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Note

On the stereochemical control of glycosylation reactions by the addition of tetrahydrofuran*

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Acetylated glycopyranosyl bromides in which the substituents at positions 1 and 2 are *cis* (1,2-*cis*-bromides) (*e.g.* **1**) react with an alcohol in the presence of certain silver salts in ether by a concerted push-pull mechanism[2,3], to yield glycosides (*e.g.* **2**) in which the substituents at positions 1 and 2 are *trans* (1,2-*trans*-glycosides). If this reaction is performed in tetrahydrofuran instead of ether, the corresponding 1,2-(ortho esters) (*e.g.* **5**) are formed[1,4] *via* oxonium ions[1] (*e.g.* **3**).

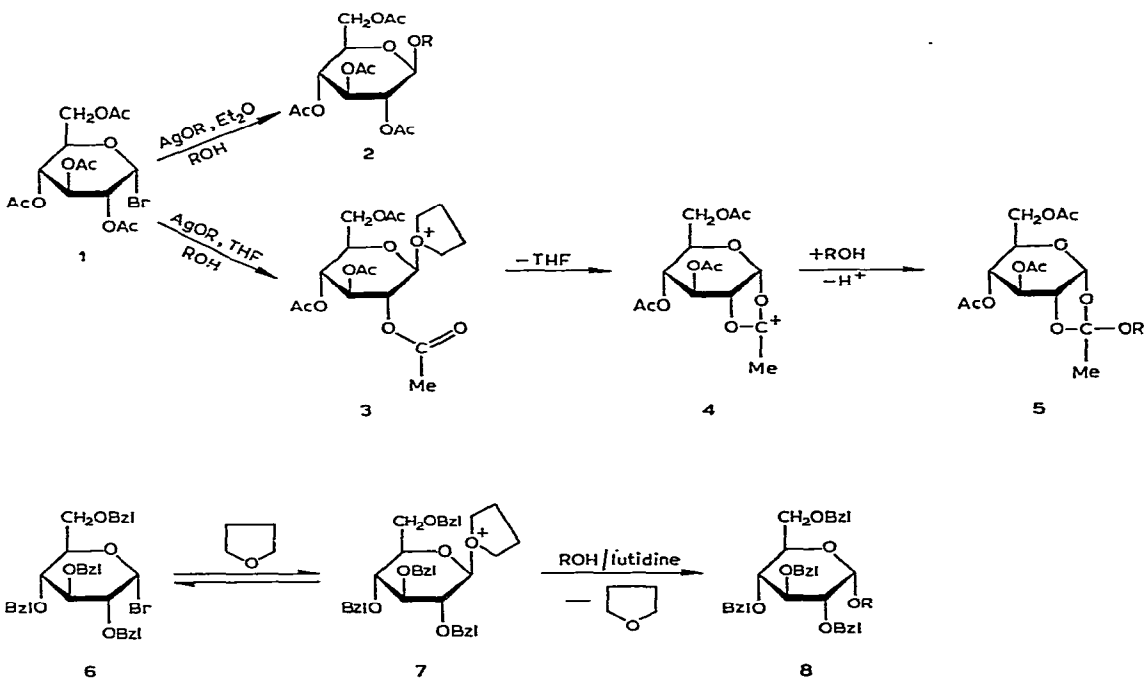

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TABLE I

GLYCOSYLATION OF METHANOL

Solvent[a]	*Mol. Ratio* **6**-*MeOH*	*Mol. Ratio THF–MeOH*	*Acid acceptor*	*Analytical method for αβ-ratio*	*Yield of glycosides (%)*	*αβ-Ratio*
CH_2Cl_2	1:300	—	Ag_2CO_3	H.p.l.c.	78	2:98
CH_2Cl_2–THF[b] (2:1)	1:300	2:1	Ag_2CO_3	H.p.l.c.	78.4	21.8:78.2
CH_2Cl_2–THF (2:1)	1:12	8:1	Ag_2CO_3	H.p.l.c.	35.1	28.8:71.2
CH_3CN	1:12	—	$Hg(CN)_2$, $HgBr_2$	T.l.c.[c]	~90	~20:80
CH_3CN–THF (2:1)	1:12	5:1	$Hg(CN)_2$, $HgBr_2$	T.l.c.[c]	~90	~40:60
CH_2Cl_2	1:300	—	2,6-Lutidine	H.p.l.c.	95	21.5:78.5
CH_2Cl_2–THF (2:1)	1:300	2.5:1	2,6-Lutidine	G.l.c.	~95	78.1:21.9
CH_2Cl_2–THF (2:1)	1:12	5:1	2,6-Lutidine	G.l.c.	~95	89.5:10.5
Et_2O–THF (2:1)	1:12	5:1	2,6-Lutidine	T.l.c.[c]	~95	~90:10
THF	1:12	>100:1	2,6-Lutidine	T.l.c.[c]	~95	~90:10

[a]Volume ratios given in parentheses. [b]Tetrahydrofuran. [c]Estimated visually after conventional detection.

TABLE II

GLYCOSYLATION OF CHOLESTEROL

Solvent[a]	*Mol. ratio 6–cholesterol*	*Acid acceptor*	*Reaction time (h)*	*Analytical method for αβ-ratio*	*Yield of glycosides (%)*	*αβ-Ratio*
CH_2Cl_2	10:6	Ag_2CO_3	12	T.l.c.[c]	12.2	~ 2:98
CH_2Cl_2–THF[b] (2:1)	1:1	Ag_2CO_3	12	T.l.c.[c]	11.8	~50:50
CH_2Cl_2–THF (2:1)	1:1	2,6-Lutidine	48	H.p.l.c.	21.8	91.9:8.1
CH_2Cl_2–THF (2:1)	1:1	2,6-Lutidine	192	C.c.[d]	23	92:8
CH_2Cl_2–THF (2:1)	6:1	2,6-Lutidine	48	T.l.c.[c]	61.8	~92:8
CH_2Cl_2–THF (2:1)	1:1	"Proton sponge"	48	C.c.	14.3	89:11
CH_2Cl_2–THF (2:1)	1:1	CF_3CO_2Ag + 2,6-lutidine	2	C.c.	5	40:60

[a]Volume ratio in parentheses. [b]Tetrahydrofuran. [c]Estimated visually. [d]Column chromatography.

We now report on the behaviour of a glycosyl bromide (**6**) having a non-participating substituent at C-2.

Schuerch *et al.*[5–7] have used onium compounds, obtained from glycosyl bromides with amines, phosphines, and sulphides, for stereochemical control of glycosylation reactions. The stable onium compounds, which were isolated prior to reaction with alcohols, had low reactivity. In contrast, oxonium ions of the type **7** are highly reactive and can be prepared easily *in situ* by using tetrahydrofuran as reaction solvent. Due to the reverse anomeric effect[8], the substituent at position 1 is equatorial, and since the oxonium ions are β, they should yield α-glycosides.

2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl bromide[9] (**6**) was treated severally with methanol and cholesterol in the presence of various acid acceptors and in the presence and absence of tetrahydrofuran. The yields of glycosides and the αβ-ratios are shown in Tables I and II. Previously unknown cholesteryl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside was isolated; the α anomer has been described[10].

The reactions of **6** in dichloromethane in the presence of silver carbonate gave β-glycosides almost exclusively, which accords with earlier results[11] and supports the mechanism proposed for glycosylation reactions in the presence of insoluble silver salts[2,3]. The proportion of the α-glycosides increased (20–50%) with increase in the amount of tetrahydrofuran added. In acetonitrile with $Hg(CN)_2.HgBr_2$ (*cf.* Ref. 12), 20% of the α-glycoside was obtained; on addition of tetrahydrofuran, the proportion was increased to 40%.

In the presence of 2,6-lutidine as acid acceptor, the αβ-ratio was 21.5:78.5 for the methyl glycosides. This ratio is similar to that obtained by using mercury salts, thus indicating a similar S_N1 mechanism. On the addition of tetrahydrofuran, the αβ-ratio was increased to 9:1 for the methyl glycosides and to 92:8 for the cholesteryl analogues. Whereas the yield of methyl glycosides was quite high, an excess of **6** had to be used in order to increase the yield of cholesteryl glycosides to 61.8%.

Attempts to accelerate the reaction by adding silver trifluoroacetate or by raising the temperature led to poorer results. The use of the "proton sponge" 1,8-bis(dimethylamino)naphthalene did not improve the results.

Thus, tetrahydrofuran can markedly influence the stereochemical course of glycosylation reactions. An excess of tetrahydrofuran can compete with the alcohol to give mainly the highly reactive oxonium ion **7** which, in turn, reacts with the alcohol to yield the α-glycoside. The method, which is simple, can be used to synthesise α-glycosides of complex alcohols, and the yields are comparable to[10,13], or better than, those for other methods[14,15], but are very low in attempted disaccharide syntheses. 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl bromide also yielded α-glycosides by the same mechanism[16].

EXPERIMENTAL

The general methods used have been described elsewhere[1]. Dichloromethane was dried over Dri-Na, distilled, and stored over molecular sieve 4Å. Ether and tetrahydrofuran were dried over sodium and distilled before use. Acetonitrile was also distilled before use. Silver carbonate[17] and silver trifluoroacetate[18] were prepared according to literature procedures.

Standard reactions. — 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl bromide[9] (**6**; 2.93 g, 4.9 mmol) was dissolved in 40 ml of the solvents mentioned in Tables I and II, and 7.4 mmol of the acid acceptor and the alcohol were added under an atmosphere of dry nitrogen.

The consumption of **6** could not be followed directly by t.l.c., since the compound decomposed during chromatography. By g.l.c. (internal standard, trimethylsilylated lactose), it was shown that the reaction with methanol was complete in 2–4 h. Reaction times for cholesterol glycosylations were determined by reaction of the unreacted **6** with excess of methanol in the presence of Ag_2CO_3. The reaction mixture was fractionated by t.l.c., and the methyl glucosides were then quantified. The glycosylation of cholesterol in the presence of lutidine was slow; after 48 h, most of **6** had been consumed, but even after 194 h, traces of **6** could be detected. Reaction times longer than 50 h did not markedly improve the yields.

The work-up procedure consisted in removal of the amines by extraction with dilute HCl, or filtration of the silver salts. After evaporation of the solvent, the reaction mixture was subjected to column chromatography in order to obtain the mixture, and hence the yield, of glycosides. The αβ-ratio was determined in some cases by fractionation of the glycoside mixture on silica gel with toluene–acetone (100:7).

The following compounds were isolated.

Cholesteryl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside, m.p. 142° (from ethanol), $[\alpha]_D^{23}$ +44° (*c* 1.2, chloroform); lit.[10] m.p. 127–128°, $[\alpha]_D^{23}$ +40°. The product previously described may have contained some β anomer.

Cholesteryl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside, m.p. 96–97° (from ethanol), $[\alpha]_D^{23}$ −0.4° (*c* 1.2, chloroform).

Anal. Calc. for $C_{61}H_{80}O_6$: C, 80.57; H, 8.86. Found: C, 80.41; H, 9.01.

The ^1H- and ^{13}C-n.m.r. spectra of the α- and the β-glucoside were very similar. The β configuration was shown by the ^{13}C signal for C-1 at 102.3 p.p.m., whereas the α compound showed the corresponding signal at 94.7 p.p.m. ($CDCl_3$, Bruker WH 90 spectrometer).

Methyl 2,3,4,6-tetra-*O*-benzyl-α- and -β-D-glucopyranoside were prepared as described by Iwashige and Saeki[19].

Determination of αβ-ratios. — (*a*) *H.p.l.c.* The high-pressure liquid chromatography system consisted of a Waters HPLC-pump, model 6000, and u.v. detector (Altex Analytical UV Detector) or differential refractometer (Waters R 401). A column (61 cm × 2 mm) of Corasil II (30–50 μm) (Waters) was used. The methyl glucoside mixtures were fractionated by using toluene–acetone (100:1) at 1 ml/min; the retention times were 3.65 (β) and 4.95 min (α). Mixtures of cholesteryl glucosides were fractionated with hexane–ethyl acetate (100:1.5) at 1 ml/min; the retention times were 31.0 (β) and 49.5 min (α).

(*b*) *G.l.c.* A Pye 104 gas chromatograph was used with a glass column (2 m × 4 mm) of 2% of OV-101 on Chromosorb W HP (80–100 mesh) and a temperature program 100° → 300° at 4°/min. Retention times for the methyl glucosides were 23.44 (β) and 26.2 min (α) at a nitrogen flow-rate of 30 ml/min.

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