV) bromide in 1,2-dichloroethane gave the 2-chloro compound **8b** or 2-bromo compound **8c** quantitatively. As the ques-

tion still remained in the configuration of the anomeric position of **8b** and **8c**, the bromo derivative **8c** was treated with silver fluoride in acetonitrile to give the fluoride **8d** in concomitance with the epoxide **7**. The $J_{3\text{ax},\text{F}}$ coupling constant of **8d** was 15.0 Hz and this value agreed with α configuration⁸⁾ of the fluorine atom, different from the β isomer **8a**.

The epoxide **7**, fluoride **8a**, chloride **8b**, and bromide **8c** are well-suited to be the glycosyl donors for the glycosylation reaction, since these derivatives are no longer the deoxysugar at **3** position and the competitive elimination reaction is suppressed.⁹⁾

Experimental

General. Melting points were taken on a Mitamura Riken flat-bulb thermometer with a heating metal block and uncorrected. Elemental analyses were done on a Perkin-Elmer 240C elemental analyzer. Nuclear magnetic resonance spectra (NMR) were obtained with a JEOL GX-500 instrument in the FT mode. Chemical shifts were expressed in parts per million from internal tetramethylsilane (δ). Coupling constants are in hertz(Hz) and splitting pattern abbreviations are: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of double doublets; br, broad. Mass spectra (MS) were obtained on a JEOL DX-300 spectrometer. Infrared spectra (IR) were recorded on a JASCO A-3 spectrophotometer. Optical rotations $[\alpha]_D$ were recorded on a JASCO DIP-181 digital polarimeter.

Table 2. ¹H NMR Data of **2–8d** in Chloroform-*d*

Com- pound	Chemical shifts, δ (multiplicity)														Aglycon (s)
	H-3eq (d)	H-3ax (d)	H-4 (dd)	H-5 (ddd)	H-6 (dd)	H-7 (dd)	H-8 (ddd)	H-9 (dd)	H-9' (dd)	Me ester (s)	NH (d)	OH-2 (br.s)	OH-3 (d)	O-Ac, N-Ac (s)	
2 ^{a)}		6.00	5.52	4.38	4.41	5.51	5.37	4.20	4.60	3.81	5.55			1.94, 2.06, 2.07, 2.08, 2.13	
3a	5.05		5.77	4.51	4.46	5.42	5.25	4.15	4.45	3.91	5.54			1.96, 2.06, 2.09, 2.11, 2.16	
3b	4.62		5.44	4.42	4.38	5.35	5.29	4.15	4.89	3.82	6.03	5.92		1.93, 2.04, 2.08, 2.09, 2.19	
3c	4.71		4.80	4.32	4.42	5.33	5.28	4.15	4.96	3.82	6.13	5.92		1.93, 2.04, 2.07, 2.09, 2.20	
3d	4.65		5.65	4.09	4.32	5.33	5.13	4.22	4.58	3.83	5.63			1.94, 2.04, 2.04, 2.11, 2.19, 2.20	
3e	4.75		5.02	4.01	4.33	5.32	5.13	4.23	4.58	3.83	5.70			1.95, 2.03, 2.04, 2.11, 2.19, 2.21	
3f	4.61		5.47	4.37	4.09	5.36	5.29	4.19	4.87	3.84	5.43			1.91, 2.04, 2.08, 2.08, 2.18	3.30
4b		4.36	5.32	4.32	4.30	5.33	5.20	3.99	4.38	3.94	5.93	5.06		1.89, 2.03, 2.08, 2.09, 2.14	
4c		4.40	5.34	4.31	4.33	5.33	5.19	4.00	4.37	3.93	6.13	5.21		1.89, 2.02, 2.09, 2.10, 2.14	
4d		4.10	5.29	4.33	5.25	5.39	5.11	4.04	4.37	3.79	6.00			1.90, 2.04, 2.09, 2.10, 2.12, 2.15	
4e		4.19	5.27	4.29	5.22	5.38	5.11	4.04	4.37	3.80	6.01			1.89, 2.04, 2.08, 2.11, 2.12, 2.14	
4f		3.98	5.49	4.27	4.65	5.26	5.35	4.05	4.24	3.85	5.44			1.91, 2.03, 2.07, 2.08, 2.14	3.54
5	2.44 ^{b)}	1.89 ^{b)}	5.26	4.13	3.93	5.41	5.22	4.13	4.80	3.82	5.42			1.88, 2.02, 2.03, 2.08, 2.15	3.27
6	2.57 ^{b)}	1.94 ^{b)}	4.86	4.07	4.13	5.33	5.43	4.11	4.32	3.82	5.14			1.89, 2.03, 2.04, 2.14, 2.15	3.32
7		3.61	5.21	4.27	4.08	5.42	5.28	4.17	4.55	3.85	5.69			1.91, 2.05, 2.08, 2.12, 2.13	
8a		4.18 ^{c)}	5.22	4.31	4.34	5.38	5.20	4.04	4.36	3.89	6.19	3.82		1.88, 2.05, 2.08, 2.09, 2.14	
8b		4.18 ^{b)}	5.22	4.32	4.38	5.44	5.16	4.03	4.40	3.91	5.66	3.39		1.90, 2.06, 2.10, 2.10, 2.13	
8c		3.83 ^{b)}	5.24	4.37	4.34	5.46	5.16	4.04	4.42	3.92	5.83	3.65		1.90, 2.07, 2.10, 2.12, 2.13	
8d		3.99 ^{c)}	5.38	4.33	4.46	5.29	5.31	4.09	4.34	3.86	6.17	4.20		1.90, 2.03, 2.05, 2.11, 2.14	

First-order coupling constants, Hz													
Compound	$J_{3eq,3ax}$	$J_{3eq,4}$	$J_{3ax,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,NH}$	$J_{6,7}$	$J_{7,8}$	$J_{8,9}$	$J_{8,9'}$	$J_{9,9'}$	$J_{OH,3ax}$	$J_{3ax,F}$
2			3.4	7.0	8.9	8.8	3.5	4.3	7.0	3.2	−12.5		
3a		3.4		10.0	10.7	9.9	1.8	7.0	5.5	2.8	−12.5		
3b		3.7		10.1	10.2	8.9	1.5	3.6	8.2	2.2	−12.5		
3c		4.0		10.1	10.4	9.5	1.8	2.0	8.6	2.3	−12.2		
3d		3.8		9.4	10.7	8.5	1.8	5.6	6.4	2.1	−12.5		
3e		4.0		10.4	10.7	8.6	1.8	5.5	6.4	2.4	−12.5		
3f		3.7		10.4	10.7	10.1	1.8	4.3	7.5	2.4	−12.5		
4b			11.0	10.7	10.0	9.5	1.8	6.9	7.0	2.4	−12.5		
4c			11.0	9.5	10.0	9.5	2.1	7.0	7.0	2.6	−12.5		
4d			10.1	10.4	11.0	10.4	2.5	6.1	6.1	2.4	−12.5		
4e			11.3	10.1	11.0	10.4	2.4	6.1	6.1	2.4	−12.5		
4f			10.7	10.4	10.8	10.4	2.1	8.5	6.1	2.2	−12.5		
5	−12.8	5.0	12.5	10.6	10.5	9.3	2.3	2.1	7.6	2.4	−12.5		
6	−12.8	4.6	12.5	10.1	10.2	9.8	2.1	8.5	5.5	2.7	−12.5		
7			0	7.6	8.5	10.1	3.7	4.9	7.0	2.8	−12.5		
8a			9.5	9.3	9.7	8.8	1.8	6.7	6.4	2.5	−12.5	7.9	−22.6
8b			9.5	9.5	9.7	10.1	2.2	7.3	5.8	2.7	−12.5	4.6	
8c			9.2	9.5	9.0	9.5	1.8	7.0	5.8	2.4	−12.5	3.4	
8d			8.9	9.8	10.7	10.1	1.0	7.5	5.8	2.0	−12.2	6.1	−15.0

a) Measured at 40°C. b) Multiplicity: dd. c) Multiplicity: ddd.

Analytical thin-layer chromatography (TLC) was conducted on precoated TLC glass sheets (silica gel 60F-254, layer thickness 0.25 mm) manufactured by E. Merck. Detection was effected with 2% concentrated sulfuric acid in ethanol.

¹H NMR data were summarized in Table 2 and MS, elemental analyses, mp, *R*_f, [α]_D, and IR data in Table 3.

Methyl 5-Acetamido-4,7,8,9-tetra-O-acetyl-2,3,5-trideoxy-D-glycero-D-galacto-non-2-enopyranosonate (2). Compound **1** (7.7 g, 15.1 mmol), freshly prepared by Kuhn's method,²⁾ was dissolved in dry benzene (70 ml). After addition of DBU (2.7 ml, 18.1 mmol), the mixture was stirred for 1 h at room temperature under argon atmosphere, washed with water and brine, dried over anhydrous Na₂SO₄, and evaporated in vacuo to give a crude material, which was chromatographed on a silica-gel column (benzene–acetone, 3:2) to give a syrup. This syrup was crystallized from hexane–ethyl acetate to give **2** (5.8 g, 81%) as white needles.

Methyl 5-Acetamido-4,7,8,9-tetra-O-acetyl-2,3-dibromo-2,3,5-trideoxy- β -D-erythro-L-manno-2-nonulopyranosonate (3a).

Method A. To a solution of **2** (280 mg, 0.59 mmol) in dichloromethane (5 ml) was added bromine (0.04 ml, 0.78 mmol) at 0°C under argon atmosphere. After stirring for 10 min, the mixture was evaporated in vacuo to give a syrup, which was crystallized from hexane–ethyl acetate to give **3a** (350 mg, 93%) as white needles.

Method B. A mixture of **2** (50 mg, 0.11 mmol) and sodium bromide (250 mg, 2.4 mmol) in acetonitrile (8 ml)–water (2 ml) was electrolyzed with platinum electrodes (1×2 cm²) 5 mm apart under a constant current density of 5 mA cm^{−2} for 2 h. The mixture was evaporated to dryness and the residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and evaporated in vacuo to give a crude material, which was treated in a similar manner as above.

Reaction of 2 with NXS (X=Br, I) in Acetonitrile (or Dimethyl Sulfoxide)–Water. To a solution of **2** (200 mg, 0.42 mmol) in acetonitrile (or dimethyl sulfoxide) (2 ml)–water (0.8 ml) was added NXS (0.48 mmol) at the temperature shown in Table 1. The mixture was stirred for 0.2–8 h

Table 3. MS, Elemental Analyses, Mp, R_f , $[\alpha]_D$, and IR Data of **2–8d**

Compound	Formula	MS ^{a)} (M+H)	Anal.			Mp ^{b)} $\theta_m/^\circ\text{C}$	R_f ^{c)}	$[\alpha]_D^{21d)}$ (c)	$\nu_{\text{max}}^{\text{KBr}}$			
			C(%)	H(%)	N(%)				NH, OH	ester	amide I	amide II
2	C ₂₀ H ₂₇ NO ₁₂	474	Calcd 50.74 Found 50.84	5.75 5.46	2.96 2.76	126—127	0.46	+79.9°(1.3)	3270	1738	1645	1565
3a	C ₂₀ H ₂₇ NO ₁₂ Br ₂	634	Calcd 37.93 Found 37.84	4.30 4.23	2.21 2.06	156—157	0.52	−57.7°(1.1)	3400	1753	1649	1560
3b	C ₂₀ H ₂₈ NO ₁₃ Br	570, 572	Calcd 42.12 Found 42.36	4.95 4.81	2.45 2.68	118—120	0.36	+38.7°(1.1)	3380	1742	1640	1522
3c	C ₂₀ H ₂₈ NO ₁₃ I	618	Calcd 38.91 Found 39.02	4.57 4.45	2.27 2.24	168—170	0.37	+66.5°(1.1)	3310	1745	1658	1555
3d	C ₂₂ H ₃₀ NO ₁₄ Br	612, 614	Calcd 43.15 Found 43.22	4.94 4.69	2.29 2.17	— ^{e)}	0.44	+2.9°(1.6)	3380	1743	1660	1540
3e	C ₂₂ H ₃₀ NO ₁₄ I	660	Calcd 40.07 Found 40.07	4.59 4.46	2.12 1.99	81—83	0.44	+12.1°(1.4)	3380	1740	1662	1538
3f	C ₂₁ H ₃₀ NO ₁₃ Br	584, 586	Calcd 43.16 Found 43.07	5.18 5.03	2.40 2.25	186—187	0.49	+35.7°(1.5)	3420	1748	1662	1565
4b	C ₂₀ H ₂₈ NO ₁₃ Br	570, 572	Calcd 42.12 Found 42.29	4.95 4.92	2.45 2.94	— ^{e)}	0.48	−41.6°(1.5)	3370	1746	1660	1540
4c	C ₂₀ H ₂₈ NO ₁₃ I	618	Calcd 38.91 Found 39.21	4.57 4.47	2.27 2.02	— ^{e)}	0.48	−56.4°(1.3)	3370	1745	1660	1540
4d	C ₂₂ H ₃₀ NO ₁₄ Br	612, 614	Calcd 43.15 Found 43.26	4.94 4.81	2.29 2.34	95—96	0.55	−38.5°(1.3)	3380	1745	1660	1540
4e	C ₂₂ H ₃₀ NO ₁₄ I	660	Calcd 40.07 Found 40.34	4.59 4.56	2.12 2.00	86—88	0.56	−51.9°(0.9)	3430	1745	1660	1538
4f	C ₂₁ H ₃₀ NO ₁₃ Br	584, 586	Calcd 43.16 Found 43.51	5.18 5.28	2.40 2.34	158—159	0.54	−69.6°(2.0)	3420	1748	1655	1540
5	C ₂₁ H ₃₁ NO ₁₃	506	Calcd 49.90 Found 50.14	6.18 6.38	2.77 2.76	— ^{e)}	0.43	−14.7°(1.5)	3400	1741	1660	1540
6	C ₂₁ H ₃₁ NO ₁₃	506	Calcd 49.90 Found 49.92	6.18 6.11	2.77 2.68	87—89	0.43	−23.7°(1.1)	3420	1742	1660	1540
7	C ₂₀ H ₂₇ NO ₁₃	490	Calcd 49.08 Found 48.97	5.56 5.55	2.86 2.89	177—178	0.46	−10.0°(1.3)	3420	1740	1650	1572
8a	C ₂₀ H ₂₈ NO ₁₃ F	510	Calcd 47.15 Found 47.48	5.54 5.43	2.75 2.86	— ^{e)}	0.26	−37.3°(0.7)	3400	1745	1660	1540
8b	C ₂₀ H ₂₈ NO ₁₃ Cl	526, 528	Calcd 45.68 Found 45.79	5.37 5.09	2.66 2.51	— ^{e)}	0.30	−66.0°(0.9)	3420	1742	1658	1540
8c	C ₂₀ H ₂₈ NO ₁₃ Br	570, 572	Calcd 42.12 Found 42.01	4.95 4.88	2.46 2.22	— ^{e)}	0.35	−91.1°(0.6)	3420	1742	1660	1540
8d	C ₂₀ H ₂₈ NO ₁₃ F	510	Calcd 47.15 Found 47.15	5.54 5.79	2.75 2.64	— ^{e)}	0.28	−26.9°(0.8)	3410	1742	1660	1540

a) Fast atom bombardment method. b) Recrystallized from hexane-ethyl acetate. c) Solvent system is benzene-acetone (3:2). d) Measured in chloroform. e) Viscous syrup.

and dried up, and the residue was chromatographed on a silica-gel column (benzene-acetone, gradient elution from 3:1 to 3:2). The fast migrating zone was a 2,3-diequatorial isomer, methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3-bromo-3,5-dideoxy- α -D-erythro-L-glucopyranosonate (**4b**) or methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-3-iodo- α -D-erythro-L-glucopyranosonate (**4c**), as a syrup and the slower migrating zone was a 2,3-diaxial isomer, methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3-bromo-3,5-dideoxy- β -D-erythro-L-manno-2-nonulopyranosonate (**3b**) or methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-3-iodo- β -D-erythro-L-manno-2-nonulopyranosonate (**3c**), which was recrystallized from hexane-ethyl acetate.

Reaction of 2 with NXS (X=Br, I) in Sodium Acetate-Acetic Acid. A solution of **2** (200 mg, 0.42 mmol), NXS (0.48 mmol), and sodium acetate (200 mg) in glacial acetic acid (2 ml) was stirred for 1–1.5 h at 20°C under argon atmosphere. After evaporation, the residue was partitioned between ethyl acetate and water. The organic layer was washed with 5% NaHCO₃, water, and brine, dried over anhydrous Na₂SO₄, and evaporated in vacuo to give a crude material, which was chromatographed on a silica-gel column (benzene-acetone, gradient elution from 3:1 to 2:1). The

fast migrating zone was a 2,3-diequatorial isomer, methyl 5-acetamido-2,4,7,8,9-penta-*O*-acetyl-3-bromo-3,5-dideoxy- α -D-erythro-L-glucopyranosonate (**4d**) or methyl 5-acetamido-2,4,7,8,9-penta-*O*-acetyl-3,5-dideoxy-3-iodo- α -D-erythro-L-glucopyranosonate (**4e**), as a syrup and the slower migrating zone was a 2,3-diaxial isomer, methyl 5-acetamido-2,4,7,8,9-penta-*O*-acetyl-3-bromo-3,5-dideoxy- β -D-erythro-L-manno-2-nonulopyranosonate (**3d**) or methyl 5-acetamido-2,4,7,8,9-penta-*O*-acetyl-3,5-dideoxy-3-iodo- β -D-erythro-L-manno-2-nonulopyranosonate (**3e**), which was recrystallized from hexane-ethyl acetate.

Reaction of 2 with NBS or 2,4,4,6-Tetrabromo-2,5-cyclohexadien-1-one (TBCD) in Methanol. To a stirred solution of **2** (100 mg, 0.21 mmol) in absolute methanol (1.5 ml) was added NBS or TBCD (0.23 mmol) at 20°C under argon atmosphere. The mixture was stirred for 0.2–2.0 h and evaporated in vacuo to give a residue. The residue was dissolved in ethyl acetate and the solution was washed with water and brine, dried over anhydrous Na₂SO₄, and evaporated in vacuo to give a syrup, which was chromatographed on a silica-gel column (benzene-acetone, 2:1). The fast migrating zone was a 2,3-diequatorial isomer, methyl (methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3-bromo-3,5-di-

deoxy- α -D-erythro-L-glucopyranosid)onate (**4f**) and the slower migrating zone was a 2,3-diaxial isomer, methyl (methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3-bromo-3,5-dideoxy- β -D-erythro-L-manno-2-nonulopyranosid)onate (**3f**), which was recrystallized from hexane-ethyl acetate.

Methyl (Methyl 5-Acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy- β -D-glycero-D-galacto-2-nonulopyranosid)onate (5). To a solution of **3f** (30 mg, 0.05 mmol) in anhydrous tetrahydrofuran (0.6 ml) was added tributylstannane (0.034 ml, 0.13 mmol). The mixture was heated for 2 h at 60 °C with stirring under argon atmosphere and evaporated in vacuo to give a syrup, which was chromatographed on a silica-gel column (benzene-acetone, 3:2) to give **5** (25 mg, 96%) as a syrup.

Methyl (Methyl 5-Acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy- α -glycero-D-galacto-2-nonulopyranosid)onate (6). To a solution of **4f** (48 mg, 0.08 mmol) in anhydrous tetrahydrofuran (1 ml) was added tributylstannane (0.05 ml, 0.19 mmol). The mixture was worked up in a similar manner as **3f** and recrystallized from hexane-ethyl acetate to give **6** (40 mg, 96%) as a white amorphous powder.

Epoxidation of 3b. To a stirred solution of **3b** (500 mg, 0.88 mmol) in anhydrous acetonitrile (4 ml) was added *N,N*-diisopropylethylamine (0.22 ml, 1.26 mmol) or DBU (0.16 ml, 1.07 mmol). The mixture was stirred for 4 h or 10 min, respectively, at room temperature and evaporated in vacuo to give a crude material, which was chromatographed on a silica-gel column (benzene-acetone, 3:2) and crystallized from hexane-ethyl acetate to give methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-2,3-anhydro-5-deoxy- β -D-erythro-L-glucopyranosonate (**7**) (83 or 92%) as white needles.

Epoxidation of 3c. To a solution of **3c** (50 mg, 0.08 mmol) in anhydrous acetonitrile (0.6 ml) was added *N,N*-diisopropylethylamine (0.02 ml, 0.11 mmol). The mixture was stirred for 2 h at room temperature and worked up in a similar manner as **3b** to give **7** (30 mg, 76%) as white needles.

Reaction of 7 with Halogenating Agents ($\text{BF}_3 \cdot \text{OEt}_2$, TiCl_4 , and TiBr_4). To a solution of **7** (200 mg, 0.41 mmol) in 1,2-dichloroethane (3 ml) was added boron trifluoride-ether complex, titanium(IV) chloride, or titanium(IV) bromide (0.45 mmol). The mixture was stirred for 10 min at room temperature and evaporated in vacuo to give a residue, which was dissolved in ethyl acetate. The organic layer was washed with saturated Na_2SO_4 solution (when boron trifluoride-ether complex was used, this operation was not required), 5% NaHCO_3 , and brine, dried over anhydrous

Na_2SO_4 , and evaporated in vacuo to give a crude syrup, which was purified by chromatography on a silica-gel column (benzene-acetone, 1:1) to give methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-2-fluoro-, chloro-, or bromo-2,5-dideoxy- β -D-erythro-L-glucopyranosonate (**8a**), (**8b**), and (**8c**), respectively, in yields as shown in Scheme 4.

Fluorination of 8c with Silver Fluoride. A mixture of **8c** (150 mg, 0.26 mmol) and silver fluoride (130 mg, 1.0 mmol) in anhydrous acetonitrile was stirred for 40 min at room temperature in the dark. The mixture was filtered through a Celite 545 bed and the solid was washed with ethyl acetate. The combined filtrates and washings were evaporated to give a residue. The residue was dissolved in ethyl acetate, washed with 5% sodium thiosulfate and brine, dried over anhydrous Na_2SO_4 , and evaporated in vacuo to give a crude material, which was chromatographed on a silica-gel column (benzene-acetone, gradient elution from 3:2 to 1:1). The fast migrating zone was the epoxide **7** (36 mg, 28%), which was obtained as white needle crystals, and the slow migrating zone was the α -fluoride, methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-2,5-dideoxy-2-fluoro- α -D-erythro-L-glucopyranosonate (**8d**) (86 mg, 64%) which was obtained as a syrup.

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