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A Reagent-Controlled S_N2-Glycosylation for the Direct Synthesis of β-Linked 2-Deoxy-Sugars

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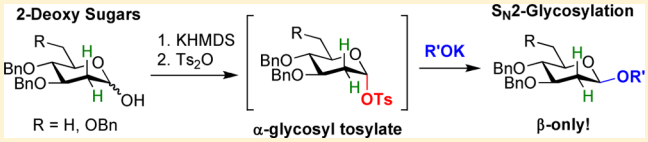
Supporting Information

ABSTRACT: The efficient and stereoselective construction of glycosidic linkages remains one of the most formidable challenges in organic chemistry. This is especially true in cases such as β-linked deoxy-sugars, where the outcome of the reaction cannot be controlled using the stereochemical information intrinsic to the glycosyl donor. Here we show that *p*-toluenesulfonic anhydride activates 2-deoxy-sugar hemiacetals in situ as electrophilic species, which react stereoselectively with nucleophilic acceptors to produce β-anomers exclusively. NMR studies confirm that, under these conditions, the hemiacetal is quantitatively converted into an α-glycosyl tosylate, which is presumably the reactive species in the reaction. This approach demonstrates that use of promoters that activate hemiacetals as well-defined intermediates can be used to permit stereoselective glycosylation through an S_N2-pathway.



INTRODUCTION

β-Linked 2-deoxy-sugars are essential for the bioactivity of many natural products (Figure 1A).[1] Furthermore, oligosaccharides composed of deoxy-sugars have been shown to possess potent biological activity.[2] Altering the composition of these sugars can modulate a natural product's bioactivity, potentially reducing undesirable side effects.[3,4] These linkages are considered to be among the most challenging to synthesize directly, however, limiting the viability of such a task.[5−7] Methods for the direct construction of β-linked phenolic glycosides and thioglycosides of 2-deoxy-sugars have been described,[8−12] but reports of the direct stereoselective synthesis of β-linked 2-deoxy-sugar disaccharides and oligosaccharides are exceedingly rare.[13−16] The mechanistic basis of selectivity in most of these latter reactions has yet to be described, and selectivity does not always translate well between systems.[17,18]

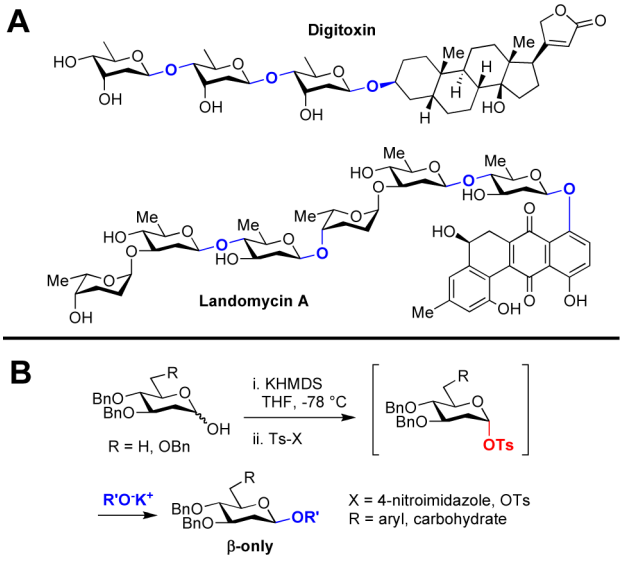


Figure 1. Occurrence of β-linked deoxy-sugars and protocol for direct glycosylation. (A) Representative biologically active natural products containing β-glycosidic deoxy-sugar linkages. (B) Activation of 2-deoxy and 2,6-dideoxy donors as glycosyl *p*-toluenesulfonates for β-specific glycosylation.

We reasoned that a glycosyl sulfonate generated in situ would undergo an S_N2-like reaction with nucleophiles if the intrinsic reactivity of the glycosyl donor were matched to the leaving group ability of the sulfonate. Aside from triflates, however, glycosyl sulfonates have been largely overlooked by the synthetic community since the 1970s.[19] We recently demonstrated that activating a hemiacetal with *N*-tosyl-4-nitroimidazole under basic conditions led to the formation of a species that reacted with strong nucleophiles to afford products exclusively as β-anomers (Figure 1B, X = 4-nitroimidazole).[10] The reaction presumably proceeds through the formation of an α-linked glycosyl tosylate that reacts through an S_N2 or S_N2-like manifold. Attempts to extend this method to less nucleophilic carbohydrate acceptors were unsuccessful. Here we report that the use of potassium hexamethyldisilazane (KHMDS)/*p*-toluenesulfonic anhydride as a promoter system permits the selective synthesis of β-linked 2-deoxy-sugar disaccharides from hemiacetals donors (Figure 1B, X = OTs). Utilizing low-temperature NMR, we demonstrate that the reaction conditions quantitatively convert the hemiacetal into an α-glycosyl tosylate, indicating that the stereoselectivity is the result of an S_N2-reaction. Together, these studies demonstrate that, through proper selection of the promoter, it is possible to

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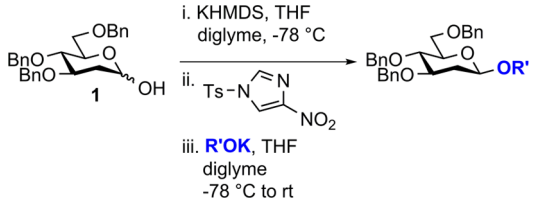
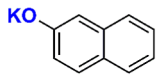
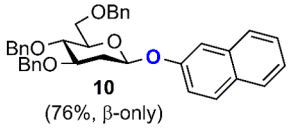
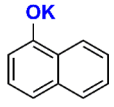
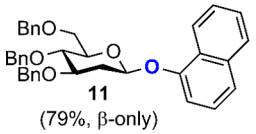
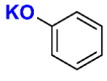
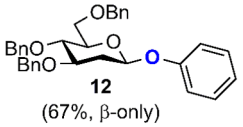
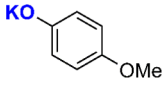
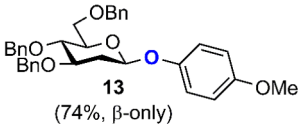
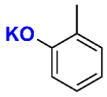
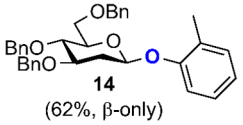
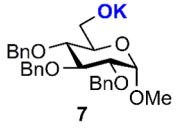
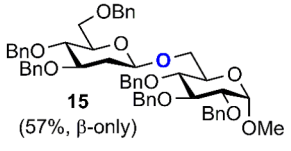
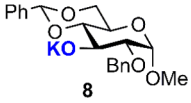
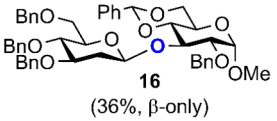
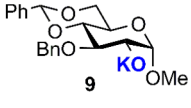
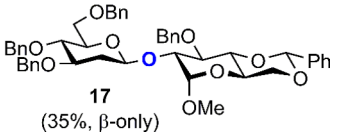
Table 1. Reaction Scope with *N*-Tosyl-4-Nitroimidazole



entry	acceptor	product (yield, α:β)
1	 **2**	 **10** (76%, β-only)
2	 **3**	 **11** (79%, β-only)
3	 **4**	 **12** (67%, β-only)
4	 **5**	 **13** (74%, β-only)
5	 **6**	 **14** (62%, β-only)
6	 **7**	 **15** (57%, β-only)
7	 **8**	 **16** (36%, β-only)
8	 **9**	 **17** (35%, β-only)

obtain direct stereoselective glycosylation reactions with 2-deoxy-sugar donors without recourse to prosthetic or directing groups.

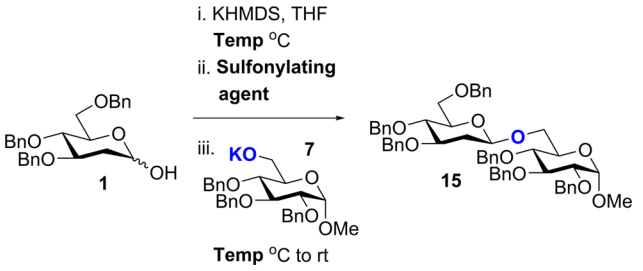
RESULTS AND DISCUSSION

Our initial studies focused on using *N*-tosyl-4-nitroimidazole[20] to activate hemiacetal **1** for glycosylation. Preliminary studies into *O*-glycosylations used phenolic nucleophiles, as aromatic 2-deoxy-sugar glycosides are a common motif in many natural products. While we had shown that this reagent readily activates hemiacetals in THF for glycosylation using thiol nucleophiles, the use of diglyme as a cosolvent was found necessary to promote *O*-glycosylation. Under these conditions, both electron-rich and electron-deficient phenolic nucleophiles reacted smoothly with 1.5 equiv of the active donor to afford the desired product exclusively as the *β*-anomer in moderate to good yield (Table 1, entries 1−5). Attempts to extend this result to carbohydrate acceptors appeared promising when the glucose derivative **7** was used in the reaction (Table 1, entry 6). The use of more hindered nucleophiles proved to be problematic, however, affording the products in low yield (Table 1, entries 7−8).

On the basis of these results, we concluded that a second round of optimization would be necessary to achieve synthetically useful yields with aliphatic acceptors. For our model study, we chose to examine the reaction between **1** and **7**. Attempts to improve this yield by increasing the donor and acceptor stoichiometry, adjusting the reaction temperature, and changing the sulfonylating agents employed proved to be ineffective (Table 2, entries 1−5). Rationalizing that a more potent sulfonylating agent would permit higher yields through complete conversion of the hemiacetal to the glycosyl sulfonate at low temperature, we turned our attention to *p*-toluenesulfonic anhydride. Using this reagent in the presence of the non-nucleophilic base tri-*tert*-butylpyrimidine (TTBP),[21] we were able to obtain the product **16** in 83% yield as a single anomer (Table 2, entry 6).

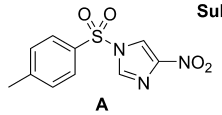
Having established the optimal reaction conditions, we decided to survey the scope of the reaction. These new conditions led to a dramatic increase in yield in the reactions between **1** and hindered acceptors **8** and **9** without compromising the selectivity (Table 3, entries 1−2 vs Table

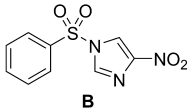
Table 2. Reaction Optimization with Carbohydrate Acceptors

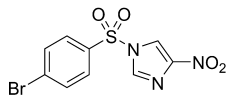


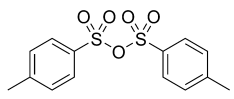
entry	donor equiv	acceptor equiv	sulfonylating agent	temp (°C)	yield (%)	α:β
1	3.0	1.0	A	−78	45	β only
2	1.5	3.0	A	−78	42	β only
3	3.0	1.0	A	−100	55	β only
4	1.5	1.0	B	−78	25	β only
5	1.5	1.0	C	−78	trace	–
6	**1.5**	**1.0**	**D**	**−78**	**83**	**β only**

Sulfonylating Agents


A


B


C


D

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1, entries 7−8). The less nucleophilic acceptor **18** also reacted with **1** in good yield and complete β-stereoselectivity. Acceptors bearing acetonides afforded products **22** and **23** in lower yields, despite the basic nature of the reaction conditions (Table 3, entries 4−5). The basis of this reduction in yield is unknown at this point; however, the reactions still afforded the product as only the β-anomer, indicating that these groups do not interfere with the selectivity of the reaction.

We next chose to examine a more reactive 2,6-dideoxy-L-arabino hexopyranose donor **24**, which represents a common motif in many bioactive natural products. These products were of particular interest to us, as the lack of oxygenation at both C2 and C6 makes these compounds somewhat unstable and prone to elimination reactions to afford the corresponding glycal.[22] This did not prove to be a problem in our hands, however, and we were again able to obtain β-linked products stereoselectively (Table 4). The primary glucose-derived alcoholic acceptor **7** reacted to afford **15** in 77% yield, while the more hindered secondary acceptors **8** and **9** afforded products **26** and **27** in 68% and 70% yield, respectively (Table 4, entries 1−3). Again, acetonide-protected acceptor **19** was less effective in the reaction, providing disaccharide **28** in moderate yield as a single isomer (Table 4, entry 4).

Together, these studies help shed light on the mechanism of the reaction. If the reaction were proceeding through an S_N1-manifold, changing the absolute configuration of one of the coupling partners would be expected to alter the stereochemical outcome. Since both D- and L-configured deoxy-donors react to form β-linked products, this study demonstrates that the reaction is not subject to stereochemical "match" and "mismatch" between donors and acceptors of different configurations.[23] The studies point to the reaction proceeding through the intermediacy of an α-linked electrophilic species that reacts through an S_N2-manifold. Furthermore, the data support our hypothesis that the stereochemical outcome of the reaction is entirely under control of the promoter.

To establish the identity of this species, we examined its low-temperature $^1H-^{13}C$ heteronuclear single-quantum correlation (HSQC) NMR spectrum. To this end, we treated a THF-d_8 solution of the potassium alkoxide of hemiacetal **1** with *p*-toluenesulfonic anhydride in an airtight NMR tube at −78 °C. This experiment revealed a correlation between a broad singlet in the ^1H NMR spectrum with a chemical shift of δ 6.11 ppm and a ^{13}C NMR signal at δ 102.3 ppm, both of which are consistent with a glycosyl sulfonate (see Supporting Information[SI]). The presence of a single anomeric carbon peak clearly demonstrates that only one anomer is formed at low temperature. This intermediate 2-deoxy-α-glucosyl tosylate persisted for nearly 2 h at −78 °C with no indication of decomposition or anomerization. The tosylate was stable at temperatures up to −5 °C, but appeared to eliminate rapidly to form the corresponding glucal above this threshold. These experiments further corroborate our working hypothesis that the reaction proceeds through the intermediacy of an α-glycosyl tosylate that reacts via an S_N2-reaction to form β-linked products specifically.

CONCLUSION

In conclusion, we have demonstrated that *p*-toluenesulfonic anhydride can activate 2-deoxy-sugar hemiacetals for β-selective glycosylation reactions. The approach works with a wide range of acceptors, and the reaction is not sensitive to the absolute configuration of the donor. Low-temperature NMR experiments establish that the reaction proceeds through the intermediacy of an α-glycosyl tosylate, which presumably reacts through an S_N2-manifold. These studies demonstrate that using a promoter system designed to convert a hemiacetal into glycosyl sulfonate where the donor reactivity is matched to the sulfonate leaving-group ability allows for the stereoselective construction of glycosidic linkages. Taken together with our previously reported TBAI/cyclopropenium cation-promoted α-selective dehydrative glycosylation reaction,[24] these results show that it is possible to obtain either anomer of a glycosidic linkage starting from the same coupling partners, simply by changing the promoter.

While it is unlikely that a single sulfonic anhydride can be used to activate all classes of glycosyl donors to effect β-selective glycosylations, the reactivity of sulfonates spans several orders of magnitude.[18] Therefore, we anticipate that this approach will be amenable to other classes of glycosyl donors. This concept of reagent control and, more specifically, using a promoter to activate hemiacetals as predefined electrophiles in situ for S_N2-glycosylation reactions will provide a particularly effective and direct approach to stereocontrolled oligosaccharide and glycoconjugate synthesis.

Table 3. Reaction Scope with 2-Deoxy-Sugars Promoted by *p*-Toluenesulfonic Anhydride

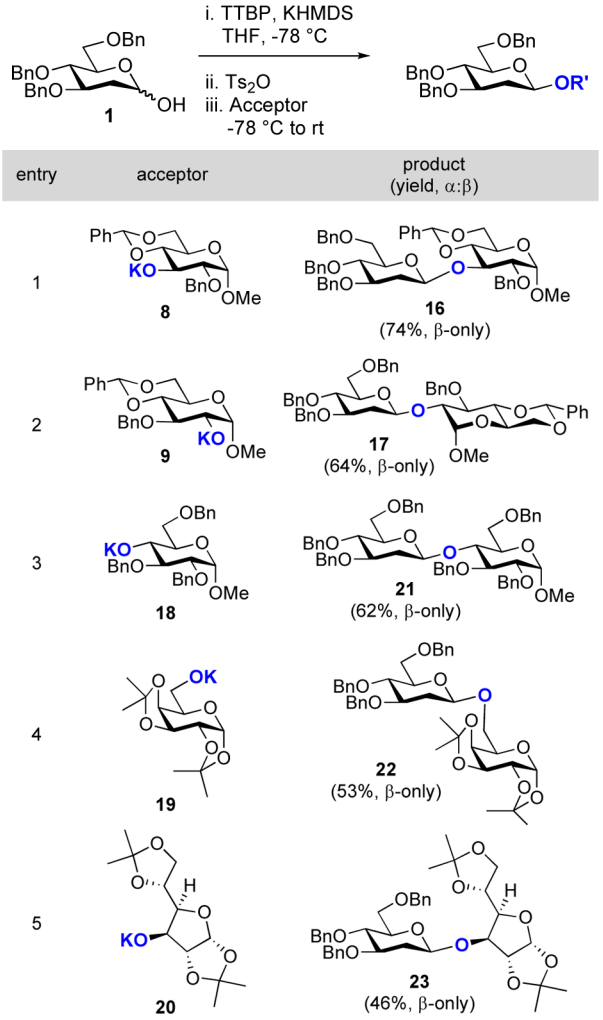

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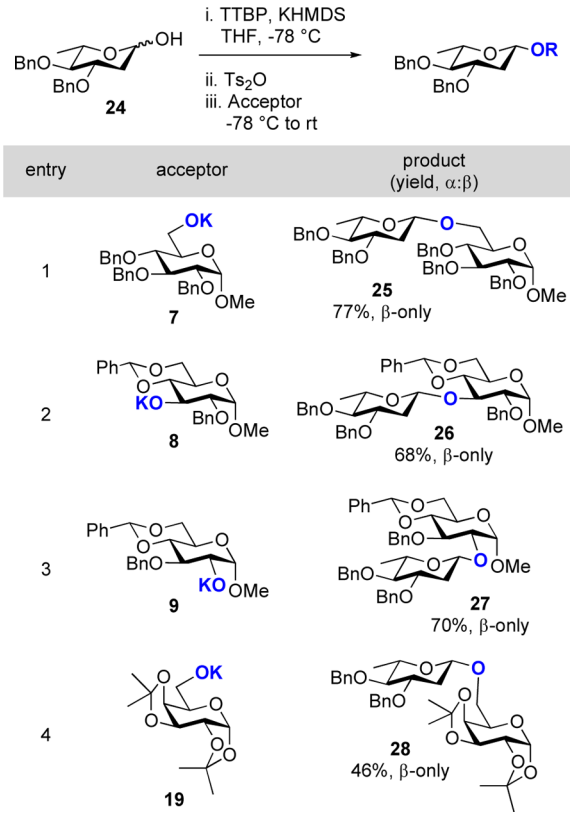
Table 4. Reaction Scope with 2,6-Dideoxy-Sugars



EXPERIMENTAL SECTION

General Experimental Procedure. A solution of donor (0.375 mmol, 1.5 equiv) and 2,4,6-tri-*tert*-butylpyrimidine (TTBP, 93.2 mg, 0.375 mmol, 1.5 equiv) in 3.0 mL THF was cooled to −78 °C and treated dropwise with potassium hexamethyldisilazane (1 M in THF, 0.375 mL, 0.375 mmol, 1.5 equiv). After 15 min, a solution of *p*-toluenesulfonic anhydride (122.4 mg, 0.375 mmol, 1.5 equiv) in 2.0 mL THF was added rapidly to the reaction. The solution was maintained at −78 °C for 30 min. Meanwhile the acceptor (0.250 mmol, 1.0 equiv) was dissolved in 2.0 mL THF, cooled to −78 °C, and treated with potassium hexamethyldisilazane (0.250 mL, 0.250 mmol, 1.0 equiv). After 15 min, this solution was transferred dropwise by syringe to the primary reaction vessel. The reaction mixture was then allowed to gradually warm to room temperature over the course of 3 h, and stirred for an additional 15 h. The reaction was quenched with several drops of saturated, aqueous ammonium chloride (NH_4Cl), diluted with water, and extracted with diethyl ether (2 × 15 mL). The pooled organic phase was washed with brine (2 × 15 mL) and then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography to afford the product as a single β-anomer.

Procedure for Low-Temperature NMR Experiment. A solution of donor **1** (21.7 mg, 0.050 mmol, 1.0 equiv) and 2,4,6-tri-*tert*-butylpyrimidine (TTBP, 13.0 mg, 0.050 mmol, 1.0 equiv) in 0.50 mL THF-d_8 was cooled to −78 °C in a dry ice/acetone bath and treated dropwise with potassium hexamethyldisilazane (1 M in THF, 50.0 μL, 0.050 mmol, 1.0 equiv). After 15 min, a solution of *p*-toluenesulfonic anhydride (17.1 mg, 0.053 mmol, 1.05 equiv) in 0.50 mL THF-d_8 was added rapidly to the reaction. The reaction was maintained at −78 °C for 30 min, transferred by syringe to a precooled 5-mm low-pressure/vacuum valve NMR tube, and promptly inserted into the NMR instrument probe precooled to −78 °C for ^{1}H NMR, ^{13}C NMR, and 2D-gradient HSQC data acquisition. The temperature was maintained for 2 h, then warmed by 10 °C every 10 min. At each 10-min interval, the ^{1}H NMR spectrum was recorded.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of all new compounds. Full VT NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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