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Directing Effect of Axial and Equatorial Anomeric Substituent in Site Specific Glycosylation of Glucopyranosides

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ABSTRACT

Regio- and stereoselective glycosylation of α- and β-octyl glucopyranoside derivatives **2c** and **2d**, respectively, with glycosyl donor **3** to obtain the corresponding 3-*O*-linked **5c** and 2-*O*-linked **4d** saccharides, respectively, is described, formation of diglycosylated products **6c** and **6d** was not observed.

Key Words: Octyl glucopyranoside; 2-Pyridyl-1-thioglucopyranoside; Iodomethane; Regioselective glycosylation.

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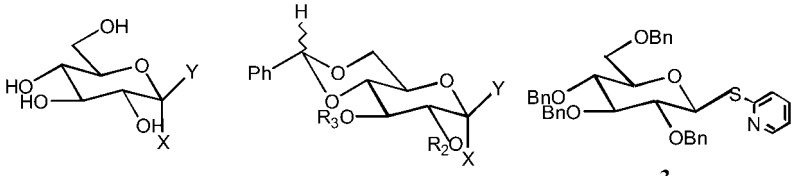
Carbohydrate biopolymers are made up of monomeric units connected to one another at several sites and in two types of anomeric linkages[1] they provide almost all variations in their structure and play essential role in many molecular processes such as fertilization, embryogenesis, and hormone activity.[2] Oligosaccharide structures change dramatically during development of cells and specific sets of oligosaccharides are expressed at distinct stages of differentiaion. The saccharide processing involves regio- and stereoselective glycosylation of carbohydrates, extent and site of glycosylation is attributed to steric crowding in the 3D structure and rate of reactivity of the hydroxyl groups.[3]

We report our initial studies on the role of anomeric substituent in the site specific glycosylation of glucopyranosides. Methyl α-(**1a**) and β-D-glucopyranoside (**1b**) were severally reacted with α,α-dimethoxy toluene in CH_2Cl_2 to obtain the corresponding 4,6-*O*-benzylidene derivatives **2a**[4] and **2b**,[5] respectively, as crystalline solids.

Axial glycoside **2a** was coupled with 2-pyridyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α/β-D-glucopyranoside (**3**) by iodomethane activation procedure[6] in CH_2Cl_2 at 40°C for 78 hr to isolate 2-*O*-glycosylated saccharide **4a** (20% yield), 3-*O*-glycosylated saccharide **5a** (48% yield), and 2,3-di-*O*-glycosylated saccharide **6a** (10% yield). Whereas coupling of equatorial glycoside **2b** with **3** under similar reaction conditions gave 2-*O*-glycosylated saccharide **4b** (23.5% yield) and 3-*O*-glycosylated saccharide **5b** (46% yield), formation of diglycosylated derivative was not observed. Stereochemistry of the newly formed *O*-glycosidic bond was established as axial.[6] **4a**–**6a** and **4b**–**5b** were fully characterized from ^{1}H NMR spectra. These experiments have indicated that in case of axial methyl glycoside acceptors marginal selectivity for



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a) X=OCH$_3$, Y=H
b) X=H, Y=OCH$_3$
c) X=nC$_8$H$_{17}$O-, Y=H
d) X=H, Y=nC$_8$H$_{17}$O-

3

2 R$_2$=R$_3$=H
4 R$_2$=sugar,R$_3$=H
5 R$_2$=H, R$_3$=sugar
6 R$_2$=R$_3$=sugar
7 R$_2$=Ac,R$_3$=sugar
8 R$_2$=sugar,R$_3$=Ac

sugar=(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)

Scheme 1.

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3-*O*-glycosylation was observed over 2-*O*- and vice versa for equatorial methyl glycoside derivatives indicating that the stereochemistry at the anomeric position played a role in directing the glycosylation site. In order to enhance the regioselectivity (site) in glycosylations we looked at the role of alkyl groups such as size and linkage (α/β) at the anomeric position. Thus glycosides possessing long chain alkyl groups at the anomeric position were considered for glycosylation. Accordingly, n-octyl α-(**1c**)[7] and -β-D-glucopyranosides (**1d**)[8] were converted to their corresponding benzylidene derivatives **2c** and **2d**, respectively, by reaction with α,α-dimethoxy toluene.[4] **2c** and **2d** were characterized from ^{1}H NMR spectra by the appearance of benzylidene acetal protons as two singlets at δ5.50 (0.8 H), δ5.40 (0.2 H), δ5.45 (0.5 H), and δ5.30 (0.5 H), respectively. **2c** and **2d** were separately coupled with glycosyl donor **3** to isolate 3-*O*-α-**5c** (58% yield) and 2-*O*-β-glycosylated **4d** (77% yield) derivatives, respectively, indicating high regioselectivity. Formation of regioisomers and diglycosylated products was not observed. **5c** and **4d** were converted to the corresponding acetyl derivatives **7c** and **8d**, respectively, for characterization by ^{1}H NMR spectra. In the ^{1}H NMR spectra of **7c**, acetyl group appeared at δ2.10 (3H, s), H-2 as a double doublet at δ5.40 ($J_{1,2} = 4.2$ Hz, $J_{2,3} = 8.1$ Hz) and H-1 appeared at δ4.30 as a doublet. Irradiation of the proton at δ5.40 resulted in the collapse of H-1 to a singlet; thus **7c** was characterized as the 3-*O*-glycosylated saccharide. In the ^{1}H NMR spectrum of **8d** the acetyl group appeared at δ2.18 (s, 3H) and H-3 at δ4.95 (0.5 H, dd) and 5.30 (0.5 H, dd, $J_{3,8} = 2$ Hz, $J_{3,4} = 8.5$ Hz). Irradiation of the protons at δ4.95 and δ5.30 did not have any effect on the multiplicity of H-1 proton that appeared as a doublet at δ4.60 ($J_{1,2} = 8.2$ Hz) indicating **8d** to be the 2-*O*-glycosylated saccharide.

In conclusion, we have shown that axial octyl glycopyranosides exhibited selective 3-*O*- and the corresponding equatorial ones the 2-*O*-glycosylation. In case of methyl glycosides the selectivity in glycosylation was not significant. Site selectivity, effect of chain length, and bulk of alkyl substituent at the anomeric position in glycosylation is under study in the light of these findings.

EXPERIMENTAL SECTION

General Methods

Flame dried glass ware, 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.

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Methyl 4,6-*O*-Benzylidene-2-*O*-(2,3,4,6-tetra-*O*-bezyl-α-D-glucopyranosyl)-α-D-glucopyranoside (4a); Methyl 4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (5a); Methyl 4,6-*O*-benzylidene-2,3-di-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (6a)

A solution of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (3.0 g, 10.3 mmol), **3** (5.8 g, 10.3 mmol), molecular sieves (100 mg) and methyl iodide (7.5 mL of 6% v/v methyl iodide solution in dichloromethane) in dichloromethane (100 mL) was refluxed for 78 hr. The reaction mixture was diluted with dichloromethane (200 mL) and filtered to remove insoluble salts. The filtrate was concentrated to a volume of 20 mL and chromatographed on a bed of silica gel [60–120 mesh, hexane : ethylacetate, (6 : 1)] to elute first 2,3-di-*O*-glycosylated derivative **6a** (0.89 g, 12%) followed by 2-*O*-glycosylated derivative **4a** (1.71 g, 28%) and 3-*O*-glycosylated product **5a** (3.14 g, 48%) as syrups.

4a: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.15–7.42 (m, 25H, Ar-H), 5.52 (d, 1H, $J = 4.5$ Hz, H-1), 5.43 (s, 1H, PhCH), 3.35–4.95 (m, 21H, $PhCH_2 \times 4$, 2-6, 1′-6′), 3.51 (s, 3H, OCH_3); Anal. calcd. for $C_{48}H_{52}O_{11}$ (804): C, 71.64; H, 6.47, Found: C, 71.32; H, 6.54.

5a: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.20–7.45 (m, 25H, Ar-H), 5.35 (d, 1H, $J = 4.5$ Hz, H-1), 5.45 (s, 1H, PhCH), 3.30–5.00 (m, 21H, $PhCH_2 \times 4$, 2–6, 1′–6′), 3.51 (s, 3H, OCH_3); Anal. calcd. for $C_{48}H_{52}O_{11}$ (804): C, 71.64; H, 6.47, Found: C, 71.39; H, 6.57.

6a: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.15–7.40 (m, 45H, Ar-H), 5.50 (s, 1H, PhCH), 3.40–5.00 (m, 36H, $PhCH_2 \times 8$, 2–6, 1′–6′, 1″–6″-H), 3.52 (s, 3H, OCH_3); Anal. calcd. for $C_{82}H_{80}O_{16}$ (1240): C, 74.21; H, 6.48, Found: C, 73.98; H, 6.57.

Methyl 4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-bezyl-α-D-glucopyranosyl)-β-D-glucopyranoside (4b); Methyl 4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-β-D-glucopyranoside (5b)

Reaction of **2b** (1.0 g, 3.5 mmol) in dichloromethane (10 mL), **3** (2.25 g, 3.5 mmol), molecular sieves (100 mg), methyl iodide (15 mL of 6% methyl iodide in dichloromethane) as described for **4a** resulted in the isolation of **3** (0.73 g, 26%) followed by 2-*O*-glycosylated derivative **5b** (410 mg, 23.5%) and 3-*O*-glycosylated derivative **4b** (0.80 g, 46%). $[\alpha]_D = -31.0^\circ$ (c 0.94, $CHCl_3$).

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4b: m.p. 155°C–157°C; $[\alpha]_D = -11^\circ$ (c 1.3, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ7.20–7.40 (m, 25H, Ar-H), 5.35 (d, 1H, $J = 6.4$ Hz, H-1′), 5.45 (s, 1H, PhCH), 3.40–5.00 (m, 21H, $PhCH_2 \times 4$, 2–6, 1′–6′), 3.58 (s, 3H, OCH_3); Anal. calcd. for $C_{48}H_{52}O_{11}$ (804): C, 71.64; H, 6.47, Found: C, 71.39; H, 6.53.

5b: syrup; $[\alpha]_D = -31^\circ$ (c 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ7.20–7.40 (m, 25H, Ar-H), 5.40 (d, 1H, $J = 6.4$ Hz, H-1), 5.45 (s, 1H, PhCH), 3.40–5.00 (m, 21H, $PhCH_2 \times 4$, 2–6, 1′–6′), 3.58 (s, 3H, OCH_3); Anal. calcd. for $C_{48}H_{52}O_{11}$ (804): C, 71.64; H, 6.47, Found: C, 71.39; H, 6.57.

n-Octyl 4,6-*O*-benzylidene-α-D-glucopyranoside (2c)

To a solution of *n*-octyl α-D-glucopyranoside (1.5 g, 5.1 mmol) in dry dichloromethane (5 mL) was added α,α-dimethoxy toluene (912 mg, 6 mmol) and a catalytic amount of p-TSA (5 mg) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 48 hr, water was added and extracted into dichloro methane. The organic phase was separated, washed with water, dried (Na_2SO_4). The residue obtained was filtered on a bed of silica gel [60–120 mesh, hexane : ethyl acetate, (1 : 1)] to obtain the title compound **2c** (1.7 g, 89%) as a crystalline solid, m.p. 74°C; ^1H NMR (200 MHz, $CDCl_3$): (diastereomeric mixture): δ7.25–7.60 (m, 5H, Ar-H), 5.30–5.50 (2s, 1H, PhCH), 4.35 (d, 1H, $J_{1,2} = 8.3$ Hz, H-1), 3.25–4.25 (m, 8H, H-2-6, OCH_2), 1.20–1.40 (m, 12H, $CH_2 \times 6$), 0.87 (t, 3H, CH_3); Anal. calcd. for $C_{21}H_{32}O_6$ (380): C, 66.31; H, 8.42, Found: C, 65.24; H, 8.51.

n-Octyl 4,6-*O*-benzylidene-β-D-glucopyranoside (2d)

To a solution of *n*-octyl β-D-glucopyranoside (4.5 g, 15.3 mmol) in dry dichloromethane (20 mL) was added α,α-dimethoxy toluene (1.9 g, 19 mmol) and a catalytic amount of p-TSA (15 mg) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 48 hr, water was added and extracted into dichloro methane. The organic phase was separated, washed with water, dried (Na_2SO_4) and concentrated. The residue obtained was filtered on a bed of silica gel [60–120 mesh, hexane : ethyl acetate, (1 : 1)] to obtain the title compound **2d** (5.1 g, 89%) as a crystalline solid, m.p. 124°C; ^1H NMR (200 MHz, $CDCl_3$): (diastereomeric mixture): δ7.25–7.60 (m, 5H, Ar-H), 5.30–5.50 (2s, 1H, PhCH), 4.35 (d, 1H, $J_{1,2} = 8.3$ Hz, H-1), 3.25–4.25 (m, 8H, H-2-6, OCH_2), 1.20–1.40 (m, 12H, $CH_2 \times 6$), 0.87 (t, 3H, CH_3); Anal. calcd. for $C_{21}H_{32}O_6$ (380): C, 66.31; H, 8.42, Found: C, 66.12; H, 8.53.

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n-Octyl 4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-bezyl-α-D-glucopyranosyl)-α-D-glucopyranoside (5c); *n*-Octyl 4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-β-D-glucopyranoside (4d)

Prepared from **2c** (1.0 g, 2.6 mmol) CH_2Cl_2 (12 mL), **3** (1.65 g, 2.6 mmol) methyl iodide (1 mL of 6% methyl iodide in dichloromethane) as described for compound **4b** to obtain the title compound **5c** (0.5 g, 48%) as a syrup: $[\alpha]_D = 60^\circ$ (c 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.05–7.40 (m, 25H, Ar-H), 5.52–5.50 (2s, 1H, PhCH), 5.35 (d, 1H, $J_{1,2} = 2.1$ Hz, H-1), 3.30–5.00 (m, 22H, H-2-6, 1′–6′, OCH_2, $PhCH_2O \times 3$, PhCH-), 1.15–1.45 (m, 12H, $CH_2 \times 6$), 0.87 (t, 3H, CH_3); Anal. calcd. for $C_{55}H_{68}O_{11}$ (904): C, 72.97; H, 7.52, Found: C, 72.78; H, 7.59.

4d: $[\alpha]_D = 14.6^\circ$ (c 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.00–7.40 (m, 25H, Ar-H), 5.25–5.50 (2s, 1H, PhCH), 3.30–5.00 (m, 22H, H-2-6, 1′–6′, OCH_2, $PhCH_2O \times 3$, PhCH-), 1.15–1.45 (m, 12H, $CH_2 \times 6$), 0.87 (t, 3H, CH_3); Anal. calcd. for $C_{55}H_{68}O_{11}$ (904): C, 72.97; H, 7.52, Found: C, 72.88; H, 7.49.

n-Octyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-bezyl-α-D-glucopyrano- syl)-α-D-glucopyranoside (7c)

2d (0.1 g, 0.09 mmol) was acetylated in pyridine (0.5 mL, 7.5 mmol) acetic anhydride (0.25 mL, 2.75 mmol) at 0°C to obtain the title compound **7c** (96 mg, 95%) as a syrup; $[\alpha]_D = 36^\circ$ (c 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.15–7.40 (m, 25H, Ar-H), 5.52 (d, 1H, $J_{1'2'} = 5.6$ Hz, H-1′), 5.42-5.30 (2s, 1H, PhCH), 4.85 (d, 1H, $J_{1,2} = 4.7$ Hz, H-2), 3.30–5.00 (m, 22H, H-1, 3-6, 2′–6′, $PhCH_2O \times 4$, $-OCH_2-$), 2.05 (s, 3H, $COCH_3$), 1.20–1.50 (m, 12H, $CH_2 \times 6$), 0.90 (t, 3H, CH_3); Anal. calcd. for $C_{57}H_{70}O_{12}$ (946): C, 72.31; H, 7.41, Found: C, 71.21; H, 7.49.

n-Octyl-3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyrano-syl)-β-D-glucopyranoside (8d)

To a solution of **4d** (200 mg, 0.22 mmol) in pyridine (0.5 mL, 7.5 mmol) at 0°C, was added acetic anhydride (0.25 mL, 2.3 mmol). The reaction mass was stirred at room temperature for 1 hr. The reaction mixture was worked up and filtered on a bed of silica gel [60–120 mesh, hexane: ethyl acetate (5 : 1)] to obtain the title compound **8d** (192 mg, 92%) as a syrup; $[\alpha]_D = 19^\circ$ (c 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.95–7.45 (m, 25H, Ar-H), 5.50–

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5.60 (2s, 1H, $J_{1'2'} = 3.2$ Hz), 5.28–5.45 (2s, 1H, 1H), 3.30–5.60 (d, 1H, $J_{1,2} = 4.7$ Hz, H-2), 3.30–5.60 (m, 22H, H-1, 3-6, 2′–6′, $PhCH_2O \times 4$, $-OCH_2-$), 5.10 (dd, $J_{2,3} = 80$ Hz, $J_{3,4} = 8.8$ Hz, H-3 merged), 2.00 (s, 3H, $COCH_3$), 1.20–1.35 (m, 12H, $CH_2 \times 6$), 0.70 (t, 3H, CH_3); Anal. calcd. for $C_{57}H_{70}O_{12}$ (946): C, 72.31; H, 7.41, Found: C, 71.31; H, 7.38.

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