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Note

Use of 2-pyridyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside as a glycosyl donor and methyl iodide as an activator for the synthesis of 1,2-*trans*-linked saccharides †

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2-Amino-2-deoxyglycopyranosides are important constituents of glycoproteins[1], glycolipids[2], and glycoside antibiotics[3]. There is much interest in the synthesis of such complex molecules due to their significant biological functions, for example, in antigen–antibody reactions[4] and in cell communication[5].

We have demonstrated that benzylated 2-pyridyl 1-thioglycopyranosides are versatile glycosyl donors that can be activated by methyl iodide for coupling reactions to give α-linked saccharides[6]. It is well known that the presence of a participating group at C-2 leads to the formation of 1,2-*trans*-linked (*i.e.*, β) products. However, initial experiments indicated that 2-pyridyl 1-thioglycopyranosides with O-2 acetylated were not activated by methyl iodide[7]. Similar observations have been made for 1-pentenyl glycosides[8], phenyl 1-thioglycosides[9], and glycals[10]. In contrast, 2-pyridyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside (**1**) was activated by methyl iodide and reacted with (*a*) 2-propanol, (*b*) *tert*-butyl alcohol, (*c*) 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose, and (*d*) 1,2,3,6-tetra-*O*-acetyl-4-*O*-(2,3-di-*O*-acetyl-α-D-glucopyranosyl)-β-D-glucopyranose[11], to give the 1,2-*trans*-linked products **2a–2d**, respectively.

The donor **1** was prepared by the reaction of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[12] with 2-mercaptopyridine–K_2CO_3 in toluene–acetone and was characterised by the ^1H NMR data. The reaction of **1** severally with 1 equiv each of the acceptors (**a**)–(**d**) in dichloromethane at 50°C for 17–36 h gave the respective 1,2-*trans*-linked (i.e., β) derivatives **2a–2d** in yields of 68–87%. The 1,2-*trans* linkage in each of **2a–2d** was indicated by the signal for H-1 (d, $J_{1,2}$ 8.2–8.5 Hz) of the GlcNAc moiety.

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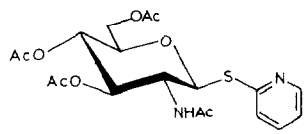
EXPERIMENTAL

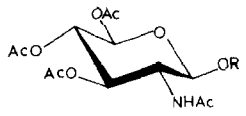
General methods.—Melting points were determined in open capillaries and are uncorrected. NMR spectra (^1H 300 MHz, ^{13}C 75 MHz) were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Varian MSL-300 spectrometer. Optical rotations were measured with a JASCO DIP-181 polarimeter on 1% solutions in $CHCl_3$. Silica gel (60–120 mesh, Acme) was used for column chromatography together with 3:1 hexane–EtOAc. TLC was performed on Silica Gel G (Acme) with detection by charring with phosphomolybdic acid. Reactions were performed in oven-dried (140°C) glassware. Dichloromethane was distilled from anhyd P_2O_5 and stored over 4A molecular sieves. Distilled MeI was used in all the reactions.

General procedure for glycosylations.—A mixture of **1** (1 mmol), dry CH_2Cl_2 (5 mL) that contained 5% of MeI, powdered 4A molecular sieves (200 mg), and the acceptor (1.1 equiv) was heated at 50°C (external bath) for 17–36 h. Each reaction was monitored by TLC and, when complete, the mixture was filtered through Celite, diluted with CH_2Cl_2 (25 mL), washed with EtOAc (5 mL), and concentrated to dryness. Column chromatography of the residue then gave the product.

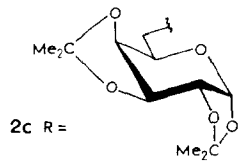
2-Pyridyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-1-thio-β-D-glucopyranoside (**1**). —To a stirred solution of 2-mercaptopyridine (1.09 g, 9.8 mmol) and anhyd K_2CO_3 (1.2 g, 10.6 mmol) in dry acetone (20 mL) was added a solution of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[12] (3 g, 8.2 mmol) in toluene (10 mL). The mixture was stirred at 50°C for 1 h, diluted with toluene (50 mL), washed with water, dried (Na_2SO_4), and concentrated, and the residue was recrystallised from hexane–ether to give **1** (2.71 g, 72%) as a yellow solid; mp 140–141°C; $[\alpha]_D$ +22°. NMR data: ^1H, δ 1.84, 2.01, 2.05, and 2.10 (4 s,



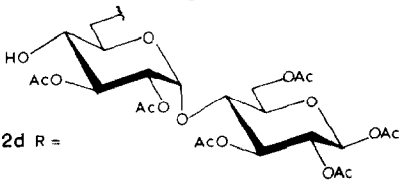
1



2a R = ^{i}Pr
2b R = ^{t}Bu



2c R =



2d R =

12 H, NAc and 3 OAc), 3.84 (ddd, 1 H, $J_{4,5}$ 7, $J_{5,6a}$ 4.5 Hz, H-5), 4.08 (dd, 1 H, $J_{6a,6b}$ 12 Hz, H-6a), 4.20 (d, 1 H, H-6b), 4.64 (dd, 1 H, $J_{1,2}$ 10.5, $J_{2,3} = J_{2,NH} = 9.5$ Hz, H-2), 5.16 (dd, 1 H, $J_{3,4}$ 7 Hz, H-4), 5.18 (dd, 1 H, H-3), 5.74 (d, 1 H, H-1), 6.24 (d, 1 H, NH), and 7.12–8.56 (m, 4 H, SPy); ^{13}C, δ 20.5, 20.6, 20.7, and 22.9 (4 q, NHCOCH_3 and 3 OCOCH_3), 52.9 (t, C-6), 62.2, 66.5, 74.3, and 75.9 (4 d, C-2/5), 82.6 (d, C-1), 120.7, 123.4, 136.6, and 149.3 (4 d, C-3/6 of SPy), 157.2 (s, C-2 of SPy), 169.2, 170.5, and 170.2 (4 s, NH$COCH_3$ and 3 $OCOCH_3$). *Anal.* Calcd for $C_{19}H_{24}N_2O_8S$: C, 51.81; H, 5.49. Found: 51.78; H, 5.37.

Isopropyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranoside (**2a**).—Reaction of **1** (0.44 g, 1 mmol) with 2-propanol (235 μL, 5 mmol) in dry CH_2Cl_2 (10 mL) that contained 5% of MeI, at 50°C for 22 h, afforded **2a** (0.31 g, 81%), isolated as a syrup; $[\alpha]_D$ −4°. NMR data: ^{1}H, δ 1.13 and 1.23 (2 d, 6 H, *J* 6.2 Hz, OCHMe_2), 1.95, 2.04, 2.05, and 2.08 (4 s, 12 H, NAc and 3 OAc), 3.6 (2 q, 1 H, OC*H*Me_2), 3.68 (ddd, 1 H, $J_{4,5}$ 10.0, $J_{5,6a}$ 4.5, $J_{5,6b}$ 2.0 Hz, H-5), 3.95 (ddd, 1 H, $J_{1,2}$ 8.3, $J_{2,3}$ 9.3, $J_{2,NH}$ 8.0 Hz, H-2), 4.13 (dd, 1 H, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.24 (dd, 1 H, H-6b), 4.85 (d, 1 H, H-1), 5.03 (dd, 1 H, $J_{3,4}$ 9.3 Hz, H-4), 5.41 (dd, 1 H, H-3), and 5.76 (d, 1 H, NH); ^{13}C, δ 20.59 (2 C), 20.6 and 21.9 (2 C), 23.2 [6 q, NHCOCH_3, 3 OCOCH_3, and OCH(CH_3)$_2$], 55.3 [d, O*C*H(CH)$_3$)$_2$], 62.3 (t, C-6), 69.1, 71.5, 72.3, and 72.0 (4 d, C-2/5), 99.1 (d, C-1), 169.4, 170.3, and 170.6 (2 C) (4 s, NH$COCH_3$ and 3 $OCOCH_3$). *Anal.* Calcd for $C_{17}H_{27}NO_9$: C, 52.43; H, 6.99. Found: C, 52.34; H, 6.89.

tert-*Butyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranoside* (**2b**).—Reaction of **1** (0.44 g, 1 mmol) with *tert*-butyl alcohol (290 μL, 5 mmol) in CH_2Cl_2 (10 mL) that contained 5% of MeI, at 50°C for 22 h, yielded **2b** (0.31 g, 77%), isolated as a syrup; $[\alpha]_D$ +10°. NMR data: ^{1}H, δ 1.23 (s, 9 H, ^{t}Bu), 1.93, 2.01, 2.02, and 2.05 (4 s, 12 H, NAc and 3 OAc), 3.58 (ddd, 1 H, $J_{1,2}$ 8.5, $J_{2,3}$ 10.5 $J_{2,NH}$ 8.5 Hz, H-2), 3.73 (ddd, 1 H, $J_{5,6a}$ 5.5, $J_{5,6b}$ 2.5, $J_{4,5}$ 10.0 Hz, H-5), 4.08 (dd, 1 H, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.22 (dd, 1 H, H-6b), 4.94 (d, 1 H, H-1), 4.98 (dd, 1 H, $J_{3,4}$ 9.5 Hz, H-4), 5.49 (dd, 1 H, H-3), 5.63 (d, 1 H, NH); ^{13}C, δ 20.7 (3 C) 23.3 and 28.5 (2 C) [6 q, NHCOCH_3, 3 OCOCH_3, and −C(CH_3)$_3$], 56.1 [s, C(CH_3)$_3$], 62.7, 69.4, 71.4, and 72.2 (2 C) (4 d, 1 t, C-2/6), 95.1 (d, C-1), 169.5, 170.1, and 170.6 (2 C) (4 s, NH$COCH_3$ and 3 $OCOCH_3$). *Anal.* Calcd for $C_{18}H_{29}NO_9$: C, 53.58; H, 7.25. Found: C, 53.49; H, 7.11.

6-O-(2-*Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl*)-1,2 : 3,4-*di-O-isopropylidene-α-D-galactopyranose* (**2c**).—Reaction of **1** (0.44 g, 1 mmol) with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (0.39 g, 1.15 mmol) in CH_2Cl_2 (10 mL) that contained 5% of MeI, for 36 h at 50°C, yielded **2c** (0.51 g, 73%) isolated as a syrup; $[\alpha]_D$ −11°. NMR data: ^{1}H, δ 1.32 (6 H), 1.45, and 1.51 (3 s, 12 H, 2 CMe_2), 1.96, 2.02, 2.09, and 2.17 (4 s, 12 H, NAc and 3 OAc), 3.54–4.65 (m, 10 H, H-2/6 and H-2′/6′), 4.71 (d, 1 H, $J_{1',2'}$ 8.5 Hz, H-1′), 5.06–5.2 (m, 2 H, H-3′,4′), 5.53 (d, 1 H, $J_{1,2}$ 5.5 Hz, H-1); ^{13}C, δ 20.3, 20.4, 20.5, 22.1, 24.0, 24.7, 25.7, and 25.8 [8 q, 2 C(CH_3)$_2$, NHCOCH_3, and 3 OCOCH_3], 53.9, 61.9, 68.1, 68.2, 68.3, 68.5, 68.8, 70.3, 70.8, 71.5, and 72.9 (8 d and 2 t, C-2/6 and C-2′/6′), 96.0 (d,

C-1′), 101.4 (d, C-1), 108.4, and 109.1 [2 s, 2 $C(CH_3)_2$], 169.1, 170.4, 170.5, and 170.7 (4 s, $NHCOCH_3$ and 3 $OCOCH_3$). *Anal.* Calcd for $C_{26}H_{39}NO_{14}$: C, 52.97; H, 6.67. Found: C, 52.89; H, 6.58.

O-(2-*Acetamido*-3,4,6-*tri*-O-*acetyl*-2-*deoxy*-α-D-*glucopyranosyl*)-(1 → 6)-O-(2,3-*di*-O-*acetyl*-α-D-*glucopyranosyl*)-(1 → 4)-1,2,3,4-*tetra*-O-*acetyl*-β-D-*glucopyranose* (**2d**). —Reaction of **1** (0.22 g, 0.5 mmol) with α-maltose 1,2,3,4,2′,3′-hexa-acetate (0.23 g, 0.39 mmol) in dry CH_2Cl_2 (10 mL) that contained 5% of MeI at 50°C for 36 h, yielded **2d** (0.38 g, 77%); mp 197–198°C (from hexane–EtOAc); $[\alpha]_D$ +43°. NMR data: ^1H, δ 1.94, 1.98, 1.99, 2.02, 2.03, 2.05, 2.07, 2.08, 2.13, and 2.15 (10 s 30 H, OAc and NAc), 3.5–5.4 (m, 20 H, H-1/6, H-2′/6′, and H-2″/6″), 5.72 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1′), and 6.17 (d, 1 H, $J_{2,NH}$ 8.5 Hz, NH); ^{13}C, δ 20.4 (2 C), 20.5 (3 C), 20.6 (2 C), 20.8 (2 C), 23.1 (10 s, $NHCOCH_3$ and 9 $OCOCH_3$), 54.6, 62.0, 62.9, 68.4, 68.6, 69.2, 70.2, 71.0, 71.5, 71.6, 72.0, 72.2, 72.3, 73.1, and 75.3 (3 t and 12 d, C-2/6, C-2′/6′, and C-2″/6″), 91.4 and 95.9 (2 d, C-1,1′), 101.2 (d, C-1″), 168.7, 169.3, 169.5, 170.0 (2 C), 170.7, and 170.8 (2 C) (10 s, $NHCOCH_3$ and 9 $OCOCH_3$). *Anal.* Calcd for $C_{38}H_{53}NO_{25}$: C, 49.40; H, 5.78. Found: C, 49.34; H, 5.62.

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