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Note

Conversion of 2-acetamido-2-deoxy-D-glucose into 2-acetamido-2,6-dideoxy-D-galactose (*N*-acetyl-D-fucosamine) and its benzyl-3-*O*-benzyl glycosides*

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INTRODUCTION

In the course of investigations on the lipopolysaccharide antigens of *Pseudomonas aeruginosa*, repeating units containing 2-acetamido-2,6-dideoxygalactose were found in the O-specific chains[1]. Preparations of an authentic reference sample of 2-acetamido-2,6-dideoxy-D-galactose from the closely related sugar 2-amino-2-deoxy-D-galactose have already been reported[2,3]. However, these methods are not suitable for large-scale preparation of the compound, because the starting amino sugar is very expensive. As there was a need for larger-scale preparations of the aminodideoxy sugar, for approaches to synthesis of the repeating units, the readily available 2-acetamido-2-deoxy-D-glucose would, in principle, provide a cheaper and more convenient precursor of 2-acetamido-2,6-dideoxy-D-galactose. Although a feasible synthesis of this acetamidodideoxy sugar from an α-glycoside of 2-acetamido-2-deoxy-D-glucose has been reported[4], we now describe an alternative synthesis that offers the possibility of conversion of both α- and β-glycosides into 2-acetamido-2,6-dideoxy-D-galactose, and presents some useful improvements.

RESULTS AND DISCUSSION

Hasegawa and Fletcher[5] reported that acetonation of 2-acetamido-2-deoxy-D-glucose with 2,2-dimethoxypropane and an acid gave a single product, 2-acetamido-2-deoxy-4,6-*O*-isopropylidene-D-glucopyranose, which on benzylation afforded mainly benzyl 2-acetamido-3-*O*-benzyl-2-deoxy-4,6-*O*-isopropylidene-β-D-glucopyranoside (**1**). Chromatographic separation was used in their preparation of **1**. In our hands, isolation of **1** from the mixture was achieved without chromatographic

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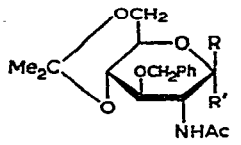
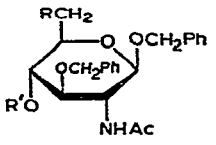
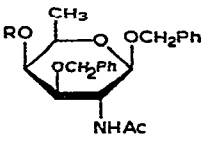


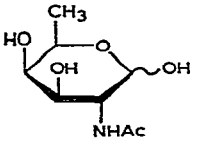
1 R = OCH_2Ph, R' = H
2 R = H, R' = OCH_2Ph



3 R = OH, R' = H
4 R = OMs, R' = Ms
5 R = H, R' = Ms



6 R = Bz
7 R = H



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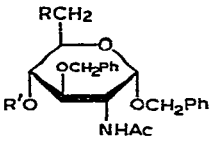
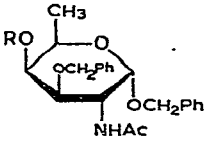


9 R = OH, R' = H
10 R = OMs, R' = Ms
11 R = H, R' = Ms



12 R = Bz
13 R = H

procedures; in some experiments, the α anomer (**2**) was also formed in isolable amount. The glycoside **1** is of particular interest, because it is a β anomer and it readily gives the 4,6-diol (**3**) on very mild, acid hydrolysis, whereas hydrolysis of the corresponding 4,6-*O*-benzylidene analog is more troublesome because the product is contaminated with benzaldehyde, a high-boiling product.

Methanesulfonylation of **3** with an excess of methanesulfonyl chloride in pyridine gave the 4,6-di-*O*-(methylsulfonyl) derivative **4** in good yield. Treatment of **4** with sodium borohydride in dimethyl sulfoxide at 85° in an atmosphere of nitrogen readily afforded a monodeoxy derivative. This method of deoxygenation was first reported by Hutchins *et al.*[6] and Bell *et al.*[7], and was successfully applied in the sugar field by Weidmann *et al.*[8]. The deoxygenation generally occurs selectively with primary sulfonates, and secondary ones are scarcely affected[8,9]. This method was thus convenient for the present work, and it was found that the 4,6-bis(methanesulfonate) **4** gave the 6-deoxy-4-methanesulfonate **5** in good (77%) yield. This compound was obtained from 2-acetamido-2-deoxy-D-glucose in five steps, whereas its α anomer had been obtained[4] in eight steps from the same starting-material.

Next, inversion of the configuration at C-4 of **5** by SN2 displacement with benzoate[4,10,11] or acetate[12] ion was attempted. However, the 4-methylsulfonyloxy group of **5** was highly resistant to displacement when sodium benzoate or sodium acetate were used in dimethyl sulfoxide or *N*,*N*-dimethylformamide. At relatively low temperatures (~100°), no reaction occurred, even after one day, and at higher temperatures (140–150°), the sulfonate **5** decomposed quite rapidly. This is in marked contrast to the situation with the α anomer[4] or a related β anomer[11]. Accordingly, in the present instance, hexamethylphosphoric triamide was employed as the solvent for reaction.

Treatment of **5** with an excess of sodium benzoate in this solvent for 24 h at 145° gave the desired product, benzyl 2-acetamido-4-*O*-benzoyl-3-*O*-benzyl-2,6-

dideoxy-β-D-galactopyranoside (**6**), without any noteworthy decomposition of the product. As this benzoate (**6**) was an amorphous solid, and its purification was troublesome, it was *O*-debenzoylated and then purified, to afford benzyl 2-acetamido-3-*O*-benzyl-2,6-dideoxy-β-D-galactopyranoside (**7**) in ~50% net yield from **5**. Catalytic hydrogenolysis of **7** gave 2-acetamido-2,6-dideoxy-D-galactose (**8**), which was identical with an authentic sample[2] prepared from 2-amino-2-deoxy-D-galactose.

The deoxygenation procedure used here was also applicable with the α anomer. The known benzyl 2-acetamido-3-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**9**), prepared according to a reported method[4,13] or by hydrolysis of **2**, was methanesulfonylated to give **10**, which was then reduced with sodium borohydride in dimethyl sulfoxide to afford the known 6-deoxy derivative (**11**) in good (74%) yield. Furthermore, treatment of **11** with sodium benzoate in hexamethylphosphoric triamide gave the known 4-benzoate (**12**). Conversion of the benzoate **12** into 2-acetamido-2,6-deoxy-D-galactose (**8**) by way of the *O*-debenzoylated compound **13** has been described in the literature[4].

This synthesis thus demonstrates the possibility of preparing 2-acetamido-2,6-dideoxy-D-galactose or 3-*O*-substituted 2-acetamido-2,6-dideoxy-D-galactopyranosides from both α- and β-glycopyranosides of 2-acetamido-2-deoxy-D-glucose. This synthetic route offers promise for the further elaboration of oligosaccharides containing a 2-acetamido-2,6-dideoxy-3-*O*-glycosyl-D-galactose residue, starting from a cheap and abundant amino sugar. In addition, compounds **7** and **13** might constitute useful "aglycons" for the synthesis of glycosides of the 2-acetamido-2,6-dideoxy-4-*O*-glycosyl-D-galactose type.

EXPERIMENTAL

General methods. — Solutions were evaporated under diminished pressure. Melting points were measured on a Thomas–Hoover "Unimelt" apparatus and not corrected. A Perkin–Elmer Model 141 automatic polarimeter and 1-dm tubes were used for measurement of specific rotations. I.r. spectra were recorded with a Perkin–Elmer 137 spectrophotometer. N.m.r. spectra were recorded at 100 MHz with a Varian HA-100 spectrometer, with tetramethylsilane ($\delta = 0.00$) as the standard. T.l.c. was performed with Silica Gel 60 G (E. Merck, 7731) as the adsorbent. Column chromatography was conducted on Silica Gel 60 (E. Merck 7734). Microanalyses were performed by W. N. Rond.

Benzylation of 2-acetamido-2-deoxy-4,6-O-isopropylidene-D-glucopyranose. — To an ice-cold solution of 2-acetamido-2-deoxy-4,6-*O*-isopropylidene-D-glucopyranose[5] (8.9 g, 34 mmol) in *N*,*N*-dimethylformamide (180 mL) were added barium oxide (54 g) and barium hydroxide octahydrate (21 g). α-Bromotoluene (24 mL, 0.2 mol) was then added dropwise with stirring. Stirring was continued for 2 h at 0° and overnight at ~25°. The mixture was then diluted with dichloromethane (500 mL), filtered to remove inorganic material, and the inorganic residue washed with dichloromethane (300 mL). The combined dichloromethane solutions were washed with water (3 ×

200 mL), dried (sodium sulfate), and evaporated, finally at 80°, to an oil by using a high-vacuum pump. The oil was stirred with water and hexane, to afford a crystalline mass that was washed with water and hexane, and dried. Recrystallization from ethanol–hexane gave crude benzyl β-glycoside **1**; yield 7 g (47%), m.p. 137–145°. The mother liquor was evaporated to an oil, which was chromatographed on a column of silica gel (100 g, suspended in chloroform) with chloroform as the eluant. After elution of α-bromotoluene and benzyl alcohol, the α anomer (**2**) of **1** was eluted as an oil that, on trituration with ethanol–hexane, afforded a crystalline solid (1.24 g, 8.2%), m.p. 127–128°, $[\alpha]_D^{24}$ +112° (*c* 1.2, chloroform).

Anal. Calc. for $C_{25}H_{31}NO_6$ (441.5): C, 68.01; H, 7.08; N, 3.17. Found: C, 68.06; H, 6.89; N, 3.09.

Continued elution of the column gave another crop (570 mg) of the β anomer **1**; the total yield of **1** was 50%. Recrystallization of **1** from ethanol–hexane gave **1** as fine needles, m.p. 152–153° (sintered at 145°), $[\alpha]_D^{22}$ −21° (*c* 0.45, chloroform) (lit.[5] m.p. 152–153°, $[\alpha]_D^{20}$ −21° in chloroform).

*Benzyl 2-acetamido-3-*O*-benzyl-2-deoxy-β-*D*-glucopyranoside* (**3**). — A solution of **1** (6.61 g, 15 mmol) in a mixture of acetic acid (50 mL) and water (30 mL) was heated for 1 h at 60° (bath) and then diluted with water (~50 mL). The resultant mixture was evaporated to dryness, and ethanol was several times added to and evaporated from the residue, which was then triturated with petroleum ether (30–60°) to give 6.02 g (100%) of **3** as a solid, m.p. 178–180°, that could be used in the next step. An analytically pure sample (0.7 g) of **3** was obtained by recrystallization of the crude solid (1.0 g) from ethanol; it had m.p. 180°, $[\alpha]_D^{26}$ −21° (*c* 1.2, methanol) {lit.[14] m.p. 183–184°, $[\alpha]_D^{25}$ −19° (*c* 0.84, methanol)}.

Anal. Calc. for $C_{22}H_{27}NO_6$ (401.5): C, 65.82; H, 6.78; N, 3.49. Found: C, 65.53; H, 6.83; N, 3.38.

*Benzyl 2-acetamido-3-*O*-benzyl-2-deoxy-4,6-di-*O*-(methylsulfonyl)-β-*D*-glucopyranoside* (**4**). — To an ice-cold solution of **3** (5.00 g, 12.5 mmol) in pyridine (70 mL) was added methanesulfonyl chloride (5.83 mL, 75 mmol) with stirring. The mixture was stirred for 1.5 h in an ice-bath and then for 1 h at ~25°. Pieces (2–3 g) of ice were now added to the mixture with stirring and cooling, and the resultant mixture was concentrated to half volume, and poured into ice–water (500 mL). After being stirred for 3 h at ~25°, the suspension was filtered, and the solid was washed with water, and recrystallized from methanol, to give 4.49 g of the product (**4**). The combined, aqueous mother liquors and washings were refrigerated overnight, affording another crop (0.56 g) of **4**. Finally, the mother liquor was extracted with chloroform. The extract was washed successively with 2M hydrochloric acid, water, saturated sodium hydrogencarbonate solution, and water, dried (sodium sulfate), and evaporated. On trituration with ethanol, the residue gave 0.41 g of crude **4**; total yield of **4**, 5.46 g (78.6%). Recrystallization from ethanol gave fine needles (4.5 g), m.p. 165–166°, $[\alpha]_D^{20}$ −12° (*c* 1, *N*,*N*-dimethylformamide); n.m.r. (Me_2SO-d_6, and external standard): δ 3.65 s and 3.57 s (3 H each, 2 Ms).

Anal. Calc. for $C_{24}H_{31}NO_{10}S_2$ (525.6): C, 51.69; H, 5.60; N, 2.51; S, 11.50. Found: C, 51.81; H, 5.41; N, 2.56; S, 11.44.

Benzyl 2-acetamido-3-O-benzyl-2,6-dideoxy-4-O-(methylsulfonyl)-β-D-glucopyranoside (**5**). — A mixture of **4** (3.34 g, 6 mmol), sodium borohydride (912 mg, 24 mmol), and dimethyl sulfoxide (15 mL) was heated for 2.5 h at 85° (bath) in an atmosphere of nitrogen, with stirring, and then poured into 2% aqueous acetic acid (50 mL). The resultant suspension was diluted with water (>200 mL), and kept overnight at ~25°. The precipitate was filtered off, washed with water, and recrystallized from ethanol, to give 2.13 g (76.5%) of needles, m.p. 194–195° (dec.), $[\alpha]_D^{20}$ −11° (*c* 0.7, chloroform); n.m.r. ($CDCl_3$, Me_2SO-d_6, internal standard): δ 2.87 (s, 3 H, Ms) and 1.40 (d, 3 H, *J* 6 Hz, CH_3).

Anal. Calc. for $C_{23}H_{29}NO_7S$ (463.6): C, 59.59; H, 6.31; N, 3.02; S, 6.92. Found: C, 59.69; H, 6.33; N, 2.78; S. 7.30.

Benzyl 2-acetamido-4-O-benzoyl-3-O-benzyl-2,6-dideoxy-β-D-galactopyranoside (**6**). — A mixture of **5** (928 mg, 2 mmol), sodium benzoate (1.000 g, 6.9 mmol), and hexamethylphosphoric triamide (15 mL) was heated for 24 h at 140–145° (bath) with stirring, cooled, and poured into ice–water (100 mL). The resultant suspension was refrigerated overnight. The precipitate was collected, washed with water, and dissolved in ethyl acetate (100 mL). The solution was dried over sodium sulfate and treated with carbon powder (Darco G-60). After removal of the sodium sulfate and carbon by filtration, the filtrate was concentrated to ~5 mL, and hexane (40–50 mL) was added. The resultant, gelatinous mixture was refrigerated overnight, and filtered. The residue was washed with hexane, to give crude **6** as a pale-brown solid (735 mg, 75%), $[\alpha]_D^{21}$ +49° (*c* 0.66, chloroform); ν_{max}^{KBr} 1720 cm^{-1} (ester). Its n.m.r. spectrum ($CDCl_3$) contained peaks (δ 7.7–7.2 p.p.m.) corresponding to 15 aromatic protons, and also revealed contamination with a small proportion of the starting material (**5**).

Benzyl 2-acetamido-3-O-benzyl-2,6-dideoxy-β-D-galactopyranoside (**7**). — To a solution of crude **6** (588 mg, ~1.2 mmol) in methanol (3 mL) was added 0.1M sodium methoxide in methanol (5 mL). The solution was kept for 30 h at ~25°, diluted with methanol, made neutral with Dowex-50W X-4 (H^+) ion-exchange resin, and evaporated to dryness. The semi-solid residue was triturated with ether, and refrigerated for 3–4 h, to give 408 mg (88%) of the crude hydroxy derivative **7**. Analytically pure **7** was obtained by chromatography on silica gel (15 g, suspended in chloroform) by successive elution with chloroform (70 mL), 1:99 (v/v) methanol–chloroform (200 mL), and 1:49 (v/v) methanol–chloroform (50 mL). Fractions containing the main product were pooled, and evaporated to a solid which, on trituration with ether, afforded a solid (318 mg, 67%), m.p. 189–191°, that, as shown by elemental analysis (Found: Cl, 2.05), contained some chloroform of solvation. This chloroform was not removed even by drying *in vacuo* at 80° or at 120–130°, but reprecipitation from ethyl acetate and hexane gave a gelatinous solid that was filtered off, washed with hexane, and dried *in vacuo* for 4 h at 78°, to give pure **7**, m.p. 193–194°, $[\alpha]_D^{22}$ −16° (*c* 0.5, chloroform).

Anal. Calc. for $C_{22}H_{27}NO_5$ (385.5): C, 68.55; H, 7.06; N, 3.63. Found: C, 68.61; H, 7.17; N, 3.60.

2-Acetamido-2,6-dideoxy-D-galactose (**8**). — *Procedure A.* To a solution of **7** (103 mg, 0.27 mmol) in a mixture of methanol (10 mL) and acetic acid (0.2 mL) was added 10% palladium-on-charcoal (120 mg), and the mixture was shaken with hydrogen (30–40 lb.in.$^{-2}$) for 25 h at ~25°. The catalyst was removed, and the solvent was evaporated with the aid of ethanol, to give an amorphous powder (55 mg, 100%). The powder was triturated with ethanol (1.4 mL), and refrigerated for 3 days, to afford crystals (38.5 mg, 70.2%), m.p. 197–199° (dec.), $[\alpha]_D^{20}$ +81° (*c* 0.75, water; equil.). Recrystallization from ethanol gave prisms, m.p. 199–200° (dec.), $[\alpha]_D^{20}$ +87° (*c* 0.5, water; equil.). The sample was identical with the authentic compound[2] by i.r. spectrum, mixed m.p., t.l.c. [20% (v/v) methanol–chloroform], and X-ray powder diffraction pattern[2].

Procedure B. Compound **12** was *O*-debenzoylated as described in the literature[4], and the resultant hydroxy compound **13** was catalytically hydrogenolyzed as just described (*A*), to give **8**, m.p. 190–191° (dec.), in ~30% overall yield from **12**.

Benzyl 2-acetamido-3-O-benzyl-2-deoxy-4,6-di-O-(methylsulfonyl)-α-D-glucopyranoside (**10**). — The 4,6-diol[4] **9** (1.0 g, 2.5 mmol) was methanesulfonylated as described for the β anomer, and the crude product was recrystallized from ethanol, to give 966 mg (73.5%) of **10** as fine needles, m.p. 169–171°, $[\alpha]_D^{23}$ +106° (*c* 0.7, chloroform).

Anal. Calc. for $C_{24}H_{31}NO_{10}S_2$ (525.6): C, 51.69; H, 5.60; N, 2.51; S, 11.50. Found: C, 51.77; H, 5.25; N, 2.43; S, 11.52.

Benzyl 2-acetamido-3-O-benzyl-2,6-dideoxy-4-O-(methylsulfonyl)-α-D-glucopyranoside (**11**). — A mixture of compound **10** (557 mg, 1.2 mmol), sodium borohydride (160 mg), and dimethyl sulfoxide (2.5 mL) was heated with stirring for 2 h at 85° (bath) under nitrogen, and then poured into 2% aqueous acetic acid (20 mL) with stirring and cooling. The crystalline precipitate was collected, and washed with water. Recrystallization from ethanol afforded pure **11** as fine needles; yield 342 mg (73.7%), m.p. 210–212° (dec.), $[\alpha]_D^{24}$ +122° (*c* 0.7, chloroform) {lit.[4] m.p. 209–210° (dec.), $[\alpha]_D^{24}$ +124° (chloroform)}.

Benzyl 2-acetamido-4-O-benzoyl-3-O-benzyl-2,6-dideoxy-α-D-galactopyranoside (**12**). — A mixture of **11** (150 mg, 0.32 mmol), sodium benzoate (160 mg, 1.11 mmol), and hexamethylphosphoric triamide (3 mL) was heated with stirring for 23 h at 140° (bath), and then cooled and poured into ice–water (40 mL). The suspension was kept for 1 h at ~25°, and the resulting precipitate was collected, washed with water, and dried. Recrystallization from ethyl acetate–hexane gave **12** as fine needles; yield 90 mg (57%), m.p. 149–150°, $[\alpha]_D^{20}$ +219° (*c* 0.55, chloroform) {lit.[4] m.p. 147–148°, $[\alpha]_D^{23}$ +195° (chloroform)}.

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