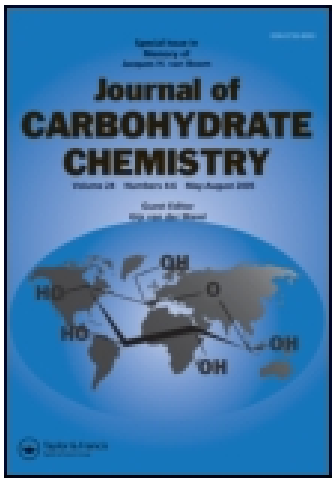

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Synthesis of Nitrogen Heterocycles from Methyl α- and β-D-Glucopyranosides

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ABSTRACT

Eight nitrogen heterocycles, mono and disubstituted tetrazoles and oxadiazoles, were synthesized from methyl D-glucopyranoside anomers. The monosubstituted tetrazoles resulted from the reaction of 6-cyanoglucopyranoside derivatives with sodium azide. By alkylation of the monosubstituted tetrazoles, the 1,5 and 2,5 disubstituted tetrazoles were obtained. The monosubstituted tetrazoles were reacted with acetic anhydride to give the oxadiazoles.

Key Words: Tetrazole; Oxadiazole; Heterocycle.

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INTRODUCTION

Tetrazoles are an increasingly popular structural unit, often used as metabolically stable surrogates for carboxylic acid groups, and as convenient lipophilic spacers in pharmaceuticals.[1] This unit also has roles in coordination chemistry as a ligand, and in various material science applications, including in specialty explosives.[2] There have been considerable achievements in the practical application of tetrazoles, especially in medicine and biochemistry.[3–5] Recent publications include the use of tetrazoles as inhibitors of monoamine oxidase,[6] as antiviral and antibacterial agents,[7,8] and antagonists of cerebellum-specific $GABA_A$ receptors[9] and angiotensin II.[10] The oxadiazoles also display biological activities such as fungicidal,[11] antibacterial[12] and glycosidase inhibitors.[13] We are interested in the synthesis of heterocycles using carbohydrates as starting materials, a strategy that offers the possibility of synthesis of compounds possessing chiral centers with the necessary enantiomeric purity required for active biological compounds. In this context, we synthesized some heterocycles using carbohydrates as starting materials.[14–17]

RESULTS AND DISCUSSION

The initial work centered on the preparation of methyl 2,3,4-tri-*O*-benzyl-6-cyano-6-deoxy-D-glucopyranoside anomers **1α** and **1β** in five conventional synthesis steps starting from methyl α(β)-D-glucopyranosides (Scheme 1). The starting materials were protected as 4,6-di-*O*-benzylidene derivatives[18] and then the C-2 and C-3 hydroxyl groups were *O*-benzylated.[19] Removal of the benzylidene group under $LiAlH_4$ reduction conditions[20] and replacement of the hydroxy group at C-6 by iodine[21] afforded the methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-iodo-α(β)-D-glucopyranosides (**4α** and **4β**). Treatment of **4α** and **4β** with potassium cyanide in DMF[22] gave nitriles **1α** and **1β**, respectively. After the preparation of these compounds, we went on to obtain the target tetrazoles.

Several methods of tetrazole synthesis are known,[2,4,5,23] but the most convenient method of synthesis of substituted tetrazoles involves the reaction of nitriles with salts of hydrazoic acid.[2,5] Thus, products **1α** and **1β** were submitted to reaction with sodium azide and ammonium chloride in DMF[16,17] to give 5-(methyl α/β-2,3,4-tri-*O*-benzyl-6-deoxy-D-glucopyranos-6-yl)tetrazole **2α** and **2β** in 81% and 73% yields, respectively.

Distinct oxadiazoles can be obtained by many methods.[12,24] In this work, we synthesized 1,3,4-oxadiazoles **3α** and **3β** in 84% and 60% yields, respectively, by the reaction of tetrazoles **2α** and **2β** with acetic anhydride and pyridine[12,16,17] at 110°C. To construct disubstituted tetrazoles, the alkylation reactions of tetrazole anions are often used.[25] However, due to the existence of the tetrazole tautomeric forms, alkylation gives mixtures of *N*(1)- and *N*(2)-alkylation isomers.[25] The ratio of these regioisomers is affected by the electronic and steric effect of the substituent.[25] Due to the two tautomeric forms of tetrazole, tetrazole **2α** when reacted with iodine derivative **4α** in the presence of anhydrous potassium carbonate in acetone,[6,17] gave a mixture of the two alkylated tetrazoles: 2,5-bis(methyl 2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranos-6-yl)-2*H*-tetrazole (**5α**) (31%) and 1,5-bis(methyl 2,3,4-tri-*O*-benzyl-6-deoxy-α-D-

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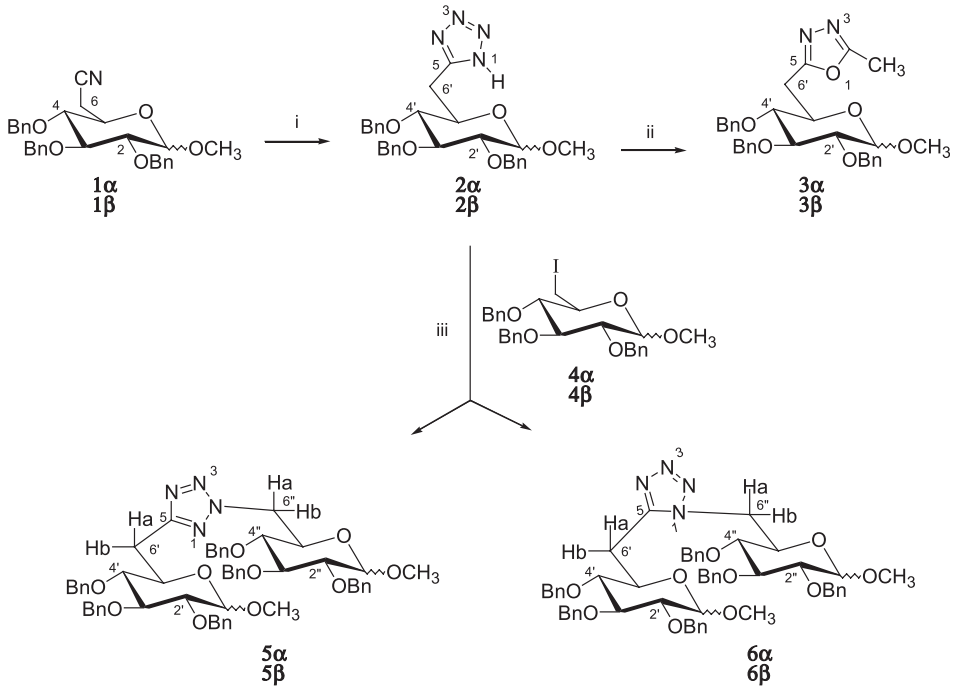

Scheme 1. Reagents, conditions and yields: i, NaN_3, DMF, NH_4Cl, 95°C, 192 h (α) and 144 h (β), 81% (α) and 73% (β); ii, acetic anhydride, pyridine, 110°C, 96 h (α) and 144 h (β), 84% (α) and 60% (β); iii, K_2CO_3, acetone, compounds **2α** and **4α**, 70°C, 120 h, **5α** (31%), **6α** (34%); compounds **2β** e **4β**, 70°C, 64 h, **5β** (50%) and **6β** (25%).

glucopyranos-6-yl)-1*H*-tetrazole (**6α**) (34%) in an approximate 1:1 ratio. Tetrazole **2β** by reaction with **4β** under the same conditions described for **2α** gave the regioisomers **5β** (50%) and **6β** (25%) in a 2:1 ratio. In a preliminary systematic conformational research (Hyperchem Pro 6.0 – Molecular Mechanics), it was observed that when the anomeric methoxy group is in the β position, there is a steric repulsion with the nucleophilic glycoside moiety, and the alkylation on the tetrazolic ring occurs preferentially at position 2. In contrast, when the anomeric methoxy group is α, the cited repulsive interaction is absent, and alkylation occurs at positions 1 and 2 in the same ratio (Scheme 1).

The structures of all the compounds obtained were confirmed by NMR spectroscopy. However, it is interesting to remark on the unequivocal characterization of the isomeric tetrazoles **5** and **6**. The literature reports that tetrazole isomers with methyl or alkyl substituents at positions 1 and 2 are readily distinguished by the ^1H and ^{13}C chemical shifts of the *N*-alkyl group. Alkyl groups bonded to *N*-1 are more shielded by *ca.* 0.15–0.35 ppm in the ^1H spectra and by *ca.* 2–6 ppm in the ^{13}C spectra relative to their corresponding *N*-2 isomers. However, HMBC experiments were carried out for confirmation and revealed that the cross correlation of H6″ with tetrazolic carbon occurs solely in derivatives **6** because of the ^3J coupling constant.

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EXPERIMENTAL

General procedures. Melting points were determined on a Mettler FP80HT apparatus and are uncorrected. Optical rotation was determined with a Perkin-Elmer 341 Polarimeter at 25°C. ^{13}C and ^{1}H NMR spectra were recorded on a Bruker Avance DRX-400 spectrometer. Chemical shifts are reported in δ units downfield from Me_4Si. Elemental analyses were carried out using a Perkin-Elmer 2400 CHN apparatus. Column chromatography was performed with silica gel 60, 70-230 mesh (Merck). The term ''standard work-up'' means that the organic layer was washed with satd NaCl solution, dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Dry solvents were prepared as follows. DMF was dried over potassium hydroxide and stirred for 24 hours at room temperature. The solution was filtered and distilled under reduced pressure. Dry pyridine was prepared after agitation with KOH for 17 h at room temperature, and then distilled. Potassium permanganate was added to refluxing acetone until its color remained purple. The solution was refluxed for 6 h more and distilled. Dry acetone was collected under desiccated K_2CO_3.

Methyl 2,3,4-tri-*O*-benzyl-6-cyano-6-deoxy-β-D-glucopyranoside 1β.[22] To a solution of methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-iodo-β-D-glucopyranoside (**4β**) (1.00 g, 1.74 mmol) in dry DMF (25 mL), KCN (0.38 g, 5.85 mmol) was added and the reaction mixture stirred at rt for 65 h. DMF was removed under reduced pressure, giving a residue. Water was added, the aqueous solution extracted with CH_2Cl_2 (4 × 30 mL), and the combined organic extracts submitted to standard work-up. The crude product was purified by column chromatography (10% EtOAc in hexane, gradually increasing the percentage of EtOAc) to give product **1β** (0.61 g, 74%) as a white solid: $[\alpha]_D$ + 32 (*c* 1.3, $CHCl_3$); mp 69–73°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.23 (m, 15H, Ar), 4.96 (d, 1H, J_{gem} 10.9 Hz, 1 × PhCH_2), 4.92 (d, 1H, J_{gem} 11.0 Hz, 1 × PhCH_2), 4.91 (d, 1H, J_{gem} 11.2 Hz, 1 × PhCH_2), 4.78 (d, 1H, J_{gem} 10.9 Hz, 1 × PhCH_2), 4.70 (d, 1H, J_{gem} 11.0 Hz, 1 × PhCH_2), 4.60 (d, 1H, J_{gem} 11.2 Hz, 1 × PhCH_2), 4.35 (d, 1H, $J_{1,2}$ 7.8 Hz, H1), 3.65 (t, 1H, $J_{3,4}$ 9.1 Hz, H3), 3.58 (s, 3H, MeO), 3.49 (ddd, 1H, $J_{5,4}$ 9.1, $J_{5,6''}$ 7.7, $J_{5,6'}$ 3.2 Hz, H5), 3.45 (dd, 1H, H2), 3.36 (t, 1H, H4), 2.70 (dd, 1H, J_{gem} 16.8 Hz, H6′), 2.43 (dd, 1H, H6″); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.3, 138.2, 137.5 (3 × C *ipso*), 128.6, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7 (15 × Ar), 116.8 (CN), 104.6 (C1), 84.2 (C3), 82.2 (C2), 79.8 (C4), 75.6, 75.2, 74.8 (3 × Ph*C*H_2), 70.5 (C5), 57.2 (MeO), 21.0 (C6).

Anal. Calcd for $C_{29}H_{31}NO_5$: C, 73.55; H, 6.60; N, 2.96. Found: C, 73.14; H, 6.59; N, 2.86.

Treating the epimer **4α** (3.15 g, 6.79 mmol) with KCN as described above for **4β**, product **1α** (2.36 g, 91%) was obtained as a whitish oil: $[\alpha]_D$ + 46.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.24 (m, 15H, Ar), 5.01 (d, 1H, J_{gem} 10.9 Hz, 1 × PhCH_2), 4.93 (d, 1H, J_{gem} 11.2 Hz, 1 × PhCH_2), 4.80 (d, 1H, J_{gem} 10.9 Hz, 1 × PhCH_2), 4.79 (d, 1H, J_{gem} 12.1 Hz, 1 × PhCH_2), 4.65 (d, 1H, J_{gem} 12.1 Hz, 1 × PhCH_2), 4.60 (d, 1H, J_{gem} 11.2 Hz, 1 × PhCH_2), 4.57 (d, 1H, $J_{1,2}$ 3.6 Hz, H1), 3.98 (t, 1H, $J_{3,4}$ 9.6 Hz, H3), 3.79 (ddd, 1H, $J_{5,4}$ 9.6, $J_{5,6'}$ 7.0, $J_{5,6''}$ 3.4 Hz, H5), 3.55 (dd, 1H, H2), 3.39 (s, 3H, MeO), 3.33 (t, 1H, H4), 2.62 (dd, 1H, J_{gem} 16.8 Hz, H6′), 2.42 (dd, 1H, H6″); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.3, 137.7, 137.5 (3 × C *ipso*), 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7 (15 × Ar), 116.9 (CN),

98.0 (C1), 81.5 (C3), 79.8 (C2 or C4), 79.7 (C2 or C4), 75.6, 75.1, 73.4 (3 × Ph*C*H_2), 66.2 (C5), 55.4 (MeO), 20.7 (C6).

Anal. Calcd for $C_{29}H_{31}NO_5$: C, 73.55; H, 6.60; N, 2.96. Found: C, 72.95; H, 6.59; N, 2.99.

5-(Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-β-D-glucopyranos-6-yl)tetrazole 2β.[16,17] To a solution of methyl 2,3,4-tri-*O*-benzyl-6-cyano-6-deoxy-β-D-glucopyranoside (**1β**) (0.17 g, 0.36 mmol) in dry DMF (10 mL), NaN_3 (0.28 g, 4.31 mmol) and NH_4Cl (0.23 g, 4.30 mmol) were added. The solution was stirred at 95°C for 144 h. DMF was removed under reduced pressure, giving a residue. Aqueous H_2SO_4 (3 mol.L^{-1}) was added until pH 1 was reached. Water was added, the aqueous solution extracted with CH_2Cl_2 (4 × 25 mL), and the combined organic extracts submitted to standard work-up. The crude product was purified by column chromatography (30% EtOAc in hexane, gradually increasing the percentage of EtOAc) to give product **2β** (0.14 g, 73%) as a white solid: $[\alpha]_D$ + 2 (*c* 1.2, Me_2SO); mp 217–219°C; ^{1}H NMR (Me_2SO-d_6, 400 MHz): δ 16.03 (br s, 1H, NH), 7.89–7.26 (m, 15H, Ar), 4.83 (d, 1H, J_{gem} 11.1 Hz, 1 × PhCH_2), 4.82 (d, 1H, J_{gem} 11.1 Hz, 1 × PhCH_2), 4.78 (d, 1H, J_{gem} 11.5 Hz, 1 × PhCH_2), 4.73 (d, 2H, J_{gem} 11.1 Hz, 2 × PhCH_2), 4.62 (d, 1H, J_{gem} 11.5 Hz, 1 × PhCH_2), 4.32 (d, 1H, $J_{1',2'}$ 7.8 Hz, H1′), 3.72 (td, 1H, $J_{5',6''}$ 9.1, $J_{5',6'}$ 3.0 Hz, H5′), 3.65 (t, 1H, $J_{3',4'}$ 9.1 Hz, H3′), 3.42 (t, 1H, H4′), 3.36 (dd, 1H, J_{gem} 15.1 Hz, H6′), 3.29–3,25 (m, 1H, H2′), 3.25 (s, 3H, MeO), 3.09 (dd, 1H, H6″); ^{13}C NMR (Me_2SO-d_6, 100 MHz): δ 153.0 (C5), 138.5, 138.4, 138.1 (3 × C *ipso*), 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 127.3 (15 × Ar), 103.3 (C1′), 83.5 (C3′), 81.6 (C2′), 80.6 (C4′), 74.4, 74.0, 73.5 (3 × Ph*C*H_2), 71.7 (C5′), 56.0 (MeO), 25.8 (C-6′).

Anal. Calcd for $C_{29}H_{32}N_4O_5$: C, 67.43; H, 6.24; N, 10.85. Found: C, 67.13; H, 6.36; N, 11.25.

Treatment of product **1α** (2.21 g, 4.66 mmol) as described above for **1β** gave product **2α** (1.94 g, 81%) as a white solid: $[\alpha]_D$ + 13.6 (*c* 1.2, $CHCl_3$); mp 218–223°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.23 (br s, 1H, NH), 7.34–7.24 (m, 15H, Ar), 4.97 (d, 1H, J_{gem} 10.9 Hz, 1 × PhCH_2), 4.89 (d, 1H, J_{gem} 11.0 Hz, 1 × PhCH_2), 4.80 (d, 1H, J_{gem} 10.9 Hz, 1 × PhCH_2), 4.76 (d, 1H, J_{gem} 12.0 Hz, 1 × PhCH_2), 4.65 (d, 1H, J_{gem} 11.0 Hz, 1 × PhCH_2), 4.62 (d, 1H, J_{gem} 12.0 Hz, 1 × PhCH_2), 4.60 (d, 1H, $J_{1',2'}$ 3.6 Hz, H1′), 4.00–3.93 (m, 1H, H5′), 3.99 (t, 1H, $J_{3',4'}$ 9.7 Hz, H3′), 3.56 (dd, 1H, H2′), 3.48 (dd, 1H, J_{gem} 15.3, $J_{6',5'}$ 3.6 Hz, H6′), 3.22 (s, 3H, MeO), 3.19 (t, 1H, $J_{4',5'}$ 9.7 Hz, H4′), 3.14 (dd, 1H, $J_{6'',5'}$ 9.7 Hz, H6″); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 153.3 (C5), 138.3, 137.8, 137.6 (3 × C *ipso*), 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7 (15 × Ar), 98.0 (C1′), 81.5 (C3′), 80.3 (C4′), 79.9 (C2′), 75.7, 75.1, 73.3 (3 × Ph*C*H_2), 67.9 (C5′), 55.4 (MeO), 25.9 (C6′).

Anal. Calcd for $C_{29}H_{32}N_4O_5$: C, 67.43; H, 6.24; N, 10.85. Found: C, 67.19; H, 5.99; N, 10.89.

2-Methyl-5-(methyl 2,3,4-tri-*O*-benzyl-6-deoxy-β-D-glucopyranos-6-yl)-1,3,4-oxadiazole 3β.[12,16,17] To a stirred solution of 5-(methyl 2,3,4-tri-*O*-benzyl-6-deoxy-β-D-glucopyranos-6-yl)tetrazole (**2β**) (0.15 g, 0.29 mmol) in dry pyridine (3 mL), acetic anhydride (9 mL, 99.10 mmol) was added. The solution was stirred at 110°C for 144 h, then cooled to rt and cold aq HCl (19 mL, 3 mol.L^{-1}) was added. Water was added, the aqueous solution extracted with CH_2Cl_2 (4 × 25 mL), and the combined organic

extracts submitted to standard work-up. The crude product was purified by column chromatography (40% EtOAc in hexane, gradually increasing the percentage of EtOAc) to give product **3β** (0.09 g, 60%) as a white solid: $[\alpha]_D$ + 13.2 (*c* 0.6, $CHCl_3$); mp 101–105°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34–7.25 (m, 15H, Ar), 4.95 (d, 1H, J_{gem} 10.9 Hz, 1 × PhCH_2), 4.93 (d, 1H, J_{gem} 11.5 Hz, 1 × PhCH_2), 4.90 (d, 1H, J_{gem} 11.7 Hz, 1 × PhCH_2), 4.78 (d, 1H, J_{gem} 10.9 Hz, 1 × PhCH_2), 4.69 (d, 1H, J_{gem} 11.7 Hz, 1 × PhCH_2), 4.66 (d, 1H, J_{gem} 11.5 Hz, 1 × PhCH_2), 4.30 (d, 1H, $J_{1',2'}$ 7.8 Hz, H1′), 3.75 (td, 1H, $J_{5',6''}$ 8.8 Hz, $J_{5',6'}$ 3.8, H5′), 3.68 (t, 1H, $J_{3',4'}$ 8.8 Hz, H3′), 3.45 (s, 3H, MeO), 3.45–3.39 (m, 1H, H2′), 3.41 (t, 1H, H4′), 3.26 (dd, 1H, J_{gem} 15.4 Hz, H6′), 2.93 (dd, 1H, H6″), 2.43 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.2 (C5), 163.7 (C2), 138.5, 138.4, 137.9 (3 × C *ipso*), 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7 (15 × Ar), 104.5 (C1′), 84.5 (C3′), 82.4 (C2′), 80.7 (C4′), 75.7, 74.9, 74.7 (3 × Ph*C*H_2), 72.0 (C5′), 56.9 (MeO), 28.3 (C6′), 10.8 (Me).

Anal. Calcd for $C_{31}H_{34}N_2O_6$: C, 70.17; H, 6.46; N, 5.28. Found: C, 69.97; H, 6.29; N, 5.32.

The treatment of tetrazole **2α** (0.20 g, 0.39 mmol) as described above for **2β** gave product **3α** (0.17 g, 84%) as a whitish oil: $[\alpha]_D$ + 42.7 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.25 (m, 15H, Ar), 5.01 (d, 1H, J_{gem} 10.8 Hz, 1 × PhCH_2), 4.95 (d, 1H, J_{gem} 10.8 Hz, 1 × PhCH_2), 4.81 (d, 1H, J_{gem} 10.8 Hz, 1 × PhCH_2), 4.78 (d, 1H, J_{gem} 12.2 Hz, 1 × PhCH_2), 4.66 (d, 1H, J_{gem} 10.8 Hz, 1 × PhCH_2), 4.63 (d, 1H, J_{gem} 12.2 Hz, 1 × PhCH_2), 4.50 (d, 1H, $J_{1',2'}$ 3.6 Hz, H1′), 4.12–4.02 (m, 1H, H5′), 4.01 (t, 1H, $J_{3',4'}$ 9.6 Hz, H3′), 3.50 (dd, 1H, H2′), 3.34 (t, 1H,$J_{4',5'}$ 9.6 Hz, H4′), 3.29 (s, 3H, MeO), 3.19 (dd, 1H, J_{gem} 15.4, $J_{6',5'}$ 3.7 Hz, H6′), 2.89 (dd, 1H, $J_{6'',5'}$ 8.4 Hz, H6″), 2.42 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 164.2 (C5), 163.6 (C2), 138.4, 137.9, 137.8 (3 × C *ipso*), 128.3, 128.0, 127.9, 127.8, 127.7, 127.6 (15 × Ar), 97.8 (C1′), 81.7 (C3′), 80.6 (C4′), 79.8 (C2′), 75.6, 74.8, 73.2 (3 × Ph*C*H_2), 67.5 (C5′), 55.2 (MeO), 27.9 (C6′), 10.7 (Me).

Anal. Calcd for $C_{31}H_{34}N_2O_6$: C, 70.17; H, 6.46; N, 5.28. Found: C, 69.98; H, 6.44; N, 5.33.

2,5-Bis(methyl 2,3,4-tri-*O*-benzyl-6-deoxy-β-D-glucopyranos-6-yl)-2*H*-tetrazole 5β and 1,5-Bis(methyl 2,3,4-tri-*O*-benzyl-6-deoxy-β-D-glucopyranos-6-yl)-1*H*-tetrazole 6β.[6,17] To a solution of 5-(methyl 2,3,4-tri-*O*-benzyl-6-deoxy-β-D-glucopyranos-6-yl)tetrazole (**2β**) (0.35 g, 0.68 mmol) and methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-iodo-β-D-glucopyranoside (**4β**) (0.39 g, 0.68 mmol) in dry acetone (120 mL), anhydrous K_2CO_3 (0.94 g, 6.81 mmol) was added. The solution was stirred at 70°C for 64 h in a pressure reactor. After cooling to rt, the solvent was removed, water was added, the aqueous solution was extracted with EtOAc (4 × 20 mL) and the combined organic extracts were submitted to standard work-up. The crude product was purified by column chromatography (10% EtOAc in hexane, gradually increasing the percentage of EtOAc) to give product **5β** (0.33 g, 50%) and **6β** (0.16 g, 25%) as white solids.

Compound **5β**: $[\alpha]_D$ + 18 (*c* 1.0, $CHCl_3$); mp 122–123°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32–7.27 (m, 30H, Ar), 4.95 (d, 1H, J_{gem} 10.9 Hz, 1 × PhCH_2), 4.94 (d, 1H, J_{gem} 10.9 Hz, 1 × PhCH_2), 4.93 (d, 1H, J_{gem} 10.9 Hz, 1 × PhCH_2), 4.92 (d, 1H, J_{gem} 11.2 Hz, 1 × PhCH_2), 4.88 (d, 1H, J_{gem} 11.1 Hz, 1 × PhCH_2), 4.86 (d, 1H, J_{gem} 11.1 Hz, 1 × PhCH_2), 4.78 (d, 2H, J_{gem} 10.9 Hz, 2 × PhCH_2), 4.73 (dd, 1H, $J_{6b'',6a''}$ 13.9, $J_{6b'',5''}$ 3.1 Hz, H-6b″), 4.72 (d, 1H, J_{gem} 11.2 Hz, 1 × PhCH_2), 4.71 (d, 1H, J_{gem} 10.9

Hz, 1 × PhCH_2), 4.67 (d, 1H, J_{gem} 11.1 Hz, 1 × PhCH_2), 4.65 (d, 1H, J_{gem} 11.1 Hz, 1 × PhCH_2), 4.56 (dd, 1H, $J_{6a'',5''}$ 7.6 Hz, H-6a″), 4.27 (d, 1H, $J_{1,2}$ 7.8 Hz, H1′ or H1″), 4.21 (d, 1H, $J_{1,2}$ 7.7 Hz, H1′ or H1″), 3.86–3.80 (m, 2H, H5′, H-5″), 3.68 (t, 1H, $J_{3,4}$ 9.1 Hz, H3′ or H3″), 3.67 (t, 1H, $J_{3,4}$ 9.1, H3′ or H3″), 3.48 (t, 1H, $J_{4',5'}$ 9.1 Hz, H4′), 3.47 (t, 1H, $J_{4'',5''}$ 9.1 Hz, H4″), 3.42–3.34 (m, 2H, H2′, H2″), 3.38 (s, 3H, MeO′ or MeO″), 3,35 (dd, 1H, $J_{6b',6a'}$ 15.3, $J_{6b',5'}$ 3.6 Hz, H6b′), 3.32 (s, 3H, MeO′ or MeO″), 3.08 (dd, 1H, $J_{6a',5'}$ 8.1 Hz, H6a′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.4 (C-5), 138.6, 138.4, 138.3, 138.2, 137.8 (6 × C *ipso*), 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5 (30 × Ar), 104.5, 104.4 (C1′, C1″), 84.7, 84.5 (C3′, C3″), 82.5, 82.2 (C2′, C2″), 81.0, 78.4 (C4′, C4″), 75.7, 75.6, 75.0, 74.9, 74.7 (6 × Ph*C*H$_2$), 72.6 (C5′), 72.4 (C5″), 56.8, 56.7 (MeO′, MeO″), 53.5 (C6″), 28.2 (C6′).

Anal. Calcd for $C_{57}H_{62}N_4O_{10}$: C, 71.08; H, 6.49; N, 5.82. Found: C, 69.97; H, 6.29; N, 5.32.

Compound **6β**: $[\alpha]_D$ + 14 (*c* 0.9, $CHCl_3$); mp 110–114°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.25 (m, 30H, Ar), 4.97 (d, 1H, J_{gem} 10.8 Hz, 1 × PhCH_2), 4.96 (d, 1H, J_{gem} 10.8 Hz, 1 × PhCH_2), 4.95 (d, 1H, J_{gem} 10.8 Hz, 1 × PhCH_2), 4.94 (d, 1H, J_{gem} 10.5 Hz, 1 × PhCH_2), 4.87 (d, 1H, J_{gem} 11.0 Hz, 1 × PhCH_2), 4.86 (d, 1H, J_{gem} 11.0 Hz, 1 × PhCH_2), 4.81 (d, 1H, J_{gem} 10.8 Hz, 1 × PhCH_2), 4.79 (d, 1H, J_{gem} 10.5 Hz, 1 × PhCH_2), 4.78 (d, 2H, J_{gem} 10.8 Hz, 2 × PhCH_2), 4.71 (dd, 1H, $J_{6b'',6a''}$ 14.5, $J_{6b'',5''}$ 2.8 Hz, H6b″), 4.67 (d, 1H, J_{gem} 11.0 Hz, 1 × PhCH_2), 4.66 (d, 1H, J_{gem} 11.0 Hz, 1 × PhCH_2), 4.38 (dd, 1H, $J_{6a'',5''}$ 7.5 Hz, H6a″), 4.22 (d, 1H, $J_{1',2'}$ 7.9 Hz, H1′), 4.18 (d, 1H, $J_{1'',2''}$ 7.9 Hz, H1″), 3.74 (ddd, 1H, $J_{5',4'}$ 9.7, $J_{5',6a'}$ 8.2, $J_{5',6b'}$ 3.2 Hz, H5′), 3.72–3.66 (m, 1H, H5″), 3.69 (t, 1H, $J_{3,4}$ 9.0 Hz, H3′ or H3″), 3.68 (t, 1H, $J_{3,4}$ 9.1 Hz, H3′ or H3″), 3.47 (dd, 1H, $J_{6b',6a'}$ 15.1 Hz, H6b′), 3.45–3.34 (m, 4H, H2′, H2″, H4′, H4″), 3.33 (s, 3H, MeO′ or MeO″), 3.29 (s, 3H, MeO′ or MeO″), 3.07 (dd, 1H, H6a′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.8 (C5), 138.4, 138.3, 138.2, 138.1, 138.0, 137.8 (6 × C *ipso*), 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5 (30 × Ar), 104.6, 104.5 (C1′, C1″), 84.4, 84.3 (C3′, C3″), 82.2, 82.0, 80.2, 78.1 (C2′, C2″, C4′, C4″), 75.6, 74.9, 74.8, 74.7 (6 × Ph*C*H$_2$), 73.4 (C5″), 73.1 (C5′), 57.0 (MeO′), 57.0 (MeO″), 47.7 (C6″), 25.7 (C6′).

Anal. Calcd for $C_{57}H_{62}N_4O_{10}$: C, 71.08; H, 6.49; N, 5.82. Found: C, 70.60; H, 6.31; N, 5.76.

By treatment of tetrazole **2α** (1.00 g, 1.94 mmol) with **4α** (1.10 g, 1.92 mmol) as described above for **2β**, product **5α** (0.57 g, 31%) and **6α** (0.64g, 34%) were obtained as whitish oils.

Compound **5α**: $[\alpha]_D$ + 47.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33–7.28 (m, 30H, Ar), 5.00 (d, 1H, J_{gem} 10.8 Hz, 1 × PhCH_2), 4.98 (d, 1H, J_{gem} 10.8 Hz, 1 × PhCH_2), 4.96 (d, 1H, J_{gem} 11.1 Hz, 1 × PhCH_2), 4.95 (d, 1H, J_{gem} 11.7 Hz, 1 × PhCH_2), 4.81 (d, 1H, J_{gem} 10.8 Hz, 1 × PhCH_2), 4.80 (d, 1H, J_{gem} 10.8 Hz, 1 × PhCH_2), 4.75 (d, 1H, J_{gem} 12.1 Hz, 1 × PhCH_2), 4.74 (d, 1H, J_{gem} 12.0 Hz, 1 × PhCH_2), 4.72 (d, 1H, J_{gem} 11.1 Hz, 1 × PhCH_2), 4.71 (d, 1H, J_{gem} 11.7 Hz, 1 × PhCH_2), 4.70 (dd, 1H, $J_{6b'',6a''}$ 14.7, $J_{6b'',5''}$ 2.8 Hz, H6b″), 4.61 (d, 1H, J_{gem} 12.1 Hz, 1 × PhCH_2), 4.59 (d, 1H, J_{gem} 12.0 Hz, 1 × PhCH_2), 4.57 (dd, 1H, $J_{6a'',5''}$ 8.3 Hz, H6a″), 4.44 (d, 1H, $J_{1'',2''}$ 3.5 Hz, H1″), 4.43 (d, 1H, $J_{1',2'}$ 3.5 Hz, H1′), 4.17–4.07 (m, 2H, H5′ and H5″), 4.01 (t, 1H, $J_{3'',4''}$ 9.4 Hz, H3″), 4.00 (t, 1H, $J_{3',4'}$ 9.4 Hz, H3′), 3.45 (dd, 1H, H2″), 3.41 (dd, 1H, H2′), 3.35 (t, 1H, $J_{4',5'}$ 9.4 Hz, H4′), 3.37–3.31 (m, 1H, H4″), 3.30 (dd, 1H, $J_{6b',6a'}$ 14.7, $J_{6b',5'}$ 3.4 Hz, H6b′), 3.19 (s, 3H, MeO′ or MeO″), 3.11

(s, 3H, MeO′ or MeO″), 3.00 (dd, 1H, $J_{6a',5'}$ 8.5 Hz, H6a′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.5 (C5), 138.6, 138.3, 138.2, 138.0, 137.8 (6 × C *ipso*), 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4 (30 × Ar), 97.8 (C1′ or C1″), 97.7 (C1′ or C1″), 81.9 (C3″), 81.8 (C3′), 81.0 (C4′), 80.0 (C2′), 79.7 (C2″), 78.3 (C4″), 75.8, 75.7, 74.9, 74.8, 73.4, 73.3 (6 × Ph*C*H$_2$), 68.4 (C5′), 68.2 (C5″), 55.2 (MeO′ or MeO″), 55.1 (MeO′ or MeO″), 53.4 (C6″), 27.9 (C6′).

Anal. Calcd for $C_{57}H_{62}N_4O_{10}$: C, 71.08; H, 6.49; N, 5.82. Found: C, 70.89; H, 6.32; N, 5.65.

Compound **6α**: $[\alpha]_D$ + 51.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34–7.26 (m, 30H, Ar), 4.99 (d, 1H, J_{gem} 10.9 Hz, 1 × PhC*H*$_2$), 4.98 (d, 1H, J_{gem} 11.0 Hz, 1 × PhC*H*$_2$), 4.96 (d, 1H, J_{gem} 12.3 Hz, 1 × PhC*H*$_2$), 4.95 (d, 1H, J_{gem} 12.5 Hz, 1 × PhC*H*$_2$), 4.81 (d, 1H, J_{gem} 10.9 Hz, 1 × PhC*H*$_2$), 4.80 (d, 1H, J_{gem} 11.0 Hz, 1 × PhC*H*$_2$), 4.76 (d, 1H, J_{gem} 11.7 Hz, 1 × PhC*H*$_2$), 4.74 (d, 1H, J_{gem} 11.7 Hz, 1 × PhC*H*$_2$), 4.73 (d, 1H, J_{gem} 12.3 Hz, 1 × PhC*H*$_2$), 4.72 (d, 1H, J_{gem} 12.5 Hz, 1 × PhC*H*$_2$), 4.63 (d, 1H, J_{gem} 11.7 Hz, 1 × PhC*H*$_2$), 4.60 (d, 1H, J_{gem} 11.7 Hz, 1 × PhC*H*$_2$), 4.48 (dd, 1H, $J_{6b'',6a''}$ 14.4, $J_{6b'',5''}$ 2.5 Hz, H6b″), 4.39 (d, 1H, $J_{1',2'}$ 3.6 Hz, H1′), 4.38 (d, 1H, $J_{1'',2''}$ 3.6 Hz, H1″), 4.15 (dd, 1H, $J_{6a'',5''}$ 8.0 Hz, H6a″), 4.00–3.86 (m, 2H, H5′ and H5″), 3.96 (t, 2H, $J_{3',4'}$ 9.4 Hz, H3′ and H3″), 3.43 (dd, 1H, H2′), 3.40 (dd, 1H, H2″), 3.32–3.23 (m, 3H, H4′, H4″ and H6b′), 3.09 (s, 3H, MeO′ or MeO″), 2.98 (s, 3H, MeO′ or MeO″), 2.81 (dd, 1H, $J_{6a',6b'}$ 15.1, $J_{6a',5'}$ 8.8 Hz, H6a′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.7 (C5), 138.5, 138.3, 138.2, 138.0, 137.9, 137.8 (6 × C *ipso*), 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6 (30 × Ar), 97.8 (C1′ or C1″), 97.7 (C1′ or C1″), 81.8 (C3′ and C3″), 80.3 (C4′), 79.8 (C2′ or C2″), 79.7 (C2′ or C2″), 78.1 (C4″), 75.7, 75.6, 74.7, 74.6, 73.3, 73.2 (6 × Ph*C*H$_2$), 69.1 (C5″), 68.7 (C5′), 55.1 (MeO′ or MeO″), 55.0 (MeO′ or MeO″), 47.5 (C6″), 25.3 (C6′).

Anal. Calcd for $C_{57}H_{62}N_4O_{10}$: C, 71.08; H, 6.49; N, 5.82. Found: C, 70.91; H, 6.35; N, 5.72.

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