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A STEREOSELECTIVE α-GLUCOSYLATION BY USE OF A MIXTURE OF 4-NITROBENZENESULFONYL CHLORIDE, SILVER TRIFLUOROMETHANESULFONATE, *N,N*-DIMETHYLACETAMIDE, AND TRIETHYLAMINE*

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ABSTRACT

Stereoselective α-glucosylation of partially protected carbohydrates with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose in dichloromethane, in the presence of a quaternary mixture of 4-nitrobenzenesulfonyl chloride, silver trifluoromethanesulfonate, *N,N*-dimethylacetamide, and triethylamine gave *O*-α-D-glucopyranosyl-(1→4)- and -(1→6)-2-acetamido-2-deoxy-D-glucopyranose (*N*-acetylmaltosamine and *N*-acetylisomaltosamine). A step-by-step synthesis of *O*-α-D-glucopyranosyl-(1→4)-*O*-[α-D-glucopyranosyl-(1→6)]-D-glucopyranose is described.

INTRODUCTION

Several procedures for α-glucosylation[1] have been published[2,3]. Most require, however, the preparation of a reactive glycosyl donor before the coupling reaction. Instead of introducing the benzyl group as a persistent protecting group, a convenient condensation reaction (Reaction *1*) may be applied to a sugar derivative having an unprotected OH-1 group (GOH; G denotes a 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl residue or equivalents)[4–7]. A ternary mixture

$$\mathrm{GOH} + \mathrm{ROH} \xrightarrow[-\mathrm{H_2O}]{} \alpha\mathrm{GOR} + \beta\mathrm{GOR} \qquad (1)$$

consisting of 4-nitrobenzenesulfonyl chloride (**3**), silver trifluoromethanesulfonate (**4**), and triethylamine (**5**) has been used for the stereoselective β-glucosylation of primary alcohols with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose[4,5] (**1**). A modification of these conditions to give selectively α-glucosides is described herein[8]. These conditions were applied to the synthesis of *O*-α-D-glucopyranosyl-(1→4)-(**25**) and -(1→6)-2-acetamido-2-deoxy-D-glucopyranoses (**27**), which constitutes

*Dedicated to Professor Raymond U. Lemieux.
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the *Shigella flexneri* O-antigens[9], as well as to the step-by-step synthesis of *O*-α-D-glucopyranosyl-(1→4)-*O*-[α-D-glucopyranosyl-(1→6)]-D-glucopyranose (**32**), which is the branching point of amylopectin and glycogen[10,11].

RESULTS AND DISCUSSION

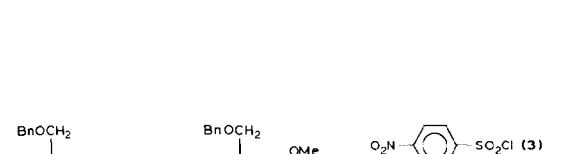
When the glucosylation of methyl 2,3,6-tri-*O*-benzyl-β-D-glucopyranoside[12] (**2**) with **1** was carried out in the presence of **3, 4,** and **5**, in *N,N*-dimethylformamide (**6**) (Run 2, Table I) instead of dichloromethane (Run 1), the proportion of α (**8**) to β anomer (**9**) rose significantly, although the yield was much decreased; the 1-*O*-formyl derivative **10** was isolated as a by-product[13]. The yield of glucosides, as well as the selectivity for the formation of the α anomer (**8**), were well improved by use of a limited amount of **6** in dichloromethane (Run 3); *N,N*-dimethylacetamide (**7**) was more effective. Thus, the glucosylation by a quaternary mixture composed of **3, 4, 5,** and **7** in dichloromethane (Run 5, Condition A) gave

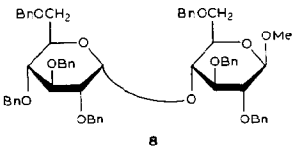
TABLE I

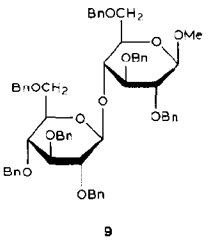
GLYCOSYLATION OF COMPOUNDS **2, 11–14, 21, 22, 30** AND **42** WITH **1**[a]

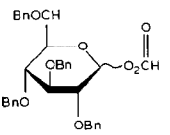
Run	*Acceptor*	*Amide*		*Time*[b] *(h)*	*Yield of glucosides (%)*	*Proportion of α-D-glucoside (%)*
		Composition	*Proportion*			
1	**2**			19	97	45
2[c]	**2**			19	58	77
3	**2**	$HCONMe_2$	2.5	18	92	88
4	**2**	AcNHMe	2.5	18	45[d]	[e]
5	**2**	$AcNMe_2$	2.5	21	86	93
6	**2**	$AcNMe_2$	3.3	16	86	93
7	**2**	$AcNMe_2$	5.0	21	73	86
8	**11**	$AcNMe_2$	2.5	18	87	88
9	**12**	$AcNMe_2$	2.5	24	85	89
10	**13**	$AcNMe_2$	2.5	18	87	90
11	**14**	$AcNMe_2$	2.5	20	91	47
12	**14**	$AcNMe_2$	5.0	18	88	73
13	**14**	$AcNMe_2$	10.0	19	54	72
14	**14**	$HCONMe_2$	5.0	24	98	66
15	**14**	$EtCONMe_2$	5.0	21	99	45
16	**14**	$EtCONMe_2$	5.0	17	95	45
17	**14**	$AcNPh_2$	5.0	22	95	41
18	**14**	$BzNMe_2$	5.0	17	94	39
19	**21**			24	76[d]	[e]
20	**21**	$AcNMe_2$	2.5	24	84[d]	[e]
21	**22**			24	79	35
22	**22**	$AcNMe_2$	5.0	24	95	68
23	**30**	$AcNMe_2$	5.0	20	82	62
24	**30**	$AcNMe_2$	2.5	20	62[d]	[e]

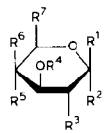
[a]The acceptor was treated with **1** (1.3 equiv.), and **3, 4,** and **5** (2.5 equiv. each) in dichloromethane. [b]At 0°. [c]In *N,N*-dimethylformamide instead of dichloromethane. [d]Yield of isolated α-D anomer. [e]Trace of β-D anomer.









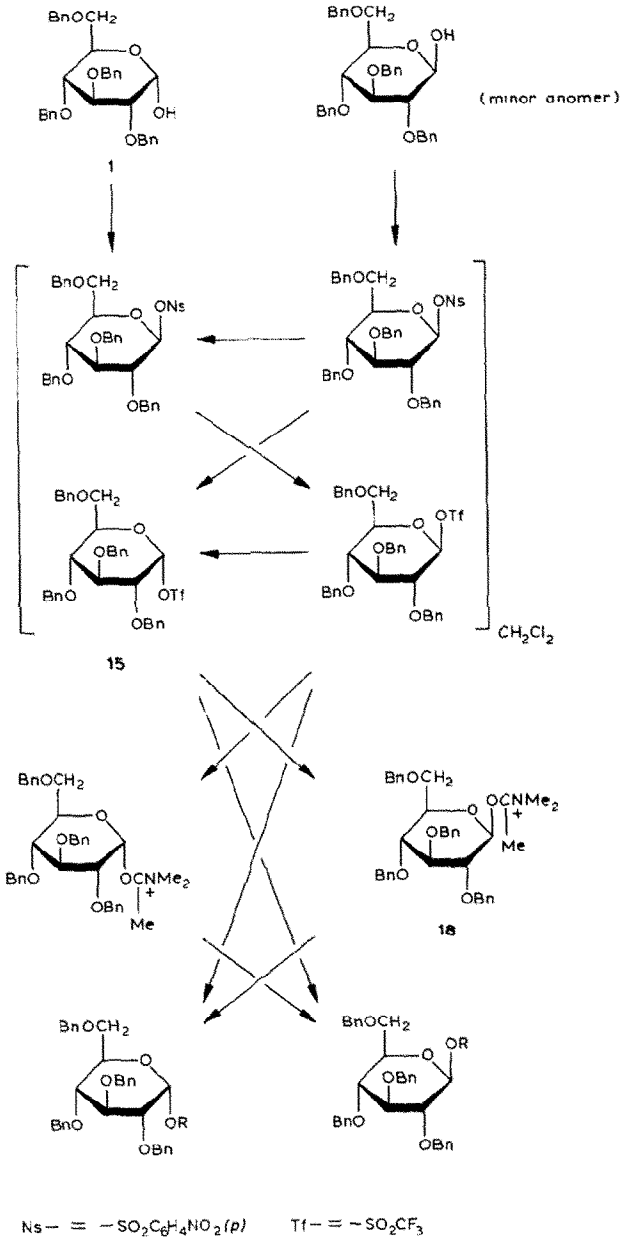


	R^1	R^2	R^3	R^4	R^5	R^6	R^7
11	H	OMe	OBn	H	OBn	H	H
12	H	OMe	OBn	H	OBn	H	CH_2OBn
13	OMe	H	OBn	Bn	H	OH	CH_2OBn
14	H	OMe	OBn	Bn	OBn	H	CH_2OH
[15	H	OSO_2CF_3	OBn	Bn	OBn	H	CH_2OBn]
16	H, Cl		OBn	Bn	OBn	H	CH_2OBn
17	OC(=NMe)Me	H	OBn	Bn	OBn	H	CH_2OBn
[18	$OC(NMe_2)Me$	H	OBn	Bn	OBn	H	CH_2OBn]
[19	H	$OCNMe_2$ (H)	OBn	Bn	OBn	H	CH_2OBn]
[20	OCNHMe (Me)	H	OBn	Bn	OBn	H	CH_2OBn]
21	H	OBn	NHAc	Bn	OH	H	CH_2OBn
22	H	OBn	NHAc	Bn	Bn	H	CH_2OH

8 in a 80% yield with an excellent stereoselectivity; use of an excess of **7** diminished the yield of glucosides (Runs 6 and 7). With *N*-methylacetamide (Run 4), the selectivity was good but the yield was poor.

The quaternary reagent used under Condition A was effective for the selective α-glycosylation of the partially benzylated pyranosides **11** (ref. 14) and **12** (ref. 15) (Runs 8 and 9). The axially oriented OH-4 group of the galactopyranoside[16] was similarly α-glycosylated without difficulty (Run 10).

The glucosylation of the primary OH group of the glycosyl acceptor[17] **14**, however, lost selectivity under Condition A (Run 11). This implies that the reactive primary alcohol may react with the hypothetical intermediate **15** (ref. 18), which we consider as the reactive intermediate (Scheme 1), to form the corresponding β-glucoside in competition[19] with **7**. Nevertheless, the selectivity was increased to an acceptable level simply by doubling the amount of **7** (Run 12, Condition B); use of an excess of **7** decreased the efficiency of the reaction (Run 13). Of the additives examined under Condition B, **7** gave the best results (Runs 14–18).



Scheme 1

Scheme 1. Plausible pathway of α-glucosylation with the quaternary reagent. The β-sulfonates may rapidly change into **15** in the presence of $[Et_3NH]^+ \cdot [OTf]^-$ in dichloromethane[17,18]. The amide **7** reacts with **15** to generate the intermediate **18** that is the immediate precursor of an α-glucoside[19]. A primary alcohol may effectively compete with **7** to give a β-glucoside. The counter anion of the intermediates, which is thought to be TfO^-, is not illustrated.

The aforementioned effect of **7** on the selectivity was also observed for the glucosylation with chloride[20] **16** and **4** (Reaction *2*).

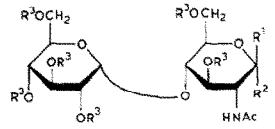
$$\mathbf{2} + \mathbf{16} \xrightarrow[CH_2Cl_2]{\mathbf{4} + \mathbf{5} + \mathbf{7}} \mathbf{8}\ (+\ \mathbf{9}) \qquad (2)$$

Thus, treatment of a mixture of the glucosyl imidate[2] **17** and **2** in

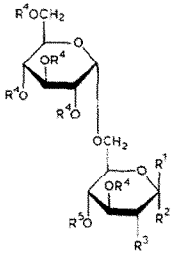
$$\mathbf{2} + \mathbf{17} \xrightarrow[CH_2Cl_2]{F_3CSO_3Me\ (\mathbf{23})} \mathbf{8} \qquad (3)$$

dichloromethane with methyl trifluoromethanesulfonate (**23**) gave **8** exclusively (Reaction *3*); the reactive intermediate **18** is thought to be involved in the reaction[19]. The aforementioned formate **10** (Run 2) appears to be formed through hydrolysis of the unreacted, less reactive intermediate having the α configuration (**19**). The intermediate **19** seems more reactive than the intermediate **20**, which may have been formed during Run 4.

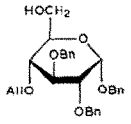
The quaternary reagents was then applied to the acceptors **21** (refs. 21, 22) and **22** (refs. 21, 23) having a 2-acetamido-2-deoxy group. In the glucosylation of OH-6 of **22**, **7** showed an apparent effect for α selectivity (Run 22). In the glucosylation of **21**, an adequate α selectivity was attained, even with the ternary reagent (Run 20). It is notable that the addition of **7** improved the yield of glucosides for **21** as well as **22**; **7** seems to prevent **15** to react with the acetamido group[24] of **21**



24 R^1 = OBn, R^2 = H, R^3 = Bn
25 R^1, R^2 = H,OH, R^3 = H



26 R^1 = H, R^2 = OBn, R^3 = NHAc, R^4 = R^5 = Bn
27 R^1, R^2 = H,OH, R^3 = NHAc, R^4 = R^5 = H
28 R^1 = H, R^2 = OBn, R^3 = OBn, R^4 = Bn, R^5 = All
29 R^1 = H, R^2 = OMe, R^3 = OBn, R^4 = R^5 = Bn



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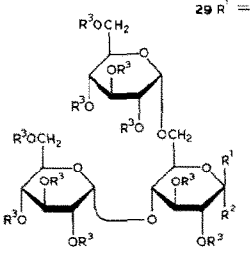
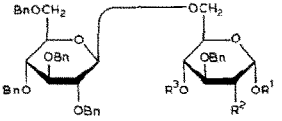
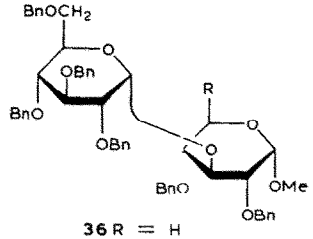


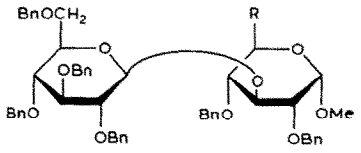
31 R^1 = H, R^2 = OBn, R^3 = Bn
32 R^1, R^2 = H,OH, R^3 = H



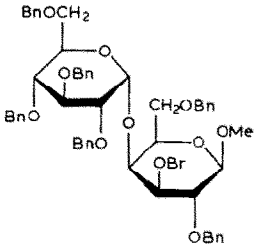
33 R^1 = Bn, R^2 = NHAc, R^3 = Bn
34 R^1 = Bn, R^2 = OBn, R^3 = All
35 R^1 = Me, R^2 = OBn, R^3 = Bn



36 R = H
37 R = CH_2OBn



38 R = H
39 R = CH_2OBn



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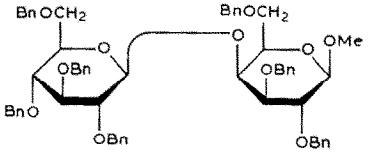

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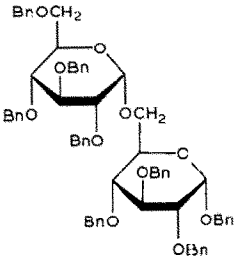

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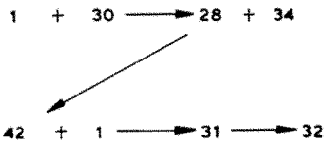

All = $CH_2—CH=CH_2$
Bn = Benzyl

and **22** to form a less reactive intermediate, such as **20**. Catalytic hydrogenation of the resulting **24** and **26** smoothly gave **25** and **27**, respectively.

The quaternary reagent was used for a new step-by-step synthesis of the branched trisaccharide **32**. The key compound[25] **30** was condensed with **1** in the presence of the quaternary reagent under Condition B (Run 23). After chromatography, the isomaltose derivative **28** was obtained in a 51% yield. After deallylation[26], the second coupling reaction of **42** with **1** by the quaternary reagent under Condition A (Run 24) gave the trisaccharide derivative **31** in a 62% yield with almost complete stereoselectivity; further catalytic debenzylation gave trisaccharide **32**. The ^{13}C-n.m.r. spectra of the debenzylated products **25**, **27**, and **32** were consistent with the structures proposed. Thus, the quaternary reagent is useful for the α-glucosylation using **1**, especially that of rather less reactive secondary alcohol groups.

EXPERIMENTAL

General. — Melting points were determined with an MP-1 melting-point apparatus (Yanagimoto); they are uncorrected. Specific rotations were measured, for solution in a jacketed 1-dm cell, with a DIP-180 automatic polarimeter (Japan Spectroscopic) at 20°. ^{1}H-N.m.r. data were recorded with a Varian S-60T spectrometer, and ^{13}C-n.m.r. data with a JEOL-PS-100 spectrometer linked to a JEOL-EC-100 computer. Column chromatography was carried out on silica gel (Kanto Kagaku); each fraction was examined by t.l.c. on silica gel (Merck, No. 7731).

Compound **2** was prepared as reported earlier[12]; m.p. 72–73°, $[\alpha]_D^{20}$ −17° (*c* 1.8, chloroform).

Anal. Calc. for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.03; H, 6.91.

Compounds **8** and **9** were identified by comparison with samples prepared by methanolysis in the presence of silver carbonate and subsequent hot benzylation with benzyl chloride and potassium hydroxide of 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-[22] and -β-D-glucopyranosyl)-α-D-glucopyranosyl bromide[28]. Compounds **36** (ref. 6), **38** (ref. 6), **29** (ref. 12), and **35** (ref. 29) were identified by comparison with the samples prepared previously.

Anal. of **29**. Calc. for $C_{62}H_{66}O_{11}$: C, 75.43; H, 6.74. Found: C, 75.41; H, 6.79.

The results of the condensation reactions are reported in Table I, the physical and analytical data of the synthesized glucosides and their derivatives in Table II, and the ^{13}C-n.m.r. data of the C-1 atoms of the protected glucosides and of the C atoms of the deprotected glucosides are in Tables III and IV, respectively; all assignments are tentative.

General procedure for glycosylation. — To a mixture of a glucosyl acceptor (0.33 mmol), 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranose (**1**, recrystallized from ethyl acetate[37], 1.3 equiv.), 4-nitrobenzenesulfonyl chloride (**3**, 2.5 equiv.), silver trifluoromethanesulfonate (**4**, 2.5 equiv.), and dichloromethane (1.8 mL), *N*,*N*-dimethylacetamide (**7**), and then triethylamine (**5**, 2.5 equiv.) were successively added under stirring at −40° bath temperature. The mixture soon became milky, and the bath temperature was gradually raised for 1 h to 0°, at which temperature the mixture was well stirred overnight. The mixture was processed as described previously[4], and then chromatographed with toluene–butanone (gradient); contamination by a trace of any nitrogenous compounds in the glucosides was removed by rechromatography on silica gel in hexane–ethyl acetate. The amount of **7** was 2.5 equiv. for a secondary alcohol (Condition A) and 5.0 equiv. for a primary alcohol (Condition B).

*Isolation of 2,3,4,6-tetra-*O*-benzyl-1-*O*-formyl-*D*-glucose* (**10**). — Chromatography of the reaction mixture of Run 2 conducted in an 85-μmol scale gave **10** (4.9 mg, 8%) as the fastest-moving syrupy product; ^{1}H-n.m.r. (CCl_4, Me_4Si): δ

TABLE II

PHYSICAL AND ANALYTICAL DATA OF COMPOUNDS

Cpd.	M.p. (degree)	Optical rotation			Mol. Form.	Anal.						Lit.
		$[\alpha]_D^{20}$ (degree)	c	Solv.[a]		Calc.			Found			
						C	H	N	C	H	N	
2	148–152	+91	0.4,	W	$C_{14}H_{25}NO_{11}$	43.86	6.57	3.65	44.41	6.92	3.39	[b]
8		+32	1.0,	C	$C_{62}H_{66}O_{11}$	75.43	6.74		75.10	6.73		
9	99–100	+22	1.0,	C	$C_{62}H_{66}O_{11}$	75.43	6.74		75.13	6.69		
24		+91	1.9,	C	$C_{63}H_{67}NO_{11}$	74.61	6.66	1.38	74.66	6.64	1.29	
26	179–181	+88	0.8,	C	$C_{63}H_{67}NO_{11}$	74.61	6.66	1.38	74.80	6.54	1.25	
27	145–148	+100	0.3,	W	$C_{14}H_{25}NO_{11}$	43.86	6.57	3.65	43.24	6.57	3.32	[c]
28		+77	1.6,	C	$C_{64}H_{68}O_{11}$	75.87	6.76		75.20	6.76		
31		+82	1.7,	C	$C_{95}H_{98}O_{16}$	76.28	6.60		76.41	6.57		
32		+139	0.3,	W	$C_{18}H_{32}O_{16}$	42.86	6.39		43.10	6.27		[d]
33	220–221	+67	0.5,	C	$C_{63}H_{67}NO_{11}$	74.61	6.66	1.38	74.78	6.66	1.48	
34	93–94	+45	1.0,	C	$C_{64}H_{68}O_{11}$	75.87	6.76		75.86	6.70		
37		+54	2.0,	C	$C_{67}H_{66}O_{11}$	75.43	6.74		75.70	6.84		[e]
39		+49	0.3,	C	$C_{62}H_{66}O_{11}$	75.43	6.74		75.27	6.79		
40		+61	1.2,	C	$C_{62}H_{66}O_{11}$	75.43	6.74		75.13	6.70		
41		+26	1.0,	C	$C_{62}H_{66}O_{11}$	75.42	6.74		75.50	6.86		
42		+43	1.6,	C	$C_{61}H_{64}O_{11}$	75.29	6.63		74.95	6.77		

[a] W = H_2O, C = $CHCl_3$. [b] Ref. 30: m.p. 144.5–146°, $[\alpha]_D^{20}$ +87→ +39° (*c* 0.9, H_2O). [c] Ref. 31: $[\alpha]_D^{25}$ +94° (H_2O). [d] Ref. 10: $[\alpha]_D^{22}$ +125° (*c* 0.9, H_2O). [e] Ref. 2; $[\alpha]_D^{20}$ +54.6° (*c* 1.62, $CHCl_3$).

TABLE III

^{13}C-N M R DATA (δ) FOR THE PROTECTED GLUCOSIDES[a]

Cpd.	C-1		C-1'→3/4		C-1''→6		C-2	$COCH_3$
	α	β	α	β	α	β		
8		104.8	96.9					
9		104.9		102.7				
24	97.0		97.0				51.5	23.3
26	97.4				96.6		52.8	23.4
28	95.2				97.8			
31[b]	94.4		96.8		97.5			
33	97.2					104.0	52.5	23.4
34	95.5					104.1		
37	97.6		97.8					
39	98.0			102.8				
40		105.4	100.2					
41		105.2		103.0				
42	95.2		97.8					

[a] At 25.1 MHz, for a solution in $CDCl_3$; signals relative to that of Me_4Si. [b] Ref. 32; δ 96.0 (C-1), 96.7 (C-1'), and 97.0 (C-1'') were assigned for a compound having a structure similar to that of **31**.

TABLE IV

^{13}C-N.M R DATA (δ) FOR GLUCOSIDES **25**, **27**, AND **32**[a]

C atom	**25**	**27**	**32**
1α	92.0	92.4	93.2
1β	96.1	96.5	97.1
2α	55.2	55.4	72.5
2β	57.9	58.0	74.7
3α	72.5	72.4	74.1
3β	75.6	75.5	75.2
4α	79.0	71.0	79.6
4β	78.3	71.0	79.2
5α	71.5	71.4	70.3
5β	77.3	77.2	77.3
6α	61.9	67.2	68.1
6β	61.9	67.2	68.1
1′	{ α101.2 β100.9		101.1
2′	74.1		74.2
3′	74.2		74.2
4′	70.7		70.8
5′	{ α 73.1 β 73.0		73.1
6′	61.9		61.8
1″		99.4	99.9
2″		72.9	72.8
3″		74.4	74.2
4″		71.0	70.7
5″		73.2	73.1
6″		61.9	61.7

[a]At 25.1 MHz, for a solution in D_2O; signals relative to that of Me_4Si (external). The assignments are based on those for 2-acetamido-2-deoxy-D-glucose[33], maltose[34–36], and isomaltose[34,36].

6.37 (d, 1 H, *J* 3 Hz, H-1) and 8.03 (s, 1 H, HCO); ^{13}C-n.m.r. ($CDCl_3$, Me_4Si): δ 94.0 (1 C, C-1) and 159.3 (1 C, CO).

α-Glucosylation with 2,3,4,6-tetra-O-benzyl-D-glucopyranosyl chloride[20] (**16**). — To a stirred mixture of **2** (36 mg, 0.078 mmol), **16** [prepared from **1** (54 mg) with an excess of cold thionyl chloride], and **4** (49.5 mg) in dichloromethane (0.42 mL), **7** (18 μL), and then **7** (27 μL) were added at −40°. Then, the bath temperature was adjusted and the time programmed as described earlier. The mixture was processed and chromatographed to give **8** (54.3 mg, 71%) and **9** (11.2 mg, 15%). Without addition of **7**, **8** and **9** were obtained in amounts of 34.1 mg (45%) and 41.2 mg (54%), respectively.

α-Glycosylation with 2,3,4,6-tetra-O-benzyl-1-O-(N-methylacetamidoyl)-β-D-glucopyranose[2] (**17**). — To a solution of **2** (37 mg, 80 μmol) and **17** (47 mg, 1.0 equiv.) in dichloromethane (0.5 mL), was added methyl trifluoromethanesulfonate (**21**, Aldrich, 9 μL, 1.0 equiv.) at −40°. The conditions of reaction and processing were as described earlier to give **8** (28.3 mg, 36%); no trace of the β anomer was isolated.

O-α-D-*Glucopyranosyl-(1→4)*-O-[α-D-*glucopyranosyl-(1→6)*]-D-*glucopyranose* (**32**). — The acceptor benzyl 4-*O*-allyl-2,3-di-*O*-benzyl-α-D-glucopyranoside (**30**, 343 mg, 0.70 mmol) was coupled with **1** under Condition B (Run 23). The faster-moving (on t.l.c.), major product (**28**, 288 mg, 0.28 mmol) was heated at reflux in a mixture of ethanol (7 mL), benzene (3 mL), and water (1 mL) containing chlorotris(triphenylphosphine)rhodium(I) (52.6 mg) for 7 h. After evaporation, the residue was heated at reflux in acetone (15 mL) containing M hydrogen chloride (0.6 mL). After evaporation, chromatography gave benzyl 2,3-di-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**42**, 248 mg, 90%). This (202 mg, 0.21 mmol) was successively coupled with **1** under Condition A (Run 24). Chromatography gave the fully benzylated trisaccharide **31** (194 mg, 62%); no trace of the β anomer was observed. This compound (118.3 mg, 80 μmol) was hydrogenated twice in acetic acid (7 mL) containing palladium-on-carbon (10%, 64 mg) in a Parr-3911 hydrogenation apparatus (340 kPa of hydrogen), followed by chromatography on silica gel in chloroform–methanol (gradient), to give **32** as a foam (18.8 mg, 47%).

Methyl 2,4,6-tri-O-benzyl-α-D-glucopyranoside (**12**). — The following procedure was more convenient, but the yield and selectivity were lower, than the previous one[15], especially for a large-scale preparation. A mixture of methyl α-D-glucopyranoside (7.5 g, 39 mmol), crushed potassium hydroxide (8.7 g), and benzyl chloride (150 mL) was vigorously stirred at 100° for 2.5 h. After processing, chromatography (silica gel, 120 g; toluene–butanone gradient) gave ~9 g (~50%) of **12**, which contained a trace amount of the 2,3,6-tribenzyl ether. After acetylation with acetic anhydride and pyridine, a similar chromatography gave the 3-acetate of **12**, which was obtained as the slower-moving material[12]. Quantitative deacetylation with methanolic sodium methoxide afforded **12**.

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