Stereoselective α-glycosidation using $FeCl_3$ as a Lewis acid catalyst

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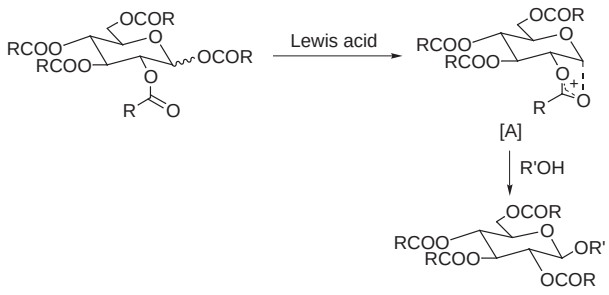
A simplified procedure for the stereoselective α-glycosidation of peracetylated sugars, carrying a participating group at C_2, with aliphatic alcohols in the presence of $FeCl_3$ as a Lewis acid is described.

In continuation of our work[1] on the study of cellular response towards liposomes and their cryoprotection through glycolipids and the interaction of phospholipid and glycolipids, we required large amounts of different pure anomers of glycolipids with varying numbers of spacer unit. In spite of a number of methods reported in the literature[2] *cis*-glycosidation is still a problem; in most of the reported syntheses partial or full protection of the sugar moiety is required, *e.g.* protection with Bn[3] or TBDMS.[4] The presence of an anchimeric assistant group, *e.g.* in the case of protection with an acyl group particularly at the C_2 position of the pyranose ring, leads to a cyclic transition state or non-isolable cyclic intermediate[5] (**A** in Scheme 1), thereby resulting in *trans*-glycosidation.

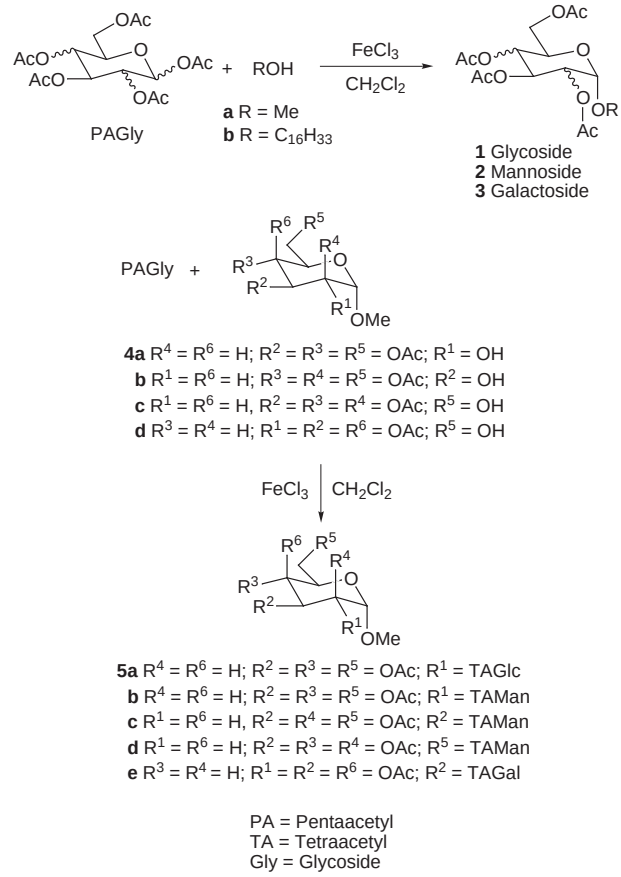
Partial or full protection of the glycosyl donor without a participating group at C_2 is not always easy. In our previous paper[3] we reported such a stereoselective α-glycosidation starting from a 2,3,4,6-tetrabenzyl monosaccharide. Even the most readily available partially-protected monosaccharide, 2,3,4,6-tetrabenzyl glucose, could be prepared by us in only 40–50% overall yield starting from the methyl glucoside.[6] The loss of product is occurring during the hydrolysis of methyl-2,3,4,6-tetrabenzyl glycoside due to the instability of the product to acidic hydrolytic conditions.

We report here for the first time α-glycosidation with a glycosyl derivative having a participating group at the C_2 position. Anomerisation of β-glucopyranosides is already known *via* treatment with titanium chloride,[7a] or mercuric bromide.[7b] Nakanishi[7c] first observed the anomerisation of tetrabenzyl β-methylglucoside to α-methylglucoside in the presence of $FeCl_3$. Srivastava[8] reported stereoselective peracetylation of different monosaccharides to give α-pentaacetyl pyranosides with $FeCl_3$. These observations lead us to try glycosidation with $FeCl_3$ starting directly from readily available peracetylated monosaccharide and aliphatic alcohols. Thus reaction of pentaacetyl sugar with alcohols in the presence of anhydrous $FeCl_3$ in CH_2Cl_2 at room temperature lead stereoselectively to the α-anomer.‡ This is the first observation of stereoselective α-glycosidation occurs inspite of the presence of the anchimeric assistant *O*-acetyl group at the C_2 position of the pyranose ring of glucose, mannose and galactose (Scheme 2, Table 1).



Scheme 1

Disaccharide moieties in which the glycosyl parts are bound α to each other are wide-spread in natural systems, *e.g.* the



Scheme 2

Table 1 Reactions of alcohols with peracetylated monosaccharides in the presence of $FeCl_3$

No.	Peracetylated sugar	Alcohol	Product	Yield (%)	Anomeric ratio[a] (α : β)
1	PAGlc	MeOH	**1a**	95	98 : 2
2	PAGlc	$C_{16}H_{33}OH$	**1b**	70	93 : 7
3	PAMan	MeOH	**2a**	90	100 : 0
4	PAMan	$C_{16}H_{33}OH$	**2b**	75	100 : 0
5	PAGal	MeOH	**3a**	88	95 : 5
6	PAGal	$C_{16}H_{33}OH$	**3b**	68	92 : 8
7	PAGlc	**4a**	**5a**	75	90 : 10
8	PAMan	**4a**	**5b**	73	100 : 0
9	PAMan	**4b**	**5c**	72	100 : 0
10	PAMan	**4c**	**5d**	70	100 : 0
11	PAGal	**4d**	**5e**	68	90 : 10

[a] The anomeric ratios were determined by GCMS or HPLC analysis.

glycoproteins in cell membranes, the immune system, receptors of different bacterial cells[9] and also the human P blood-group system.[10] They are therefore of great interest for cell-cell recognition. We found that triacetyl-α-methylglycosides **4** react, in the presence of ferric chloride, with different pentaacetyl monosaccharides to give heptaacetyl disaccharides **5** in high yield where the monosaccharide moiety is stereoselectively α-orienteded to the glycosyl donor.

This work was supported by the Deutsche Forschungsgemeinschaft (Sonderforschungsbereich 197).

Notes and References

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‡ *General procedure*: To a solution of pentaacetylmonosaccharide (2 g) in CH_2Cl_2 below 5 °C was added slowly $FeCl_3$ (1 equiv.), and the mixture was stirred for 5 min. An equimolar amount of alcohol was then added to the reaction mixture portionwise over 15 min. and stirred at room temperature. Continuous TLC monitoring showed no significant formation of the β-anomer. After completion of the reaction, indicated by the disappearance of the alcohol by TLC (there is always some transformation of the alcohol to the acetate due to transesterification) the reaction mixture was poured into sat. aq. sodium hydrogen carbonate and extracted with Et_2O. Chromatography of the resultant mixture gave the expected glycoside. GCMS and HPLC analysis showed it to be the α-anomer (Table 1), Pure anomer can be obtained *via* preparative TLC. ^{13}C and ^{1}H NMR and mass spectroscopic and other analytical data are identical to those reported previously (ref. 3).

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Received in Cambridge, UK, 22nd April 1998; revised manuscript received, 15th June 1998; 8/04533J