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The utility of glycoside copper chelates for effecting regioselective glycosidation

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Abstract—Regio- and stereoselective glycosidation of the C-3 hydroxyl of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside and methyl 4,6-*O*-benzylidene-α-D-galactopyranoside, via formation of the respective copper chelate, is described.

1. Introduction

It is now well established that carbohydrates are involved in a multitude of biological processes including cell recognition, cell differentiation and cell adhesion.[1] Moreover, it has been demonstrated that a number of protein–carbohydrate interactions mediate critical biological processes such as cell signalling in growth and differentiation events, fertilisation and inflammatory responses.[1] As such, carbohydrates and their derivatives are being considered as a new generation of therapeutic agents.[2] In recent years there has been considerable improvement in chemical and enzymatic methods for oligosaccharide synthesis,[3] and in particular, one-pot strategies for chemical oligosaccharide assembly have been developed.[4] However, many chemical synthetic strategies still rely heavily upon extensive protecting group manipulations, limiting their efficiency. We,[5] and others,[6] have recently reported the ability to protect regioselectively the C-3 hydroxyl of a range of 4,6-*O*-benzylidene glucopyranosides, by prior formation of copper chelates. This is particularly useful since the C-3 hydroxyl group is generally considered the least reactive hydroxyl group of the C-2 C-3 diol pair, and hence this methodology overrides the natural reactivity of the system. We were therefore interested to investigate whether this methodology could be extended to allow regioselective formation of glycosidic bonds between the C-3 hydroxyl of the copper chelate acceptor and, for example, bromide donors. Previous results[7] have illustrated that regioselective glycosidation, with minimal reliance on protecting groups, can indeed be achieved by employing stannylene acetals, and this suggested that such an approach may also be plausible utilising copper chelates.

2. Results and discussion

To determine whether copper chelates were indeed capable of effecting regioselective glycosidation, methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) and methyl 4,6-*O*-benzylidene-α-D-galactopyranoside (**2**) were utilised as substrates. The copper chelates were prepared by initial treatment of the 4,6-*O*-benzylidene gluco- or galactopyranoside diols with sodium hydride (2 equiv.) and then freshly prepared, pre-dried copper(II) chloride[8] (1 equiv.) was added. Previous work had illustrated that acylation of the copper chelates could be effected at room temperature, however reflux temperatures were essential for efficient alkylation reactions.[5,6] Extension of this methodology to incorporate regioselective glycosidation reactions with the bromide donors (**3**) and (**4**) was initially performed at room temperature. However, such conditions proved ineffective for accessing the desired disaccharide targets, with starting material being returned in all cases. However, when the reactions were performed at reflux in THF, efficient entry to the 1,3-linked disaccharide products was achieved as outlined in Scheme 1 and Table 1.[9,10]

These results illustrate that in all cases it was possible to form regio- and stereoselectively the α-1,3-linked disaccharides (**5a**)–(**8a**) via pre-formation of the copper chelates. Only small quantities of the regioisomeric

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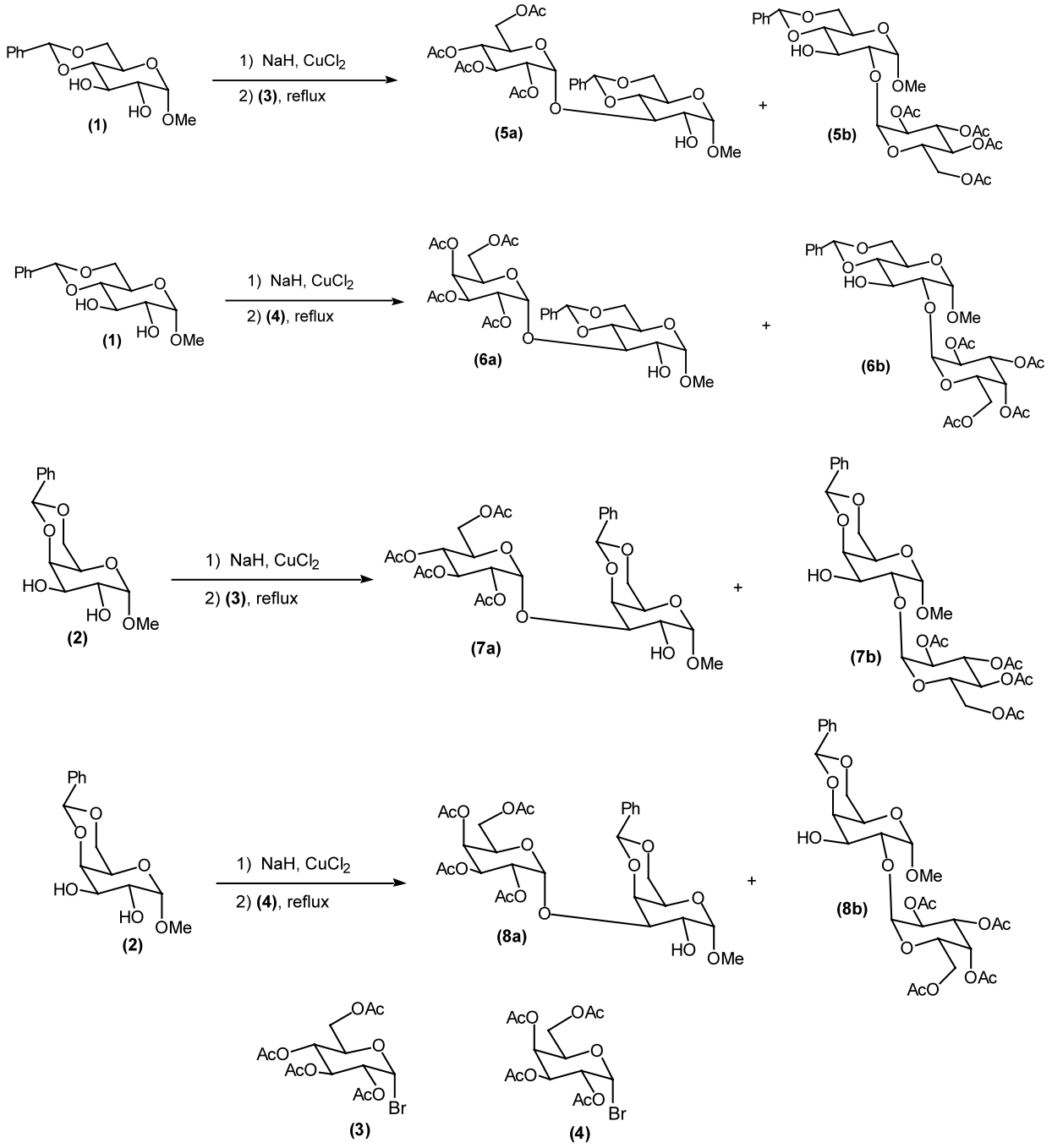

Scheme 1.

Table 1.

Acceptor	Donor	Yield α-1,3-linked disaccharide (%)	Yield α-1,2-linked disaccharide(%)
(**1**)	(**3**)	(**5a**) 51	(**5b**) 16
(**1**)	(**4**)	(**6a**) 55	(**6b**) 10
(**2**)	(**3**)	(**7a**) 49	(**7b**) 14
(**2**)	(**4**)	(**8a**) 46	(**8b**) 11

α-1,2-linked disaccharides (**5b**)–(**8b**) were formed and the β-anomers of the 1,2- and 1,3-linked isomers were never detected.[11] In all cases the regio- and stereoselectivities of the reactions were assessed by extensive NMR analyses of the 1,2- and 1,3-linked disaccharides and their fully acylated analogues. For comparative purposes, ^{1}H NMR data were also obtained for crude reaction mixtures, and yields and isomeric ratios deter-

Table 2.

Acceptor	Donor	Yield α-1,3-linked disaccharide (%)	Yield α-1,2-linked disaccharide(%)
(**1**)	(**3**)	(**5a**) 18	(**5b**) 55
(**1**)	(**4**)	(**6a**) 16	(**6b**) 47
(**2**)	(**3**)	(**7a**) 22	(**7b**) 45
(**2**)	(**4**)	(**8a**) 15	(**8b**) 46

mined in this way paralleled those reported above for the purified regioisomers. Interestingly, when copper acetate was instead utilised for generation of the copper chelate,[5b] or silver triflate was employed for activation of the bromopyranoside donors, no reaction resulted, with only starting material being returned. Attempts were also made to convert the bromide donors into the more reactive iodide donors, in-situ, by addition of catalytic quantities of tetra-butyl ammonium iodide (TBAI). However, worse selectivities were obtained in these experiments, with the TBAI appearing to interfere with the formation of the copper chelate.

A series of control reactions was also performed, to verify that pre-formation of the copper chelates was indeed essential for effecting regioselective glycosidation. Thus the diol substrates (**1**) and (**2**) were treated with sodium hydride (2 equiv.) and the bromide donors (**3**) and (**4**) (1.2 equiv.) to yield mixtures of the α-1,2-linked and α-1,3-linked products, with the α-1,2-linked isomers always predominating (Table 2). Reactions performed in the absence of sodium hydride afforded complex mixtures of products.

In conclusion, we have described an efficient method for effecting regio- and stereoselective glycosidation of the C-3 hydroxyl of methyl 4,6-*O*-benzylidene-α-D-gluco- and galactopyranoside, with two bromopyranoside donors, to afford α-1,3-linked disaccharides. For the first time, it has been demonstrated that formation of glycoside copper chelates can direct glycosidation onto the least reactive hydroxyl of a 1,2-diol pair. This therefore circumnavigates the need for protection–deprotection of the more reactive hydroxyl group.

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9. **Standard reaction conditions for forming α-1,3-linked disaccharides**: the glycopyranoside substrate (**1**) or (**2**) (typically 0.5 mmol) was dissolved in THF (10 cm^3 distilled over sodium/benzophenone) at room temperature under argon. Sodium hydride (typically 1.0 mmol, 2 equiv.) was added and the reaction mixture left to stir for 1 h. After this time a thick white slurry resulted and hydrogen evolution ceased. Anhydrous copper(II) chloride (freshly prepared and dried,[7] typically 0.5 mmol, 1 equiv.) was added to the slurry which immediately went to complete dissolution as a dark green solution. After stirring for no longer than 20 min, the glycosyl donor (**3**) or (**4**) (typically 0.6 mmol, 1.2 equiv.) was added to the solution and the mixture stirred at reflux for 24 h. Water (typically 3 cm^3) and aqueous ammonia solution (typically 3 cm^3) were then added to afford a dark blue solution. The organic layer was separated and the aqueous layer extracted with ethyl acetate (typically 3×10 cm^3). The organic fractions were combined, dried ($MgSO_4$), filtered and the solvent removed in vacuo to give a pale yellow oil. This oil was purified by column chromatography on silica gel (typically hexane:ether, 1:4 plus 1% triethylamine) to afford the α-1,3-linked disaccharide (**5a**), (**6a**), (**7a**) or (**8a**).
10. The structures of the compounds were confirmed by ^1H and ^{13}C NMR, IR, mass spectrometry and HRMS.
11. $J_{1,2}$ for (**5a**), (**6a**), (**7a**), (**8a**) = 4.96–5.20 Hz, indicative of α-configuration.