Facile Synthesis of 4-Acylamino-2,6-anhydro-2,3,4-trideoxy-D-*glycero*-D-*galacto*-non-2-enoic Acids

Xue-Long SUN, Toshitsugu KAI, Makoto TANAKA, Hiroaki TAKAYANAGI, and Kimio FURUHATA*

School of Pharmaceutical Sciences, Kitasato University, 5–9–1 Shirokane, Minato-ku, Tokyo 108, Japan.
Received April 10 1995; accepted June 6, 1995

The title compounds were synthesized from 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (5, KDN) by a new method which is similar to the Ritter reaction. The structures of these compounds were elucidated from the MS, elemental analysis, ^{1}H-NMR and ^{13}C-NMR data, and the stereochemistry of methyl 4-benzoylamino-5,7,8,9-tetra-*O*-acetyl-2,6-anhydro-2,3-dideoxy-D-*glycero*-D-*galacto*-non-2-enonate (13) was determined by X-ray crystallographic analysis.

Key words sialic acid; 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid; KDN; sialidase inhibitor; Ritter reaction; acetonitrile

Sialic acids are biologically important carbohydrates[1–6] with a vast range of functions extending from cell-recognition processes through to involvement in immunologic events.[7,8] An Australian research group has developed synthetic inhibitors of influenza virus sialidase, including 4-amino- and 4-guanidino derivatives of 5-*N*-acetyl-2,6-anhydro-2,3,5-trideoxy-D-*glycero*-D-*galacto*-non-2-enoic acid (**1**, Neu5Ac2ene), which were designed based on the protein structural data from a complex of the influenza sialidase with an inhibitor.[9] Recently, the formation of allylic acetamides from methyl 3-deoxy-ulonate, methyl 2,4,5,7-tetra-*O*-acetyl-deoxy-L-*arabino*-2-heptalo-pyranosonate (**2**), methyl 2,4,7,8,9-penta-*O*-acetyl-5-deacetamido-neuraminate (**3**), and methyl 2,4,7,8,9-tetra-*O*-acetyl-*N*-acetyl-neuraminate (**4**) under Ritter reaction conditions[10] was reported by Driguez *et al.*[11] and Starkey *et al.*[12]

We have reported the synthesis of *N*-glycosides of *N*-acetylneuraminic acid (Neu5Ac) and 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (**5**, KDN) under Vorbruggen reaction conditions using tin(IV) chloride as the catalyst and acetonitrile as the solvent. In these reactions, a 4-acetamido group was substituted for the 4-*O*-acetyl group of **4**, and methyl 2,4,5,7,8,9-hexa-*O*-acetyl-3-deoxy-D-*glycero*-D-*galacto*-2-nonulopyranosonate (**6**), and the corresponding 4-acetamido derivatives were also isolated as by-products in trace quantities.[13–15] Therefore, it was necessary to examine in detail the formation of the 4-amido derivatives from **6** under Ritter-type reaction conditions. We report herein a facile stereoselective methodology for the introduction of nitrogen at the C-4 position on KDN by the treatment of **6** with several nitriles and Lewis acids. The methyl 5,7,8,9-tetra-*O*-acetyl-4-acylamino-2,6-anhydro-2,3,4-trideoxy-D-*glycero*-D-*galacto* and D-*talo*-2-enonates were synthesized in high yields from **6** using various nitriles as the solvent and tin(IV) chloride or trimethylsilyl triflate (TMSOTf) as the catalyst. The structures of the synthesized derivatives were elucidated mainly on the basis of the proton nuclear magnetic resonance (^{1}H-NMR) spectral data. The proton assignments were based on published data from spin-decoupling experiments. Furthermore, the allylic acetamide structure of methyl 4-benzoylamino-5,7,8,9-tetra-*O*-acetyl-2,6-anhydro-2,3-dideoxy-D-*glycero*-D-*galacto*-non-2-enonate (**13**) was confirmed by X-ray crystallographic analysis.

Results and Discussion

Crystalline KDN (**5**) was prepared in high purity and high yield by the aldol condensation of D-mannose with oxalacetic acid without formation of 4-*epi*-KDN.[13,16] Compound **6** was prepared from **5** by the reported method.[16] The target compound, methyl 4-acetylamino-5,7,8,9-tetra-*O*-acetyl-2,6-anhydro-2,3,4-trideoxy-D-*glycero*-D-*galacto*-non-2-enonate, was synthesized from an acetonitrile solution of **6** in the presence of tin(IV) chloride (2 eq) as a catalyst at room temperature. The reaction mixture was subjected to careful chromatographic separation, affording a mixture of two epimers in 22% yield and the starting material in 62% yield. The ratio of epimeric methyl 4-acetylamino-5,7,8,9-tetra-*O*-acetyl-

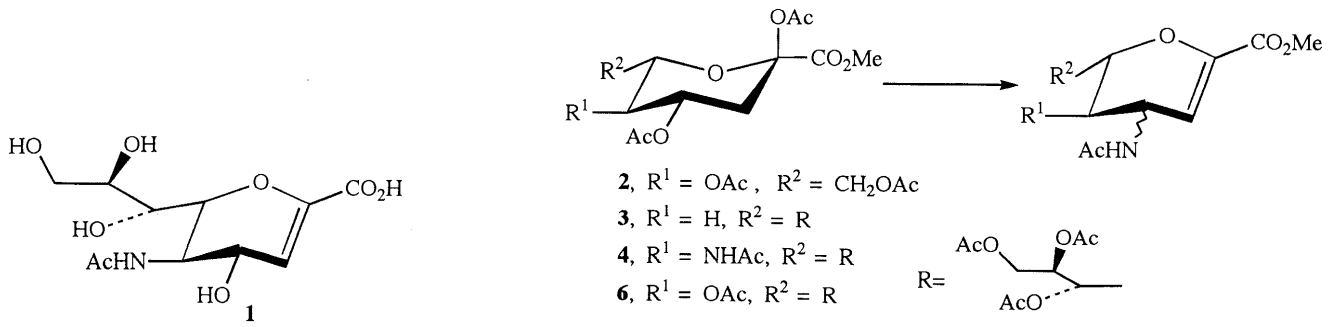
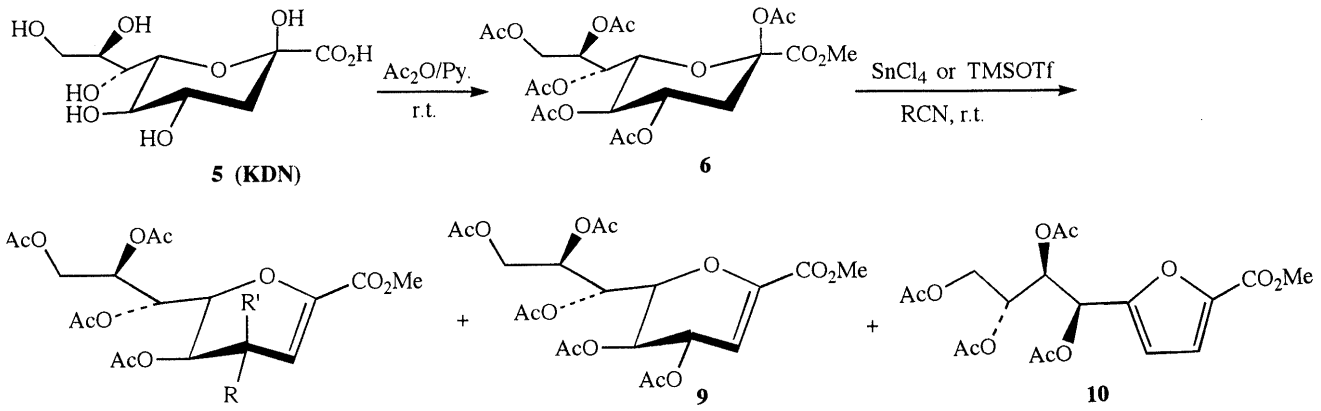


Chart 1

* To whom correspondence should be addressed.



7 R = $NHCOCH_3$, R' = H
8 R = H, R' = $NHCOCH_3$
11 R = $NHCOCH_2CH_3$, R' = H
12 R = H, R' = $NHCOCH_2CH_3$
13 R = $NHCOC_6H_5$, R' = H
14 R = H, R' = NHCO CCl_3
15 R = $NHCOCCl_3$, R' = H

Chart 2

Table 1. Isolation Yield of 4-Amido-KDN2en Derivatives

Run	Reagent and solvent	Catalyst	Time (h)	Total yield (%)	Ratio of α- and β-isomers	By-product (%)		
						9	**10**	**6**[a]
1	MeCN	$SnCl_4$ (2eq)	12	22	1:3			62
2	MeCN	$SnCl_4$ (10eq)	12	10	0:10	30	40	
3	MeCN	TMSOTf (2eq)	3	86	4:1		9	
4	EtCN	$SnCl_4$ (2eq)	12	30	7:8			55
5	EtCN	$SnCl_4$ (10eq)	12	7	0:7	25	35	
6	C_6H_5CN	$SnCl_4$ (2eq)	12	18.5	1:36			68
7	C_6H_5CN	$SnCl_4$ (10eq)	12	48	1:48			
8	Cl_3CCN	$SnCl_4$ (2eq)	12	72	3:8			15

a) Recovered starting material (**6**).

Table 2. Proton Chemical Shifts and Coupling Constants in $CDCl_3$

Compd.	Chemical shift (ppm)			Coupling constant (Hz)	
	H-3	H-4	H-5	$J_{3,4}$	$J_{4,5}$
7	5.94	4.90	4.92	2.4	8.4
8	6.00	4.92	4.99	5.7	5.1
11	5.39	4.91	4.93	2.1	8.1
12	5.99	4.94	4.99	5.1	5.7
13	6.00	5.05	5.08	2.3	8.5[a]
14	6.05	4.64	5.32	3.1	8.4
15	6.15	4.86	4.97	5.7	5.7

a) Determined in pyridine-d_5.

2,6-anhydro-2,3,4-trideoxy-D-*glycero*-D-*galacto*-non-2-enonate (**7**) and methyl 4-acetylamino-5,7,8,9-tetra-*O*-acetyl-2,6-anhydro-2,3,4-trideoxy-D-*glycero*-D-*talo*-non-2-enonate (**8**) was approximately 3 : 1. The presence of the acetamido group in **7** and **8** was indicated by the infrared (IR) spectra, which showed characteristic acetamido group absorptions at 1680 and 1682 cm^{-1}, respectively. When TMSOTf was used instead of tin(IV) chloride, the total yield of **7** and **8** increased to 86% after chromatographic separation, and the ratio of **7** and **8** changed to 1 : 4. Treatment of **6** with an excess amount of tin(IV) chloride (10 eq) in acetonitrile gave **7** and **8** in 10% yield together with a large amount of methyl 4,5,7,8,9-penta-*O*-acetyl-2,6-anhydro-2,3-dideoxy-D-*glycero*-D-*galacto*-non-2-enonate (**9**) and (1′*S*,2′*R*,3′*R*)-methyl 5-(1′,2′,3′,4′-tetra-*O*-acetylbutyl) furoate (**10**) as shown in Chart 2.

The structures of **7** and **8** were elucidated from the ^{1}H-NMR and ^{13}C-NMR spectral data in comparison with those of **9**[18] and from a comparison of the ^{1}H-NMR spectral data with those of the corresponding *N*-acetylneuraminic acid derivatives.[19,20] Selected ^{1}H-NMR data are shown in Table 2. In particular, a doublet due to NH on an acetamido group was observed for both epimers, at 5.74 ppm for **7** and 5.39 ppm for **8**. The orientation of H-4 was easily deduced from the values of the coupling constants between H-3 and H-4, and H-4 and H-5. The coupling constants $J_{3,4}$ = 2.4 Hz and $J_{4,5}$ = 8.4 Hz indicate β-configuration for **7**, and the coupling constants, $J_{3,4}$ = 5.7 Hz and $J_{4,5}$ = 5.1 Hz indicate α-configuration for **8**. ^{1}H-NMR studies of Neu5Ac2en (**1**) and 4-*epi*-Neu5Ac2en indicated that the coupling constant between H-3 and H-4 of **1** ($J_{3,4}$ = 3.3 Hz) is smaller than

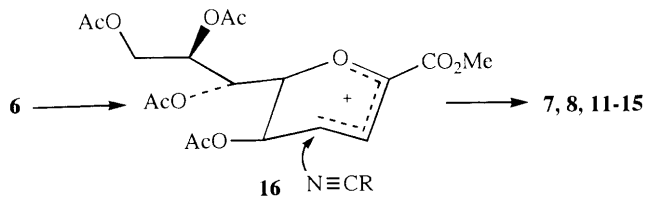


Chart 3

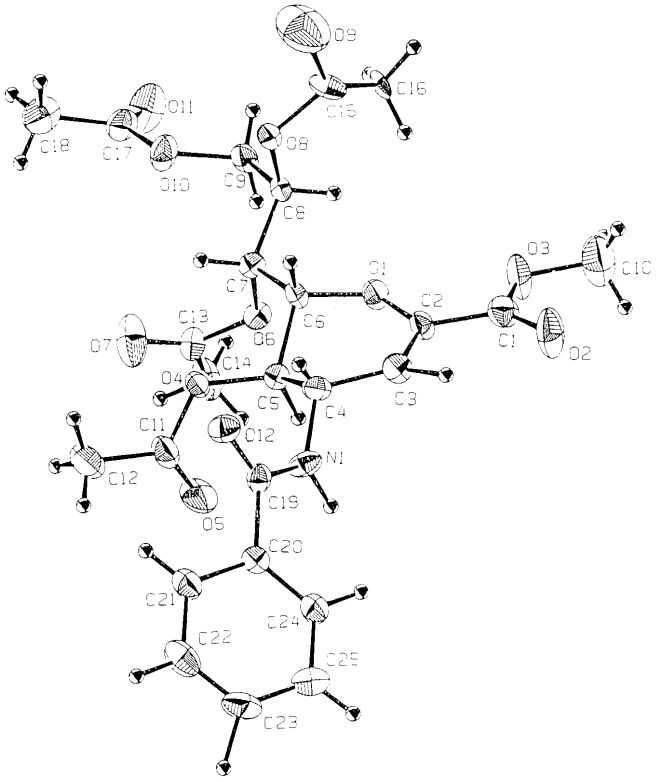


Fig. 1. ORTEP Drawing of **13**

that of 4-*epi*-Neu5Ac2en ($J_{3,4}=5.4$ Hz).[20] The coupling constant $J_{3,4}$ of the α-isomer (**7**) at C-4 is also smaller than that of the β-isomer (**8**), and the H-3 and H-4 singnals of the 4α-isomer are observed at higher field than those of the 4β-isomer. In the same manner, treatment of **6** in propionitrile, benzonitrile, and trichloroacetonitrile with tin(IV) chloride gave the corresponding 4-amido derivatives (**11**—**15**). The total yield and ratio of the products varied depending upon the reaction conditions as shown in Table 1. In the case of benzonitrile, only methyl 4-benzoylamino-5,7,8,9-tetra-*O*-acetyl-2,6-anhydro-2,3-dideoxy-D-*glycero*-D-*galacto*-non-2-enonate (**13**) was obtained. However, we could not obtain compounds **14** and **15** using trimethylsilyl triflate as a catalyst in trichloroacetonitrile. These compounds may be derived from an allyl carbocation of type **16** *via* the known reaction intermediate (Chart 3).[11] Details of the reaction mechanism will be reported in due course.

We conducted an X-ray crystallographic analysis of **13**, because only **13** afforded good crystals on recrystallization from ethyl acetate–*n*-hexane. An ORTEP drawing in Fig. 1 shows that the conformation of the pyranose ring of **13** is a normal half chair ($^6H_5$), with similar features to those of other general glycals.[21,22] The absolute configuration at C-4 was assigned as *S* (α-configuration). Furthermore,

Table 3. Atomic Coordinates (10^4) with Their Standard Deviations in Parentheses and Equivalent Isotropic Temperature Factors of **13**

Atom	*x*	*y*	*z*	B_{eq}
O(1)	0.4199 (3)	0.2014 (2)	0.358 (1)	3.8 (3)
O(2)	0.5554 (4)	0.2879 (2)	0.184 (2)	7.1 (5)
O(3)	0.4371 (4)	0.2723 (2)	0.058 (2)	6.0 (4)
O(4)	0.4666 (3)	0.0949 (2)	0.174 (1)	3.0 (3)
O(5)	0.5113 (5)	0.0444 (2)	0.425 (1)	7.1 (5)
O(6)	0.3313 (3)	0.1165 (2)	0.292 (1)	3.2 (3)
O(7)	0.3116 (5)	0.0477 (2)	0.500 (1)	7.3 (5)
O(8)	0.2638 (3)	0.2044 (2)	0.729 (1)	3.4 (3)
O(9)	0.2398 (6)	0.2729 (3)	0.976 (2)	11.6 (7)
O(10)	0.1702 (3)	0.1258 (2)	0.629 (1)	4.8 (3)
O(11)	0.0588 (4)	0.1111 (3)	0.436 (2)	7.1 (5)
O(12)	0.6242 (3)	0.1276 (2)	1.055 (1)	4.0 (3)
N(1)	0.6176 (3)	0.1364 (3)	0.638 (2)	3.8 (4)
C(1)	0.4987 (6)	0.2646 (3)	0.198 (2)	4.5 (5)
C(2)	0.4909 (5)	0.2231 (3)	0.361 (2)	3.3 (4)
C(3)	0.5503 (5)	0.2069 (3)	0.490 (2)	3.8 (4)
C(4)	0.5464 (7)	0.1631 (4)	0.638 (2)	3.3 (5)
C(5)	0.4784 (5)	0.1339 (3)	0.548 (2)	2.8 (4)
C(6)	0.4090 (5)	0.1674 (3)	0.554 (2)	2.8 (4)
C(7)	0.3318 (4)	0.1441 (3)	0.519 (2)	2.9 (4)
C(8)	0.2670 (5)	0.1797 (2)	0.492 (2)	2.7 (4)
C(9)	0.1896 (5)	0.1598 (3)	0.433 (2)	3.6 (5)
C(10)	0.4406 (6)	0.3128 (4)	−0.107 (3)	8.4 (8)
C(11)	0.4119 (6)	0.0511 (3)	0.634 (2)	4.3 (5)
C(12)	0.4904 (6)	0.0153 (3)	0.828 (2)	6.3 (6)
C(13)	0.3135 (5)	0.0698 (3)	0.309 (2)	3.7 (5)
C(14)	0.2984 (7)	0.0504 (3)	0.065 (2)	5.5 (6)
C(15)	0.2520 (6)	0.2525 (3)	0.711 (2)	4.0 (5)
C(16)	0.2458 (6)	0.2720 (3)	0.534 (1)	3.4 (4)
C(17)	0.1014 (5)	0.1049 (4)	0.606 (2)	4.4 (5)
C(18)	0.0859 (5)	0.0749 (3)	0.833 (2)	5.8 (6)
C(19)	0.6515 (5)	0.1207 (3)	0.849 (2)	3.2 (4)
C(20)	0.7260 (5)	0.0947 (3)	0.807 (2)	3.1 (4)
C(21)	0.7422 (5)	0.0590 (3)	0.982 (2)	4.1 (5)
C(22)	0.8112 (6)	0.0357 (3)	0.959 (2)	5.7 (6)
C(23)	0.8619 (6)	0.0467 (4)	0.777 (3)	5.4 (6)
C(24)	0.7771 (5)	0.1049 (3)	0.624 (2)	4.2 (5)
C(25)	0.8465 (6)	0.0826 (4)	0.606 (2)	5.2 (6)

^{1}H-NMR data for **13** (Table 2) indicate that the pyranose ring has the same conformation in the crystalline state and in solution.

In conclusion, we have developed a facile synthetic method for the preparation of 4-acylamino-2,3-didehydro-2,4-dideoxy-KDN derivatives. The ratio of the isomers varies depending on the catalyst used, and the configuration of the 4-acylamido group in these products was determined by X-ray crystallographic analysis and from the ^{1}H-NMR spectral data.

Experimental

General Procedures Melting points were measured on a Yamato melting point apparatus without correction. Fast atom bombardment mass spectra (FAB-MS) were taken on a JEOL JMS-DX 300. Optical rotations were measured with a JASCOJIP-4 digital polarimeter (at 21 °C). IR spectra were obtained on a Perkin–Elmer 983G infrared spectrometer. The ^{1}H-NMR spectra were determined with Varian VXR-300 and XL-400 spectrometers, in the solution state, with tetramethylsilane (TMS) as an internal reference. Thin-layer chromatography (TLC) was performed on Kieselgel 60 F_{254} (Merck) plates, and spots were detected under ultraviolet (UV) irradiation or by spraying 5% sulfuric acid solution. Column chromatography was conducted on Silica gel 60 (70—230 mesh) (Merck).

Methyl 4-Acetylamino-5,7,8,9-tetra-*O*-acetyl-2,6-anhydro-2,3-dideoxy-D-*glycero*-D-*galacto*-non-2-enonate (7) and Methyl 4-Acetylamino-

5,7,8,9-tetra-*O*-acetyl-2,6-anhydro-2,3-dideoxy-D-*glycero*-D-*talo*-non-2-enonate (8) Procedure 1: Tin(IV) chloride (488 mg, 1.87 mmol) was added to a solution of **6** (500 mg, 0.936 mmol) in acetonitrile (20 ml) at room temperature. The mixture was stirred at room temperature for 24 h, then saturated sodium hydrogen carbonate aqueous solution (10 ml) was added with stirring, and the whole was concentrated to dryness under reduced pressure. The residue was extracted with dichloromethane (30 ml × 3), and the combined extracts were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated to a syrup *in vacuo*. The syrup was purified by silica gel column chromatography with *n*-hexane–acetone to yield **7** (71 mg, 16%) and **8** (27 mg, 6%). Both of them were crystallized from chloroform–*n*-hexane to give colorless prisms.

Procedure 2: A solution of trimethylsilyl triflate (0.2 ml, 1 mmol) in acetonitrile (1 ml) was added to a solution of **6** (267 mg, 0.50 mmol) in acetonitrile (10 ml) at 0 °C. The mixture was stirred at room temperarure for 3 h until the starting material was no longer detectable by TLC ($CHCl_3$–MeOH). Potassium carbonate (150 mg, 2 mol eq) was then added and the mixture was stirred for a further 15 min. Solids were removed by filtration and concentration of filtrate under reduced pressure gave a residue, which was purified by silica gel chromatography (*n*-hexane–acetone) to yield **7** (37 mg, 16%), **8** (165 mg, 70%), and **10** (18 mg, 9%). All of them were crystallized from chloroform–*n*-hexane to give colorless prisms.

7: mp 98—99 °C. FAB-MS *m/z*: 474 ($M^+ + 1$) (*m*-NBA as matrix). *Anal.* Calcd for $C_{20}H_{27}NO_{12}$: C, 50.74; H, 5.71; N, 2.96. Found: C, 50.60; H, 5.76; N, 2.85. $[\alpha]_D$ +20° (*c* = 0.27, MeOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1742 (COO), 1680 (CON). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.94 (1H, d, *J* = 2.4 Hz, 3-H), 4.90 (1H, ddd, *J* = 8.4, 7.5, 2.4 Hz, 4-H), 4.92 (1H, dd, *J* = 10.2, 8.4 Hz, 5-H), 4.31 (1H, dd, *J* = 10.2, 2.7 Hz, 6-H), 5.51 (1H, dd, *J* = 6.9, 2.7 Hz, 7-H), 5.35 (1H, ddd, *J* = 6.9, 6.6, 2.4 Hz, 8-H), 4.21 (1H, dd, *J* = 12.3, 6.6 Hz, 9-H), 4.56 (1H, dd, *J* = 12.3, 2.4 Hz, 9-H), 5.74 (1H, d, *J* = 7.5 Hz, NH), 3.79 (3H, s, $COOCH_3$), 2.05, 2.05, 2.06, 2.07 (each 3H, s, OAc), 1.95 (3H, s, NAc). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 20.46, 20.72 20.78, 20.83 ($CO\underline{C}H_3$), 23.14 ($NHCO\underline{C}H_3$), 48.60 (4-C), 52.50 ($COO\underline{C}H_3$), 61.74 (9-C), 66.34 (7-C), 66.75 (5-C), 66.96 (8-C), 75.63 (6-C), 110.06 (3-C), 144.27 (2-C), 161.49 ($N\underline{C}OCH_3$), 1.69.73, 169.81, 170.35, 170.55 ($\underline{C}OCH_3$), 170.99 ($\underline{C}OOCH_3$).

8: mp 71—73 °C. FAB-MS *m/z*: 474 ($M^+ + 1$) (*m*-NBA as matrix). *Anal.* Calcd for $C_{20}H_{27}NO_{12}$: C, 50.74; H, 5.71; N, 2.96. Found: C, 50.45; H, 5.75; N, 2.69. $[\alpha]_D$ −77° (*c* = 0.53, MeOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1744 (COO), 1682 (CON). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.00 (1H, d, *J* = 5.7 Hz, 3-H), 4.92 (1H, ddd, *J* = 8.1, 5.7, 5.1 Hz, 4-H), 4.99 (1H, dd, *J* = 9.9, 5.1 Hz, 5-H), 4.15 (1H, dd, *J* = 9.9, 3.0 Hz, 6-H), 5.51 (1H, dd, *J* = 5.4, 3.0 Hz, 7-H), 5.37 (1H, ddd, *J* = 6.6, 5.4, 3.3 Hz, 8-H), 4.19 (1H, dd, *J* = 12.6, 6.6 Hz, 9-H), 4.68 (1H, dd, *J* = 12.6, 3.3 Hz, 9-H), 3.80 (3H, s, $COOCH_3$), 5.39 (1H, d, *J* = 5.7 Hz, NH), 2.02, 2.06, 2.07, 2.09 (each 3H, s, OAc), 1.99 (3H, s, NAc). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 20.43, 20.57, 20.73, 20.89 ($CO\underline{C}H_3$), 23.15 ($NHCO\underline{C}H_3$), 48.86 (4-C), 52.59 ($COO\underline{C}H_3$), 61.93 (9-C), 67.49 (7-C), 65.18 (5-C), 70.74 (8-C), 72.53 (6-C), 107.11 (3-C), 145.37 (2-C), 161.56 ($N\underline{C}OCH_3$), 169.55, 169.59, 169.65, 170.06 ($\underline{C}OCH_3$), 170.57 ($\underline{C}OOCH_3$).

10: mp 89—93 °C. FAB-MS *m/z*: 415 ($M^+ + 1$) (*m*-NBA as matrix). *Anal.* Calcd for $C_{18}H_{22}NO_{11}$: C, 52.17; H, 5.31. Found: C, 52.35; H, 5.17. $[\alpha]_D$ −29° (*c* = 0.61, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.07 (1H, d, *J* = 3.9 Hz, 3-H), 6.42 (1H, d, *J* = 3.9 Hz, 4-H), 6.12 (1H, d, *J* = 3.3 Hz, 6-H), 5.58 (1H, dd, *J* = 9.3, 3.3 Hz, 7-H), 5.22 (1H, ddd, *J* = 5.1, 3.0, 9.3 Hz, 8-H), 4.24 (1H, dd, *J* = 12.6, 3.0 Hz, 9′-H), 4.13 (1H, dd, *J* = 12.6, 5.1 Hz, 9-H), 3.86 (3H, s, $COOCH_3$), 2.03, 2.06, 2.08, 2.09 (each 3H, s, OAc). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 20.3495, 20.567, 20.718 ($CO\underline{C}H_3$), 51.923 ($COO\underline{C}H_3$), 61.556 (C-9), 65.775 (C-6), 68.185 (C-8), 69.366 (C-7), 111.147 (C-4), 118.286 (C-3), 144.732 (C-2), 152.916 (C-5), 158.615 (C-1), 169.301, 169.542, 169.664, 170.492 ($COCH_3$).

Methyl 4-Propionylamino-5,7,8,9-tetra-*O*-acetyl-2,6-anhydro-2,3-dideoxy-D-*glycero*-D-*galacto*-non-2-enonate (11) and Methyl 4-Propionylamino-5,7,8,9-tetra-*O*-acetyl-2,6-anhydro-2,3-dideoxy-D-*glycero*-D-*talo*-non-2-enonate (12) Tin(IV) chloride (175 mg, 0.66 mmol) was added to a solution of **6** (200 mg, 0.33 mmol) in propionitrile (15 ml) at room temperature. The mixture was processed by procedure **1** as described for **7** and **8** to yield **11** (28 mg, 14%) and **12** (32 mg, 16%). Both of them were crystallized from ethyl acetate–*n*-hexane to give colorless prisms.

11: mp 84—85 °C. FAB-MS *m/z*: 488 ($M^+ + 1$) (*m*-NAB as matrix). *Anal.* Calcd for $C_{21}H_{29}NO_{12}$: C, 51.74; H, 5.95; N, 2.87. Found: C, 51.46; H, 6.08; N, 2.64. $[\alpha]_D$ +37° (*c* = 0.51, MeOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1743 (COO), 1682 (CON). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.93 (1H, d, *J* = 2.4 Hz, 3-H), 4.91 (1H, ddd, *J* = 8.1, 6.9, 2.1 Hz, 4-H), 4.93 (1H, dd, *J* = 10.2, 8.1 Hz, 5-H), 4.32 (1H, dd, *J* = 10.2, 2.4 Hz, 6-H), 5.51 (1H, dd, *J* = 6.9, 2.4 Hz, 7-H), 5.36 (1H, ddd, *J* = 6.6, 6.3, 2.4 Hz, 8-H), 4.20 (1H, dd, *J* = 13.2, 6.3 Hz, 9-H), 4.56 (1H, dd, *J* = 13.2, 2.7 Hz, 9-H), 5.69 (1H, d, *J* = 6.9 Hz, NH), 3.79 (3H, s, $COOCH_3$), 1.12 (3H, t, *J* = 7.8 Hz, CH_3), 2.18 (2H, q, *J* = 7.8 Hz, CH_2), 2.05, 2.06, 2.07, 2.08 (each 3H, s, OAc).

12: mp 183—185 °C. FAB-MS *m/z*: 488 ($M^+ + 1$) (*m*-NBA as matrix). *Anal.* Calcd for $C_{21}H_{29}NO_{12}$: C, 51.74; H, 5.95; N, 2.87. Found: C, 51.87; H, 6.13; N, 2.71. $[\alpha]_D$ −91° (*c* = 0.41, MeOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1742 (COO), 1680 (CON). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.99 (1H, d, *J* = 5.1 Hz, 3-H), 4.94 (1H, ddd, *J* = 8.1, 5.7, 5.1 Hz, 4-H), 4.99 (1H, dd, *J* = 9.6, 5.7 Hz, 5-H), 4.13 (1H, dd, *J* = 9.6, 2.7 Hz, 6-H), 5.51 (1H, dd, *J* = 5.4, 2.7 Hz, 7-H), 5.36 (1H, ddd, *J* = 6.9, 5.4, 2.4 Hz, 8-H), 4.19 (1H, dd, *J* = 12.3, 6.9 Hz, 9-H), 4.68 (1H, dd, *J* = 12.3, 2.4 Hz, 9-H), 3.80 (3H, s, $COOCH_3$), 5.37 (1H, d, *J* = 8.1 Hz, NH), 1.16 (3H, t, *J* = 7.2 Hz, CH_3), 2.23 (2H, q, *J* = 7.2 Hz, CH_2), 1.98, 2.06, 2.07, 2.09 (each 3H, s, OAc).

Methyl 4-Benzoylamino-5,7,8,9-tetra-*O*-acetyl-2,6-anhydro-2,3-dideoxy-D-*glycero*-D-*galacto*-non-2-enonate (13) Tin(IV) chloride (488 mg, 1.87 mmol) was added to a solution of **6** (500 mg, 0.936 mmol) in benzonitrile (20 ml) at room temperature.

The mixture was processed by procedure **1** as described for **7** and **8** to yield **13** (235 mg, 47%). It was crystallized from ethyl acetate–*n*-hexane to give colorless prisms.

13: mp 125—127 °C. FAB-MS *m/z*: 536 ($M^+ + 1$) (*m*-NBA as matrix). *Anal.* Calcd for $C_{25}H_{29}NO_{12}$: C, 56.07; H, 5.42; N, 2.62. Found: C, 56.15; H, 5.52; N, 2.75. $[\alpha]_D$ +62° (*c* = 0.63, MeOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1742 (COO), 1660 (CON). ^{1}H-NMR (300 MHz, $CDCl_3$), δ: 6.06 (1H, d, *J* = 2.3 Hz, 3-H), 5.05 (1H, m, 4-H), 5.08 (1H, m, 5-H), 4.38 (1H, dd, *J* = 10.2, 2.1 Hz, 6-H), 5.55 (1H, dd, *J* = 6.9, 2.1 Hz, 7-H), 5.39 (1H, ddd, *J* = 6.9, 6.3, 2.7 Hz, 8-H), 4.21 (1H, dd, *J* = 12.3, 6.3 Hz, 9-H), 4.57 (1H, dd, *J* = 12.3, 2.7 Hz, 9-H), 6.54 (1H, d, *J* = 5.7 Hz, NH), 3.77 (3H, s, $COOCH_3$), 7.45—7.72 (5H, m, C_6H_5), 2.05, 2.06, 2.09, 2.10 (each 3H, s, OAc). ^{1}H-NMR (300 MHz, pyridine-d_5) δ: 6.24 (1H, d, *J* = 2.3 Hz, 3-H), 5.67 (1H, ddd, *J* = 2.3, 8.4, 8.5 Hz, 4-H), 5.63 (1H, dd, *J* = 10.2, 8.5 Hz, 5-H), 4.88 (1H, dd, *J* = 10.2, 2.1 Hz, 6-H), 5.95 (1H, dd, *J* = 6.9, 2.1 Hz, 7-H), 5.86 (1H, ddd, *J* = 6.9, 6.3, 2.7 Hz, 8-H), 4.46 (1H, dd, *J* = 12.3, 6.3 Hz, 9-H), 4.89 (1H, dd, *J* = 12.3, 2.7 Hz, 9-H), 9.59 (1H, d, *J* = 8.4 Hz, NH), 3.68 (3H, s, $COOCH_3$), 7.40, 8.22 [(3H, m), (2H, dd, *J* = 12.3, 2.7 Hz), C_6H_5], 2.00, 2.01, 2.04, 2.10 (each 3H, s, OAc).

Methyl 4-Trichloroacetylamino-5,7,8,9-tetra-*O*-acetyl-2,6-anahydro-2,3-dideoxy-D-*glycero*-D-*galacto*-non-2-enonate (14) and Methyl 4-Trichloroacetylamino-5,7,8,9-tetra-*O*-acetyl-2,6-anhydro-2,3-dideoxy-D-*glycero*-D-*talo*-non-2-enonate (15) Tin(IV) chloride (175 mg, 0.66 mmol) was added to a solution of **6** (200 mg, 0.33 mmol) in trichloroacetonitrile (15 ml) at room temperature. The mixture was processed by procedure **1** as described for **7** and **8** to yield **14** (102 mg, 55%) and **15** (30 mg, 17%).

14: FAB-MS *m/z*: 578 ($M^+ + 1$) (*m*-NBA as matrix). *Anal.* Calcd for $C_{20}H_{24}Cl_3NO_{12}$: C, 41.59; H, 4.16; N, 2.43. Found: C, 41.80; H, 4.36; N, 2.75. $[\alpha]_D$ +39° (*c* = 0.23, MeOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1744 (COO), 1710 (CON). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.05 (1H, d, *J* = 3.1 Hz, 3-H), 5.46 (1H, dd, *J* = 6.0, 2.4 Hz, 7-H), 5.34 (1H, ddd, *J* = 6.9, 3.0, 6.0 Hz, 8-H), 5.32 (1H, dd, *J* = 10.2, 8.4 Hz, 5-H), 4.64 (1H, dd, *J* = 8.4, 3.1 Hz, 4-H), 4.60 (1H, dd, *J* = 12.6, 3.0 Hz, 9-H), 4.20 (1H, dd, *J* = 10.2, 2.4 Hz, 6-H), 4.15 (1H, dd, *J* = 12.6, 6.9 Hz, 9-H), 3.79 (3H, s, $COOCH_3$), 2.04, 2.06, 2.09, 2.10 (each 3H, s, OAc).

15: FAB-MS *m/z*: 578 ($M^+ + 1$) (*m*-NBA as matrix). *Anal.* Calcd for $C_{20}H_{24}Cl_3NO_{12}$: C, 41.59; H, 4.16; N, 2.43. Found: C, 41.40; H, 4.28; N, 2.36. $[\alpha]_D$ −9° (*c* = 0.47, MeOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1742 (COO), 1710 (CON). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.15 (1H, d, *J* = 5.7 Hz, 3-H), 5.54 (1H, dd, *J* = 6.6, 2.1 Hz, 7-H), 5.41 (1H, ddd, *J* = 6.0, 2.4, 6.6 Hz, 8-H), 4.97 (1H, dd, *J* = 11.1, 4.8 Hz, 5-H), 4.84 (1H, dd, *J* = 5.7, 4.8 Hz, 4-H), 4.58 (1H, dd, *J* = 12.6, 2.4 Hz, 9-H), 4.49 (1H, dd, *J* = 11.1, 2.1 Hz, 6-H), 4.19 (1H, dd, *J* = 12.6, 6.0 Hz, 9-H), 3.80 (3H, s, $COOCH_3$), 2.06, 2.07, 2.09, 2.13 (each 3H, s, OAc).

X-Ray Crystallographic Analysis of 13 A crystal having approximate dimensions of 0.20 × 0.20 × 0.20 mm was used for the analysis. The cell dimensions and diffraction intensities were measured on a Rigaku AFC-5R diffractometer using graphite-monochromated Cu K_α radiation (*l* = 1.54178 Å) and a 12 kW rotating anode generator at 23 °C. Empirical formula: $C_{25}H_{29}NO_{12}$. Crystal system: orthorhombic. Lattice parameters: *a* = 17.42(1) Å, *b* = 28.225(2) Å, *c* = 5.385(1) A°, *V* = 2648(4) Å^3. Space group: P_{212121}. *Z* value: 4. Density (calculated): 1.642 g cm^{-3}. The data were collected using the ω–2θ scan technique in the range of 2θ

$<140.0°$. Scans of $(1.63+0.30\tan\theta)°$ were made at a speed of $16.0° \min^{-1}$. In total, 2865 reflections were collected and corrected for Lorentz and polarization factors but not for absorption. The structure was elucidated by a direct method using TEXSAN.[23] The non-hydrogen atoms were refined anisotropically by full-matrix, least-squares refinement. A difference Fourier synthesis was calculated, and the positions of all hydrogen atoms were found. They were refined isotropically. The final R value was 6.8%, where $R=S||F_O|-|F_C||/S|F_O|$. The final R_w values was 6.2%, where $R_w=[(\Sigma_w(|F_O|-|F_C|)^2/S_wF_O^2)]^{1/2}$. The final atomic parameters for **13** are given in Table 3.

References and Notes

1) Corfied A. P., Schauer R., "Sialic Acids Chemistry, Metabolism and Function, Cell Biology Monographs," Vol. 10, ed. by Schauer R., Springer Verlag, New York, 1982, pp. 5—39.
2) Bretscher M. S., *Scientific American*, **253**, 86—95 (1985).
3) DeNinno M. P., *Synthesis*, **1991**, 583—593.
4) Lubieau A., Le Gallic J., *J. Carbohydr. Chem.*, **10**, 263—268 (1991).
5) Estenne G., Sarol A., Doutheau A., *J. Carbohydr. Chem.*, **10**, 181—195 (1991).
6) Ogura H., "Carbohydrates—Synthetic Methods and Applications in Medicinal Chemistry," ed. by Ogura H., Hasegawa A., Suami T., Kodansha-VCH, 1992, pp. 282—303.
7) Roth J., Zuber C., Wanger P., Blaha I., Bitter-Suermann D., Heitz P. U., *Lab. Invest.*, **62**, 55—60 (1988).
8) Reutter W., Kottgen E., Bauer C., Gerok W., "Sialic Acids Chemistry, Metabolism and Function, Cell Biology Monographs," Vol. 10, ed. by Schauer R., Springer Verlag, Vienna, New York, 1982, pp. 263—305.
9) Itzstein M. V., Wu W. Y., Kok G. B., Pegg M. S., Dyason J. C., Jin B., Phan T. V., Smythe M. I., White H. F., Oliver S. W., Colman P. M., Varghese J. N., Ryan D. M., Woods J. M., Bethell R. C., Hotham V. J., Cameron J. M., Penn C. R., *Nature* (London), **363**, 418—423 (1993).
10) Ritter J. J., Minieri P. P., *J. Am. Chem. Soc.*, **70**, 4045—4050 (1948).
11) Driguez P. A., Barrere B., Quash G., Doutheau A., *Carbohydr. Res.*, **262**, 297—310 (1994).
12) Starkey I. D., Mahmoudian M., Noble D., Smith P. W., Cherry P. C., Howes P. D., Sollis S. L., *Tetrahedron Lett.*, **36**, 299—302 (1995).
13) Ogura H., Fujita H., Furuhata K., Ito M., Shitori Y., *Chem. Pharm. Bull.*, **34**, 1479—1484 (1986).
14) Nakamura M., Furuhata K., Yamazaki T., Ogura H., *Chem. Pharm. Bull.*, **39**, 3140—3144 (1991).
15) Sun X.-L., Haga N., Ogura H., Takayanagi H., *Chem. Pharm. Bull.*, **42**, 2352—2356 (1994).
16) Nakamura M., Furuhata K., Yamazaki K., Ogura H., Kamiya H., Ida H., *Chem. Pharm. Bull.*, **37**, 2204—2206 (1989).
17) Nakamura M., Furuhata K., Ogura H., *Chem. Pharm. Bull.*, **36**, 4807—4813 (1988).
18) Nakamura M., Takeda K., Takayanagi H., Asai N., Ibata N., Ogura H., *Chem. Pharm. Bull.*, **41**, 26—30 (1993).
19) Schreiner E., Zbiral E., Kleineidane R. G., Schauer R., *Justus Liebigs Ann. Chem.*, **1991**, 129—134.
20) Itzstein M. V., Jin B., Wu W. Y., Chandler M., *Carbohydr. Res.*, **244**, 181—185 (1993).
21) Kumar V., Kessier J., Scott M. E., Patcuardhan B. H., Tanenbaum S. W., Flashner M., *Carbohydr. Res.*, **94**, 123—130 (1981).
22) Furuhata K., Sato S., Goto M., Takayanagi H., Ogura H., *Chem. Pharm. Bull.*, **36**, 1872—1876 (1988).
23) TEXRAY Structure Analysis Package, Molecular Structure Corporation (1985).