Synthesis of O-β-D-Glucopyranosyl-(1→2)-O-β-D-glucopyranosyl-(1→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→2)-O-β-D-glucopyranosyl-(1→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 glycosylation[1] has shown that the ternary system of *p*-nitrobenzenesulfonyl chloride (NsCl, Ns=$-SO_2C_6H_4NO_2(p-)$, silver trifluoromethanesulfonate (AgOTf, Tf=$-SO_2CF_3$), and triethylamine (Et_3N) 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→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 ($MeSO_3H$) and $CoBr_2$[12] 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 ^{13}C NMR spectrum in D_2O 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 $CHCl_3$ (3.0 ml) containing AcBr (1.05 ml) and H_2O (0.23 ml) at room temperature for 2 h.[11] Evaporation and coevaporation with toluene gave a syrup which was dissolved in $MeNO_2$ (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 $NaHCO_3$ (5%). An organic layer was evaporated to dryness to give a syrup which was then heated in $PhCH_2Cl$ (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 $NaHCO_3$ (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 ($CDCl_3$, TMS): δ=2.00 (s, 3H, CH_3CO), 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_3N μl	CH_2Cl_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=$(CH_2Cl)_2$-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 θ_m/°C	$[\alpha]_D^{20}$(*c*, solv)[a]	Mol. form	Calcd/% C	Calcd/% H	Found/% C	Found/% H	δ_C ($CDCl_3$, TMS)[b] C-1	C-1′	C-1″	CH_3CO
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)				73.04	6.69	98.2	101.2	—	21.0
7	—	+21° (1.8, C)	$C_{57}H_{62}O_{12}$	72.90	6.65	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)	$C_{18}H_{32}O_{16}\cdot H_2O$	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=$CHCl_3$, W=H_2O. b) Measured at 25.1 MHz. c) Ref. 6, mp 128—129 °C, $[\alpha]_D^{22}$ +55° (*c* 1.1, $CHCl_3$).

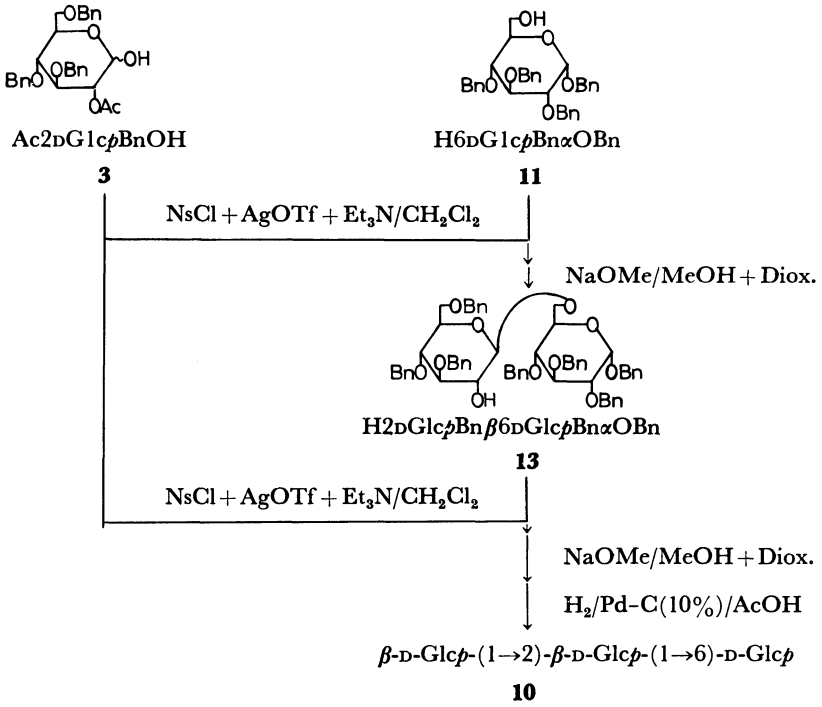
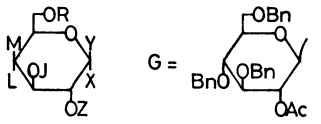
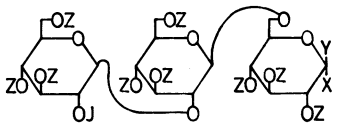


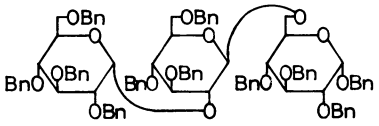
Fig. 1. Synthetic diagram[5] for the trisaccharide **10** (Bn=-CH_2Ph, Ns=-$SO_2C_6H_4NO_2$(*p*-), Tf=-SO_2CF_3).



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 processing[12] 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→2)-O-(3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-(1→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 **I**[14] (84 mg, 0.156 mmol, α:β≈95:5), **13** (116.2 mg, 0.12 mmol), NsCl (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 $(CH_2Cl)_2$–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→2)-O-(3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-(1→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→2)-O-β-D-glucopyranosyl-(1→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-6α), 70.0 (C-6β), 70.8 (C-4′ and -4″), 70.9 (C-4α and -4β), 71.7 (C-5α), 72.8 (C-2α), 74.0 (C-3α), 75.0 (C-2″), 75.4 (C-2β), 76.2 (C-3β), 77.0 (C-5β, -3′, and -3″), 77.5 (C-5′ and -5″), 81.2 (C-2′), 93.5 (C-1α), 97.4 (C-1β), 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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