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Functionalization of 2-Deoxy-2,3-dehydro-*N*-acetylneuraminic Acid Methyl Ester[1)]

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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 bromide[4)] in acetonitrile-water (Pt-Pt electrodes) to give the 2β,3α-dibromide **3a**[5)] as white crystals in 93 or 98% yield, respectively (Table 1, Entries 1, 2). In ^{1}H NMR sepctrum 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 ^{1}H 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 combinations[7)] 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

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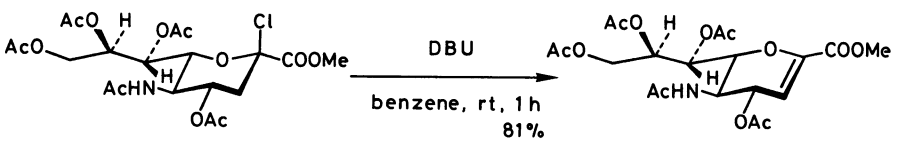


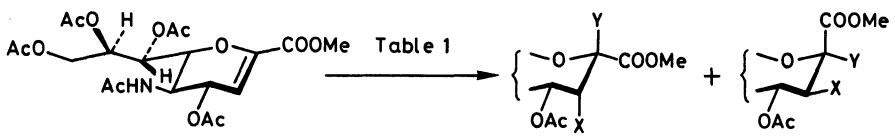
1 2

Scheme 1.

Table 1. Reaction of **2** with X^+-Y^-

Entry	Reaction System	Reaction		Product (Yield/%[a])			
		Temp/°C	Time/h	X	Y	**3** series	**4** series
1	Bromine CH_2Cl_2	0	0.2	Br	Br	**3a** (93)	—
2	NaBr, −e MeCN-H_2O	20	2.0	Br	Br	**3a** (98)	—
3	NBS MeCN-H_2O	20	6.0	Br	OH	**3b** (39)	**4b** (59)
4	NBS DMSO-H_2O	−20	0.5	Br	OH	**3b** (8)	**4b** (84)
5	NBS MeCN-H_2O	60	1.0	Br	OH	**3b** (71)	**4b** (26)
6	NBS MeCN-H_2O	80	0.2	Br	OH	**3b** (73)	**4b** (23)
7	NIS MeCN-H_2O	20	8.0	I	OH	**3c** (56)	**4c** (38)
8	NIS MeCN-H_2O	60	0.5	I	OH	**3c** (72)	**4c** (24)
9	NCS MeCN-H_2O	60	12.0	Cl	OH	—	—[b]
10	NBS AcONa-AcOH	20	1.5	Br	OAc	**3d** (41)	**4d** (41)
11	NIS AcONa-AcOH	20	1.0	I	OAc	**3e** (80)	**4e** (11)
12	NCS AcONa-AcOH	20	6.0	Cl	OAc	—	—[b]
13	NBS MeOH	20	1.0	Br	OMe	**3f** (37)	**4f** (55)
14	TBCD[c] CH_2Cl_2-MeOH	20	0.2	Br	OMe	**3f** (45)	**4f** (48)
15	NIS MeOH	20	2.0	I	OMe	—	—[b]

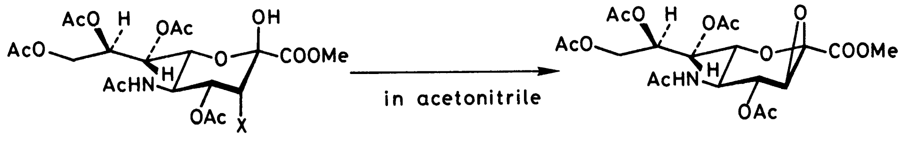
a) Isolated yield. b) **2** was recovered. c) 2,4,4,6-Tetrabromo-2,5-cyclohexadien-1-one.



2 **3** series **4** series

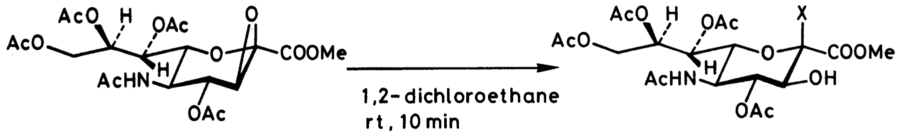
a: X = Br, Y = Br
b: X = Br, Y = OH
c: X = I , Y = OH
d: X = Br, Y = OAc
e: X = I , Y = OAc
f: X = Br, Y = OMe

Scheme 2.



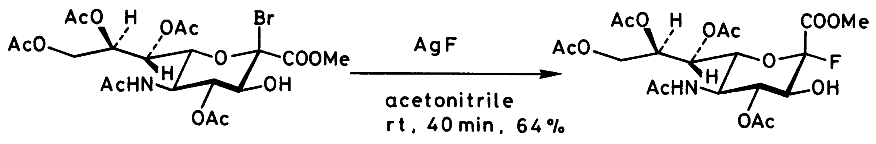
3b X=Br	(iPr)$_2$NEt, 4 h	83%	7
	DBU, 10 min	92%	
3c X=I	(iPr)$_2$NEt, 2 h	76%	

Scheme 3.



7	$BF_3 \cdot OEt_2$	8a X=F (97%)
	$TiCl_4$	8b X=Cl (95%)
	$TiBr_4$	8c X=Br (98%)

Scheme 4.



8c 8d

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 ^{1}H 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 (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-3ax and fluoro group of the product was 22.6 Hz in ^{1}H 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 question 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 $J_{3ax,F}$ coupling constant of **8d** was 15.0 Hz and this value agreed with α configuration[8] 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. ^{1}H NMR Data of **2**—**8d** in Chloroform-*d*

Compound	Chemical shifts, δ (multiplicity)														
	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)	Aglycon (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	

Compound	First-order coupling constants, Hz											
	$J_{3eq,3ax}$	$J_{3eq,4}$	$J_{3ax,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,NH}$	$J_{6,7}$	$J_{7,8}$	$J_{8,9}$	$J_{8,9'}$	$J_{9,9'}$	$J_{OH,3ax}$	$J_{3ax,F}$
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.

^{1}H NMR data were summarized in Table 2 and MS, elemental analyses, mp, R_f, $[\alpha]_D$, 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 Na_2SO_4, 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 cm^2) 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 Na_2SO_4, 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. C(%)	H(%)	N(%)	Mp[b] θ_m/°C	R_f[c]	$[\alpha]_D^{21}$[d] (c)	ν_{max}^{KBr} NH, OH	ester	amide I	amide II
2	$C_{20}H_{27}NO_{12}$	474	Calcd	50.74	5.75	2.96	126—127	0.46	+79.9°(1.3)	3270	1738	1645	1565
			Found	50.84	5.46	2.76							
3a	$C_{20}H_{27}NO_{12}Br_2$	634	Calcd	37.93	4.30	2.21	156—157	0.52	−57.7°(1.1)	3400	1753	1649	1560
			Found	37.84	4.23	2.06							
3b	$C_{20}H_{28}NO_{13}Br$	570, 572	Calcd	42.12	4.95	2.45	118—120	0.36	+38.7°(1.1)	3380	1742	1640	1522
			Found	42.36	4.81	2.68							
3c	$C_{20}H_{28}NO_{13}I$	618	Calcd	38.91	4.57	2.27	168—170	0.37	+66.5°(1.1)	3310	1745	1658	1555
			Found	39.02	4.45	2.24							
3d	$C_{22}H_{30}NO_{14}Br$	612, 614	Calcd	43.15	4.94	2.29	—[e]	0.44	+2.9°(1.6)	3380	1743	1660	1540
			Found	43.22	4.69	2.17							
3e	$C_{22}H_{30}NO_{14}I$	660	Calcd	40.07	4.59	2.12	81—83	0.44	+12.1°(1.4)	3380	1740	1662	1538
			Found	40.07	4.46	1.99							
3f	$C_{21}H_{30}NO_{13}Br$	584, 586	Calcd	43.16	5.18	2.40	186—187	0.49	+35.7°(1.5)	3420	1748	1662	1565
			Found	43.07	5.03	2.25							
4b	$C_{20}H_{28}NO_{13}Br$	570, 572	Calcd	42.12	4.95	2.45	—[e]	0.48	−41.6°(1.5)	3370	1746	1660	1540
			Found	42.29	4.92	2.94							
4c	$C_{20}H_{28}NO_{13}I$	618	Calcd	38.91	4.57	2.27	—[e]	0.48	−56.4°(1.3)	3370	1745	1660	1540
			Found	39.21	4.47	2.02							
4d	$C_{22}H_{30}NO_{14}Br$	612, 614	Calcd	43.15	4.94	2.29	95—96	0.55	−38.5°(1.3)	3380	1745	1660	1540
			Found	43.26	4.81	2.34							
4e	$C_{22}H_{30}NO_{14}I$	660	Calcd	40.07	4.59	2.12	86—88	0.56	−51.9°(0.9)	3430	1745	1660	1538
			Found	40.34	4.56	2.00							
4f	$C_{21}H_{30}NO_{13}Br$	584, 586	Calcd	43.16	5.18	2.40	158—159	0.54	−69.6°(2.0)	3420	1748	1655	1540
			Found	43.51	5.28	2.34							
5	$C_{21}H_{31}NO_{13}$	506	Calcd	49.90	6.18	2.77	—[e]	0.43	−14.7°(1.5)	3400	1741	1660	1540
			Found	50.14	6.38	2.76							
6	$C_{21}H_{31}NO_{13}$	506	Calcd	49.90	6.18	2.77	87—89	0.43	−23.7°(1.1)	3420	1742	1660	1540
			Found	49.92	6.11	2.68							
7	$C_{20}H_{27}NO_{13}$	490	Calcd	49.08	5.56	2.86	177—178	0.46	−10.0°(1.3)	3420	1740	1650	1572
			Found	48.97	5.55	2.89							
8a	$C_{20}H_{28}NO_{13}F$	510	Calcd	47.15	5.54	2.75	—[e]	0.26	−37.3°(0.7)	3400	1745	1660	1540
			Found	47.48	5.43	2.86							
8b	$C_{20}H_{28}NO_{13}Cl$	526, 528	Calcd	45.68	5.37	2.66	—[e]	0.30	−66.0°(0.9)	3420	1742	1658	1540
			Found	45.79	5.09	2.51							
8c	$C_{20}H_{28}NO_{13}Br$	570, 572	Calcd	42.12	4.95	2.46	—[e]	0.35	−91.1°(0.6)	3420	1742	1660	1540
			Found	42.01	4.88	2.22							
8d	$C_{20}H_{28}NO_{13}F$	510	Calcd	47.15	5.54	2.75	—[e]	0.28	−26.9°(0.8)	3410	1742	1660	1540
			Found	47.15	5.79	2.64							

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-*gluco*-2-nonulopyranosonate (**4b**) or methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-3-iodo-α-D-*erythro*-L-*gluco*-2-nonulopyranosonate (**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% $NaHCO_3$, water, 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 3:1 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-*gluco*-2-nonulopyranosonate (**4d**) or methyl 5-acetamido-2,4,7,8,9-penta-*O*-acetyl-3,5-dideoxy-3-iodo-α-D-*erythro*-L-*gluco*-2-nonulopyranosonate (**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 Na_2SO_4, 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-*gluco*-2-nonulopyranosid)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-*gluco*-2-nonulopyranosonate (**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 ($BF_3 \cdot OEt_2$, $TiCl_4$, 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-*gluco*-2-nonulopyranosonate (**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-*gluco*-2-nonulopyranosonate (**8d**) (86 mg, 64%) which was obtained as a syrup.

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