A synthesis of 6-amino-6-deoxy-D-mannose*

The 6-amino-6-deoxyhexoses are of interest in view of the occurrence[1] of 6-amino-6-deoxy-D-glucose in kanamycin A. As part of a program in this laboratory on the hydrolytic susceptibility of various substituted glycosides, the methyl α-D-glycoside of 6-amino-6-deoxy-D-mannopyranose was required. This report describes the synthesis of methyl 6-amino-6-deoxy-α-D-mannopyranoside hydrochloride (**4**) from D-mannose in a sequence of high-yielding steps.

The 4,6-benzylidene acetal[2] of methyl α-D-mannopyranoside[3] was acetylated to give the 2,3-diacetate[4] (**1**). Treatment of **1** with *N*-bromosuccinimide by the procedure of Hanessian[5] gave crystalline methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-bromo-6-deoxy-α-D-mannopyranoside (**2**). Treatment of the bromo derivative **2** with sodium azide in *N*,*N*-dimethylformamide gave the corresponding 6-azido derivative **3**. Removal of the ester groups from **3** by catalytic transesterification, followed by reduction of the azido group and conversion of the resultant amine into the hydrochloride salt gave the crystalline glycoside **4**.

The sequence affords an excellent preparative procedure for the amino glycoside **4** because all steps are amenable to large-scale work and no chromatographic purifications are required. The glycoside **4** can be obtained in over 60% net yield from the starting material **1** if the intermediates **2** and **3** are not recrystallized to high purity. The useful new reaction described by Hanessian[5], as used in the conversion of **1** into **2**, is particularly advantageous because it obviates the necessity of generating a good leaving group at C-6 by a less effective procedure; the conventional method involving selective sulfonylation of an unsubstituted glycoside at C-6 leads to mixtures of esters that may be troublesome to separate, and yields of the desired 6-ester are frequently low.

The glycoside **4** was further characterized as its crystalline *N*-acetylated derivative (**5**). Hydrolysis of the glycoside **4** gave 6-amino-6-deoxy-D-mannose hydrochloride (**6**) as a syrup. Details of characterization of the intermediates and products **1**–**6**, including n.m.r. spectral data, are given in the experimental section.

A synthesis of the syrupy amino sugar **6**, by way of methyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-mannopyranoside, was reported recently in the patent literature[6]. Crystalline methyl 6-acetamido-6-deoxy-α-D-mannopyranoside (**6**), having constants in good agreement with those found in the present work, was obtained from methyl α-D-mannopyranoside in ~15% net yield by a 6-step sequence.

EXPERIMENTAL

General methods. — Melting points were determined with a Thomas–Hoover

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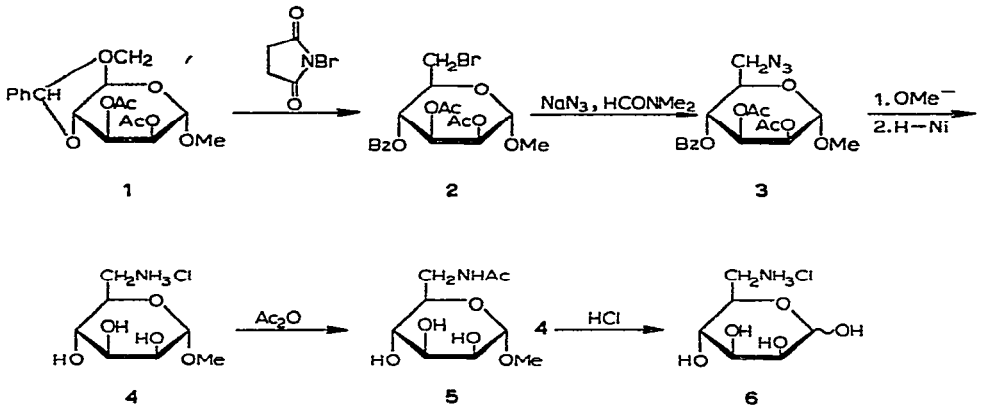
apparatus and are uncorrected. Specific rotations were determined in a 2-dm polarimeter tube. I.r. spectra were measured with a Perkin–Elmer Model 137 "Infracord" i.r. spectrophotometer. N.m.r. spectra were measured with Varian A-60, A-60A, or HA-100 spectrometers. Unless otherwise noted, spectra were measured at 35–40° with solutions (5–15%) in chloroform-*d* with an internal standard of tetramethylsilane



1 2 3

4 5 6

(τ = 10.00), or in deuterium oxide with sodium 4,4-dimethyl-4-silapentane-1-sulfonate (τ = 10.00) as the internal standard. Elemental analyses were performed by W. N. Rond. X-Ray powder diffraction data give interplanar spacings, Å, for CuKα radiation. The camera diameter was 114.54 mm. Relative intensities were estimated visually; s, strong; m, moderate; w, weak; v, very. The strongest lines are numbered (1, strongest), double numbers indicate approximately equal intensities. Unless otherwise noted, R_F values refer to t.l.c. on Silica Gel G (E. Merck, Darmstadt, Germany), activated at 110°, with the developer indicated. Zones were detected with sulfuric acid or with ninhydrin. Paper chromatography was performed by downward irrigation on Whatman No. 1 paper, with detection by ninhydrin and by alkaline silver nitrate.

Methyl 2,3-di-O-acetyl-4,6-O-benzylidene-α-D-mannopyranoside (**1**). — A solution of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside[2] (4.0 g) in a mixture of acetic anhydride (4 ml) and pyridine (200 ml) was heated for 3.5 h on a steam bath and was then kept for 4 h at room temperature. The solution was poured into ice–water (175 ml), whereupon an oil separated. The water layer was decanted and evaporated, and the residue was triturated with ether (100 ml). The ether solution was added to the oil, and the mixture was evaporated to give a pale-yellow syrup. The latter was dissolved in ethanol (200 ml), and the solution was passed through a bed of decolorizing carbon. The solution was evaporated to a syrup, which was converted into a solid mass by evaporating several small portions of methanol from it. The solid product, yield 4.4 g (87%), was sufficiently pure for subsequent conversions. It was chromatographically homogeneous and had m.p. 59–63°, $[\alpha]_D^{20}$ +21.4 ±0.6° (*c* 2, chloroform); R_F 0.35 [1:1 petroleum ether (b.p. 65–100°)–ether];

λ_{max}^{KBr} 5.75 (OAc), 14.35 μm (aryl); n.m.r. data (60 MHz, chloroform-*d*): τ 2.67 (5-proton multiplet, phenyl), τ 4.45 (1-proton singlet, benzylic H), τ 4.69 (2-proton multiplet, H-2,3), τ 5.35 (1-proton narrow multiplet, H-1), τ 5.61–6.26 (4-proton multiplet, H-4,5,6,6'), τ 6.62 (3-proton singlet, OMe), τ 7.85, 8.00 (3-proton singlets, OAc).

Anal. Calc. for $C_{18}H_{22}O_8$: C, 59.01; H, 6.05. Found: C, 58.89; H, 5.87.

This product was obtained by Coxon[3] as a syrup, $[\alpha]_D^{25}$ +23.1 (chloroform), in unspecified yield, after purification by column chromatography. The n.m.r. spectral data reported for **1** by Coxon[3] are in agreement with those measured in the present work.

*Methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-bromo-6-deoxy-*α*-*D*-mannopyranoside* (**2**). — To a suspension of *N*-bromosuccinimide (6.45 g, 0.0363 mole) in dry carbon tetrachloride (250 ml) was added the benzylidene acetal **1** (12.0 g, 0.0333 mole) followed by barium carbonate (10 g). The mixture was refluxed for 1.5 h, cooled to 0°, and filtered. The filtrate was evaporated, and the resultant syrup was crystallized from ethanol to give **2** as white needles, yield 10.4 g (71%), m.p. 119–120°, $[\alpha]_D^{20}$ +21.1 ±0.1° (*c* 2.3, chloroform); R_F 0.47 (1:1 petroleum ether (b.p. 65-110°)–ether); λ_{max}^{KBr} 5.78, 5.85 (OAc, OBz), 6.31, 6.40, 6.80 (aryl C=C), 14.1 μm (aryl); n.m.r. data (60 MHz, chloroform-*d*): τ 2.1, 2.6 (2- and 3-proton multiplets, phenyl), τ 4.60–4.90 (multiplets, 3 protons, H-2,3,4). τ 5.26 (1-proton, narrow multiplet, H-1), τ 5.92 (1-proton multiplet, H-5), τ 6.53 (5-proton multiplet, H-6,6', OMe), τ 7.85, 8.12 (3-proton singlets, OAc).

Anal. Calc. for $C_{18}H_{21}BrO_8$: C, 48.55; H, 4.75; Br, 17.95. Found: C, 48.15; H, 4.65; Br, 17.76.

*Methyl 2,3-di-*O*-acetyl-6-azido-4-*O*-benzoyl-6-deoxy-*α*-*D*-mannopyranoside* (**3**). — A solution of the 6-bromo derivative **2** (14 g) in *N*,*N*-dimethylformamide (120 ml) containing sodium azide (20 g) was stirred for 18 h at 51° and then poured into ice–water (500 ml), whereupon the product **3** crystallized, yield almost quantitative, m.p. 65°. Recrystallization from ethanol gave pure **3**; yield 10.5 g (78%), m.p. 71–72°, $[\alpha]_D^{20}$ +15.3 ±0.6° (*c* 2.3, chloroform); R_F 0.47 (1:1 petroleum ether (b.p. 65–110°)–ether); λ_{max}^{KBr} 4.80 (azide), 5.73, 5.83 (OAc, OBz), 6.30, 6.38, 6.79, 6.95 (aryl C=C), 14.05 μm (aryl); n.m.r. data (60 MHz, chloroform-*d*): τ 2.1, 2.55 (2- and 3-proton multiplets, phenyl), τ 4.40–4.80 (multiplets, 3 protons, H-2,3,4), τ 5.25 (1-proton, narrow multiplet, H-1), τ 5.93 (1-proton multiplet, H-5), τ 6.55 (multiplet, 5 protons, H-6,6', OMe), τ 7.85, 8.14, (3-proton singlets, OAc).

Anal. Calc. for $C_{18}H_{21}N_3O_8$: C, 53.07; H, 5.20; N, 10.31. Found: C, 52.87; H, 5.33; N, 10.06.

Methyl 6-amino-6-deoxy-α-D-mannopyranoside hydrochloride (**4**). — To a solution of the azido derivative **3** (1.67 g) in anhydrous methanol (20 ml) was added a small piece of sodium and the solution was kept for 18 h at room temperature. Solid carbon dioxide was added to neutralize the base and the solution was evaporated to a syrup. The latter was dissolved in water (20 ml) and washed with two 10-ml portions of chloroform. The combined chloroform solution was extracted with water (20 ml). The combined aqueous solutions were evaporated to 35 ml and then stirred

for 5 h at 50° with Raney nickel* (8 g). Filtration of the suspension and evaporation of the filtrate gave the free base of the title compound **4** as a syrup.

The syrup was dissolved in methanol (15 ml), 12M hydrochloric acid (1.1 ml) was added, and the solution was evaporated. Methanol (four 15-ml portions) was evaporated from the residue to remove excess hydrogen chloride, and the residue was crystallized from hot ethanol (15 ml); yield 2.0 g (71%), m.p. 161–162° (dec.), $[\alpha]_D^{20}$ +65.7 ±0.4° (*c* 2.2, water); R_F 0.67 (5:5:3:1 pyridine–ethyl acetate–water–acetic acid); $R_{2\text{-amino-2-deoxyglucose}}$ 1.07 (papergram, 5:5:3:1 pyridine–ethyl acetate–water–acetic acid); λ_{max}^{KBr} 3.1 (broad, NH_3^+), 5.28, 6.22, 6.42, 6.73 μm (NH_3^+); azide, carbonyl, and aryl ring-absorptions absent; n.m.r. data (100 MHz, 70°, deuterium oxide): τ 5.19 (1-proton doublet, $J_{1,2}$ 1.7 Hz, H-1), τ 5.7 (HOD, observed at τ 5.5 at 25°), τ 6.04 (1-proton quartet, $J_{2,3}$ 3.0 Hz, H-2), τ 6.09-6.60 (4-proton multiplet, H-3,4,5,6), τ 6.58 (3-proton singlet, OMe), τ 6.82 (1-proton quartet, $J_{5,6'}$ 8.0 Hz, $J_{6,6'}$ 13.2 Hz, H-6'); X-ray powder diffraction data: 8.25 w, 7.04 vw, 6.03 m, 5.47 s (3,3), 5.18 w, 4.67 s (3,3), 4.41 w, 4.14 w, 3.86 w, 3.69 vs (2), 3.51 vs (1), 3.22 m, 3.09 w, 3.00 vw, 2.94 m, 2.82 w, 2.76 w, 2.70 m.

Anal. Calc. for $C_7H_{16}ClNO_5$: C, 36.60; H, 7.02; Cl, 15.44; N, 6.10. Found: C, 36.54; H, 7.07; Cl, 15.23; N, 6.27.

Methyl 6-acetamido-6-deoxy-α-D-mannopyranoside (**5**). — To a solution of the hydrochloride salt **4** (0.50 g) in methanol (25 ml) was added 10 ml of Amberlite IRA-400 (OH^-) ion-exchange resin, together with acetic anhydride (1 ml), and the mixture was kept for 18 h at room temperature. The resin was filtered off, the filtrate was evaporated to low volume, and ether was added. Refrigeration of the solution gave the product **5** as leaflets, yield 0.22 g (43%), m.p. 171°, $[\alpha]_D^{20}$ +63.5 ±1.5° (*c* 2, water) [lit.[6] m.p. 171–172°, $[\alpha]_D^{30.5}$ +70° (*c* 2, methanol)]; R_F 0.67 (5:5:3:1 pyridine–ethyl acetate–water–acetic acid); λ_{max}^{KBr} 2.95 (OH) 6.10, 6.43 μm (NHAc); n.m.r. data (60 MHz, 70°, deuterium oxide): τ 5.25 (1-proton narrow doublet, H-1), τ 6.61 (3-proton singlet, OMe), τ 7.98 (3-proton singlet, NAc).

Anal. Calc. for $C_9H_{17}NO_6$: C, 45.95; H, 7.28; N, 5.95. Found: C, 45.83; H, 7.24; N, 5.94.

6-Amino-6-deoxy-D-mannose hydrochloride (**6**). — The glycoside **4** (0.5 g) in M hydrochloric acid (10 ml) was refluxed for 4 h, and the solution was evaporated to a syrup. Water (three 10-ml portions) was evaporated from the syrup to remove hydrochloric acid, the product was redissolved in water and decolorized with activated carbon. The solution was evaporated to give the amino sugar **6** as a colorless, ninhydrin-positive syrup that was essentially homogeneous by t.l.c. on cellulose (Eastman Chromagram Sheet No. 6065 with fluorescent indicator, 4:1:1 butyl alcohol–acetic acid–water), R_F 0.15, and by paper chromatography (5:5:3:1 ethyl acetate–pyridine–water–acetic acid), $R_{2\text{-amino-2-deoxyglucose}}$ 0.63.

The n.m.r. spectrum of **6** at 60 MHz in deuterium oxide showed the H-1 signals

*Raney nickel catalyst No. 28; the Raney Catalyst Division of the W. R. Grace Co., Chattanooga, Tennessee.

of the two pyranose anomers as narrow signals ($J_{1,2} \leqslant 1$ Hz) of approximately equal intensity, at τ 4.78 and 5.04.

The 2-hydroxy-1-naphthylmethylene Schiff-base derivative of **6**, prepared by the method of Jolles and Morgan[7], was obtained from methanol–acetone as an amorphous yellow powder that softened at 128° and decomposed at 140–150°.

Anal. Calc. for $C_{17}H_{19}O_6N$: N, 4.20. Found: N, 4.23.

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