Carbohydrate Research, 70 (1979) 155–160

Note

The synthesis of derivatives of 3,6-diamino-3,6-dideoxy-D-galactose

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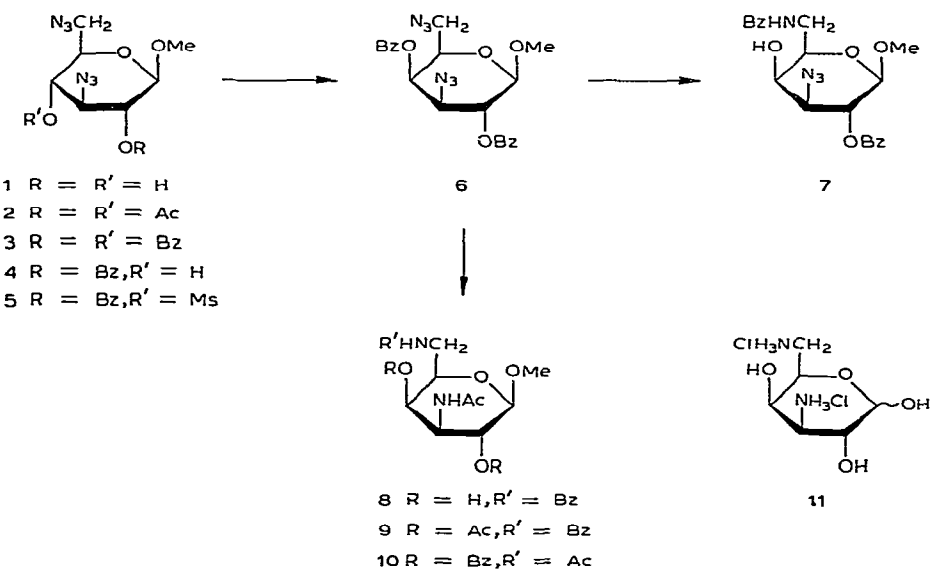
(Received November 14th, 1977; accepted for publication, February 14th, 1978)

Several diaminodideoxy monosaccharides have been isolated as components of antibiotics and found in bacterial polysaccharides[1,2]. 3,6-Diamino-3,6-dideoxy-D-galactose has not been encountered in Nature and has not been synthesized. It was therefore of interest to develop a method for the synthesis of this amino sugar and investigate its properties. This communication describes the synthesis of some derivatives of 3,6-diamino-3,6-dideoxy-D-galactose.

Methyl 3,6-dichloro-3,6-dideoxy-β-D-allopyranoside, used as starting material, was prepared by the method of Dean *et al.*[3] from methyl β-D-glucopyranoside by chlorination with sulfuryl chloride. The dichlorodideoxy sugar reacted with sodium azide in *N*,*N*-dimethylformamide for 14 h at 100° and chromatographic purification on silica gel gave methyl 3,6-diazido-3,6-dideoxy-β-D-glucopyranoside (**1**) as a syrup in 93% yield. In order to characterize its structure, the azide **1** was treated with



1 R = R′ = H
2 R = R′ = Ac
3 R = R′ = Bz
4 R = Bz, R′ = H
5 R = Bz, R′ = Ms

6

7

8 R = H, R′ = Bz
9 R = Ac, R′ = Bz
10 R = Bz, R′ = Ac

11

acetic anhydride in pyridine to afford the 2,4-diacetate **2** in 62% yield. Selective benzoylation at OH-2 of **1** with benzoyl chloride in pyridine at −40° yielded the 3,6-diazido-2-benzoate **4** in 62% yield, along with a trace of the 3,6-diazido-2,4-dibenzoate **3**. The location of the benzoyl group in **4** was confirmed by p.m.r. analysis, which showed the H-2 resonance appearing at a field (τ 4.94) lower than the resonances of the other ring protons. Subsequent treatment of **4** with mesyl chloride in pyridine afforded the 4-mesylate **5** in 87% yield.

For the synthesis of 3,6-diamino-3,6-dideoxy-D-galactose, the important step was configurational inversion at C-4 of the glucoside **5** with sodium benzoate, which was obtained by treatment in hexamethylphosphoric triamide for 14 h at 100°, to give methyl 3,6-diazido-2,4-di-*O*-benzoyl-3,6-dideoxy-β-D-galactopyranoside (**6**) in 54% yield, after column chromatography. The *galacto* configuration of **6** was established by: (a) the signal of H-4 of **6** appeared at a field (τ 4.40) lower by 0.43 p.p.m. than that of the corresponding resonance of **3**, indicating that the H-4 proton of **6** was oriented equatorially[4]; (b) the H-4 resonance of **6** was observed as a double doublet (*J* 4 and ~1 Hz) characteristic of a galactopyranoside[5].

Catalytic reduction of the galactoside **6** in methanol for 19 h with 5% palladium-on-carbon, followed by treatment with acetic anhydride, yielded the unexpected 3-azido-6-benzamido-2-benzoate **7** as a major product in 40% yield. Its structure was determined by p.m.r. and i.r. spectroscopy. The p.m.r. spectrum showed that the signal of H-2 ring proton appeared as a one-proton quartet (*J* 8 and 10 Hz) at a field (τ 4.69) lower than that of all the other protons, indicating that O-2 was substituted by a benzoyl group. Furthermore, new signals, disappearing after addition of deuterium oxide, appeared at τ 1.47 as a one-proton broad singlet for the amide proton of the benzamido group and at τ 4.40 as a one-proton broad doublet (*J* 6 Hz) for the hydroxyl group proton, respectively. This indicates that the benzoyl group at O-4 had migrated to the newly generated amino group at C-6. Similar benzoyl migration has been reported for the hydrogenation of 3-azido-4-*O*-benzoyl-2,3,6-trideoxy-D-*ribo*-hexose[6]. The i.r. spectrum of **7** showed characteristic absorptions in the OH and NH regions at 3370 cm^{-1}, in the N_3 region at 2120 cm^{-1}, in the CO region at 1710 cm^{-1}, and in the CON regions at 1650 and 1550 cm^{-1}.

Prolonged hydrogenation of **6** in the presence of 10% palladium-on-carbon for 3 days, followed by *N*-acetylation gave the 3-acetamido-6-benzamidogalactoside **8** in 89% yield as a single product. The i.r. spectrum of this compound did not show any absorption of ester groups. The structure of **8** was further confirmed by conversion into the 2,4-diacetate **9** (82% yield). The p.m.r. spectrum of **9** showed resonances of the amide protons of the benzamido group as a one-proton broad singlet at τ 3.10 and as one-proton doublet (*J* 7 Hz) at τ 4.00. This indicates that C-6 and C-2 of **8** and **9** are substituted by benzamido and acetamido groups, respectively. Similar treatment of **6** with 10% palladium-on-carbon for 26 h, except for the addition of acetic anhydride, gave the expected methyl 3,6-diacetamido-2,4-di-*O*-benzoyl-3,6-dideoxy-β-D-galactopyranoside (**10**) in high yield.

Hydrolysis of the 3,6-diacetamido galactoside **10** with 6M hydrochloric acid

gave, in 92% yield, 3,6-diamino-3,6-dideoxy-D-galactose dihydrochloride (**11**) as an extremely hygroscopic powder.

EXPERIMENTAL

General methods. — Melting points were determined with a Yanagimoto apparatus and are uncorrected. Optical rotations were measured with a Yanagimoto OR-50 polarimeter. The i.r. spectra were determined with a Hitachi 215 spectrometer by the potassium bromide disk method and the p.m.r. spectra with a Hitachi R-24 60-MHz instrument for solutions in chloroform-*d* using tetramethylsilane as the internal standard, unless otherwise stated. Thin-layer chromatography (t.l.c.) was performed on Silica gel G 60 (Merck) and column chromatography on Silica gel 60 (70–230 mesh, Merck).

Methyl 3,6-diazido-3,6-dideoxy-β-D-glucopyranoside (**1**). — A solution of methyl 3,6-dichloro-3,6-dideoxy-β-D-allopyranoside[3] (1.262 g) in *N,N*-dimethylformamide (13 ml) was heated with sodium azide (2.9 g) on a boiling-water bath for 14 h, and t.l.c. (1:3, v/v chloroform–ethyl acetate) showed complete disappearance of the starting material. The mixture was cooled and diluted with chloroform, and the insoluble material was removed by filtration through Celite. The filtrate was evaporated to a syrup, which was purified by column chromatography on silica gel (150 g) with 1:1 (v/v) benzene–ethyl acetate as eluent to afford **1** (1.235 g, 93%) as a syrup, which could not be crystallized. For characterization, a portion (500 mg) of this syrup was acetylated with acetic anhydride (6 ml) in pyridine (6 ml) to give methyl 2,4-di-*O*-acetyl-3,6-diazido-3,6-dideoxy-β-D-glucopyranoside (**2**) (417 mg, 62%) that crystallized from ethanol, m.p. 66–67°, $[\alpha]_D^{22}$ −55.0° (*c* 1.0, chloroform); ν_{max}^{KBr} 2100 (N_3) and 1760 cm^{-1} (OAc); p.m.r.: τ 5.15 (t, 1 H, $J_{3,4} = J_{4,5} = 10$ Hz, H-4), 5.65 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 6.53 (s, 3 H, OCH_3), and 7.89 (s, 6 H, 2 $COCH_2$),

Anal. Calc. for $C_{11}H_{16}N_6O_6$: C, 40.24; H, 4.92; N, 25.60. Found: C, 40.48; H, 4.77; N, 25.18.

Partial benzoylation of methyl 3,6-diazido-3,6-dideoxy-β-D-glucopyranoside (**1**). — To a solution of **2** (1.235 g) in pyridine (50 ml) was added benzoyl chloride (0.72 ml, 1.2 mol. equiv.) at −40°. The bath temperature was kept for 3 h at −20°, for 24 h at 0°, and the mixture was stirred for 2 days at room temperature. T.l.c. (4:1, v/v, chloroform–ethyl acetate) indicated the presence of one major and two minor components. The reaction mixture was extracted with chloroform, and the extract was washed successively with dilute sulfuric acid, saturated sodium hydrogencarbonate, and water, and dried (sodium sulfate). Chromatographic separation of the components on silica gel (200 mg) with 4:1 (v/v) benzene–ethyl acetate as eluent afforded methyl 3,6-diazido-2,4-di-*O*-benzoyl-β-D-glucopyranoside (**3**) (30 mg, 1%), which was crystallized from ethanol, m.p. 83–84°, $[\alpha]_D^{22}$ −36.3° (*c* 1.0, chloroform); ν_{max}^{KBr} 2100 (N_3) and 1730 cm^{-1} (OBz); p.m.r.: τ 1.7–2.7 (m, 10 H, 2 COC_6H_5), 4.78 (q, 1 H, $J_{2,3}$ 10 Hz, H-2), 4.83 (t, 1 H, $J_{3,4} = J_{4,5} = 10$ Hz, H-4), 5.40 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), and 6.47 (s, 3 H, OCH_3).

Anal. Calc. for $C_{21}H_{20}N_6O_6$: C, 55.75; H, 4.46. Found: C, 55.94; H, 4.38.

Elution with 2:1 (v/v) benzene–ethyl acetate followed by crystallization gave methyl 3,6-diazido-2-*O*-benzoyl-3,6-dideoxy-β-D-glucopyranoside (**4**) (1.087 g, 62%), m.p. 140–141°, $[\alpha]_D^{21}$ +7.9° (*c* 1.0, chloroform); ν_{max}^{KBr} 3500 (OH), 2100 (N_3), and 1720 cm^{-1} (OBz); p.m.r.: τ 1.8–2.7 (m, 5 H, COC_6H_5), 4.94 (bq, 1 H, H-2), 5.49 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 6.47 (s, 3 H, OCH_3), and 7.03 (bs, 1 H, OH exchanges in D_2O).

Anal. Calc. for $C_{14}H_{16}N_6O_5$: C, 48.54; H, 4.64; N, 24.13. Found: C, 48.28; H, 4.43; N, 23.89.

Further elution with ethyl acetate yielded the starting material (68 mg, 4%).

*Methyl 3,6-diazido-2-*O*-benzoyl-3,6-dideoxy-4-*O*-mesyl-β-D-glucopyranoside* (**5**). — Mesyl chloride (0.2 ml) was added dropwise over a period of 15 min to an ice-cooled solution of **4** (400 mg) in pyridine (1.6 ml) with stirring. After being stirred overnight at 4°, the reaction mixture was processed in the usual way. Crystallization from ethanol gave **5** (422 mg, 87%), m.p. 178–179°, $[\alpha]_D^{20}$ +15.8° (*c* 1.0, chloroform); ν_{max}^{KBr} 2100 (N_3), 1740 (OBz), 1360, and 1180 cm^{-1} (SO_2); p.m.r.: τ 1.8–2.7 (m, 5 H, COC_6H_5), 4.80 (q, 1 H, $J_{2,3}$ 8 Hz, H-1), 6.47 (s, 3 H, OCH_3), and 6.81 (s, 3 H, SO_2CH_3).

Anal. Calc. for $C_{15}H_{18}N_6O_7S$: C, 42.25; H, 4.26; N, 19.71; S, 7.52. Found: C, 42.37; H, 4.17; N, 19.47; S, 7.71.

*Methyl 3,6-diazido-2,4-di-*O*-benzoyl-3,6-dideoxy-β-D-galactopyranoside* (**6**). — A solution of **5** (500 mg) in hexamethylphosphoric triamide (10 ml) containing sodium benzoate (2.5 g) was heated on a boiling-water bath for 14 h, and at this time t.l.c. (9:1, v/v benzene–ethyl acetate) indicated that the starting material had disappeared. The reaction mixture was diluted with chloroform and filtered through Celite. After decolorization with activated carbon, the filtrate was evaporated with a small amount of silica gel, and the residue obtained was deposited on top of a silica gel column (50 g). Sequential elution with petroleum ether (b.p. 30–70°), benzene, and 9:1 (v/v) benzene–ethyl acetate gave **6** (288 mg, 54%), which was crystallized from ethanol, m.p. 118°, $[\alpha]_D^{20}$ +171.6° (*c* 1.0, chloroform); ν_{max}^{KBr} 2150 (N_3) and 1730 cm^{-1} (OBz); p.m.r.: τ 1.8–2.7 (m, 10 H, 2 COC_6H_5), 4.40 (q, 1 H, $J_{3,4}$ 4, $J_{4,5}$ ~1 Hz, H-4), 4.48 (q, 1 H, $J_{2,3}$ 10 Hz, H-2), 5.39 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), and 6.50 (s, 3 H, OCH_3).

Anal. Calc. for $C_{21}H_{20}N_6O_6$: C, 55.75; H, 4.46; N, 18.58. Found: C, 56.03; H, 4.41; N, 18.47.

*Hydrogenation of methyl 3,6-diazido-2,4-di-*O*-benzoyl-3,6-dideoxy-β-D-galactopyranoside* (**6**). — (*a*). Compound **6** (100 mg) was hydrogenated in methanol (5 ml) in the presence of 5% palladium-on-carbon catalyst (200 mg) for 19 h at ambient temperature and pressure. T.l.c. (9:1, v/v, chloroform–methanol) showed the presence of a trace of the starting material (R_F 0.97) with formation of three new products (R_F 0.88, 0.78 (major), and 0.58). The catalyst was removed by filtration and the filtrate was treated with acetic anhydride (0.2 ml) in the usual way. Evaporation of the solvent followed by crystallization from ethanol afforded methyl 3-azido-

6-benzamido-2-*O*-benzoyl-3,6-dideoxy-β-D-galactopyranoside (**7**) (84 mg, 90%, m.p. 209–210°, $[\alpha]_D^{22}$ +25.4° (*c* 0.7, dimethyl sulfoxide); R_F 0.78; ν_{max}^{KBr} 3370 (OH, NH), 2120 (N_3), 1710 (CO), 1650, and 1550 cm^{-1} (NHBz); p.m.r.: τ 1.47 (bs, 1 H, N*H*COC$_6$H$_5$, exchanges in D_2O), 1.9–2.5 (m, 10 H, NHC$_6$*H*$_5$, COC$_6$*H*$_5$), 4.40 (d, 1 H, *J* 6 Hz, OH exchanges in D_2O), 4.69 (q, 1 H, $J_{2,3}$ 10 Hz, H-2), 5.39 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), and 6.61 (s, 3 H, OCH_3).

Anal. Calc. for $C_{21}H_{22}N_4O_6$: C, 59.14; H, 5.24. Found: C, 59.53; H, 5.35.

(*b*). Compound **6** (200 mg) was hydrogenated in methanol (3.6 ml) containing 10% palladium-on-carbon (441 mg) for 3 days. The filtered solution was treated with acetic anhydride (1 ml). T.l.c. (9 : 1, v/v, chloroform–methanol) indicated the presence of a single compound having R_F 0.58. Evaporation of the solvent gave a crystalline mass (133 mg, 89%), which was recrystallized from ethanol–methanol to give methyl 3-acetamido-6-benzamido-3,6-dideoxy-β-D-galactopyranoside (**8**), m.p. 263–264°, $[\alpha]_D^{22}$ +33.8° (*c* 0.4, methanol); ν_{max}^{KBr} 3340 (OH, NH), 1660, and 1550 cm^{-1} (NHAc, NHBz); p.m.r.: τ 1.61 (bs, 1 H, N*H*COC$_6$H$_5$, exchanges in D_2O), 2.1–2.7 (m, 5 H, NHCOC$_6$*H*$_5$), 5.10 (bd, 2 H, 2 OH, exchange in D_2O), 5.88 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 6.63 (s, 3 H, OCH_3), and 8.10 (s, 3 H, $NHCOCH_3$).

Anal. Calc. for $C_{16}H_{22}N_2O_6 \cdot 0.5\ H_2O$: C, 56.63; H, 6.84; N, 8.26. Found: C, 56.31; H, 6.47; N, 7.91.

Compound **8** (133 mg) was further characterized as its acetate **9** (136 mg, 82%) which was crystallized from ethanol–ether, m.p. 236–239°, $[\alpha]_D^{25}$ −64.1° (*c* 1.0, chloroform); ν_{max}^{KBr} 3330 (NH), 1750, 1740 (CO), 1670, 1640, and 1540 cm^{-1} (NHAc, NHBz); p.m.r.: τ 3.10 (bs, 1 H, N*H*COC$_6$H$_5$, exchanges in D_2O), 4.00 (d, 1 H, *J* 7 Hz, N*H*COCH$_3$, exchanges in D_2O), 4.78 (d, 1 H, $J_{3,4}$ 4 Hz, $J_{4,5}$ ~1 Hz, H-2), 5.55 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 6.52 (s, 3 H, OCH_3), 7.76, 7.93 (2 s, 6 H, 2 $COCH_3$), and 8.10 (s, 3 H, NHCOC*H*$_3$).

Anal. Calc. for $C_{20}H_{26}N_2O_8$: C, 56.85; H, 6.22; N, 6.63. Found: C, 56.72; H, 6.33; N, 6.49.

(*c*). Hydrogenation of **6** (300 mg) in methanol (7 ml) containing acetic anhydride (1.4 ml) for 26 h in the presence of 10% palladium-on-carbon (120 mg) gave a syrup (320 mg, 99%). Crystallization from ethanol–ether afforded exclusively methyl 3,6-diacetamido-2,4-di-*O*-benzoyl-3,6-dideoxy-β-D-galactopyranoside (**10**), m.p. 242–243°, $[\alpha]_D^{24}$ +71.5° (*c* 1.3, chloroform); ν_{max}^{KBr} 3280 (NH), 1730 (CO), 1660, and 1550 cm^{-1} (NHAc); p.m.r.: τ 1.9–2.9 (m, 10 H, 2 COC$_6$H$_5$), 3.65 (bt, 2 H, N*H*COCH$_3$, exchange in D_2O), 4.42 (q, 1 H, $J_{3,4}$ 8 Hz, $J_{4,5}$ = ~1 Hz, H-4), 4.63 (q, 1 H, $J_{2,3}$ 10 Hz, H-2), 5.31 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 6.39 (s, 3 H, OCH_3), 8.00, and 8.23 (2 s, 6 H, NHCOC*H*$_3$).

Anal. Calc. for $C_{25}H_{28}N_2O_8 \cdot H_2O$: C, 59.74; H, 6.03; N, 5.58. Found: C, 59.67; H, 5.92; N, 5.71.

3,6-Diamino-3,6-dideoxy-D-galactose dihydrochloride (**11**). — A solution of **10** (258 mg) in 6M hydrochloric acid (13 ml) was heated for 5 h on a boiling-water bath. The solution was cooled and extracted with ether. The aqueous phase was decolorized with activated carbon and evaporated. Addition to and evaporation from

the resulting syrup of methanol–ethanol yielded a white crystalline powder (**11**, 97 mg, 92%). Compound **11** was extremely hygroscopic and its m.p. could not be determined, $[\alpha]_D^{25}$ +46.3° (30 min)→+50.4° (24 h, *c* 2.9, water); ν_{max}^{Nujol} 3400–3200 (OH, NH_3^+), 2130, 1610, and 1500 cm^{-1} (NH_3^+).

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