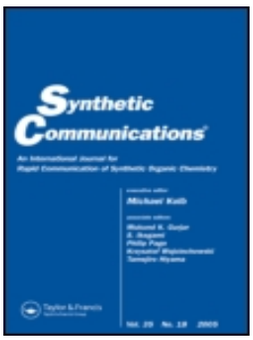

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Controlled Acetolysis of 3,6-Anhydro-5-*o*-benzyl-1,2-*o*-isopropylidene-α-D-glucofuranose: Synthesis of 1-(3′,6′-Anhydro-α-D-glucofuranosyl)thymine

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ABSTRACT

Controlled acetolysis of 1,2-*O*-isopropylideneglucofuranose derivative **1** in Ac_2O:AcOH:H_2SO_4 at 0°C is reported to isolate 2-acetoxy dimethylmethylenoxy glucofuranose derivative **2** in quantitative yield. Utility of **2** for the synthesis of alpha linked nucleoside **5a** is demonstrated.

Acetolysis reaction of sugars has been well studied to prepare activated 1-*O*-acetyl saccharide synthons in carbohydrate chemistry.[1–3]

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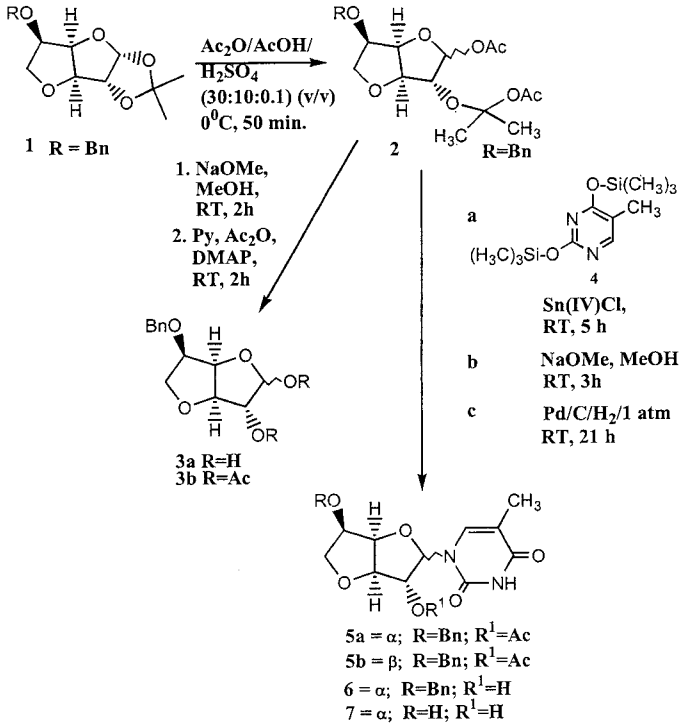
The reaction has been earlier performed by reacting 1,2-*O*-isopropylidene gluco-[4] and xylofuranose[5] derivatives with acetolysis mixture prepared from acetic anhydride, acetic acid, and concentrated H_2SO_4 either in a ratio of 1:10:0.3–0.8 (v/v)[6] or 7:3:0.1 (v/v)[7] to obtain 1,2-di-*O*-acetyl derivatives.

During our work to prepare α-linked bicyclonucleoside analogues, acetolysis of 3,6-anhydro-5-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**1**) was studied to prepare glycosyl donor possessing a non participating C-2 neighboring group. We have found reaction of **1** with acetolysis mixture containing Ac_2O:AcOH:conc. H_2SO_4 in a ratio of 30:10:0.1 (v/v) at 0°C for 50 min was the best reaction condition required to obtain 1-*O*-acetyl-2-acetoxy-(α,α-dimethyl)-methylenoxy-3,6-anhydro-5-*O*-benzyl-α/β-D-glucofuranose (**2**) in quantitative yield (Sch. 1). Formation of **2** was evident from the appearance of gem-dimethyl groups at δ 1.41, 1.45, 1.48, and 1.58 integrating for six protons, acetyl groups appeared as singlets at δ 2.02, 2.05, 2.07, and 2.10 integrating for six



Scheme 1.

protons, anomeric proton (H-1) appeared at δ 6.18 and δ 6.25 integrating for one proton. Formation of **2** was also indicated from the ^{13}C NMR spectrum from the appearance of quaternary carbon appearing at δ 111.8 and δ 112.7 and anomeric C-1 at δ 95.6 and δ 93.0. **2** was deacetylated by reacting with a catalytic amount of NaOMe at RT to give 3,6-anhydro-5-*O*-benzyl-1,2-dihydroxy-α/β-D-glucofuranose (**3a**), m.p.: 108–110°C in quantitative yield. **3a** was acetylated to the known 1,2-di-*O*-acetyl-3,6-anhydro-5-*O*-benzyl-α/β-D-glucofuranose (**3b**) and was characterized by comparison of ^{1}H NMR spectrum with that reported in literature.[8] **2** was coupled with *bis*(trimethylsilyl)thymine (**4**) in CH_2Cl_2 at 0°C by use of Sn(IV)Cl as an activator to isolate a mixture of bicyclonucleosides, 1-(2′-*O*-acetyl-3′,6′-anhydro-5′-*O*-benzyl-α-D-glucofuranosyl)thymine (**5a**) and 1-(2′-*O*-acetyl-3′,6′-anhydro-5′-*O*-benzyl-β-D-glucofuranosyl)thymine (**5b**) in 65% yield.[9] **5a** was characterized from ^{1}H NMR spectrum from the appearance of H-1′ at δ 6.18 (d, $J_{1',2'} = 3.0$ Hz), H-2′ at δ 5.42 (d), and 5-CH_3 at δ 1.90 (s, 3H); thus indicating **5a** to be the α- linked bicyclonucleoside. **5b** was characterized as the β-nucleoside by comparison of the spectral data with that reported in literature.[10] **5a** was deacetylated to obtain 1-(3′,6′-anhydro-5′-*O*-benzyl-α-D-glucofuranosyl)thymine (**6**) and was characterized from ^{1}H NMR. **6** on hydrogenolysis gave 1-(3′,6′-anhydro-α-D-glucofuranosyl)thymine (**7**) and was characterized from the appearance of H-1′ at δ 5.35 (d, $J_{1',2'} = 5.8$ Hz), H-6 at δ 7.23 (s, 1H) and 5-CH_3 at δ 1.72 (s, 3H).

In conclusion, controlled acetolysis of 3,6-anhydro-1,2-*O*-isopropylidene glucofuranose derivative has been achieved to isolate the acetoxy-α,α-dimethylmethylenoxy saccharide an intermediate useful for preparation of α-linked nucleoside.

EXPERIMENTAL SECTION

General Methods

Flame dried glassware, commercially available solvents and reagents were used without further purification unless otherwise stated. Melting points were measured using capillary tubes and are uncorrected. ^{1}H NMR spectra were measured with a Varian Gemini (200 MHz) spectrometer, with TMS as an internal standard using $CDCl_3$, as solvent, ^{13}C NMR spectra were taken with a Varian Gemini (50 MHz) spectrometer with solutions in deuterochloroform. Mass spectra were obtained on a VG 70-70H instrument.

1-*O*-Acetyl-2-acetoxy(α,α-dimethyl)methylenoxy-3,6-anhydro-5-*O*-benzyl- α/β-D-glucofuranose (2). To a solution of 3,6-anhydro-5-*O*-benzyl-1,2-*O*-isopropylidene-α/β-D-glucofurnaose (**1**) (5.0 g, 13.80 mmol) was added freshly prepared acetolysis mixture (12 mL) using Ac_2O: AcOH:conc. H_2SO_4 (30:10:0.1) (v/v) ratio at 0°C. The reaction mixture was stirred at 0°C for 50 min. TLC indicated the completion of the reaction. The reaction mixture was quenched by addition of chilled water (100 mL) was added and stirred for about 25 min and extracted the compound into $CHCl_3$ (100 mL × 2). Combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (100 mL), water (100 mL), dried (Na_2SO_4) and concentrated to obtain a thick syrup that was filtered on a bed of SiO_2 (60–120 mesh) by eluting with EtOAc:hexane (3:7) to obtain the title compound **2** as a thick syrup (4.3 g, 89.0%). ^{1}H NMR ($CDCl_3$): δ 1.41, 1.45, 1.48, 1.58 (4s, 6H, 2 × CH_3), 2.02, 2.05, 2.07, 2.10 (4s, 6H, $OCOCH_3$), 3.80–4.05 (m, 2H, H-6,6′), 4.12–4.30 (m, 2H, H-3,4), 4.38–4.58 (m, 3H, H-2, 2 × OCH_2Ph), 5.30–5.35, 5.42–5.48 (2m, 1H, H-5α,β), 6.18, 6.25 (2d, 1H, H-1α,β, J = 3.50 Hz), 7.20–7.38 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 20.50, 20.90 (MeCO), 25.90, 26.30 (CH_3), 27.20, 28.10 (CH_3), 69.40, 70.90, 71.40, 72.60, 77.50, 78.50, 78.80, 79.00, 80.60 (CH_2Ph,C-2,3,4,6), 93.00, 95.60 (C-1β,α), 111.80, 112.70 (C-5β,α), 127.40, 127.70, 128.30, 137.30 (Ar), 169.70 (CO). IR (Neat): 1740 cm^{-1} (C=O), 1223 cm^{-1} (C-O). FAB-MS: m/z 417 $(M + 23)^+$. Anal. calcd. for $C_{20}H_{26}O_8$: C, 60.90; H, 6.64. Found: C, 61.09; H, 6.75.

3,6-Anhydro-5-*O*-benzyl-1,2-dihydroxy-α,β-D-glucofuranose (3a). To a solution of **2** (0.95 g, 2.40 mmol) in CH_3OH (5 mL) was added a catalytic amount of NaOMe 1 N (0.1 mL) and left at room temperature for 2 h. The reaction mixture was neutralized with IR 120 H^+, filtered and washed with methanol. The filtrate was concentrated to obtain **3a** (0.6 g, 99.3%) as a white crystalline solid (m.p.: 108–110°C); $[\alpha]_D$ +111.50°C (c 1.0, MeOH). ^{1}H NMR ($CDCl_3$-DMSO-d_6): δ 3.48–3.58 (dd, 1H, $J_{6,6'}$ = 15.2 Hz, $J_{5,6}$ = 7.5 Hz, H-6), 3.75–4.02 (m, 2H, H-5,6′), 4.26–4.40 (2m, 1H, H-4α,β), 4.50, 4.70 (2d, 2H, J = 12.5 Hz, 2 × OCH_2Ph), 4.52–4.63 (2m, 1H, H-3α,β), 5.20–5.25 (d, 0.25H, $J_{1',2'}$ = 6.0 Hz, H-2β), 5.30–5.40 (m, 0.75H, H-2α), 5.70–5.82 (m, 0.25H, H-1β), 5.84–5.90 (d, 0.75H, H-1α), 7.20–7.30 (m, 5H, Ar-H). FAB-MS: m/z 275 $(M + 23)^+$. IR (KBr): 3305, 3360 cm^{-1} (OH), 1047, 1000 cm^{-1} (C-O). Anal. calcd. for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.74; H, 6.44.

1-(2′-*O*-Acetyl-3′,6′-anhydro-5′-*O*-benzyl-α-D-glucofuranosyl)thymine (5a). To a solution of **2** (4.25 g, 12.17 mmol) in dry CH_2Cl_2 (120 mL) was added *bis*(trimethyl-silyl)thymine (**4**) (3.94 g, 14.6 mmol) and $SnCl_4$

(1.68 mL) in CH_2Cl_2 (60 mL) under N_2 atmosphere. The reaction mixture was stirred at room temperature for 5 h. After completion of the reaction, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution (55 mL) and filtered on a bed of celite. The filtrate was separated, diluted with water (100 mL) and extracted into CH_2Cl_2 (100 mL × 2). The combined organic phase was separated, dried (Na_2SO_4) and concentrated to obtain a diastereometric mixture of **5a** and **5b** and residue (4.63 g). The residue was chromatographed (SiO_2, 60–120 mesh) by eluting with EtOAc:$CHCl_3$(1:8) to elute first the title compound **5a** (1.78 g, 36%) as a syrup followed by **5b** (1.40 g, 29%) as thick syrup; **5a** $[\alpha]_D + 4.85^\circ$ (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.84 (s, 3H, $OCOCH_3$), 1.92 (s, 3H, 5-CH_3), 3.80 (dd, 1H, $J_{6',6''} = 9.10$ Hz, $J_{5',6'} = 6.10$ Hz, H-6′), 4.05 (dd, 1H, $J_{5',6''} = 6.10$ Hz, H-6″), 4.10–4.14 (m, 1H, H-5′), 4.20–4.30 (m, 2H, H-3′,4′), 4.40, 4.54 (2d, 2H, $J = 7.30$ Hz, 2 × OCH_2Ph), 5.42 (d, 1H, $J_{1',2'} = 3.0$ Hz, H-2′), 6.18 (d, 1H, H-1′), 7.18–7.38 (m, 6H, 5Ar-H, 1H, H-6), 9.01 (s, 1H, NH). FAB-MS: m/z 403 $(M + 1)^+$. IR (Neat): 1693 (C=O). Anal. calcd. for $C_{20}H_{22}O_7N_2$: C, 59.70; H, 5.51; N, 6.96. Found: C, 59.58; H, 5.49; N, 6.89.

1-(3′,6′-Anhydro-5′-*O*-benzyl-α-D-glucofuranosyl)thymine (6). To a solution of **5a** (0.31 g, 0.77 mmol) in CH_3OH (5 mL) was added a catalytic amount of NaOMe (1 N, 0.1 mL) and left at room temperature for 3 h. The reaction mixture was neutralized with IR 120 H^+, filtered and washed with methanol. The filtrate was concentrated to obtain **6** (0.25 g, 88.4%) as light yellow thick syrup, $[\alpha]_D$ -24° (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.82 (s, 3H, 5-CH_3), 3.70–3.98 (m, 3H, H-5′,6′,6″), 4.07–4.32 (m, 3H, H-2′,3′,4′), 4.40, 4.50 (2d, 2H, $J = 10.5$ Hz, 2 × OCH_2Ph), 6.18 (d, 1H, $J = 5.8$ Hz, H-1′), 7.20–7.38 (m, 6H, 5Ar-H, H-6), 8.70 (s, 1H, NH). IR (Neat): 1690 cm^{-1} (CO). FAB-MS: m/z 360 $(M + 1)^+$. Anal. calcd. for $C_{18}H_{20}O_6N_2$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.85, H, 5.68; N, 7.65.

1-(3′,6′-Anhydro-α-D-glucofuranosyl)thymine (7). To a solution of **6** (0.12 g, 0.33 mmol) in CH_3OH (8 mL) was added 5% Pd/C (5 mg) and hydrogenated (1 atm) for 21 h. After completion of the reaction the catalyst was filtered and residue washed with methanol. The filtrate was concentrated to obtain the title compound **7** (0.042 g, 53.50%) as a syrup. $[\alpha]_D + 10.5^\circ$ (c 1.0, H_2O). ^{1}H NMR (D_2O): δ 1.72 (s, 3H, 5-CH_3), 3.40–3.60 (m, 2H, H-6′,6″), 3.75–3.85 (m, 1H, H-5), 3.90–4.80 (m, 3H, H-2′,3′,4′), 5.35 (d, 1H, $J_{1',2'} = 5.8$ Hz, H-1′), 7.23 (s, 1H, H-6). Anal. calcd. for $C_{11}H_{14}O_6N_2$: C, 48.89; H, 5.22; N, 10.37. Found: C, 48.69; H, 5.18; N, 10.29.

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