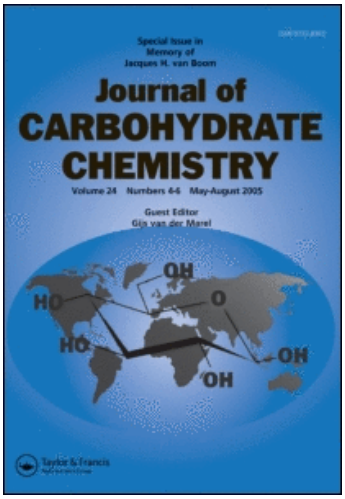

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1,6-CYCLIZATION REACTIONS OF SELECTED ALDOHEXOPYRANOSES *via* THEIR 1-*O*-TOSYL DERIVATIVES

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ABSTRACT

2,3,4,6-Tetra-*O*-acetyl-D-gluco-, D-galacto- and D-mannopyranoses were tosylated with *p*-tolenesulfonyl chloride to afford their 1-*O*-tosyl derivatives which were cyclized "in situ" in a methanolic solution of sodium methoxide. 1,6-Cyclization products were obtained only with D-glucose and D-galactose derivatives. Cyclization of derivatives of D-glucose i.e. 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl chloride, 3,4,6-tri-*O*-acetyl-1,2-anhydro-α-D-glucopyranose (Brigl's anhydride) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide enabled the estimation of the influence of configuration at C-1 and C-2 on the course of cyclization. All product mixtures were separated by capillary gas chromatography (CGC) and their components were identified by coinjection with standards.

INTRODUCTION

Among anhydrohexoses, the group of 1,6-anhydroglycosans has been most extensively studied.[1] These compounds can be prepared by introduction of a leaving group at the anomeric carbon atom of an appropriate hexopyranose derivative, which initiates the 1,6-cyclization. Possible leaving groups include, *inter alia*,

trimethylammonium,[2] *O*-aryl,[3] *S*-aryl,[4] fluoride[5] and *S*-alkyl[6] ones. We decided to investigate the cyclization of 1-*O*-tosyl derivatives based on the results described by Schuerch[7] in glycoside synthesis. The course of the 1,6-cyclization reaction is controlled by the configuration at C-2; according to Lemieux, the successful outcome of the cyclization depends on the possibility of formation of an α-1,2-epoxide (e.g., the Brigl's anhydride) as an intermediate during the first step of the reaction.[8]

RESULTS AND DISCUSSION

O-Tosylation products of 2,3,4,6-tetra-*O*-acetyl-D-galacto-, D-gluco- and D-mannopyranose were treated with a methanolic solution of sodium methoxide and the products were converted into per-*O*-acetylated derivatives. The mixtures were analyzed by capillary gas chromatography and the components were identified by co-injection with standards. The relative percentages of per-*O*-acetylated 1,6-anhydrohexopyranoses and methyl glycopyranosides formed in the methanolic solution of sodium methylate were determined from CGC peaks areas. The product distributions and the retention times of the compounds mentioned above are listed in the Table.

The qualitative and quantitative estimation of products formed after cyclization indicates that 1-*O*-tosyl derivatives having the D-gluco and D-galacto configuration undergo analogous cyclization reactions while the derivatives having D-manno configuration do not cyclize. It is presumed that the configuration at C-2 influences the path of the reaction, as was suggested by Lemieux.[9,10] The 1,2-epoxide is the most probable intermediate in both the cyclization and ring-opening reactions. The transformations of the α-1,2-epoxide afford 1,6-anhydro-D-gluco- and D-galactopyranose as well as methyl β-D-gluco- and β-D-galacto-pyranosides (Scheme 1). This mechanism is supported by the results obtained for 1,2-anhydro-1-deoxy-3,4,6-tri-*O*-acetyl-β-D-glucopyranose as well as 1-chloro-1-deoxy-3,4,6-tri-*O*-acetyl-β-D-glucopyranose. In both cases, we obtained the same product distribution.

In contrast, the reaction of 1-*O*-tosyl-2,3,4,6-tetra-*O*-acetyl-D-mannopyranose with methoxide, which should proceed via the β-1,2-epoxide, affords mainly methyl α-D-mannopyranoside (Scheme 2).

TABLE

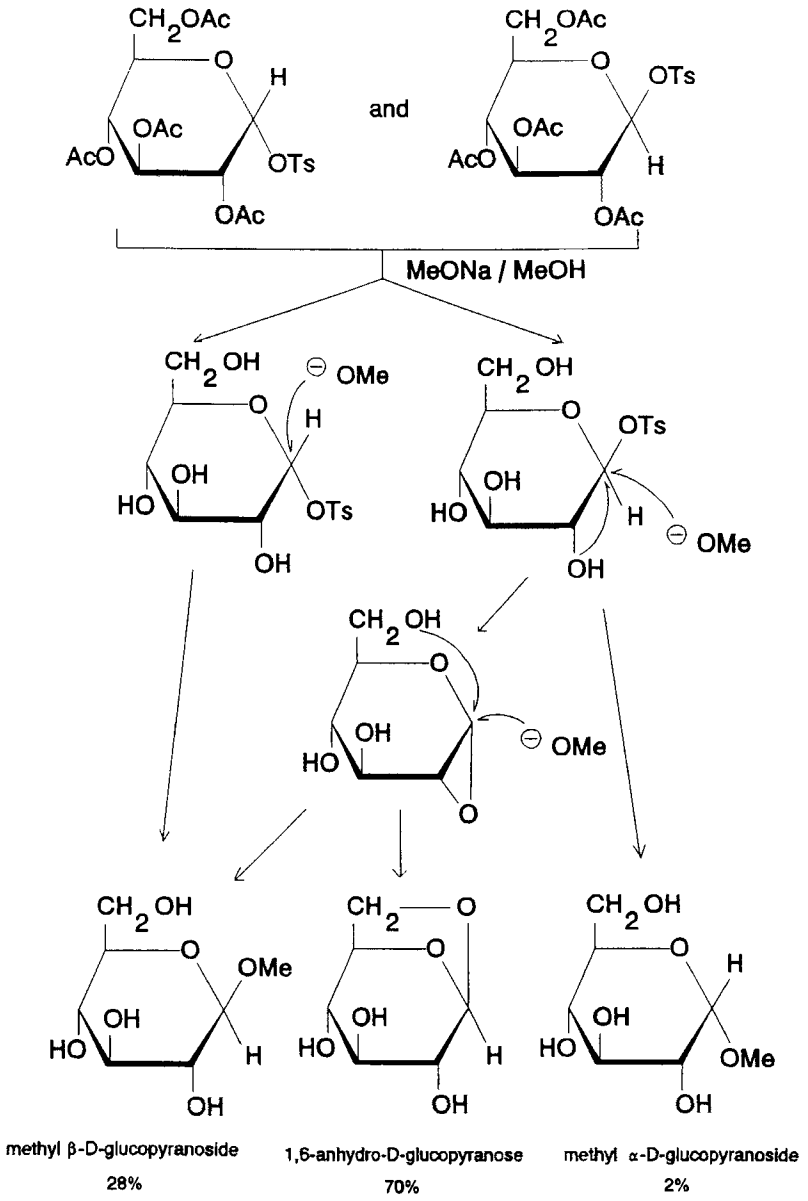
Relative percentages[a] and retention times in CGC of components present in the mixtures obtained after reactions of selected hexopyranose derivatives with sodium methylate solution

parent compound	1,6-anhydro-hexopyranose	methyl α-D-glycopyranoside	methyl β-D-glycopyranoside
1-*O*-tosyl-2,3,4,6-tetra-*O*-acetyl-D-glucopyranose	70% 12.1 min	2% 16.0 min	28% 16.8 min
1-chloro-1-deoxy-3,4,6-tri-*O*-acetyl-β-D-glucopyranose	75% 12.1 min	-	25% 16.8 min
1,2-anhydro-3,4,6-tri-*O*-acetyl-α-D-glucopyranose	75% 12.1 min	-	25% 16.8 min
1-bromo-1-deoxy-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose	8% 12.1 min	-	92% 16.8 min
1-*O*-tosyl-2,3,4,6-tetra-*O*-acetyl-D-galactopyranose	80% 12.0 min	2% 15.2 min	15%[b] 16.2 min
1-*O*-tosyl-2,3,4,6-tetra-*O*-acetyl-D-mannopyranose	-	96% 15.1 min	4% 16.0 min

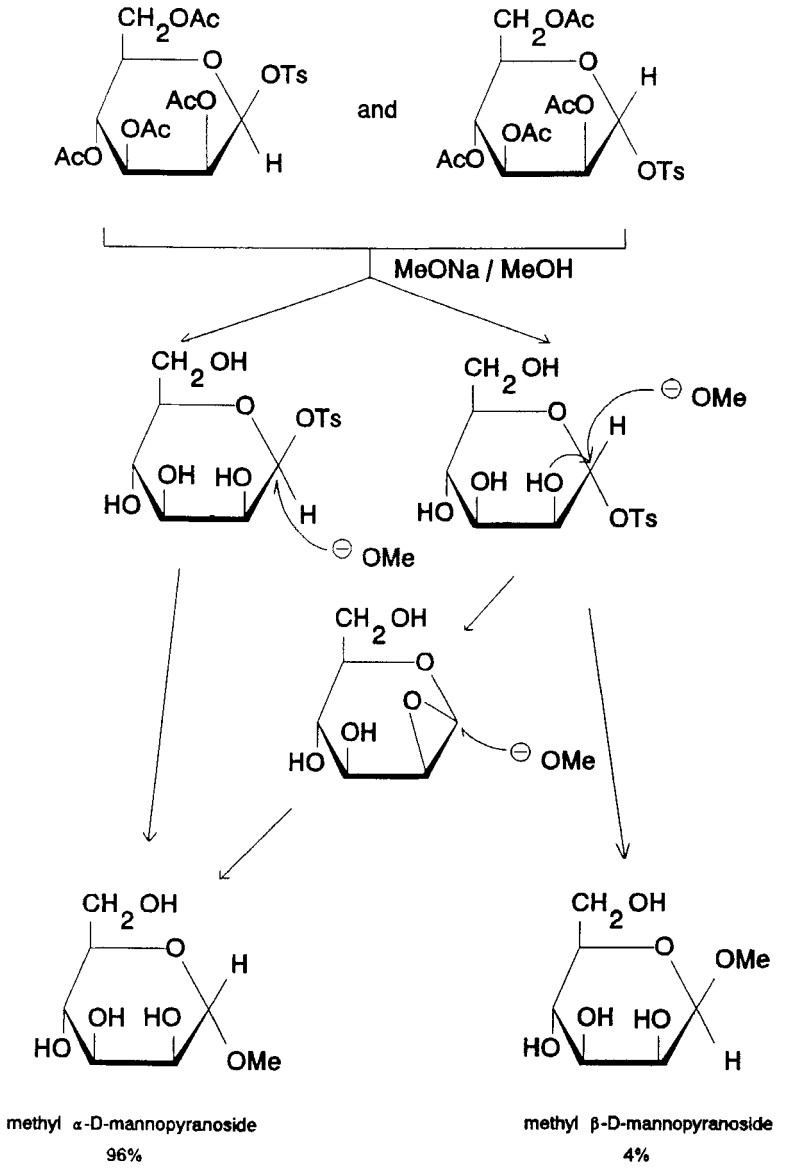
a. calculated from CGC peak areas
b. 3% of unidentified compounds were also present

The absence of any traces of per-*O*-acetylated hexopyranoses (i.e., the absence of free C-1-OH group among the products of the cyclization reactions) suggests indirectly that the total tosylation of the anomeric hydroxyl group of 2,3,4,6-tetra-*O*-acetylhexopyranoses took place quantitatively. The absence of 1-chloro-1-deoxy-per-*O*-acetylhexopyranoses in the mixtures after *O*-tosylation reactions was demonstrated by CGC and TLC analyses using authentic samples as the reference standards. In spite of many attempts we did not succeed in isolation of pure 1-*O*-tosyl derivatives of the examined hexoses.

The formation of 1-*O*-tosyl-2,3,4,6-tetra-*O*-acetylhexopyranoses (as a mixture of α and β anomer in ratio 1:3) in the reaction of tetra-*O*-acetylglycopyranoses with tosyl chloride in pyridine is supported by ^{1}H NMR analysis. The 100 MHz ^{1}H NMR spectrum of our products with D-gluco configuration (δ=6.1, d, $J_{1,2}$=3.2 Hz, H-1 for the α anomer and δ=5.5, d, $J_{1,2}$=10 Hz, H-1 for the β anomer) are in accordance with the corresponding values of the 1-*O*-tosyl derivatives which were obtained under the Schuerch method[7] (reaction of silver *p*-toluenesulfonate with acetylglucopyranosyl bromide in acetonitrile).



SCHEME 1



methyl α-D-mannopyranoside
96%

methyl β-D-mannopyranoside
4%

SCHEME 2

In conclusion we suggest that the 1-*O*-tosyl derivatives obtained during tosylation of 2,3,4,6-tetra-*O*-acetyl-D-gluco- and D-galactopyranoses with TsCl in pyridine are useful intermediates for the synthesis of 1,6-anhydrosugars. Treatment of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose with *p*-toluenesulfonyl chloride on a preparative scale (ca. 1 g of the substrate) gave crystalline 2,3,4-tri-*O*-acetyl-1,6-anhydro-D-glucopyranose (mp 102-104 °C) in a 53% yield.

EXPERIMENTAL

General procedures. CGC analyses were conducted using a CHROM-5 (Laboratorni Pristroje, Prague) gas chromatograph equipped with a flame ionization detector (FID) and a glass capillary column (35 m x 0.3 mm) coated with a Carbowax 20M TPA stationary phase (film thickness 0.2 μm on $BaCO_3$).[11] Hydrogen with a flow rate of 2mL/min was used as a carrier gas. The temperature of the detector and the injector were 250 and 270 °C, respectively. The oven temperature was programmed as follows: 140 °C, 4 °C/min. ^{1}H NMR spectra were determined on a Tesla BS 567A spectrometer with pyridine-*d* and acetonitrile-*d* as the solvents and TMS as an internal standard. The following compounds were synthesized according to the referenced methods: 2,3,4,6-tetra-*O*-acetyl-D-galactopyranose,[12,13] 2,3,4,6-tetra-*O*-acetyl-D-gluco-pyranose,[12,13] 2,3,4,6-tetra-*O*-acetyl-D-mannopyranose,[12,13] Brigl's anhydride,[8] 3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl chloride,[8] 2,3,4,6-tetra-*O*-acetyl-α-D-gluco-pyranosyl bromide,[14] methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside,[15] methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside,[16] methyl 2,3,4,6-tetra-*O*-acetyl-α-D-galacto-pyranoside,[17] methyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside,[16] methyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside,[18] and 1,6-anhydro-D-glucopyranose,[19].

***O*-Tosylation of selected 2,3,4,6-tetra-*O*-acetyl-D-hexopyranoses.** 2,3,4,6-Tetra-*O*-acetyl-D-galactopyranose, D-glucopyranose and D-mannopyranose (25 mg; 0.07 mmol each) were placed in three screw capped glass vials to which 40 mg (0.2 mmol) of *p*-toluenesulfonyl chloride (TsCl) and 0.6 mL of dry pyridine were added. The solvent was then expelled under a nitrogen stream and the products immediately reacted with methanolic sodium methoxide solution.

Reaction of selected hexopyranose derivatives with sodium methoxide in methanol. To each of six ampoules containing either the *O*-tosylation products of 2,3,4,6-tetra-*O*-acetyl-D-hexopyranoses (from reaction 1); 50 mg (0.17 mmol) of 3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl chloride; 50 mg (0.15 mmol) of Brigl's anhydride or 50 mg (0.12 mmol) of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide was added 2 mL (0.34 mmol) of 0.17 M methanolic solution of sodium methoxide. The tightly closed vials were heated at 80 °C for 2.5 h. Volatile constituents were then removed under a nitrogen stream and the residue was acetylated with 0.5 mL of acetic anhydride in the presence of anhydrous sodium acetate at 100 °C for 1 h. The products were analyzed by capillary gas chromatography.

Preparation of 2,3,4-tri-*O*-acetyl-1,6-anhydro-D-glucose. 1.04 g (3 mmol) of 2,3,4,6-tetra-*O*-acetyl-D-glucose and 4.56 g (24 mmol) of p-toluenesulfonyl chloride were dissolved in 7.5 mL of dry pyridine and left for 70 h at room temperature, after which sodium methoxide methanol solution was added (to attain pH ≈ 9.5) and the mixture was heated at 80 °C for 1 h. After removal of the solvents, the residue was acetylated with 20 mL of acetic anhydride in the presence of anhydrous sodium acetate at 100 °C for 1 h. The acetic anhydride was evaporated, the residue was extracted with chloroform and the solution was concentrated to dryness (0.7 g of product). Crystallization from ethanol-ethyl acetate gave crystalline 2,3,4-tri-*O*-acetyl-1,6-anhydro-D-glucose (0.45 g, 53 %: mp 102-104 °C,)[19] which identity was confirmed by CGC.

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