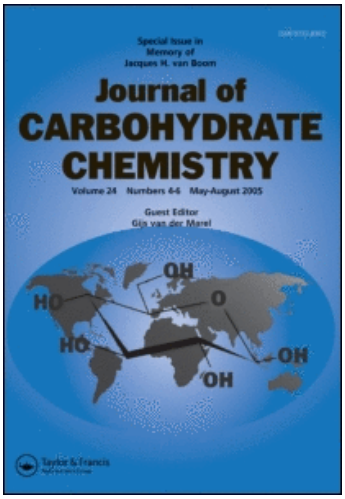

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Cyclization of *N*(Tetra-*O*-acetyl-d-gluco- and d-Mannopyranosyl)-Pyridinium Salts in a Methanolic Solution of Sodium Methylate

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CYCLIZATION OF *N*-(TETRA-*O*-ACETYL-D-GLUCO- AND D-MANNOPYRANOSYL)-PYRIDINIUM SALTS IN A METHANOLIC SOLUTION OF SODIUM METHYLATE

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ABSTRACT

N-(2,3,4,6-Tetra-*O*-acetyl-α-D-gluco-, β-D-gluco- and β-D-mannopyranosyl)-pyridinium salts were obtained and their structures were determined by 2D ^{1}H NMR spectroscopy. The compounds obtained were treated with a methanolic solution of sodium methylate. The β-anomer of the D-gluco derivative cyclizes *via* Brigl's anhydride but the α anomer is competitively transformed according to the S_N2 and S_N1 mechanisms. The β-D-manno derivative does not cyclize under the conditions used. Comparison of the qualitative and quantitative results of the reaction studied enabled 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) as exhaustively *O*-acetylated derivatives and their components were identified by coinjection with authentic materials.

INTRODUCTION

The title compounds can be recognized as *N*-glycosides that are quaternary ammonium salts. Fischer[1] first prepared *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-pyridinium bromide in the reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide with dry pyridine at room temperature in the presence of phenol. Its conformational structure was elucidated by Lemieux and Morgan[2] on the basis of the coupling constants taken

from its ^{1}H NMR (100 MHz) spectrum. Lemieux and Morgan[3] obtained evidence that the reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide with pyridine at high dilution (ca. 2% w/v) gave a high yield of *N*-(tetra-*O*-acetyl-β-D-glucopyranosyl)pyridinium bromide. When the initial concentrations were higher, up to ca. 35% (w/v), a syrupy product was obtained which contained α and β anomers in a ratio of ca. 1:1. The addition of tetrabutylammonium bromide or perchlorate[4] favours the formation of mostly α-anomer.

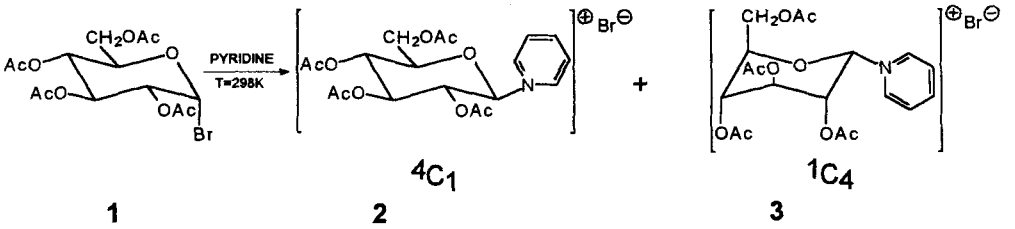
Lemieux[4] proposed the mechanism for the formation of β anomer *via* direct replacement of the bromide ion of tetra-*O*-acetyl-α-D-glucopyranosyl bromide by pyridine, but the formation of α anomer *via* a 1,2-acetoxonium cation. He extended the study to include the corresponding ribosyl bromide and some additional nitrogen bases, i.e., 4-methylpyridine, 2-pyridone, and nicotine amide. The above mentioned salts showed a reverse anomeric effect which accounts for their abnormal ring $^1C_4$ conformation. The influence of the anomeric and reverse anomeric effect on conformational equilibrium ($^1C_4 \leftrightarrow {}^4C_1$) of *N*-substituted *N*-pentopyranoside has been investigated by Paulsen and coworkers.[5]

Appropriate hexopyranose derivatives having a leaving group at the anomeric carbon atom[6-13] or at C-6[14-16] can undergo 1,6-cyclization. The purpose of this study was to investigate the cyclization of the isolated isomers of *N*-(tetra-*O*-acetyl-D-gluco and mannopyranosyl)pyridinium salts in a methanolic solution of sodium methylate.

RESULTS AND DISCUSSION

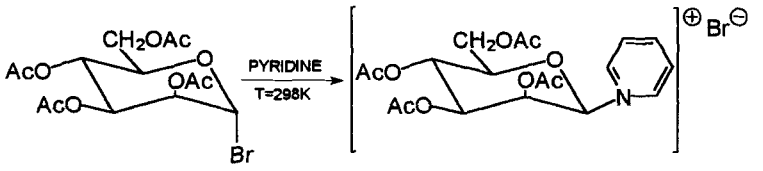
Reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (1) with dry pyridine (34.4%) at room temperature provides α and β anomers of *N*-(2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl)pyridinium bromide (Scheme 1, compounds **2** and **3**) in a ratio of ca. 1:3 determined on the basis of the ^{1}H NMR spectra of the crude product. The reported literature ratio of the same products was 1:1.[3] From the reaction mixture the β anomer (**2**) was isolated by crystallization[3] and the α anomer (**3**) was purified by HPLC (see Experimental) and finally as its *O*-trifluoroacetyl derivative (an oil).

The structures or these anomers were determined by 2D ^{1}H NMR (500 MHz) spectroscopy and were compared with the data given in the literature.[3] The following



1 2 3

Scheme 1



4 5

Scheme 2

coupling constants observed confirmed the conformations of **2** and **3** drawn in Scheme 1: $J_{1,2}$ = 8.8 Hz, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 9.3 Hz, $J_{4,5}$ = 9.3 Hz for **2** and $J_{1,2}$ = 2.4 Hz, $J_{2,3}$ = 2.9 Hz, $J_{3,4}$ = 2.9 Hz for **3**. The large vicinal proton couplings in the spectrum of **2** indicate large dihedral angels (ca. 180°) and are in contrast to the small couplings and corresponding small dihedral angles due to vicinal protons on **3**. Compound **3** was isolated by HPLC which insured its high purity. It is noteworthy to explain why the α anomer **(3)** was not isolated under Lemieux procedure.[3] Many attempts at its purification by this method turned out to be ineffective. In each case the α anomer **(3)** was almost free of the β anomer **(2)** but was contaminated with phenol. For our studies we needed starting material of high purity, which required multiple HPLC separations.

The similar reaction of tetra-*O*-acetyl-α-D-mannopyranosyl bromide with pyridine affords only the β anomer of *N*-(2,3,4,6-tetra-*O*-acetyl-D-mannopyranosyl)-pyridinium bromide (Scheme 2, compound **5**). The structure of **5** was determined using 2D ^{1}H NMR spectroscopy.

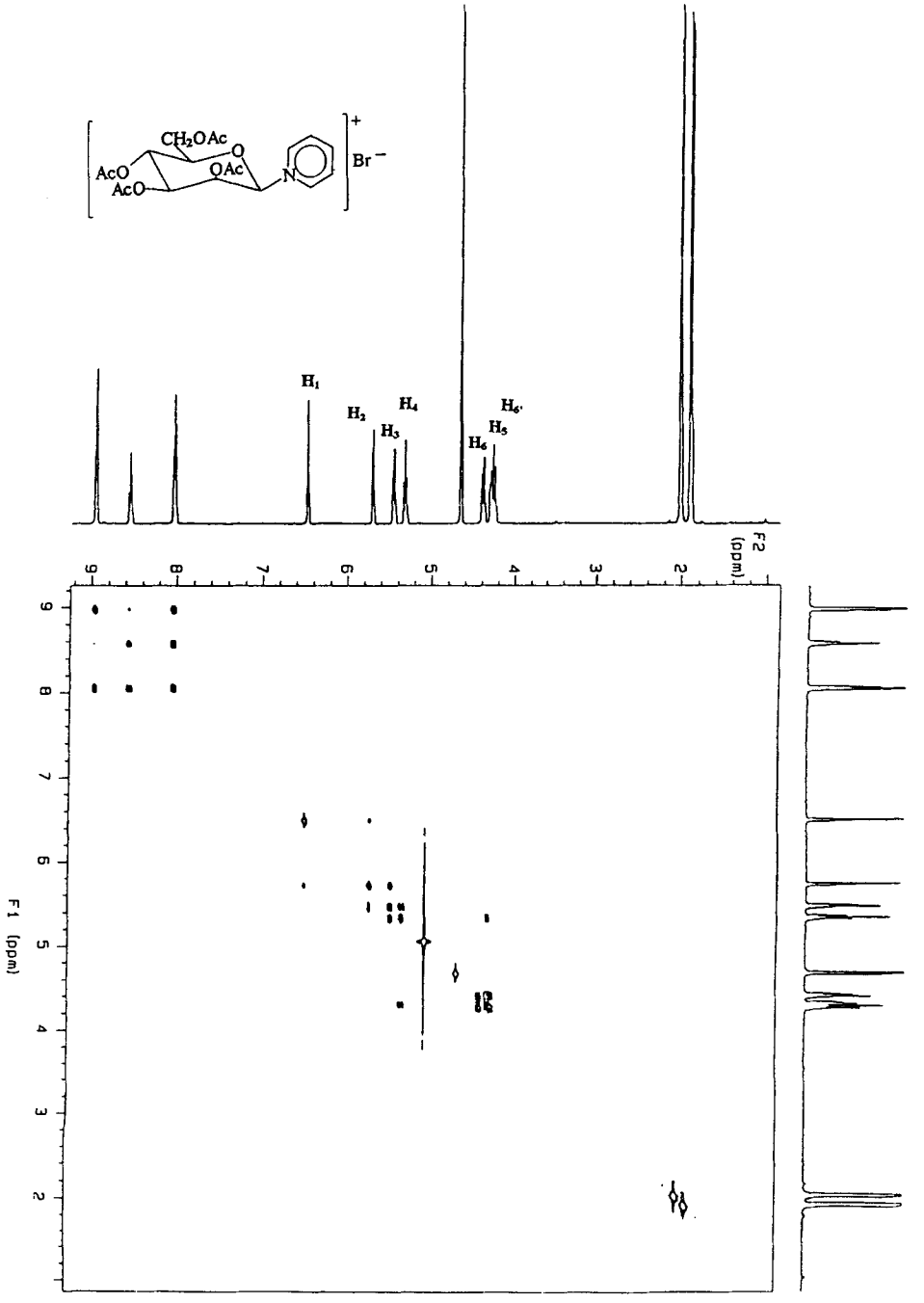


Figure 500 MHz 2D ^{1}H NMR spectrum of compound 5 in D_2O

Table. Relative percentages* and retention times in CGC of components present in the mixtures obtained after reactions of **2, 3a** and **5** with sodium methylate.

CGC peak	per *O*-acetyl derivative of	RT (retention time)	Relative yields [%]
	compound **2**		
1	1,6-anhydro-D-glucopyranose	15.76	81
2	methyl β-D-glucopyranoside	18.37	16
3 + 4	anomers of D-glucopyranose	21.90, 22.25	3
	compound **3a**		
1	1,6-anhydro-D-glucopyranose	16.62	62
2	methyl α-D-glucopyranoside	18.61	8
3	methyl β-D-glucopyranoside	19.25	29
4 + 5	anomers of D-glucopyranose	21.90, 22.25	1
	compound **5**		
1	methyl α-D-mannopyranoside	18.16	83
2 + 3 +4 + 5	unknown	18.24, 18.72, 19.02, 19.34	14
6	D-mannopyranose	22.21	3

* calculated from CGC peaks areas

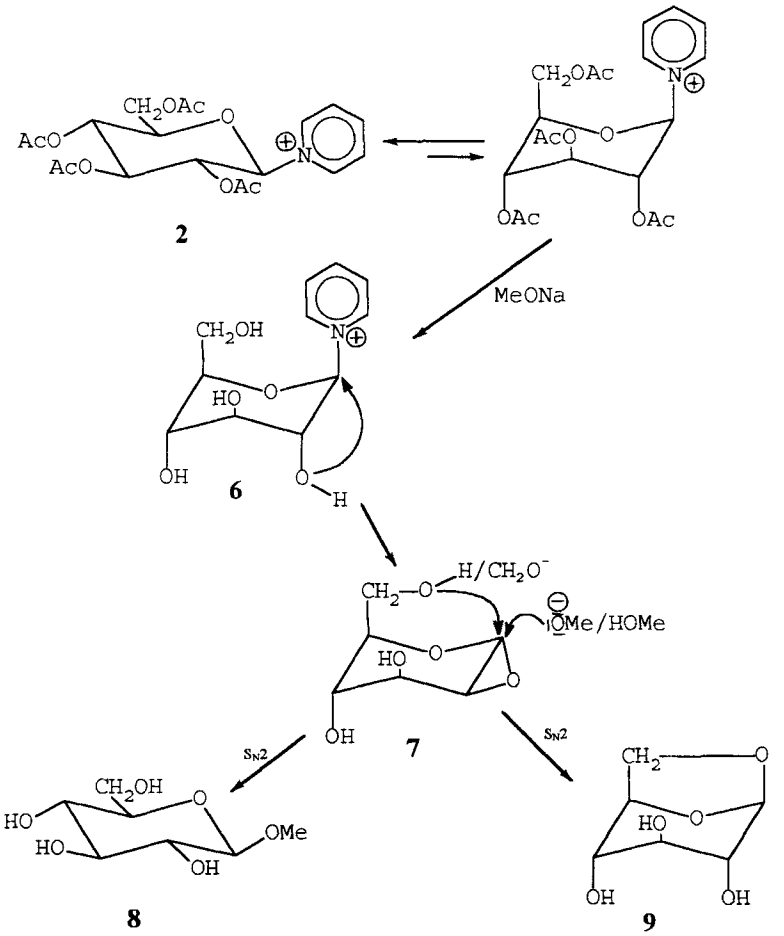
The coupling constants $J_{3,4}$ = 9.8 Hz and $J_{4,5}$ = 9.8 Hz taken from its 2D ^1H NMR spectrum (Figure) verify the $^4C_1$ conformation of compd **5**.

The *N*-(tetra-*O*-acetyl-D-glycopyranosyl)pyridinium salts (compounds **2**, **3** and **5**) each have as a leaving group a positive charged nitrogen atom bonded to the anomeric carbon atom. These salts are thus subject to intramolecular 1,6-cyclization or intermolecular substitution in the presence of strong bases, e.g., sodium methylate.

Each of the pyridinium salts was reacted in methanolic sodium methylate (pH = 9) at a temperature of 85 °C and the products formed were separated using capillary gas chromatography (CGC) as their exhaustively *O*-acetylated derivatives. The products from the reactions were identified using CGC by coinjection with authentic samples. The results obtained are collected in Table.

Based on the gas chromatographic (qualitative and quantitative) results we can state that both anomers of *N*-(tetra-*O*-acetyl-D-glucopyranosyl)pyridinium salt undergo 1,6-cyclization with high yields while the analogous derivative with the α-D-manno configuration (**5**) does not cyclize.

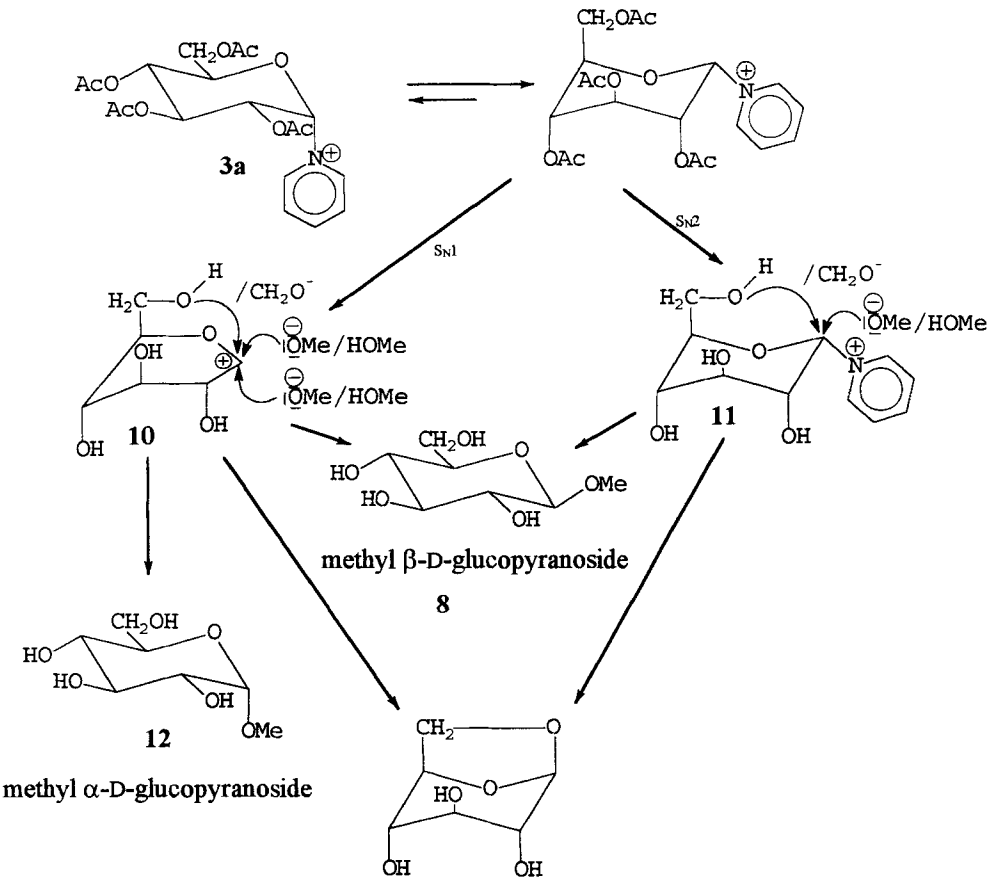
The transformation of the compound **2** (β-anomer) into 1,6-anhydro-D-glucose (**9**) most probably goes *via* the 1,2-epoxide (**7**) as was suggested by Lemieux[17-19]



Scheme 3

(Scheme 3). The $^1C_4$ or boat conformation of compound **2** or **6** is necessary for 1,2-epoxide formation. The 1,2-epoxide opening reaction can occur by intramolecular (C-6-*O*) or intermolecular (Me*O*⁻/MeOH) nucleophilic attack on C-1 to give 1,6-anhydro-D-glucopyranose (**9**) or methyl β-D-glucopyranoside (**8**), respectively. No traces of methyl α-D-glucopyranoside in the reaction mixture were observed suggesting that the transformation goes according to the sole S_N2 mechanism (Scheme 3).

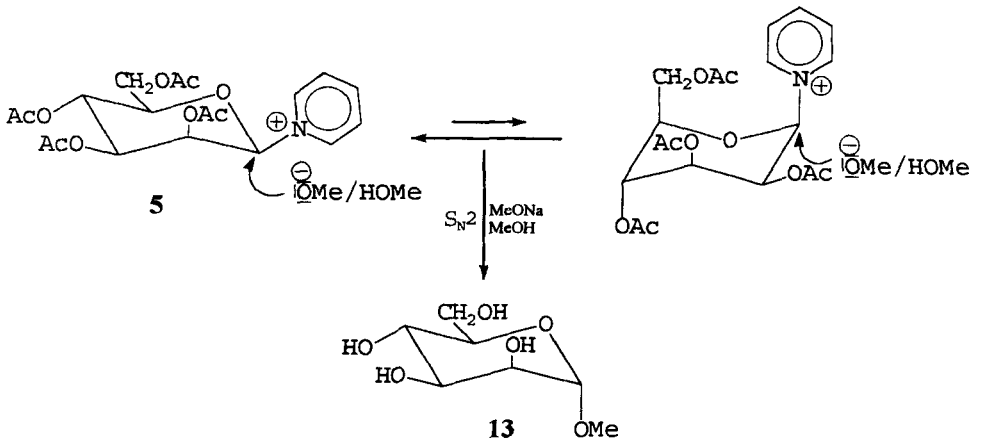
In contrast, the transformation of compound **3a** (α-D-gluco) with methoxide/methanol is more complicated and probably takes place in two ways, i.e., according to S_N2 and S_N1 mechanisms (Scheme 4).



Scheme 4

Direct intra- or intermolecular attack (S_N2) on C-1 of compound **3a** $^1C_4$ conformation leads to 1,6-anhydro-D-glucopyranose **(9)** or methyl β-D-glucopyranoside **(8)** formation but only to the latter product, resulting from the $^4C_1$ conformation.

Methyl α-D-glucopyranoside **(12,** 8%) can be formed from **3a** with carbocation intermediate **(10)** reacting with MeO^- or MeOH. The reaction pathway can also produce the β-glucoside **(8).** Compound **3a** is also an excellent precursor for the 1,6-cyclization reaction. From the mixture containing 62 % of β anomer **(2)** and 38 % of α anomer **(3)** 1,6-anhydrohexopyranose **(9)** was obtained in 68 % yield (See Experimental).



methyl α-D-mannopyranoside

Scheme 5

The analogous transformation of compound **5** (β-D-manno) afforded methyl α-D-mannopyranoside as the main product (Scheme 5). Comparing the structures of compounds **3a** and **5** the intramolecular transformation via an S_N1 mechanism would appear possible, but in fact no cyclization reaction was observed starting with **5**.

The high concentration of α-D-mannopyranoside **(13)** and the absence of the β-isomer in the reaction mixture strongly suggests that transformation of **5** with MeO^- or MeOH occurs by an S_N2 mechanism alone.

EXPERIMENTAL

General Procedures. Reactions were monitored using TLC silica gel plates 60 F-254 (Merck), eluent: tetrachloromethane-acetone, 3:1 (v/v). The identification of compounds obtained was performed by ^1H NMR spectroscopy. A Varian Unity Plus 500 MHz, with D_2O as solvent and TMS as an external standard and 2D COSY technique at temperature of 25 °C were used. Their optical rotations were measured in aqueous solutions using a Jasco J-20 polarimeter. The products formed after the cyclization reaction of **2**, **3a** and **5** were separated as their per-*O*-acetylated derivatives using a gas chromatograph equipped with a DB fused silica column (60 m x 0.258 mm id). The

column was installed inside a Carlo Erba Vega 6180 gas chromatograph. The gas chromatograph was equipped with a cold on-column injector, flame ionization detector (FID) and an integrator (CE Instruments DP-700). Hydrogen was used as a carrier gas at a flow-ratio of 2 mL/min (measured at room temperature). The program was from 140-160 °C at 5 °C/min, 160-200 °C at 6 °C/min, and 200-240 °C at 8 °C/min with a final hold at 240 °C for 10 min. All compounds formed in the reactions were identified by coinjection with standards. The following compounds were synthesized according to the referenced methods: methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside,[20] methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside,[21] methyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside,[22] and 1,6-anhydro-D-glucopyranose.[23]

***N*-(Tetra-*O*-acetyl-α-D-glucopyranosyl)pyridinium bromide (3).** Compound **3** was isolated from the mixture by RP-HPLC on a Kromasil KR-100 C-8, 7 μm (ϕ 50.8, l=250 mm, Eka-Nobel Sweden) column. 2 % of THF in 0.2 M aqueous trimethylammonium phosphate buffer (pH=3) was used as an eluent. Fractions containing the α anomer were collected, concentrated under reduced pressure to ca. half volume, then applied on the same column equilibrated with 0.1 % of TFA (v/v) in water. Elution was carried out using a linear gradient from 0 to 6 % of THF in 0.1 % aqueous solution of THF. Fractions containing α anomer (**3a**) were collected and lyophilized. All preparative separations were performed at the flow rate of ca. 50 mL/min and controlled using 2238 Uvicord S II with a UV monitor at λ = 226 nm (Pharmacia-LKB, Sweden).

***N*-(Tetra-*O*-acetyl-β-D-glucopyranosyl)pyridinium bromide (2)** was obtained according to Fischer and Raske[1] procedure and purified by crystallization from butanone (mp 165-167 °C); $[\alpha]_D$= -4.7° (*c* 1.5, water), ca.70% yield. ^{1}H NMR: (δ) 9.30-8.07 (m, 5H, Py); 6.10 (d, 1H, H-1, $J_{1,2}$ = 8.8 Hz); 5.39 (t, 1H, H-2, $J_{2,3}$ = 9.5 Hz); 5.56 (t, 1H, H-3, $J_{3,4}$ = 9.3 Hz); 5.29 (t, 1H, H-4, $J_{4,5}$ = 9.3 Hz); 4.36 (m, 2H, H-5 and H-6); 4.23 (d, 1H, H-6', $J_{6,6'}$ = 11.2 Hz); 2.01-1.82 (12H, 4 x *O*Ac).

***N*-(Tetra-*O*-acetyl-α-D-glucopyranosyl)pyridinium trifluoroacetate (3a)** A mixture of compounds **2** and **3** (3g) obtained using the Lemieux procedure[3] was purified chromatographically (four times) using HPLC and the phosphate buffer was removed as above. Pure compound **3a** (150 mg) was obtained as a syrup, ($[\alpha]_D$=16.7°; *c* 10, water), which decomposed after a few hours at room temperature. ^{1}H NMR: (δ) 9.00-8.06 (m, 5H, Py); 6.70 (d, 1H, H-1, $J_{1,2}$ = 2.4 Hz); 5.45 (t, 1H, H-2, $J_{2,3}$ = 2.9 Hz); 5.30 (t, 1H,

H-3, $J_{3,4}$ = 2.9 Hz); 5.05 (q, 1H, H-4, $J_{4,5}$ = 2.9 Hz), 4.75 (m, 1H, H-5); 4.55 (dd, 1H, H-6, $J_{5,6}$ = 5.9 Hz, $J_{6,6'}$ = 12.7 Hz); 4.33 (dd, 1H, H-6', $J_{5,6'}$ = 2.9 Hz); 2.12-1.83 (12H, 4 x *O*Ac).

***N*-(Tetra-*O*-acetyl-β-D-mannopyranosyl)pyridinium bromide (5).** Tetra-*O*-acetyl-α-D-mannopyranosyl bromide, 1 g (2.3 mM) was dissolved in 49 mL of dry pyridine and the reaction mixture was kept at room temperature. After 2 days the solvent was evaporated and the raw crystalline residue was crystallized from butanone. The compound was recrystallized to constant physical properties, mp 197-198 °C, $[\alpha]_D$= -17° (*c* 1.5, water), ca. 80% yield. ^{1}H NMR: (δ) 8.98-8.04 (m, 5H, Py); 6.49 (s, 1H, H-1); 5.72 (d, 1H, H-2, $J_{2,3}$ = 1.9 Hz); 5.46 (dd, 1H, H-3, $J_{3,4}$ = 9.8 Hz); 5.34 (t, 1H, H-4, $J_{4,5}$ = 9.8 Hz); 4.31 (dq, 1H, H-5 $J_{5,6}$ = 19 Hz, $J_{5,6'}$ = 3.4 Hz); 4.41 (dd, 1H, H-6, $J_{6,6'}$ = 12.7 Hz); 4.27 (dd, 1H, H-6'); 2.04-1.98 (12H, 4 x *O*Ac).

Anal. Calcd for $C_{19}O_9H_{24}NBr$ C, 46.54; H, 4.93; N, 2.86. Found: C, 46.25; H, 4.89; N, 2.80.

Preparation of 2,3,4-tri-*O*-acetyl-1,6-anhydro-D-glucopyranose (9). 0.57 g (1.16 mM) of an anomeric mixture of *N*-(tetra-*O*-acetyl-D-glucopyranosyl)pyridinum bromide (38% of α anomer **(2)** and 62% of β one **(3)**, taken from its ^{1}H NMR spectrum) was dissolved in 113.7 mL of absolute methanol. Then 2 mL (0.34 mM) of 0.17 M sodium methoxide in methanol was added and the mixture was kept 3 days at room temperature. During that time every 8 h one drop of the same solution of sodium methoxide was added to hold pH≈9.5. The mixture was concentrated under reduced pressure to a thick syrup and then *O*-acetylated with 7.2 mL of acetic anhydride in 7.2 mL of dry pyridine during 24 h at room temperature. The crude product was isolated in the usual manner. Crystallization from ethanol-ethyl acetate gave crystalline 2,3,4-tri-*O*-acetyl-D-glucose (0.23 g, 66% : mp 102-104 °C), lit.[23] mp 108-109 °C which identity was confirmed by CGC.

Cyclization reactions (on a microscale). 0.01 mM of compounds **2, 3a** and **5** were each placed in three screw capped glass vials to which 0.25 mL of dry methanol and 25 μL of 0.37 M methanolic solution of sodium methoxide were added. The reaction mixtures were heated for 2 h at 80 °C, cooled, neutralized with acetic acid and concentrated to dryness under a nitrogen stream. The residue was exhaustively *O*-

acetylated with 0.3 mL of acetic anhydride in the presence of catalytic amounts of sodium acetate during 1 h at 100 C. The products were analyzed by CGC.

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