Carbohydrate Research, 135 (1985) 319–323
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Direct conversion of D-glucosamine into D-gulosamine

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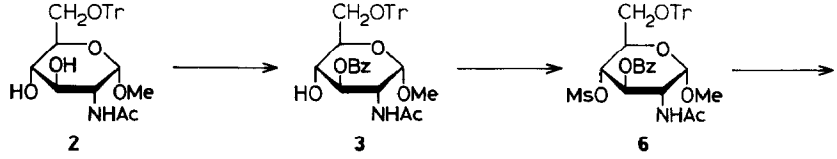
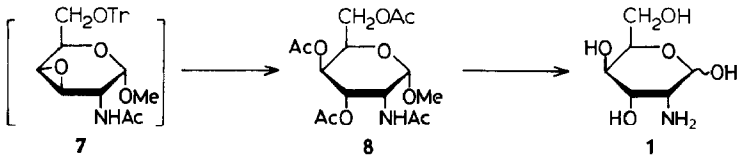
(Received January 19th, 1984; accepted for publication, April 20th, 1984)

D-Gulosamine, 2-amino-2-deoxy-D-gulose (**1**), has been isolated[1] from the antibiotics streptothricin and streptolidin B, and its structure has been established by three research groups. Tarasiejska and Jeanloz[2] synthesized **1** by epimerization of D-galactosamine at C-3, and Kuhn and Bister[3] prepared **1** starting from D-xylose. One synthetic approach to **1** from D-glucosamine was reported by Gross *et al.*[4,5]. We describe here a convenient synthesis of **1** by a stereoselective reaction starting from a readily accessible derivative of D-glucosamine.

Benzoylation of methyl 2-acetamido-2-deoxy-6-*O*-trityl-α-D-glucopyranoside[6] (**2**) with benzoyl chloride (1.5 mol eq.) in pyridine afforded preferentially the 3-benzoate (**3**) in 86% yield. The structure of **3** was confirmed by converting **3** into the known compounds methyl 2-acetamido-3-*O*-benzoyl-α-D-glucopyranoside[7] (**4**) and methyl 2-acetamido-4,6-di-*O*-acetyl-3-*O*-benzoyl-α-D-glucopyranoside[7] (**5**). Conventional mesylation of **3** gave the 4-methanesulfonate **6** in almost quantitative yield. Treatment of **6** in a suspension of sodium hydride in DMF gave the 3,4-





0008-6215/85/$ 03.30

epoxide (**7**), which was converted stereoselectively by diaxial opening into methyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-gulopyranoside[2] (**8**) in 88% yield. The overall yield of **8** from **2** was 72%. Acid hydrolysis of **8** in 2 M HCl gave **1** hydrochloride, which was converted into the penta-*O*-acetyl derivative[3] (**9**) by conventional acetylation.

EXPERIMENTAL

General methods. — Melting points were determined with a Mitamura Riken micro apparatus and ae uncorrected. Solutions were evaporated under diminished pressure at a bath temperature <40°. Specific rotations were measured in a 1-dm tube with a JEOL DIP-4 polarimeter. Column chromatography on silica gel was performed with Wakogel C-300, and t.l.c. on glass plates coated with Merck Kieselgel 60 F_{254}; compounds were detected by u.v. light and by spraying the plates with sulfuric acid followed by heating. Preparative t.l.c. (p.l.c.) was performed on glass plates (20 × 20 cm) coated with Merck Kieselgel 60 PF_{254}. I.r. spectra were recorded with a Hitachi Model-225 spectrometer. ^{1}H-N.m.r. spectra were recorded with a Varian EM-390 spectrometer. Chemical shifts for $CDCl_3$ solutions are relative to internal tetramethylsilane. High-resolution mass spectra were taken on a Hitachi M-80 mass spectrometer. Elemental analyses were perormed by Mr. Saburo Nakada of the University, to whom our thanks are due.

Methyl 2-acetamido-2-deoxy-6-O-trityl-α-D-glucopyranoside (**2**). — This compound was prepared according to a reported procedure[6]. To obtain the pure α anomer of **2**, the mixture was chromatographed on SiO_2 (toluene containing 1% triethylamine, and then 1:10 ethanol–toluene containing 1% of triethylamine). Fractions having R_F 0.44 in t.l.c. (1:3 ethanol–toluene) were collected and evaporated to afford pure α-**2** (R_F 0.36 in t.l.c. employing the same solvent system as used for β-**2**); m.p. 138–141°, [lit.[6] 140–143°], $[\alpha]_D^{17}$ +35.9° (*c* 1.53, $CHCl_3$), [lit.[6] $[\alpha]_D^{27}$ +38 ±2° (*c* 1.53, $CHCl_3$)].

Methyl 2-acetamido-3-O-benzoyl-2-deoxy-6-O-trityl-α-D-glucopyranoside (**3**). — To a solution of **2** (1.44 g, 3.02 mmol) in pyridine (15 mL) was added benzoyl chloride (0.53 mL, 4.54 mmol) under ice cooling. The solution was stirred for 3 h and evaporated. The residue was partitioned between dichloromethane (100 mL) and water (100 mL), and the aqueous layer was extracted with dichloromethane (100 mL × 2). The combined organic extracts were dried (Na_2SO_4) and evaporated to afford a brown syrup. The syrup was chromatographed on SiO_2 (60 g, 1:2 ethyl acetate–hexane). Fractions having R_F 0.55 in t.l.c. (2:1 ethyl acetate–hexane) were evaporated to afford **3** (1.50 g, 86%); m.p. 114–116°, $[\alpha]_D^{22}$ +53.9° (*c* 0.84, $CHCl_3$); ν_{max}^{KBr} 3470, 3260, 3060, 2900, 1725, 1650, 1540, 1450, 1375, 1265, 1120, and 1045 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 1.80 (3 H, s, NAc), 2.53–2.83 (1 H, br s, OH), 3.26–3.89 (4 H, m, H-4,5,6 and 6′), 3.40 (3 H, s, OCH_3), 4.40 (1 H, dt, $J_{1,2}$ 4, $J_{2,3}$ 9, $J_{2,NH}$

9 Hz, H-2), 4.74 (1 H, d, $J_{1,2}$ 4 Hz, H-1), 5.28 (1 H, dd, $J_{2,3}$ 9, $J_{3,4}$ 11 Hz, H-3), 5.85 (1 H, d, $J_{2,NH}$ 9 Hz, NH), and 7.08–8.11 (20 H, m, OBz and CPh_3).

Anal. Calc. for $C_{35}H_{35}NO_7$: M^+, 581.2411. Found: *m/z* 581.2388.

*Methyl 2-acetamido-3-*O*-benzoyl-2-deoxy-α-*D*-glucopyranoside* (**4**). — A solution of **3** (74.8 mg, 0.13 mmol) in 60% aqueous acetic acid (2.0 mL) was boiled under reflux for 40 min and then evaporated. The residue was chromatographed on SiO_2 (10 g, 1:15 ethanol–toluene). Fractions having R_F 0.28 in t.l.c. (1:5 ethanol–toluene) were evaporated to afford **4** (34.0 mg, 78%) as a colorless syrup; $[\alpha]_D^{21}$ +91.2° (*c* 1.70, $CHCl_3$), [lit.[7] $[\alpha]_D^{26}$ +99° (*c* 2.93, $CHCl_3$)]; $\nu_{max}^{CHCl_3}$ 3600, 3440, 3020, 1710, 1670, 1510, 1275, 1205, 1120, and 1055 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 1.78 (3 H, s, NAc), 2.30–2.57 (1 H, br s, OH), 2.99–3.30 (1 H, br s, OH), 3.39 (3 H, s, OCH_3), 3.57–4.20 (4 H, m, H-4,5,6 and 6′), 4.39 (1 H, dt, $J_{1,2}$ 4, $J_{2,3}$ 9, $J_{2,NH}$ 9 Hz, H-2), 4.73 (1 H, d, $J_{1,2}$ 4 Hz, H-1), 5.35 (1 H, dd, $J_{2,3}$ 9, $J_{3,4}$ 10 Hz, H-3), 6.18 (1 H, d, $J_{2,NH}$ 9 Hz, NH), and 7.15–8.15 (5 H, m, OBz).

Anal. Calc. for $C_{16}H_{22}NO_7$: M + H, 340.1394. Found: *m/z* 340.1377.

*Methyl 2-acetamido-4,6-di-*O*-acetyl-3-*O*-benzoyl-2-deoxy-α-*D*-glucopyranoside* (**5**). — Compound **4** (26.0 mg, 0.07 mmol) was acetylated with acetic anhydride (0.7 mL) in pyridine (0.7 mL) for 2 days. The mixture was evaporated and the residue purified by preparative t.l.c. (1:10 ethanol–toluene). A fraction having R_F 0.59 in t.l.c. (1:5 ethanol–toluene) was extracted with $CHCl_3$ and evaporated to afford **5** (24.9 mg, 77%); m.p. 133–134°, [lit.[7] m.p. 140–141°], $[\alpha]_D^{20}$ +55.3° (*c* 0.80, $CHCl_3$), [lit.[7] $[\alpha]_D^{25}$ +52° (*c* 0.80, $CHCl_3$)]; ν_{max}^{KBr} 3350, 2950, 1740, 1720, 1660, 1530, 1450, 1385, 1370, 1310, 1280, 1270, 1245, 1225, 1125, 1110, 1070, 1040, and 1025 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 1.86 (3 H, s, NAc), 1.91 and 2.11 (each 3 H, each s, 2 × OAc), 3.43 (3 H, s, OCH_3), 3.90–4.35 (3 H, m, H-5,6 and 6′), 4.50 (1 H, dt, $J_{1,2}$ 4, $J_{2,3}$ 9, $J_{2,NH}$ 9 Hz, H-2), 4.83 (1 H, d, $J_{1,2}$ 4 Hz, H-1), 5.31 and 5.50 (each 1 H, each t, $J_{2,3} = J_{3,4} = J_{4,5}$ = 9 Hz, H-3 and H-4), and 7.20–8.10 (5 H, m, OBz).

Anal. Calc. for $C_{20}H_{25}NO_9$: C, 56.73; H, 5.95; N, 3.30. Found: C, 57.01; H, 5.97; N, 3.36.

*Methyl 2-acetamido-3-*O*-benzoyl-2-deoxy-4-*O*-mesyl-6-*O*-trityl-α-*D*-glucopyranoside* (**6**). — To a solution of **2** (1.47 g, 2.53 mmol) in pyridine (15 mL) was added mesyl chloride (0.59 mL, 7.58 mmol) under ice cooling. The solution was stirred for 8 h and then evaporated. The residue was partitioned between dichloromethane (100 mL) and water (100 mL), and the aqueous layer was extracted with dichloromethane (100 mL × 2). The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed on SiO_2 (60 g, 1:1 ethyl acetate–hexane), and fractions having R_F 0.26 on t.l.c. (1:1 ethyl acetate–hexane) were evaporated to afford **6** (1.58 g, 95%) as colorless needles; m.p. 202–204°, $[\alpha]_D^{20}$ +30.9° (*c* 0.97, $CHCl_3$); ν_{max}^{KBr} 3420, 2930, 1730, 1690, 1490, 1350, 1265, 1180, and 1040 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 1.82 (3 H, s, NAc), 2.36 (3 H, s, OSO_2CH_3), 3.20–3.61 (2 H, m, H-6 and 6′), 3.51 (3 H, s, OCH_3), 3.87–4.15 (1 H, m, H-5), 4.52 (1 H, dt, $J_{1,2}$ 4, $J_{2,3}$ 9, $J_{2,NH}$ 9 Hz, H-2), 4.87 (1 H, d, $J_{1,2}$ 4 Hz, H-1),

4.90 (1 H, t, $J_{3,4} = J_{4,5} = 9$ Hz, H-4), 5.54 (1 H, t, $J_{2,3} = J_{3,4} = 9$ Hz, H-3), 5.90 (1 H, d, $J_{2,NH}$ 9 Hz, NH), and 6.90–8.20 (20 H, m, OBz and $OCPh_3$).

Anal. Calc. for $C_{36}H_{37}NO_9S$: C, 65.54; H, 5.65; N, 2.12; S, 4.86. Found: C, 65.25; H, 5.71; N, 1.90; S, 4.52.

*Methyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-*D*-gulopyranoside* (**8**). — Sodium hydride (60% emulsion in mineral oil, 0.295 g, 7.36 mmol) was washed with hexane (4 mL × 3), and suspended in DMF (4 mL). To this suspension was added a solution of **6** (1.62 g, 2.45 mmol) in DMF (16 mL) under ice cooling. The mixture was heated for 2 h at 100° with stirring and EtOH (5 mL) was added. The mixture was evaporated and the residue partitioned between dichloromethane (100 mL) and water (100 mL). The aqueous layer was extracted with dichloromethane (100 mL × 2), and the combined organic extracts were dried (Na_2SO_4), and evaporated to afford 1.23 g of the crude 3,4-epoxide **7** (R_F 0.51, 1:5 ethanol–toluene) as a brown solid that was subjected to the next reaction without further purification.

The solid was dissolved in 1,4-dioxane (12 mL), and M HCl (12 mL) was added. The mixture was heated for 30 min at 70° with stirring. The mixture was made neutral with M NaOH, diluted with water (100 mL), and washed with ethyl acetate (50 mL). The aqueous layer was evaporated to afford a brown solid (R_F 0.27, 1:1 ethanol–toluene). The solid was acetylated with acetic anhydride (12 mL) in pyridine (12 mL) for 14 h. The mixture was evaporated, and the residue was diluted with water (80 mL) and extracted with ethyl acetate (80 mL × 3). The organic extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed on SiO_2 (30 g, 1:10 ethanol–toluene), and fractions having R_F 0.33 in t.l.c. (1:5 ethanol–toluene) were evaporated to afford 0.782 g (88%) of **8**. An analytical sample was obtained by recrystallization from ethyl acetate and hexane; m.p. 121–122°, [lit.[2] m.p. 123–124°], $[\alpha]_D^{20}$ +70.5° (*c* 0.91, $CHCl_3$), [lit.[2] $[\alpha]_D^{21}$ +76° (*c* 0.91, $CHCl_3$)]; ν_{max}^{KBr} 3300, 2960, 1745, 1645, 1530, 1370, 1235, 1220, 1105, and 1035 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 1.96 (3 H, s, NAc), 2.05 (3 H, s, OAc), 2.14 (6 H, s, 2 × OAc), 3.14 (3 H, s, OCH_3), 3.97–4.48 (3 H, m, H-5,6, and 6′), 4.55 (1 H, dt, $J_{1,2} = J_{2,3} = 4$ Hz, $J_{2,NH}$ 9 Hz, H-2), 4.70 (1 H, d, $J_{1,2}$ 4 Hz, H-1), and 4.98 and 5.07 (each 1 H, each t, $J_{2,3} = J_{3,4} = J_{4,5} = 4$ Hz, H-3 and 4), 5.85 (1 H, d, $J_{2,NH}$ 9 Hz, NH).

Anal. Calc. for $C_{15}H_{23}NO_9$: C, 49.86; H, 6.42; N, 3.88. Found: C, 49.58; H, 6.29; N, 3.94.

*2-Amino-2-deoxy-α,β-*D*-gulose* (**1**) *hydrochloride*. — A suspension of **8** (0.300 g, 0.83 mmol) in 2M HCl (3 mL) was boiled under reflux for 7 h, and the acid was removed by evaporation with EtOH (2 mL × 3). The residual brown solid was dissolved in MeOH (10 mL), and the solution passed through a Celite–active carbon pad. The colorless filtrate was evaporated to afford **1** (0.165 g, 92%) as colorless crystals (R_F 0.23, 1:1 $CHCl_3$–EtOH). An analytical sample was obtained by recrystallization from acetone and MeOH; m.p. 145–160° (dec), [lit.[2] m.p. 150–170° (dec)], $[\alpha]_D^{21}$ +5.6° (3 min) → −18.6° (4 h, equil.) (*c* 0.90, H_2O), [lit.[2] $[\alpha]_D^{22}$ +6.0° (10 min) → −18° (36 h, equil.) (*c* 0.90, H_2O)]; ν_{max}^{KBr} 3320, 2920, 1610, and 1490

cm^{-1}; ^{1}H-n.m.r. (D_2O–DSS): δ 3.31–4.77 (6 H, m, H-2,3,4,5,6, and 6'), and 5.03 and 5.32 (total 1 H, each d, $J_{1,2}$ 9 and 4 Hz, H-1, α/β = 3:1).

*2-Acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α,β-*D*-gulopyranose* (**9**-*α and* **9**-*β*). — The crude **1** obtained from **8** (0.90 g) was acetylated with acetic anhydride (10 mL) in pyridine (10 mL) for 16 h. The mixture was evaporated, and the residue passed through active alumina (2 g) with $CHCl_3$ as eluant. The eluate was evaporated and the residue chromatographed on SiO_2 (70 g, 1:20 ethanol–toluene). Fractions having R_F 0.33 in t.l.c. (1:5 ethanol–toluene) were evaporated to afford **9**-*β* (0.59 g, 61%) as colorless crystals. Fractions having R_F 0.25 in t.l.c. (1:5 ethanol–toluene) were evaporated to afford **9**-*α* (0.19 g, 20%) as an amorphous solid. An analytical sample of **9**-*β* was obtained by recrystallization from EtOH and petroleum ether.

Compound **9**-*α* had $[\alpha]_D^{22}$ +81.7° (*c* 1.33, $CHCl_3$), [lit.[3] $[\alpha]_D^{22}$ +88 ±1° (*c* 1.33, $CHCl_3$)]; ν_{max}^{KBr} 3400, 1750, 1660, 1520, 1370, 1220, and 1100 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 1.96 (3 H, s, NAc), 2.05 (3 H, s, OAc), 2.18 (6 H, s, 2 × OAc), 2.20 (3 H, s, OAc), 3.89–4.49 (3 H, m, H-5,6, and 6'), 4.72 (1 H, dt, $J_{1,2} = J_{2,3} = 4$, $J_{2,NH}$ 9 Hz, H-2), 5.08 and 5.12 (each 1 H, each t, $J_{2,3} = J_{3,4} = J_{4,5} = 4$ Hz, H-3 and 4), 5.71 (1 H, d, $J_{2,NH}$ 9 Hz, NH), and 6.16 (1 H, d, $J_{1,2}$ 4 Hz, H-1).

Anal. Calc. for $C_{16}H_{23}NO_{10}$: M, 389.1320. Found: *m/z* 389.1320.

Compound **9**-*β* had m.p. 175°, [lit.[3] m.p. 176°]; $[\alpha]_D^{20}$ −18.7° (*c* 1.39, $CHCl_3$), [lit.[3] $[\alpha]_D^{22}$ −18.5° (*c* 1.39, $CHCl_3$)]; ν_{max}^{KBr} 3280, 1755, 1650, 1550, 1375, 1300, 1210, and 1070 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 1.94 (3 H, s, NAc), 2.04 (3 H, s, OAc), 2.10 (3 H, s, OAc), 2.17 (6 H, s, 2 × OAc), 4.00–4.37 (3 H, m, H-5,6, and 6'), 4.54 (1 H, dt, $J_{1,2}$ 9, $J_{2,3}$ 4, $J_{2,NH}$ 9 Hz, H-2), 5.02 and 5.19 (each 1 H, each t, $J_{2,3} = J_{3,4} = J_{4,5} = 4$ Hz, H-3 and 4), 5.85 (1 H, d, $J_{2,NH}$ 9 Hz, NH), 5.90 (1 H, d, $J_{1,2}$ 9 Hz, H-1).

Anal. Calc. for $C_{16}H_{23}NO_{10}$: C, 49.87; H, 5.89; N, 3.56. Found: C, 49.50; H, 5.39; N, 3.58.

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