

Synthesis of *O*- β -D-Glucopyranosyl-(1 $\rightarrow$ 2)-*O*- β -D-glucopyranosyl-(1 $\rightarrow$ 6)-D-glucopyranose; Dehydrative β -D-Glucosylation Using 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-D-glucopyranose

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A step-by-step synthesis of *O*- β -D-glucopyranosyl-(1 $\rightarrow$ 2)-*O*- β -D-glucopyranosyl-(1 $\rightarrow$ 6)-D-glucopyranose through the dehydrative β -D-glucosylation using 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-D-glucopyranose and the ternary system of *p*-nitrobenzenesulfonyl chloride, silver trifluoromethanesulfonate, and triethylamine is described.

Our continuing study of glycosylation¹⁾ has shown that the ternary system of *p*-nitrobenzenesulfonyl chloride (NsCl, Ns=–SO₂C₆H₄NO₂(*p*-), silver trifluoromethanesulfonate (AgOTf, Tf=–SO₂CF₃), and triethylamine (Et₃N) induces selective β -D-glucosylation of glycosyl acceptors with the D-glucosyl donor having a free OH group at C-1 such as 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose (**1**).²⁾ However, in any reaction with less reactive acceptors it almost always loses its selectivity.³⁾ To improve such an undesirable aspect, the benzyloxyl group at C-2 of **1** was replaced with an acetoxyl group, since an acyloxyl group at C-2 plays an important role in β -D-glycosylation using the 1-*O*-sulfonates.⁴⁾ Expectedly, the D-glucosylation with 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-D-glucopyranose (**3**) yielded β -D-glucosides with excellent selectivity, while that with 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose preferred to form α -D-glucosides.⁵⁾

1,2,3,4,6-Penta-*O*-acetyl- β -D-glucopyranose (**2**) was readily converted into a D-glucosyl donor **3**⁶⁾ (α : β ≈85:15) via a continuous four-stage through process.

D-Glucosylation of the primary OH group of methyl 2,3,4-tri-*O*-benzyl- α -D-glucopyranoside **4**⁷⁾ with **3** through the ternary system at 0°C for 20 h gave the corresponding β -D-glucoside **5** in a 62% yield (Table 1). The β -selectivity was retained even in the D-glucosylation of the less reactive secondary OH group of methyl 2,3,6-tri-*O*-benzyl- β -D-glucopyranoside **6**⁸⁾ though the yield of the reaction was lowered. Thus, the β (1 $\rightarrow$ 4)-linked disaccharide **7** was selectively obtained at a 46% yield. The selectivity was also maintained in the D-glucosylation of the axial OH group of the galactose derivative **8**.⁹⁾ Therefore, it is concluded that the acetoxyl group at C-2 controls the selectivity in dehydrative D-glucosylation irrespective of the type of OH group of D-glucosyl acceptor to produce β -D-glucoside in comparison with the previous experiments using **1**.³⁾

Using the β -D-glucosylation described above, a linear trisaccharide **10** was synthesized as illustrated in Fig. 1. The first D-glucosylation of the acceptor **11**^{10,11)} with **3** was carried out using the ternary system; the gentiobiose derivative **12** was obtained

selectively at a 61% yield. After deacetylation, the second glucosylation was performed by the ternary system to give the β -D-glucoside **14** at a 34% yield; an appreciable amount of the α -D-glucoside was isolated. In contrast to this, the use of **1** instead of **3** yielded the α -D-glucoside **15** as a significant by-product. A mixture of methanesulfonic acid (MeSO₃H) and CoBr₂¹²⁾ was useful for the first D-glucosylation to give **12** at a 41% yield. However, it was not at all useful for a second glucosylation of **13** with **3**. Deacetylation and successive hydrogenolysis of **14** afforded the trisaccharide **10**, whose ¹³C NMR spectrum in D₂O was consistent with its proposed structure—6-*O*- β -sophorosyl-D-glucose.¹³⁾

Experimental

Instrumentation for measuring the physical characteristics of the products was described in previous papers.^{2,3,12)} The D-glucosylation with the ternary system and the following processes were carried out in a manner which was detailed before.^{2,3,5)} The results of D-glucosylation are summarized in Table 1. The analytical and physical data of the products are listed in Table 2.

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-D-glucopyranose (**3**).

1,2,3,4,6-Penta-*O*-acetyl- β -D-glucopyranose (**2**, Kyowa, 1.0 g, 2.56 mmol) was treated in CHCl₃ (3.0 ml) containing AcBr (1.05 ml) and H₂O (0.23 ml) at room temperature for 2 h.¹¹⁾ Evaporation and coevaporation with toluene gave a syrup which was dissolved in MeNO₂ (2.5 ml). 2,6-Dimethylpyridine (0.95 ml) and EtOH (1.15 ml) were added to the solution, which was then kept at room temperature overnight. The mixture was diluted with chloroform and washed with aq NaHCO₃ (5%). An organic layer was evaporated to dryness to give a syrup which was then heated in PhCH₂Cl (14 ml) containing powdered KOH (7 g) for 2 h at 110°C. Filtration and evaporation gave a syrup which was then stirred in aq AcOH (80%, 70 ml) for 2 h at room temperature. The mixture was diluted with toluene and an organic layer was washed with aq NaHCO₃ (5%) and water. After an evaporation, chromatography on a silica gel using a toluene–2-butanone system (gradient) gave a homogeneous syrup (*R*_f 0.18, toluene:2-butanone=6:1). This was crystallized from diisopropyl ether to afford **3** (0.37 g, 29%); ¹H NMR (CDCl₃, TMS): δ =2.00 (s, 3H, CH₃CO), 3.44 (d, 1H, *J* 4.0 Hz, OH), 5.38 (dd, 1H, *J*=3.8 and 4.0 Hz, H-1).

TABLE 1. THE RESULTS OF GLUCOSYLATION USING THE TERNARY REAGENT^{a)}

Run	3 /mg	Acceptor mg	NsCl mg	AgOTf mg	Et ₃ N μ l	CH ₂ Cl ₂ ml	Time ^{b)} h	β -Glucoside obtained	Yield %	Solvent ^{c)} for column chromatography ^{d)}
1	64.0	4 46.4	37.7	43.7	24.0	0.50	20	5	62	TB ^{e)}
2	64.0	6 46.4	37.7	43.7	24.0	0.50	24	7	46	TB ^{e)}
3	101.4	8 67.0	54.4	63.1	34.0	0.78	45	9	65	TB ^{e)}
4	320	11 270	189	219	119	2.7	24	12	61	TB ^{e)}
5	93.2	13 142	54.8	63.8	34.2	0.75	48	14	34	DE ^{e)}

a) The molar ratio of **3** to acceptor was 1.3 and that of each component of the ternary reagent to acceptor was 1.7. b) At 0 °C. c) TB=toluene-2-butanone, DE=(CH₂Cl)₂-AcOEt. d) On silica gel. e) A small amount of the α -glucoside was isolated (<5%).

TABLE 2. PHYSICAL AND ANALYTICAL DATA OF COMPOUNDS

Cpd	Mp $\theta_m/^\circ\text{C}$	$[\alpha]_D^{25}(\epsilon, \text{solv})^a)$	Mol. form	Calcd/%		Found/%		δ_C (CDCl ₃ , TMS) ^{b)}			CH ₃ CO
				C	H	C	H	C-1	C-1'	C-1''	
3 ^{c)}	129—130	+53° (1.0, C)	C ₂₉ H ₃₂ O ₇	70.71	6.55	70.57	6.51	α 90.5 β 95.8	—	—	20.9
5	127—128	+15° (4.3, C)	C ₅₇ H ₆₂ O ₁₂	72.90	6.65	73.04	6.69	98.2	101.2	—	21.0
7	—	+21° (1.8, C)				72.74	6.72	104.8	100.5	—	21.0
9	—	+28° (3.4, C)				72.68	6.73	98.6	102.1	—	21.0
10	—	—1° (0.8, W)	C ₁₈ H ₃₂ O ₁₆ ·H ₂ O	41.38	6.56	41.49	6.27	—	—	—	—
12	129—131	+15° (0.2, C)	C ₆₃ H ₆₆ O ₁₂	75.29	6.63	74.73	6.69	95.5	101.2	—	21.0
13	100—103	+39° (1.3, C)	C ₆₁ H ₆₄ O ₁₁	74.53	6.55	74.77	6.49	95.6	103.7	—	—
14	—	+28° (1.1, C)	C ₉₀ H ₉₄ O ₁₇	74.67	6.54	73.96	6.46	95.2	102.1	100.4	20.9
15	—	+67° (0.6, C)	C ₉₅ H ₉₈ O ₁₆	76.28	6.60	76.33	6.61	94.9	104.0	94.2	—
16	—	+34° (2.6, C)				76.08	6.60	95.5	102.0	102.4	—
17	—	+31° (1.0, C)	C ₈₈ H ₉₂ O ₁₆	75.19	6.60	75.31	6.82	95.4	102.9	103.9	—

a) C=CHCl₃, W=H₂O. b) Measured at 25.1 MHz. c) Ref. 6, mp 128—129 °C, $[\alpha]_D^{25} +55^\circ$ (ϵ 1.1, CHCl₃).

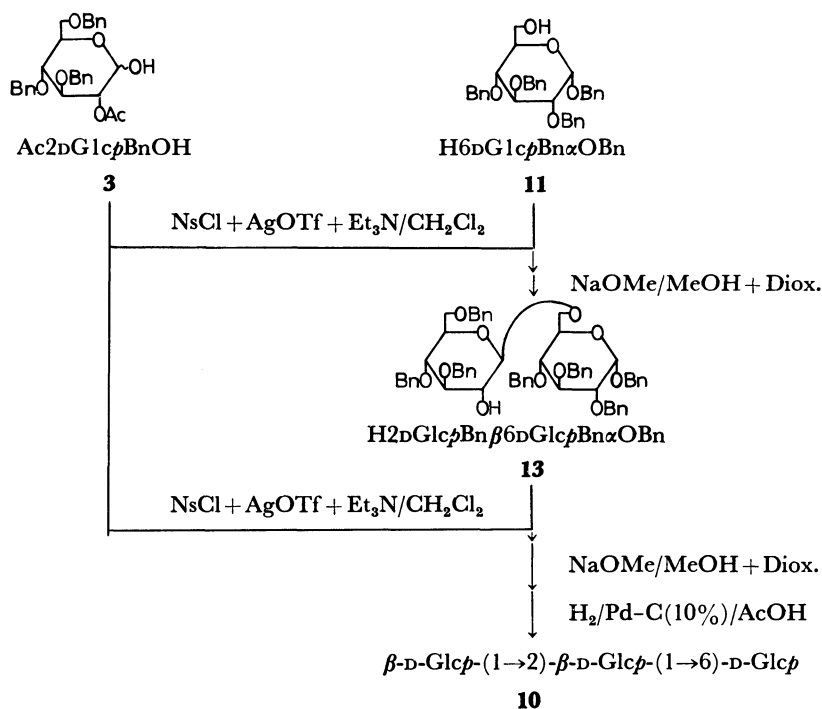
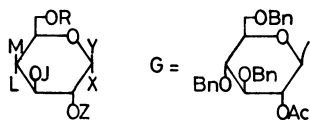
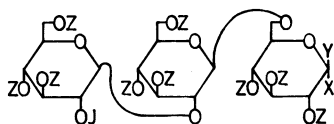


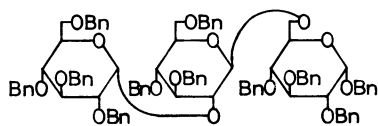
Fig. 1. Synthetic diagram⁶⁾ for the trisaccharide **10** (Bn=—CH₂Ph, Ns=—SO₂C₆H₄NO₂(*p*), Tf=—SO₂CF₃).



Cpd	X	Y	Z	J	L	M	R
1	OH,	H	Bn	Bn	OBn	H	Bn
2	H	OAc	Ac	Ac	OAc	H	Ac
4	OMe	H	Bn	Bn	OBn	H	H
5	OMe	H	Bn	Bn	OBn	H	G
6	H	OMe	Bn	Bn	OH	H	Bn
7	H	OMe	Bn	Bn	OG	H	Bn
8	OMe	H	Bn	Bn	H	OH	Bn
9	OMe	H	Bn	Bn	H	OG	Bn
12	OBn	H	Bn	Bn	OBn	H	G



Cpd	X	Y	Z	J
10	OH,	H	H	H
14	OBn	H	Bn	Ac
16	OBn	H	Bn	Bn
17	OBn	H	Bn	H



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Alternative Synthesis of Benzyl 6-O-(2-O-Acetyl-3,4,6-tri-O-benzyl- β -D-glucopyranosyl)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (12). To a stirring mixture of **11**^{10,11} (82 mg, 0.17 mmol), **3** (90 mg, 0.17 mmol), and CoBr_2 (36.5 mg, 0.17 mmol) in CH_2Cl_2 (0.45 ml), MeSO_3H (3.3 μl , 0.05 mmol) was added at 20 °C and stirring was continued for 2 h. After processing¹² and chromatography the product was shown to be **12** (69 mg, 41%).

Benzyl 2,3,4-Tri-O-benzyl-6-O-(3,4,6-tri-O-benzyl- β -D-glucopyranosyl)- α -D-glucopyranoside (13). Compound **12** (127.6 mg, 0.126 mmol) was treated with a mixture of methanolic NaOMe (0.3%, 4.3 ml) and 1,4-dioxane (4 ml) at 20 °C overnight. Chromatography on a silica gel with toluene-2-butanone system gave **13** (112.3 mg, 92%).

Benzyl O-(2,3,4,6-Tetra-O-benzyl- α - and - β -D-glucopyranosyl)-(1 $\rightarrow$ 2)-O-(3,4,6-tri-O-benzyl- β -D-glucopyranosyl)-(1 $\rightarrow$ 6)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (15 and 16).

Triethylamine (22 μl , 0.158 mmol) was added into a stirred mixture of **14** (84 mg, 0.156 mmol, α : β ≈95:5), **13** (116.2 mg, 0.12 mmol), NaCl (35 mg, 0.158 mmol), and AgOTf (40 mg, 0.156 mmol) in CH_2Cl_2 (0.65 ml) at -40 °C. The bath temperature was gradually raised to 0 °C, at which temperature the reaction was continued overnight. After

processing, chromatography on a silica gel with toluene-2-butanone (gradient) gave a syrup (46.6 mg, 39%) consisting of **15** and **16**. Rechromatography of this syrup on silica gel using $(\text{CH}_2\text{Cl}_2)_2$ - AcOEt (gradient) gave pure **16** (25.1 mg, 21%) and then **15** (19.2 mg, 16%).

Benzyl O-(3,4,6-Tri-O-benzyl- β -D-glucopyranosyl)-(1 $\rightarrow$ 2)-O-(3,4,6-tri-O-benzyl- β -D-glucopyranosyl)-(1 $\rightarrow$ 6)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (17). The trisaccharide derivative **14** (79.5 mg, 0.055 mmol) was treated in a mixture of methanolic NaOMe (0.4%, 2 ml) and 1,4-dioxane (4 ml) at 20 °C overnight. After chromatography on silica gel with toluene-2-butanone system gave **17** (73.8 mg, 96%).

Compound **17** (47 mg, 0.033 mmol) was heated in PhCH_2Cl (0.8 ml) containing NaH (60%, 40 mg) at 135 °C for 16 h to give the aforementioned fully benzylated trisaccharide **16** (25 mg, 50%).

O- β -D-Glucopyranosyl-(1 $\rightarrow$ 2)-O- β -D-glucopyranosyl-(1 $\rightarrow$ 6)-D-glucopyranose (10). Two hydrogenolyses of **17** (47.4 mg, 0.034 mmol) in AcOH (6 ml) containing Pd-C (10%, 40 mg) under H_2 (340 kPa) and subsequent chromatography on silica gel with CHCl_3 - MeOH (1:1) gave glassy **10** (10.0 mg, 59%); ^{13}C NMR (D_2O , ext. TMS): δ =62.0 (C-6'), 62.2 (C-6''), 69.9 (C-6 α), 70.0 (C-6 β), 70.8 (C-4' and -4''), 70.9 (C-4 α and -4 β), 71.7 (C-5 α), 72.8 (C-2 α), 74.0 (C-3 α), 75.0 (C-2''), 75.4 (C-2 β), 76.2 (C-3 β), 77.0 (C-5 β , -3', and -3''), 77.5 (C-5' and -5''), 81.2 (C-2'), 93.5 (C-1 α), 97.4 (C-1 β), 102.6 (C-1'), and 103.8 (C-1'').

Similar hydrogenolysis of **16** (25 mg, 0.017 mmol) gave **10** (4 mg, 48%).

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