Regioselectivity in glycosylation reactions of 3,4-diols of α- and β-methyl glycosides derived from N-DMM-d-glucosamine

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Introduction
There are many examples in the literature of selective glycosylations at the 4-position of 3,4-diols derived from N-protected glucosamine, leaving a free 3-OH for a second glycosylation.

In 1998, Magnusson and Ellervik reported reactions of selective galactosylation of 3,4-diols derived from N-protected glucosamine. Based on these experiments, they developed the synthesis of Leα trisaccharide and SLeα tetrasaccharide through a sequential double glycosylation (Ellervik and Magnusson, 1998). More recently, a number of publications reported that 4-OH of acceptors derived from β-D-glucosamine with different protecting groups at N-2 and O-6 was preferentially, and in some cases exclusively, glycosylated under a variety of conditions (Figueroa-Pérez and Verez-Bencomo, 1998; Cao et al., 1999; Gan et al., 1999; Zhang et al., 1999; Xia et al., 2000, 2002, 2003; Ercegovic et al., 2001; Gu et al., 2002; Yang et al., 2003; Xue et al., 2004; Gourmala et al., 2005; Tanaka et al., 2005). Taking into account these results, there are no simple reasons to explain this regioselection. However, recently it was proposed, at least for acceptor 1, the "stereo hindrance" effect of the N-Phth group (Fig. 1) to explain the exclusive 4-OH glycosylation (Gourmala et al., 2005).

Figure 1

Methodology
Continuing with our studies on the reactivity of N-protected glucosaminyl acceptors (Bohn et al., 2006), we decided to examine the influence of the anomeric carbon configuration in the regioselectivity of some 3,4-diols derived from N-dimethylmaleoyl (N-DMM)-D-glucosamine (Aly et al., 1998) against a donor derived from D-galactofuranose using the trichloroacetimidate method (Schmidt and Toepfer, 1991).

The 2a,b and 3a,b diols were selected, considering that the presence of α-oriented C-1 methoxyl in 2a,b, would force the N-DMM group to locate near C-3, thus reducing the accessibility of hydroxyl to that position, which would lead to a predominantly 4-OH glycosylation.

A donor derived from D-galactofuranose (4) (Gallo-Rodriguez et al., 1999; Wang and Ning, 2003) was chosen due to the recent discovery that furanosic sugars are constituents of a wide range of products of biological importance (Lederkremer and Colli, 1995; Wang and Ning, 2003), and also because it is known that the generated glycosidic bond is solely β, which simplifies product analysis (Gallo-Rodriguez et al., 1996, 1999, 2002; Wang and Ning, 2003).

Results
Surprisingly, the coupling of acceptor 2a with 1.1 equivalents of galactofuranosyl imidate 4 under activation with trimethylsilyl triflate at -30 °C gave only 1→3 disaccharide (5a) in a 68% yield. The 1→4 disaccharide was not detected neither by TLC nor by 1H-NMR. However, glycosylation of diol 2b under the same reaction conditions gave a mixture of regioisomers, 5b and 6a, in a 3.2:1 ratio. The coupling of 3a with
4 generated a 1:1 mixture of 7a and 8a, while from 3b a mixture of 7b and 8b in a 1: 2.9 ratio was obtained. Same product ratio was observed by 1H-NMR of crude reaction mixtures.

The assignation of regioisomeric structures was corroborated by acylation of the obtained disaccharides.

Conclusions
Based on the results obtained using the trichloroacetimide method for glycosylation, it can be observed that with acceptors derived from N-dimethylmaleoyl glucosamine that have an β anomeric configuration, contrary to expectations, 3-OH becomes more reactive towards the donor derived from D-galactofuranose (4). On the contrary, when using β anomers the reaction regioselectivity varies.

This observation leads us to believe that in the α anomer might be a hydrogen bridge-type bond between 3-OH and one of the carbonyls of N-DMM, which would trigger such oxygen in the glycosylation reaction. This fact would not be observed with β anomers, since the N-DMM ring accommodates far from 3-OH, thus not allowing the formation of such bonds. This hypothesis is confirmed when modeling both anomers by DFT (at B3LYP/6-31 + G ** level), and noting that the planar ring disposition of the protective group in one and other case are markedly different, being 3-OH and one of the carbonyls of N-DMM closer to each other in the case of the α anomer (Fig. 1).

On the other hand, it can be seen how the protecting group used at 6-position affects the 4-OH reactivity. As previously reported (Bohn et al., 2006), when using an electron-donor protecting group (OBN) the reactivity of 4-OH is increased compared with those acceptors that have an electron-withdrawing group (OBz) at 6 position. When using acceptor 3b, the influence of the substituent at O-6 will be responsible for obtaining higher amounts of the (1→4)-disaccharide (8b).

Figure 1. Structures optimized by DFT (at B3LYP/6-31 + G ** level, more stable conformer) of methyl 2-deoxy-2-dimethylmaleimide-6-O-methyl-α-D-glucopyranoside (a) and its β-anomer (b). Dotted lines show strong hydrogen bridge-type bond interactions.

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References
- Figueroa-Pérez S. and Verez-Bencomo V. (1998) Synthesis of dimeric Lewis X antigenic determinant with azido-type spacer arm by a


