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STEREOSELECTIVE SYNTHESIS OF α-D-GLUCOPYRANOSIDES VIA 6-SILYL-α-D-GLUCOPYRANOSYL BROMIDES

C. P. Fei and T. H. Chan*

Department of Chemistry, McGill University,

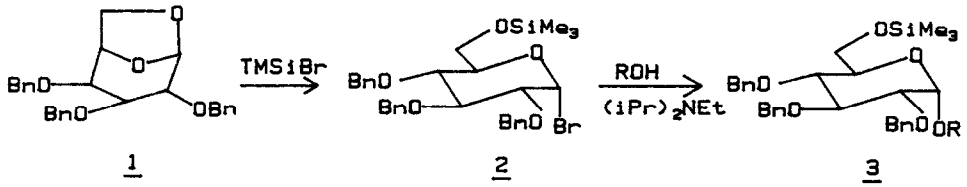
Montreal, Quebec, Canada. H3A 2K6.

ABSTRACT: Bromotrimethylsilane cleaved 2,3,4-tri-O-benzyl-1,6-anhydro-β-D-glucopyranose (1) to give 2,3,4-tri-O-benzyl-6-O-trimethylsilyl- α-D-glucopyranosyl bromide (2). Reaction of 2 with ROH/diisopropylethylamine gave the corresponding α-glucopyranosides.

One of the problems in the synthesis of complex oligosaccharides is the stereoselective formation of the glycosidic linkage.[1] In the D-gluco series, the synthesis usually starts from the α-D-glucopyranosyl halides. The β-anomer is prepared by taking advantage of the neighboring group assisted procedure with an acyl-substituent at the C-2 position.[2] The synthesis of the α-anomer is more demanding. It is necessary to choose a starting α-D-pyranosyl halide with a non-neighboring group active substituent at C-2. An *in situ* anomerisation procedure[3] is then employed to cause an equilibration between the α- and the β-D-glycopyranosyl halide followed by a faster substitution reaction at the less stable β-D-halide. We wish to report here a procedure for the stereoselective synthesis of α-D-glucopyranosides which appears to rely on the neighboring group participation of a siloxy group at C-6.

While bromotrimethylsilane reacts with 2-methoxytetrahydropyran to give the corresponding 2-pyranosyl bromide,[4] it is unreactive towards the fully protected methyl D-glucopyranoside.[5] We reasoned that a strained ether linkage at the anomeric centre may be more susceptible to cleavage.[6] Indeed, bromotrimethylsilane cleaved 2,3,4-tri-O-benzyl-1,6-anhydro-β-D-glucopyranose (1) cleanly to give 2, 3, 4-tri-O-benzyl-6-O-trimethylsilyl-α-D-glucopyranosyl bromide (2).

While compound 2 could be isolated[7] if necessary, the synthesis of glycosides can be performed more easily by adding the appropriate ROH with diisopropylethylamine to a solution of 2 generated *in situ* (Scheme 1).[8]



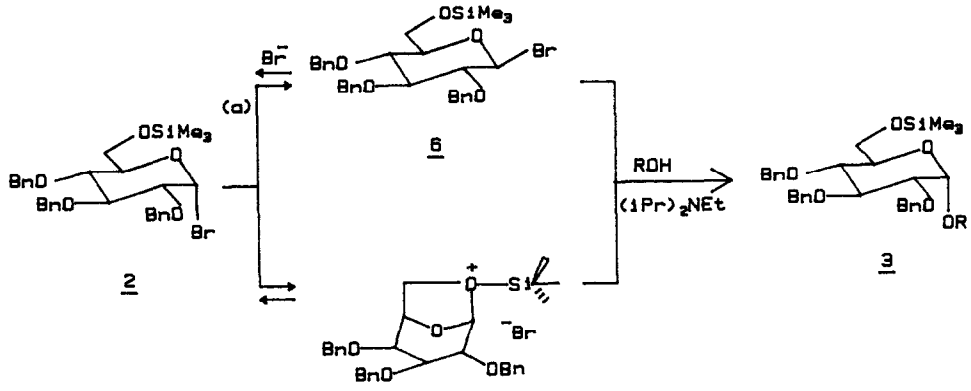
1 2 3

SCHEME 1

The glucopyranoside 3 isolated has predominantly the α-stereochemistry at the anomeric centre (Table). In addition to the simple alcohols, β-trimethylsilylethanol can also replace the bromide to give the corresponding glucopyranoside with exclusive α-stereochemistry. One advantage of the reaction is that the trimethylsilyl protecting group at the 6-OH position can be unmasked readily. Thus, compound 4 was obtained by treatment of 3 (R=CH_3) with methanol. Coupling of 4 with 2 under similar reaction conditions gave the disaccharide 5 with α-stereochemistry at the new glycosidic linkage.

Bromotriethylsilane also cleaved the anhydro ether linkage in 1 to give the 6-O-triethylsilyl derivative of 2. The reaction was much slower and the α-glucopyranosyl bromide was formed in about 30% yield even after 15 days at 35-40°. Nevertheless, coupling of the glucopyranosyl bromide with methanol/diiso- propylethylamine gave the methyl 2,3,4-tri-O-benzyl-6-O-triethylsilyl-α-D-glucopyranoside with no indication of the β-anomer.

We attribute the α-stereoselectivity in the formation of the glycosidic linkage not to an anomerization of the α-glucopyranosyl bromide to the β-bromide (6, scheme 2, path a)[3] but to the intervention of the intermediate 7 (scheme 2, path b) by neighboring group participation of the 6-siloxy group.[8] This is based on the following observations. (1) The use of ammonium bromide salt to cause equilibration of the α-and β-bromides (2 6) was not necessary in the present synthesis.(2) When methanol was reacted with 2 without the use of diisopropylethylamine, the α-anomer of methyl D-glucopyranoside was formed predominantly as well.



SCHEME 2

(3) Furthermore, when diisopropylethylamine alone was used without the presence of nucleophile, the anhydroglucose 1 could be obtained from 2. Evidently, 2 exists in equilibrium with 7, and nucleophillic opening of the bicyclic structure 7 to give 3 occurs preferentially with α-stereoselectivity. We are exploring the application of this approach to the synthesis of other α-glycosides.

Acknowledgement: We thank NSERC and FCAR for financial support of this work.

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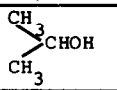
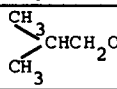
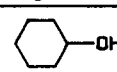
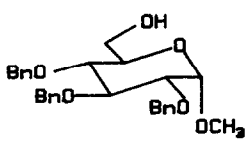
6. J. Thiem and B. Meyer, Chem. Ber., 113:3075(1980).

7. Physical properties of 2: ^{1}H NMR: H_1: 6.46 ppm(d,J=3.8Hz); ^{13}C nmr: C_1:92.1; C_2:79.9; C_3:82.2; C_4:76.4; C_5:72.8: C_6:60.8; C-Si:-0.3; $[\alpha]_D^{22}$=+89.5° ($CHCl_3$, C=1.6).

8. Typical procedure: To 108 mg. (0.25 mmoli) of 1 dissolved in 0.15 ml of $CHCl_3$ was added 306 mg. (2.0 mmol) of bromotrimethylsilane. The reaction was left in the dark at room temperature for 7 days. Solvent and excess reagent was removed in vacuo, Compound 2 so obtained was redissolved in 0.4 ml of $CHCl_3$ and 0.1 ml of diisopropylethylamine. Then 0.5 mmol of ROH was added and allowed to react for 8 hrs at rt. The product was isolated by flash chemotography on silica gel with 4:1 hexane/ethylacetate as eluent.

9. The influence of the 6-substituent on the stereoselectivity of the glycosidic linkage formation was noted previously. J. M. Frechet and C. Schuerch. J. Amer. Chem. Soc., 94:604(1972).

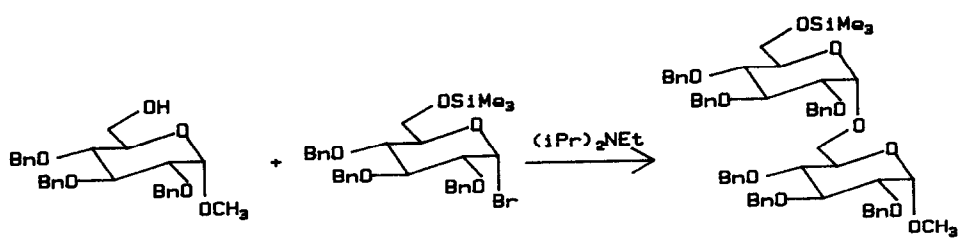
TABLE: Formation of α-D-glucopyaniosides 3 according to Scheme 1

ROH=	Yield % (isolated)	Optical rotation[a] of 3 $[\alpha]_D^{22}$	Anomeric ratio[b] α=β
CH_3OH	70	+ 16.1° (C=1.6,$CHCl_3$)	6:1
	61	+ 26.0° (C=0.95,$CHCl_3$)	15:1
	72	+ 36.6° (C=1.4,$CHCl_3$)	15:1
	44	+ 43.9° (C=1.3,$CHCl_3$)	no β
$Me_3SiCH_2CH_2CH_2OH$	60	+ 39.1° (C=2.7,$CHCl_3$)	no β
	43	+ 48.7° (C=1.0,$CHCl_3$)	10:1

a: Optical rotation was measured with a JASCO-DIP-140 Polarimeter.

b: Anomeric ratio was determined by ^{13}C nmr using C-1 α at 94-98 ppm and C-1 β at 102-104 ppm.

c: Ratio was determined by weight of isolated compounds.



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