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Stereoselective Synthesis of 2-Hydroxy-α-mannopyranosides from Glucal Donors

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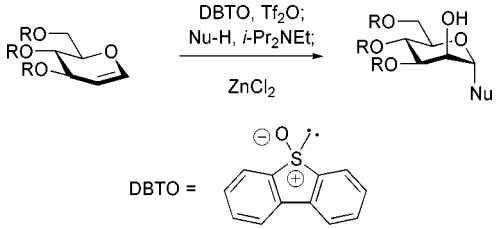
ABSTRACT



Direct synthetic access to 2-hydroxy-α-mannopyranosides from glucal donors is accomplished via a one-pot stereoselective oxidative glycosylation reaction, employing the reagent combination of dibenzothiophene bis(triflate) and dibenzothiophene-5-oxide.

The key roles that carbohydrates play in vital biological processes,[1] such as immune response, inflammation, cell proliferation, and metastasis, has resulted in the development of numerous glycosylation processes for the assembly of complex glycoconjugates.[2] Of these methods, glycal carbohydrate donors have been widely investigated and employed in the preparation of C(2)-branched or C(2)-derivatized oligosaccharides as a result of the versatile reactivity of the C(1)−C(2)-glycal π-system.[3] In this context, the glycal assembly method has been elegantly demonstrated as a convenient means for the preparation of 2-hydroxy gluco- and galactopyranosides via the corresponding α-1,2-anhydropyanosides.[3a] However, the direct preparation of α-*manno*pyranosides from glycal donors (Scheme 1, **1** → **2**) has

Scheme 1

remained elusive, despite their prevalence in nature as exemplified by α-mannose-rich oligosaccharides in a host of *N*-linked protein glycoforms.[4] To date, the most efficient method for the glucal-to-mannopyranoside transformation (**1** → **2**) relies on a multistep modification of the traditional glycal assembly procedure in which inversion of the C(2)-stereocenter is required following glycal oxidation.[5] We now report a new process that allows, for the first time, direct synthetic access to 2-hydroxy-α-mannopyranosides from glucal donors.

Previous work from our laboratories has shown that the reagent combination of diphenylsulfide bis(triflate) and excess diphenylsulfoxide can effect direct stereoselective

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(2) (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155−173. (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212−235. (c) Sinaÿ, P. *Pure Appl. Chem.* **1991**, *63*, 519−528. (d) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531. (e) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095−1121. (f) *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker, Inc.: New York, 1997; Chapters 12−22. (g) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137−2160.

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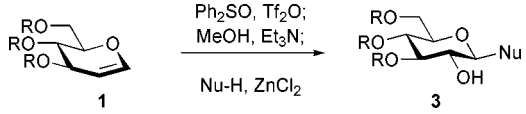
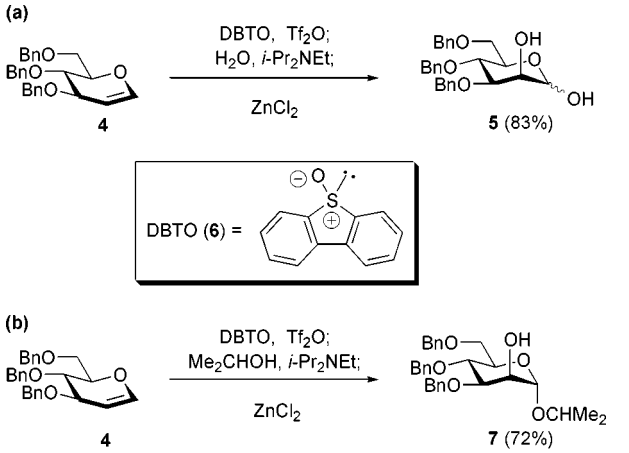
oxidative glycosylations.[6] This allows for the one-pot conversion of glucal substrates to 2-hydroxyglucopyranosides via stereoselective oxygen atom transfer from the sulfoxide reagent to the C(2)-position of the glycal donor (Scheme 2, **1** → **3**). This discovery led us to pursue the prospect of achieving complementary stereochemical control in our sulfonium-mediated oxidative glycosylation reaction to address the long-standing challenge of direct mannopyranoside synthesis from glucals, especially in light of the abundance of mannopyranose residues in nature.

Scheme 2



It was envisioned that the structure of the sulfoxide reagent in this transformation would have a significant influence on the stereochemical course in the oxidative glycosylation reaction. This hypothesis was verified when dibenzothiophene-5-oxide (DBTO, **6**) was employed as the sulfoxide reagent in combination with triflic anhydride in the glucal activation/oxidation process. The use of this reagent pair led to a dramatic reversal in the stereochemical outcome of the oxidative glycosylation, resulting in the stereoselective formation of 2-hydroxy*manno*pyranosides (Scheme 3). For example, treatment of a mixture of tri-*O*-benzyl-D-glucal (**4**) and DBTO (5 equiv) with Tf_2O (2 equiv) at −78 °C led to complete activation of the glycal (Scheme 3a); subsequent introduction of water as a nucleophile/glycosyl acceptor in the presence of diisopropylethylamine and $ZnCl_2$ provided 3,4,6-tri-*O*-benzyl-D-mannopyranose (**5**) in 83% yield (7:1, α:β) as a single C(2)-diastereomer. No glucopyranose products were detected. Similarly, when **4** is activated with DBTO and Tf_2O, employing 2-propanol (3 equiv) as the glycosyl acceptor (Scheme 3b), 2-propyl 3,4,6-tri-*O*-benzyl-mannopyranoside (**7**, 72%) is isolated as the only product of oxidative glycosylation. These results highlight several key aspects of this novel transformation, including (1) the establishment of DBTO and Tf_2O as a new glycal activating agent; (2) the demonstration of exquisite stereochemical control over the newly formed C(2)-stereocenter in the oxidative glycosylation reaction simply by appropriate selection of the sulfoxide reagent; and (3) the first realization of a method for direct stereoselective conversion of glucals to mannopyranosides.

Scheme 3



A proposed mechanism for this stereoselective glycosylation reaction is summarized in Scheme 4. The initial step is believed to be the activation of DBTO with triflic anhydride to form dibenzothiophene bis(triflate) (**8**) in situ.[7] The electrophilic species **8** can subsequently activate the glycal nucleophile from the more sterically accessible α-face to generate the oxocarbenium species **9**, which incorporates a latent sulfide leaving group at C(2). In the presence of excess DBTO, addition of a second equivalent of the sulfoxide from the β-face would afford the anomeric oxosulfonium intermediate **10**. Following addition of the hydroxyl nucleophilic acceptor (R′OH, 3 equiv) and the acid scavenger diisopropylethylamine, nucleophilic addition of the first equivalent of the acceptor (R′OH) to the oxosulfonium center of **10** would lead to heterolytic cleavage of the S−O bond, resulting in concomitant intramolecular displacement of dibenzothiophene from C(2). The result would entail formation of the β-1,2-anhydropyranoside **11**, as well as the byproducts dibenzothiophene (**12**) and the acceptor-derived sulfonium salt **13** (which is hydrolyzed upon aqueous workup of the reaction to regenerate the acceptor and DBTO). The final stages of the oxidative glycosylation can then proceed by Lewis acid ($ZnCl_2$) mediated epoxide ring opening by

(3) Review: (a) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380−1419. For C2-nitrogen substituents, see: (b) Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244−1251. (c) Leblanc, Y.; Fitzsimmons, B. J.; Springer, J. P.; Rokach, J. *J. Am. Chem. Soc.* **1989**, *111*, 2995−3000. (d) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811−5819. (e) Czernecki, S.; Ayadi, E. *Can. J. Chem.* **1995**, *73*, 343−350. (f) Rubinstenn, G.; Esnault, J.; Mallet, J.-M.; Sinaÿ, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1327−1336. (g) Du Bois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 3179−3180. (h) Das, J.; Schmidt, R. R. *Eur. J. Org. Chem.* **1998**, 1609−1613. (i) Di Bussolo, V.; Liu, J.; Huffman, L. G. *Angew. Chem. Int. Ed.* **2000**, *39*, 204−207. (j) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Vega, J. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 2525−2529. For C2-halo-substituents, see: (k) Lemieux, R. U.; Levine, S. *Can. J. Chem.* **1965**, *43*, 2190−2198. (l) Tatsuta, K.; Fujimoto, K.; Kinoshita, M.; Umezawa, S. *Carbohydr. Res.* **1977**, *54*, 85−104. (m) Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696−699. (n) Burkart, M. D.; Zhang, Z.; Hung, S.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1997**, *119*, 11743−11746. For C2-sulfur/selenium substituents, see: (o) Jaurand, G.; Beau, J.-M.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1981**, 572−573. (p) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 2723−2726. (q) Preuss, R.; Schmidt, R. R. *Synthesis* **1988**, 694−697. (r) Perez, M.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 75−78. (s) Grewal, G.; Kaila, N.; Franck, R. W. *J. Org. Chem.* **1992**, *57*, 2084−2092. (t) Roush, W. R.; Sebesta, D. P.; James, R. A. *Tetrahedron* **1997**, *53*, 8837−8852. For C2-carbon substituents, see: (u) Linker, T.; Sommermann, T.; Kahlenberg, F. *J. Am. Chem. Soc.* **1997**, *119*, 9377−9384. (v) Beyer, J.; Madsen, R. *J. Am. Chem. Soc.* **1998**, *120*, 12137−12138.

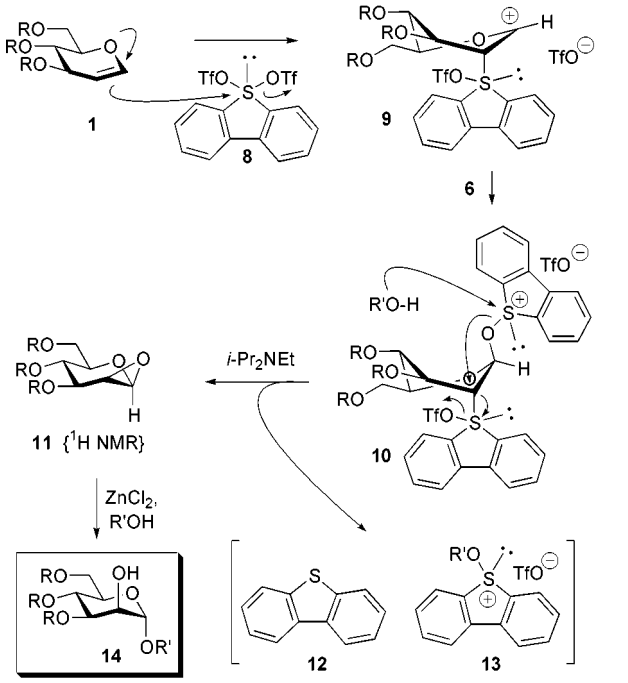
(4) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683−720.

(5) Seeberger, P. H.; Eckhardt, M.; Gutteridge, C. E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10064−10072.

(6) Di Bussolo, V.; Kim, Y.-J.; Gin, D. Y. *J. Am. Chem. Soc.* **1998**, *120*, 13515−13516.

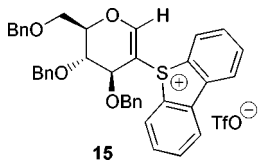
(7) It is unclear whether the activated sulfoxide intermediate **8** exists/reacts as a sulfonium species or a σ-sulfurane species.

Scheme 4



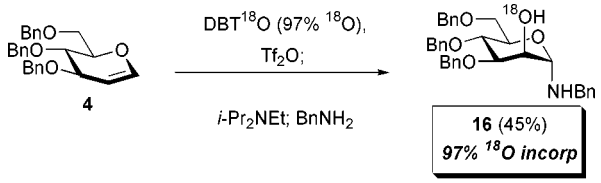
the excess acceptor R′OH to generate the 2-hydroxy mannopyranoside product **14** in a one-pot procedure.

Several lines of evidence are consistent with the mechanistic hypothesis outlined in Scheme 4. In the oxidative glycosylation of 2-propanol with tri-*O*-benzyl-D-glucal (**4**, Scheme 3) using DBTO and Tf_2O, 0.93 equiv of dibenzothiophene (**12**) was isolated at the end of the reaction. In addition, the C(2)-vinyl sulfonium triflate salt **15** was also



isolated (13%) as a byproduct of this reaction, presumably a result of elimination of the H(2) proton from the proposed oxocarbenium intermediate **9**.[8] To unambiguously establish that the oxidation process proceeds by oxygen atom transfer from DBTO to the C(2)-position of the 2-hydroxymannopyranoside product (Scheme 4), an oxidative glycosylation of benzylamine (a non-oxygen nucleophile) was performed with ^{18}O-labeled DBTO (97% ^{18}O) and Tf_2O (Scheme 5). This reaction led to the isolation of the C(1)-benzylamino-2-hydroxy-α-mannopyranoside **16** in 45% yield with 97% ^{18}O-incorporation, thereby verifying the source of oxygen transfer in the transformation.[9] Finally, tracking of the oxidative glycosylation reaction by NMR clearly revealed the formation of the β-1,2-anhydropyranoside **11** following introduction of the acceptor and acid scavenger. It should be emphasized that although product analysis and detection of **11** are consistent with Scheme 4, the details of the initial glucal activation process, especially the origin of the dramatic

Scheme 5



stereochemical reversal in the oxygen transfer process as it relates to sulfoxide structure (i.e., Ph_2SO vs DBTO), are at present under investigation.[10]

To better define the scope of this method for the one-pot synthesis of 2-hydroxymannopyranosides, a series of oxidative glycosylations were performed from selectively protected glucal donors and hydroxy acceptors (Figure 1).[11] In this respect, donors incorporating benzyl ether, isopropylidene

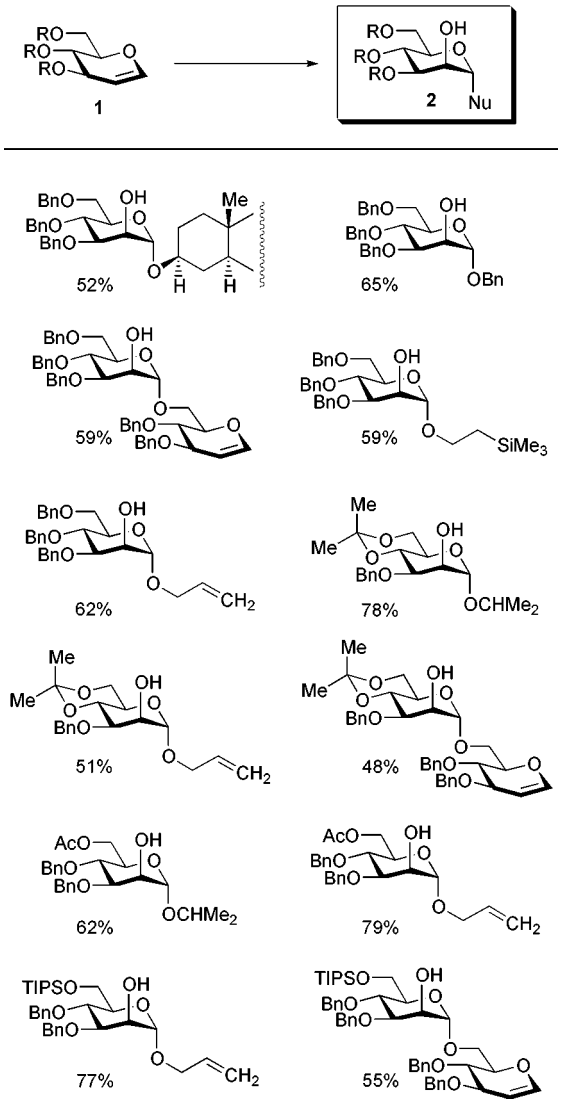


Figure 1. 2-Hydroxy-α-mannopyranosides derived from glucal donors.

ketal, hindered silyl ethers,[12] and acetate ester protective groups were found to be compatible with this method. In addition, a host of 2-hydroxy-α-mannopyranosides can be prepared with a variety of hydroxy nucleophiles, such as dihydrocholesterol, 2-propanol,[13] benzyl alcohol, trimethylsilylethanol, and allyl alcohol, many of which also function as convenient anomeric protective groups in carbohydrate synthesis. Finally, more complex carbohydrate nucleophiles such as 3,4-di-*O*-benzyl-D-glucal can also function as useful acceptors to generate the corresponding disaccharides, which show promise for oligosaccharide synthesis.[14]

In summary, a new method for the synthesis of 2-hydroxymannopyranosides has been established. This procedure, employing DBTO and Tf_2O as a new reagent combination for glucal activation, involves a net 1,2-transdiaxial functionalization of the glucal double bond. This method allows, for the first time, a one-pot conversion of glucal donors to 2-hydroxymannopyranosides, a transformation that has traditionally required at least a three- or four-step synthetic sequence. This method should not only facilitate synthetic access to biologically important mannose-rich oligosaccharides, but it may also provide an intriguing method for stereoselective oxygen transfer to electron-rich olefins in general.

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Supporting Information Available: Experimental details and spectral/analytical data for the glycoside products. This material is available free of charge via the Internet at http://pubs.acs.org.

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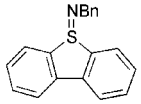
(8) The use of excess DBTO served to minimize the formation of the unwanted byproduct **15**, presumably a result of increased stabilization of the putative oxocarbenium intermediate arising from glycal activation (i.e., **9** → **10**).

(9) The corresponding benzylsulfilimine derivative **17** was also isolated as a byproduct, which is consistent with the presumed acceptor-induced epoxide ring closure in Scheme 4.



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(10) One hypothesis is that the reagent combination of Ph_2SO and Tf_2O reacts as a monomeric pyramidalized sulfonium salt (i.e., $[Ph_2SOTf]^+ \cdot [TfO]^-$) that assumes an axial β-approach onto the glucal in a chairlike transition structure, leading to a net transfer of oxygen to the α-face of C(2) of the glucal. Conversely, the DBTO·Tf_2O reagent may react as a neutral pseudotrigonalbipyramidal σ-sulfurane **8** or perhaps as a bis(sulfonium) salt (i.e., $[(C_6H_4)_2SOS[(C_6H_4)_2]^{2+} \cdot 2[TfO]^-$), which assumes a sterically favorable α-approach onto the glucal (i.e., *trans* to the C(3)-substituent), leading to a net transfer of oxygen to the β-face of the glucal (Scheme 4). Attempts to identify the putative intermediates **9** and/or **10** are underway to gain insight into the validity of such a hypothesis.

(11) In these reactions, 0.5 equiv of 2,4,6-tri-*tert*-butylpyridine can be introduced at the outset of the reaction to neutralize trace amounts of triflic acid that could potentially lead to unproductive glucal decomposition.

(12) For the oxidative glycosylation of allyl alcohol with 3,4-di-*O*-benzyl-6-*O*-triisopropylsilyl-D-glucal, 7% of the corresponding 2-hydroxy-β-D-glucopyranoside was also isolated.

(13) Although fairly unhindered secondary alcohols can be oxidatively mannosylated with this procedure, more hindered secondary alcohol acceptors, such as methyl 2,3,6-tri-*O*-benzyl-D-glucopyranose, were ineffective, presumably a result of inefficient addition of the nucleophile to the putative oxosulfonium salt **10** in the epoxide ring closure step. Efforts are currently underway to develop a procedure for the mannosylation of hindered acceptors by introducing a sacrificial nucleophile to form the intermediate anhydropyranoside prior to epoxide opening with the desired acceptor.

(14) The excess carbohydrate acceptor can be recovered at the end of the reaction.