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β-Stereoselective Mannosylation Using 2,6-Lactones

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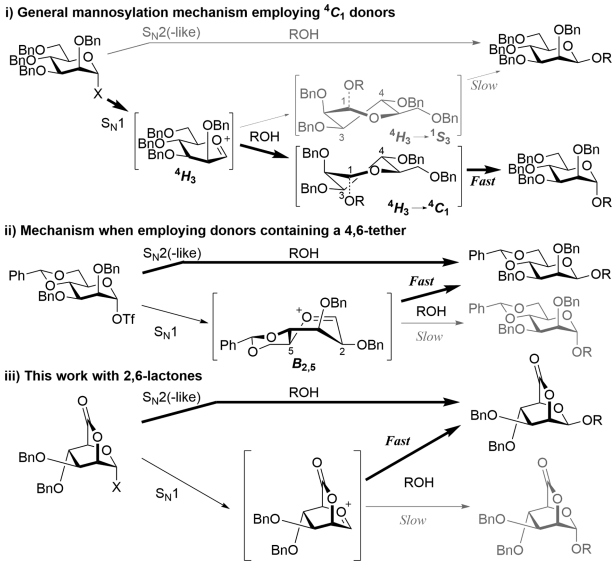
Supporting Information

ABSTRACT: β-Stereoselective mannosylation using donors bearing the 2,6-lactone moiety is described. In general, glycosylation is a nucleophilic substitution reaction between an alcoholic nucleophile and a sugar moiety containing a leaving group at the anomeric position. Owing to stereoelectronic effects, the reaction tends to proceed via an S_N1 mechanism to afford α-glycosides. We found that the introduction of a 2,6-lactone bridge can circumvent the competing S_N1 reaction, affording β-glycosides with stereoinversion via S_N2(-like) mechanisms. Glycosyl trichloroacetimidates are particularly efficient when activated by a combined catalyst of $AuCl_3$ and 3,5-bis(trifluoromethyl)phenyl thiourea. In addition, the product stereoselectivity was highly dependent on the concentration of the reaction. Moreover, even when the reaction proceeds via an S_N1 mechanism, the corresponding glycosyl cation appears to present sterically a β-directing nature. Overall, 2,6-lactones were promising structures for achieving β-mannosylations.

The S_N2-S_N1 borderline poses a critical problem in stereoselective transformations[1] and has cast a shadow over the field of glycosylation. In particular, the construction of the 1,2-*cis*-β-glycosidic linkages (e.g., β-mannosylation) remains puzzling due to the absence of neighboring group participation, and as such, significant efforts have been put into establishing current methodologies.[2] In terms of diastereoselectivity in the S_N1 system, the Woerpel and Deslongchamps models have helped us to understand its origin.[3] Chemical mannosylations via an S_N1 mechanism are postulated to proceed through a glycosyl cation in a half-chair conformation, otherwise known as $^4H_3$,[4] as illustrated in Scheme 1-i. Nucleophilic addition to the cation is favored from the α-face as the generating lone pair of the ring oxygen is expected to be antiperiplanar to the incoming nucleophile, which induces the most stable conformer, $^4C_1$. Attack at the β-face, however, is predicted to produce a skew-boat conformer, $^1S_3$, due to pseudoaxial attack, and as such, this route is disfavored. Overall, glycosylation via an S_N1 mechanism tends to produce α-glycosides. Thus, to construct β-mannosidic linkages via an S_N1 mechanism, the oxocarbenium ions must be distorted,[3b,5] the nucleophile must be delivered (pseudo)intermolecularly,[6] or the α-face must be shielded by remote participation.[5a] An alternative strategy involves the stereoinversion of an α-nucleofuge via an S_N2 or S_N2-like reaction, where nucleophilic attack occurs against the contact ion pair of the glycosyl cation and the departing anion. However, an S_N2(-like) reaction at the anomeric position has only been observed in limited examples, likely due to the intrinsic contribution of the ring-oxygen lone pair blurring the boundary between S_N1 and S_N2. Among the classical examples is a heterogeneous reaction between a glycosyl halide and a silver salt.[7] As for glucosylation and galactosylation, Taylor et al. have recently demonstrated reactions proceeding via associative mechanisms.[8] Alternatively, taking advantage of the electrostatic nature of the protective groups on glycosyl donors has been considered a suitable means to overwhelm the S_N1 reaction. More specifically, the disarming effects[9] of electron withdrawing groups destabilizes the glycosyl cation and enhances the S_N2 pathway.[10] Notably, Crich et al. accomplished an S_N2-like mannosylation employing an α-triflate with the 4- and 6-oxygen functions tethered (Scheme 1-ii).[11] In this case, the 4,6-benzylidene group fixes the geometry around O5-C5-C6-O6 to maximize the electron withdrawing nature, increasing the energetic barrier to the glycosyl cation,[12] which results in a predominant S_N2-like reaction. Additionally, a 4,6-benzylidene-

Scheme 1. Mechanistic Overview in Mannosylations[a]



[a]Examples of S_N2-like mannosylation reactions are limited, and the S_N1 mechanism yields predominantly α-stereoselectivity via the $^4H_3$-glycosyl cation, as outlined in part i. In contrast, the 4,6-tethered α-triflates result in an S_N2(-like) reaction, and their glycosyl cations direct β-stereoselectivity via the $B_{2,5}$-conformer (part ii). We herein demonstrate β-stereoselective mannosylation reactions using 2,6-lactones (part iii). The donors employed result in an S_N2(-like) reaction, and the distorted glycosyl cations direct β-stereoselectivity.

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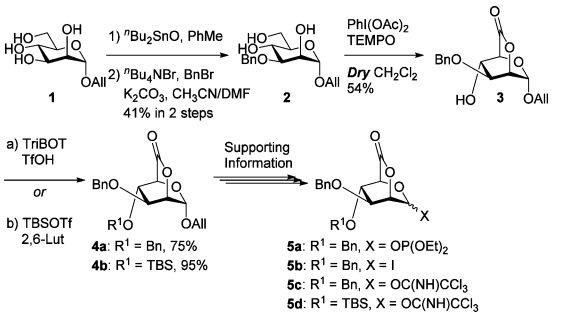
containing mannosyl cation is assumed to adopt a $B_{2,5}$ conformation, which is prone to nucleophilic attack at the β-face.[13] Although the chemistry of 4,6-tethered donors has been frequently updated by a number of groups,[14] this chemistry is not free from limitations with regards to the 4,6-tether and the size of the 2- and 3-substituents.[11a,b] In addition, a novel type of donor could deepen our understanding of the glycosylation mechanism, and in this context, we herein report the use of 2,6-lactones to produce 1,2-*cis*-β-glycosylations (Scheme 1-iii).

We speculated that the n_O-O-C1-X geometry should have a significant effect on the S_N1-reaction rate. When n_O and C-X are antiperiplanar, as in $^4C_1$, the X group should leave relatively easily, whereas a less effective overlap will likely retard the S_N1 reaction, favoring an S_N2-reaction. In addition, the carbonyl group at the O-2 position should function as an electron withdrawing group.[15] On the basis of these speculations, we designed and prepared a series of glycosyl donors containing 2,6-lactones. The conformation bridged by the 2,6-lactone moiety should be restricted to a conformation between $^5S_1$, $^{2,5}B$, and ^2S_O, which lessens the n_O-$\sigma^*_{C\text{-}X}$ overlap compared with $^4C_1$. As outlined in Scheme 2, 2,6-lactones are easily prepared in a

Scheme 2. Preparation of 2,6-Lactones



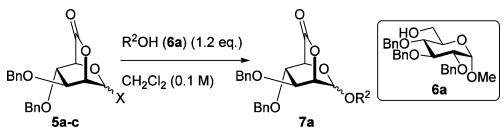
few steps from allyl mannoside **1**, which itself could be easily prepared by Fischer glycosylation.[16] Compound **1** was subjected to ^{n}Bu$_2$SnO-catalyzed O-3 selective benzylation,[17] with the subsequent TEMPO oxidation leading to the desired 2,6-lactone **3** under anhydrous conditions to permit ring-closure. The O-4 position could then be either benzylated[18] or silylated to give **4a** or **4b**, respectively. Manipulation at the C-1 position gave glycosyl donors **5a**–**d** (see Supporting Information for details), with the glycosyl iodide **5b** being stable to silica gel column chromatography. Although the intermediacy of glycosyl iodides has been discussed,[19] they have rarely been isolated, with the exception of the disarmed per-*O*-acetylated glucose.[20] Therefore, the unusual stability of **5b** may indicate that the 2,6-lactone system exhibits the desired disarming effect.

We carried out the glycosylation reaction of primary sugar alcohol **6a** with donors **5a**–**c** as outlined in Table 1. With the appropriate configurations and conditions, diethyl phosphites[21] and iodides[22] have been reported to behave as leaving groups with partial stereoinversion. The reaction using phosphite **5a*α*** proceeded stereoselectively to give the corresponding ***β***-glycoside with an anomeric ratio of 9:1. Furthermore, α-glycosyl iodide **5b*α*** proceeded with perfect β-stereoselectivity, although the reaction rate was rather slow. As shown in entry 3, the stereoselectivity decreased when using an anomeric mixture, i.e., **5b*αβ***, suggesting that this reaction proceeded with partial stereoinversion. Trichloroacetimidate **5c*α*** resulted in an even faster reaction with good β-stereoselectivity in the presence of a $AuCl_3$ and 3,5-bis(trifluoromethyl)phenyl thiourea cocatalyst system. Again, a poorer stereoselectivity was observed when the β-imidate **5c*β*** was employed. These promising results prompted us to investigate further the substrate scope and concentration effects of the reaction using **5c*α*** (Table 2).

Recently, Crich et al. clearly demonstrated that the stereoselectivity of glycosylation reactions is highly dependent on substrate concentration where either triflate or trichloroacetimidate are the leaving group.[13b,23] Indeed, our glycosylation reaction exhibits a clear tendency toward improved β-stereoselectivity in more concentrated solutions, indicating that β-glycosides result from S_N2(-like) reactions whereas α-glycosides are formed via an S_N1 mechanism. This trend was observed in the reaction with glycosyl acceptors **6a**–**e**. Interestingly, **5d**, which has a sterically demanding TBS substituent, afforded good β-stereoselectivity (entry 6). Moreover, the obtained glycosides **7a** could be converted to mannosides **8** by gentle reduction with $NaBH_4$, or to mannuronates **9** by solvolysis, as shown in Scheme 3.

We then attempted to gain some insight into the mechanisms of these reactions. Although it is clear that β-stereoselectivity, at least partially, arises from an S_N2(-like) mechanism, we examined the nature of the glycosyl cation. Thus, we chose to carry out *C*-glycosylation via the glycosyl cation (Table 3), as *C*-allylation has been used to probe steric effects originating from glycosyl cations.[3a,25] The reaction yielded β-*C*-glycosides with perfect stereoselectivity irrespective of the leaving group geometry, indicating that the glycosyl cation has a β-directing nature when electrostatics and hydrogen bonding are ignored. This also explains why β-trichloroacetimidate did not exhibit α-stereoselective properties

Table 1. Glycosylation of 6a with 2,6-Lactones 5a–c



entry	donor	X	conditions	yield (α:β ratio)
1[a]	**5a*α***	-OP(OEt)$_2$ (α)	TMSOTf	91% (1:9)
2	**5b*α***	-I (α)	^{i}Pr$_2$NEt, Ph$_3$PO	37% (β only)
3	**5b*αβ***	-I (α:β = 2:1)	^{i}Pr$_2$NEt, Ph$_3$PO	18% (1:2.3)
4	**5c*α***	-OC(NH)CCl$_3$ (α)	$AuCl_3$, (Ar^{F}NH)$_2$CS	78% (1:16)
5	**5c*β***	-OC(NH)CCl$_3$ (β)	$AuCl_3$, (Ar^{F}NH)$_2$CS	48% (1:1)

[a]R^{1}OTMS **6a′** was used instead of R^{1}OH (**6a**). Ar^F = 3,5-Bis(trifluoromethyl)phenyl.

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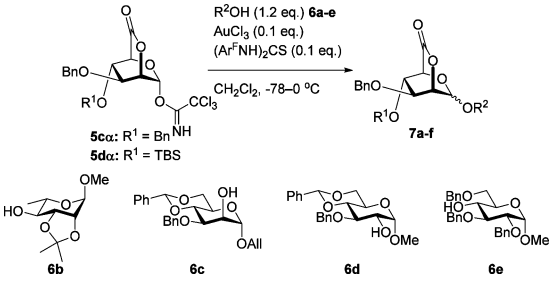
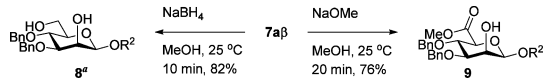
Table 2. Substrate Scope and the Effect of Concentration on β-Stereoselectivity



entry	donor	R^2OH, glycoside	yield (α:β ratio)[a] 0.1 M	1.5 M
1	**5cα**	**6a**, **7a**	78% (1:16)	93% (1: > 99)
2	**5cα**	**6b**, **7b**	83% (1:6.9)	81% (1:10)
3	**5cα**	**6c**, **7c**	77% (1:10)	93% (1: > 99)
4	**5cα**	**6d**, **7d**	88% (1:3.0)	93% (1:47)
5	**5cα**	**6e**, **7e**	7% (1:10)	25% (1:12)
6	**5dα**	**6a**, **7f**	52% (1:8.0)	70% (1:12)

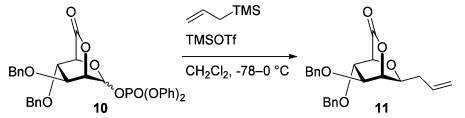
[a]The α:β ratios were determined by HPLC based on authentic samples. The α-anomers of **7b**–**e** were prepared separately by alternative routes (see, Scheme S1 in Supporting Information), and the other glycosides were isolated from each reaction. Because the $^1J_{CH}$ values at the anomeric position are different from those of typical glycosides (179.0 Hz for **7aα** and 169.6 Hz for **7aβ**),[24] the anomeric configuration was confirmed by NOE correlations between H-1 and H-3.

Scheme 3. Derivatization of the Obtained Glycosides



[a]$^1J_{CH}$ for C-1′ was 158.4 Hz, which confirmed the anomeric configuration of **7aβ**.[24]

Table 3. *C*-Allylation of Glycosyl Phosphate 10

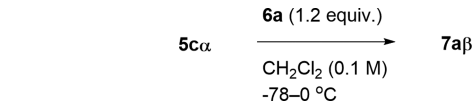


entry	donor	yield (α:β ratio)
1	**10α** (α only)	99% (1: > 99)
2	**10αβ** (α:β = 1:1)	98% (1: > 99)

(Table 1, entry 5). Thus, a partial S_N2(-like) reaction should yield the α-glycosides and the residual S_N1 reaction will produce β-glycosides.[26]

With respect to the cocatalyst, we were inspired to use the combined $AuCl_3$ and the thiourea catalyst based on Schmidt et al.'s glucosylation and galactosylation reactions (where $AuCl_3$ functions via acid–base catalysis)[27] and by recent findings on the thiourea in glycosylations.[28] We observed that β-stereoselectivity was diminished in the absence of both thiourea and $AuCl_3$ (Table 4). Compared to TMSOTf, $AuCl_3$ alone induced β-stereoselectivity (entries 1 and 3),[27] whereas thiourea promoted such selectivity. However, thiourea appeared not to participate in the reaction with TMSOTf (entry 4). Indeed, ^1H and ^{19}F NMR experiments clearly showed that the addition of $AuCl_3$ desymmetrized the thiourea (Figure 1). In addition, we observed activation of the donor in the presence of $AuCl_3$ and

Table 4. Glycosylation Reactions in the Presence and Absence of Thiourea



entry	activator	$(Ar^FNH)_2CS$	yield (α:β ratio)
1	$AuCl_3$	–	86% (1:5)
2	$AuCl_3$	+	78% (1:16)
3	TMSOTf	–	64% (1:2)
4	TMSOTf	+	94% (1:2)

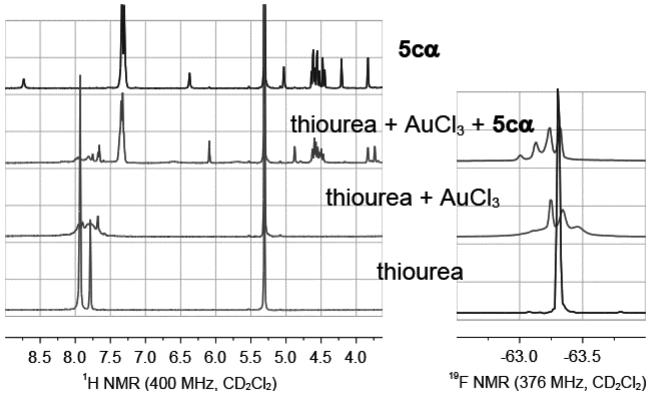


Figure 1. NMR experiments.

thiourea, which contrasts with Schmidt et al.'s observation that $AuCl_3$ alone does not affect the imidate donor.[27] Although the function of the thiourea moiety in glycosylation reactions has recently been discussed,[28] in our case, we expect that the gold binds to sulfur and enhances the acidity of a single thiourea N–H group. As interactions also appeared to take place between the hydroxy moiety and the thiourea, further studies are required to gain a better understanding of the reaction mechanisms involved.[29]

In summary, we successfully developed and employed glycosyl donors bearing a 2,6-lactone moiety in 1,2-*cis*-β-glycosylation reactions. The reactions proceeded mainly with concentration-dependent stereoinversion, more specifically via S_N2-like mechanisms, with the glycosyl cation generated from the donor being sterically β-directing. This methodology can serve as an alternative route to those using 4,6-tethered donors, and is expected to contribute to a wider understanding of the S_N2-S_N1 borderline, in particular in the field of carbohydrate chemistry. Detailed mechanistic studies and application to other types of donors are now in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08874.

Full experimental procedures, spectral data for all unknown compounds (PDF)

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Notes

The authors declare no competing financial interest.

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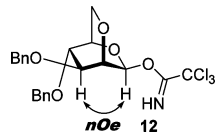

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