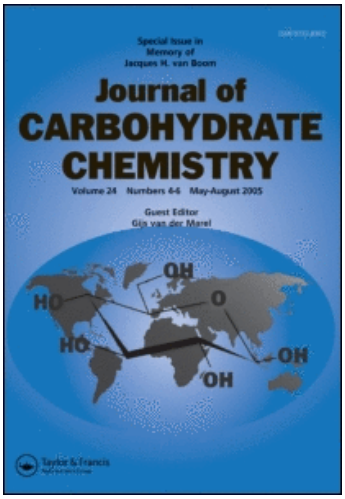


Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Synthesis of Sialic Acid Analogues with the Oxime Group at C-4 Or C-5 of KDN

Toshitsugu Kai[a]; Xue-Long Sun[a]; Hiroaki Takayanagi[a]; Kimio Furuhata[a]
[a] School of Pharmaceutical Sciences, Kitasato University, Tokyo, Japan

To cite this Article Kai, Toshitsugu , Sun, Xue-Long , Takayanagi, Hiroaki and Furuhata, Kimio(1997) 'Synthesis of Sialic Acid Analogues with the Oxime Group at C-4 Or C-5 of KDN', Journal of Carbohydrate Chemistry, 16: 4, 521 — 532
To link to this Article: DOI: 10.1080/07328309708007331
URL: http://dx.doi.org/10.1080/07328309708007331

J. CARBOHYDRATE CHEMISTRY, 16(4&5), 521-532 (1997)

SYNTHESIS OF SIALIC ACID ANALOGUES WITH THE OXIME GROUP AT C-4 OR C-5 OF KDN[1]

Toshitsugu Kai, Xue-Long Sun, Hiroaki Takayanagi and Kimio Furuhata*

School of Pharmaceutical Sciences, Kitasato University,
5-9-1 Shirokane, Minato-ku, Tokyo 108, Japan

Final Form March 3, 1997

ABSTRACT

The readily available methyl (methyl 3-deoxy-5,8:7,9-di-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (**7**) was converted in five synthetic steps into methyl (methyl 4-acetamido-3,4-dideoxy-β-D-*glycero*-D-*talo*-2-nonulopyranosid)onate (**11**). Selective protection of the C-4, C-7, C-8 and C-9 hydroxy groups of methyl (methyl 3-deoxy-8,9-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-2-nonulpyranosid)onate (**2**) followed by oxidation of the C-5 hydroxy group and then its oximination gave 5-hydroxyimino derivatives (**15** and **16**).

INTRODUCTION

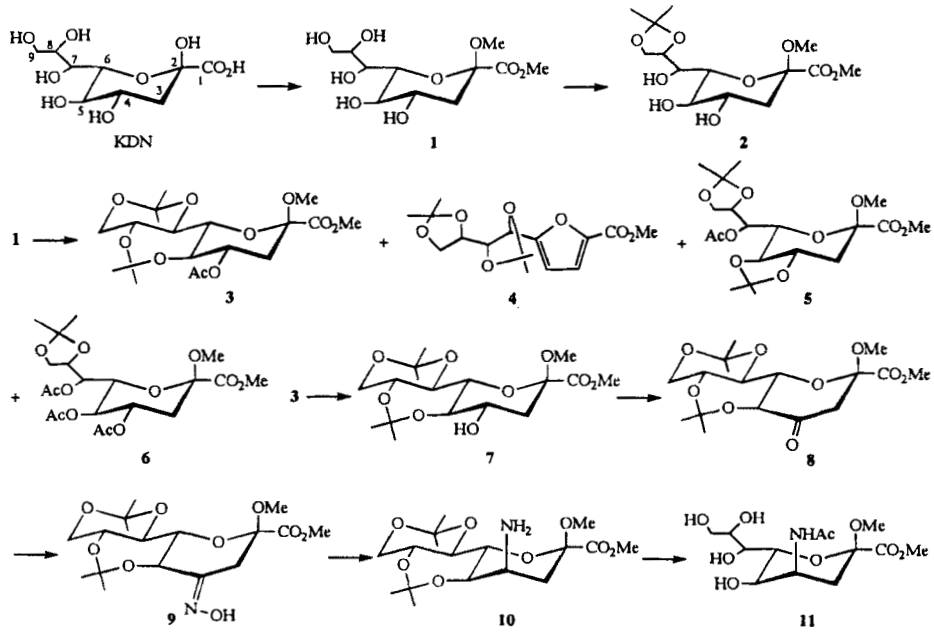
Since a chemical method for the preparation of crystalline 3-deoxy-D-*glycero*-D-*galacto*-2-nonulopyranosonic acid (KDN) on a large scale has been established, we have synthesized various analogues.[2,3] These KDN analogues are of considerable interest as potential modifiers of neuraminidase inhibitors.

The use of protective agents in the manipulation of carbohydrate materials is a long established practice. A key element in this is the need for regioselective protection of the carbohydrate materials to facilitate further processing. In a previous paper we described the synthesis of partially *O*-acetylated *N*-acetylneuraminic acid.[4,5] We have been interested in various *O*-isopropylidene derivatives of KDN as starting materials for the synthesis of other sialic acids. We describe herein a regioselective synthesis giving a high yield of 8,9-*O*-isopropylidene[5] and 5,8:7,9-di-*O*-isopropylidene derivatives of methyl (methyl 3-deoxy-β-

D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (**1**). Moreover, this prompted us to attempt the syntheses of some derivatives of C-4 and C-5 positions on **1** with novel modification.

RESULTS AND DISCUSSION

Previously, we reported a facile method for preparation of methyl (methyl 3-deoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (**1**),[2] which was extremely useful for the synthesis of sialic acid analogues. We tried to synthesize the C-4 or C-5 hydroxyimino derivatives from **1** as a starting material. Protection of the C-8 and C-9 hydroxy groups on **1** was carried out with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate to give isopropylidene monoketal (**2**)[6] in 90% yield as a crystalline product. Surprisingly, treatment of **1** with an excess amount of 2,2-dimethoxypropane and *p*-toluenesulfonic acid in toluene for 6 h at 80 °C and then acetylation with acetic anhydride and pyridine afforded isopropylidene diketal, methyl (methyl 4-*O*-acetyl-3-deoxy-5,8:7,9-di-*O*-ispropylidene-β-D-*glycero*-D-*galacto*-2-nonulopyranosid)-onate (**3**) in 75% yield, after purification by recrystallization from diisopropyl ether. In this reaction, by-products were isolated in minor quantities by silica gel column chromatography to give furan derivative (**4**), 7-*O*-acetyl-4,5-*O*-isopropylidene ketal derivative of **2** (**5**), and 4,5,7-tri-*O*-acetyl derivative of **2** (**6**). As a related compound to **7**, the 7,9-*O*-isopropylidene monoketal derivative of *N*-acetylneuraminic acid was reported by Hasegawa *et al.*[7] **3** was deacetylated under Zemplen conditions, and then the oxidation at the C-4 position of **7** was carried out by treatment with a stoichiometric amount of ruthenium tetraoxide in tetrachloromethane to give ketone (**8**) in 96% as a crystalline compound. The structures of the isopropylidene diketals (**3**, **7**, and **8**) were proposed as shown in Scheme 1, but the positions of isopropylidene diketal methyl protons from ^{1}H NMR data did not fully support these structures. Therefore, the structure of **8** was confirmed by X-ray crystallographic analysis as shown in Figure 1. Oximation of **8** by treatment with hydroxylamine afforded a single oxime (**9**) in good yield. We propose, on the basis of ^{1}H NMR chemical shift data[8,9] that the (*E*)-isomer, which places the hydroxy group of the C=N-OH substituent *cis* to the methylene group, is preferentially formed. For further investigation, **9** was converted into its 4-amino-H-4$_{eq}$ derivative (**10**) by catalytic hydrogenation with platinum(IV) oxide in methanol. Subsequent acetylation of the 4-amino group and removal of the isopropylidene diketal under acidic conditions gave the desired methyl (methyl 4-acetamido-3,4-dideoxy-β-D-*glycero*-D-*talo*-2-nonulopyranosid)onate (**11**). This compound was identified on the basis of its ^{1}H NMR spectral data. In particular, a doublet due to the NH acetamido group was observed at δ 7.92. The orientation of H-4 was easily deduced from the value of the coupling constant, $J_{4,5}$ = 4.5 Hz.



Benzoylation at 4-OH of **2** was regioselectively carried out by treatment of **2** with benzoic anhydride and excess pyridine to give the 4-*O*-benzoate of **2** (**12**) in good yield.

Furthermore, benzoylation of **2** with 3.3 molar equivalents of benzoyl chloride in pyridine at 0 °C gave the desired 4,7-di-*O*-benzoate of **2** (**13**) in 78% yield. The structure of **13** was assigned on the basis of its ^{1}H NMR spectra. The benzoylated positions of **13** were confirmed to be at C-4 and C-7 by the downfield shift of the signals for H-4 and H-7 owing to *O*-acylation effects. The oxidation at the C-5 position of **13** was carried out by treatment with ruthenium tetraoxide to give ketone (**14**) in good yield. Oximation of **14** gave two isomers (**15** and **16**).

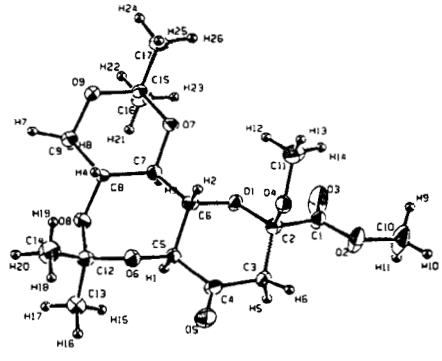
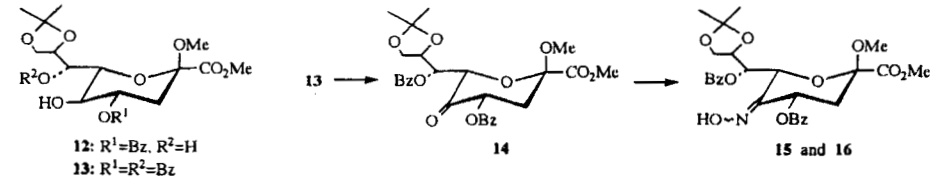


Fig. 1



In conclusion, we have developed a convenient method for protection of C-5, C-7, C-8 and C-9, and C-4, C-7, C-8 and C-9 of hydroxy groups of **1**, respectively. We utilized

these derivatives to synthesize the hydroxyimino derivatives of KDN (**9**, **15** and **16**) and the 4-acetamido derivative **11**.

EXPERIMENTAL

General methods. Melting points were measured on a Yazawa melting point apparatus without correction. Optical rotations were measured with a JASCO JIP-4 digital polarimeter (at 23 °C). IR spectra were recorded as a film on NaCl plate with a JASCO A-2 infrared spectrometer. The NMR spectra were determined with a Varian VXR-300 (300 MHz) spectrometer, in the solution sate, with tetramethylsilane (TMS) as an internal reference. Column chromatography was conducted on Silica gel 60 (70-230 mesh, Merck). Thin-layer chromatography (TLC) was performed on Silica gel 60 (Merck) plates, and spots were detected under ultraviolet (UV) irradiation or by spraying with 5% sulfuric acid. Solvent evaporations were conducted *in vacuo*.

Methyl (Methyl 3-Deoxy-8,9-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (2). 2,2-Dimethoxypropane (0.52 g, 5 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg) were added with stirring for 1 h at room temperature to **1** (1.19 g, 4 mmol) dissolved in acetone (30 mL). The mixture was treated with Dowex-1 (OH^-) anion-exchange resin (1 g) to remove the acid, and the resin filtered off and washed with acetone (20 mL). The combined filtrate and washings were concentrated, and the residue was purified by crystallization from acetone to give **2** (1.22 g, 90%) as colorless needles: mp 135-136 °C; $[\alpha]_D$ -58.5° (*c* 1, MeOH); IR ν_{max} 1730, 3380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67 (t, 1H, $J_{3ax,3eq}$ = 12.0 Hz, H-3_{ax}), 2.37 (dd, 1H, $J_{3eq,4}$ = 5.0 Hz, H-3_{eq}), 4.02 (m, 1H, H-4), 3.59 (t, 1H, $J_{5,6}$ = 9.0 Hz, 5-H), 3.70 (dd, 1H, $J_{6,7}$ = 1.0 Hz, H-6), 3.85 (dd, 1H, $J_{7,8}$ = 7.0 Hz, H-7), 4.18 (m, 1H, H-8), 3.96–4.16 (2H, H_2-9), 3.23 (s, 3H, OMe), 3.80 (s, 3H, CO_2Me), 1.31, 1.40 (2s, each 3H, CMe_2); (C_5D_5N) δ 2.22 (dd, 1H, $J_{3ax,3eq}$ = 12.5 Hz, $J_{3ax,4}$ = 11.5 Hz, H-3_{ax}), 2.87 (dd, 1H, $J_{3eq,4}$ = 5.0 Hz, H-3_{eq}), 4.68 (ddd, 1H, $J_{4,5}$ = 9.0 Hz, H-4), 4.50 (t, 1H, $J_{5,6}$ = 9.0 Hz, H-5), 4.37 (dd, 1H, $J_{6,7}$ = 1.5 Hz, H-6), 4.78 (dd, 1H, $J_{7,8}$ = 6.0 Hz, H-7), 4.81 (q, 1H, $J_{8,9}$ = $J_{8,9'}$ = 6.0 Hz, H-8), 4.39 (dd, 1H, $J_{9,9'}$ = 9.0 Hz, H-9), 4.46 (dd, 1H, H-9'), 3.53 (s, 3H, OMe), 3.66 (s, 3H, CO_2Me), 1.39 and 1.49 (2s, each 3H, CMe_2).

Anal. Calcd for $C_{14}H_{24}O_9$ (336.33): C, 50.00; H, 7.19. Found: C, 50.05; H 7.22.

Methyl (Methyl 4-*O*-Acetyl-3,4-dideoxy-5,8:7,9-di-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (3). An excess amount of 2,2-dimethoxypropane (5 g, 48 mmol) and *p*-toluenesulfonic acid monohydrate were added to a stirred suspension of **1** (0.89 g, 3 mmol) in toluene (50 mL). The reaction mixture was stirred at 80 °C for 6 h. Dry pyridine (5 mL) and acetic anhydride (2 mL) were added to a

reaction mixture at room temperature and the mixture was stirred for 4 h, and then concentrated to dryness. The residue was dissolved in ethyl acetate (50 mL) and successively washed with water and 3% $NaHCO_3$, and dried over sodium sulfate and filtered. The filtrate was condensed and the resulting crystalline powder was recrystallized from diisopropyl ether to give **3** (0.94 g, 75%) as colorless needles. The solvent of recrystallization was evaporated off to give a syrup. The syrupy residue was separated and purified by silica gel column chromatography with diisopropyl ether. The first eluate was concentrated in vacuo to give **4** (78 mg, 8%) as a white powder. The second eluate was concentrated to give **5** (25 mg, 2%) as a white powder. The third eluate was concentrated in vacuo to give **3** (87 mg, 7%) as colorless needles. The fourth eluate was concentrated in vacuo to give **6** (27 mg, 6%) as a white powder.

3: mp 168–169 °C; $[\alpha]_D$ -56.0° (*c* 1, MeOH); IR ν_{max} 1740, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74 (dd, 1H, $J_{3ax,3eq}$ = 12.5 Hz, $J_{3ax,4}$ = 11.5 Hz, H-3_{ax}), 2.47 (dd, 1H, $J_{3eq,4}$ = 5.5 Hz, H-3_{eq}), 5.22 (ddd, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 3.65 (t, 1H, $J_{5,6}$ = 9.5 Hz, H-5), 3.49 (dd, 1H, $J_{6,7}$ = 7.5 Hz, H-6), 3.67–3.81 (m, 4H, H-7, H-8, H_2-9), 1.28, 1.30, 1.37, and 1.50 (4s, each 3H, 2 CMe_2), 2.02 (s, 3H, OAc).

Anal. Calcd for $C_{19}H_{30}O_{10}$ (418.43): C, 54.54; H, 7.23. Found: C, 54.56; H, 7.31.

4: $[\alpha]_D$ +21.2° (*c* 1.0, MeOH); IR ν_{max} 1520, 1595, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.11 (d, 1H, $J_{3,4}$ = 3.5 Hz, H-3), 6.47 (d, 1H, H-4), 4.96 (d, 1H, $J_{6,7}$ = 7.5 Hz, H-6), 4.26 (t, 1H, $J_{7,8}$ = 7.5 Hz, H-7), 4.17 (ddd, 1H, $J_{8,9}$ = 4.0 Hz, $J_{8,9'}$ = 5.5 Hz, H-8), 3.93 (dd, 1H, $J_{9,9'}$ = 8.5 Hz, H-9), 4.08 (dd, 1H, H-9'), 3.86 (s, 3H, CO_2Me), 1.21, 1.28, 1.44, and 1.48 (4s, each 3H, 2 CMe_2).

Anal. Calcd for $C_{16}H_{22}O_7$ (326.34): C, 58.88; H, 6.80. Found: C, 58.72; H, 6.85.

5: $[\alpha]_D$ -32.2° (*c* 1.0, MeOH); IR ν_{max} 1740, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88 (t, 1H, $J_{3ax,3eq}$ = $J_{3ax,4}$ = 11.5 Hz, H-3_{ax}), 2.55 (dd, 1H, $J_{3eq,4}$ = 5.0 Hz, H-3_{eq}), 3.86 (ddd, 1H, $J_{4,5}$ = 8.5 Hz, H-4), 3.16 (dd, 1H, $J_{5,6}$ = 9.5 Hz, H-5), 3.97 (dd, 1H, $J_{6,7}$ = 3.0 Hz, H-6), 5.35 (dd, 1H, $J_{7,8}$ = 3.5 Hz, H-7), 4.40 (dt, 1H, $J_{8,9}$ = 6.5 Hz, $J_{8,9'}$ = 3.0 Hz, 8-H), 3.90 (dd, 1H, $J_{9,9'}$ = 9.5 Hz, H-9), 3.97 (dd, 1H, H-9'), 3.29 (s, 3H, OMe), 3.81 (s, 3H, CO_2Me), 2.15 (s, 3H, OAc), 1.33, 1.38, and 1.43 (3s, each 3H, 6H, and 3H, 2 CMe_2).

Anal. Calcd for $C_{19}H_{30}O_{10}$ (418.43): C, 54.54; H, 7.22. Found: C, 54.72; H, 7.36.

6: $[\alpha]_D$ -26.0° (*c* 1.1, MeOH); IR ν_{max} 1740, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84 (dd, 1H, $J_{3ax,3eq}$ = 13.0 Hz, $J_{3ax,4}$ = 11.5 Hz, H-3_{ax}), 2.51 (dd, 1H, $J_{3eq,4}$ = 5.0 Hz, H-3_{eq}), 5.33 (ddd, 1H, $J_{4,5}$ = 10.0 Hz, H-4), 4.93 (t, 1H, $J_{5,6}$ = 10.0 Hz, H-5), 4.07 (dd, 1H, $J_{6,7}$ = 2.0 Hz, H-6), 5.27 (dd, 1H, $J_{7,8}$ = 2.0 Hz, H-7), 4.35 (q, 1H, $J_{8,9}$ = $J_{8,9'}$ = 6.5 Hz, H-8), 3.90 (dd, 1H, $J_{9,9'}$ = 9.0 Hz, H-9), 4.05 (dd, 1H, H-9'), 3.29 (s, 3H, OMe), 3.81 (s, 3H, CO_2Me), 1.32, 1.38 (2s, each 3H, CMe_2), 1.99 (s, 3H, OAc), 2.01 (s, 3H, OAc), 2.11 (s, 3H, OAc).

Anal. Calcd for $C_{20}H_{30}O_{12}$ (462.44): C, 51.94; H, 6.54. Found: C, 51.84; H, 6.72.

Methyl (Methyl 3,4-Dideoxy-5,8:7,9-di-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (7). A 0.1 M sodium methoxide solution (0.1 mL) was added to a solution of **3** (418 mg, 1 mmol) in dry methanol (20 mL) and the mixture was kept for 1 h at room temperature, then deionized on Dowex-50 (H^+) resin at 0 °C. The resin was filtered off and washed with methanol (20 mL). The filtrate and washing were combined and concentrated to give **7** (360 mg, 96%) as a colorless powder: $[\alpha]_D$ -78.8° (*c* 1, MeOH); IR ν_{max} 1750, 3500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74 (dd, 1H, $J_{3ax,3eq}$ = 13.0 Hz, $J_{3ax,4}$ = 11.5 Hz, H-3_{ax}), 2.58 (dd, 1H, $J_{3eq,4}$ = 5.5 Hz, H-3_{eq}), 3.95 (ddd, 1H, $J_{4,5}$ = 8.5 Hz, H-4), 3.48 (dd, 1H, $J_{5,6}$ = 10.0 Hz, H-5), 3.38 (dd, 1H, $J_{6,7}$ = 7.5 Hz, H-6), 3.74 (dd, 1H, $J_{7,8}$ = 7.0 Hz, H-7), 3.69 (ddd, 1H, $J_{8,9}$ = 9.5 Hz, $J_{8,9'}$ = 2.5 Hz, H-8), 3.70 (dd, 1H, $J_{9,9'}$ = 10.5 Hz, H-9), 3.78 (dd, 1H, H-9'), 3.24 (s, 3H, OMe), 3.80 (s, 3H, CO_2Me), 2.30 (br s, 1H, OH-4).

Anal. Calcd for $C_{17}H_{28}O_9$ (376.39): C, 54.24; H, 7.50. Found: C, 54.49; H, 7.64.

Methyl (Methyl 3-Deoxy-5,8:7,9-di-*O*-isopropylidene-4-oxo-β-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (8). $NaIO_4$ (3.2 g, 13.8 mmol) and $RuO_2 \cdot 2H_2O$ (0.4 g, 3 mmol) were dissolved in H_2O (50 mL), and RuO_4 was extracted two times with tetrachloromethane (20 mL).[10] This solution was added to a stirred solution of **7** (0.2 g, 0.53 mmol) in tetrachloromethane (10 mL). The mixture was stirred at room temperature for 3 h. The reaction was stopped by addition of 2-propanol (1 mL), and stirring was continued for 30 min. The mixture was filtered over celite and washed 2 times with tetrachloromethane. The combined solution were concentrated to dryness. The crude product was purified by recrystallization with diisopropyl ether to give **8** (178 mg, 90%) as colorless prisms: mp 150-151 °C; $[\alpha]_D$ -129.2° (*c* 1, MeOH); IR ν_{max} 1690, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.75 (dd, 1H, $J_{3ax,3eq}$ = 14.5 Hz, $J_{3ax,5}$ = 1.0 Hz, H-3_{ax}), 2.88 (d, 1H, H-3_{eq}), 4.23 (dd, 1H, $J_{5,6}$ = 10.0 Hz, H-5), 3.71 (dd, 1H, $J_{6,7}$ = 8.0 Hz, H-6), 3.93 (br t, 1H, $J_{7,8}$ = 8.0 Hz, H-7), 3.68–3.79 (m, 3H, H-8, H_2-9), 3.28 (s, 3H, OMe), 3.83 (s, 3H, CO_2Me), 1.31, 1.38, 1.42, and 1.53 (4s, each 3H, 2 CMe_2); (C_5D_5N) δ 3.28 (dd, 1H, $J_{3ax,3eq}$ = 14.5 Hz, $J_{3ax,5}$ = 1.0 Hz, H-3_{ax}), 3.11 (d, 1H, H-3_{eq}), 4.82 (br d, 1H, $J_{5,6}$ = 10.0 Hz, 5-H), 4.00 (dd, 1H, $J_{6,7}$ = 8.0 Hz, H-6), 4.16 (dd, 1H, $J_{7,8}$ = 8.5 Hz, H-7), 3.91 (dd, 1H, $J_{8,9'}$ = 5.0 Hz, H-8), 3.85 (d, 1H, $J_{9,9'}$ = 12.0 Hz, H-9), 3.92 (dd, 1H, H-9'), 3.46 (s, 3H, OMe), 3.64 (s, 3H, CO_2Me), 1.41, 1.42, 1.48, and 1.49 (4s, each 3H, 2 CMe_2); ^{13}C NMR (75 MHz, C_5D_5N) δ 19.2, 24.4, 24.5, and 29.4 (each, 2 $\underline{C}Me_2$), 49.2 (C-3), 51.3 (2-OMe), 52.7 ($CO_2\underline{Me}$), 62.8 (C-9), 63.1 (C-8), 73.1 (C-5), 75.6 (C-7), 76.6 (C-6), 99.0 (-$O_2\underline{C}Me_2$), 100.6 (-$O_2\underline{C}Me_2$), 102.6 (C-2), 167.8 (C-1), 199.0 (C-4).

Anal. Calcd for $C_{17}H_{28}O_9$ (374.39): C, 54.54; H, 7.00. Found: C, 54.64 H, 7.22.

Methyl (Methyl 3-Deoxy-5,8:7,9-di-*O*-isopropylidene-4-hydroxyimino-β-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (9). A solution of **8** (187 mg, 0.5 mmol) and $NH_2OH \cdot HCl$ (69 mg, 1 mmol) in dry pyridine (5mL) was stirred at room temperature for 16 h. The solution was concentrated and then the pyridine was removed by codistilling with toluene 2 times. The residue was dissolved in ethyl acetate (50 mL), and the solution was washed with water (15 mL) and then brine (15 mL), and dried over sodium sulfate and filtered. The filtrate was concentrated to dryness to give **9** (187 mg, 96%) as a colorless amorphous solid: $[\alpha]_D$ -101.4° (*c* 1, MeOH); IR ν_{max} 1755, 3250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.28 (dd, 1H, $J_{3ax,3eq}$ = 15.0 Hz, $J_{3ax,5}$ = 1.0 Hz, H-3_{ax}), 3.72 (d, 1H, H-3_{eq}), 4.30 (d, 1H, $J_{5,6}$ = 10.0 Hz, H-5), 3.64 (dd, 1H, $J_{6,7}$ = 8.0 Hz, H-6), 3.69–3.88 (m, 4H, H-7, H-8, H_2-9), 3.27 (s, 3H, OMe), 3.83 (s, 3H, CO_2Me), 9.58 (s, 1H, NOH), 1.32, 1.38, 1.56(3s, 3H, 6H, 3H, 2 CMe_2); (C_5D_5N) δ 2.93(d, 1H, $J_{3ax,3eq}$ = 15.0 Hz, H-3_{ax}), 4.21 (d, 1H, H-3_{eq}), 4.76 (d, 1H, $J_{5,6}$ = 9.5 Hz, H-5), 4.03 (dd, 1H, $J_{6,7}$ = 8.0 Hz, H-6), 4.10 (t, 1H, $J_{7,8}$ = 8.0 Hz, H-7), 3.88–3.99 (m, 3H, H-8, H_2-9), 3.85 (t, 1H, $J_{9,9'}$ = 10.0 Hz, H-9'), 3.50 (s, 3H, OMe), 3.66 (s, 3H, CO_2Me), 13.19 (s, 1H, NOH), 1.40, 1.49 (2s, 3H, 9H, 2 CMe_2).

Anal. Calcd for $C_{17}H_{27}NO_9$ (389.40): C, 52.43; H, 6.99; N, 3.60. Found: C, 52.26; H, 7.10; N, 3.48.

Methyl (Methyl 4-Amino-3,4-dideoxy-5,8:7,9-di-*O*-isopropylidene-β-D-*glycero*-D-*talo*-2-nonulopyranosid)onate (10). A solution of **9** (200 mg, 0.52 mmol) in methanol (20 mL) was hydrogenated with hydrogen over platinum oxide (0.1 g) at room temperature for 24 h under an atmospheric pressure. The reaction mixture was filtered, and the filtrate was concentrated to dryness. The crude product was purified by chromatography on silica gel column with $CHCl_3$ – MeOH (50:1) and crystallized with cyclohexane to give **10** (156 mg, 80%) as a colorless needles: mp 139–140 °C; $[\alpha]_D$ -73.6° (*c* 1.1, MeOH); IR ν_{max} 1755, 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.98 (dd, 1H, $J_{3ax,3eq}$ = 14.5 Hz, $J_{3ax,4}$ = 5.0 Hz, H-3_{ax}), 2.24 (dd, 1H, $J_{3eq,4}$ = 2.5 Hz, H-3_{eq}), 3.19 (br ddd, 1H, $J_{4,5}$ = 3.5 Hz, H-4), 3.67 (dd, 1H, $J_{5,6}$ = 9.5 Hz, H-5), 3.77 (dd, 1H, $J_{6,7}$ = 4.5 Hz, H-6), 3.81 (dd, 1H, $J_{7,8}$ = 9.5 Hz, H-7), 3.63 (dd, 1H, $J_{8,9}$ = 6.5 Hz, $J_{9,9'}$ = 10.0 Hz, H-9), 3.71 (dd, 1H, H-9'), 2.82 (br s, 2H, NH_2-4), 1.30, 1.33, 1.38, and 1.51 (4s, each 3H, 2 CMe_2), 3.27 (3H, s, OMe), 3.79 (3H, s, CO_2Me).

Anal. Calcd for $C_{17}H_{29}NO_8$ (375.41): C, 54.39; H, 7.79; N, 3.73. Found: C, 54.30; H, 7.91; N, 3.88.

Methyl (Methyl 4-Acetamido-β-D-*glycero*-D-*talo*-2-nonulopyranosid)-onate (11). To a solution of **10** (113 mg, 0.3 mmol) in pyridine (0.5 mL) was added acetic anhydride (1 mL). The mixture was stirred at room temperature for 10 h and concentrated. The residue was dissolved in chloroform (20 mL) and the organic layer was

washed twice with water and then brine. The solution was dried with anhydrous Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by chromatography on silica gel with $CHCl_3$–MeOH (50:1) to give methyl (methyl 4-acetamido-5,7:8,9-di-*O*-isopropylidene-3,4-dideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate as a colorless amorphous powder: ^{1}H NMR ($CDCl_3$) δ 2.05 (dd, 1H, $J_{3ax,3eq}$ = 16.0 Hz, $J_{3ax,4}$ = 4.5 Hz, H-3_{ax}), 2.08 (dd, 1H, $J_{3eq,4}$ = 2.5 Hz, H-3_{eq}), 4.58 (dddd, 1H, $J_{4,5}$ = 5.0 Hz, $J_{4,NH}$ = 10.0 Hz, H-4), 3.75 (dd, 1H, $J_{5,6}$ = 10.5 Hz, 5-H), 3.51 (dd, 1H, $J_{6,7}$ = 7.5 Hz, H-6), 3.78 (dd, 1H, d, $J_{7,8}$ = 9.5 Hz, H-7), 3.63–3.71 (m, 3H, H-8, H_2-9), 6.49 (d, 1H, NH-4), 1.99 (s, 3H, NAc), 1.26, 1.32, 1.37, and 1.50 (4s, each 3H, 2 CMe_2), 3.33 (s, 3H, OMe), 3.80 (s, 3H, CO_2Me).

A solution of *N*-acetyl derivative of **10** in methanol (1 mL) was added to 1 N HCl (0.5 mL). The mixture was stirred at room temperature for over night, and concentrated to dryness to give **11** (81 mg, 80%) as a colorless amorphous powder: $[\alpha]_D$ -40.3° (*c* 0.62, MeOH); IR ν_{max} 1530, 1640, 1740, 3400 cm^{-1}; ^{1}H NMR (C_5D_5N) δ 2.28 (dd, 1H, $J_{3ax,4}$ = 14.5 Hz, $J_{3ax,4}$ = 4.5 Hz, 3-H_{ax}), 2.50 (dd, 1H, $J_{3eq,4}$ = 4.0 Hz, H-3_{eq}), 5.03 (ddd, 1H, $J_{4,5}$ = 9.0 Hz, H-4), 4.77 (dd, 1H, $J_{5,6}$ = 4.5 Hz, H-5), 4.89 (dd, 1H, $J_{6,7}$ = 10.0 Hz, H-6), 4.83 (dd, 1H, $J_{7,8}$ = 9.0 Hz, H-7), 4.65 (ddd, 1H, $J_{8,9}$ = 5.5 Hz, $J_{8,9'}$ = 3.0 Hz, H-8), 4.38 (dd, 1H, $J_{9,9'}$ = 11.0, H-9), 4.53 (dd, 1H, H-9'), 7.93 (d, 1H, $J_{NH,4}$ = 9.0 Hz, NH-4), 2.05 (s, 3H, NAc), 3.46 (s, 3H, OMe), 3.58 (s, 3H, CO_2Me).

Anal. Calcd for $C_{13}H_{23}NO_9$ (337.32): C, 46.29; H, 6.87; N, 1.97. Found: C, 46.31; H, 6.94; N, 1.90.

Methyl (Methyl 4-*O*-Benzoyl-3-deoxy-8,9-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (12). Benzoic anhydride (0.23 g, 1 mmol) was added to stirred solution of **2** (168 mg, 0.5 mmol) in pyridine (3 mL). The mixture was stirred at room temperature for 16 h and methanol (1 mL) was added to it. The reaction mixture was stirred for 30 min and concentrated to a syrup, which was chromatographed on a silica gel column ($CHCl_3$–MeOH = 50:1) to give **12** (185 mg, 85%) as a colorless powder: $[\alpha]_D$ -5.0° (*c* 1.23, MeOH); IR ν_{max} 1590, 1605, 1725, 1755, 3500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.88 (dd, 1H, $J_{3ax,3eq}$ = 13.0 Hz, $J_{3ax,4}$ = 11.5 Hz, H-3_{ax}), 2.58 (dd, 1H, $J_{3eq,4}$ = 5.0 Hz, H-3_{eq}), 5.46 (ddd, 1H, $J_{4,5}$ = 9.0 Hz, H-4), 3.95 (t, 1H, $J_{5,6}$ = 9.0 Hz, H-5), 3.88 (dd, 1H, $J_{6,7}$ = 1.5 Hz, H-6), 3.93 (dd, 1H, $J_{7,8}$ = 9.0 Hz, H-7), 4.21 (ddd, 1H, $J_{8,9}$ = 4.0 Hz, $J_{8,9'}$ = 7.0 Hz, H-8), 4.08 (dd, 1H, $J_{9,9'}$ = 8.5 Hz, H-9), 4.15 (dd, 1H, H-9'), 3.28 (s, 3H, OMe), 3.78 (s, 3H, CO_2Me), 1.31, 1.41 (2s, each 3H, CMe_2), 7.40–8.05 (5H, phenyl group).

Anal. Calcd for $C_{21}H_{28}O_{10}$ (440.43): C, 57.27; H, 6.41. Found: C, 56.98; H, 6.39.

Methyl (Methyl 4,7-Di-*O*-benzoyl-3-deoxy-8,9-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (13). Benzoyl chloride (1.4 g, 10

mmol) was added to stirred solution of **2** (1.0 g, 3 mmol) in pyridine at 0 ℃. The mixture was stirred at room temperature for 2 h and concentrated to a syrup. This was dissolved in ethyl acetate (50 mL) and the solution was washed with ice-cold 0.5 N HCl, 3% $NaHCO_3$, and brine, and dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to a syrup, which was chromatographed on a silica gel column ($CHCl_3$ – MeOH= 100 : 1) and crystallized with diisopropyl ether to give **13** (1.3 g, 78%) and **12** (0.2 g, 15%) as colorless needles: mp 105-106 ℃; $[\alpha]_D$ -4.1° (*c* 1.16, MeOH); IR ν_{max} 1590, 1605, 1725, 1775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83 (dd, 1H, $J_{3ax,3eq}$ = 13.0 Hz, $J_{3ax,4}$ = 11.5 Hz, H-3_{ax}), 2.61 (dd, 1H, $J_{3eq,4}$ = 5.0 Hz, H-3_{eq}), 5.54 (ddd, 1H, $J_{4,5}$ = 10.0 Hz, H-4), 3.52 (dt, 1H, $J_{5,6}$ = 10.0 Hz, $J_{5,OH}$ = 4.0 Hz, H-5), 4.04 (dd, 1H, $J_{6,7}$ = 2.0 Hz, H-6), 5.58 (dd, 1H, $J_{7,8}$ = 2.0 Hz, H-7), 4.61 (q, 1H, $J_{8,9}$ = $J_{8,9'}$ = 6.0 Hz, H-8), 4.10 (dd, 1H, $J_{9,9'}$ = 9.0 Hz, H-9), 4.19 (dd, 1H, H-9'), 3.40 (s, 3H, OMe), 3.81 (s, 3H, CO_2Me), 1.35, 1.41 (2s, each 3H, CMe_2), 7.37–8.16 (5H, phenyl group).

Anal. Calcd for $C_{28}H_{32}O_{11}$ (544.54): C, 61.76; H, 5.92. Found: C, 61.66; H, 5.01.

Methyl (Methyl 4,7-Di-*O*-benzoyl-3-deoxy-8,9-*O*-isopropylidene-5-oxo-β-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (14). A RuO_4 solution in tetrachloromethane was prepared as described for **8**. This solution was added to a stirred solution of **13** (0.27 g, 0.5 mmol) in tetrachloromethane (10 mL). The mixture was stirred at room temperature overnight. The reaction was stopped by the addition of 2-propanol (1 mL), and stirring was continued for 30 min. The mixture was filtered over celite and washed 2 times with tetrachloromethane. The combined solution was concentrated to dryness in vacuo. The crude product was purified by chromatography on silica gel column with $CHCl_3$ – MeOH (50 : 1) to give **14** (210 mg, 78%) as a colorless amorphous powder: $[\alpha]_D$ -53.4° (*c* 1.0, MeOH); IR ν_{max} 1590, 1605, 1715, 1750, 1790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.53 (t, 1H, $J_{3ax,3eq}$ = $J_{3ax,4}$ = 12.5 Hz, H-3_{ax}), 2.89 (dd, 1H, $J_{3eq,4}$ = 7.0 Hz, H-3_{eq}), 5.97 (dd, 1H, H-4), 4.74 (br d, 1H, $J_{6,7}$ = 2.0 Hz, H-6), 5.80 (dd, 1H, $J_{7,8}$ = 8.5 Hz, H-7), 4.48 (dt, 1H, $J_{8,9}$ = 6.0 Hz, H-8), 4.02 (d, 2H, H_2-9), 3.46 (s, 3H, OMe), 3.83 (s, 3H, CO_2Me), 1.35, 1.40 (2s, each 3H, CMe_2), 7.3–8.8 (10H, phenyl groups).

Anal. Calcd for $C_{28}H_{30}O_{11}$ (542.52): C, 61.99; H, 5.57. Found: C, 61.72; H, 5.53.

Methyl (Methyl 4,7-Di-*O*-benzoyl-3-deoxy-5-hydroxyimino-8,9-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (15) and its isomer (16). A solution of **14** (150 mg, 0.28 mmol) and $NH_2OH \cdot HCl$ (69 mg, 1 mmol) in dry pyridine (2 mL) was stirred at 40 ℃ for 3 h. The solution was concentrated and then the pyridine was removed by codistilling with toluene several times. The residue was dissolved in chloroform (20 mL) and the organic layer was washed twice with water and then brine. The solution was dried with anhydrous Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by chromatography on silica gel (*n*-hexane–ethyl

Table Positional Parameters and B_{eq} for **8**

Atom	x	y	z	B_{eq}/Å^2
O1	0.8938(4)	0.9431(2)	0.9809(4)	2.7(2)
O2	1.1778(4)	0.8399(3)	1.0040(6)	5.0(3)
O3	0.9940(5)	0.8297(3)	1.1094(6)	6.5(3)
O4	1.0335(4)	0.9096(2)	0.8120(5)	3.3(2)
O5	1.1277(4)	1.1124(3)	0.8760(6)	5.8(3)
O6	0.8740(4)	1.1357(2)	0.8614(5)	3.3(2)
O7	0.6399(4)	0.9444(2)	0.8821(5)	3.0(2)
O8	0.6745(4)	1.1398(2)	0.9680(5)	3.4(2)
O9	0.4433(4)	1.0034(2)	0.8567(4)	3.3(2)
C1	1.0587(6)	0.8596(4)	1.0322(8)	3.1(3)
C2	1.0225(6)	0.9274(4)	0.9477(7)	2.6(3)
C3	1.1116(7)	0.9916(4)	0.973(1)	3.5(4)
C4	1.0594(6)	1.0649(4)	0.9241(8)	3.5(4)
C5	0.9152(6)	1.0760(4)	0.9426(8)	2.7(3)
C6	0.8419(7)	1.0047(4)	0.9068(9)	2.6(4)
C7	0.6998(6)	1.0083(4)	0.9403(8)	2.6(4)
C8	0.6337(6)	1.0779(4)	0.8891(8)	2.6(3)
C9	0.4893(9)	1.0733(5)	0.909(1)	3.6(5)
C10	1.2295(8)	0.7784(4)	1.079(1)	6.9(5)
C11	0.9533(7)	0.8487(4)	0.7683(8)	4.6(4)
C12	0.7775(6)	1.1826(4)	0.9167(8)	3.3(4)
C13	0.8280(6)	1.2280(4)	1.0352(9)	4.7(4)
C14	0.7355(8)	1.2311(4)	0.805(1)	5.8(5)
C15	0.5049(6)	0.9400(4)	0.9075(7)	2.6(3)
C16	0.4788(6)	0.9272(4)	1.0518(7)	4.0(4)
C17	0.4568(6)	0.8772(4)	0.8234(8)	3.8(4)
H1	0.896(7)	1.088(4)	1.038(8)	7(2)
H2	0.846(7)	0.990(4)	0.835(7)	4(2)
H3	0.696(7)	1.001(4)	1.035(8)	7(2)
H4	0.648(6)	1.096(3)	0.781(6)	6(2)
H5	1.126(7)	0.994(4)	1.087(9)	7(2)
H6	1.194(5)	0.979(3)	0.931(6)	3(2)
H7	0.425(7)	1.115(4)	0.848(8)	9(3)
H8	0.482(8)	1.070(5)	0.977(7)	4(3)
H9	1.1785	0.7342	1.0700	9.5
H10	1.3162	0.7657	1.0520	9.5
H11	1.2332	0.7905	1.1718	9.5
H12	0.8620	0.8605	0.7863	5.8
H13	0.9613	0.8366	0.6798	5.8
H14	0.9694	0.8042	0.8221	5.8
H15	0.8590	1.1951	1.1051	5.6
H16	0.9001	1.2592	1.0116	5.6
H17	0.7638	1.2591	1.0741	5.6
H18	0.8069	1.2602	0.7702	7.8
H19	0.6984	1.2040	0.7375	7.8
H20	0.6728	1.2684	0.8360	7.8
H21	0.5100	0.9703	1.1043	4.5
H22	0.3881	0.9243	1.0712	4.5
H23	0.5198	0.8849	1.0873	4.5
H24	0.3662	0.8726	0.8273	4.5
H25	0.4792	0.8864	0.7300	4.5
H26	0.4956	0.8312	0.8469	4.5

$B_{eq} = (4/3)\Sigma_i\Sigma_j \beta_{ij} (\boldsymbol{a}_i \cdot \boldsymbol{a}_j)$.

acetate = 4 : 1) to give **15** (105 mg, 67%) and its isomer **16** (26 mg, 15%) as a colorless amorphous powder, respectively.

15: $[\alpha]_D$ -32.8°(*c* 1.0, MeOH); IR ν_{max} 1590, 1605, 1720, 1755, 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.81 (dd, 1H, $J_{3ax,3eq}$ = 15.5 Hz, $J_{3ax,4}$ = 5.0 Hz, H-3_{ax}), 2.39 (dd, 1H, $J_{3eq,4}$ = 5.0 Hz, H-3_{eq}), 5.82 (t, 1H, H-4), 5.31 (d, 1H, $J_{6,7}$ = 2.5 Hz, H-6), 6.39 (dd, 1H, $J_{7,8}$ = 6.5 Hz, H-7), 4.64 (q, 1H, $J_{8,9}$ = 6.0 Hz, H-8), 4.17 (d, 2H, H_2-9), 3.37 (s, 3H, OMe), 3.77 (s, 3H, CO_2Me), 8.65 (br s, 1H, NOH), 1.30, 1.35 (2s, each 3H, CMe_2), 7.2–7.9 (10H, phenyl groups).

Anal. Calcd for $C_{28}H_{31}NO_{11}$ (557.54): C, 60.35; H, 5.61; N, 2.51. Found: C, 60.30; H, 5.75; N, 2.62.

16: $[\alpha]_D$ -26.6° (*c* 1.0, MeOH); IR ν_{max} 1590, 1605, 1720, 1755, 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.95 (dd, 1H, $J_{3ax,3eq}$ = 15.5 Hz, $J_{3ax,4}$ = 4.0 Hz, H-3_{ax}), 2.26 (dd, 1H, $J_{3eq,4}$ = 4.0, H-3_{eq}), 6.41 (t, 1H, H-4), 4.97 (d, 1H, $J_{6,7}$ = 2.0 Hz, H-6), 5.79 (dd, 1H, $J_{7,8}$ = 7.8 Hz, H-7), 4.63 (dt, 1H, $J_{8,9} = J_{8,9'}$ = 6.0 Hz, H-8), 4.12 (dd, 1H, $J_{9,9'}$ = 8.0 Hz, H-9), 4.15 (dd, 1H, H-9'), 3.40 (s, 3H, OMe), 3.61 (s, 3H, CO_2Me), 1.37, 1.42 (s, each 3H, CMe_2), 7.2–8.1 (10H, phenyl groups).

Anal. Calcd for $C_{28}H_{31}NO_{11}$ (557.54): C, 60.35; H, 5.61; N, 2.51. Found: C, 60.26; H; 5.88, N, 2.38.

Crystal Data for 8. A crystal with the dimensions of 0.4×0.2×0.2 mm^3 was used for the structure determination. The cell dimensions and diffraction intensities were measured on a Rigaku four-circle diffractometer (AFC-5R), using graphite monochromated CuK_α radiation. Crystal Data: $C_{17}H_{26}O_9$, Orthorhombic, space group $P2_12_12_1$, a = 10.401(7), b = 18.013(4), c = 10.092(5) Å, V = 1891(3) $Å^3$, Z = 4, D_{calcd} = 1.315 g/cm^3. In total, 1301 independent reflections with the range of 2θ = 139.6° were collected by use of the 2θ-ω scan mode with a scanning rate of 16° min^{-1} (ω). In total, 1629 independent reflections with I>3.00s(I) were obtained and corrected for Lorentz and polarization factors, but not for absorption. The structure was solved by direct methods using the program MITHRIL.[11] The positions of all hydrogen atoms were located in the difference Fourier map. Atomic scattering factors were taken from the International Table for X-Ray Crystallography.[12] All calculations were performed using the TEXSAN[13] crystallographic software package from Molecular Structure Corporation. The final R value was 5.4%. The final atomic parameters for **8** are given in the Table.

REFERENCES

1. Presented at the *XVIIIth International Carbohydrate Symposium*, Milan, Italy, July 21-26, 1996.

2. T. Kai, X.-L. Sun, M. Tanaka, H. Takayanagi and K. Furuhata, *Chem. Pharm. Bull.*, **44**, 208 (1996).
3. M. Nakamura, K. Furuhata, T. Yamasaki and H. Ogura, *Chem. Pharm. Bull.*, **39**, 3140 (1991).
4. H. Ogura, K. Furuhata, S. Sato, K. Anazawa, M. Itoh and Y. Shitori, *Carbohydr. Res.*, **167**, 77 (1987).
5. K. Anazawa, K. Furuhata and H. Ogura, *Chem. Pharm. Bull.*, **36**, 4976 (1988).
6. S. David, A. Malleron and B. Cavaye, *Carbohydr. Res.*, **260**, 233 (1994).
7. A. Hasegawa, T. Murase, M. Ogawa, H. Ishida and M. Kiso, *J. Carbohydr. Chem.*, **9**, 415 (1990).
8. P. J. Beynon, P. M. Collins and W. G. Overrend, *J. Chem. Soc. (C)*, 272 (1969).
9. D. R. Groves, J. C. Wilson and M. von Itzstein, *Aust. J. Chem.*, **48**, 1217 (1995).
10. H. Nakata, *Tetrahedron*, **19**, 1959 (1963).
11. C. J. Gilmore; MITHRIL, an integrated direct methods computer program, *J. Appl. Crystallogr.*, **17**, 42, Univ. of Glasgow, Scotland, 1984.
12. International Tables for X-Ray Crystallography, Vol. IV, Kynoch Press, Birmingham, 1974, pp 72-149.
13. TEXSAN-TEXRAY Structure Analysis Package, Molecular Structure Corporation, 1985.