Studies on Sialic Acids. XXV. Synthesis of the α- and β-*N*-Glycosides of 3-Deoxy-D-*glycero*-D-*galacto*-2-nonulosonic Acid (KDN)

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Several α- and β-*N*-glycosides of 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (1, KDN) were synthesized under Vorbrüggen and Williamson reaction conditions. Two hexa-*O*-acetyl derivatives of 1 were treated with trimethylsilyl derivatives of pyrimidine, 5-fluoropyrimidine and 5-methylpyrimidine, and azidotrimethylsilane to give mixtures of α- and -β-*N*-glycoside derivatives of 1. Two penta-*O*-acetyl-2-chloro derivatives of 1 were treated with the sodium salts of 2,4(1*H*,3*H*)-pyrimidinedione, 5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione and 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione to give only the α-*N*-glycosides. The anomeric configurations of these compounds could be elucidated on the basis of the coupling pattern of C-1 in ^{13}C-nuclear magnetic resonance spectral analysis.

Keywords 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN); glycosylation; *N*-glycoside; ^{13}C-NMR; sialic acid; 3-deoxy-D-nonulosonic acid

We have synthesized 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (**1**, KDN) and several *O*-glycosides of **1** under Koenigs–Knorr and Williamson reaction conditions, using 2-halogenous derivatives as glycosyl donors.[1,2] The anomeric configurations of these *O*-glycosides could be elucidated by means of proton nuclear magnetic resonance (^{1}H-NMR) and circular dichroism (CD) spectral analysis. In studies on *N*-acetylneuraminic acid, several *N*-glycosides were synthesized[3] and biological activities of these derivatives were reported. As part of a program on the synthesis of glycoconjugates binding **1**, we wish to report the synthesis of several α- and β-*N*-glycosides of **1** under Vorbrüggen and Williamson reaction conditions. The anomeric configurations of these *N*-glycosides could be elucidated on the basis of the coupling pattern in gated proton-decoupled and selective proton-decoupled ^{13}C-NMR spectral analyses.

Syntheses of **1** and the glycosyl donors (**2**, **3**, **4**, **5**) were performed on the basis of reported procedures[1,2,4,5] (Chart 1). A synthetic modification of a carbohydrate needs a large quantity of starting material because the overall yield is usually low. We developed a facile procedure which reproducibly yields hundred gram quantities of **1** in high purity and high yield by utilizing the aldol condensation reaction. The obtained **1** was utilized for the synthesis of the glycosyl donors (**2**, **3**, **4**, **5**). Treatment of **1** with cesium carbonate and benzyl bromide or iodomethane in *N*,*N*-dimethylformamide (DMF) and subsequent acetylation with acetic anhydride gave benzyl and methyl 2,4,5,7,8,9-hexa-*O*-acetyl-3-deoxy-D-*glycero*-D-*galacto*-2-nonulopyranosonates (**2**, **4**) in 47 and 41% yields, respectively. These derivatives (**2**, **4**) were treated with hydrogen chloride in acetic acid to give benzyl and methyl 4,5,7,8,9-penta-*O*-acetyl-2-chloro-2,3-dideoxy-D-*glycero*-D-*galacto*-2-nonulopyranosonates (**3**, **5**) in 94 and 91% yields, respectively. The physical properties of **2**, **3** and **4** were in good agreement with published values.[1,2,5] The structure of **5** was elucidated by ^{1}H-NMR comparison with **3**. The ^{1}H-NMR data are summarized in Table I.

Glycosylation reactions of **2** or **4** with trimethylsilyl derivatives of pyrimidine, 5-fluoropyrimidine and 5-methyl pyrimidine in the presence of tin(IV) chloride under Vorbrüggen reaction conditions gave benzyl 4,5,7,8,9-penta-*O*-acetyl-2,3-dideoxy-2-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-D-*glycero*-β-D-*galacto*-2-nonulopyranosonate (**7a**), **7b** and **7c** in 11, 18 and 6% yields, respectively. However, the α-anomers (**6a**—**c**) were obtained in poor yields (0—1%). The reaction of **5** and azidotrimethylsilane gave methyl 4,5,7,8,9-penta-*O*-acetyl-2-azido-2,3-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosonate (**6d**) in 12% yield and the β-anomer (**7d**) in 14% yield. On the other hand, the condensation reactions of **3** or **5** with the sodium salts of 2,4(1*H*,3*H*)-pyrimidinedione, 5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione and 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione

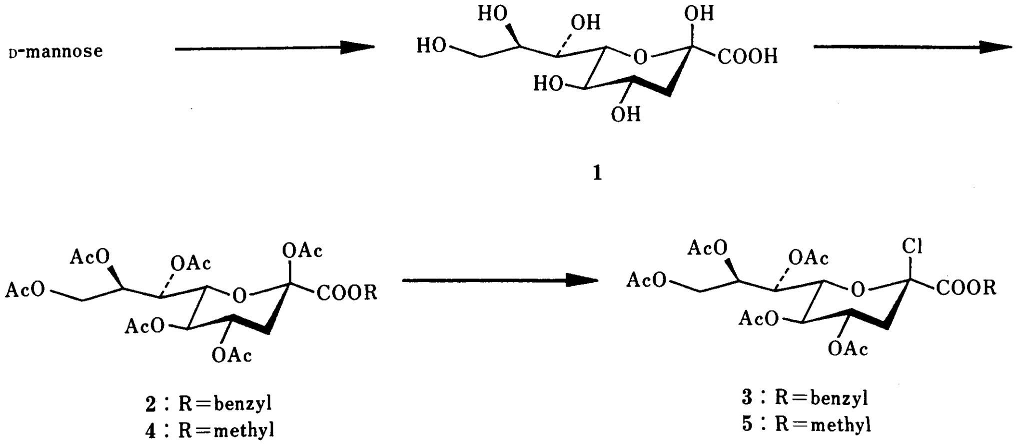
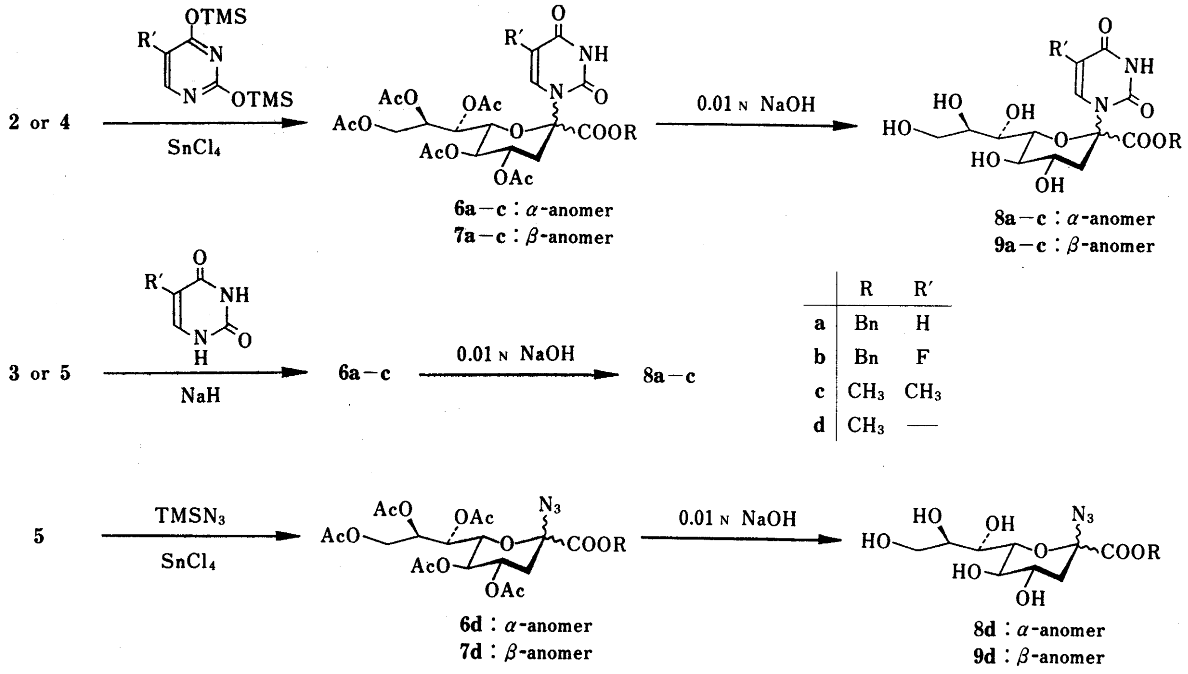


Chart 1



	R	R′
a	Bn	H
b	Bn	F
c	CH_3	CH_3
d	CH_3	—

Chart 2

Table I. Proton Chemical-Shift and Spin-Coupling Data at 300 MHz for **2**, **3**, **4**, **5**, **6a—d**, **7a—d**, **8a—d** and **9a—d**

Compound No.	Chemical shifts (δ)													Spin couplings (Hz)									
	H-3ax	H-3eq	H-4	H-5	H-6	H-7	H-8	H-9	H-9′	$COOCH_2Ph$	$COOCH_3$	$COCH_3$	Olefine	$J_{3ax,3eq}$	$J_{3ax,4}$	$J_{3eq,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$	$J_{8,9}$	$J_{8,9'}$	$J_{9,9'}$
2	2.08	2.26	5.26	4.96	4.19	5.39	5.16	4.15	4.40	5.15, 5.23		1.99—2.11		13.5	11.4	5.2	9.8	10.2	2.2	6.1	5.9	2.6	12.5
3	2.24	2.84	5.44	4.95	4.48	5.47	5.22	4.10	4.34	5.22, 5.34		2.00—2.07		14.0	11.3	5.0	10.0	10.5	2.3	8.0	5.0	2.5	12.5
4	2.06	2.60	5.24	4.95	4.17	5.37	5.13	4.12	4.42		3.77	1.99—2.14		13.8	11.8	5.2	9.7	10.0	2.4	6.3	5.8	2.7	12.5
5	2.24	2.86	5.45	4.96	4.48	5.48	5.23	4.10	4.36		3.87	2.01—2.10		13.9	11.1	5.0	9.6	10.3	2.4	8.0	4.9	2.6	12.5
6a	1.90	3.36	5.56	4.92	3.89	5.35	5.17	4.08	4.22	5.16, 5.30		1.95—2.15	5.80, 7.65	13.8	10.0	5.3	8.5	10.3	2.0	7.9	5.0	2.8	12.5
7a	2.25	3.30	5.30	5.09	3.97	5.45	5.06	4.08	4.24	5.16, 5.21		2.02—2.09	5.73, 7.65	13.8	9.6	5.5	8.2	9.5	3.0	8.2	5.0	2.8	12.5
6b	1.98	3.35	5.54	4.92	4.00	5.35	5.21	4.09	4.23	5.17, 5.35		1.96—2.17	7.78	13.8	9.5	5.3	8.7	10.3	2.0	8.0	5.0	2.8	12.5
7b	2.29	3.27	5.07	5.03	3.89	5.35	5.18	4.12	4.49	5.24		1.99—2.18	7.64	14.5	11.0	3.9	9.6	9.6	2.0	6.2	5.9	2.5	12.5
6c	1.91	3.30	5.54	4.93	3.99	5.39	5.25	4.12	4.29		3.82	1.98—2.15	7.46	13.8	10.2	5.6	8.6	10.2	1.9	8.8	5.0	2.5	12.5
7c	2.21	3.16	5.08	5.07	3.83	5.36	5.12	4.13	4.58		3.81	2.00—2.12	7.45	14.5	11.5	3.2	—	9.8	2.0	5.5	6.0	2.3	12.5
6d	1.82	2.63	5.05	4.90	3.92	5.37	5.37	4.16	4.32		3.89	2.01—2.15		13.0	11.6	5.0	9.4	10.2	1.5	—	4.1	2.0	12.6
7d	2.07	2.31	4.89	5.22	4.27	5.43	5.24	4.10	4.46		3.88	1.99—2.09		13.3	—	5.0	9.8	10.0	2.0	7.0	5.1	2.2	12.5
8a	1.63	2.97	4.13	3.55	3.61	3.83	—	—	3.71	5.10, 5.29			5.77, 7.96	13.5	11.2	5.2	8.8	10.0	1.1	9.0	—	1.8	12.0
9a	2.01	2.98	4.53	3.67	3.91	3.59	3.65	3.57	3.75	5.10, 5.19			5.71, 7.87	14.7	9.0	5.6	8.3	9.0	1.1	8.5	6.0	2.8	11.6
8b	1.62	2.97	4.13	3.55	3.60	3.83	—	—	3.72	5.10, 5.30			8.15	13.5	11.0	5.3	8.5	10.0	1.1	9.0	—	2.0	11.2
9b	2.00	2.95	—	3.63	3.53	—	—	—	—	5.14, 5.24			8.01	15.0	9.8	4.8	8.9	10.0	0.5	4.2	—	—	—
8c	1.60	2.93	4.16	—	—	3.87	3.66	—	—		3.74		7.85	13.4	11.0	5.3	8.7	—	0.5	8.7	—	—	—
9c	2.06	2.89	3.92	3.63	3.46	3.78	3.63	3.57	3.72		3.72		7.65	14.0	11.8	5.0	9.0	9.0	0.8	9.0	5.0	2.2	11.5
8d	1.60	2.53	—	—	—	—	—	3.60	—		3.81			13.0	11.8	4.8	—	—	—	—	5.0	—	12.0
9d	1.80	2.18	3.85	3.50	3.95	3.84	3.73	3.60	3.76		3.79			14.5	11.5	5.0	8.9	10.1	1.0	9.3	5.5	2.8	12.0

Data for **2**, **3**, **4**, **5**, **6a—d** and **7a—d** were recorded in $CDCl_3$. Data for **8a—d** and **9a—d** were recorded in D_2O.

gave the corresponding α-anomers (**6a—c**) in 36, 28 and 20% yields, respectively. In this reaction, the β-anomer could not be obtained. These compounds were deprotected with 0.01 N sodium hydroxide solution to give the corresponding esters (**8a—d**, **9a—d**) in 35—68% yields.

We first attempted to confirm the stereochemistry at the anomeric configurations of these *N*-glycosyl derivatives by examination of the ¹H-NMR and CD spectra in comparison with those of the *O*-glycosyl derivatives.[1,2] Figure 1 shows the CD spectra of the α-anomers (**8a—d**) and the β-anomers (**9a—d**). Based on the CD spectra of the *O*-glycosyl derivatives, the peak around 220—230 nm is assigned to the n-π* Cotton effect of the carboxyl group and the negative Cotton effect was assigned to the α-anomer and the positive one to the β-anomer. But this method is not suitable for these *N*-glycosyl derivatives (**8a—c**, **9a—c**) which contain a chromophore such as a pyrimidine group. The spectra of the azido derivatives (**8d**, **9d**) were in accordance with the above results. Table I shows the ¹H-NMR data of the α-anomers (**6a—d**, **8a—d**) and the β-anomers (**7a—d**, **9a—d**). Empirical studies of **1** and *N*-acetylneuraminic acid indicated that the H-3(eq) signal of the α-anomer is usually observed at lower field than that of the β-anomer. The differences between the chemical shifts of H-3(eq) of the α-anomers (**6a—d**, **8a—d**) and those of the β-anomers (**7a—d**, **9a—d**) were +0.06, +0.08, +0.14, +0.32, −0.01, +0.02, +0.04, and +0.35 ppm, respectively. The values except those of the azido derivatives (**6d**, **7d**, **8d**, **9d**) are smaller than those of the *O*-glycosyl derivatives owing to the anisotropy of the

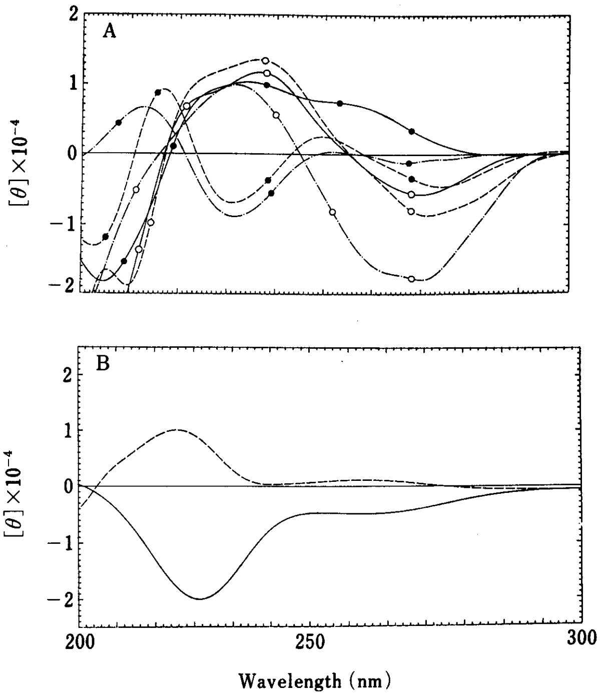


Fig. 1. CD Curves of **8a**—**d** and **9a**—**d** in MeOH at 20 °C

A. —○—, **8a**; —●—, **9a**; ---○---, **8b**; ---●---, **9b**; —·—○—·—, **8c**; —·—●—·—, **9c**. B. ——, **8d**; ---, **9d**.

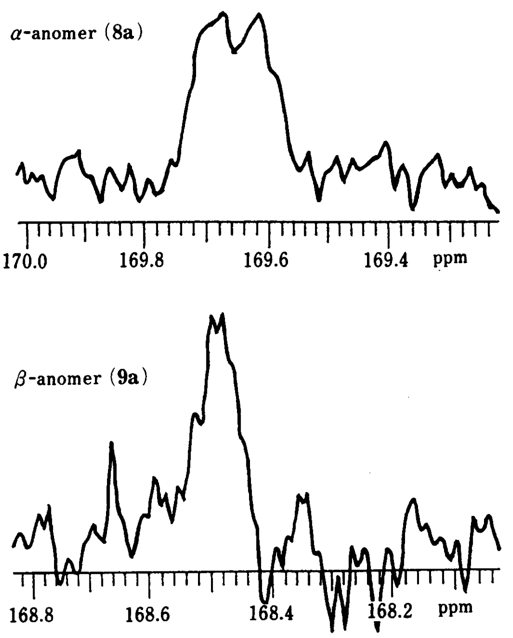


Fig. 2. C-1 Coupling Pattern of **8a** and **9a**

pyrimidine group. In conclusion, it was not possible to elucidate the stereochemistry at the anomeric position of the pyrimidine derivatives (**6a**—**c**, **7a**—**c**, **8a**—**c**, **9a**—**c**) from the CD and ^{1}H-NMR spectra. The stereochemistry at the anomeric position of the azido derivatives (**6d**, **7d**, **8d**, **9d**) could be elucidated by those methods, as could that of the *O*-glycosyl derivatives of **1**.

In studies on *N*-acetylneuraminic acid, Haverkamp *et al.*[6] and Hori *et al.*[7] have developed a method to deduce the anomeric configuration on the basis of the coupling pattern of C-1 in gated proton-decoupled or selective proton-decoupled ^{13}C-NMR spectra. We attempted to apply this method to elucidate the anomeric configuration of the *N*-glycosides of **1**. Figure 2 shows the C-1 coupling patterns of **8a** and **9a** in the gated proton-decoupled ^{13}C-NMR in D_2O at 100 MHz. The values of $J_{C1,3ax}$ (α-anomer (**8a**): 6 Hz, β-anomer (**9a**): 1 Hz) were confirmed by selective decoupling of H-3eq and ester benzyl protons. Similar measurements of the other derivatives (**8b**—**d**, **9b**—**d**) were carried out and the same results were obtained. Therefore the anomeric configurations of the *N*-glycosides could be elucidated by this method.

In conclusion, we have synthesized the α- and β-*N*-glycosyl derivatives of **1** under Vorbrüggen and Williamson reaction conditions. The anomeric configuration of these compounds could be elucidated on the basis of the coupling pattern of C-1 in the ^{13}C-NMR spectra.

Experimental

Melting points were measured with a Yamato melting point apparatus and the results are uncorrected. Optical rotations were measured with a JASCO JIP-4 digital polarimeter. Thin layer chromatography (TLC) was performed on Silica gel GF-254 (Merck) plates, and spots were detected by ultraviolet (UV) irradiation and by spraying with 5% sulfuric acid solution. Fast atom bombardment mass spectra (FAB-MS), and infrared (IR) spectra were measured with JEOL JMS-DX300 and JASCO FT/IR-7300 instruments, respectively. CD spectra were measured in a 0.1 cm cell with a JASCO J-720 spectropolarimeter. The ^{1}H-NMR spectra were measured with Varian VXR-300 and XL-400 spectrometers. Tetramethylsilane (TMS) in $CDCl_3$ or sodium 3-(trimethylsilyl)-1-propanesulfonate (DDS) in D_2O was used as an internal reference. Column chromatography was conducted on Silica gel 60 (70—230 mesh).

3-Deoxy-D-*glycero*-D-*galacto*-2-nonulosonic Acid (1) Oxalacetic acid (73.3 g, 0.555 mol) was added to water (440 ml) at 5 °C, and its solution was adjusted to pH 11 with 10 M sodium hydroxide. D-Mannose (300 g, 1.66 mol) was added, and the mixture was stirred for 2 h at room temperature (the pH was maintained at 11 by adding 10 M sodium hydroxide). The solution was acidified (pH 6) with Dowex-50(H^+) resin in the presence of nickel(II) chloride (1.71 g, 13.2 mmol) at 50 °C, stirred for 1 h (the solution was kept at pH 6 with Dowex-50(H^+) resin), then filtered and evaporated. Purification of **1** was achieved by column chromatography on Dowex-50(H^+) resin with 0.3 N formic acid, and the eluate was concentrated under reduced pressure to give **1** (109 g, 73% from oxalacetic acid) as a colorless amorphous solid. $[\alpha]_D^{23}$ −40.7° ($c=2.4$, H_2O). FAB-MS *m/z*: 269 ($M^+ + 1$). *Anal.* Calcd for $C_9H_{16}O_9\cdot 2H_2O$: C, 35.53; H, 6.63. Found: C, 35.24; H, 6.51. IR ν_{max}^{KBr} cm^{-1}: 3385, 1745. ^{1}H-NMR (300 MHz, D_2O) δ: 1.69 (1H, dd, $J=12.9$, 11.8 Hz, 3_{ax}-H), 2.12 (1H, dd, $J=12.9$, 5.0 Hz, 3_{eq}-H), 3.45 (1H, dd, $J=9.2$, 9.8 Hz, 5-H), 3.52 (1H, dd, $J=11.5$, 6.3 Hz, 9-H), 3.62 (1H, ddd, $J=9.0$, 6.3, 2.4 Hz, 8-H), 3.70—3.76 (2H, m, 7 and 9-H), 3.85 (1H, dd, $J=10.0$, 9.8 Hz, 6-H), 3.86 (1H, ddd, $J=11.8$, 9.2, 5.0 Hz, 4-H).

Benzyl 2,4,5,7,8,9-Hexa-*O*-acetyl-3-deoxy-D-*glycero*-β-D-*galacto*-2-nonulopyranosonate (2) Anhydrous cesium carbonate (6.07 g, 18.6 mmol) was added to a solution of **1** (10.0 g, 37.2 mmol) in water (50 ml) at room temperature, and the solution was evaporated to dryness. The amorphous residue was suspended in DMF (50 ml), and benzyl bromide (12.7 g, 74.4 mmol) was added. The mixture was stirred for 18 h, then acetic anhydride (68.3 g, 0.669 mol), pyridine (52.9 g, 0.669 mol) and 4-dimethylaminopyridine (0.454 g, 3.72 mmol) were added at 5 °C. The whole was stirred for 18 h at room temperature, poured into 0.5 N HCl (1400 ml) and extracted with ethyl acetate (300 ml × 3). This extract was washed with sodium hydrogen carbonate solution and brine, dried and concentrated. The residual syrup was purified on a column of silica gel with ether–hexane (1 : 1) to yield **2** (10.7 g, 47%) as an amorphous powder. $[\alpha]_D^{25}$ −17.4° ($c=1.0$, $CHCl_3$). FAB-MS *m/z*: 611 ($M^+ + 1$). *Anal.* Calcd for $C_{28}H_{34}O_{15}$: C, 55.08; H, 5.61. Found: C, 55.29; H, 5.78. IR ν_{max}^{KBr} cm^{-1}: 2960, 1745.

Benzyl 4,5,7,8,9-Penta-*O*-acetyl-2-chloro-2,3-dideoxy-D-*glycero*-β-D-*galacto*-2-nonulopyranosonate (3) A solution of **2** (4.0 g, 6.55 mmol) in acetic acid (40 ml) and acetyl chloride (4 ml) was saturated with dry hydrogen chloride at 5 °C. After being stirred for 8 h at room temperature, the solution was evaporated, and the residue was purified on a column of silica gel with ether–hexane (1 : 1) to yield **3** (3.61 g, 94%) as colorless plates, mp 108—110 °C (ether–hexane). $[\alpha]_D^{25}$ −61.9° (c=0.32, $CHCl_3$). Electron impact mass spectra (EI-MS) m/z: 586 (M^+). *Anal.* Calcd for $C_{26}H_{31}ClO_{13}$: C, 53.20; H, 5.32. Found: C, 53.12; H, 5.42. IR ν_{max}^{KBr} cm^{-1}: 2950, 1430, 1360.

Methyl 2,4,5,7,8,9-Hexa-*O*-acetyl-3-deoxy-D-*glycero*-β-D-*galacto*-2-nonulopyranosonate (4) Anhydrous cesium carbonate (3.64 g, 11.1 mmol) was added to a solution of **1** (6.00 g, 22.3 mmol) in water (30 ml) at room temperature, and the solution was evaporated to dryness. The amorphous residue was suspended in DMF (30 ml), and iodomethane (6.33 g, 44.6 mmol) was added. The mixture was stirred for 18 h, then acetic anhydride (40.9 g, 0.401 mol), pyridine (31.7 g, 0.401 mol) and 4-dimethylaminopyridine (0.272 g, 2.23 mmol) were added at 5 °C. The whole was stirred for 18 h at room temperature, poured into 0.5 N HCl (840 ml) and extracted with ethyl acetate (180 ml × 3). This extract was washed with sodium hydrogen carbonate solution and brine, dried and concentrated. The residual syrup was purified on a column of silica gel with ether–hexane (1 : 1) to yield **4** (4.90 g, 41%) as colorless prisms, mp 104—105 °C (ether–hexane). $[\alpha]_D^{19}$ −20.4° (c=0.71, $CHCl_3$). EI-MS m/z: 534 (M^+). *Anal.* Calcd for $C_{22}H_{30}O_{15}$: C, 49.44; H, 5.66. Found: C, 49.49; H, 5.70. IR ν_{max}^{KBr} cm^{-1}: 2950, 1750, 1440, 1370, 1230.

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2-chloro-2,3-dideoxy-D-*glycero*-β-D-*galacto*-2-nonulopyranosonate (5) A solution of **4** (2.00 g, 3.74 mmol) in acetic acid (20 ml) and acetyl chloride (2 ml) was saturated with dry hydrogen chloride at 5 °C. After being stirred for 8 h at room temperature, the solution was evaporated to dryness, and the residue was purified on a column of silica gel with ether–hexane (1 : 1) to yield **5** (1.74 g, 91%) as an amorphous powder. $[\alpha]_D^{22}$ −95.3° (c=0.44, $CHCl_3$). FAB-MS m/z: 511 (M^++1). *Anal.* Calcd for $C_{20}H_{27}ClO_{13}$: C, 47.02; H, 5.33. Found: C, 47.31; H, 5.45. IR ν_{max}^{KBr} cm^{-1}: 2962, 1752, 1236.

Benzyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dideoxy-2-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-D-*glycero*-α- and -β-D-*galacto*-2-nonulopyranosonates (6a, 7a) a) Tin(IV) chloride (1.72 g, 6.60 mmol) was added to a solution of **2** (2.00 g, 3.30 mmol) and trimethylsilylpyrimidine (1.69 g, 6.60 mmol) in acetonitrile (66 ml). The mixture was stirred for 24 h at room temperature, then sodium hydrogen carbonate (2.21 g, 26.4 mmol) in water (10 ml) was added under stirring. After evaporation of the solution, the residue was extracted with dichloromethane (50 ml × 3). The extract was washed with brine, dried and concentrated. The residual syrup was purified on a column of silica gel with ether to yield the α-anomer (**6a**) (18 mg, 1%) and the β-anomer (**7a**) (238 mg, 11%), each as an amorphous powder.

b) Sodium hydride (68.0 mg, 1.70 mmol) was added to a solution of 2,4(1*H*,3*H*)-pyrimidinedione (190 mg, 1.70 mmol) in DMF at room temperature. The mixture was stirred for 1 h, then **3** (1.00 g, 1.70 mmol) was added at room temperature, and stirring was continued for 5 h. Then the solution was poured into water (200 ml) and extracted with ethyl acetate (50 ml × 3). This extract was washed with brine, dried and concentrated. The residual syrup was purified on a column of silica gel with ether to yield the α-anomer (**6a**) (406 mg, 36%) as an amorphous powder.

α-Anomer (**6a**): $[\alpha]_D^{24}$ −36.8° (c=0.29, $CHCl_3$). FAB-MS m/z: 663 (M^++1). *Anal.* Calcd for $C_{30}H_{34}N_2O_{15}$: C, 54.38; H, 5.17; N, 4.23. Found: C, 54.59; H, 5.33; N, 4.09. IR ν_{max}^{KBr} cm^{-1}: 3481, 1751, 1698, 1233.

β-Anomer (**7a**): $[\alpha]_D^{24}$ −6.4° (c=0.31, $CHCl_3$). FAB-MS m/z: 663 (M^++1). *Anal.* Calcd for $C_{30}H_{34}N_2O_{15}$: C, 54.38; H, 5.17; N, 4.23. Found: C, 54.63; H, 5.26; N, 4.11. IR ν_{max}^{KBr} cm^{-1}: 1757, 1700, 1225.

Benzyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dideoxy-2-(2,4-dioxo-5-fluoro-1,2,3,4-tetrahydropyrimidin-1-yl)-D-*glycero*-α- and -β-D-*galacto*-2-nonulopyranosonates (6b, 7b) a) Tin(IV) chloride (1.72 g, 6.60 mmol) was added to a solution of **2** (2.00 g, 3.30 mmol) and 5-fluorotrimethylsilylpyrimidine (1.80 g, 6.60 mmol) in acetonitrile (66 ml). The solution was processed as described for **6a** and **7a** to give the α-anomer (**6b**) (24 mg, 1%) as colorless needles and the β-anomer (**7b**) (401 mg, 18%) as an amorphous powder.

b) Sodium hydride (68.0 mg, 1.70 mmol) was added to a solution of 5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione (220 mg, 1.70 mmol) in DMF at room temperature. The mixture was stirring for 1 h, then **3** (1.00 g, 1.70 mmol) was added at room temperature. The solution was processed as described for **6a** to give the α-anomer (**6b**) (324 mg, 28%) as colorless needles.

α-Anomer (**6b**): mp 157—160 °C (ether). $[\alpha]_D^{24}$ −26.6° (c=0.35, $CHCl_3$). FAB-MS m/z: 681 (M^++1). *Anal.* Calcd for $C_{30}H_{33}FN_2O_{15}\cdot H_2O$: C, 51.58; H, 5.05; N, 4.01. Found: C, 51.83; H, 4.85; N, 3.88. IR ν_{max}^{KBr} cm^{-1}: 3229, 1754, 1711, 1225.

β-Anomer (**7b**): $[\alpha]_D^{24}$ −44.3° (c=0.27, $CHCl_3$). FAB-MS m/z: 681 (M^++1). *Anal.* Calcd for $C_{30}H_{33}FN_2O_{15}$: C, 52.94; H, 4.88; N, 4.11. Found: C, 53.01; H, 5.02; N, 3.92. IR ν_{max}^{KBr} cm^{-1}: 3231, 1751, 1236.

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2,3-dideoxy-2-(2,4-dioxo-5-methyl-1,2,3,4-tetrahydropyrimidin-1-yl)-D-*glycero*-α- and -β-D-*galacto*-2-nonulopyranosonates (6c, 7c) a) Tin(IV) chloride (1.95 g, 7.48 mmol) was added to a solution of **4** (2.00 g, 3.74 mmol) and 5-methyltrimethylsilylpyrimidine (2.02 g, 7.48 mmol) in acetonitrile (75 ml). The solution was processed as described for **6a** and **7a** to give the β-anomer (**7c**) (135 mg, 6%) as an amorphous powder.

b) Sodium hydride (78.0 mg, 1.96 mmol) was added to a solution of 5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (247 mg, 1.96 mmol) in DMF at room temperature. The mixture was stirred for 1 h, then **5** (1.00 g, 1.96 mmol) was added at room temperature. The solution was processed as described for **6a** to give the α-anomer (**6c**) (240 mg, 20%) as an amorphous powder.

α-Anomer (**6c**): $[\alpha]_D^{20}$ −53.9° (c=0.29, $CHCl_3$). FAB-MS m/z: 601 (M^++1). *Anal.* Calcd for $C_{25}H_{32}N_2O_{15}$: C, 50.00; H, 5.37; N, 4.66. Found: C, 50.12; H, 5.44; N, 4.39. IR ν_{max}^{KBr} cm^{-1}: 1752, 1698, 1236.

β-Anomer (**7c**): $[\alpha]_D^{20}$ −71.6° (c=0.21, $CHCl_3$). FAB-MS m/z: 601 (M^++1). *Anal.* Calcd for $C_{25}H_{32}N_2O_{15}$: C, 50.00; H, 5.37; N, 4.66. Found: C, 50.02; H, 5.65; N, 4.41. IR ν_{max}^{KBr} cm^{-1}: 1751, 1698, 1234.

Methyl 4,5,7,8,9-Penta-*O*-acetyl-2-azido-2,3-dideoxy-D-*glycero*-α- and -β-D-*galacto*-2-nonulopyranosonates (6d, 7d) Tin(IV) chloride (1.95 g, 7.48 mmol) was added to a solution of **4** (2.00 g, 3.74 mmol) and azidotrimethylsilane (860 mg, 7.48 mmol) in acetonitrile (75 ml). The solution was processed as described for **6a** and **7a** to give the α-anomer (**6d**) (232 mg, 12%) and the β-anomer (**7d**) (271 mg, 14%), each as an amorphous powder.

α-Anomer (**6d**): $[\alpha]_D^{20}$ −46.7° (c=0.33, $CHCl_3$). FAB-MS m/z: 518 (M^++1). *Anal.* Calcd for $C_{20}H_{27}N_3O_{13}$: C, 46.42; H, 5.26; N, 8.12. Found: C, 46.71; H, 5.50; N, 8.03. IR ν_{max}^{KBr} cm^{-1}: 2123, 1749, 1218.

β-Anomer (**7d**): $[\alpha]_D^{20}$ −41.5° (c=0.21, $CHCl_3$). FAB-MS m/z: 518 (M^++1). *Anal.* Calcd for $C_{20}H_{27}N_3O_{13}\cdot 1/2H_2O$: C, 45.63; H, 5.36; N, 7.98. Found: C, 45.58; H, 5.30; N, 7.85. IR ν_{max}^{KBr} cm^{-1}: 2125, 1747, 1220.

Benzyl 2,3-Dideoxy-2-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-D-*glycero*-α- and -β-D-*galacto*-2-nonulopyranosonates (8a, 9a) A solution of **6a** or **7a** (100 mg, 0.151 mmol) in 0.01 N NaOH (76 ml) was stirred for 1 h at room temperature. The solution was neutralized with acetic acid and evaporated to dryness. The residual syrup was purified on a column of silica gel with CH_2Cl_2–EtOH (10 : 1) to yield the α-anomer (**8a**) (42 mg, 61%) or the β-anomer (**9a**) (33 mg, 48%) as an amorphous powder.

α-Anomer (**8a**): $[\alpha]_D^{24}$ −83.1° (c=0.17, EtOH). FAB-MS m/z: 453 (M^++1). *Anal.* Calcd for $C_{20}H_{24}N_2O_{10}$: C, 53.10; H, 5.35; N, 6.19. Found: C, 52.94; H, 5.09; N, 6.36. IR ν_{max}^{KBr} cm^{-1}: 3395, 1745, 1695.

β-Anomer (**9a**): $[\alpha]_D^{20}$ −35.2° (c=0.19, EtOH). FAB-MS m/z: 453 (M^++1). *Anal.* Calcd for $C_{20}H_{24}N_2O_{10}$: C, 53.10; H, 5.35; N, 6.19. Found: C, 52.96; H, 5.51; N, 5.82. IR ν_{max}^{KBr} cm^{-1}: 3393, 1750, 1684.

Benzyl 2,3-Dideoxy-2-(2,4-dioxo-5-fluoro-1,2,3,4-tetrahydropyrimidin-1-yl)-D-*glycero*-α- and -β-D-*galacto*-2-nonulopyranosonates (8b, 9b) A solution of **6b** and **7b** (100 mg, 0.147 mmol) in 0.01 N NaOH (74 ml) was stirred for 1 h at room temperature. The solution was processed as described for **8a** and **9a** to give the α-anomer (**8b**) (43 mg, 63%) or the β-anomer (**9b**) (24 mg, 35%) as an amorphous powder.

α-Anomer (**8d**): $[\alpha]_D^{20}$ −97.7° (c=0.23, EtOH). FAB-MS m/z: 471 (M^++1). *Anal.* Calcd for $C_{20}H_{23}FN_2O_{10}$: C, 51.07; H, 4.93; N, 5.96. Found: C, 50.83; H, 4.81; N, 5.71. IR ν_{max}^{KBr} cm^{-1}: 3394, 1701.

β-Anomer (**9d**): $[\alpha]_D^{20}$ −65.9° (c=0.18, MeOH). FAB-MS m/z: 471 (M^++1). *Anal.* Calcd for $C_{20}H_{23}FN_2O_{10}$: C, 51.07; H, 4.93; N, 5.96. Found: C, 50.91; H, 4.99; N, 5.75. IR ν_{max}^{KBr} cm^{-1}: 3395, 1705.

Methyl 2,3-Dideoxy-2-(2,4-dioxo-5-methyl-1,2,3,4-tetrahydropyrimidin-1-yl)-D-*glycero*-α- and -β-D-*galacto*-2-nonulopyranosonates (8c, 9c) A solution of **6c** or **7c** (100 mg, 0.166 mmol) in 0.01 N NaOH (83 ml) was stirred for 1 h at room temperature. The solution was processed as described for **8a** and **9a** to give the α-anomer (**8c**) (44 mg, 68%) or the β-anomer (**9c**) (26 mg, 40%) as an amorphous powder.

α-Anomer (**8c**): $[\alpha]_D^{20}$ −89.6° (c=0.42, MeOH). FAB-MS m/z: 391 (M^++1). *Anal.* Calcd for $C_{15}H_{22}N_2O_{10}\cdot 1/2H_2O$: C, 45.11; H, 5.80; N, 7.01. Found: C, 45.38; H, 5.81; N, 6.84. IR ν_{max}^{KBr} cm^{-1}: 3400, 1699.

β-Anomer (**9c**): $[\alpha]_D^{20}$ −104.8° (c=0.25, MeOH). FAB-MS m/z: 391 (M^++1). *Anal.* Calcd for $C_{15}H_{22}N_2O_{10}\cdot H_2O$: C, 44.12; H, 5.92; N, 6.86. Found: C, 44.39; H, 6.07; N, 6.59. IR ν_{max}^{KBr} cm^{-1}: 3396, 1701.

Methyl 2-Azido-2,3-dideoxy-D-*glycero*-α- and -β-D-*galacto*-2-nonulopyranosonates (8d, 9d) A solution of **6d** or **7d** (100 mg, 0.193 mmol) in 0.01 N NaOH (96 ml) was stirred for 1 h at room temperature. The solution was processed as described for **8a** and **9a** to give the α-anomer (**8d**) (31 mg, 52%) or the β-anomer (**9d**) (40 mg, 68%) as an amorphous powder.

α-Anomer (**8d**): $[\alpha]_D^{20}$ −92.6° (c=0.49, MeOH). FAB-MS m/z: 308 ($M^+ + 1$). *Anal.* Calcd for $C_{10}H_{17}N_3O_8 \cdot 1/2H_2O$: C, 37.98; H, 5.74; N, 13.29. Found: C, 38.17; H, 5.69; N, 13.53. IR ν_{max}^{KBr} cm^{-1}: 3383, 2939, 2122, 1741.

β-Anomer (**9d**): $[\alpha]_D^{20}$ −81.7° (c=0.31, MeOH). FAB-MS m/z: 308 ($M^+ + 1$). *Anal.* Calcd for $C_{10}H_{17}N_3O_8 \cdot 2/3H_2O$: C, 37.62; H, 5.58; N, 13.16. Found: C, 37.62; H, 5.56; N, 12.87. IR ν_{max}^{KBr} cm^{-1}: 3238, 2109, 1745.

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