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Note

Stereoselective and mild method for the synthesis of *C*-D-glucosylarenes in high yield*

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2,3,4,6-Tetra-*O*-benzyl-1-*O*-trifluoroacetyl-α-D-glucopyranose (**1**) is shown to react smoothly with aryl ethers in the presence of a Lewis acid in dichloromethane at room temperature to afford *C*-D-glucosylarenes with high stereoselectivity and in very high yield.

Much attention has been focused on the stereoselective synthesis of *C*-glycosyl compounds, not only for the preparation of naturally occurring examples[1b], but also for the homologation of sugars to serve as chiral templates for more-complex synthetic targets[2]. For this purpose, it is important to select both the leaving group at the anomeric position and the activator in the alkylation. Many reports on the synthesis of 1-allyl 1-*C*-glycosyl derivatives have appeared recently[3–5], but only Schmidt *et al.*[6] and Williams *et al.*[7], using *O*-glycosyl-trichloroacetimidates and pyridyl thioglycosides, respectively, have synthesized *C*-glycosylarenes stereoselectively. We have found that D-glucosyl 4-nitrobenzoate[8] and 3,5-dinitrobenzoate[1a] react with aryl ethers to give *C*-β-D-glucosylarenes in most cases. We now report a highly stereoselective and mild method for the synthesis of *C*-D-glucosylarenes from **1** in high yields.

RESULTS AND DISCUSSION

Compound **1** reacted with aryl ethers to afford generally the β anomers. The yield of *C*-D-glucosylarene depended on the reactivity of the aryl ether and the Lewis acid. The best catalyst was $BF_3 \cdot Et_2O$, but anhydrous $AlCl_3$ gave a low yield because HCl in $AlCl_3$ cleaves the benzyl groups in **1** giving many by-products. Anhydrous $ZnBr_2$ is a weak Lewis acid and the yields were very low, even at extended reaction-times. Interestingly, when **1** reacted with 1,3-bis(trimethylsilyl)oxybenzene in the presence of $BF_3 \cdot Et_2O$, the α anomer was the only product,

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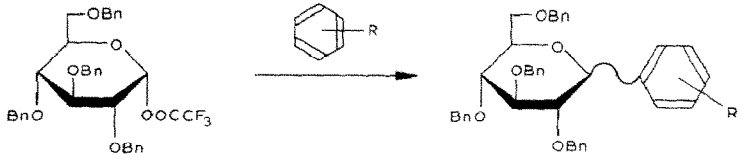
TABLE I

C-D-GLUCOSYLARENES FROM TETRA-*O*-BENZYL-α-D-GLUCOSYL TRIFLUOROACETATE (**1**)

Aryl ethers	*Lewis acid*	*Reaction conditions (~25°)*	*C-D-Glucosyl-arene*	*Yield (%)*	*Ratio of anomers (α:β)*
R = 1,3,5-$(MeO)_3$	$BF_3 \cdot Et_2O$	CH_2Cl_2, 5 min	R = 2,4,6-$(MeO)_3$	99	0:1
	$AlCl_3$	CH_2Cl_2, 5 min		91	0:1
	$ZnBr_2$	CH_2Cl_2, 5 min	(**3**)	61	0:1
R = 1,3-$(MeO)_2$	$BF_3 \cdot Et_2O$	CH_2Cl_2, 5 min	R = 2,4-$(MeO)_2$ (**4**)	81	0:1
Anisole	$BF_3 \cdot Et_2O$	CH_2Cl_2, 5 min	R = 4-MeO (**5,6**)	86	1:4
R = 1,3-$(Me_3SiO)_2$	BF_3Et_2O	CH_2Cl_2, 5 min	R = 2,4-$(OH)_2$	95	1:0
	$AlCl_3$	CH_2Cl_2, 5 min		85	1:2.3
	$ZnBr_2$	CH_2Cl_2, 15 min	(**7,8**)	67	0:1



1 2–8

and if anhydrous $AlCl_3$ or $ZnBr_2$ was used, an α,β mixture was obtained in which the β anomer preponderated. Anisole also gave a 1:4 α,β anomeric mixture.

In the synthesis of allyl *C*-glycosyl compounds, the α anomer is always the main product. The allyl group is rather small and the difference in stability between the α and β anomers is very small. Consequently, the oxocarbonian ion derived from **1** by the SN1 mechanism should preferentially accept nucleophiles from the α (axial) side through operation of the anomeric effect[9]. In the case of *C*-glucosylarenes, the β anomer is much more stable than the α anomer, and it may be supposed that the stability of the *C*-glucosylarene controls the stereochemistry of the reaction rather than the anomeric effect, as in the *C*-glucosylation of 1,3,5-trimethoxybenzene, 1,3-dimethoxybenzene and anisole. If the aryl ether group is large, as with 1,3-di(trimethylsilyloxy)benzene, it becomes difficult for it to approach C-1 of the oxocarbonium ion and so the anomeric effect again controls the reaction pathway. In this instance, the α anomer is obtained instead of the β anomer, as shown by Schmidt *et al.*[6] when D-glucosyl trichloroacetimidate was treated with the same nucleophile. We have also found 1,3-di(trimethylsilyloxy)-benzene reacted with **1** using anhydrous $AlCl_3$ or $ZnBr_2$ as the catalyst to give an anomeric mixture in which the β anomer preponderated.

The determination of the configuration of benzylated *C*-glycosylarenes is very difficult, and Schmidt *et al.*[6] assigned the configuration of compounds **3, 4** and **8** after debenzylation. We found by using ^1H–^1H shift-correlation spectra that the two benzylic protons of compounds **5** and **6** were not equivalent and coupled each

other to give two doublets. In addition to these doublets, there was another doublet which coupled with a quartet (J 4.8 Hz, H-1′ and H-2′ of the α anomer) and a triplet (J 10 Hz, H-1′ and H-2′ of the β anomer). The ^{13}C-n.m.r. chemical shifts of compound **6** were readily assigned by ^{1}H–^{13}C shift-correlation spectroscopy and following the usual sequence of ^{13}C-n.m.r. chemical shifts of sugar-ring carbons of glucopyranosides. After studying the ^{13}C-n.m.r. spectra of several pairs of benzylated *C*-glucosylarenes, we found that the chemical shifts ($\delta_{C'}$) of the corresponding carbon atoms of the sugar ring in the β anomers were almost the same and shifts for the α anomers were similar to those of the β anomers. If there were *ortho*-substituted groups in the aglycon, $\delta_{C\text{-}1'}$ and $\delta_{C\text{-}2'}$ of the α and β anomers became small. However, the difference of $\delta_{C'}$ for the corresponding carbon atoms of the sugar ring, between the α and β anomers, was very obvious. The $\delta_{C'}$ values of the β anomers were 3–6 p.p.m. larger than those of the α anomers. This pattern may also be seen in the *O*-glucopyranosides and used to determine the configuration of benzylated *C*-D-glucopyranosylarenes[10]; see Table II.

EXPERIMENTAL

General methods. — M.p.s are uncorrected. Spectra were recorded with the following instruments; ^{1}H-n.m.r., Varian XL-300 (300 MHz) and Varian 400 (400 MHz); ^{1}H–^{1}H and ^{1}H–^{13}C shift-correlation spectra, Varian 400; ^{13}C-n.m.r., JEOL JMN-FX 100 (100 MHz); mass spectra, VG 20-250 g.l.c.–m.s., and VG ZAB GC g.l.c.–m.s. The ^{1}H-n.m.r. spectra were recorded with Me_4Si as the internal standard and ^{13}C-n.m.r. with Me_2SO-d_6 as solvent and internal standard (39.6 p.p.m.). Preparative t.l.c. was performed on silica gel (10–40 μm).

2,3,4,6-Tetra-O-benzyl-1-O-trifluoroacetyl-α-D-glucopyranose (**1**). — A mixture of 0.5 g (0.93 mmol) of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose[11], 0.15 g of CF_3CO_2Na and 3 mL of $(CF_3CO)_2O$ was heated to reflux for 30 min with stirring. After cooling, the mixture was diluted with CH_2Cl_2 (10 mL), and then filtered through silica gel (60–80 μm). The silica gel was washed with CH_2Cl_2 (2 × 10 mL), and the combined organic solution was concentrated *in vacuo* to give **1** (0.65 g, 100%) as a colorless syrup; ^{1}H-n.m.r. (300 MHz, $CDCl_3$): δ 6.45 (d, 1 H, J 3.4 Hz,

TABLE II

^{13}C-N.M.R. CHEMICAL SHIFTS (δ) OF SUGAR RING CARBONS OF *C*-D-GLUCOSYLARENES

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
3	75.2	78.7	86.5	78.2	80.2	69.1
4	74.3	78.8	86.2	78.0	83.2	68.9
5	77.8	72.4	80.5	72.2	80.0	69.9
6	80.0	78.4	85.8	78.3	83.4	69.9
7	73.8	77.5	81.2	74.0	79.4	68.9
8	74.8	78.4	86.9	78.4	82.6	69.4

H-1), 3.60–5.50 (m, 15 H, sugar-ring protons and benzylic CH_2), and 7.10–7.60 (m, aryl protons). This compound was not purified further and used directly in the following reaction.

C-Glucosylarenes (general method). — Two drops of $BF_3 \cdot Et_2O$ (or 10 mg of anhydrous $AlCl_3$ or 10 mg of anhydrous $ZnBr_2$) was added to a mixture of 58.5 mg (0.093 mmol) of **1** and 0.186 mmol of aryl ether in 2 mL of CH_2Cl_2 with stirring at room temperature under nitrogen. After 5 min (or 15 min for anhydrous $ZnBr_2$), 10 mL of 20% HCl was added and the mixture was extracted with ether. The extract was dried ($MgSO_4$) and evaporated *in vacuo* to give the crude product, which was purified by preparative t.l.c. using the following eluents: *A*, 7:3 cyclohexane–ether; or *B*, 4:1 cyclohexane–EtOAc.

*1-(2,3,4,6-Tetra-*O*-benzyl-β-*D*-glucopyranosyl)-2,4,6-trimethoxybenzene*[6] (**3**). — The crude product was purified by preparative t.l.c. (eluent *A*) to give a yellow suryp; $[\alpha]_D^{25}$ +1.0° (*c* 8.0, Me_2CO); ^{1}H-n.m.r. (300 MHz, Me_2SO-d_6): δ 3.75, 3.78, 3.79 (3s, 3 × 3 H, 3 OCH_3), 4.02 (d, 1 H, *J* 12 Hz, H-1′), 3.40–5.00 (m, 15 H, sugar-ring protons and benzylic CH_2), 6.25, 6.28 (2s, 2 H, H-3,5), and 6.80–7.50 (m, 20 H, aryl protons).

*2,4-Dimethoxy-1-(2,3,4,6-tetra-*O*-benzyl-β-*D*-glucopyranosyl)benzene*[6] (**4**). — From the preparative t.l.c. (eluent *A*), the product was obtained as a yellow syrup, $[\alpha]_D^{25}$ +25.9° (*c* 1.4, Me_2CO); ^{1}H-n.m.r. (300 MHz, Me_2SO-d_6): δ 3.75, 3.78 (2s, 2 × 3 H, 2 OCH_3), 4.00 (d, 1 H, *J* 10 Hz, H-1′), 3.50–5.00 (m, 15 H, sugar-ring protons and benzylic CH_2), and 6.50–7.50 (m, 23 H, aryl protons).

*4-Methoxy-1-(2,3,4,6-tetra-*O*-benzyl-α-*D*-glucopyranosyl)benzene* (**5**). — This was obtained by preparative t.l.c. (eluent *A*), as a yellow syrup, $[\alpha]_D^{25}$ +16.0° (*c* 2.0, Me_2CO); ^{1}H-n.m.r. (400 MHz, Me_2SO-d_6): δ 3.78 (s, 3 H, OCH_3), 5.16 (d, 1 H, *J* 4.8 Hz, H-1′), 3.90 (q, 1 H, *J* 4.8 Hz, H-2′), 3.00–5.00 (m, 15 H, sugar-ring protons and benzylic CH_2), and 6.90–7.60 (m, 24 H, aryl protons); *m/z* (e.i.): 630.2963 (M^+).

Anal. Calc. for $C_{41}H_{42}O_6$: C, 78.07; H, 6.72. Found: C, 77.82; H, 6.69.

*4-Methoxy-1-(2,3,4,6-tetra-*O*-benzyl-β-*D*-glucopyranosyl)benzene* (**6**). — This was obtained by preparative t.l.c. (eluent *A*) as colorless crystals, m.p. 108.5–109.0°, $[\alpha]_D^{25}$ −5.3° (*c* 0.8, Me_2CO): ^{1}H-n.m.r. (400 MHz, Me_2SO-d_6): δ 3.75 (s, 3 H, OCH_3), 4.42 (d, 1 H, *J* 10 Hz, H-1′), 3.50 (t, 1 H, *J* 10 Hz, H-2′), 3.50–5.50 (m, 15 H, sugar-ring protons and benzylic CH_2), and 6.50–3.50 (m, 24 H, aryl protons).

Anal. Calc. for $C_{41}H_{42}O_6$: C, 78.07; H, 6.72. Found: C, 78.26; H, 6.89.

*2,4-Dihydroxy-1-(2,3,4,6-tetra-*O*-benzyl-α-*D*-glucopyranosyl)benzene* (**7**). — This was obtained by preparative t.l.c. (eluent *B*) as a yellow syrup, $[\alpha]_D^{25}$ +53.0° (*c* 1.4, Me_2CO); ^{1}H-n.m.r. (300 MHz, Me_2SO-d_6: δ 5.70 (d, 1 H, *J* 4.0 Hz, H-1′), 3.50–5.00 (m, 15 H, sugar-ring protons and benzylic CH_2), and 6.50–7.50 (m, 23 H, aryl protons); *m/z* (e.i.): 632.2776 (M^+).

Anal. Calc. for $C_{40}H_{40}O_7$: C, 75.93; H, 6.37. Found: C, 75.74; H, 6.33.

*2,4-Dihydroxy-1-(2,3,4,6-tetra-*O*-benzyl-β-*D*-glucopyranosyl)benzene*[6] (**8**). — This was obtained by preparative t.l.c. (eluent *B*) as colorless crystals, m.p. 141.5–

142.0°, $[\alpha]_D^{25}$ −15.5° (*c* 0.9, Me_2CO); ^{1}H-n.m.r. (300 MHz, Me_2SO-d_6): δ 4.28 (d, 1 H, *J* 9.0 Hz, H-1′), 3.50–5.00 (m, 15 H, sugar-ring protons and benzylic CH_2), and 6.30–7.50 (m, 23 H, aryl protons).

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