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An unusual example of steric buttressing in glycosylation

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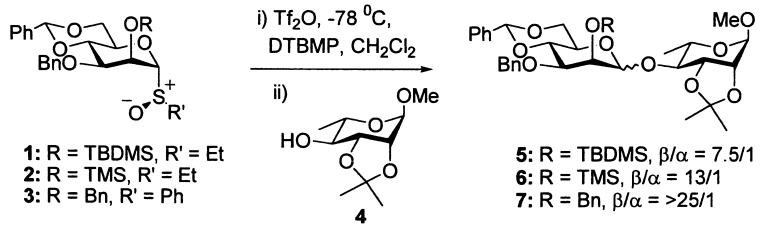
Abstract

An unusual example of steric buttressing is presented in which a 'remote' *tert*-butyldimethylsilyl protecting group dramatically influences the stereoselectivity of a glycosylation reaction.

Steric buttressing is a phenomenon in which a group remote from the site of a reaction serves to limit the conformational space of a system leading, typically, to a rate enhancement. This effect is sometimes seen as being entropic, with minimization of the entropic cost of the transition state, or enthalpic due to a loss of steric strain in the course of a reaction.[1,2] Here, we present a highly unusual example of steric buttressing in which a pair of regioisomeric mannosyl donors, differing only in the placement of two 'non-participating' groups, result in widely differing diastereoselectivities when coupled to a common alcohol.

In previous work in this laboratory we have adapted Kahne's sulfoxide glycosylation method[3] to the synthesis of β-mannopyranosides.[4] We have demonstrated inter alia that secondary alcohol **4** may be coupled to a series of 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosyl sulfoxides (**1**–**3**) in dichloromethane at –78°C following activation with triflic anhydride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) resulting in the highly selective formation of β-mannosides (**5**–**7**) (Scheme 1). Following a series of detailed low temperature NMR experiments we interpret the formation of the β-anomer in terms of an S_N2-like reaction in which **4** displaces triflate from



Scheme 1.

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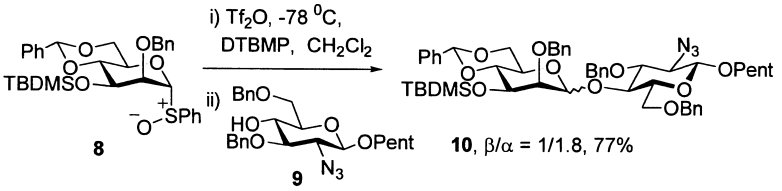
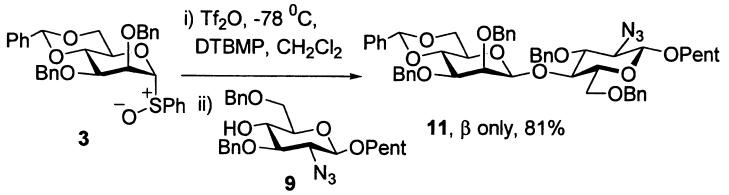
the α-mannosyl triflate formed in situ.[5] The α-anomer of the product is thought to arise from a competing S_N1 reaction going via a free oxacarbenium ion. The effect of the steric bulk of the *O*-2 protecting group on this coupling was noteworthy with the larger groups retarding the S_N2-like process and so leading to the erosion of stereoselectivity. Nevertheless, even with the bulky 2-*O*-TBDMS group, a 7:1 β:α-ratio was feasible (Scheme 1).

Thus, it was reasonable to assume that the transposition of the 2-*O*-TBDMS and 3-*O*-benzyl groups of **3**, as in **8**, with the removal of the steric bulk further from the reaction center, would lead to high β-selectivity. However, coupling of **8**[6] with **9**[7] under our standard conditions (Scheme 2) resulted in the formation of a very disappointing 1:1.8 β:α mixture of anomers, albeit in good yield.[8] When **9** was coupled with the known 2,3-di-*O*-benzyl donor **3** under identical conditions (Scheme 3) the excellent β-selectivity that we typically observe was restored. We were therefore led to the conclusion that the poor selectivity observed with **8** was a function of the remote 3-*O*-silyl group.

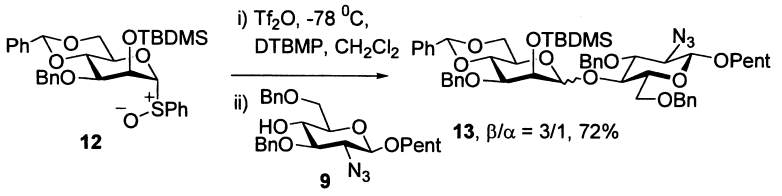


Scheme 2.



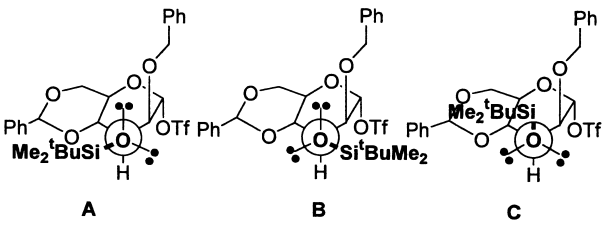
Scheme 3.

This conclusion was confirmed when the regioisomer (**12**)[9] of **8** gave reasonable β-selectivity on coupling with **9** under the standard conditions (Scheme 4).[10]



Scheme 4.

In the absence of obvious conformational changes to the pyranose ring, we attribute the poor selectivity observed with the 3-*O*-silylated donor to a steric buttressing phenomenon. Scheme 5 shows the three possible staggered conformations around the C3–O3 bond. Of these the first (**A**)



Scheme 5.

is disfavored by the steric interaction between the bulky silyl group and the rigid benzylidene ring. In the two remaining conformers (**B**) and (**C**) the steric interaction between the silyl group and the 2-*O*-benzyl group is minimized by rotating the benzyl group toward and over C1. Such a conformation necessarily retards β-face attack on the α-triflate and so distorts the reaction surface in favor of the S_N1 pathway and in doing so leads to the erosion in selectivity observed. In the case of the various 3-*O*-benzyl donors used previously the conformation about the C3–O3 bond corresponding to **A** suffers from no particularly unfavorable interactions. This, in turn, allows the O2 protecting group to rotate away from the C1 and so permits entry of the nucleophile in the S_N2-like process.

There has been much effort focused recently in preparative carbohydrate chemistry on the effects of protecting groups on glycosyl donors, with a view toward establishing a calibrated scale of reactivity,[11,12] such as is needed for the efficient one-pot synthesis of oligosaccharides.[12,13] The above observations indicate that even 'remote' steric interactions cannot be neglected when constructing such scales. It is also entirely possible that similar buttressing effects have a role to play, positive or negative, in other solid-supported glycosylation methods in which a donor is linked to the support via a silyl group located on O3.[14,15] Finally, we note that although the adroit manipulation of protecting groups has contributed enormously to our understanding of glycosyl donor reactivity patterns in recent years, organic chemistry still has much to learn from the multiple subtleties of carbohydrate chemistry.

Acknowledgements

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