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The Glucosylation of Several Alcohols with Tetra-*O*-benzyl-*α*-D-glucopyranose and a Mixture of *p*-Nitrobenzenesulfonyl Chloride, Silver Trifluoromethanesulfonate, and Triethylamine

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Synopsis. A novel glucosylation of several alcohols using 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose and a ternary mixture of *p*-nitrobenzenesulfonyl chloride, silver trifluoromethanesulfonate, and triethylamine is presented.

The development of methods for the glycosylation is important in carbohydrate chemistry.[1] Recently, several syntheses of glucosides using 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (**1**) have been reported.[2] We ourselves have briefly communicated a two-stage glucosylation using a novel procedure for generating the reactive sulfonate[3] from **1** and a ternary mixture of *p*-nitrobenzenesulfonyl chloride (NsCl), silver trifluoromethanesulfonate (AgOTf), and triethylamine (Et_3N).[4] This report will present a further finding that the one-stage treatment of an equimolar mixture of **1** and an alcohol with the ternary mixture in dichloromethane afforded the corresponding glucosides containing the *β*-anomer predominantly, as is shown in Table 1. This constitutes a convenient method for the preparation of *β*-glucoside from **1**. The self-condensation of **1**, yielding octa-*O*-benzyl-α,α- and α,*β*-trehalose (**7a** and **7b**),[5] was prevented in the one-stage glucosylation of alcohols with a primary hydroxyl group. Silver chloride and *p*-nitrobenzenesulfonic acid were deposited in the course of the reaction. Thus, the overall reaction is written by Eq. 1, where G denotes the tetra-*O*-benzyl-D-glucopyranosyl moiety:

$$\alpha\mathrm{GOH} + \mathrm{ROH} + \mathrm{NsCl} + \mathrm{AgOTf} + \mathrm{Et_3N} \longrightarrow \alpha,\beta\mathrm{GOR} + \mathrm{AgCl} + \mathrm{NsOH} + \mathrm{Et_3N{\cdot}TfOH}. \quad (1)$$

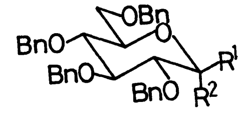
It should be noted that the self-condensations of **1** were unavoidable in the one-stage glucosylation of alcohols with a secondary hydroxyl group. The ternary mixture cannot be stored even at 0 °C, since an appreciable amount of bis(*p*-nitrophenyl) sulfoxide is formed.[6]

TABLE 1. GLUCOSYLATION OF ALCOHOLS WITH TETRA-*O*-BENZYL-α-D-GLUCOPYRANOSE (**1**) AND A MIXTURE OF *p*-NITROBENZENESULFONYL CHLORIDE, SILVER TRIFLUOROMETHANESULFONATE, AND TRIETHYLAMINE

Run	R[b)]	Method[c)]	Yield/%			Recov./%
			Glucosides (α/β)	(Net Yield)[d)]	**7a**+**7b**	**1**
1	Me	/2/	76 (16/60)	(83)	16	8
2	Me	/1/	68 (11/57)	(96)	0	29
3	Cm	/2/	67 (18/49)	(72)	23	7
4	Cm	/1/	75 (15/60)	(96)	0	22
5	Ch	/2/	64 (17/47)	(78)	21	18
6	Ch	/1/	69 (19/50)	(84)	12	18
7	Ct	/1/	56 (16/40)	(72)	17	22[e)]
8	Dh	/1/	76 (13/60)	(93)	0	18[f)]

a) Yields are based on the weight of products separated chromatographically, referring to that of **1** charged. b) Ch=cyclohexyl, Cm=cyclohexylmethyl, Ct=5α-cholestan-3*β*-yl, Dh=6-(2,4-dinitroanilino)hexyl, Me=methyl. c) /1/=one-stage treatment, /2/=two-stage treatment. d) Yields based on the **1** used. e) The recovery of the alcohol was 37%. f) The recovery of the alcohol was 23%.

	R[1]	R[2]
1	H	OH
2a	H	OMe
2b	OMe	H
3a	H	OCm
3b	OCm	H
4a	H	OCh
4b	OCh	H
5a	H	OCt
5b	OCt	H
6a	H	ODh
6b	ODh	H
7a	H	OαG
7b	OαG	H



Bn=benzyl
Ch=cyclohexyl
Cm=cyclohexylmethyl
Ct=5α-cholestan-3*β*-yl
Dh=6-(2,4-dinitroanilino)hexyl
Me=methyl
αG=2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl

Experimental

General. The instruments used are identical with those mentioned in the foregoing papers,[5,7] except for the JEOL JDX-7F X-ray powder diffractometer (Cu *K*α ray, λ=153.2 pm, Ni filter). The dichloromethane (Wako), cyclohexylmethanol (Tokyo Kasei), cyclohexanol (Koso), and triethylamine (Wako) were distilled and stored over molecular sieves (Linde 3A) before use. Compound **1**,[7] *p*-nitrobenzenesulfonyl chloride (Tokyo Kasei), 5α-cholestan-3α-ol (Tokyo Kasei), and 6-(2,4-dinitroanilino)-1-hexanol (mp 76—77 °C, Found: C, 50.55, H, 6.05, N, 15.03%. Calcd for $C_{12}H_{17}N_3O_5$: C, 50.88, H, 6.05; N, 14.83%), prepared by the treatment of 6-amino-hexanol (Aldrich) with 2,4-dinitrofluorobenzene (Wako) and $NaHCO_3$ in aq ethanol, as well as silver trifluoromethanesulfonate, made by the neutralization of Ag_2CO_3 (Wako) with aq trifluoromethanesulfonic acid (Kanto Denka Kogyo), were stored *in vacuo* over P_2O_5.

General Procedure for One-stage Glucosylation. To a mixture of **1** (180 mg, 0.33 mmol), alcohol (0.33 mmol), *p*-nitrobenzenesulfonyl chloride (74 mg, 0.33 mmol), and silver trifluoromethanesulfonate (86 mg, 0.33 mmol) in dichloromethane (1.8 ml), we added triethylamine (47 μl, 0.33 mmol) at −40 °C (bath temperature) and the resulting mixture was stirred well. The bath temperature gradually rose at the rate of 1.0 °C/min to 0 °C, at which temperature the mixture was then stirred for 3 h. After the addition of powdered $NaHCO_3$ (*ca.* 0.1 g) and stirring at room temperature, the mixture was filtered, evaporated, and chromatographed on silica gel (Kanto Kagaku), using three kinds of solvent systems: benzene and butanone (Solvent A), hexane and ethyl acetate (Solvent B), and chloroform and ethyl acetate (Solvent C),

TABLE 2. PHYSICAL DATA OF GLUCOSIDES

	Solvents for Chromatog.[a]		Mp/°C (Recryst. from)[b]	$[\alpha]_D^{20}$ (c, $CHCl_3$)	Found (%)			Calcd for: (%)			
					C	H	N		C	H	N
2a[c]	Solv. A	s	—	+28° (1.0)	75.73	6.92		$C_{35}H_{38}O_6$	75.79	6.90	
2b[d]		f	74—75 (HX)	+11° (5.6)	75.85	6.92					
3a	Solv. B	s	—	+33° (1.0)	76.73	7.48		$C_{41}H_{48}O_6$	77.36	7.55	
3b		f	103—104 (HX)	+4° (1.6)	77.52	7.56					
4a	Solv. B	s	—	+45° (1.3)	77.26	7.44		$C_{40}H_{46}O_6$	77.14	7.45	
4b		f	105—106 (IP)	+8° (1.6)	77.40	7.50					
5a	Solv. B	s	123—125 (IP)	+67° (0.5)	80.44	9.07		$C_{61}H_{82}O_6$	80.40	9.01	
5b		f	120—123 (IP)	+20° (1.0)	79.89	8.90					
6a	Solv. C	f	—	+25° (1.0)	68.32	6.08	4.95	$C_{46}H_{51}N_3O_{10}$	68.55	6.38	5.21
6b		s	—	+9° (1.0)	68.43	6.26	5.06				

a) For the solvent systems, see **Experimental.** f=faster-moving, s=slower-moving. b) HX=hexane, IP=isopropyl ether. c) O. T. Schmidt, T. Auer, and H. Schmadel, *Chem. Ber.*, **93**, 556 (1960), $[\alpha]_D^{20}$ +32.2° (c 5, $CHCl_3$). d) P. W. Austin, F. E. Hardy, J. G. Buchanan, and J. Baddiley, *J. Chem. Soc.*, **1964**, 2128, mp 68—69 °C, $[\alpha]_D^{20}$ +11° (c 5.3, dioxane).

respectively; these solvents were also used for TLC on silica gel (Merck, 7731).

General Procedure for Two-stage Glucosylation.[4,8] To an equimolar mixture of **1** (180 mg, 0.33 mmol), *p*-nitrobenzenesulfonyl chloride (74 mg), and silver trifluoromethanesulfonate (86 mg) in dichloromethane (1.8 ml), we added triethylamine (47 μl, 0.33 mmol) at −40 °C. After the bath temperature was risen to −10 °C, the mixture was stirred for 30 min. An alcohol (0.33 mmol) was then added, and agitation was continued at 0 °C for 3 h. Work-up was done as has been described above.

*Self-condensation of **1** with the Ternary Mixture.* To a mixture of **1** (90 mg, 0.17 mmol), *p*-nitrobenzenesulfonyl chloride (37 mg), and silver trifluoromethanesulfonate (43 mg) in dichloromethane (0.9 ml), we added triethylamine (24 μl) at −40 °C. The bath temperature rose to room temperature at the rate of 1.0 °C/min. The processed reaction mixture was chromatographed using Solvent A (gradient, 100: 1—20: 1) to give **7a** (17.5 mg, 20%) and then **7b** (36.6 mg, 42%). Compounds **7a** and **7b** were identified with those prepared before.[7]

*Alternative Synthesis of **5a**.* Ethyl 2.3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranoside[9] (40 mg, 0.83 mmol) in dichloromethane (0.5 ml) was treated with Br_2 in dichloromethane (0.62 g/ml, 22 μl) at room temperature for 10 min. After evaporation to dryness, the syrup thus obtained was reacted with 5α-cholestan-3β-ol (32 mg, 0.083 mmol), tetrabutylammonium bromide[10] (27 mg, 0.083 mmol), and 2,6-lutidine (10 μl, 0.083 mmol) in dichloromethane (0.5 ml) overnight. Chromatography using Solvent A (40: 1), followed by recrystallization from hexane, afforded **5a** (59 mg, 78%) (Found: C, 79.39; H, 8.83%).

*Alternative Synthesis of **5b**.* A mixture of 3β-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5α-cholestan[11] (0.14 g, 0.2 mmol), KOH (0.35 g), and benzyl chloride (1.4 ml) was heated at 100 °C for 16 h. After processing, chromatography sing Solvent A (40: 1) and recrystallization from hexane gave **5b** (0.08 g, 73%) (Found: C, 79.44; H, 8.70%).

Isolation of p-*Nitrobenzenesulfonic Acid and Silver Chloride.* The reaction mixture of glucosylation carried out on a 0.33-mmol scale using cyclohexylmethanol was filtered to give a solid. Subsequent washings of solid with methanol on evaporation afforded hydroscopic crystals of *p*-nitrobenzenesulfonic acid (42 mg, 62%), identified with the authentic sample by determining their IR (KBr) spectra. A washed solid (≈40 mg, >80%) on the filter was identified with AgCl by determining its X-ray powder diffraction.

Examination of the Stability of the Ternary Mixture. To a mixture of *p*-nitrobenzenesulfonyl chloride (73.8 mg, 0.33 mmol) and silver trifluoromethanesulfonate (85.7 mg, 0.33 mmol) in dichloromethane (1.8 ml), we added triethylamine (47 μl, 0.33 mmol) at −40 °C; the bath temperature was programmed as it was in the one-stage treatment. The mixture was then directly poured onto a column of silica gel, which was subsequently chromatographed with benzene. Bis(*p*-nitrophenyl)sulfoxide (8.2 mg, 17%) (mp 181.5 °C, UV_{max} (95% C_2H_5OH) 268 nm (ε 1.8×10^4) [lit,[12] mp 178—180 °C, UV_{max} (95% (C_2H_5OH) 268 nm (ε 1.82×10^4)], Found: C, 49.33, H, 2.66; N, 9.71. M^+-16. 276,[13] Calcd for $C_{12}H_8N_2O_5S$: C, 49.32; H, 2.76; N, 9.58%, MW 292. 27) and the slower-moving *p*-nitrobenzenesulfonyl chloride (55.7 mg, 75%), identified with an authentic sample by determining the mp, IR (KBr), and MS (M^+ 221, $M^+ + 2$. 223), were thus obtained.

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