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Super arming of a glycosyl donor using a molecular lever

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ABSTRACT

Novel thiomannosyl donors with a 2,3-(phenyl-1,2-ethylidine) tethering group were designed so that the phenyl group would act as a molecular lever and force the pyranoside into its most reactive conformation. It was demonstrated that this type of molecular leverage could increase the reaction rate at least 200 times.

Introduction

Being able to manipulate the conformation of monosaccharides is important for understanding and controlling carbohydrate reactivity and stereoselectivity.[1–3] In such work protecting groups, which are ubiquitous in carbohydrate chemistry,[4–6] play a crucial role as they decrease or in unusual cases enhance the reactivity of carbohydrates in glycosylation reactions.[7–9]

The concept of 'armed' and 'disarmed' was developed by Fraser-Reid and co-workers and refers to ether and ester protected carbohydrates, in which the ether protected derivatives display superior reactivity in glycosylations, compared to that of the ester protected derivatives.[10] The disarming effect of the ester protection group, is due to its larger electron-withdrawing effect compared to ether protection groups[11] (both groups actually lower the reactivity compared to OH[12]). It has also been found that cyclic acetal/ketal protecting groups have a disarming effect,[13] which has been attributed to the more rigid structures (torsional disarming) and electronic effects.[14] While protecting groups themselves are electron-withdrawing and deactivating, the fact that an OH, OR, or other polar group at C3 and C4 in a pyranose is less electron-withdrawing when located axial compared to equatorial[15–17] can cause protecting groups that induce conformational change to increase the reactivity of the carbohydrate. Thus, bulky TBS groups that force an axial rich conformation[18,19] or protecting groups that, by tethering OH groups, induce a ring flip,[20] can cause highly reactive 'super armed' carbohydrate derivatives. However the steric hindrance caused by such protecting groups is not always ideal as it can seriously affect stereoselectivity.

In the present communication we introduce a new principle where a phenyl group acting as molecular lever is used to force the pyranoside into its reactive conformer.

The *cis*-decalin system is capable of chair–chair inversions at close to the same rate as cyclohexane,[21–23] and NMR studies indicate that *cis*-1,4-dioxadecalin also undergoes rapid conformational change.[24] This lent credibility to the design where a *cis*-fused six-membered tethering group which includes an equatorial 'loving' substituent in the axial position could enforce a chair-chair inversion of the pyranoside. The substituent being 'uncomfortable' in the unfavorable axial position would act as a molecular lever and enforce a conformational flip of the entire system. The phenethylidene group was chosen, as the phenyl group is sterically demanding, and presumably can be attached and removed through the phenacyl derivative. Using a thiomannopyranoside as the carbohydrate derivative, we envisaged preparing the diastereomeric pairs **5**–**6** and **9**–**10** (Fig. 1). In (*S*)-configured **5** and **9**, the equatorial position of phenyl is consistent with the pyranose ring being in the favorable (and unreactive) $^4C_1$ conformation. However in (*R*)-configured **6** and **10**, the phenyl group as the molecular lever would strive to be in an equatorial position and induce a conformational change of the pyranose ring causing it to adopt the reactive $^1C_4$ conformation.

Results and discussion

Starting from **1**,[25] alkylation of the 2-OH and 3-OH positions was conducted via the tin acetal using Bu_2SnO followed by

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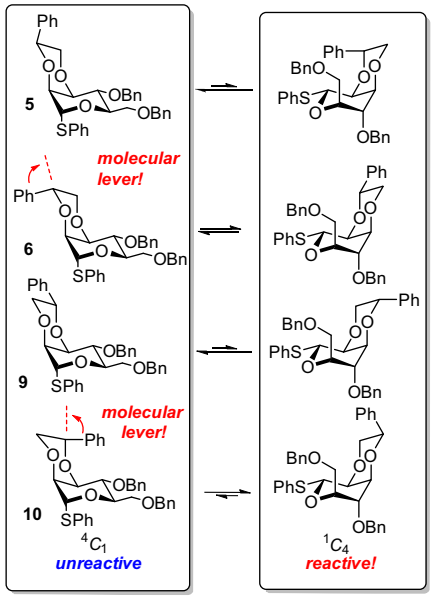


Figure 1. Diastereomeric pairs **5**/**6** and **9**/**10** prepared in this work. In **6** and **10** the phenyl group acts as a molecular lever and flips the saccharide into the 'super armed' conformation.

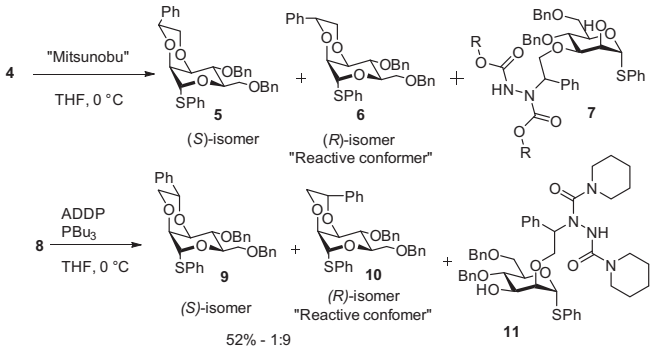


Table 1
Mitsunobu cyclizations

Entry	Azodicarboxylate	Phosphine	Solvent	**5**[a]	**6**[a]	**7**[a]	**4**[a]
1	DIAD	PPh_3	THF	24	4	47	—
2	DEAD	PPh_3	THF	20	4	57	—
3	DEAD	PPh_3	Tol	—	—	—	—
4	DBAD	PPh_3	THF	7	4	—	58
5	ADDP	PBu_3	THF	34	39	—	14

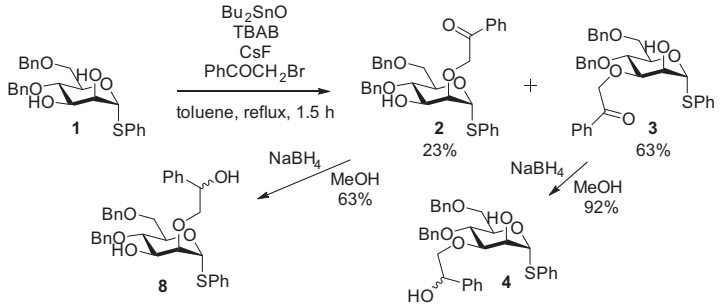
[a] Isolated yield (%).

treatment with tetrabutylammonium bromide, CsF and α-bromoacetophenone to give ketone **2** in 23% yield and ketone **3** in 63% yield.[26] Ketone **3** was then reduced with $NaBH_4$ to give **4** in 92% yield as a 1:2 mixture of diastereomeric benzylic alcohols (Scheme 1). Cyclization of **4** under standard Mitsunobu conditions using diisopropyl azodicarboxylate (DIAD) gave very little of compounds **5** and **6** and mostly byproduct **7** (Table 1, entry 1). Switching from DIAD to DEAD provided no significant difference in yield (entry 2), while changing the solvent from THF to toluene, resulted in no reaction (entry 3). Use of the more bulky di-*tert*-butyl-diazene-1,2-dicarboxylate (DBAD) resulted in a very sluggish reaction with low conversion (entry 4). The formation of **7** is probably due to the small difference in pK_a between the 2-OH and the NH-amide of the azodicarboxylate,[27] therefore ADDP (1,1′-(azodicarbonyl) dipiperidine) was tried as it can deprotonate 'acids' with a pK_a range of 11.7–13.[28] With ADDP we obtained increased yields of **5** (34%) and **6** (39%) with no evident formation of **7** (entry 5).

Ketone **2** was reduced with $NaBH_4$ to give **8** in 63% yield as a 1:1 mixture of two diastereomeric alcohols (Scheme 1). Next, **8** was cyclized using the same optimized conditions as for **4**. This provided an inseparable 1:9 mixture of **9**:**10** in 52% yield (Table 1). By-product **11** and only one diastereoisomer of **8** were also isolated as an inseparable 1:1 mixture in 26% yield.

Thioglycosides **5**, **6**, **9**, and **10** were analyzed by NMR spectroscopy and the coupling constants of the three donors are summarized in Table 2. Compounds **5** and **9** have similar coupling constants to **1**, that is, they are in the $^4C_1$ conformation, and therefore the configuration of the 2′ or 3′ stereocenter must be (*S*) to allow the phenyl group to be equatorial (Fig. 2).

This was confirmed by the coupling constants of the attached cyclic system ($J_{2',3'ax} = 8.8$ and $J_{2',3'eq} = 5.5$ Hz for **5**). As a consequence of this **6** and **10** must be the (*R*)-isomers. For **6,** coupling constants of $J_{1,2} = 4.1$ Hz and $J_{3,4} = 5.8$ Hz together with small couplings in the attached ring ($J_{2',3'}$) were consistent with the compound being an ca. 1:1 mixture of $^4C_1$ and $^1C_4$ conformations or an intermediate in between the two conformations. Compound **10**, on the other hand, had a large coupling constant of $J_{1,2} = 8.2$ Hz and a small one of $J_{3,4} = 2.3$ Hz, which was consistent with the $^1C_4$ conformation. The $J_{2',3'}$ coupling constants of 10.3 Hz and 3.2 Hz confirm this as they show the phenyl group had adopted an equatorial orientation and thus would function as a molecular lever. The difference in the conformational behavior of **6** and **10** was readily explained by their structures. In **6**, the axial phenyl-group associated with the $^4C_1$ conformer has 1,3-diaxial interactions with hydrogen and a lone-pair and therefore would not be as destabilized as the $^4C_1$ conformer of **10** in which the phenyl group had 1,3-diaxial interactions with carbon (Fig. 1).



Scheme 1. Alkylation via the tin acetal and subsequent reduction of ketone **3** with $NaBH_4$.