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*C*2-Acetamidomannosylation. Synthesis of 2-*N*-acetylamino-2-deoxy-α-D-mannopyranosides with glucal donors

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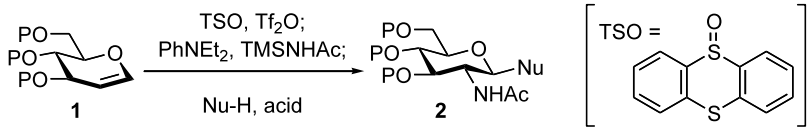
Abstract—A one-pot *C*2-acetamidomannosylation reaction for the synthesis of 2-*N*-acetylamino-2-deoxy-α-D-mannopyranosides from glucals is described. Glucal donors are activated by the reagent combination of 2,8-dimethyldibenzothiophene-5-oxide (DMDBTO) and trifluoromethanesulfonic anhydride. Upon subsequent addition of *N*-(TMS)acetamide and an appropriate glycosyl acceptor, the corresponding *C*2-acetamidomannopyranosides are formed.

*C*2-Azaglycosides are ubiquitous building blocks in biologically important glycoconjugates including glycoproteins, peptidoglycans, glycolipids, and glycosaminoglycans.[1] Numerous methods for the synthesis of *C*2-azaglycosides have been developed, many of which employ glycals[2] as the starting material. The preparation of *C*2-aza*gluco*pyranosides from glucals is well studied and can be accomplished via a variety of elegant methods.[3] On the other hand, only a handful of processes exist for the multi-step synthesis of *C*2-aza*manno*pyranosides from glycals. These include: (1) the Lemieux four-step synthesis of D-mannosamine from 3,4,6-tri-*O*-acetyl-D-glucal via a 2-oximinoglucoside as the key intermediate;[4] (2) preparation of protected mannosamines via IBX-mediated intramolecular cyclization of glycals with *C*3-*N*-arylcarbamates;[3c] (3) oxyamination of 2,3-glycals to afford the corresponding 2-*N*-tosyl-aminomannoside;[5] and (4) the preparation of several *C*2-azamannosides from 3,4,6-tri-*O*-acetyl-D-galactal through the sequential steps of Ferrier rearrangement, [3,3]-sigmatropic rearrangement, and dihydroxylation.[6] To date, no method is available for the direct conversion of glycals to 2-amido-2-deoxy-mannosides despite their critical roles as biosynthetic precursors to neuraminic acids.[7]

Recently, we disclosed the *C*2-acetamidoglycosylation reaction, which involves a one-pot synthesis of naturally occurring *C*2-acetamidoglucosides from glucals.[8] In the reaction, a glucal donor **1** (Eq. (1)) is activated by the reagent combination of thianthrene-5-oxide (TSO) and Tf_2O. Upon subsequent sequential addition of *N*-(TMS)acetamide and a glycosyl acceptor (Nu-H), 2-*N*-acetylamino-2-deoxy-β-D-glucopyrannoside **2** was obtained in good yield with excellent diastereoselectivity.

To expand this process for the preparation of 2-aza-2-deoxy-mannopyranosides, a variety of aromatic sulfoxide reagents[9] were screened for this process to probe the effect of sulfoxide structure on diastereoselectivity of the nitrogen transfer reaction. Of the sulfoxides tested, only dibenzothiophene-5-oxide (DBTO) led to the formation of the α-D-mannopyrannoside as the major diastereomer (Scheme 1). For instance, when the glycosyl donor 3,4,6-tri-*O*-benzyl-D-glucal (**3**) was activated by DBTO·Tf_2O followed by the sequential introduction of *N*-(TMS)acetamide and 2-propanol, the *C*2-amidomannoside **4** and the corresponding glucoside **5** were obtained in a 2:1 ratio, respectively.[10]



(1)

Keywords: acetamidomannosylation; glycosylation; nitrogen transfer.

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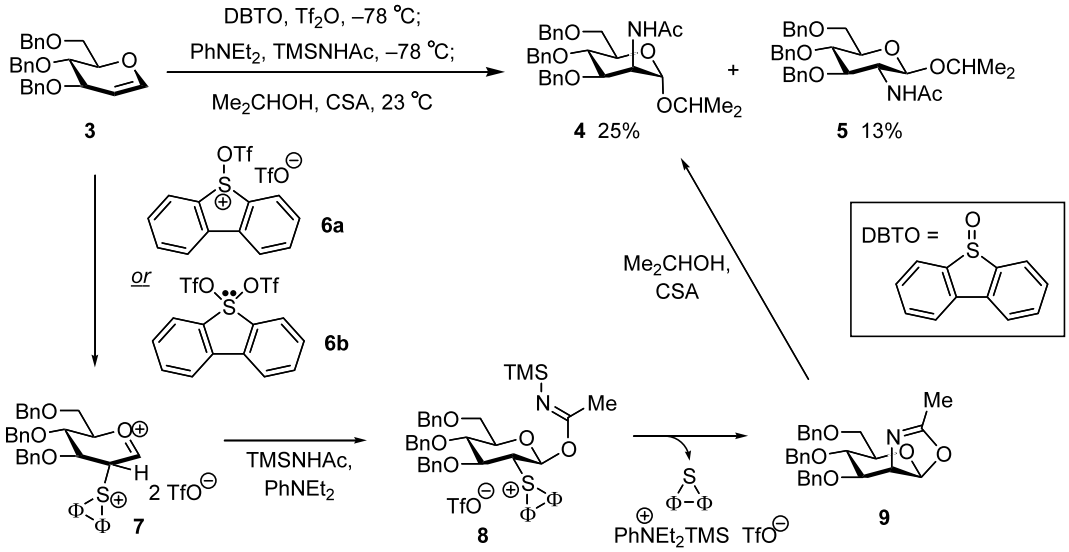
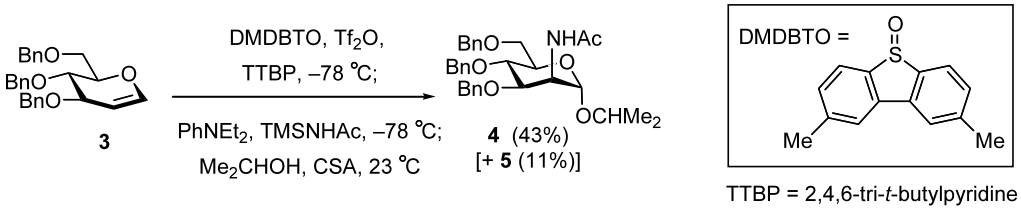
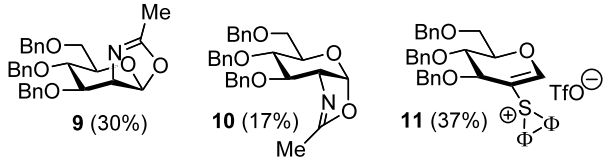


Scheme 1.



(2)

The proposed mechanism for the formation of **4** can be thought of as electrophilic activation of the glucal enol ether from the α-face by either the sulfonium triflate **6a** or σ-sulfurane **6b**[11] (generated in situ) to afford oxocarbenium **7**.[12] Upon the addition of *N*-(TMS)acetamide and $PhNEt_2$ as an acid scavenger, nucleophilic addition of the amide oxygen to the *C*1 position of **7** gives glycosyl imidate **8**. Subsequent intramolecular expulsion of dibenzothiophene at *C*2 by the imidate nitrogen with concomitant *N*-desilylation leads to the formation of β-mannosyl oxazoline **9**. Finally, acid-promoted ring opening of **9** at the anomeric position[13] affords the *C*2-acetamidomannoside **4**.



Consistent with the proposed *N*-transfer pathway is the observation that oxazolines **9** and **10** can be isolated prior to the addition of glycosyl acceptor and acid promoter in 30% and 17% yield respectively, reflective of the manno:gluco diastereomeric ratio of the product glycosides. Moreover, the major by-product of the reaction was found to be the vinyl sulfonium salt **11**,[10] which is likely formed via the elimination of the *C*2-proton from the oxocarbenium intermediate **7**.

In order to enhance both the yield and diastereoselectivity of the reaction, several derivatives of DBTO were prepared and screened for the reaction. It was observed that 2,8-dimethyldibenzothiophene-5-oxide (DMDBTO)[14] led to both an enhancement of yield as well as higher diastereoselectivity for the *C*2-azamannosides.[15] For example (Eq. (2)), the *C*2-acetamidomannosylation of 2-propanol with 3,4,6-tri-*O*-benzyl-D-glucal (**3**) afforded α-mannoside **4** and β-glucoside **5** in 54% combined yield in a 4:1 ratio.

Using the *C*2-acetamidomannosylation reaction, a variety of *C*2-azamannosides (**12**–**19**, Chart 1) were prepared from the corresponding glucals.[16] Interestingly, the diastereoselectivity varies significantly with the nature of the protective group on the glucal donor. In the reactions with 3,4,6-tri-*O*-alkyl protected glucals, a 3–4:1 mixture of α-mannoside and β-glucoside is typically observed (**12**, **15**, **16**, **18**). However, when an acyl protective group is present at the 6-*O*-position of the glucal substrate, the α-mannoside product was the only detectable diastereomer (**13**, **14**, **17**, **19**), presumably a result of altered conformational biases in the glucal donor[17] leading to enhanced facial selectivity in approach of $DMDBTO{\cdot}Tf_2O$ onto the glucal. Primary and secondary alcohols ranging from simple alkyl alcohols to selectively protected carbohydrates and amino acids can be employed as glycosyl acceptors. In addition, *N*-nucleophiles such as sodium azide also serve as an effective nucleophile, leading to the formation of *C*2-acetamidomannosyl azides (**18**, **19**).

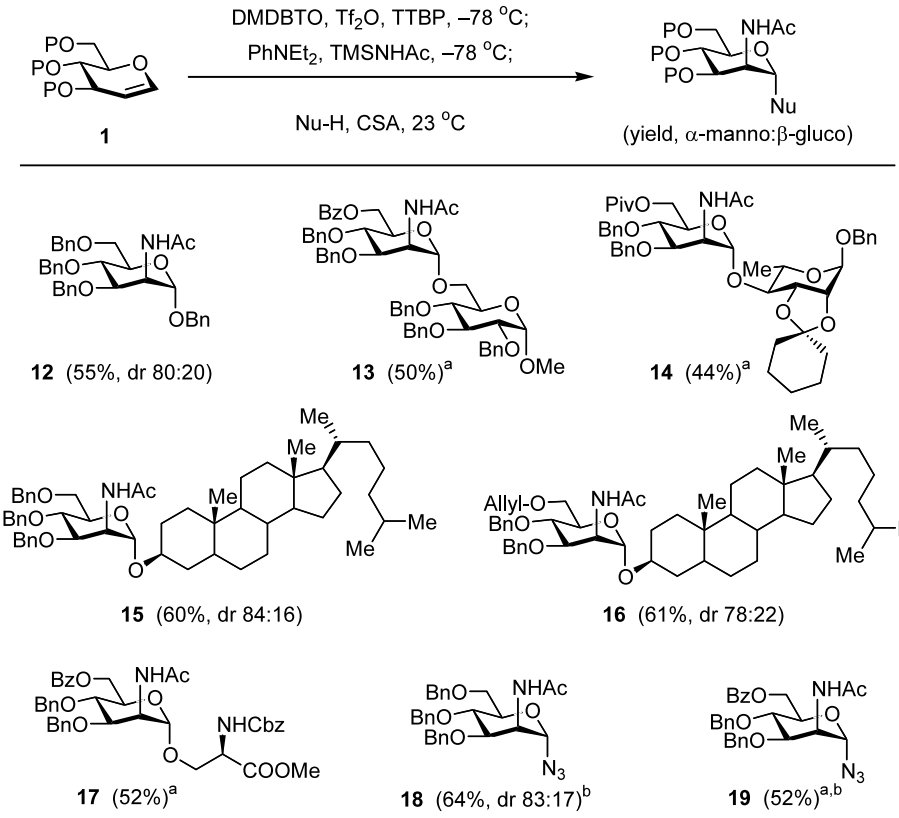


Chart 1. [a]Only the α-mannopyranoside diastereomer was detected. [b]Glycosyl acceptor = NaN_3; with $Cu(OTf)_2$ as the glycosylation promoter.

In summary, a *C*2-acetamidomannosylation reaction for the synthesis of 2-*N*-acetylamino-2-deoxy-α-D-mannopyranosides from glucals has been developed. The reagent combination of DMDBTO and Tf_2O was employed to activate the glucal donor. Subsequent nitrogen transfer at *C*2 from *N*-(TMS)acetamide followed by one-pot glycosylation provides the corresponding *C*2-acetamidomannopyranosides with good to excellent diastereoselectivity. This method represents the first direct synthesis of *C*2-azamannosides from glycals and should prove to be useful in glycoconjugate synthesis.

Acknowledgements

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9. Several diphenyl sulfoxide derivatives, as well as phenyl pyridyl sulfoxide, phenoxathiin-5-oxide, and dibenzothiophene-5-oxide were investigated.
10. It is worth noting that a similar change in diastereoselectivity was observed in the *C*2-oxidative glycosylation reactions, where the reagent combination of DBTO and Tf_2O was also used for glucal activation. See: Kim, J.-Y.; Di Bussolo, V.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 303–306 and references cited therein.
11. Sulfurane formation was proposed in the reaction of DBTO and trifluoroacetic anhydride at low temperature. See: Sato, S.; Zhang, S.-Z.; Furukawa, N. *Heteroat. Chem.* **2001**, *12*, 444–450.
12. In the case of DBTO·Tf_2O for acetamidoglucosylation (Eq. (1)), the sulfonium reagent likely approaches the β-face of the glucal. See Ref. 8b.
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14. DMDBTO can be easily prepared from commercially available dibenzothiophene in three steps: (1) bromination (Bremner, J. B.; Keller, P. A.; Pyne, S. G.; Robertson, A. D.; Skelton, B. W.; White, A. H.; Witchard, H. M. *Aust. J. Chem.* **2000**, *53*, 535–540); (2) methylation (Gilman, H.; Wilder, G. R. *J. Org. Chem.* **1957**, *22*, 523–526); and (3) oxidation (Ho, T.-L.; Wong, C. M. *Synthesis* **1972**, *10*, 561–562).
15. The enhancement of yield is likely due to the increased solubility of the sulfonium or sulfurane species formed from DMDBTO.
16. *Typical procedure*: Tf_2O (40 μL, 0.24 mmol, 2.0 equiv.) was added to a solution of **3** (50 mg, 0.12 mmol, 1.0 equiv.), DMDBTO (55 mg, 0.24 mmol, 2.0 equiv.), and TTBP (30 mg, 0.12 mmol, 1.0 equiv.) in CH_2Cl_2 (2.0 mL) at −78°C. The reaction mixture was stirred at this temperature for 1 h, then $PhNEt_2$ (76 μL, 0.48 mmol, 4.0 equiv.) was added, followed by *N*-(TMS)acetamide (47 mg, 0.36 mmol, 3.0 equiv.). The mixture was immediately warmed to 23°C and stirred at this temperature for 1 h. A solution of (+)-3-dihydrocholesterol (140 mg, 0.36 mmol, 3.0 equiv.) and CSA (56 mg, 0.24 mmol, 2.0 equiv.) in 1.0 mL dichloromethane was added via cannula and reaction was stirred for 24 h. The mixture was concentrated under vacuum and the residue immediately purified by silica gel flash column chromatography (4:1 hexane/EtOAc, 3:1 PhH/EtOAc) to afford **15** (52 mg, 50% yield) and the corresponding β-gluco diastereomer (10 mg, 10%).
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