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Short Note

2,3,4,6-Tetra-*O*-benzyl-1-*C*-phenyl-α-D-glucopyranosyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranoside

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Abstract: The title compound **1** was synthesized by the coupling reaction of 2,3,4,6-tetra-*O*-benzyl-1-*C*-phenyl-α-D-glucopyranose (**2**) with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**3**) in the presence of 5 mol% bismuth(III) triflate in dichloromethane at 0 °C.

Keywords: trehalose mimic; ketose; 1-*C*-phenyl-glucopyranose; glucose; bismuth triflate

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Trehalose is a non-reducing disaccharide which is composed of two glucopyranosyl units linked to each other in α-configuration. Trehalose is well-known for its various biological functions, and current attention is focused on the biologically novel functions of trehalose analogs, such as binding potentials to E-selectin and shiga toxins, and antibacterial activities [1–3]. Therefore, it is of increasing importance to design and synthesize novel non-reducing disaccharides which are structurally-classified as trehalose analogs.

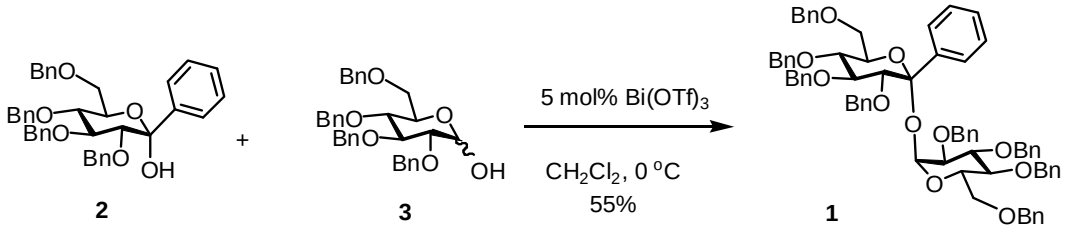
Our recent studies showed the synthetic approaches to two types of non-reducing disaccharides from aldoses and/or ketoses by bismuth(III) triflate ($Bi(OTf)_3$)-catalyzed dehydrative glycosidations [4–6]. One was non-reducing disaccharides composed of two aldoses which linked with each other by self-condensations [5]. The other was a hybrid type of non-reducing disaccharides composed of aldose and ketose by the cross-condensations [6]. The latter condensation was the ketosylation reaction that utilized the ketohexopyranoses carrying the methyl group at the anomeric centers, *i.e.*, the 1-*C*-methyl-hexopyranose derivatives, as the glycosyl donors by using only 5 mol% $Bi(OTf)_3$. Since some ketohexopyranose derivatives having a functional group such as an alkyl, alkynyl, alkene, and aryl group at the anomeric carbon centers are readily prepared from the corresponding glycono-1,5-lactone derivatives and appropriate organometallic reagents, it is expected that various kinds of structurally novel non-reducing disaccharides can be created using such ketohexopyranose derivatives. We also

achieved the synthesis of a non-reducing disaccharide using the 1-*C*-butyl-**D**-glucopyranose derivative employing the same procedure [7].

We designed a novel non-reducing disaccharide using the 1-*C*-phenyl-**D**-glucopyranose derivative as a trehalose analog. This paper describes the synthesis of 2,3,4,6-tetra-*O*-benzyl-1-*C*-phenyl-**D**-glucopyranosyl 2,3,4,6-tetra-*O*-benzyl-**D**-glucopyranoside (**1**) by the $Bi(OTf)_3$-catalyzed ketosylation of 2,3,4,6-tetra-*O*-benzyl-1-*C*-phenyl-**D**-glucopyranose (**2**) [8,9] into 2,3,4,6-tetra-*O*-benzyl-**D**-glucopyranose (**3**) [10].

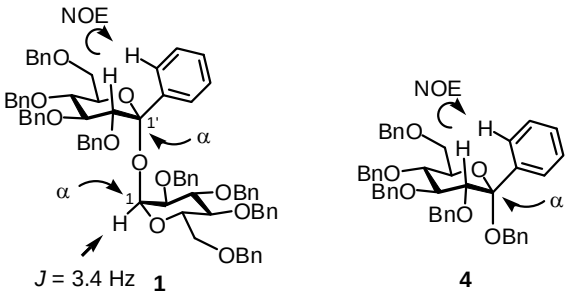
The ketosylation of **2** with **3** was investigated using $Bi(OTf)_3$ as shown in Scheme 1. The condensation reaction of **2** with **3** in the presence of 5 mol% $Bi(OTf)_3$ in dichloromethane at 0 °C for 15 h afforded **1** in a good yield of 55%. The benzyl 2,3,4,6-tetra-*O*-benzyl-1-*C*-phenyl-α-**D**-glucopyranoside (**4**) was obtained in 11% yield as a major by-product. Compound **4** would be formed by the reaction of **2** with benzyl alcohol generated by the degradation of **2** and/or **3**. A similar reaction at room temperature reduced the yield of **1** (12%) and increased the yield of **4** (26%).

Scheme 1. Synthesis of the title compound **1**.



The configuration of the two glycosidic linkages of **1** was determined by NOE and ^{1}H-NMR experiments. The NOE interaction between aromatic-ortho H and H-2' as shown in Figure 1 was observed. This observation inevitably indicated the equatorial orientation of the phenyl group and determined the α-ketopyranosidic linkage. The α-aldopyranosidic linkage was confirmed by the coupling constant (J = 3.4 Hz) of H-1. Thus, both the glycosidic linkages of **1** were α. The ketopyranosidic linkage of **4** was similarly determined as an α by the NOE interaction.

Figure 1. NOE interaction.



Experimental

*2,3,4,6-Tetra-O-benzyl-1-C-phenyl-α-**D**-glucopyranosyl 2,3,4,6-tetra-O-benzyl-α-**D**-glucopyranoside* (**1**)

To a suspension of $Bi(OTf)_3$ (4.7 mg, 0.007 mmol), **2** (47.3 mg, 0.09 mmol) and $CaSO_4$ (*ca*. 100 mg) in CH_2Cl_2 (3.5 mL) was added **3** (83.2 mg, 0.13 mmol) at 0 °C under an Ar atmosphere. The resulting

mixture was stirred for 15 h. The reaction was then quenched by addition of a sat. $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with CH_2Cl_2, and the organic layer was washed with water and a sat. NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative silica gel TLC (ethyl acetate/hexane = 1/3) to give **1** (R_f = 0.58, 55.3 mg, 55%) and **4** (R_f = 0.65, 10.1 mg, 11%) both as colorless oils. Compound **1**: $[\alpha]_D^{21}$ +49° (*c* 0.74, $CHCl_3$). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 3.32 (1H, d, *J* = 9.7 Hz, H-2'), 3.33–3.37 (2H, m, H_a-6, H_a-6'), 3.42 (1H, dd, *J* = 3.4 Hz, *J* = 10.3 Hz, H-2), 3.47 (1H, dd, *J* = 2.8 Hz, *J* = 11.0 Hz, H_b-6'), 3.62–3.64 (1H, m, H_b-6), 3.65 (1H, t, *J* = 8.9 Hz, H-4), 3.80 (1H, t, *J* = 9.6 Hz, H-4'), 4.121 (1H, t, *J* = 9.6 Hz, H-3), 4.124 (1H, d, *J* = 11.0 Hz, C*H*$_2$Ph), 4.16 (1H, t, *J* = 9.7 Hz, H-3'), 4.28–4.30 (1H, m, H-5), 4.35 (1H, d, *J* = 12.3 Hz, C*H*$_2$Ph), 4.44–4.62 (8H, m, H-5', C*H*$_2$Ph), 4.75 (1H, d, *J* = 11.0 Hz, C*H*$_2$Ph), 4.83–4.92 (5H, m, C*H*$_2$Ph), 4.99 (1H, d, *J* = 11.0 Hz, C*H*$_2$Ph), 5.03 (1H, d, *J* = 3.4 Hz, H-1), 7.14–7.33 (43H, m, Ph), 7.83 (2H, d, *J* = 7.6 Hz, Armatic ortho-H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 68.2 (C-6), 68.6 (C-6'), 70.5 (C-5), 71.4 (C-5'), 73.2 (*C*H_2Ph), 73.3 (*C*H_2Ph), 73.4 (*C*H_2Ph), 74.7 (*C*H_2Ph), 75.0 (*C*H_2Ph), 75.1 (*C*H_2Ph), 75.47 (*C*H_2Ph), 75.51 (*C*H_2Ph), 78.21 (C-4), 78.22 (C-4'), 80.5 (C-2), 81.8 (C-3), 83.1 (C-3'), 85.5 (C-2'), 92.1 (C-1), 101.3 (C-1'), 127.1–128.4 (Ph), 138.0–138.7 (Ph). HRMS (ESI): *m/z* calcd for $C_{74}H_{74}O_{11}Na^+$: 1161.5123; found: 1161.5142. Anal. Calcd for $C_{74}H_{74}O_{11}\cdot H_2O$: C, 76.79; H, 6.62. Found: C, 76.97; H, 6.82. Compound **4**: $[\alpha]_D^{24}$ +41° (*c* 0.55, $CHCl_3$). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 3.38 (1H, d, *J* = 9.6 Hz, H-2), 3.74 (1H, d, *J* = 10.3 Hz, H_a-6), 3.80–3.85 (3H, m, H-4, H_b-6, C*H*$_2$Ph), 3.90 (1H, dd, *J* = 3.4 Hz, *J* = 10.3 Hz, H-5), 4.25 (1H, t, *J* = 8.9 Hz, H-3), 4.37 (2H, s, C*H*$_2$Ph), 4.46 (1H, d, *J* = 10.3 Hz, C*H*$_2$Ph), 4.61 (1H, d, *J* = 12.3 Hz, C*H*$_2$Ph), 4.63 (1H, d, *J* = 13.1 Hz, C*H*$_2$Ph), 4.70 (1H, d, *J* = 12.4 Hz, C*H*$_2$Ph), 4.86–4.88 (2H, m, C*H*$_2$Ph), 4.94 (1H, d, *J* = 11.0 Hz, C*H*$_2$Ph), 7.10–7.41 (28H, m, Ph), 7.72 (2H, d, *J* = 8.2 Hz, Armatic ortho-H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 63.7 (*C*H_2Ph), 68.9 (C-6), 72.3 (C-5), 73.4 (*C*H_2Ph), 75.1 (*C*H_2Ph), 75.5 (*C*H_2Ph), 75.7 (*C*H_2Ph), 78.6 (C-4), 83.1 (C-3), 85.8 (C-2), 101.5 (C-1), 127.3–128.4 (Ph), 138.3–138.8 (Ph). HRMS (ESI): *m/z* calcd for $C_{47}H_{46}O_6Na^+$: 729.3187; found: 729.3216. Anal. Calcd for $C_{47}H_{46}O_6\cdot 2/3H_2O$: C, 78.53; H, 6.64. Found: C, 78.42; H, 6.61.

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