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Glycosylation of 4,7,8,9-Tetra-*O*-acetyl-2-deoxy-2*β*,3*β*-epoxy-*N*-acetylneuraminic Acid Methyl Ester[1)]

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Reaction of the 2*β*,3*β*-epoxyneuraminic acid derivative prepared from 2,3-dehydroneuraminic acid derivative with primary or secondary alcohol gave the corresponding glycoside(s) or ortho ester.

In the course of our glycosylation study on *N*-acetylneuraminic acid we have prepared some new glycosyl donors such as 2,3-dibromo-, 2,3-epoxy-, and 2-halo-3-hydroxy-*N*-acetylneuraminic acid derivatives from tetra-*O*-acetyl-2-deoxy-2,3-dehydro-*N*-acetylneuraminic acid methyl ester (**1**).[2)] We have already reported that the 2,3-dibromo compound is well-suited for the stereoselective *β*-glycosylation since the bromo group prevents the elimination reaction.[3)] We report here glycosylation of the 2,3-epoxy ccmpound **2**[2)] whose epoxy ring is *β*-oriented (Scheme 1). If the glycosylation reaction occurs in S_N2 type, **2** is suited to give *α*-glycosides.

Treatment of **2** with methanol in the presence of *d*-camphor-10-sulfonic acid or Amberlyst 15 catalyst (catalytic amount) gave only methyl *α*-glycoside **3** in nearly quantitative yield. To determine the anomeric configuration the glycoside **3** was treated with phenyl chlorocarbonothioate[4)] in the presence of 4-dimethylaminopyridine (DMAP) to give **5**, which was reduced with tributylstannane to the known *α*-glycoside **6**[5)] quantitatively. Antimony pentachloride (1.0 equiv) in methanol was also effective catalyst for this glycosylation. By use of 2 equivalents of methanol in the presence of antimony pentachloride or trimethylsilyl triflate (TMSOTf) catalyst, however, an inseparable mixture of *α*- and *β*-glycosides was obtained.

Treatment of **2** with methyl 2,3,4-tri-*O*-benzyl-*α*-D-glucoside (**8**)[6)] in the presence of boron trifluoride-ether complex or titanium(IV) chloride gave methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,5-dideoxy-2-fluoro-*β*-D-*erythro*-L-*gluco*-2-nonulopyranosonate (**12**)[2)] or methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2-chloro-2,5-dideoxy-*β*-D-*erythro*-L-*gluco*-2-nonulopyranosonate (**7**)[2)] without any glycosides. The hydroxy-*β*-glycoside **9** was

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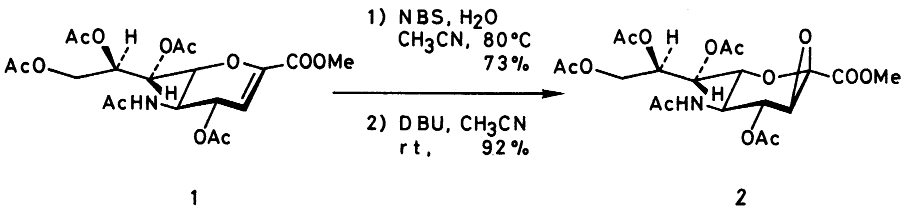
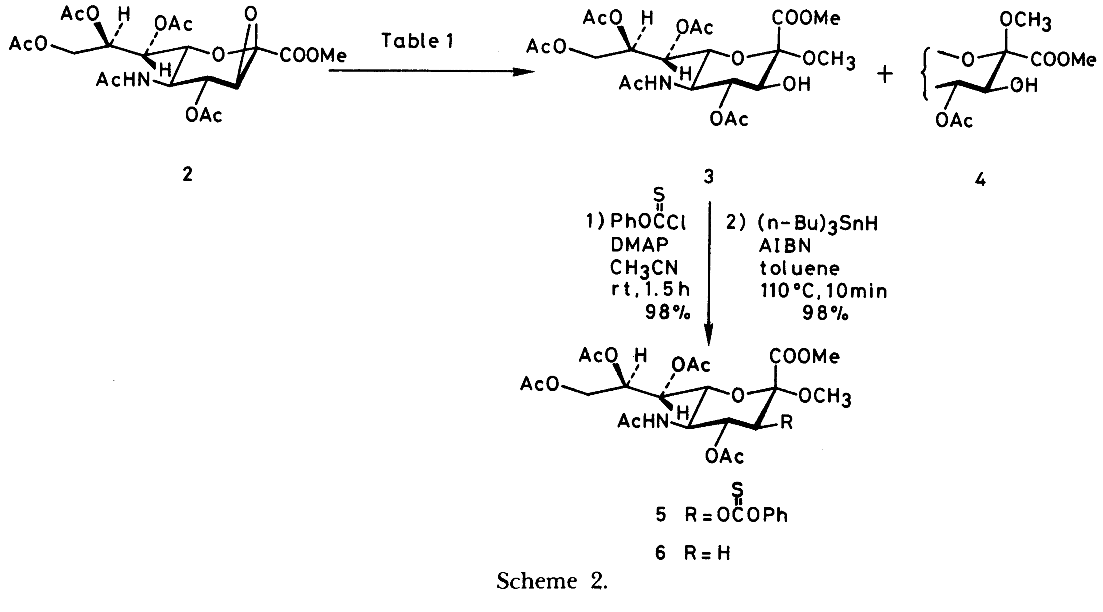


Scheme 1.



Scheme 2.

Table 1. Reaction of the Epoxide **2** and Methanol

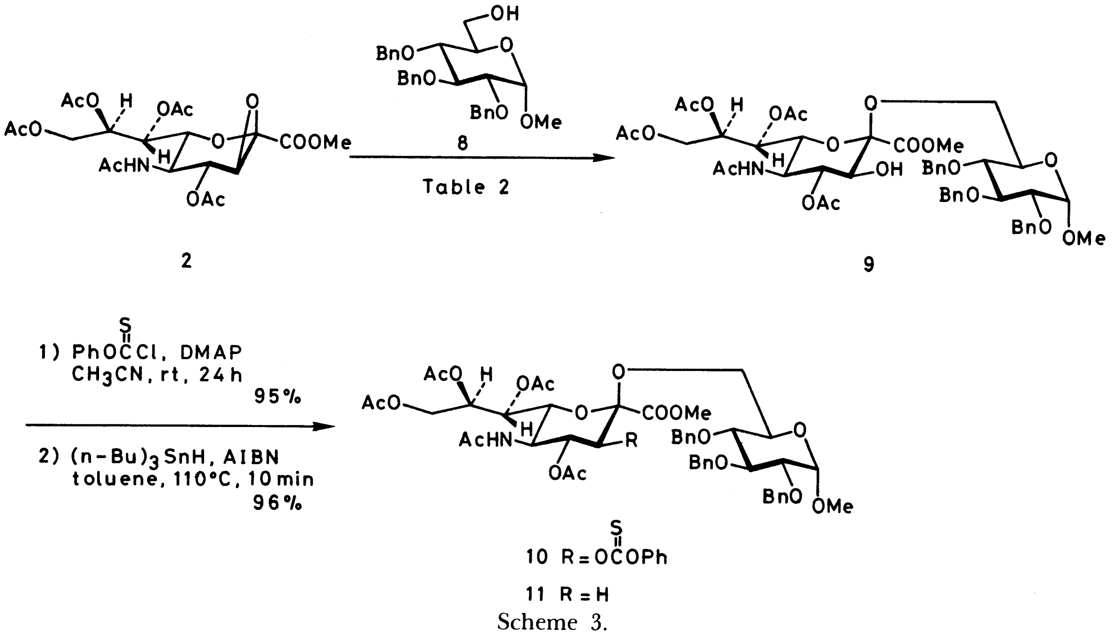
Catalyst(equiv)	MeOH (equiv)	Solvent	Reaction		Yield/% of Product	
			Temp	Time	**3**	**4**
CSA (cat.)		Methanol	rt	15 min	99[a)]	
Amberlyst 15 (cat.)		Methanol	rt	15 min	98[a)]	
$SbCl_5$ (1.0)		Methanol	rt	15 min	89[a)]	
$SbCl_5$ (1.0)	2.0	$ClCH_2CH_2Cl$	0 °C	15 min	41[b)]	20[b,c)]
TMSOTf (1.0)	2.0	$ClCH_2CH_2Cl$	0 °C	15 min	62[b)]	29[b)]

a) Isolated yield. b) Determined by ^{1}H NMR. c) Methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2-chloro-2,5-dideoxy-*β*-D-*erythro*-L-*gluco*-2-nonulopyranosonate (**7**) was also obtained in 37% yield.

Table 2. Reaction of the Epoxide **2** and Glucose Derivative **8**[a)]

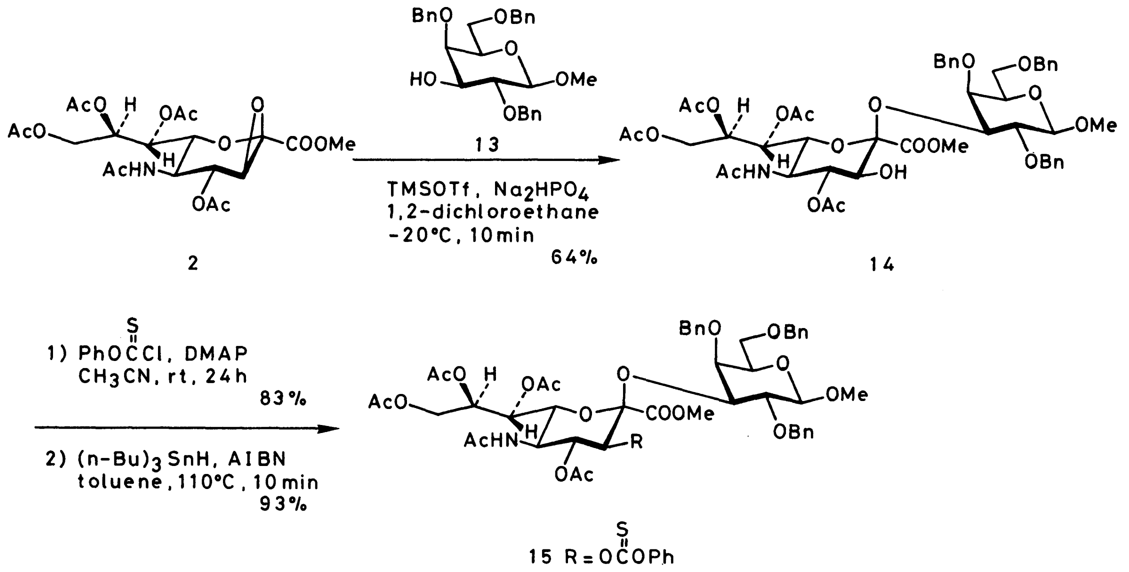
Catalyst(equiv)	Solvent	Reaction		Yield/%[b)] of **9**
		Temp	Time/h	
CSA (cat.)	$ClCH_2CH_2Cl$	rt	0.5	no reaction
$BF_3 \cdot OEt_2$ (1.0)	THF	rt	0.2	c)
$TiCl_4$ (1.0)	$ClCH_2CH_2Cl$	rt	0.2	d)
$SbCl_5$ (1.0)	$ClCH_2CH_2Cl$	rt	0.2	49
TMSOTf[e)] (1.0)	$ClCH_2CH_2Cl$	0 °C	0.2	56

a) Two equivalents of **8** were used. b) Isolated yield. c) Methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,5-dideoxy-2-fluoro-*β*-D-*erythro*-L-*gluco*-2-nonulopyranosonate (**12**) was obtained in 80% yield. d) Methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2-chloro-2,5-dideoxy-*β*-D-*erythro*-L-*gluco*-2-nonulopyranosonate (**7**) was obtained in 80% yield. e) Na_2HPO_4 was used as a buffer.

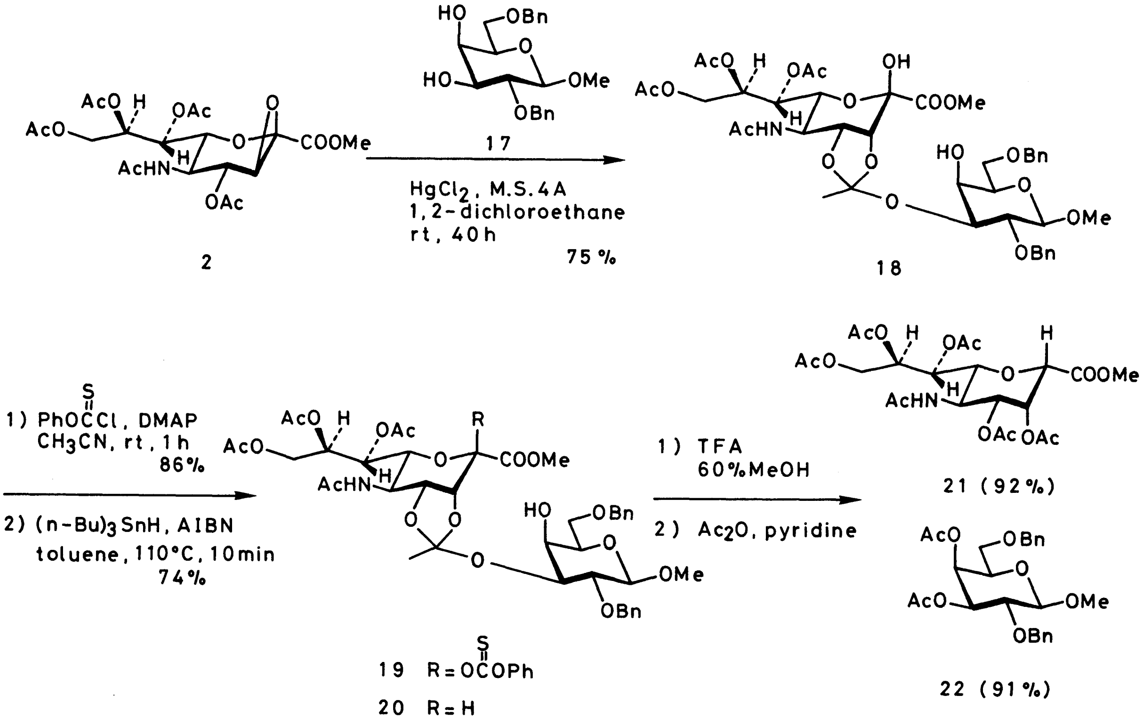


Scheme 3.

obtained in a moderate yield by the use of either antimony pentachloride or trimethylsilyl triflate. In the ^{1}H NMR spectrum of **9**, the coupling constant $J_{7,8}$ was 1.5 Hz and the $\Delta\delta|\text{H-9}'\text{-H-9}|$ value was 0.94 ppm. In cases of the carbonothioate **10** and the glycoside **11**, the $J_{7,8}$ values were 1.5 and 2.2 Hz and the $\Delta\delta|\text{H-9}'\text{-H-9}|$ values were 0.94 and 0.94 ppm, respectively. As **11** was determined to be a *β*-glycoside by comparing its physical data with those of the authentic sample,[3)] it is safe to deduce the anomeric configuration of **9** from the $J_{7,8}$ and $\Delta\delta|\text{H-9}'\text{-H-9}|$ values in ^{1}H NMR spectrum.[7,8)] Similarly, reaction of **2** with methyl 2,4,6-tri-*O*-benzyl-*β*-D-galactopyranoside (**13**)[9)] afforded in 64% yield only *β*-glycoside **14**, whose $J_{7,8}$ was 1.8 Hz and $\Delta\delta|\text{H-9}'\text{-H-9}|$ value was 1.02 ppm. To make sure that the anomeric position was *β* configuration, the hydroxy-glycoside **14** was carbonothioated and reduced in the same manner as above to give the protected 3-*O*-(2*β*-neuraminyl)galactoside **16**, which was identical with the authentic sample.[3)] Although the reaction of **2** with the acceptor **13** in the presence of mercury(II) chloride catalyst gave no glycosides, treatment of **2**



Scheme 4.



Scheme 5.

with a less sterically hindered acceptor **17** afforded an unstable product **18** in 75% yield. In its ^{1}H NMR spectrum, the coupling constant $J_{7,8}$ was 4.2 Hz and the $\Delta\delta|$H-9′-H-9$|$ value was 0.89 ppm, which were fit for neither α- nor β-glycoside. The product **18** was treated with phenyl chlorocarbonothioate to determine the structure. In spite of the presence of a carbonothioate group in **19** as evident from its ^{1}H NMR spectrum, the signal corresponding to H-3 of **19** was not shifted toward lower field. The carbonothioated **19** was reduced with tributylstannane to give **20**, which exhibited $J_{2ax,3eq}$ coupling constant as 2.4 Hz. From these data a series of compounds obtained by the reaction of **2** with **17** was revealed to be the ortho esters as illustrated in Scheme 5. Treatment of **20** with dilute trifluoroacetic acid in aqueous methanol gave almost instantaneously two degradation products, which were treated with acetic anhydride in pyridine to afford the acetylated compounds **21** and **22**. These compounds were characterized by IR, ^{1}H NMR, and mass spectra.

In summary, the epoxide **2** gave α-glycosides by the use of highly reactive acceptors such as methanol, and

β-glycosides by sugar derivatives such as a 6-unprotected glucoside and a 3-unprotected galactoside in the presence of antimony pentachloride or trimethylsilyl triflate. On the other hand, the ortho ester was yielded in the presence of mercury(II) chloride catalyst. The anomeric configuration of neuraminic acid derivatives was able to be determined from the $J_{7,8}$ coupling constant and the $\Delta\delta|\text{H-9}'\text{-H-9}|$ value in ^{1}H NMR spectrum. For example, 2β-glycosides showed ca. 2 Hz in $J_{7,8}$ and ca. 1 ppm of $\Delta\delta|\text{H-9}'\text{-H-9}|$ value, whereas 2α-glycosides showed more than 7 Hz in $J_{7,8}$ coupling constant and less than 0.5 ppm of $\Delta\delta|\text{H-9}'\text{-H-9}|$ value. These values in glycosides remain unaltered even if 3 position of NeuAc unit is substituted by any group.

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; m, mutiplet; 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.

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 Tables 3, 4, and 5, and MS, elemental analyses, mp, R_f, $[\alpha]_D$, and IR data in Table 6.

Reaction of the Epoxide 2 and Methanol. Procedure A

Table 3. ^{1}H NMR Data of NeuAc Unit at 500 MHz in Chloroform-d

Compound	Chemical shifts, δ (multiplicity)																	
	H-2ax (d)	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)	Phenyl (m)	Aglycon (s)
3			3.82[a]	5.15	4.22	4.54	5.28	5.37	4.08	4.32	3.84	5.63		3.02	1.89, 2.03, 2.08 2.09, 2.14		3.46
5			5.87	5.50	4.42	4.63	5.31	5.36	4.10	4.32	3.82	5.52			1.92, 2.04, 2.06 2.09, 2.16	7.04—7.44	3.51
6		2.57	1.94	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
9			3.85[a]	5.05	4.21	4.30	5.35	5.24	4.04	4.98	3.80	5.39		2.53	1.87, 1.97, 2.04 2.06, 2.14		
10			5.87	5.43	4.41	4.44	5.41	5.28	4.08	5.02	3.68	5.63			1.88, 1.98, 2.05 2.06, 2.17	6.85—7.50	
11		2.47	1.88	5.16	4.11	4.27	5.38	5.27	4.13	5.07	3.72	5.49			1.86, 1.97, 2.01 2.05, 2.13		
14			3.90[a]	5.00	4.08	4.02	5.17	5.09	3.96	4.98	3.54	4.52		3.68	1.72, 1.93, 2.01 2.02, 2.08		
15			5.82	5.32	4.25	3.94	5.15	5.18	3.95	5.22	3.51	3.95			1.65, 1.99, 2.00 2.03, 2.09	6.90—7.65	
16		2.70	1.80	4.98	3.99	3.91	5.15	5.15	4.00	4.99	3.54	3.86			1.64, 1.98, 2.00 2.03, 2.06		
18		4.60		4.47	3.87	4.23	5.32	5.25	4.04	4.93	3.68	5.84	5.48		1.69, 1.93, 2.03 2.07, 2.13		
19		4.72		4.44	4.18	4.15	5.38	5.14	4.20	4.65	3.71	6.64			1.72, 1.92, 1.93 2.06, 2.13	7.10—7.50	
20	4.28	4.74[a]		4.53	3.39	3.79	5.24	5.30	4.18	4.61	3.66	5.69			1.65, 1.95, 2.03 2.06, 2.12		
21	4.37	5.71[a]		5.22	4.25	3.88	5.39	5.30	4.20	4.73	3.75	5.87			1.90, 1.99, 2.05 2.07, 2.13, 2.17		

Compound	First-order coupling constants, Hz												
	$J_{2ax,3ex}$	$J_{3eq,3ax}$	$J_{3eq,4}$	$J_{3ax,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,NH}$	$J_{6,7}$	$J_{7,8}$	$J_{8,9}$	$J_{8,9'}$	$J_{9,9'}$	$J_{OH,3ax}$
3				9.8	10.1	11.0	10.1	2.1	7.9	6.1	2.6	−12.5	6.1
5				8.6	10.4	11.0	9.8	2.1	8.0	6.3	2.5	−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	
9				9.5	10.4	10.7	10.1	2.1	1.5	9.2	2.3	−12.5	7.3
10				9.8	9.8	10.1	9.5	2.0	1.5	9.2	2.1	−12.5	
11		−12.9	5.1	10.8	11.2	10.4	10.4	2.3	2.2	9.3	2.2	−12.5	
14				9.5	9.8	10.0	10.1	2.0	1.8	9.2	2.4	−12.5	7.0
15				9.8	10.4	10.5	10.5	2.1	2.1	8.9	2.2	−12.5	
16		−13.4	4.6	11.6	11.2	10.7	10.4	1.8	b)	8.5	2.1	−12.5	
18			5.2		8.2	10.7	9.8	2.1	4.2	7.9	2.1	−12.5	
19			5.5		7.6	10.0	9.2	2.7	2.7	7.6	2.1	−12.5	
20	2.4		5.8		7.6	11.3	8.2	1.8	5.5	6.7	2.4	−12.5	
21	1.2		3.5		10.7	9.4	9.8	2.1	4.9	7.3	2.4	−12.5	

a) Multiplicity: dd. b) Not assigned owing to the complexity of the spectrum.

Table 4. ^{1}H NMR Data of Glc or Gal Unit at 500 MHz in Chloroform-*d*

Compound	Chemical shifts, δ (multiplicity)									First-order coupling constants, Hz							
	H-1 (d)	H-2 (dd)	H-3 (dd)	H-4 (dd)	H-5 (ddd)	H-6 (dd)	H-6′ (dd)	OMe (s)	OH-4 (d)	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$J_{OH,4}$
9	4.90	3.64	3.99	3.72	3.79	3.88	4.09	3.36		3.7	9.5	9.2	8.9	2.0	2.3	−10.9	
10	4.93	3.67	3.99	3.84	3.82	3.87	4.19	3.36		3.7	9.5	8.9	9.0	1.0	2.0	−10.3	
11	4.89	3.61	3.97	3.70	3.74	3.80	3.81	3.35		3.7	9.5	9.2	10.1	2.5	2.0	−10.8	
14	4.35	3.87	4.39	4.10	3.82	3.69	3.73	3.49		7.0	9.2	3.1	1.0	6.7	6.3	−10.0	
15	4.38	3.84	4.42	4.08$^{a)}$	3.88	3.77	3.79	3.47		7.3	9.8	3.1	0	7.2	7.1	−10.2	
16	4.34	3.75	4.09	3.94$^{a)}$	3.77	3.68	3.71	3.46		7.3	9.8	2.8	0	6.1	6.1	−9.8	
18	4.28	3.51	3.67	4.01	3.57	3.72	3.78	3.55	2.98	7.6	9.5	3.7	0	6.1	4.6	−10.1	1.5
19	4.29	3.53	3.70	3.90$^{b)}$	3.58	3.75	3.81	3.56	2.68	7.9	9.8	3.4	0.5	5.4	5.8	−10.1	2.5
20	4.27	3.50	3.69	3.95	3.56	3.72	3.79	3.55	2.64	7.9	9.5	3.4	0	5.8	5.5	−9.8	2.5
22	4.38	3.58	4.98	5.42	3.83	3.49	3.57	3.59		7.6	10.1	3.7	1.0	6.7	6.3	−9.8	

a) Multiplicity: d. b) Multiplicity: ddd.

Table 5. ^{1}H NMR Data of Other Groups at 500 MHz in Chloroform-*d*

Compound	Chemical shifts, δ (multiplicity)					First-order coupling constants, Hz
	PhCH_2 (AB quartet)			Ph (m)	O-Ac (s)	J_{gem}
9	4.74 and 4.89,	4.76 and 4.82,	4.85 and 4.97	7.23—7.45		−11.0, −11.9, −11.0
10	4.78 and 4.85,	4.88 and 4.96,	4.92 and 5.00	6.85—7.50		−11.9, −11.0, −11.0
11	4.70 and 4.87,	4.75 and 4.82,	4.84 and 4.97	7.20—7.50		−10.8, −12.0, −11.0
14	4.54 and 4.56,	4.74 and 4.87,	4.88 and 4.90	7.20—7.50		−11.9, −11.3, −13.7
15	4.60,$^{a)}$	4.82 and 5.02,	4.95 and 5.03	6.90—7.65		−11.9, −13.7
16	4.56,$^{a)}$	4.68 and 4.88,	4.79 and 4.80	7.20—7.50		−11.0, −12.5
18	4.57 and 4.61,	4.63 and 4.81,		7.25—7.50		−11.9, −11.0
19	4.58 and 4.60,	4.62 and 4.85,		7.10—7.50		−10.0, −10.7
20	4.57 and 4.61,	4.61 and 4.85,		7.23—7.45		−12.2, −11.0
22	4.44 and 4.55,	4.61 and 4.85,			1.94, 2.01	−11.9, −11.9

a) Multiplicity: s.

Table 6. MS, Elemental Analyses, Mp, R_f, $[\alpha]_D$, and IR Data of **3**—**22**

Compound	Formula	MS$^{a)}$ (M+H)	Anal.				Mp θ_m/°C	R_f	$[\alpha]_D$ (c)$^{b)}$ (Temp)	ν_{max}^{KBr}			
				C(%)	H(%)	N(%)				NH, OH	ester	amide I	amide II
3	$C_{21}H_{31}NO_{14}$	522	Calcd	48.37	5.99	2.69	—$^{c)}$	0.27$^{d)}$	−34.3°(1.1)	3430	1743	1660	1540
			Found	48.35	5.89	2.75			(15 °C)				
5	$C_{28}H_{35}NO_{15}S$	658	Calcd	51.14	5.36	2.13	—$^{c)}$	0.56$^{d)}$	−18.4°(1.2)	3430	1748	1660	1540
			Found	50.85	5.43	2.32			(15 °C)				
6	$C_{21}H_{31}NO_{13}$	506	Calcd	49.90	6.18	2.77	87—89$^{e)}$	0.43$^{d)}$	−23.7°(1.1)	3420	1742	1660	1540
			Found	50.11	6.01	2.92			(21 °C)				
9	$C_{48}H_{59}NO_{19}$	955	Calcd	60.43	6.23	1.47	—$^{c)}$	0.46$^{d)}$	+11.5°(1.3)	3430	1743	1665	1540
			Found	60.71	6.45	1.39			(21 °C)				
10	$C_{55}H_{63}NO_{20}S$		Calcd	60.60	5.82	1.29	—$^{c)}$	0.60$^{f)}$	−5.6°(2.6)	3400	1748	1665	1540
			Found	60.23	5.78	1.44			(20 °C)				
11	$C_{48}H_{59}NO_{18}$	938	Calcd	61.46	6.34	1.49	—$^{c)}$	0.52$^{f)}$	+23.3°(1.0)	3400	1748	1665	1540
			Found	61.59	6.34	1.31			(29 °C)				
14	$C_{48}H_{59}NO_{19}$	955	Calcd	60.43	6.23	1.47	—$^{c)}$	0.48$^{f)}$	−15.7°(1.0)	3380	1743	1670	1540
			Found	60.56	6.57	1.59			(11 °C)				
15	$C_{55}H_{63}NO_{20}S$		Calcd	60.60	5.82	1.29	—$^{c)}$	0.64$^{f)}$	+9.1°(0.7)	3420	1752	1660	1540
			Found	60.91	5.75	1.46			(12 °C)				
16	$C_{48}H_{59}NO_{18}$	938	Calcd	61.46	6.34	1.49	—$^{c)}$	0.58$^{f)}$	+5.3°(1.0)	3400	1743	1660	1540
			Found	61.23	6.27	1.08			(29 °C)				
18	$C_{48}H_{53}NO_{19}$		Calcd	57.00	6.18	1.62	—$^{c)}$	0.40$^{d)}$	+31.8°(1.2)	3400	1745	1660	1540
			Found	56.72	6.08	1.87			(11 °C)				
19	$C_{48}H_{57}NO_{20}S$		Calcd	57.65	5.75	1.40	—$^{c)}$	0.54$^{f)}$	−9.5°(1.0)	3400	1748	1660	1530
			Found	57.83	5.41	1.42			(12 °C)				
20	$C_{41}H_{53}NO_{18}$		Calcd	58.08	6.30	1.65	—$^{c)}$	0.40$^{f)}$	+12.3°(0.9)	3420	1742	1660	1530
			Found	57.82	6.07	1.36			(11 °C)				
21	$C_{22}H_{31}NO_{14}$	534	Calcd	49.53	5.86	2.63	—$^{c)}$	0.26$^{f)}$	+49.8°(1.6)	3370	1748	1660	1540
			Found	49.50	5.79	2.38			(12 °C)				
22	$C_{25}H_{30}O_8$	459	Calcd	65.49	6.60		—$^{c)}$	0.54$^{g)}$	+6.5°(2.0)		1740		
			Found	65.44	6.73				(12 °C)				

a) Fast atom bombardment method. b) Measured in chloroform. c) Viscous syrup. d) Solvent system is benzene–acetone (3:2). e) Recrystallized from hexane–ethyl acetate. f) Solvent system is benzene–acetone (2:1). g) Solvent system is benzene–ethyl acetate (6:1).

(*d*-camphor-10-sulfonic acid or SbCl$_5$ catalyst in the presence of large excess methanol). To a solution of **2** (100 mg, 0.20 mmol) in absolute methanol (2.5 ml) was added *d*-camphor-10-sulfonic acid (cat. amount) or antimony pentachloride (26 µl, 0.20 mmol) at room temperature under argon atmosphere. After stirring for 15 min, the mixture was evaporated to dryness, and the residue was dissolved in ethyl acetate. The solution was washed with 5% NaHCO$_3$ and brine, dried over anhydrous Na$_2$SO$_4$. The solvent was removed in vacuo to give a syrupy residue, which was chromatographed on a silica-gel column (benzene–acetone, 1:1) to give methyl glycoside of methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-5-deoxy-α-D-*erythro*-L-*gluco*-2-nonulopyranosonate (**3**) as a syrup.

Procedure B (Amberlyst 15 catalyst in the presence of large excess methanol). A mixture of **2** (100 mg, 0.20 mmol) and Amberlyst 15 (cat. amount) in absolute methanol (2.5 ml) was stirred for 15 min under argon atmosphere. It was filtered and the resin was washed well with methanol. The combined filtrate and washings were evaporated to a syrup, which was purified in the same manner as procedure A.

Procedure C (SbCl$_5$ catalyst in the presence of 2 equiv of methanol). To a solution of **2** (100 mg, 0.20 mmol) in 1,2-dichloroethane (2.0 ml) containing 0.2 M (1M=1 mol dm^{-3}) methanol (2.0 ml) was added antimony pentachloride (26 µl, 0.20 mmol) at 0 °C under argon atmosphere. The mixture was stirred for 15 min, diluted with chloroform, washed with 5% NaHCO$_3$ and brine, dried over anhydrous Na$_2$SO$_4$, and evaporated to dryness. The residue was purified in the same manner as procedure A. The fast migrating zone was methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2-chloro-2,5-dideoxy-β-D-*erythro*-L-*gluco*-2-nonulopyranosonate (**7**)2) (40 mg, 37%) and the slow migrating zone was an inseparable mixture of **3** (41%) and **4** (20%).

Procedure D (TMSOTf catalyst in the presence of 2 equiv of methanol). To a solution of **2** (100 mg, 0.20 mmol) in 1,2-dichloroethane (2.0 ml) containing 0.2 M methanol was added trimethylsilyl triflate (40 µl, 0.20 mmol) at 0 °C under argon atmosphere. The mixture was worked up in the same manner as above to give **3** (62%) and **4** (29%).

Methyl (Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-5-deoxy-3-*O*-[phenoxy(thiocarbonyl)]-α-D-*erythro*-L-*gluco*-2-nonulopyranosid)onate (5). A solution of **3** (50 mg, 0.096 mmol), 4-dimethylaminopyridine (50 mg, 0.41 mmol), and phenyl chlorocarbonothioate (27 µl, 0.20 mmol) in anhydrous acetonitrile (1.0 ml) was stirred for 1.5 h at room temperature under argon atmosphere. The mixture was evaporated to dryness and the residue, which was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over anhydrous Na$_2$SO$_4$, and evaporated in vacuo to give a crude material, which was chromatographed on a silica-gel column (benzene–acetone, 5:2) to give **5** (64 mg, 98%) as a colorless syrup.

Methyl (Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-α-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (6). To a solution of **5** (20 mg, 0.030 mmol) in toluene (1.0 ml) were added tributylstannane (20 µl, 0.074 mmol) and AIBN (cat. amount) under argon atmosphere. The mixture was heated at 110 °C for 10 min, evaporated to dryness and the residue was chromatographed on a silica-gel column (benzene-acetone, 2:1) to give crystals. Recrystallization from hexane-ethyl acetate gave **6** (15 mg, 98%) as white needles.

Reaction of the Epoxide 2 and 8. Procedure A (BF$_3$·OEt$_2$ catalyst). To a stirred solution of **2** (20 mg, 0.041 mmol) and **8**6) (40 mg, 0.086 mmol) in tetrahydrofuran (0.6 ml) was added boron trifluoride-ether complex (5.2 µl, 0.041 mmol) at room temperature under argon atmosphere. After stirring for 0.2 h, the solvent was removed and the residue was dissolved in ethyl acetate. The solution was washed with 5% NaHCO$_3$ and brine, dried over anhydrous Na$_2$SO$_4$, and evaporated in vacuo to give a crude syrup, which was chromatographed on a silica-gel column (benzene-acetone, 1:1). Unreacted **8** (35 mg) was recovered and then methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,5-dideoxy-2-fluoro-β-D-*erythro*-L-*gluco*-2-nonulopyranosonate (**12**)2) (16.7 mg, 80%) was obtained.

Procedure B (TiCl$_4$ catalyst). To a solution of **2** (20 mg, 0.041 mmol) and **8** (40 mg, 0.086 mmol) in 1,2-dichloroethane (0.6 ml) was added titanium(IV) chloride (4.5 µl, 0.041 mmol) at room temperature under argon atmosphere. The mixture was stirred for 0.2 h, diluted with ethyl acetate, washed with saturated Na$_2$SO$_4$ and brine, dried over anhydrous Na$_2$SO$_4$, and evaporated in vacuo to give a residue, which was treated in the same manner as procedure A to give **8** (30 mg) and **7** (17.3 mg, 80%).

Procedure C (SbCl$_5$ catalyst). To a solution of **2** (20 mg, 0.041 mmol) and **8** (40 mg, 0.086 mmol) in 1,2-dichloroethane (0.6 ml) was added antimony pentachloride (5.2 µl, 0.041 mmol) at room temperature under argon atmosphere. The mixture was stirred for 0.2 h, diluted with ethyl acetate, washed with 5% NaHCO$_3$ and brine, dried over anhydrous Na$_2$SO$_4$, and evaporated in vacuo to give a crude material, which was chromatographed on a silica-gel column (benzene–acetone, 2:1) to give methyl 2,3,4-tri-*O*-benzyl-6-*O*-[methyl(5-acetamido-4,7,8,9-tetra-*O*-acetyl-5-deoxy-β-D-*erythro*-L-*gluco*-2-nonulopyranosyl)onate]-α-D-glucopyranoside (**9**) (19 mg, 49%) as a syrup.

Procedure D (TMSOTf catalyst). To a mixture of **2** (20 mg, 0.041 mmol), **8** (40 mg, 0.086 mmol), anhydrous disodium hydrogenphosphate (20 mg), and 1,2-dichloroethane (0.6 ml) was added trimethylsilyl triflate (8 µl, 0.041 mmol) at 0 °C under argon atmosphere. It was stirred for 0.2 h at the same temperature and worked up in the same manner as above to give **9** (22 mg, 56%).

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-[methyl(5-acetamido-4,7,8,9-tetra-*O*-acetyl-5-deoxy-3-*O*-[phenoxy(thiocarbonyl)]-β-D-*erythro*-L-*gluco*-2-nonulopyranosyl)onate]-α-D-glucopyranoside (10). A solution of **9** (22 mg, 0.023 mmol), 4-dimethylaminopyridine (6 mg, 0.049 mmol), and phenyl chlorocarbonothioate (7 µl, 0.051 mmol) in anhydrous acetonitrile (0.3 ml) was stirred for 24 h at room temperature under argon. The mixture was evaporated to dryness, and the residue was dissolved in ethyl acetate, washed with water and brine, dried over anhydrous Na$_2$SO$_4$, and evaporated in vacuo to give a crude material. This was chromatographed on a silica-gel column (benzene–acetone, 5:2), triturated with hexane–ethyl acetate, and washed with hexane to give **10** (24 mg, 95%).

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-[methyl(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranosyl)onate]-α-D-glucopyranoside (11). To a solution of **10** (20 mg, 0.018 mmol) in toluene (1 ml) were added tributylstannane (10 µl, 0.037 mmol) and AIBN (cat. amout) under argon atmosphere. The mixture was heated at 100 °C for 15 min and the solvent was removed in vacuo to give a crude material, which was chromatographed on a silica-gel column (benzene–acetone, 2 : 1) to give **11** (16.5 mg, 96%) as a syrup.

Methyl 2,4,6-Tri-*O*-benzyl-3-*O*-[methyl(5-acetamido-4,7,8,9-tetra-*O*-acetyl-5-deoxy-*β*-D-*erythro*-L-*gluco*-2-nonulopyranosyl)onate]-*β*-D-galactopyranoside (14). To a mixture of **2** (20 mg, 0.041 mmol), **13**[10] (40 mg, 0.086 mmol), anhydrous disodium hydrogenphosphate (20 mg), and 1,2-dichloroethane (0.3 ml) was added trimethylsilyl triflate (8 μl, 0.041 mmol) at −20 °C under argon atmosphere. It was stirred for 10 min, diluted with ethyl acetate, washed with 5% $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was chromatographed on a silica-gel column (benzene–acetone, 2 : 1) to give **14** (25 mg, 64%) as a syrup.

Methyl 2,4,6-Tri-*O*-benzyl-3-*O*-[methyl(5-acetamido-4,7,8,9-tetra-*O*-acetyl-5-deoxy-3-*O*-[phenoxy(thiocarbonyl)]-*β*-D-*erythro*-L-*gluco*-2-nonulopyranosyl)onate]-*β*-D-galactopyranoside (15). A solution of **14** (18 mg, 0.019 mmol), 4-dimethylaminopyridine (6 mg, 0.049 mmol), and phenyl chlorocarbonothioate (5 μl, 0.036 mmol) in anhydrous acetonitrile (0.3 ml) was stirred for 24 h at room temperature under argon atmosphere. After evaporation, the residue was partitioned between ethyl acetate and water. The organic layer was separated, 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, 4 : 1) to give **15** as a syrup.

Methyl 2,4,6-Tri-*O*-benzyl-3-*O*-[methyl(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-*β*-D-*glycero*-D-*galacto*-2-nonulopyranosyl)onate]-*β*-D-galactopyranoside (16). To a solution of **15** (15 mg, 0.014 mmol) in toluene (1 ml) were added tributylstannane (7 μl, 0.026 mmol) and AIBN (cat. amount) under argon atmosphere. The mixture was heated at 110 °C for 10 min and evaporated to dryness. The residue was chromatographed on a silica-gel column (benzene–acetone, 4 : 1) to give a syrup. This was triturated with hexane-ethyl acetate and washed with hexane to give **16** (12 mg, 93%).

Reaction of the Epoxide 2 with 17. A mixture of **2** (100 mg, 0.20 mmol), **17**[10] (160 mg, 0.43 mmol), mercury(II) chloride (60 mg, 0.22 mmol), powdered molecular sieves 4A (200 mg), and 1,2-dichloroethane (3 ml) was stirred for 40 h. The reaction mixture was filtered and the solid was washed with chloroform. The combined filtrate and washings were washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo to give a residue, which was chromatographed on a silica-gel column (benzene–acetone, 3 : 2) to give the ortho ester **18** (132 mg, 75%).

To a solution of **18** (100 mg, 0.12 mmol) and 4-dimethylaminopyridine (60 mg, 0.49 mmol) in anhydrous acetonitrile (1.5 ml) was added phenyl chlorocarbonothioate (18 μl, 0.13 mmol) under argon atmosphere. The mixture was stirred for 1 h at room temperature, evaporated to dryness, and the residue was partitioned between ethyl acetate and water. The ethyl acetate layer was separated, 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, 3 : 2) to give **19** (100 mg, 86%).

To a mixture of **19** (80 mg, 0.08 mmol), anhydrous sodium acetate (40 mg), and toluene (3 ml) was added tributylstannane (43 μl, 0.16 mmol) under argon atmosphere. The mixture was heated at 110 °C for 10 min, diluted with ethyl acetate, washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was chromatographed on a silica-gel cloumn (benzene–acetone, 3 : 2), triturated with hexane–ethyl acetate, and washed with hexane to give **20** (50 mg, 74%).

To a solution of **20** (100 mg, 0.12 mmol) in 60% aq methanol (3 ml) was added trifluoroacetic acid (1 drop) at room temperature. After stirring for 10 min, the mixture was evaporated to dryness and the residue was treated with acetic anhydride (0.4 ml) and pyridine (0.8 ml) for 10 h at room temperature under argon atmosphere. The resulting mixture was evaporated to a syrup, which was chromatographed on a silica-gel column (benzene–ethyl acetate, 6 : 1, followed by benzene–acetone, 1 : 1) to give methyl 3,4-di-*O*-acetyl-2,6-di-*O*-benzyl-*β*-D-galactopyranoside (**22**) (50 mg, 92%) and methyl 5-acetamido-3,4,7,8,9-penta-*O*-acetyl-2,5-dideoxy-D-*erythro*-L-*manno*-2-nonulopyranosonate (**21**) (51 mg, 91%) as a syrup.

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