Carbohydrate Research, 175 (1988) 311–316
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

2-Acetamido-2-deoxy-D-gluco- and -D-manno-furanose: a simple preparation of 2-acetamido-2-deoxy-D-mannose*,†

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(Received October 27th, 1987; accepted for publication, November 30th, 1987)

Sialic acids are accessible synthetically by chain extension of 2-acetamido-2-deoxy-D-glucose or -D-mannose with oxaloacetate[1]. However, due to epimerisation at C-2 under alkaline conditions, mixtures of four products are formed, the fractionation of which is sometimes difficult.

The *aldehydo*-2-acetamido-2-deoxyhexoses[2,3] are unstable compounds and cannot be used, without difficulties, for aldol condensations under basic conditions. 2-Acetamido-2-deoxyhexofuranoses are much more stable compounds if HO-3 is not substituted. They readily undergo condensation reactions even under weakly basic conditions and side reactions such as epimerisation or β-elimination are not significant. Hitherto, the glucofuranose derivative **3**, required for the synthesis of the *manno* analogue **5** and of sialic acid derivatives, was accessible only in low yield[4]. We now describe a simple method for preparing **3** and **5** in high yields.

Under non-aqueous conditions, strong Lewis acids such as $FeCl_3$ or $BF_3 \cdot Et_2O$ act on 2-acetamido-2-deoxy-D-glucopyranose in boiling acetone to yield the oxazoline **1c**. At lower temperatures, in addition to **1c**, the furanose derivative **3** is obtained, which decomposes to a mixture of enofuranoses during work-up under strongly alkaline conditions. The results suggest that the reaction is thermodynamically controlled. It is assumed that the action of a strong Lewis acid leads to **3**, which is transformed into **1c**, according to the sequence: 2-acetamido-2-deoxy-D-glucose →**3** →**1a** →**1b** →**1c**. Reaction with $FeCl_3$ produces crude **1c**, which can be used either directly or can be purified by chromatography on silica gel. On the other hand, reaction with boron trifluoride yields a less pure product.

The ^{1}H-n.m.r. spectrum of **1c** shows a characteristic downfield shift (δ 6.17)

*Dedicated to Professor Rezső Bognár in the year of his 75th birthday.
†Presented, in part, at the XIIth International Carbohydrate Symposium, Utrecht, The Netherlands, July 1–7, 1984.
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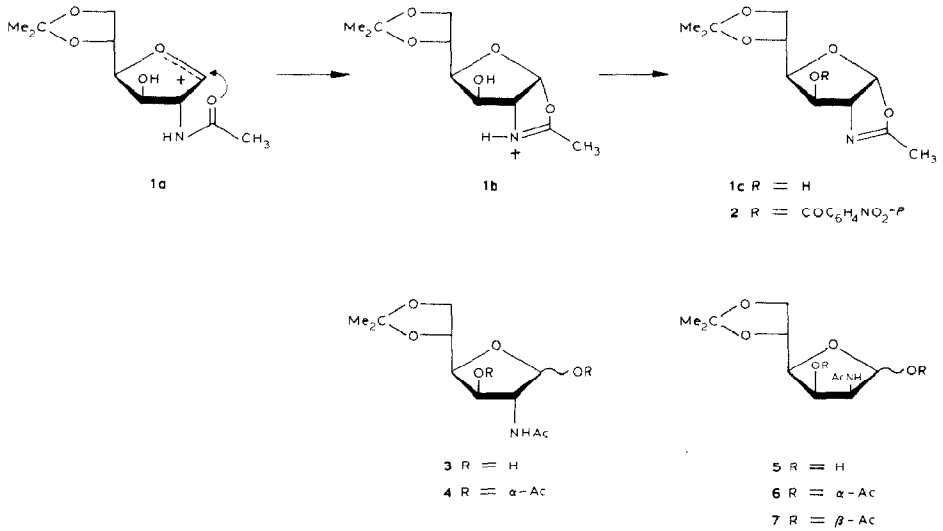
0008-6215/88/$ 03.50

for the H-1 resonance and no coupling between H-2 and H-3. Furthermore, the fragment $C_5H_9O_2^+$ (61%) in the mass spectrum is in accordance with the furanose structure[4,5]

Acylation of HO-3 in **1c** may partially cleave the oxazoline ring and, as a consequence, the 4-nitrobenzoate **2** is obtained only in moderate yield. Mild conditions (*e.g.*, aqueous 0.5% acetic acid) readily and selectively cleaved the oxazoline in **1c** to yield **3** as a 3:2 $\alpha\beta$-mixture. The crystalline α anomer, which is identical (^{1}H-n.m.r. data) with the compound described by Hasegawa *et al.*[4], was characterised as the 1,3-diacetate **4**[4] and as a semicarbazone. Whereas, with strong base, **3** is converted into an enofuranose[6], the use of a weakly basic anion-exchange resin results in epimerisation to give the mannofuranose derivative **5**, which could be isolated from the equilibrium mixture (*gluco:manno* 35:65) by chromatography on silica gel and obtained as a 4:1 $\alpha\beta$-mixture. Since **3** and **5** crystallise as a 1:1 adduct, pure **5** can be isolated in crystalline form by concentrating the mother liquor. ^{1}H-N.m.r. spectra [in $(CD_3)_2SO$] prove the 35:65 ratio for the *gluco:manno* isomers as well as the 1:1 composition of the crystalline adduct of **3** and **5** (integration of well-separated NH and HO-1 resonances). The 1:1 adduct of **3** and **5** may be used again for epimerisation. This method is much simpler than the isolation of **5** by chromatography. Acetylation of **5** gives an $\alpha\beta$-mixture (**6** and **7**).



Thus, the mannofuranose derivative **5** may be prepared in a one-pot synthesis *via* the sequence **1c→3→5**.

2-Acetamido-2-deoxy-D-mannose is accessible by epimerisation of the D-*gluco* isomer only in low yield since the equilibrium favours the latter[7] (80%). In contrast, the equilibrium between **3** and **5** favours the *manno* isomer, thereby permitting a synthesis of 2-acetamido-2-deoxy-D-mannose in higher yield. Thus, treatment of the mixture (35:65) of the furanose derivatives **3** and **5** with dilute acetic

acid gives a mixture of pyranoses, which is freeze-dried and extracted with 1-propanol[1], yielding 2-acetamido-2-deoxy-D-mannose in 94% purity. When **5** is deprotected, the desired amino sugar is obtained pure.

The furanose derivatives **3** and **5** are reactive compounds[8] which can be used for chain elongation, *e.g.*, by aldol condensation[9], Wittig reaction[10], and hydrogen cyanide addition[10].

EXPERRIMENTAL

General methods. — Melting points were determined in capillary tubes with a Büchi apparatus and are uncorrected. Optical rotations were measured at 20° with a Perkin–Elmer 241 polarimeter and i.r. spectra with a Perkin–Elmer 297 spectrophotometer. ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ or $(CD_3)_2SO$ (internal Me_4Si) with a Varian EM 360 (60 MHz), Varian EM 390 (90 MHz), or Bruker 300 instrument (300 MHz). The apparent coupling constants (Hz) reported are the directly observed line-spacings. The mass spectrum was obtained with a ZAB spectrometer coupled to a Multispec data-system (VG Instruments). The purity of products was determined by t.l.c. on Silica Gel 60 F_{254} (Merck) with detection by charring with sulfuric acid. Column chromatography was performed on Silica Gel 60 (70–230 mesh, Merck), which was used without pretreatment. For flash chromatography, a Chromatospac Prep apparatus (Jobin–Yvon) was used. Solvent was removed by rotatory evaporation under reduced pressure.

2-Methyl-(1,2-dideoxy-5,6-O-isopropylidene-α-D-glucofurano-[2,1-d]-2-oxazoline (**1c**). — (*a*) *Using $FeCl_3$.* Anhydrous $FeCl_3$ (45 g, 0.277 mol) was added to a suspension of 2-acetamido-2-deoxy-D-glucopyranose (30 g, 0.135 mol) in dry acetone (600 mL), and the mixture was stirred and boiled under reflux for 20 min with exclusion of moisture. The solution was cooled to 0° and stirred, and diethylamine (77 g) and acetone (400 mL) were added followed dropwise by a solution of sodium carbonate (64 g) in water (400 mL). Acetone, diethylamine, and some water were removed *in vacuo* at <30° (bath). The mixture was then extracted with ether (5 × 200 mL), and the combined extracts were dried ($MgSO_4$) and concentrated at room temperature to give **1c** as a brownish syrup (23.8 g, 72%). The crude product contained traces of a less polar enofuranose but could be used for the preparation of **3** and **5**. Column chromatography on silica gel (160 g, quenched with a trace of diethylamine), using ether and ether–methanol (10:1), yielded **1c** (20.3 g, 62%), isolated as a syrup, R_F 0.35 (ether–methanol, 10:1), $[\alpha]_D^{20}$ −40° (*c* 1, chloroform); ν_{max}^{film} 3200 (OH), 1660 (C=N) cm^{-1}. ^{1}H-N.m.r. data (300 MHz, $CDCl_3$): δ 6.17 (d, 1 H, $J_{1,2}$ 5 Hz, H-1), 4.46 (qd, 1 H, $J_{2,3}$ ~0, $J_{2,Me}$ 1.5 Hz, H-2), 4.40 (d, 1 H, $J_{3,4}$ 2.8 Hz, H-3), 4.33 (ddd, 1 H, $J_{5,6}$ 6.2, $J_{5,6'}$ 4.9 Hz, H-5), 4.15 (dd, 1 H, $J_{6,6'}$ 8.7 Hz, H-6), 4.02 (dd, 1 H, H-6'), 3.76 (dd, 1 H, $J_{4,5}$ 7.7 Hz, H-4), 3.20 (s, 1 H, HO-3), 2.03 (d, 3 H, $J_{2,Me}$ 1.5 Hz, N=C–Me), 1.42 (s, 3 H, Me), and 1.36 (s, 3 H, Me). E.i.-mass spectrum: *m/z* 228.0843 [$M^+ - CH_3$, $C_{10}H_{14}NO_5^+$ (25.7%); calc. 228.0870], 101.0597 [$C_5H_9O_2^+$ (61.2%); calc. 101.0594].

(*b*) *Using* BF_3. To a suspension of 2-acetamido-2-deoxy-D-glucopyranose (20 g, 0.09 mol) in dry acetone (400 mL) was added $BF_3 \cdot Et_2O$ (40.0 g, 0.28 mol). The mixture was stirred and boiled under reflux for 12 min with the exclusion of moisture, then cooled in ice, treated with triethylamine (130 mL), and added dropwise with stirring to a cooled solution of sodium carbonate (145 g) in water (1 L). Further treatment as in (*a*) yielded crude **1c** (17.0 g) which contained ~6% of a less polar enofuranose. Chromatography as in (*a*) gave **1c** (14.4 g, 65%).

The 3-(4-nitrobenzoate) **2** of **1c**, prepared conventionally, was eluted from a column of silica gel (30 g) with ether–hexane (4:1, 350 mL) and then ether–methanol (9:1, 250 mL) to give a product (25%), m.p. 165° (from ethyl acetate), $[\alpha]_D^{20}$ −89° (*c* 2.9, chloroform); ν_{max}^{KBr} 1720 (C=O), 1680 (C=N) cm^{-1}. ^{1}H-N.m.r. data (60 MHz, $CDCl_3$): δ 8.20–8.42 (m, 4 H, aromatic protons), 6.25 (d, 1 H, $J_{1,2}$ 5 Hz, H-1), 5.68 (d, 1 H, $J_{3,4}$ 3 Hz, H-3), 4.64 (qd, 1 H, $J_{2,3}$ ~0, $J_{2,Me}$ 1.5 Hz, H-2), 2.12 (d, 3 H, $J_{2,Me}$ 1.5 Hz, N=C–Me), 1.42 (s, 3 H, Me), and 1.26 (s, 3 H, Me).

Anal. Calc. for $C_{18}H_{20}N_2O_8$: C, 55.10; H, 5.14; N, 7.14. Found: C, 55.14; H, 5.17; N, 7.26.

*2-Acetamido-2-deoxy-5,6-*O*-isopropylidene-*D*-glucofuranose* (**3**). — To a solution of **1c** (15.5 g, 63.8 mmol), obtained by the $FeCl_3$ method, were added cold methanol (500 mL) and cold aqueous 1% acetic acid (500 mL). The solution was left for 24 h at room temperature and then extracted with ether (100 mL), and the residue was repeatedly concentrated with water *in vacuo* and then concentrated at room temperature. After freeze-drying, **3** was obtained as a 2:1 αβ-mixture (14.9 g, 90%). Crystallisation of this product (3.29 g) from ether–methanol gave the pure α-anomer* (1.80 g), m.p. 149–150°, $[\alpha]_D^{20}$ +31° (*c* 1, methanol) {lit.[4] m.p. 145–147°, $[\alpha]_D$ +9° (*c* 0.8)}; R_F 0.23 (ether–methanol, 10:1); the ^{1}H-n.m.r. data (CD_3OD) accorded with those reported[4]. ^{1}H-N.m.r. data [300 MHz, $(CD_3)_2SO$]: δ 8.04 (d, 0.33 H, $J_{2,NH}$ 8 Hz, NHβ), 7.87 (d, 0.66 H, $J_{2,NH}$ 8 Hz, NHα), 6.56 (d, 0.66 H, $J_{1,HO\text{-}1}$ 4 Hz, HO-1α), 6.18 (d, 0.33 H, $J_{1,HO\text{-}1}$ 6 Hz, HO-1β), 5.30 (d, 0.66 H, $J_{3,HO\text{-}3}$ 5 Hz, HO-3α), 5.27 (dd, 0.66 H, $J_{1,2}$ 4.8 Hz, H-1α), 5.17 (d, 0.33 H, $J_{3,HO\text{-}3}$ 5 Hz, HO-3β), 4.97 (dd, 0.33 H, $J_{1,2}$ 1.0 Hz, H-1β), 1.84 (s, 2 H, NAcα), 1.82 (s, 1 H, NAcβ), 1.32 (s, 1 H, Meβ), 1.31 (s, 2 H, Meα), 1.26 (s, 1 H, Meβ), and 1.25 (s, 2 H, Meα).

Treatment of **3** (200 mg, 0.77 mmol) with semicarbazide (200 mg) and sodium acetate (200 mg) in methanol (2.5 mL) and water (1.0 mL) for 2 h gave the semicarbazone (210 mg, 85%), m.p. 218–220°, $[\alpha]_D^{20}$ +5° (*c* 1, methyl sulfoxide). ^{1}H-N.m.r. data [60 MHz, $(CD_3)_2SO$]: δ 10.0 (s, 1 H, NH), 7.98 (d, 1 H, $J_{2,NH}$ 8 Hz, NH), 7.25 (d, 1 H, $J_{1,2}$ 4.6 Hz, H-1), 6.40 (s, 2 H, $CONH_2$), 1.89 (s, 3 H, AcN), and 1.27 (s, 6 H, 2 Me).

Anal. Calc. for $C_{12}H_{22}N_4O_6$: C, 45.28; H, 6.96; N, 17.60. Found: C, 45.18; H, 7.37; N, 17.40.

*2-Acetamido-1,3-di-*O*-acetyl-2-deoxy-5,6-*O*-isopropylidene-α-*D*-glucofuran-*

*During recrystallisation from ether–methanol, some decomposition to enofuranoses was observed.

ose (**4**). — A solution of crystalline **3** (1.60 g, 6.17 mmol) in pyridine (15 mL) and acetic anhydride (10 mL) was left for 2 days at 0° and then concentrated *in vacuo*. Column chromatography of the residue on silica gel (50 g), using dichloromethane–methanol (100:1), yielded **4** (1.94 g, 91%), isolated as a syrup, $[\alpha]_D^{20}$ +92° (*c* 1.45, chloroform). The ^{1}H-n.m.r. data corresponded to those reported[4].

*2-Acetamido-2-deoxy-5,6-O-isopropylidene-*D*-mannofuranose* (**5**). — To a solution of **3** (20 g, 77 mmol; freeze-dried product) in water (200 mL) was added Amberlite IRA-68 (HO^-) resin (40 mL, 20–25 mesh), and the mixture was stirred for 12 h at room temperature and then filtered. The resin was washed with water, and the combined filtrate and washings were concentrated *in vacuo* and then freeze-dried to give a 35:65 syrupy mixture of **3** and **5**. Repeated recrystallisation from ether–methanol (3:1) gave a 1:1 mixture, m.p. 139–140°.

Anal. Calc. for $C_{11}H_{19}NO_6$: C, 50.57; H, 7.33; N, 5.36. Found: C, 50.91; H, 7.01; N, 5.39.

A solution of the above 35:65 mixture (20 g, 77 mmol) of **3** and **5** in water (20 mL) was applied to a column of silica gel (1250 g). Flash chromatography was monitored by t.l.c. (R_F values: **3**, 0.23; **5**, 0.15; ether–methanol, 10:1). Elution with ether–methanol (10:1, 6 L) gave a mixture (4.60 g) enriched with **3** which may be used for further epimerisation. Elution with ether–methanol (5:1, 3 L) gave **5** (8.40 g, 42%) as a syrupy 4:1 $\alpha\beta$-mixture, containing only traces of **3**.

The 35:65 mixture of **3** and **5** (26.6 g, 101.9 mmol) was dissolved in dry ethanol (200 mL) with heating. The solution was concentrated to half volume and cooled to −15° to give a crystalline 1:1 mixture of **3** and **5**. The mother liquors were concentrated to half volume and dry ether (100 mL) was added. Crystallisation at −15° gave pure α-**5** (7.06 g, 26.5%). From the mother liquor, more α-**5** (2 g) containing a few percent of **3** was obtained. Compound **5** had m.p. 132–133°, $[\alpha]_D^{20}$ +59° → +49° (1 h; *c* 1, methanol). ^{1}H-N.m.r. data [300 MHz, $(CD_3)_2SO$]: δ 7.94 (d, 0.8 H, $J_{2,NH}$ 8 Hz, NHα), 7.40 (d, 0.2 H, $J_{2,NH}$ 8.4 Hz, NHβ), 6.39 (d, 0.8 H, $J_{1,HO\text{-}1}$ 6.7 Hz, HO-1α), 5.28 (d, 0.8 H, $J_{3,HO\text{-}3}$ 5.3 Hz, HO-3β), 5.11 (dd, 0.2 H, H-1β), 5.09 (dd, 0.8 H, $J_{1,2} = J_{1,HO\text{-}1}$ = 6.2 Hz, H-1α), 4.91 (d, 0.2 H, $J_{3,HO\text{-}3}$ 5.7 Hz, HO-3β), 1.90 (s, 0.6 H, AcNβ), 1.85 (s, 2.4 H, AcNα), 1.30 (s, 3 H, Me), and 1.28 (s, 3 H, Me).

Anal. Calc. for $C_{11}H_{19}NO_6$: C, 50.57; H, 7.33; N, 5.36. Found: C, 50.50; H, 7.07; N, 5.34.

*2-Acetamido-1,3-di-O-acetyl-2-deoxy-5,6-O-isopropylidene-α-*D*-mannofuranose* (**6**) *and -β-*D*-mannofuranose* (**7**). — A solution of **5** (200 mg, 0.58 mmol) in cold pyridine (5 mL) and acetic anhydride (2.5 mL) was stored for 24 h at 0° and then concentrated *in vacuo*. Elution of the residue from silica gel (20 g) with toluene–ethanol (10:1) gave **6** (169 mg, 49%) and **7** (82 mg, 24%).

Compound **6** had m.p. 129–130° (from ether–hexane), $[\alpha]_D^{20}$ +72° (*c* 1, chloroform). ^{1}H-N.m.r. data (60 MHz, $CDCl_3$): δ 6.35 (d, 1 H, $J_{2,NH}$ 9.2 Hz, NH), 6.10 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 5.73 (dd, 1 H, H-3), 4.90 (ddd, 1 H, H-5), 2.13 (s, 3 H, AcO), 2.10 (s, 3 H, AcO), 2.00 (s, 3 H, AcN), 1.40 (s, 3 H, Me), and 1.30 (s, 3 H, Me).

Anal. Calc. for $C_{15}H_{23}NO_8$: C, 52.17; H, 6.71; N, 4.06. Found: C, 52.39; H, 6.58; N, 3.97.

Compound **7** was a syrup, $[\alpha]_D^{20}$ −2.8° (*c* 1, chloroform). ^{1}H-N.m.r. data (60 MHz, $CDCl_3$): δ 6.24 (d, $J_{1,2}$ 5.2 Hz, H-1), 5.85–5.60 (m, 2 H, H-3 and NH), 4.88 (ddd, H-5), 2.13 (s, 3 H, AcO), 2.11 (s, 3 H, AcO), 2.00 (s, 3 H, AcN), 1.38 (s, 3 H, Me), and 1.30 (s, 3 H, Me).

*2-Acetamido-2-deoxy-*D*-mannopyranose.* — To a solution of **1c** (10.5 g, 43.2 mmol; crude product), obtained by the $FeCl_3$ method, in cold 1:1 methanol–water (750 mL) was added acetic acid (3.75 mL). The solution was stored for 24 h at room temperature, then concentrated as described for **3**, stirred with Amberlite IRA-68 (HO^-) resin (250 mL) for 24 h at room temperature, and worked-up as described for **5**. The solution containing **3** and **5** (35:65) was extracted with ether (100 mL), acetic acid (10 mL) was added, and the mixture was heated for 60 min at 60°, then concentrated under reduced pressure, and freeze-dried to give a syrup containing ManNAc and GlcNAc (65:35). The syrup was extracted[1] with 1-propanol (4 × 250 mL) at 70°, the extracts were combined and concentrated, and the semicrystalline residue was recrystallised from water–acetone to give the title compound (1.82 g), m.p. 112–114°, $[\alpha]_D^{20}$ +11° (*c* 2, water); lit.[1] m.p. 113–115°, $[\alpha]_D^{20}$ +10° (water). From the mother liquor, second (2.05 g) and third (1.25 g) crops were obtained, containing a few percent of GlcNAc (^{1}H-n.m.r. spectroscopy). The overall yield based on **1c** was 5.12 g (49–50%), of which 3.30 g contained ~6% GlcNAc. The latter product may be purified by recrystallisation from water–acetone.

ACKNOWLEDGMENTS

We thank Ms. Andrea Schaeffner for typing the manuscript, and the Deutsche Forschungsgemeinschaft SFB 136 and the Fonds der Chemischen Industrie for financial support.

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