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Note

Preparation of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allononitrile from D-glucose *

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2,5-Anhydro-3,4,6-tri-*O*-benzoyl-D-allononitrile (**1**) has been extensively used in the synthesis of *C*-nucleosides [1] with potential antitumour and/or antiviral properties. Three independent syntheses of **1** have already been described starting from D-ribose [2–4]. We now report a new synthesis of **1** from D-glucose.

5,6-Di-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-β-L-idofuranose (**2**), readily available from D-glucose [5], was *O*-deacetylated to give **3** and subsequently mesylated † to give **4**. Acid-catalysed solvolysis of **4** (ethylene glycol, TsOH) [7] afforded the 2,5-anhydro derivative **5** which was further benzoylated to give **6**. Treatment of **6** with potassium benzoate (DMF, 100°C) afforded the 4,6-di-*O*-benzoyl derivative **7** (38% from **2**). Solvolysis of **7** (DMF, $CaCO_3$, 160°C) gave a mixture of 2,5-anhydro-3(and 4),6-di-*O*-benzoyl-D-allose ethylene acetals (**8**, most likely formed via a cyclic benzoxonium ion [8]), which was subsequently benzoylated in a crude form to give 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allose ethylene acetal (**9**, 80% from **7**).

The *allo* configuration of **9** is unambiguously proved by the significantly higher value of the proton–proton coupling constant $J_{3,4} = 5.2$ Hz, compared to the corresponding value for **7** ($J_{3,4} \sim 0$ Hz).

Treatment of **9** with a mixture of trifluoroacetic acid and aq hydrochloric acid gave the unstable aldehyde **10**, which was immediately converted into the corresponding oxime **11**. Reaction of **11** with mesyl chloride in pyridine gave **1** (37% from **9**). ^{1}H NMR and ^{13}C NMR data, as well as the melting point and optical rotation, of **1** were in good agreement with those already reported [2–4].

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† Compound **4** was mentioned, without detailed characterisation, by Ogawa et al. [6].

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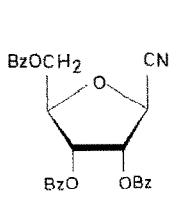
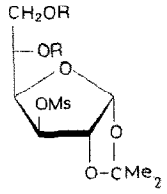


1



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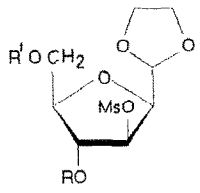
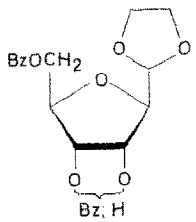
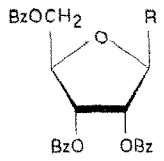
3 R = H
4 R = Ms



5 R = H; R' = Ms
6 R = Bz; R' = Ms
7 R = R' = Bz



8



9 R = 

10 R = CHO
11 R = CHNOH

Although this new synthesis of **1** consists of more synthetic steps (11) and has a lower overall yield (8%) than the earlier preparations from D-ribose [2–4] (4–5 steps; overall yields, $\geqslant 30\%$), it uses inexpensive and readily available starting materials, and it may be that some of the intermediates will have other synthetic uses.

1. Experimental

General methods.—Melting points were determined on a Büchi SMP 20 apparatus and were not corrected. Optical rotations were measured on an automatic polarimater Polamat A (Karl Zeiss, Jena). NMR spectra were recorded on a Bruker AC 250 E instrument and chemical shifts are expressed in ppm values, downfield to tetramethylsilane. Thin-layer chromatography was performed on DC Alufolien Kieselgel 60 F_{254} (Merck) and column chromatography was carried out using Kieselgel 60 (< 0.063 mm; Merck).

1,2-O-Isopropylidene-3-O-methanesulfonyl-β-L-idofuranose (**3**).—To a solution of 5,6-di-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-β-L-idofuranose [5] (**2**; 7.6 g, 19.94 mmol) in dry methanol (27 mL) was added a solution of sodium methoxide in methanol (*c* 0.1 mol/L; 27 mL). The mixture was stirred for 2 h at room temperature and then neutralised [Amberlite IR-120(H^+) resin; 10 g], filtered, and evaporated. The syrupy residue was crystallised from CH_2Cl_2–hexane to give chromatographically pure **3** (5.02 g, 91%); mp 97°C. Recrystallised from CH_2Cl_2–hexane, **3** had mp 126–128°C; $[\alpha]_D$ −31.2° (*c* 0.76, acetone); ^1H NMR ($CDCl_3$): δ 1.34 and 1.53 [2 s, 6 H, $C(CH_3)_2$], 2.2–2.4 (bs, 2 H, 2 OH), 3.12 (s, 3 H, CH_3SO_2), 3.73 (dd, 1 H, $J_{6a,6b}$ 11.5, $J_{5,6b}$ 6.2 Hz, H-6b), 3.79 (dd, 1 H, $J_{5,6a}$ 4 Hz, H-6a), 4.03 (m, 1 H, $J_{4,5}$ 7.1 Hz, H-5), 4.36 (dd, 1 H, $J_{3,4}$ 2.9 Hz, H-4), 4.84 (dd, 1 H, $J_{1,2}$ 3.8, $J_{2,3}$ 0.2 Hz, H-2), 5.12 (d, 1 H, H-3), 6.0 (d, 1 H, H-1); ^{13}C NMR ($CDCl_3$): δ 26.6 and 26.3 [$C(CH_3)_2$], 38.6 (CH_3SO_2), 63.1 (C-6), 69.7 (C-5), 79.3, 80.7, 83.8 (C-2,3,4), 104.2 (C-1), 112.9 [$C(CH_3)_2$]. Anal. Calcd. for: $C_{10}H_{18}O_8S$: C, 40.26; H, 6.04; S, 10.74. Found: C, 39.90; H, 6.10; S, 10.41.

1,2-O-Isopropylidene-3,5,6-tri-O-methanesulfonyl-β-L-idofuranose (**4**).—To a stirred and ice-cooled solution of **3** (3.71 g, 13.34 mmol) in dry pyridine (40 mL) was added mesyl chloride (4.27 mL, 55.17 mmol). The mixture was stored at +4°C for 48 h, then poured onto ice acidified with aq hydrochloric acid (1:1) to pH 2, and extracted with chloroform (3 × 100 mL). The combined extracts were washed with brine and dried (Na_2SO_4), and the solvent was evaporated. Recrystallisation of the residue from EtOH gave pure **4** (4.88 g, 81%); mp 147–148°, $[\alpha]_D$ −39.4° (*c* 1.27, chloroform); ^1H NMR ($CDCl_3$): δ 1.33 and 1.53 [2 s, 6 H, $C(CH_3)_2$], 3.12, 3.18, and 3.19 (3 s, 9 H, 3 CH_3SO_2), 4.4–4.66 (m, 3 H, $J_{6a,6b}$ 12.2 Hz, H-4,6a,6b), 4.9 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-2), 5.05 (m, 1 H, $J_{5,6a}$ 5.8, $J_{5,6b}$ 2.7, $J_{4,5}$ 9 Hz, H-5), 5.11 (d, 1 H, $J_{3,4}$ 3 Hz, H-3), 6.01 (d, 1 H, H-1); ^{13}C NMR ($CDCl_3$): δ 26.2 and 26.6 [$C(CH_3)_2$], 37.6 and 38.9 (2 CH_3SO_2), 67.0 (C-6), 76.8, 77.3, 79.4, and 83.2 (C-2,3,4,5), 104.5 (C-1), 113.3 [$C(CH_3)_2$]. Anal. Calcd. for: $C_{12}H_{22}O_{12}S_3$: C, 31.69; H, 4.84; S, 21.14. Found: C, 32.03; H, 5.08; S, 21.14.

2,5-Anhydro-3,6-di-O-methanesulfonyl-D-glucose ethylene acetal (**5**).—A solution of **4** (4.85 g; 10.68 mmol) and toluene-*p*-sulfonic acid (0.231 g, 1.21 mmol) in ethylene glycol (58 mL) was stirred at 100°C for 13 h. The mixture was then poured into satd aq $NaHCO_3$ (100 mL) and extracted with ethyl acetate (4 × 60 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated in vacuo. The syrupy residue was crystallised from EtOH to afford 1.54 g (40%) of analytically pure **5**; mp 120–121°C; $[\alpha]_D$ +51.1° (*c* 2.36, acetone). The mother liquor was concentrated to give an oil which was chromatographed on silica gel with 1:1 CH_2Cl_2–EtOAc as eluent, to yield an additional 0.781 g of **5**. The total yield of pure **5** was 2.316 g (60%). ^1H NMR ($CDCl_3$): δ 3.13 and 3.17 (2 s, 6 H, 2 CH_3SO_2), 3.81–4.01 (m, 4 H, dioxolane), 4.04 (m, 1 H, $J_{4,5}$ 6 Hz, H-5), 4.05 (dd, 1 H, $J_{1,2}$ 5.1, $J_{2,3}$ 4.2 Hz, H-2), 4.26–4.43 (m, 3 H, H-4,6a,6b), 4.93 (dd, 1 H, $J_{3,4}$ 1.5 Hz, H-3), 5.06 (d, 1 H, H-1), 5.28 (d, 1 H, $J_{4,OH}$ 3.5 Hz, OH); ^{13}C NMR ($CDCl_3$): δ 36.6 and 37.5 (2 CH_3SO_2), 65.0 (dioxolane), 69.4 (C-6), 76.2 (C-5), 79.8 (C-2), 83.6 (C-4), 85.2 (C-3), 101.6 (C-1). Anal. Calcd. for $C_{10}H_{18}O_{10}S_2$: C, 33.14; H, 4.91; S, 17.67. Found: C, 33.05; H, 4.95; S, 17.42.

2,5-Anhydro-4-O-benzoyl-3,6-di-O-methanesulfonyl-D-glucose ethylene acetal (**6**). —To a solution of **5** (2.99 g; 8.25 mmol) in dry pyridine (5 mL) and dry dichloromethane (40 mL) was added benzoyl chloride (4.31 mL, 37.12 mmol) at 0°C. The mixture was stored at room temperature for 48 h, then acidified with aq hydrochloric acid (1 : 1) to pH 2 and extracted with dichloromethane. The extracts were combined, successively washed with water and satd aq $NaHCO_3$, dried (Na_2CO_3), and concentrated. Column chromatography of the residue (98 : 2 → 9 : 1 CH_2Cl_2–EtOAc) gave **6** (3.71 g, 96%) as a colourless syrup; $[\alpha]_D$ +12.2° (*c* 0.84, chloroform); ^1H NMR ($CDCl_3$): δ 3.13 and 3.23 (2 s, 6 H, 2 CH_3SO_2), 3.92–4.08 (m, 4 H, dioxolane), 4.09 (dd, 1 H, $J_{2,3}$ 3.6, $J_{1,2}$ 6.2 Hz, H-2). 4.36 (m, 1 H, $J_{5,6a}$ 4.6, $J_{4,5}$ 2.7 Hz, H-5), 4.57 (d, 2 H, H-6a,6b), 5.2 (d, 1 H, H-1), 5.3 (dd, 1 H, $J_{3,4}$ 0.4 Hz, H-3), 5.52 (dd, 1 H, H-4), 7.43–8.13 (m, 5 H, aromatic); ^{13}C NMR ($CDCl_3$): δ 37.6 and 38.6 (2 CH_3SO_2), 65.4 and 65.5 (dioxolane), 67.7 (C-6), 78.2 (C-4), 81.0 (C-2), 81.9 (C-3), 82.4 (C-5), 101.1 (C-1), 128.3, 128.6, 129.8, and 133.9 (aromatic), 165.2 (C=O).

2,5-Anhydro-4,6-di-O-benzoyl-3-O-methanesulfonyl-D-glucose ethylene acetal (**7**). —To a solution of **6** (3.52 g; 7.55 mmol) in *N*,*N*-dimethylformamide (100 mL) was added potassium benzoate (12.57 g, 78.48 mmol). The mixture was stirred for 10 h at 100°C, then filtered, and the precipitate was washed with 1 : 1 benzene–hexane (2 × 10 mL). The filtrate and washings were combined, poured into water (300 mL), and extracted with dichloromethane (4 × 60 mL). The combined extracts were washed with water (2 × 50 mL) and dried (Na_2CO_3), and solvents were evaporated in vacuo. The solid residue was recrystallised from CH_2Cl_2–hexane to give **7** (3.25 g, 88%); mp 135–136°C; $[\alpha]_D$ +13.6° (*c* 4.99, chloroform); ^1H NMR ($CDCl_3$): δ 3.16 (s, 3 H, CH_3SO_2), 3.9–4.1 (m, 4 H, dioxolane), 4.11 (dd, 1 H, $J_{1,2}$ 6, $J_{2,3}$ 3.3 Hz, H-2), 4.47 (dt, 1 H, $J_{4,5}$ 2.5, $J_{5,6}$ 4.8 Hz, H-5), 4.68 (d, 2 H, H-6a,6b), 5.24 (d, 1 H, H-1), 5.34 (d, 1 H, $J_{3,4}$ ~ 0 Hz, H-3), 5.61 (d, 1 H, H-4), 7.4–8.15 (m, 10 H, aromatic); ^{13}C NMR ($CDCl_3$): δ 38.6 (CH_3SO_2), 63.6 (C-6), 65.4 and 65.5 (dioxolane), 79.0 (C-4), 80.9 (C-2), 82.5 (C-5), 82.9 (C-3), 101.2 (C-1), 128.3, 128.4, 128.5, 129.5, 129.8, 129.9, 133.1, and 133.8 (aromatic), 165.1 and 166.2 (2 C=O). Anal. Calcd. for $C_{23}H_{24}O_{10}S$: C, 56.10; H, 4.87; S, 6.50. Found: C, 56.11; H, 4.92; S, 6.45.

2,5-Anhydro-3,4,6-tri-O-benzoyl-D-allose ethylene acetal (**9**).—To a solution of **7** (0.155 g; 0.315 mmol) in 3 mL of 95% *N*,*N*-dimethylformamide (5% of H_2O) was added calcium carbonate (0.063 g, 0.315 mmol). The mixture was stirred for 12 h at 160°C, then concentrated in vacuo, and the remaining oily residue was dried by co-distillation with toluene–ethanol. The resulting crude mixture (**8**) of 3- and 4-*O*-benzoyl derivatives was dissolved in dry pyridine (4.5 mL) and allowed to react with benzoyl chloride (0.18 mL, 1.55 mmol) for 24 h at room temperature. The mixture was then poured onto ice, acidified with aq hydrochloric acid (1 : 1) to pH 2, and extracted with dichloromethane. The extract was washed with water and satd aq $NaHCO_3$, dried (Na_2CO_3), and evaporated to dryness. Short-column chromatography (9 : 1 toluene–EtOAc) of the residue gave **9** (0.13 g; 80%) as a colourless oil; $[\alpha]_D$ +44.9° (*c* 1.36, chloroform); ^1H NMR ($CDCl_3$): δ 3.85–4.13 (m, 4 H, dioxolane), 4.47 (dd, 1 H, $J_{2,3}$ 3.1, $J_{1,2}$ 2.1 Hz, H-2), 4.53 (dd, 1 H, $J_{5,6a}$

4.2, $J_{6a,6b}$ 11.5 Hz, H-6a), 4.65 (m, 1 H, H-5), 4.73 (dd, 1 H, $J_{5,6b}$ 3.8 Hz, H-6b), 5.17 (d, 1 H, H-1), 5.76 (dd, 1 H, $J_{4,5}$ 6.6, $J_{3,4}$ 5.2 Hz, H-4), 5.84 (dd, 1 H, H-3), 7.25–8.15 (m, 15 H, aromatic); ^{13}C NMR ($CDCl_3$): δ 63.9 (C-6), 65.5 and 65.6 (dioxolane), 71.9 (C-3), 72.4 (C-4), 78.8 (C-5), 82.6 (C-2), 102.1 (C-1), 128.9, 129.2, 132.9, and 133.2 (aromatic), 165.1–166.1 (3 partially overlapping C=O). FAB-mass spectrum: *m/z* 519.2 (MH^+), 396.9 (MH^+ – BzOH), 105.0 ($PhCO^+$), 73 ($C_3H_4O_2^+$).

*2,5-Anhydro-3,4,6-tri-*O*-benzoyl-*D*-allose oxime* (**11**).—To a solution of **9** (0.5 g, 0.96 mmol) in trifluoroacetic acid (2.4 mL) was added aq HCl (1:1, 0.6 mL). The mixture was stirred for 12 h at room temperature, then concentrated to a volume of 1 mL, treated with satd aq $NaHCO_3$ to pH 8–9, and extracted with dichloromethane. The extract was washed with satd aq $NaHCO_3$, dried (Na_2SO_4), and evaporated. The crude product **10** (0.42 g; 0.89 mmol) was dissolved in dry EtOH and treated with sodium acetate (0.264 g, 3 mmol) and hydroxylamine hydrochloride (0.141 g, 2 mmol). The mixture was stirred for 16 h at room temperature, then concentrated, and the residue was partitioned between water and dichloromethane. The organic phase was separated, washed (H_2O), dried (Na_2SO_4), and concentrated. Short-column chromatography (7:3 cyclohexane–acetone) of the residue gave **11** (0.451 g, 96% from **9**) as a 4.5:1 mixture of *E* and *Z* isomers; ^{1}H NMR ($CDCl_3$): δ 8.8 (bs =NOH, *E* isomer), 9.2 (bs =NOH, *Z* isomer); ^{13}C NMR ($CDCl_3$): *E* isomer: δ 64.0 (C-6), 72.5, 73.5, 78.5, and 80.2 (C-2,3,4,5), 128.3, 128.4, 128.8, 129.7, 133.2, and 133.4 (aromatic), 147.7 (C-1), 165.2, 165.3, and 166.2 (3 C=O); *Z* isomer; δ 150.8 (C-1).

*2,5-Anhydro-3,4,6-tri-*O*-benzoyl-*D*-allononitrile* (**1**).—A solution of oxime **11** (0.27 g, 0.55 mmol) in dry pyridine (1.5 mL) was added dropwise over 0.5 h to a stirred solution of methanesulfonyl chloride (0.55 mL, 19.4 mmol) in pyridine (1.5 mL) at −15°C. The mixture was allowed to warm up to room temperature and stirred for a further 24 h. Ice (0.5 g) was added with stirring and solvents were removed by co-distillation with toluene, to give a brown oil which was chromatographed on a column of silica gel (15 g) eluting with 7:3 cyclohexane–acetone, to afford **1** (0.102 g; 39%) as a colourless syrup, $[\alpha]_D$ +23.6° (*c* 0.5, chloroform); lit. [2] $[\alpha]_D$ +23.8° (chloroform); lit. [4] $[\alpha]_D$ +24.4° (chloroform). Recrystallised from EtOH, **1** had mp 82–83°C; lit. [2] mp 78.5–80°C; lit. [4] mp 77–78°C; ^{1}H NMR ($CDCl_3$): δ 4.6 (dd, 1 H, $J_{6a,6b}$ 13.4, $J_{5,6b}$ 5.1 Hz, H-6a), 4.72 (m, 1 H, $J_{4,5}$ 5.1, $J_{5,6b}$ 3.3 Hz, H-5), 4.74 (dd, 1 H, H-6b), 4.98 (d, 1 H, $J_{2,3}$ 4.4 Hz, H-2), 5.86 (t, 1 H, $J_{3,4}$ 5.1 Hz, H-4), 6.0 (dd, 1 H, H-3), 7.13–8.17 (m, 15 H, aromatic); ^{13}C NMR ($CDCl_3$): δ 63.2 (C-6), 69.4, 71.9, 74.4, and 80.9 (C-2,3,4,5), 115.7 (CN), 128.2, 128.5, 128.6, 129.2, 129.7, 129.8, 129.9, 133.4, 133.8, and 134.0 (aromatic), 164.8, 165.0, and 166.1 (3 C=O).

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