

69. A New Synthesis of *N*-Acetylneuraminic Acid

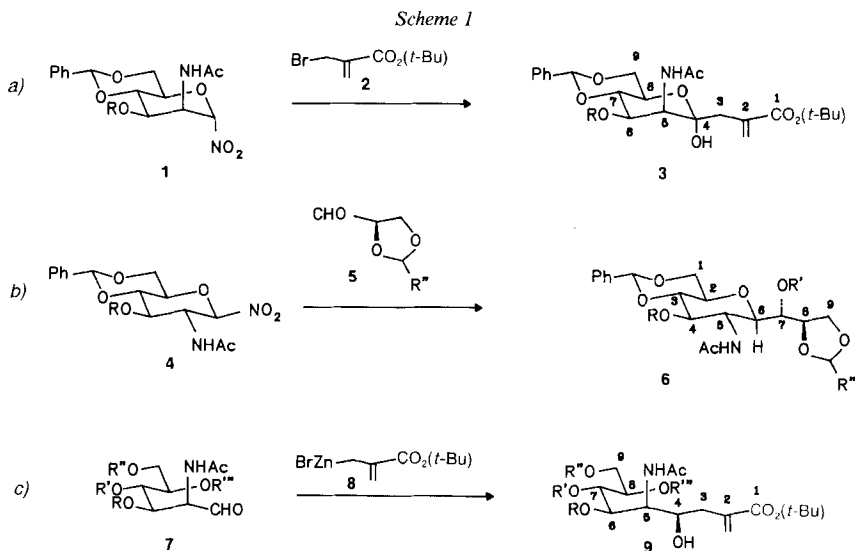
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A new synthesis of *N*-acetylneuraminic acid (Neu5Ac; **28**) via the aldehyde **10** is described. The aldehyde **10** was obtained from *N*-acetyl-D-glucosamine (**11**; 5 steps, overall yield *ca.* 6%) or from D-glucono-1,5-lactone (**17**; 6 steps, overall yield *ca.* 57%). Thus, on the one hand, *N*-acetyl-D-mannosamine (**12**), obtained from **11**, was transformed into the known dithioacetal **14** and hence into the (ethylthio)dihydrooxazole **16** which was cleaved under weakly acidic conditions to the aldehyde **10**. On the other hand, the known ester **18**, obtained from **17**, was sulfonated and further transformed via the azide **20** into the *N*-acetyl-D-mannonate **22**. Reduction of **22** to **23** and oxidation of **23** with 'periodinane' again gave **10**. The aldehyde **10** was treated with the organozinc reagent **8** obtained from *tert*-butyl 2-(bromomethyl)acrylate (**2**) to yield predominantly **24** which was transformed (two steps) into the 2-methylidene-D-glycero-D-galacto-nononic acid **27** and hence into Neu5Ac (**28**).

Introduction. – The well recognized biological importance of sialic acids and their conjugates has been taken as a motive for a number of syntheses of *N*-acetylneuraminic acid (Neu5Ac; **28**), the only sialic acid occurring in the human species (see [1–6] and ref. cit. therein). We have recently presented two syntheses [7] [8] of Neu5Ac which are complementary to each other in that each one may be adopted to the preparation of different analogues, the first one for analogues modified at C(1) to C(6), the second one for analogues modified at C(6) to C(9) (*Scheme 1a* and *1b*, respectively). Both syntheses



involved a C–C bond formation between a 1-deoxy-1-nitrohexose (**1** or **4**) as a nucleophilic partner and a suitable, electrophilic C(3) equivalent, the (bromomethyl)acrylate **2** in the first and cyclohexylidene-D-glyceraldehyde **5** in the second case (\rightarrow **3** and **6**, respectively).

The transformation of the intermediate **3** into Neu5Ac required the diastereoselective reduction at C(4) to an intermediate of type **9**. Such an intermediate might also be obtained by a diastereoselective (reductive) hydroxyalkylation of an aldehyde derivative of ManNAc (**7**) with the organozinc derivative **8** obtained from **2** (*Scheme 1c*)¹). The product **9** possesses only one OH group (at C(4)) which may, thus, be more easily modified than in the reduction product of **3** which possesses two OH groups (at C(4) and C(8)). The synthesis according to *Scheme 1c* was realized to establish a convenient access to C-glycosides of Neu5Ac and to intermediates allowing modifications of the C(4) substituent.

Results. – The known aldehyde **10** was first obtained by a modification of *Sinay's* procedure [19] (*Scheme 2*). The preparation of *N*-acetyl-D-mannosamine (ManNAc; **12**) by base-catalyzed epimerization of *N*-acetyl-D-glucosamine (GlcNAc; **11**) [20] requires a tedious isolation and leads in a yield of *ca.* 8% to 93–96% pure **12**. Formation of the dithioacetal **13** from **12** and the protection of **13** to give **14** [19] [21] are high-yield reactions. Hydrolysis of the dithioacetal **14** under various conditions [22–24] gave the aldehyde **10** at the best in low yields. During the treatment of **14** with HgO and HgCl₂ in MeCN, we observed (TLC) the rapid formation of a new compound, which turned out to be a Hg complex **15** of the crystalline dihydrooxazole **16**. The latter was obtained in 90% yield after treatment of the reaction mixture with aqueous KI solution. Treatment of **16** with HgCl₂/HgO gave back the Hg complex **15**.

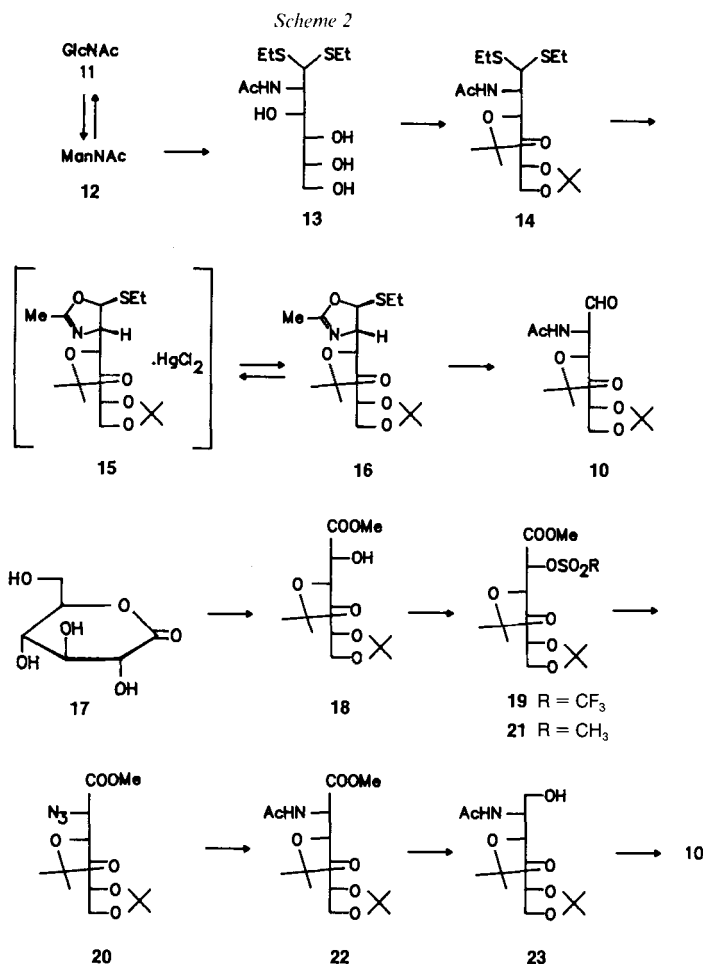
Comparison of the ¹H-NMR spectra of **15** and **16** revealed a shift to lower fields of the following signals: H–C(1) ($\Delta\delta = -0.27$ ppm), H–C(2) ($\Delta\delta = -0.36$ ppm), CH₂S ($\Delta\delta = -0.05$ ppm), and CH₃–C=N ($\Delta\delta = 0.31$ ppm). The signal of H–C(4) showed a very small shift ($\Delta\delta = 0.06$ ppm) to higher fields. These results indicate that the imino and not the ethylthio group functions as a ligand for Hg²⁺. *Harmon et al.* [25] obtained in a similar reaction the two diastereoisomeric *gluco*-configured analogues of **16**; in our case, only one diastereoisomer was formed.

The presence of a dihydrooxazole ring is indicated by an IR band at 1675 cm⁻¹ (C=N) and the absence of bands between 1510 and 1580 cm⁻¹ characteristic of secondary amides. The ¹H-NMR spectrum of **16** revealed a ³*J*(H–C(1), H–C(2)) value of 6.3 Hz, in keeping with a *trans*-configuration. The large ⁵*J*(CH₃–C=N, H–C(2)) value of 1.5 Hz is typical for 2-methyl-substituted dihydrooxazoles [26]. Thio-substituted dihydrooxazoles are only rarely found [25] [27], and no complete NMR or structural data have been published so far. The crowded ¹H-NMR spectrum (400 MHz) could easily be analyzed, and a 2D-¹H, ¹³C-shift-correlation experiment allowed unambiguous assignment of all ¹³C signals (see *Exper. Part*). In addition, **16** was characterized by a ¹⁵N-NMR signal at –158.82 ppm.

The structure of **16** was established by X-ray analysis (*Fig. 1*). Bond lengths and angles (*cf. Fig. 2*) for **16** are quite similar to those found for dihydrooxazoles or for thio-glycosides [28]. Selective hydrolysis of **16** by treatment with dilute HOAc under continuous removal of EtSH gave the aldehyde **10** in good yield (95%).

In spite of the improved transformation of **16** into **10**, the tedious and low-yield preparation of **12** is an obstacle for the preparation of large amounts of **10**. In an

¹) In most partial syntheses [9–18] of Neu5Ac, suitably protected D-mannosamine derivatives were chain-elongated by reaction with either oxaloacetic acid, potassium di(*tert*-butyl) oxaloacetate, bromopyruvate, nitromethane, or phosphoranes.



alternative approach to **10**, **18** was obtained on a large scale from D-glucono-1,5-lactone (**17**; one step, 84%) according to *Chittenden* and coworkers [29], and was transformed via the crystalline triflate **19** into the *manno*-azide (**20**; 86% from **18**; Scheme 2)². The azide **20** was also prepared in a somewhat lower yield (75%) by treatment of the mesylate **21** with LiN₃ in DMF. Hydrogenation of **20** in AcOEt/Ac₂O 1:1 (*v/v*) at atmospheric pressure in the presence of 10% Pd/C afforded **22** in almost quantitative yield. The ester **22** was reduced with LiBH₄ in THF/MeOH at 0° to give **23** (92%).

Oxidation of **23** with DMSO in the presence of the pyridine-SO₃ [30] or the Et₃N-SO₃ complex led to the aldehyde **10** in modest yields. Oxidation with the 'periodinane' of *Dess* and *Martin* [31] gave the delicate aldehyde **10** in a yield of *ca.* 85%, containing *ca.* 5–7% impurities (¹H-NMR).

²) It is important to use well dried Bu₄NN₃ for this transformation of **19** into **20**. Commercial Bu₄NN₃ (TCI, Japan) was dried by azeotropic removal of H₂O with toluene, and finally *in vacuo*.

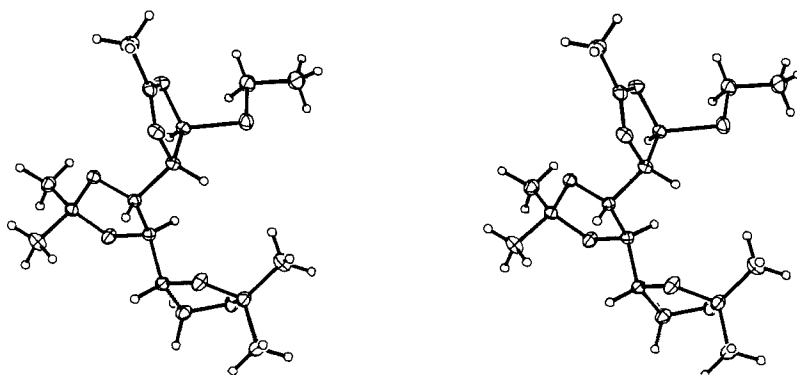


Fig. 1. Stereoview of 16

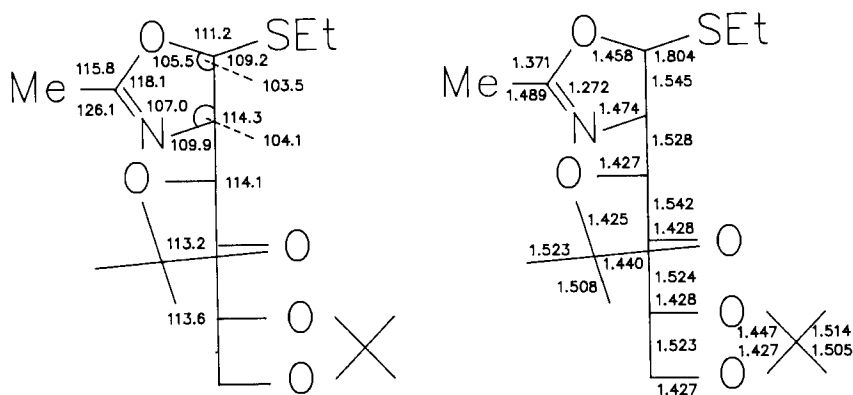
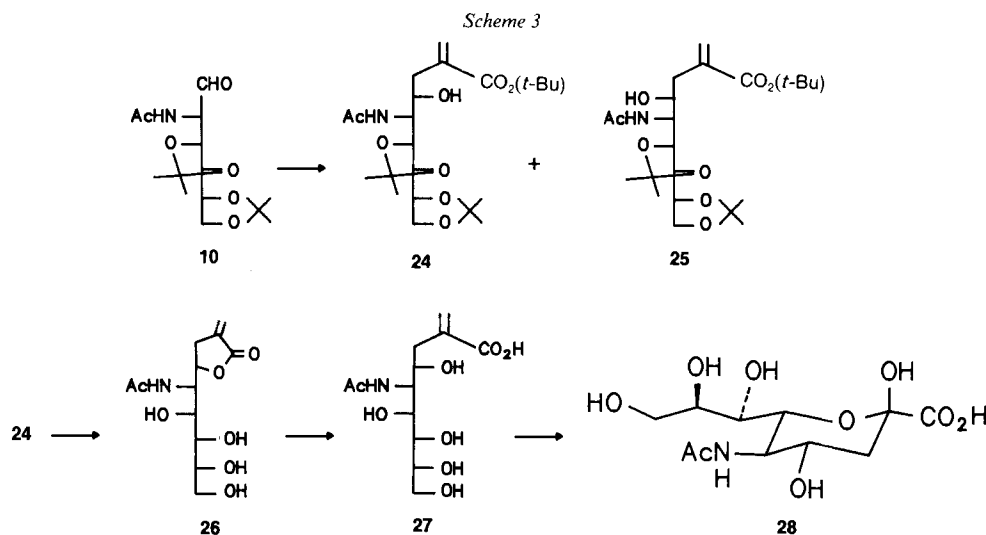


Fig. 2. Selected bond lengths and bond angles of 16

Reaction of crude **10** with the organozinc reagent **8** formed from *tert*-butyl 2-(bromo-methyl)prop-2-enoate³) (**2**) and 'black-powder' Zn [32], additionally activated by the use of trimethyl borate as a co-solvent [33], gave 70% of a 79:21 mixture of the diastereoisomers **24** and **25** (Scheme 3). Using acid-activated Zn dust [34] in the presence of 3.5 equiv. of hexamethylphosphorous triamide (HMPT) and 5 equiv. of Me₃SiCl [35] at -78° followed by cleavage of the intermediary *O*-trimethylsilyl ethers with Bu₄NF · 3 H₂O in AcOH/AcOEt gave **24** and **25** in overall yields of 80% (**24/25** 85:15, HPLC).

We finally obtained **24** and **25** in yields of over 90% from **10** and with a diastereoselectivity of ca. 80% (HPLC) using the highly reactive Zn/Ag couple on graphite [36]. The isomers **24** and **25** could be easily separated by column chromatography. On the basis of the 'chelation model' [37], it is expected that the major product **24** should be *D-glycero-D-galacto*-configured, but the crowded ¹H-NMR spectra of **24** and **25** were very similar to each other even at 400 MHz and did not allow an unambiguous assignment of the configuration.

³) We thank Dr. H. Braunschweiger, Sandoz AG, Basel, for a generous gift of this compound.



Concentrated aqueous HCl solution hydrolyzed **24** to the nonono-1,4-lactone **26** which was saponified with 0.5N aq. NaOH. The acid **27** was obtained by ion-exchange chromatography of its sodium salt on *Dowex 1 × 8/HCOO⁻* resin. Ozonolysis of **27** at -60° gave *N*-acetylneuraminic acid (**28**) in 80% yield (38.4% after recrystallization [11]). This product could not be distinguished from an authentic sample of **28** (m.p., mixed m.p., specific rotation, and ¹H-NMR- and ¹³C-NMR spectrum [7] [38]).

We thank the *Swiss National Science Foundation* and *Sandoz AG*, Basel, for generous support, and Dr. *R. Prewé* for performing the X-ray analysis.

Experimental Part

General. See [7] [8].

N-Acetyl-*D*-mannosamine (**12**; 21.8 g, 8.7%) was obtained from *N*-acetyl-*D*-glucosamine (**11**; 250 g, 1.13 mol) according to [20] as a hygroscopic, yellowish foam. Purity 93–96% by HPLC (*HPX 87 H*, 0.006N H₂SO₄, 0.66 ml/min). M.p. 103–106° ([20]: 105–108°). $[\alpha]_{\text{D}}^{20} = +11.2$ ($c = 1$, H₂O, 24 h; [20]: 10 ($c = 1$, H₂O, 24 h)).

2-Acetamido-2-deoxy-*D*-mannose Diethyl Dithioacetal (**13**). From **12** (22.1 g, 99.91 mmol), 28.13 g (86.0%) of **13** were obtained according to [19]. M.p. 149–151° ([19]: 150–152°), $[\alpha]_{\text{D}}^{20} = -17.3$ ($c = 1.3$, EtOH, [19]: -16.3 ($c = 1.24$, EtOH)). ¹³C-NMR (50 MHz, D₂O): 14.05 (*q*, CH₃); 14.49 (*q*, CH₃); 22.31 (*q*, CH₃); 26.04 (*t*, CH₂S); 27.00 (*t*, CH₂S); 52.45 (*d*); 53.95 (*d*); 63.63 (*t*); 69.17 (*t*); 69.61 (*t*); 71.10 (*t*); 174.67 (*s*).

2-Acetamido-2-deoxy-3,4:5,6-di-*O*-isopropylidene-aldehydo-*D*-mannose Diethyl Dithioacetal (**14**). A suspension of **13** (10 g, 30.53 mmol) and powdered CaSO₄ · ½ H₂O (40.0 g, 275.6 mmol) in dry acetone (750 ml) was vigorously stirred under Ar, and FeCl₃ (2.0 g, 12.33 mmol) was added at once under exclusion of moisture. The suspension was stirred for 4 h, Na₂CO₃ · 10 H₂O (50.0 g, 175 mmol) added, and the mixture stirred for 1 additional h. After filtration through *Celite* and evaporation of the filtrate followed by coevaporation with toluene (4 times), the yellow oil was flash chromatographed (gradient hexane/Et₂O 1:1→2:3) giving **14** (11.45 g, 92.0%) as a colourless oil which solidified upon standing. M.p. 55–57°, b.p. 110–112°/0.2 mbar. $[\alpha]_{\text{D}}^{20} = +21.4$ ($c = 2.1$, CHCl₃; [19]: 20.7 ($c = 8.2$, CHCl₃)). IR 3420*m* (br.), 2990*s*, 2930*m*, 2875*w*, 1680*s*, 1500*m*, 1450*w*, 1380*s*, 1370*s*, 1150*s*,

1070s. $^1\text{H-NMR}$ (200 MHz): 1.27 (s, CH_3); 1.31 (t, $J = 8.0$, CH_3); 1.37 (s, CH_3); 1.38 (t, CH_3); 1.39 (s, CH_3); 1.43 (s, CH_3); 2.01 (s, CH_3); 2.68 (q, $J = 8.0$, CH_2S); 2.77 (q, $J = 8.0$, CH_2S); 3.81 (dd, $J = 4.6, 7.9$, $\text{H-C}(6)$); 3.94 (dd, $J = 5.8, 7.9$, $\text{H-C}(6)$); 3.96 (dd, $J = 7.5, 7.9$, $\text{H-C}(4)$); 4.02 (ddd, $J = 4.6, 5.8, 7.9$, $\text{H-C}(5)$); 4.17 (dd, $J = 3.23, 7.5$, $\text{H-C}(3)$); 4.29 (d, $J = 2.3$, $\text{H-C}(1)$); 4.57 (ddd, $J = 2.3, 3.2, 10.0$, $\text{H-C}(2)$); 5.71 (br. d, $J = 10.0$, NH, exchangeable with D_2O). $^{13}\text{C-NMR}$ (50 MHz): 14.17 (q, CH_3); 14.77 (q, CH_3); 23.41 (q, CH_3); 25.43 (q, CH_3); 25.67 (t, CH_2S); 26.50 (q, CH_3); 27.05 (t, CH_2S); 27.60 (q, CH_3); 27.81 (q, CH_3); 52.44 (d); 54.86 (d); 67.66 (t); 77.12 (d); 79.83 (d); 80.70 (d); 109.62 (s); 110.35 (s); 170.04 (s). CI-MS: 408 ($[M + 1]^+$), 346. Anal. calc. for $\text{C}_{18}\text{H}_{33}\text{NO}_2\text{S}_2$ (407.59): C 53.04, H 8.16, N 3.44, S 15.73; found: C 53.06, H 8.02, N 3.25, S 15.44.

2,1-O-(1-Aza-1-propene-1,2-diyl)-2-deoxy-3,4:5,6-di-O-isopropylidene-aldehydo-D-mannose S-Ethyl Monothioacetal (**16**). To a soln. of **14** (10.0 g, 24.53 mmol) in anh. MeCN (150 ml), HgO (15.0 g, 69.26 mmol) and HgCl_2 (15.0 g, 55.25 mmol) were added. After stirring for 1 h, the mixture was filtered through *Celite* and the solvent evaporated. Addition of CHCl_3 (150 ml) resulted in the precipitation of a white solid. The filtrate obtained by passage through *Celite* was diluted with CHCl_3 (150 ml) and washed twice with 1M KI, H_2O , and brine (10 ml each), and the org. layer was processed in the usual way. Recrystallization of the residue from hexane/ Et_2O afforded **16** (7.7 g, 90.8%). M.p. 84–86°. $[\alpha]_{\text{D}}^{20} = -224.8$ ($c = 1.4$, CHCl_3). IR (KBr): 2980m, 2960m, 2920m, 1880m, 1675s, 1485m, 1450m, 1385s, 1375s, 1365m, 1335m, 1260s, 1250s, 1240s, 1230s, 1210s, 1165m, 1150m, 1120m, 1070s, 1055m, 1040m, 1000m. $^1\text{H-NMR}$ (400 MHz): 1.25 (t, $J = 7.9$, CH_3); 1.27 (s, CH_3); 1.31 (s, CH_3); 1.35 (s, CH_3); 1.37 (s, CH_3); 1.95 (d, $J = 1.5$, CH_3); 2.70, 2.76 (qAB, $J = 7.9, 7.9$, -13.0 , CH_2S); 3.78 (dd, $J = 7.5, 7.6$, $\text{H-C}(4)$); 3.96 (dd, $J = 4.5, 7.9$, $\text{H-C}(6)$); 4.08 (ddd, $J = 4.5, 6.2, 7.5$, $\text{H-C}(5)$); 4.13 (dd, $J = 6.2, 7.9$, $\text{H-C}(6)$); 4.17 (ddd, $J = 1.5, 3.1, 6.3$, $\text{H-C}(2)$); 4.22 (dd, $J = 3.1, 7.6$, $\text{H-C}(3)$); 5.55 (d, $J = 6.3$, $\text{H-C}(1)$). $^1\text{H-NMR}$ (400 MHz, CD_3CN): 1.27 (s, CH_3); 1.28 (t, CH_3); 1.31 (s, CH_3); 1.36 (s, CH_3); 1.37 (s, CH_3); 1.90 (d, $J = 1.3$, $\text{H-C}(2)$); 2.70, 2.72 (qAB, $J = 12.9, 7.4, 7.4$, CH_2S); 3.73 (t, $J = 7.4$, $\text{H-C}(4)$); 3.87 (dd, $J = 4.5, 8.0$, $\text{H-C}(6)$); 4.02–4.13 (m, $\text{H-C}(3)$, $\text{H-C}(2)$, $\text{H-C}(5)$, $\text{H-C}(6)$); 5.62 (d, $J = 5.7$, $\text{H-C}(1)$). $^{13}\text{C-NMR}$ (50 MHz): 14.18 (q, CH_3); 14.75 (q, CH_3); 25.04 (q, CH_3); 25.19 (q, CH_3); 26.41 (q, CH_3); 26.97 (q, CH_3); 27.11 (q, CH_3); 67.30 (t, $\text{C}(6)$); 73.55 (d, $\text{C}(2)$); 77.85 (d, $\text{C}(4)$); 80.16 (d, $\text{C}(3)$); 84.14 (d, $\text{C}(1)$); 109.68 (s); 109.86 (s); 164.42 (s, C=N). $^{15}\text{N-NMR}$ (40.56 MHz, CH_3NO_2 external standard): -158.82 . CI-MS: 346 ($[M + 1]^+$). Anal. calc. for $\text{C}_{16}\text{H}_{27}\text{NO}_3\text{S}$ (345.46): C 55.63, H 7.88, N 4.06, S 9.28; found: C 55.66, H 7.97, N 4.03, S 9.16.

[2,1-O-(1-Aza-1-propene-1,2-diyl)-2-deoxy-3,4:5,6-di-O-isopropylidene-aldehydo-D-mannose S-Ethyl Monothioacetal]mercury Dichloride (**15**) from **16**. A mixture of HgCl_2 (1.7 g, 6.26 mmol) and HgO (1.4 g, 6.46 mmol) was added to a soln. of **16** (1.0 g, 2.89 mmol) in dry MeCN. After stirring for 30 min, the mixture was filtered through *Celite* and the solvent evaporated. The oily residue was immediately flash-chromatographed (toluene/ EtOAc 3:1) to give **15** which decomposed within 20–30 min. The decomposition was slower in the presence of added HgCl_2 . $^1\text{H-NMR}$ (400 MHz, CD_3CN ; registered immediately after chromatography): 1.26 (t, $J = 7.4$, CH_3); 1.28 (s, CH_3); 1.29 (s, CH_3); 1.33 (s, CH_3); 1.39 (s, CH_3); 2.21 (d, $J = 1.2$, CH_3); 2.77 (q, $J = 7.4$, CH_2); 3.67 (dd, $J = 7.8, 8.0$, $\text{H-C}(4)$); 3.87 (dd, $J = 5.6, 7.7$, $\text{H-C}(6)$); 4.09–4.13 (m, $\text{H-C}(5)$, $\text{H-C}(6)$); 4.38 (ddd, $J = 5.8, 2.3, 1.2$, $\text{H-C}(2)$); 4.44 (dd, $J = 8.0, 2.3$, $\text{H-C}(3)$); 5.89 (d, $J = 5.8$, $\text{H-C}(1)$).

2-Acetamido-2-deoxy-3,4:5,6-di-O-isopropylidene-aldehydo-D-mannose (**10**). From **16**. To a soln. of **16** (3.5 g, 10.13 mmol) in THF (250 ml), 5% aq. AcOH soln. (160 ml) was added at once. N_2 was bubbled through the vigorously stirred soln. for 3 h. Solid NaHCO_3 was added (pH \rightarrow 8), and after the evolution of gas had ceased, the mixture was extracted 8–10 times with EtOAc (50 ml each). The combined org. layers were processed in the usual way. The colourless, syrupy residue (3.1 g, 95%) was immediately used. $[\alpha]_{\text{D}}^{20} = +36.8$ – 40.1 ($c = 1$, CHCl_3 ; [19]: 39 ($c = 6.59$, CHCl_3)). IR: 3430m (br.), 3350m (br.), 1735s, 1680s, 1500m, 1370s, 1060s. $^1\text{H-NMR}$ (200 MHz): 1.35–1.40 (m, 4 CH_3); 2.08 (s, CH_3); 3.92–4.24 (m, 5H); 4.69 (ddd, $J = 0.5, 6.5, 6.5$, $\text{H-C}(2)$); 6.52 (d, $J = 6.5$, NH); 9.72 (d, $J = 0.5$, CHO). $^{13}\text{C-NMR}$ (50 MHz): 22.73 (q, CH_3); 25.04 (q, CH_3); 26.51 (q, CH_3); 26.75 (q, CH_3); 26.87 (q, CH_3); 59.84 (d); 67.78 (t); 76.77 (d); 79.04 (d); 79.75 (d); 110.05 (s); 110.61 (s); 170.24 (s); 197.90 (d).

From **23**. A soln. of **23** (3.1 g, 10.2 mmol) in dry CH_2Cl_2 (100 ml) was added to a stirred soln. of periodinane [31] (4.75 g, 11.2 mmol) in 50 ml of dry CH_2Cl_2 over 15 min. After 30 min, the homogeneous mixture was diluted with Et_2O (250 ml) and poured into sat., cold NaHCO_3 soln. (100 ml) containing $\text{Na}_2\text{S}_2\text{O}_3$ (12.5 g, 79.06 mmol). After stirring for 15 min, the layers were separated. The aq. layer was extracted 5 times with Et_2O (100 ml each). The combined org. layers were washed with sat. NaHCO_3 soln. and brine (10 ml each), and dried (Na_2SO_4). The solvents were evaporated below 20° . The slightly yellowish residue (2.6 g, 85%) was immediately used for further transformations. It could be stored at -20° under Ar for at least 12 h. $[\alpha]_{\text{D}}^{20} = +37$ – 40.5 ($c = 1$, CHCl_3).

Methyl 3,4:5,6-Di-O-isopropylidene-D-gluconate (**18**). To D-glucono-1,5-lactone (**17**; 356.0 g, 2 mol) in 1,1-dimethoxyethane (600 ml), dry acetone (200 ml), and abs. MeOH (60 ml), $\text{TsOH} \cdot \text{H}_2\text{O}$ (4.0 g, 21.03 mmol) was added. After stirring for 12 h, the homogeneous soln. was neutralized with NaHCO_3 and filtered. Solvents were evaporated below 30° . A soln. of the syrupy residue in CH_2Cl_2 (500 ml) was washed twice with H_2O (50 ml each)

and dried (Na_2SO_4). Distillation of the residue obtained after evaporation of the filtrate through a 25-cm *Vigreux* column gave **18** (489.0 g, 84.3%). B.p. 129–130°/0.9 Torr ([29]: 122–124°/0.7 Torr). $[\alpha]_{\text{D}}^{20} = +10.3$ ($c = 1$, CHCl_3 ; [29]: 10.0 ($c = 1$, CHCl_3)). $^{13}\text{C-NMR}$ (50 MHz): 25.24 (q , CH_3); 26.50 (q , CH_3); 26.65 (q , CH_3); 27.13 (q , CH_3); 52.64 (q , CH_3O); 67.86 (t); 69.42 (d); 76.46 (d); 77.26 (d); 80.87 (d); 109.83 (s); 110.04 (s); 172.95 (s).

Methyl 3,4 : 5,6-Di-O-isopropylidene-2-O-(trifluoromethanesulfonyl)-D-gluconate (19). A soln. of **18** (11.0 g, 37.89 mmol) in abs. CH_2Cl_2 (100 ml) was cooled to -10° , and precooled dry pyridine (10 ml) was added. A soln. of trifluoromethanesulfonic anhydride (14.2 g, 50.33 mmol) in anh. CH_2Cl_2 (20 ml) was added over 30 min under vigorous stirring. The mixture was neutralized at 0° with sat. aq. NaHCO_3 soln. The org. layer was processed in the usual way. The residue was co-evaporated repeatedly (5 times) with toluene. The remaining yellowish crystals (14.9 g, 93.1%) were pure enough for further transformations. An anal. sample was obtained by flash chromatography (toluene/EtOAc 10:1) and crystallization from EtOAc/hexane: 14.36 g (89.7%). M.p. 66–67°. $[\alpha]_{\text{D}}^{20} = +44.2$ ($c = 1.1$, CHCl_3). IR (KBr): 2995 m , 2960 w , 2940 w , 2920 w , 2900 w , 1740 s , 1440 m , 1390 m , 1380 s , 1350 s , 1300 s , 1250 m , 1200 m , 1185 s , 1120 m , 1105 w , 1070 s , 1060 s , 1000 m . $^1\text{H-NMR}$ (400 MHz): 1.35 (s , CH_3); 1.38 (s , CH_3); 1.39 (s , CH_3); 1.40 (s , CH_3); 3.87 (dd , $J = 7.4$, 8.6, H–C(4)); 3.90 (dd , $J = 6.0$, 8.7, H–C(6)); 3.91 (s , CH_3); 4.07 (ddd , $J = 6.0$, 8.6, 6.2, H–C(5)); 4.21 (dd , $J = 6.2$, 8.7, H–C(6)); 4.55 (dd , $J = 1.9$, 7.4, H–C(3)); 5.33 (d , $J = 1.9$, H–C(2)). $^{13}\text{C-NMR}$ (50 MHz): 25.04 (q , CH_3); 26.14 (q , CH_3); 26.14 (q , CH_3); 27.25 (q , CH_3); 53.51 (q , CH_3O); 68.14 (t); 77.00 ($2d$); 79.35 (d); 80.57 (d); 110.24 (s); 111.51 (s); 118.44 (q , $J = 319.5$, CF_3); 165.47 (s). CI-MS: 364 ($[M - \text{CO}_2\text{CH}_3 + 1]^+$). Anal. calc. for $\text{C}_{14}\text{H}_{21}\text{F}_3\text{SO}_9$ (422.38): C 39.81, H 5.01; found: C 39.81, H 5.20.

Methyl 3,4 : 5,6-Di-O-isopropylidene-2-O-(methanesulfonyl)-D-gluconate (21). To a soln. of **18** (50.0 g, 172.23 mmol) in dry CH_2Cl_2 (250 ml) and Et_3N (27 ml, 193.71 mmol), methanesulfonyl chloride (22.0 g, 192.0 mol) was added over 30 min so that the temp. did not exceed 30° . The mixture was stirred for additional 2 h, diluted with CH_2Cl_2 (250 ml), poured onto ice/ NaHCO_3 , filtered, and processed in the usual way. Column chromatography (silica gel, toluene/EtOAc 10:1) afforded **21** (56.0 g, 88.3%) as white crystals. M.p. 86–88°. $[\alpha]_{\text{D}}^{20} = +19.8$ ($c = 4.40$, CHCl_3). IR (KBr): 2995 m , 2960 w , 2940 w , 2920 w , 2895 w , 1780 s , 1420 s , 1400 w , 1375 m , 1365 m , 1295 m , 1250 s , 1220 s , 1150 s , 1120 w , 1105 m , 1070 s , 1080 w , 1020 m . $^1\text{H-NMR}$ (400 MHz): 1.35 (s , CH_3); 1.38 (s , CH_3); 1.41 (s , CH_3); 1.45 (s , CH_3); 3.86 (s , CH_3O); 3.95 (dd , $J = 5.1$, 8.7, H–C(6)); 3.96 (dd , $J = 7.6$, 8.6, H–C(4)); 4.08 (ddd , $J = 5.1$, 6.2, 8.6, H–C(5)); 4.19 (dd , $J = 6.2$, 8.7, H–C(6)); 4.50 (dd , $J = 1.8$, 7.6, H–C(3)); 5.28 (d , $J = 1.8$, H–C(2)). $^{13}\text{C-NMR}$ (50 MHz): 25.19 (q , CH_3); 26.33 (q , CH_3); 26.43 (q , CH_3); 27.22 (q , CH_3); 53.05 (q , CH_3O); 67.89 (t); 75.98 (d); 76.91 (d); 77.11 (d); 79.49 (d); 110.18 (s); 110.82 (s); 167.58 (s). CI-MS: 369 ($[M + 1]^+$), 311. Anal. calc. for $\text{C}_{14}\text{H}_{24}\text{SO}_9$ (368.41): C 45.64, H 6.57, S 8.70; found: C 45.79, H 6.52, S 8.91.

Methyl 2-Azido-2-deoxy-3,4 : 5,6-di-O-isopropylidene-D-mannonate (20). From **19**. To a soln. of **19** (5.0 g, 11.93 mmol) in dry MeCN (50 ml), Bu_4NN_3 (4.0 g, 14.06 mmol) was added under exclusion of moisture. After stirring for 20 min, the mixture was diluted with CH_2Cl_2 (300 ml), washed with H_2O (20 ml), and processed in the usual way. Flash chromatography (toluene/EtOAc 10:1) afforded **19** (3.58 g, 95.9%) as an oil which solidified upon standing. M.p. 20–21°. $[\alpha]_{\text{D}}^{20} = +21.5$ ($c = 1.3$, CHCl_3). IR: 2990 m , 2960 w , 2940 w , 2890 w , 2110 s , 1750 s , 1455 m , 1435 m , 1385 s , 1370 s , 1340 w , 1240 s , 1155 m , 1070 s , 1025 m . $^1\text{H-NMR}$ (400 MHz): 1.32 (s , CH_3); 1.38 (s , CH_3); 1.40 (s , CH_3); 1.41 (s , CH_3); 3.81 (s , CH_3O); 3.95 (dd , $J = 4.6$, 8.5, H–C(6)); 4.0–4.05 (m , H–C(5), H–C(4)); 4.13 (dd , $J = 5.5$, 8.5, H–C(6)); 4.29 (d , $J = 3.5$, H–C(2)); 4.37 (dd , $J = 3.5$, 6.5, H–C(3)). $^{13}\text{C-NMR}$ (50 MHz): 25.26 (q , CH_3); 26.30 (q , CH_3); 26.82 (q , CH_3); 27.24 (q , CH_3); 52.52 (q , CH_3O); 62.92 (d); 67.58 (t); 76.73 (d); 77.56 (d); 80.65 (d); 109.92 (s); 110.32 (s); 167.67 (s , COO). CI-MS: 316 ($[M + 1]^+$), 288, 258, 230. Anal. calc. for $\text{C}_{13}\text{H}_{21}\text{NO}_6$ (315.33): C 49.52, H 6.71, N 13.32; found: C 49.51, H 6.57, N 13.19.

From **21**. Dry LiN_3 (12.2 g, 249.18 mmol) was added to a soln. of **21** (37.0 g, 100.4 mmol) in dry DMF (150 ml). After stirring at 50° overnight under Ar, the mixture was processed as indicated above to yield 27.05 g (85.4%).

Methyl 2-Acetamido-2-deoxy-3,4 : 5,6-di-O-isopropylidene-D-mannonate (22). A soln. of **20** (31.5 g, 99.9 mmol) in EtOAc/ Ac_2O (250 ml, 1:1) was hydrogenated at atmospheric pressure in the presence of 10% Pd/C (1.0 g). After 24 h, filtration through *Celite* and removal of the solvents by repeated co-evaporation with toluene (5 times) and Et_2O (3 times) gave a white solid which was recrystallized from EtOAc/hexane to yield **22** (30.5 g, 92.0%). Evaporation of the mother liquor and recrystallization of the residue afforded additional 1.6 g (4.8%). M.p. 117–119°. $[\alpha]_{\text{D}}^{20} = +33.5$ ($c = 1.1$, CHCl_3). IR (KBr): 3255 s (br.), 3065 s , 2990 s , 2960 w , 2940 m , 2900 m , 1700 s , 1635 s , 1565 s , 1455 m , 1440 m , 1385 s , 1375 s , 1350 w , 1330 w , 1310 w , 1300 w , 1265 s , 1240 s , 1215 s , 1200 s , 1175 s , 1160 s , 1105 s , 1065 s , 1015 w , 1000 w . $^1\text{H-NMR}$ (400 MHz): 1.34 (s , CH_3); 1.35 (s , CH_3); 1.36 (s , CH_3); 1.45 (s , CH_3); 2.02 (s , CH_3); 3.78 (s , CH_3O); 3.95 (dd , $J = 4.8$, 8.5, 1 H); 4.01 (dd , $J = 6.4$, 8.2, 1 H); 4.05 (dd , $J = 5.0$, 8.5, 1 H); 4.13–4.17 (m , 2 H); 4.73 (dd , $J = 4.8$, 8.5, 1 H); 6.44 (br. d , $J = 6.5$, exchangeable with D_2O , NH). $^{13}\text{C-NMR}$ (50 MHz): 23.07 (q , CH_3); 25.28 (q , CH_3); 26.65 (q , CH_3); 26.93 (q , CH_3); 27.23 (q , CH_3); 52.52 (s); 54.91 (q , CH_3O); 67.74 (t); 77.14 (d); 78.89 (d); 80.81 (d); 110.08 (s); 110.52 (s); 169.82 (s); 170.30 (s). CI-MS: 332 ($[M + 1]^+$). Anal. calc. for $\text{C}_{15}\text{H}_{25}\text{NO}_7$ (331.37): C 54.37, H 7.61, N 4.22; found: C 54.23, H 7.72, N 4.04.

2-Acetamido-2-deoxy-3,4 : 5,6-di-O-isopropylidene-D-mannitol (**23**). LiBH_4 (1.0 g, 45.9 mmol) was added in 5 portions over 30 min at 0° under N_2 to a soln. of **22** (15.0 g, 45.26 mmol) in anh. THF (100 ml). Abs. MeOH (5 ml) was added over 1 h, and the mixture was stirred for another h at r.t. After quenching of the excess of LiBH_4 by adding EtOAc (10 ml), the solvents were evaporated finally by co-evaporation with MeOH (5 times 20 ml), and the remaining white solid was flash-chromatographed (SiO_2 deactivated with 0.2% Et_3N ; gradient EtOAc/hexane 1:3→3:1, containing 0.1% of Et_3N) to yield **23** (12.7 g, 92.3%). M.p. 68–70° ([19]: oil). $[\alpha]_{\text{D}}^{20} = +31.9$ ($c = 1.19$, MeOH), $[\alpha]_{\text{D}}^{20} = +14.6$ ($c = 6.19$, CHCl_3); [19]: 34 ($c = 2.75$, MeOH). IR: 3420s (br.), 3360m (br.), 2990s, 2940m, 2890m, 1730w, 1670s, 1520s, 1505m, 1455m, 1385s, 1370s, 1240s, 1150s, 1070s. $^1\text{H-NMR}$ (400 MHz): 1.37 (q, CH_3); 1.41 (q, CH_3); 1.42 (q, CH_3); 1.43 (q, CH_3); 2.01 (s, CH_3CO); 3.6 (br. s, OH, exchangeable with D_2O); 3.83–3.91 (m, 4 H); 4.02–4.14 (m, 3 H); 4.17 (dd, $J = 6.2, 8.6$); 6.5 (br. s, NH, exchangeable with D_2O). $^{13}\text{C-NMR}$ (50 MHz): 23.29 (q, CH_3); 25.23 (q, CH_3); 26.51 (q, CH_3); 27.07 (q, CH_3); 27.07 (q, CH_3); 53.54 (d); 62.56 (t); 67.85 (t); 77.11 (d); 79.83 (d); 79.90 (d); 109.90 (s); 110.09 (s); 170.64 (s). CI-MS: 606 ($[2M + 1]^+$), 549, 304 ($[M + 1]^+$), 246. Anal. calc. for $\text{C}_{14}\text{H}_{25}\text{NO}_6$ (303.36): C 55.43, H 8.31, N 4.62; found: C 55.22, H 8.35, N 4.84.

tert-Butyl 5-Acetamido-2,3,5-trideoxy-6,7:8,9-di-O-isopropylidene-2-methylidene-D-glycero-D-galacto-nononate (**24**) and tert-Butyl 5-Acetamido-2,3,5-trideoxy-6,7:8,9-di-O-isopropylidene-2-methylidene-D-glycero-D-talono-nononate (**25**). Graphite (2.5 g, 208.14 mmol) was heated under Ar for 20 min at 150°. Under vigorous stirring, freshly cut clean K (0.98 g, 25.06 mmol) was added in several pieces over 5–10 min. Heating and stirring was continued for 30 min, and the bronze-coloured C_8K was allowed to cool to r.t. and suspended in anh. THF (100 ml). A mixture of anh. ZnCl_2 (1.7 g, 12.47 mmol) and AgOAc (0.21 g, 1.26 mol) was added in 3 portions. After heating under reflux for 30 min, the mixture was cooled to –78° and a soln. of tert-butyl 2-(bromomethyl)prop-2-enoate (**2**; 2.8 g, 12.66 mmol) and **10** (3.0 g, 9.96 mmol) in anh. THF (20 ml) was slowly added through a syringe. After stirring for 30 min at –78°, the mixture was allowed to warm up to 0° over 1 h. The mixture was filtered through *Celite*, and the filtrate was evaporated to give an oil (**24/25** = 88–91:8.8–11.1, HPLC, *Zorbax Sil*, EtOAc/hexane 3:1, 1.5 ml/min). Column chromatography (SiO_2 , EtOAc/hexane 2:1) afforded **24** (3.7 g, 83.7%) and then **25** (0.42 g, 9.5%).

Data for **24**: M.p. 84–86°. $[\alpha]_{\text{D}}^{20} = +9.65$ ($c = 0.2$, CHCl_3). IR (KBr): 3380s (br.), 3100w, 2990s, 2920m, 1725s, 1660w, 1635s, 1565m, 1555m, 1550m, 1480w, 1455w, 1435m, 1380m, 1370s, 1330m, 1315m, 1255m, 1240m, 1215s, 1160s, 1150s, 1110w, 1070s. $^1\text{H-NMR}$ (400 MHz): 1.32 (s, CH_3); 1.33 (s, CH_3); 1.36 (s, CH_3); 1.37 (s, CH_3); 1.46 (s, 3 CH_3); 2.00 (s, CH_3); 2.38–2.41 (m, 2 H–C(3)); 3.23 (br. s, OH, exchangeable with D_2O); 3.82 (dd, $J = 6.5, 8.4, 1$ H); 3.86 (ddd, $J = 0.2, 4.9, 8.3, 1$ H); 3.99 (ddd, $J = 6.3, 6.4, 8.3, 1$ H); 4.08–4.17 (m, 4 H); 5.60 (d, $J = 1.2, 1$ H, $\text{CH}_2=$); 6.1 (br. m, NH); 6.12 (d, $J = 1.5, 1$ H, $\text{CH}_2=$). $^{13}\text{C-NMR}$ (50 MHz): 23.37 (q, CH_3); 25.35 (q, CH_3); 26.49 (q, CH_3); 27.48 (q, CH_3); 27.55 (q, CH_3); 27.95 (3q, CH_3); 37.51 (t); 53.97 (d); 67.68 (t); 69.04 (d); 77.21 (d); 80.02 (d); 80.37 (d); 81.17 (d); 109.69 (s); 110.02 (s); 127.59 (t); 138.36 (s); 167.08 (s); 170.05 (s). CI-MS: 444 ($[M + 1]^+$), 388. Anal. calc. for $\text{C}_{22}\text{H}_{37}\text{NO}_8$ (443.54): C 59.58, H 8.41, N 3.16; found: C 59.81, H 8.62, N 3.07.

Data for **25**: $[\alpha]_{\text{D}}^{20} = +10.7$ ($c = 1.9$, CHCl_3). IR: 3440s (br.), 3360s (br.), 2900s, 2940m, 2920w, 1700s, 1680s, 1630m, 1520m, 1480w, 1455m, 1385s, 1370s, 1345m, 1315m, 1230m (br.), 1150s, 1075s. $^1\text{H-NMR}$ (400 MHz): 1.34 (s, CH_3); 1.36 (s, CH_3); 1.38 (s, CH_3); 1.41 (s, CH_3); 1.47 (s, 3 CH_3); 2.01 (s, CH_3); 2.39 (ddd, $J = < 0.5, 8.7, 12.7, 12.7$, H–C(3)); 2.53 (ddd, $J = < 0.5, 1.9, 14.4$, H–C(3)); 3.82–3.87 (m, 2 H); 3.98 (dd, $J = 6.1, 8.6, 1$ H); 4.00 (dd, $J = 6.9, 8.6, 1$ H); 4.10–4.12 (m, 2 H); 4.17 (dd, $J = 6.1, 8.6, 1$ H); 4.27 (br. s, OH, exchangeable with D_2O); 5.65 (d, $J = 1.3, 1$ H, $\text{CH}_2=$); 6.4 (d, $J = 1.3, 1$ H, $\text{CH}_2=$); 6.45 (br. d, $J = 6.1$, NH). $^{13}\text{C-NMR}$ (50 MHz): 23.24 (q); 25.24 (q); 26.48 (q); 26.85 (q); 27.13 (q); 27.93 (q); 35.75 (t); 57.77 (d); 68.14 (t); 71.74 (d); 77.39 (d); 79.23 (d); 80.05 (d); 80.88 (s); 109.94 (s); 110.17 (s); 126.68 (s); 138.67 (t); 167.03 (s); 171.34 (s). CI-MS: 444 ($[M + 1]^+$), 388. Anal. calc. for $\text{C}_{22}\text{H}_{37}\text{NO}_8$ (443.54): C 59.58, H 8.41, N 3.16; found: C 59.62, H 8.41, N 3.26.

5-Acetamido-2,3,5-trideoxy-2-methylidene-D-glycero-D-galacto-nonono-1,4-lactone (**26**). A suspension of **24** (1.5 g, 3.38 mmol) in conc. HCl soln. (5 ml) was vigorously stirred for 20 min, abs. MeOH (10 ml) was added, and the solvents were evaporated at 30°. After repeated co-evaporation with toluene (2×10 ml), the residue was dried for 12 h (10^{-3} Torr) and dissolved in abs. MeOH (1.5 ml). Dry Et_2O (50 ml) was slowly added under vigorous stirring. After standing at 5° for 12 h, **26** (0.93 g, 95%) was filtered off and dried. M.p. 175–177° (dec.). $[\alpha]_{\text{D}}^{20} = -14.3$ ($c = 0.95$, MeOH). IR (KBr): 3400s (br.), 2940m, 1760s, 1670s, 1550s, 1435m, 1400m, 1375m, 1325w, 1285m, 1260m, 1220w, 1170w, 1135m, 1090m, 1070w, 1025s. $^1\text{H-NMR}$ (400 MHz, D_2O): 1.98 (s, CH_3); 2.77 (dddd, $J = 2.6, 2.9, 4.8, 17.6$, H–C(3)); 3.17 (dddd, $J = 2.6, 2.9, 8.6, 17.6$, H–C(3)); 3.48 (dd, $J = 1.0, 9.0$, H–C(7)); 3.64 (dd, $J = 6.3, 11.8$, H–C(9)); 3.77 (ddd, $J = 2.8, 6.3, 9.0$, H–C(8)); 3.86 (dd, $J = 2.8, 11.8$, H–C(9)); 4.01 (dd, $J = 1.0, 10.4$, H–C(6)); 4.27 (dd, $J = 1.5, 10.4$, H–C(5)); 5.23 (ddd, $J = 1.6, 4.8, 8.6$, H–C(4)); 5.81 (dd ($= r'$), $J = 2.6, 2.6, 1$ H, $\text{CH}_2=$); 6.19 (dd ($= r'$), $J = 2.9, 2.9, 1$ H, $\text{CH}_2=$). $^{13}\text{C-NMR}$ (50 MHz, D_2O): 22.09 (q, CH_3); 30.00 (t); 53.07 (d); 63.64 (t); 68.07 (d); 69.51 (d); 71.07 (d); 77.42 (d); 123.29 (t); 134.45 (s); 173.88 (s); 175.16 (s).

MS-CI: 290 ($[M + 1]^+$), 272. Anal. calc. for $C_{12}H_{19}NO_7$ (289.28): C 49.82, H 6.62, N 4.84; found: C 49.89, H 6.43, N 4.88.

5-Acetamido-2,3,5-trideoxy-2-methylidene-D-glycero-D-galacto-nononic Acid (27). A suspension of **26** (0.9 g, 3.11 mmol) in aq. NaOH (0.5N, 25 ml) was stirred for 30 min, diluted with H_2O (25 ml) and purified by ion-exchange chromatography (100 g *Dowex I* \times 8/ $HCOO^-$, elution by $0 \rightarrow 0.04N$ aq. $HCOOH$). Fractions containing the product were collected, diluted with H_2O to twice of volume and lyophilized. Recrystallization ($MeOH/CH_2Cl_2$ 1:4) yielded **27** (866 mg, 85.5%). M.p. 140–142° (dec.). $[\alpha]_D^{20} = -44.0$ ($c = 0.5$, H_2O). 1H -NMR (400 MHz, D_2O): 2.09 (s, CH_3); 2.47 (ddd, $J = 0.7, 7.6, 14.0$, H–C(3)); 2.52 (ddd, $J = 0.5, 6.0, 14.0$, H–C(3)); 3.49 (d, $J = 8.9$, H–C(7)); 3.66 (dd, $J = 6.2, 11.5$, H–C(9)); 3.75 (ddd, $J = 2.7, 6.2, 8.9$, H–C(8)); 3.85 (dd, $J = 2.7, 11.5$, H–C(9)); 3.93 (d, $J = 10.3$, H–C(6)); 3.97 (dd, $J = 1.0, 10.3$, H–C(5)); 4.35 (ddd, $J = 1.0, 6.0, 7.6$, H–C(4)); 5.82 (d, $J = 0.7, 1$ H, $CH_2=$); 6.32 (d, $J = 0.5, 1$ H, $CH_2=$). ^{13}C -NMR (50 MHz, D_2O): 22.37 (q, CH_3); 36.57 (t); 53.45 (d); 63.71 (t); 67.77 (d); 68.22 (d); 69.81 (d); 71.04 (d); 129.51 (t); 136.88 (s); 170.67 (s); 174.50 (s). FAB-MS: 308 ($[M + 1]^+$), 290. Anal. calc. for $C_{12}H_{21}NO_8 \cdot H_2O$ (325.45): C 44.29, H 7.12, N 4.30; found: C 44.11, H 7.16, N 4.53.

5-Acetamido-3,5-dideoxy-D-glycero-D-galacto-2-nonulosonic Acid (= N-Acetylneuraminic Acid; Neu5Ac; 28). A soln. of **27** (650 mg, 2.0 mmol) in THF/ H_2O 9:1 (10 ml) was ozonized at -60° over 30 min, HPLC on *HPX 87 H* (0.006N H_2SO_4 , 0.66 ml/min) showed no **27** at this time. Then O_2 was bubbled through the soln. for 10 min at 0° . Evaporation below 20° gave a white solid which was dissolved in H_2O (100 ml) and freeze-dried to yield **28** (494 mg, 80.0%) which was crystallized from $H_2O/AcOH$ (0.8/12 ml) at 5° for 3 d to give pure **28** (237 mg, 38.4%) after drying at 10^{-5} mbar over P_4O_{10} and KOH. M.p. 180–182° (dec.) ($[11]$: 181–183° (dec.)). $[\alpha]_D^{20} = -33.1$ ($c = 0.9$, H_2O ; $[11]$: -32.1 ($c = 1.03$, H_2O)). 1H -NMR (400 MHz, D_2O) and ^{13}C -NMR (50 MHz, D_2O) in agreement with previously published data.

REFERENCES

- [1] A. P. Corfield, R. Schauer, in 'Sialic Acids, Chemistry, Metabolism and Function', 'Cell Biology Monographs', Ed. R. Schauer, Springer Verlag, Wien–New York, 1982, Vol. 11, pp. 5–50.
- [2] R. Jäckh, *Chemie in unserer Zeit* **1975**, *10*, 139.
- [3] S. S. Ng, J. A. Dain, in 'Biological Roles of Sialic Acids', Eds. A. Rosenberg and E. L. Schengrund, Plenum Press, New York, 1976, pp. 59–102.
- [4] W. Reutter, E. Kottgen, C. Bauer, W. Gerok, in 'Sialic Acids, Chemistry, Metabolism and Function', 'Cell Biology Monographs', Ed. R. Schauer, Springer Verlag, New York, 1982, Vol. 10, pp. 263–305.
- [5] T. Wiegandt, *Angew. Chem.* **1968**, *80*, 89.
- [6] 'Ganglioside Structure, Function and Biological Potential', Eds. R. W. Ledeen, R. K. Yu, M. M. Rapport, and K. Suzuki, in 'Adv. Exp. Med. Biol.', Plenum Press, New York, 1984, Vol. 174.
- [7] F. Baumberger, A. Vasella, *Helv. Chim. Acta* **1986**, *69*, 1205.
- [8] R. Julina, I. Müller, A. Vasella, R. Wyler, *Carbohydr. Res.* **1987**, *164*, 415.
- [9] J. W. Cornforth, M. E. Daines, A. Gottschalk, *Proc. Chem. Soc.* **1957**, 25; J. W. Cornforth, M. E. Firth, A. Gottschalk, *Biochem. J.* **1958**, *68*, 57; J. W. Cornforth, P. M. Carroll, *Biochim. Biophys. Acta* **1960**, *39*, 162.
- [10] M. J. How, M. D. A. Halford, M. Stacey, E. Vickers, *Carbohydr. Res.* **1969**, *11*, 313.
- [11] R. Kuhn, G. Baschang, *Liebigs Ann. Chem.* **1962**, *659*, 156.
- [12] W. Gielen, *Z. Physiol. Chem.* **1967**, *348*, 329.
- [13] W. Wesemann, F. Zilliken, *Liebigs Ann. Chem.* **1966**, *695*, 209.
- [14] H. Mack, P. Brossmer, *Tetrahedron Lett.* **1987**, *28*, 191.
- [15] A. Y. Khorlin, I. M. Privalova, *Carbohydr. Res.* **1970**, *13*, 373.
- [16] L. Benzing-Nguyen, M. B. Perry, *J. Org. Chem.* **1978**, *43*, 551.
- [17] J.-M. Beau, P. Sinaÿ, *Carbohydr. Res.* **1978**, *65*, 1; J.-M. Beau, P. Sinaÿ, J. P. Kamerling, J. F. G. Vliegthart, *ibid.* **1978**, *67*, 65; J. F. G. Vliegthart, P. Sinaÿ, *ibid.* **1980**, *82*, 125; J.-M. Beau, R. Schauer, *Eur. J. Biochem.* **1980**, *106*, 531.
- [18] G. H. De Vries, S. B. Binkley, *Arch. Biochem. Biophys.* **1972**, *451*, 243.
- [19] J.-M. Beau, P. Rollin, P. Sinaÿ, *Carbohydr. Res.* **1977**, *53*, 187.
- [20] R. Kuhn, G. Baschang, *Liebigs Ann. Chem.* **1960**, *636*, 164.
- [21] R. Bisaz, Dissertation, ETH, Nr. 5500, 1975.
- [22] M. Miljkovic, D. Dropkin, P. Hagel, M. Habash-Marino, *Carbohydr. Res.* **1984**, *128*, 11.

- [23] M. Balogh, A. Carnelis, P. Laszlo, *Tetrahedron Lett.* **1984**, 25, 3313.
- [24] N. J. Cussans, S. V. Ley, D. H. R. Barton, *J. Chem. Soc., Perkin Trans. 1* **1979**, 1654.
- [25] R. E. Harmon, G. Wellman, S. K. Gupta, *Chem. Ind.* **1973**, 19, 951.
- [26] R. A. Wohl, J. Cannie, *J. Org. Chem.* **1973**, 38, 1787.
- [27] R. S. El'konson, A. V. Eremeev, *Khim. Geterotsikl. Soedin.* **1984**, 2, 206.
- [28] P. B. Rérat, C. Rérat, *Acta Crystallogr.* **1964**, 17, 1119; H. A. Karapetyan, Y. T. Struchkov, A. V. Kameritzky, *Cryst. Struct. Commun.* **1981**, 10, 1461, 1471; R. Parthasarathy, R. E. Davis, *Acta Crystallogr.* **1967**, 23, 1049; R. L. Girling, G. A. Jeffrey, *ibid.*, Sect. B **1973**, 29, 1006; D. C. Carter, J. R. Ruble, G. A. Jeffrey, *Carbohydr. Res.* **1982**, 102, 59.
- [29] H. Regeling, E. de Rouville, G. J. F. Chittenden, *Recl. Trav. Chim. Pays-Bas* **1987**, 106, 461.
- [30] Y. Hamada, T. Shioiri, *Chem. Pharm. Bull.* **1982**, 30, 1921.
- [31] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, 48, 4156.
- [32] R. D. Rieke, P. T.-J. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, 46, 4324.
- [33] A. Lindert, M. W. Rathke, *J. Org. Chem.* **1970**, 35, 3966.
- [34] R. D. Smith, H. E. Simmons, *Org. Synth.* **1961**, 41, 72.
- [35] J. Horiguchi, I. Kuwajima, S. Matuzawa, E. Nakamura, *Tetrahedron Lett.* **1986**, 27, 4025, 4029; A. Alexis, J. Berlan, Y. Besace, *ibid.* **1986**, 27, 1047.
- [36] R. Csuk, A. Fürstner, H. Weidmann, *J. Chem. Soc., Chem. Commun.* **1986**, 775.
- [37] N. T. Anh, *Topics Curr. Chem.* **1980**, 88, 145; M. Chérest, H. Felkin, M. Prudent, *Tetrahedron Lett.* **1968**, 2199.
- [38] J. Haverkamp, H. Van Halbeek, L. Dorland, J. F. G. Vliegthart, R. Pfeil, R. Schauer, *Eur. J. Biochem.* **1982**, 122, 305.