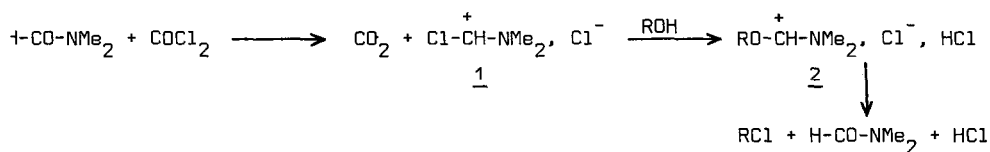


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**Abstract :** Starting from a free hemiacetalic hydroxyl group, the glycosylation is performed by means of the DMF-COCl<sub>2</sub> Vilsmeier-Haack reagent and silver tosylate. The nature of the reactive species is discussed.

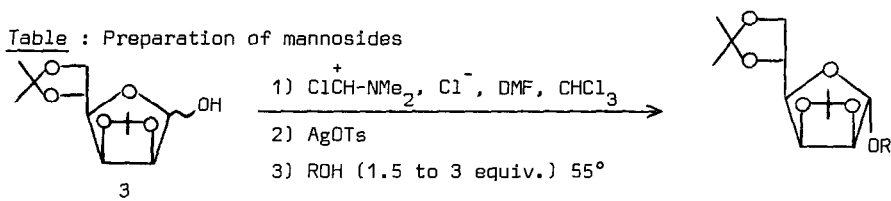
Work done by our group concerning the formation of the glycosidic bond led us to finding the use of positively charged starting groups centred at C-1<sup>2</sup>. In this respect, the use of Vilsmeier-Haack type reagents, obtained by the reaction of phosgene with N,N-dimethylformamide (DMF), is known in sugar chemistry to transform a primary alcohol into the corresponding chloride<sup>3</sup> :



Thus, treatment of 2,3;5,6-di-O-isopropylidene-D-mannofuranose 3 with 1.15 equiv. of the salt 1 and between 2 and 5 equiv. of DMF in chloroform as a solvent provides a solution reactive towards alcohols by heating. Exclusively  $\alpha$ -mannosides are thus obtained in good yields. However, the competition between the alcohol and the chloride anion leads to some  $\alpha$ -mannosyl chloride 4; this drawback is avoided if the reactive solution is treated, prior to the glycosylation, with silver tosylate, in order to remove chloride anions. Our results are listed in the Table.

A  $^1\text{H}$  NMR spectrum recorded at  $-50^\circ$  of the mixture, prepared at  $-50^\circ$ , of 1 and 3 in the presence of DMF shows characteristic signals of  $\alpha$ -mannosyl chloride 4 ( $\text{H}_1$ , 6.1 ppm) and of two species which we assume to be the  $\alpha$  and  $\beta$  iminium salts 6a and 6b at C-1 ( $\text{H}_1$ , s, 6.5 and d, 5.6 ppm ;  $\text{NMe}_2$  : s, 3.22 and 3.52, s, 3.30 and 3.66 ppm ;  $-\text{CH}-$  : s, 8.95, s, 9.90 ppm ; 4/6a/6b : approximately 1/6/3). The signals of 1 are no longer present ( $\text{NMe}_2$  : s, 4.1 ;  $-\text{CH}-$ , s, 11.18 ppm<sup>5</sup>).

Table : Preparation of mannosides



| ROH                          | Yield <sup>a)</sup><br>% | $[\alpha]_{\text{D}}^{20}$<br>c in $\text{CHCl}_3$ | $^1\text{H NMR}$ ( $\delta$ , $\text{CDCl}_3$ )                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|------------------------------|--------------------------|----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| $\text{CH}_3\text{OH}$       | 95 (90)                  | +49.5°<br>4.65                                     | m, 3.89-4.89, 7 H ; $-\text{OCH}_3$ , s, 3.31                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| $(\text{CH}_3)_2\text{CHOH}$ | 95 (85)                  | +53°<br>1.45                                       | $\text{H}_1$ , s, 5.1 ; m, 3.67-4.83, 6 H ; $\text{CH}(\text{CH}_3)_2$ , d, 1.1 (2 Hz)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| $(\text{CH}_3)_3\text{COH}$  | 90 (50)                  | +50.1°<br>1.25                                     | $\text{H}_1$ , s, 5.27 ; m, 3.98-4.90, 6 H ; $(\text{CH}_3)_3$ , s, 1.24                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                              | 72                       | +75.3°<br>1.7                                      | $\text{H}_1$ , s, 5.1 ; m, 3.90-4.90, 6 H ; $\text{CH}_3$ , s, 0.85 ; $\text{CH}_3$ , s, 0.82 ; m, 0.5-2.5, 22 H                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                              | 75 <sup>b)</sup>         | +22°<br>2.4                                        | $\text{H}_1$ , s, 5.23 ; $\text{H}_2$ , d, 4.61 (6 Hz) ; $\text{H}_3$ , dd, 4.76 (3.5 Hz) ; $\text{H}_5$ , m, 4.41, $\text{H}_6$ , $\text{H}_6'$ , $\text{H}_4$ , m, 3.92-4.24 ; $\text{H}'_1$ , d, 5.82 (3.5 Hz) ; $\text{H}'_2$ , d, 4.57 ; $\text{H}'_4$ , $\text{H}'_5$ , $\text{H}'_6$ , m, 3.92-4.24                                                                                                                                                                                                                                                                 |
|                              | 80 (40)                  | -9.5°<br>1.8                                       | $\text{H}_1$ , s, 5.05 ; $\text{H}_2$ , d, 4.63 (6 Hz) ; $\text{H}_3$ , dd, 4.78 (3.5 Hz) ; $\text{H}_4$ , dd, 3.97 (7.5 Hz) ; $\text{H}_5$ , m, 4.39 ( $J_4$ 7.5 Hz, $J_{6a}$ 5.75 Hz, $J_{6b}$ 4 Hz) ; $\text{H}_{6a}$ and $\text{H}_{6b}$ , 4.13 and 3.93 ( $J_{6a-6b}$ 8.5 Hz) ; $\text{H}'_1$ , d, 5.52 (5 Hz) ; $\text{H}'_2$ , dd, 4.31 (2.5 Hz) ; $\text{H}'_3$ , dd, 4.61 (8 Hz) ; $\text{H}'_4$ , dd, 4.21 (2 Hz) ; $\text{H}'_5$ , 3.97 ; $\text{H}'_{6a}$ and $\text{H}'_{6b}$ , 3.75 and 3.64 ( $J_{5'-6'a}$ 6.5 Hz, $J_{5'-6'b}$ 7 Hz, $J_{6'a-6'b}$ 10 Hz). |
|                              | 61                       | -29.9°<br>0.9<br>(MeOH)                            | $\text{H}_1$ , s, 5.42 ; $\text{H}_2$ , d, 4.67 (6 Hz) ; $\text{H}_3$ , dd, 4.78 (3.5 Hz) ; $\text{H}_4$ , dd, 4.27 (7 Hz) ; $\text{H}_5$ , 4.39 ( $J_4$ 7 Hz, $J_6$ 6 Hz, $J_6'$ 5 Hz) ; $\text{H}_6$ , $\text{H}_6'$ , 4.07 ( $J_{6-6'}$ 8.5 Hz) ; $\text{H}'_1$ , AB, 3.94, 4.07 (9 Hz) ; $\text{H}'_3$ , d, 3.71 (7.5 Hz)                                                                                                                                                                                                                                              |

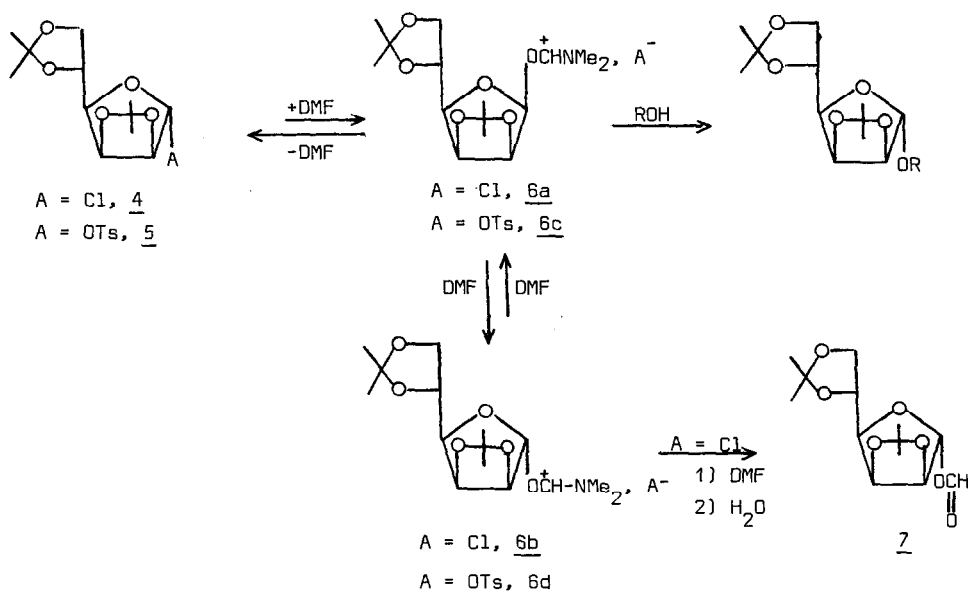
a) As pure isolated products with satisfactory microanalyses ( $\text{C} \pm 0.3$  ;  $\text{H} \pm 0.2$  %) ; between brackets : yields without prior treatment by  $\text{AgOTs}$ .

b) Accompanied by 10 % of the mannoside resulting from the rearrangement of the 1,2;5,6-di-O-isopropylidene- $\alpha$ -D-glucofuranose into the 1,2;3,5-di-O-isopropylidene- $\alpha$ -D-glucofuranose <sup>4</sup>.

By heating at room temperature, all the signals of 6a and 6b disappear without line broadening and are replaced by those of the complex formed between DMF and HCl ( $\text{HOCH-NMe}_2^+$ ,  $\text{Cl}^-$ :  $\text{NMe}_2$ , s, 3.11 and s, 3.23;  $-\text{CH}-$ , s, 8.41 ppm) whereas the intensity of the signals of 4 increases.

After addition of silver tosylate the signals of 4 disappear and are replaced by those of the  $\alpha$ -tosyl mannoside 5.

We know<sup>7</sup> that condensation of an alcohol with either 4 or 5 gives a mixture of  $\alpha$ - and  $\beta$ -mannosides, so we believe that DMF plays a specific role to give only  $\alpha$ -mannosides. It can exert a very strong solvating effect at C-1 on the reactive species or, possibly, form a small amount of a very reactive  $\beta$  iminium salt at C-1, 6a or 6c, through the equilibrium shown below :



The latter assumption is substantiated by three facts :

- A glycosylation performed with 4, silver tosylate and DMF gives qualitatively the same results, namely the  $\alpha$  mannoside.
- The same overall reaction (as in the Table) but run in the presence of a five fold molar excess of hexamethylphosphotriamide gives, as do the oxyphosphonium salts<sup>7</sup>, a mixture of  $\alpha$ - and  $\beta$ -mannosides.
- The hydrolysis of the reaction mixture of 3, and 1 gives the  $\alpha$ -mannosyl formate 7 ( $\text{H}_1$ , s, 6.21;  $-\text{CHO}$ , s, 8.1; Me, s, 1.35, 6 H, s, 1.45, 3 H, s, 1.49 ppm, 3 H).

We are now investigating the scope of this reaction which is somewhat related to previous results<sup>8</sup>, and explains them.

BIBLIOGRAPHY AND NOTES

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- <sup>9</sup> *A typical condensations runs as it follows : a solution of 520 mg of 3 and 290 mg (1.15 equiv.) of 1 in CHCl<sub>3</sub> (5 ml) is allowed to stand 0.5 h ; DMF (1.7 equiv.), AgOTs (2.3 equiv.) and 780 mg (3 equiv.) of 1,2;3,4-di-O-isopropylidene-α-D-galactopyranoside are successively added. The solution is refluxed for 3 - 4 h. After cooling, half of the solvent is evaporated, the residue is diluted with ether (100 ml), filtered, washed (H<sub>2</sub>O, saturated HNaCO<sub>3</sub> and H<sub>2</sub>O) dried and concentrated. By elution (AcOEt/hexane, 2/3 v/v) through a silicagel column, 803 mg of pure mannoside is obtained (80 %).*

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