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C2-Hydroxyglycosylation with Glycal Donors. Probing the Mechanism of Sulfonium-Mediated Oxygen Transfer to Glycal Enol Ethers

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Abstract: The C2-hydroxyglycosylation reaction employing the reagent combination of a diaryl sulfoxide and triflic anhydride offers a novel method for glycal assembly whereby a hydroxyl functionality is stereoselectively installed at the C2-position of a glycal donor with concomitant glycosylation of a nucleophilic acceptor. Mechanistic investigations into this reaction revealed a novel process for sulfonium-mediated oxidation of glycal enol ethers in which the sulfoxide oxygen atom is stereoselectively transferred to the C2-position of the glycal. ^{18}O-labeling studies revealed that the S-to-C2 oxygen-transfer process involves initial formation of a C1−O linkage followed by O-migration to C2, leading to the generation of an intermediate glycosyl 1,2-anhydropyranoside that serves as an in situ glycosylating agent. These findings are consistent with the initial formation of a C2-sulfonium−C1-oxosulfonium pyranosyl species upon activation of the glycal donor with $Aryl_2SO{\cdot}Tf_2O$.

Introduction

The development of new methods for the preparation of complex oligosaccharides and glycoconjugates is a challenging endeavor in organic synthesis and glycobiology. Glycosylation is a critical function that modulates important cellular processes[1] and has prompted the development of numerous chemical methods for the construction of glycosidic bonds.[2] The use of glycal substrates in oligosaccharide synthesis is an attractive strategy for carbohydrate synthesis, as selective functionalization at the C2-position of the glycal enol ether and anomeric bond formation can be achieved in the glycosylation process. Elegant methods are available by which oxygen,[3] nitrogen,[4] halide,[5] sulfur, selenium,[6] carbon,[7] and hydrogen[8] substituents can be introduced at the C2-position to provide synthetic glycoconjugates of varied structure and function. In particular, oxidative glycosylation methods in which an oxygen substituent is directly introduced at the C2-position of a glycal donor have seen extensive utility in carbohydrate synthesis. This "glycal assembly" approach, which typically involves direct glycal epoxidation[9] followed by oxirane ring opening of the resulting 1,2-anhydropyranoside[10] by a nucleophilic glycosyl acceptor, has seen recent remarkable advances in the context of the preparation of complex natural products, immunostimulants, and cell-surface oligosaccharides.[11]

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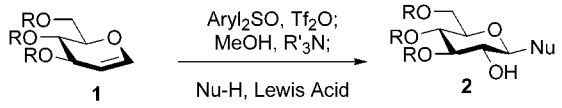
Scheme 1

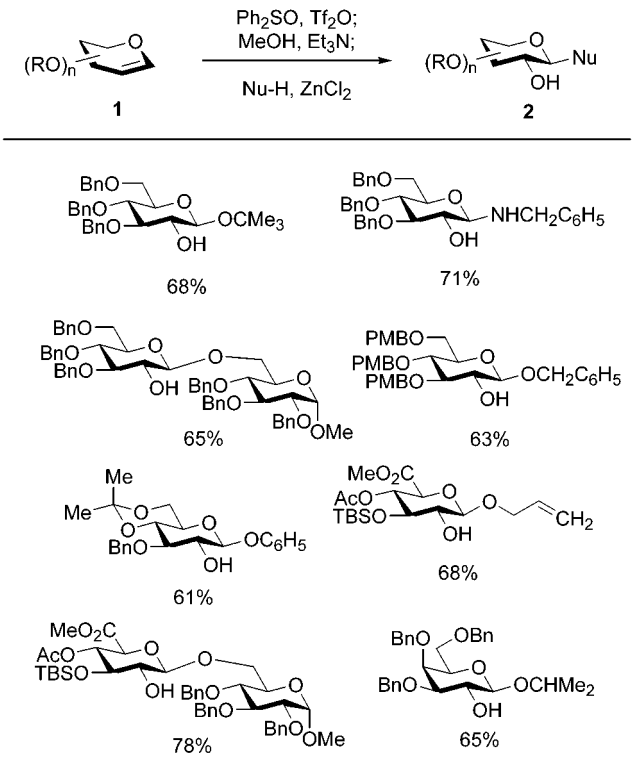


Existing methods for glycal epoxidation involve the use of well-known alkene oxidants such as peroxyacids and dioxirane reagents.[9] Recently, we have developed a new method for C2-hydroxyglycosylation (Scheme 1) with glycal donors (**1**),[12] wherein a mixture of excess diaryl sulfoxide and Tf_2O is employed as the glycal oxidant. Following initial glycal activation with this reagent combination, subsequent sequential addition of methyl alcohol and a tertiary amine (R'_3N), followed by the glycosyl acceptor (Nu-H) and a Lewis acid such as $ZnCl_2$, yields C2-hydroxypyranosides **2** in a one-pot procedure. The process offers a new method for sulfonium-mediated oxygen transfer to glycals and thus presents a novel means for glycoconjugate construction. We report herein our investigations into the identification and characterization of reactive glycosyl intermediates in the process, thereby providing key insights into the pathway of oxygen transfer.

Results and Discussion

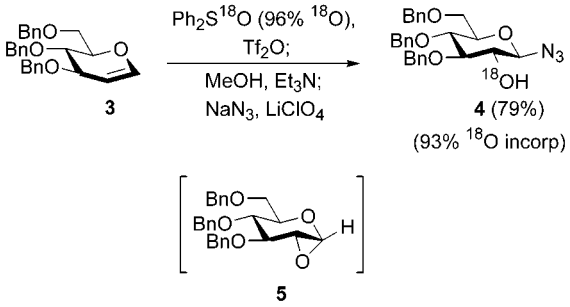
The C2-hydroxyglycosylation reaction depicted in Scheme 1 involves a one-pot procedure, in which an oxygen-transfer reagent is generated in situ from the addition of triflic anhydride (1.5 equiv) to a solution of glucal **1** (1 equiv), diphenyl sulfoxide (3 equiv), and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 3−4 equiv) in dichloromethane at −78 °C. After 1 h at −40 °C, anhydrous methyl alcohol (1 equiv) and triethylamine (3 equiv) are introduced. The reaction is allowed to proceed at 23 °C for 1 h, at which time the glycosyl acceptor (Nu-H, 2−3 equiv) and a Lewis acid ($ZnCl_2$, 1−2 equiv) are added to afford the C2-hydroxy-β-D-glucopyranoside product **2** in good yields and high diastereoselectivity. The method was found to be amenable to the preparation of a variety of O- and N-glycoconjugates (Chart 1).[12,13]

Chart 1



Proposed Reaction Pathways. The transformation in Scheme 1 provides a useful method for oxygen transfer to glycal donors with concomitant anomeric bond construction. The reaction pathway appears to involve a novel process for oxygen transfer to glycals, especially in light of the paucity of existing methods for sulfoxide-mediated oxidation of electron-rich alkenes.[14] A number of reaction pathways can be envisioned for the oxidative glycosylation, although it is likely that the mechanism of the transformation proceeds via initial electrophilic activation of the glycal donor by the $Ph_2SO{\cdot}Tf_2O$ complex.

Scheme 2



Our initial observations revealed several key aspects of the C2-hydroxyglucosylation. First, nearly stoichiometric quantities of Ph_2S are generated in these glycosylation reactions, which is indicative of the sulfoxide reagent serving as the oxidant. This hypothesis was tested by an ^{18}O-labeling experiment (Scheme 2) in which $Ph_2S^{18}O$ (96% ^{18}O incorporation) was employed as the sulfoxide reagent in an oxidative glycosylation with tri-*O*-benzyl-D-glucal (**3**) as the donor and sodium azide as a non-oxygen nucleophilic acceptor. The C2-hydroxy glycosyl azide **4** (79%) is formed with 93% ^{18}O incorporation (as measured by FAB^+ mass spectrometry) along with 0.7 equiv of Ph_2S. This result clearly indicates that the oxidation process proceeds through a stereoselective oxygen transfer from the sulfoxide reagent to the C2-position of the glycal donor. Second, monitoring of the oxidative glycosylation reaction with tri-*O*-benzyl-D-glucal (**3**) by ^1H NMR revealed that the 1,2-anhydropyranoside **5** was formed as the principal carbohydrate species in solution following the addition of MeOH, prior to the

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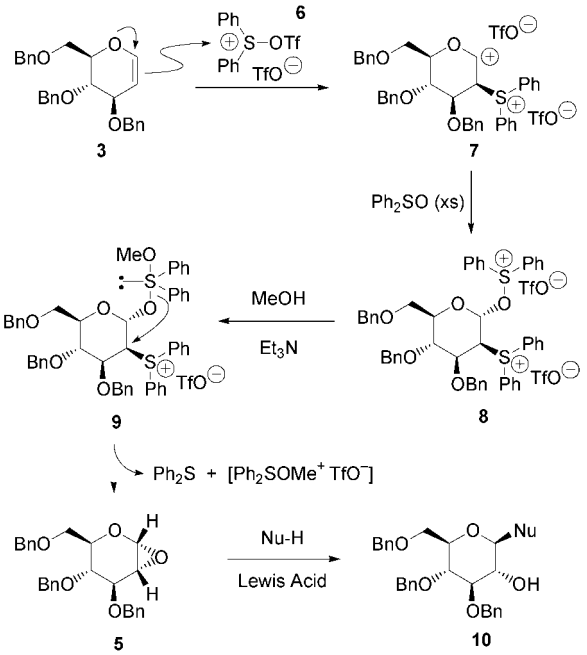
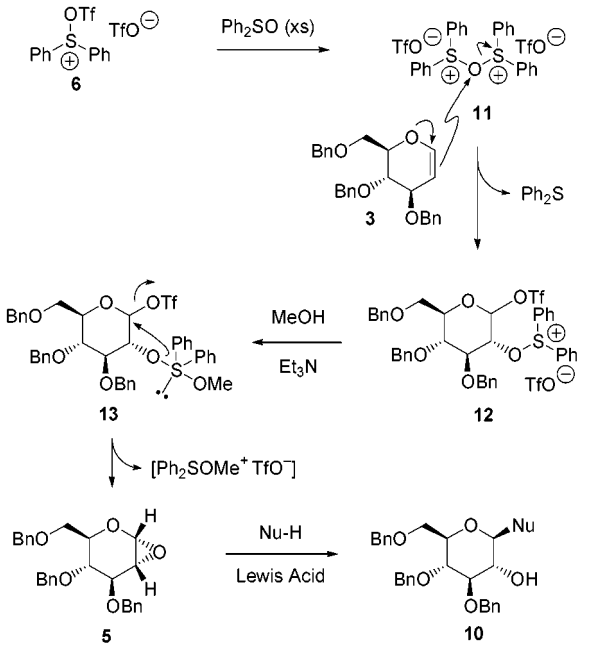
Scheme 3



Scheme 4



introduction of the nucleophilic acceptor.[15] Thus, the formation of the C2-hydroxyglycoside products illustrated by **4** is likely the result of nucleophilic ring opening of 1,2-anhydropyranoside intermediates such as **5**. It is also significant that the formation of the α-glucal epoxide **5** occurs only after the addition of the nucleophile (i.e., MeOH) to the activated glycal intermediate. Finally, the formation of the C2-hydroxyglycoside products proceed efficiently only in the presence of excess sulfoxide reagent. These initial observations provide a useful mechanistic framework from which plausible reaction pathways for the oxygen-transfer process can be investigated.

Two possible reaction pathways for Ph_2SO-mediated C2-hydroxyglycosylation consistent with the above observations are illustrated in Schemes 3 and 4. In the first (Scheme 3), the reagent combination of $Ph_2SO{\cdot}Tf_2O$ is considered to generate diphenylsulfide bis(triflate) (**6**) in situ, which can engage in electrophilic activation of the glycal donor at C2. The resulting C2-functionalization of **3** generates a C2-sulfonium−C1-oxocarbenium (or glycosyl) triflate intermediate **7**, which incorporates electrophilic sites at C1 and C2. In the presence of excess sulfoxide reagent, O-substitution of excess Ph_2SO at the anomeric position leads to the C2-sulfonium−C1-oxosulfonium pyranosyl intermediate **8**. Addition of an initial hydroxyl nucleophile such as MeOH then leads to addition of the alcohol at the anomeric oxosulfonium group, generating a transient anomeric σ-sulfurane species **9**. Fragmentation of **9** with concomitant intramolecular displacement of the C2-sulfonium substituent results in formation of the observed 1,2-anhydropyranoside **5**, accompanied by expulsion of Ph_2S and $Ph_2SOMe^+{\cdot}TfO^-$, which is hydrolyzed to Ph_2SO upon aqueous workup. Finally, introduction and glycosylation of the nucleophilic acceptor (Nu-H) by **5** generates the C2-hydroxy-β-glucopyranoside **10**. It is worth noting that the stereochemical course of the reaction involves a glucal → β-glucopyranoside transformation by way of the α-1,2-anhydropyranoside **5**. According to Scheme 3, this requires a sterically demanding β-approach of the sulfonium reagent **6** onto the glycal **3** (i.e., syn to the C3-alkoxy substituent) to provide **7**/**8**. This is plausible, given that the sulfonium electrophile would assume a favorable β-axial approach onto the C2-position of the glucal[16] in a chairlike transition structure, resulting in a net 1,2-trans-diaxial functionalization of the endocyclic π-system in **3** to form **8**.

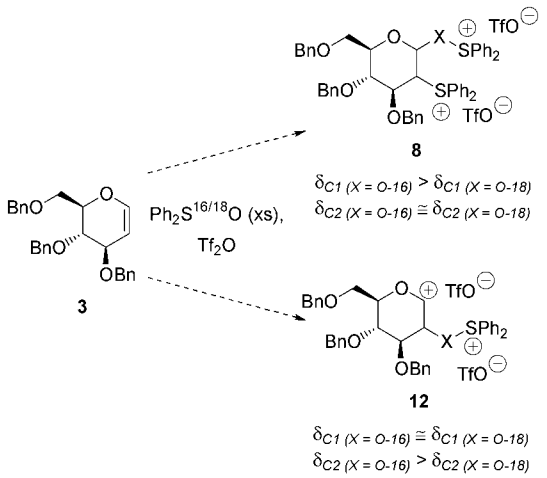
An alternate reaction pathway (Scheme 4) invokes a different sulfonium reagent in the glycal activation process. In situ generation of diphenylsulfide bis(triflate) (**6**) in the presence of excess Ph_2SO leads to the formation of the oxygen-bridged bis(sulfonium) salt **11** prior to glycal activation. If electrophilic activation of glycal **3** were to occur by addition of the C2-π-nucleophile onto a *sulfonium* center within **11**, the reaction pathway depicted in Scheme 3 would ensue. Alternatively, addition of the C2-π-nucleophile of **3** to the bridging *oxygen* functionality in **11** results in expulsion of Ph_2S and formation of the C2-oxosulfonium−C1-pyranosyl triflate intermediate **12**. Upon introduction of 1 equiv of MeOH as a sacrificial nucleophile, its addition to the C2-oxosulfonium functionality in **12** initiates the scission of the S−O bond, leading to intramolecular expulsion of the anomeric triflate functionality at C1 to generate the observed 1,2-anhydropyranoside intermediate (i.e., **12** → **13** → **5**). In this proposed reaction pathway (Scheme 4), the stereochemical course of the activation process is distinct from that of Scheme 3. In this case, α-approach of **11**, consistent with reagent approach under steric control, leads to initial transfer of the oxygen atom to the α-face of the glycal at C2.[17] Nevertheless, this reaction pathway is also consistent with the above observations in the C2-hydroxyglycosylation reaction, which include (1) the transfer of an oxygen atom from the sulfoxide reagent to the C2-position of the glycal donor; (2) the requirement for excess sulfoxide reagent for the reaction to proceed; (3) the generation of Ph_2S as a principal byproduct;

(15) This assignment was verified by independent synthesis. See ref 9c.

(16) β-Approach of electrophilic reagents onto the C2-position of protected glucal substrates are not uncommon. See, for example, refs 3, 5a,b, and 6a.

(17) For examples of α-approach of electrophilic reagents onto the C2-position of protected glucal substrates, see ref 6c−f.

Scheme 5

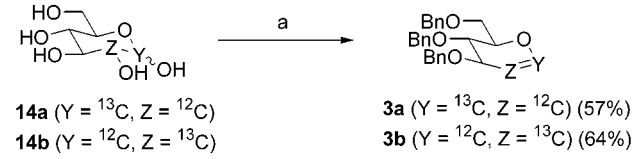


and (4) the formation of the 1,2-anhydropyranoside **5** as a key intermediate in the O-transfer process.

Detection of Reactive Glycosyl Intermediates. A key feature which distinguishes between the reaction pathways outlined in Schemes 3 and 4 is the stage at which the C2−O bond is formed during the C2-hydroxyglycosylation reaction. In Scheme 3, glycal oxidation proceeds by formation of the α-C1−O bond prior to oxirane formation; in Scheme 4, the α-C2−O linkage is established prior to oxirane formation. Thus, detection and characterization of the putative reactive intermediates **8** and **9** (Scheme 3) or **12** and **13** (Scheme 4) would reveal the course of oxygen delivery from sulfoxide to glycal.

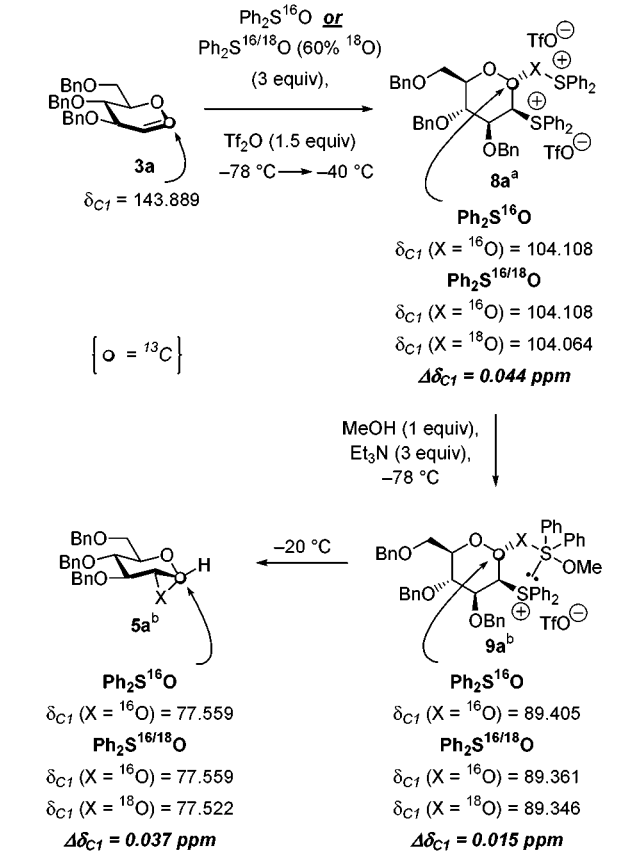
To determine whether the initial glycosyl intermediate formed in the oxidative glycosylation incorporates a C1−O or a C2−O linkage, low-temperature NMR monitoring of the glycal activation process was performed, employing heavy-atom ^{18}O-labeled sulfoxide reagents. It is known that ^{13}C NMR resonances experience a small but significant upfield chemical shift perturbation (i.e., ∼0.01−0.05 ppm) when directly bound to ^{18}O relative to that of a ^{13}C−^{16}O linkage;[18] consequently, this technique should be amenable to establishing the nature of C−O connectivity in the reactive glycosyl intermediates generated in the C2-hydroxyglycosylation process. Activation of a glycal donor **3** (Scheme 5) with the reagent combination of Ph_2SO·Tf_2O would, according to the proposed pathways in Schemes 3 and 4, generate two different intermediates, either **8** or **12**. If the C1-oxosulfonium intermediate **8** were formed as the initial species with $Ph_2S^{18}O$ as the sulfoxide reagent, an upfield ^{13}C1 chemical shift perturbation would be observed relative to reaction with unlabeled $Ph_2S^{16}O$.[19] Conversely, if the C2-oxosulfonium intermediate **12** were generated in the activation process, a ^{13}C2 upfield chemical shift perturbation in the range of 0.01−0.05 ppm would be observed with $Ph_2S^{18}O$ as the

Scheme 6 [a]



[a] Reagents and conditions: (a) Ac_2O, HBr, AcOH; Zn, $CuSO_4$; $PhCH_2Cl$, KOH.

Scheme 7 [a]



[a] δ_{C1} values measured at −40 °C. [b] δ_{C1} values measured at −20 °C.

sulfoxide reagent.[20] To this end, both the ^{13}C1- and ^{13}C2-labeled 3,4,6-tri-*O*-benzyl-D-glucal substrates **3a** and **3b** (Scheme 6) were prepared from ^{13}C1- and ^{13}C2-labeled glucose (**14a/b**), respectively,[21] and employed in this study to ensure adequate detection and unambiguous assignment of both the ^{13}C1 and ^{13}C2 resonances of the putative reactive intermediates.

The first series of low-temperature ^{13}C NMR investigations employed the ^{13}C1-labeled glucal **3a** (Scheme 7, δ_{C1} = 143.889 in CD_2Cl_2) with a focus on the reaction pathway in Scheme 3. Upon treatment of this donor with the reagent combination of $Ph_2S^{16}O$ (3 equiv) and Tf_2O (1.5 equiv) at −78 °C, followed

(18) See, inter alia: (a) Jameson, C. J. *J. Chem. Phys.* **1977**, *66*, 4983−4988. (b) Risley, J. M.; Van Etten, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 252−253. (c) Darensbourg, D. J. *J. Organomet. Chem.* **1979**, *174*, C70−C76. (d) Vederas, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 374−376. (e) Vederas, J. C. *Can. J. Chem.* **1982**, *60*, 1637−1642. (f) Risley, J. M.; Van Etten, R. L. In *NMR—Basic Principles and Progress*; Gunther, H., Ed.; Springer-Verlag: Berlin, 1990; Vol. 22, pp 81−168.

(19) Any chemical shift perturbation at ^{13}C2 in **8** would likely be too small to be observed at low temperature. ^{18}O chemical shift perturbations on β- and γ-^{13}C signals can be detected, although magnitudes of $\Delta\delta$ are typically <0.01 ppm. See, for example: (a) Moore, R. N.; Diakur, J.; Nakashima, T. T.; McLaren, S. L.; Vederas, J. C. *J. Chem. Soc., Chem. Commun.* **1981**, 501−502. (b) Mega, T. L.; Van Etten, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 12056−12059.

(20) It is worth noting that in the proposed formation of either diphenylsulfide bis(triflate) (**6**) or bis(sulfonium) species (**11**), 50% of the triflate anions could conceivably incorporate ^{18}O if rapid exchange of the triflate anions were to occur at the sulfonium center(s). A mechanism involving oxygen transfer from sulfoxide to triflate to glycal is unlikely, as this would erode the amount of ^{18}O incorporation on the C2-hydroxyglycoside product. The possibility of incorporation of ^{18}O into 50% of the triflate anions in the activation process might also lead to a ^{13}C1 upfield chemical shift perturbation in the intermediates **7** (Scheme 3) or **12/13** (Scheme 4) if a covalent C1−O-triflate bond were to exist in these species; however, if this were the case, the relative intensity of the upfield-shifted ^{13}C1−^{18}O resonance would be significantly diminished compared with the amount of ^{18}O incorporation in the sulfoxide reagent.

(21) Shull, B. K.; Wu, Z.; Koreeda, M. *J. Carbohydr. Chem.* **1996**, *15*, 955−964.

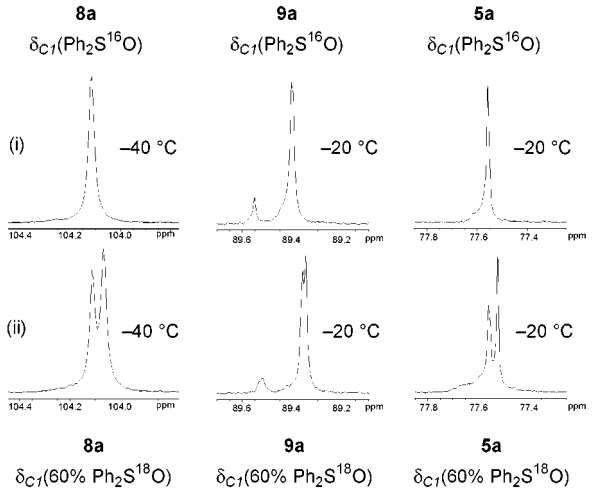


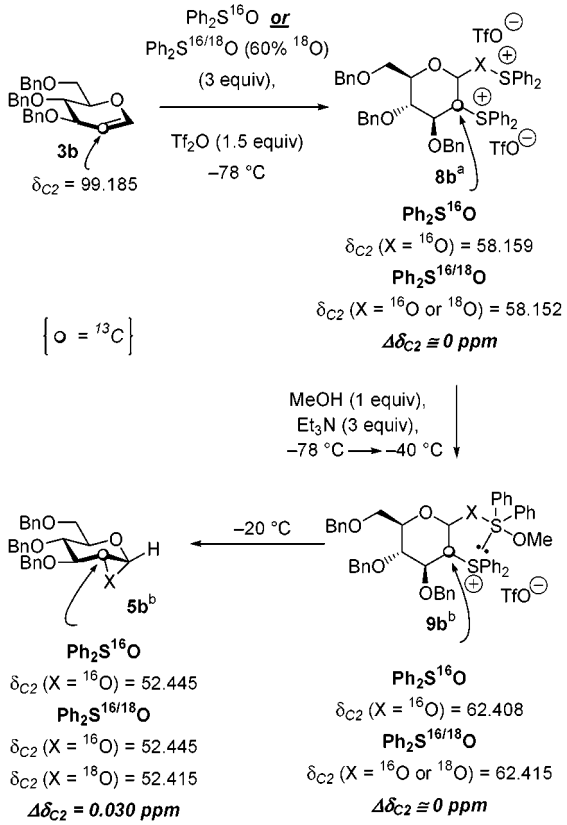
Figure 1.

by warming to −40 °C, a principal glycosyl intermediate, assigned as **8a** (Scheme 7, Figure 1i), bearing a ^{13}C1 resonance at δ104.108 was observed. Recooling of the reaction to −78 °C and subsequent addition of the initial sacrificial nucleophile (MeOH, 1 equiv) and Et_3N (3 equiv) led to the immediate formation of a second glycosyl intermediate, assigned as **9a**. Upon warming of the reaction to −20 °C, steady conversion to the 1,2-anhydropyranoside **5a** (δ_{C1} = 77.559)[15] was observed.

With the detection of two principal intermediates in the oxidative glycosylation reaction prior to oxirane formation, the analogous ^{13}C1 NMR tracking experiment was performed employing 60% ^{18}O-labeled diphenyl sulfoxide to probe the structure of the reactive species.[22] Treatment of **3a** with 60% $Ph_2S^{18}O$ and Tf_2O (3.0 and 1.5 equiv, respectively) led to the formation of an intermediate **8a** with two distinct ^{13}C1 resonances, one at δ 104.108 and a second of slightly larger intensity at δ 104.064 (Scheme 7, Figure 1ii). This chemical shift perturbation ($\Delta\delta_{C1}$ = 0.044 ppm upfield) upon incorporation of $Ph_2S^{18}O$ as the oxidant is indicative of a ^{13}C1−^{18}O bond, consistent with the initial intermediate of glycal activation being the glycosyl oxosulfonium species **8a**. Subsequent addition of MeOH (1 equiv) and Et_3N (3 equiv) at −78 °C and warming to −20 °C afforded the intermediate **9a** with two ^{13}C1 resonances, one at δ 89.361 and the other at δ 89.346. It should be noted that these two $^{16/18}$O isotopomer ^{13}C1 resonances in **9a** could not be resolved at temperatures below −20 °C due to peak broadening; however, upon warming to −20 °C during the conversion to the 1,2-anhydropyranoside **5a**, the $\Delta\delta$ value of 0.015 ppm could be clearly discerned in **9a** (Figure 1ii). Given the marked upfield ^{13}C1 chemical shift of this second intermediate (**9a**) compared to that of the first (**8a**), it is reasonable to propose that the introduction of MeOH generates the glycosyl sulfurane intermediate **9a**, which leads to the 1,2-anhydropyranoside **5a**. Finally, examination of the ^{13}C1 resonances in the 1,2-anhydropyranoside **5a** revealed, not surprisingly, two signals, one at δ 77.559 (^{13}C1−^{16}O) and the other at δ 77.522 (^{13}C1−^{18}O). These initial experiments therefore are consistent with the formation of the intermediates **8** and **9** of Scheme 3,

(22) The chemical shift perturbation values ($\Delta\delta$) to be measured are small (0.01−0.05 ppm), and minor chemical shift fluctuations of this magnitude may occur between NMR experiments, especially at variable temperatures. Thus, use of 60% ^{18}O-labeled Ph_2SO, as opposed to >90% ^{18}O incorporation, ensures the detection of isotope-induced $\Delta\delta$ values in the form of two distinct resonances of nearly equal intensity.

Scheme 8 [a]

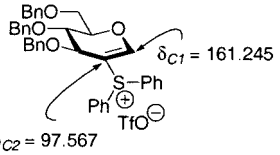


[a] δ_{C2} values measured at −40 °C. [b] δ_{C2} values measured at −20 °C.

both bearing a C1 linkage to the sulfoxide oxygen atom prior to formation of the 1,2-anhydropyranoside **5**.[23]

To evaluate the alternative pathway of Scheme 4 for oxygen transfer in the C2-hydroxyglucosylation reaction, the analogous complementary ^{13}C2 NMR tracking experiments were performed with ^{13}C2-labeled tri-*O*-benzyl-D-glucal (**3b**, δ_{C2} 99.185). Activation of **3b** (Scheme 8, Figure 2) with either $Ph_2S^{16}O$ or $Ph_2S^{16/18}O$ (60% ^{18}O incorporation) and Tf_2O in CD_2Cl_2 at low temperature generates the first glycosyl intermediate **8b** with only a single discernible ^{13}C2 resonance at δ 58.152, even when 60% $Ph_2S^{18}O$ was employed (Scheme 8, Figure 2).[24] Following the addition of MeOH and Et_3N to **8b**, the second intermediate **9b** is generated, incorporating a single ^{13}C2 resonance (δ 62.415), even when 60% $Ph_2S^{16/18}O$ was employed. Finally, conversion of the second intermediate **9b** to the 1,2-anhydropyranoside **5b** at −20 °C produced two ^{13}C2 resonances when

(23) In all of the low-temperature NMR experiments reported herein, initial activation of the glucal is accompanied by the formation of ∼20% of the C2-sulfonium glucal (below) as a byproduct, presumably a result of elimination of H2 from the putative reactive glycosyl species **7** (Scheme 3). This minor competitive pathway could not be avoided, as small temperature fluctuations (i.e., elevations) are inevitably associated with the transfer of the NMR reaction tube to the precooled NMR probe following introduction of Tf_2O. The formation of the C2-sulfonium glucal is also consistent with the pathway depicted in Scheme 3, if it is indeed formed in a manifold diverted from the productive pathway.



(24) Two-bond ^{18}O−C1−^{13}C2 chemical shift perturbations (typically <0.01 ppm; see ref 19) were not detected, presumably due to some degree of peak broadening at low temperature.

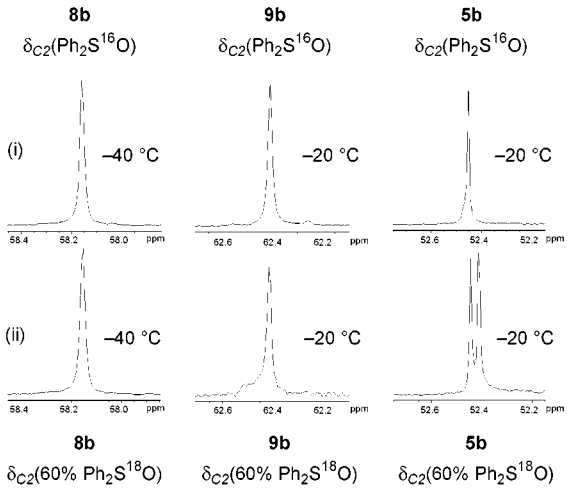
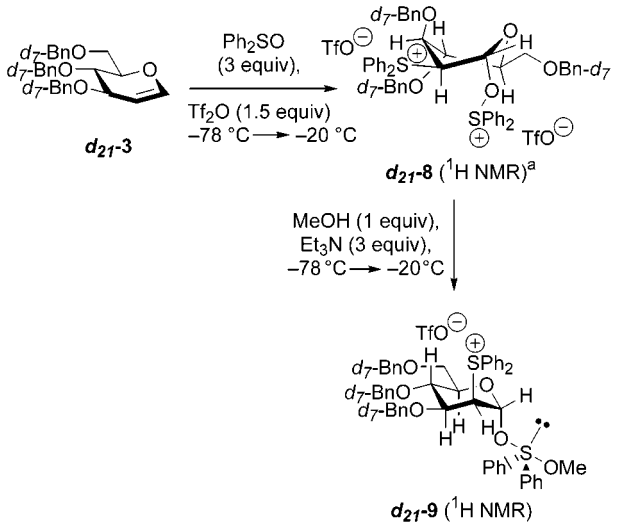


Figure 2.

60% $Ph_2S^{18}O$ was employed, one at δ 52.445 ($^{13}C2-^{16}O$) and the other at δ 52.415 ($^{13}C2-^{18}O$), revealing an ^{18}O-isotope-induced $\Delta\delta_{C2}$ value of 0.030 ppm upfield. These results indicate that both of the glycosyl intermediates **8b** and **9b** are devoid of a C2−O linkage, which is *not* consistent with the expectations for reaction via Scheme 4. Only when **9b** is converted to the 1,2-anhydropyranoside **5b** through the formation of a C2−O linkage is the ^{18}O-heavy-atom $^{13}C2$ chemical shift perturbation detected.[25]

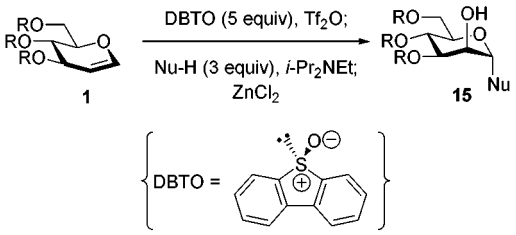
These heavy-atom labeling investigations confirm the C1-to-C2 pathway (consistent with Scheme 3) for oxygen transfer from the sulfoxide reagent to the glycal donor and thus reveal key details concerning the structures of the initial activated glycal intermediates. Further structural characterization of the activated glycosyl intermediates by ^1H NMR analysis allows insight into the stereochemical and conformational properties of **8** and **9**. These studies employed tri-*O*-d_7-benzyl-D-glucal (***d*$_{21}$-3**, Scheme 9)[26] as the glucal donor in the C2-hydroxyglycosylation in order to facilitate identification and assignment of the pyranoside ^1H resonances within the intermediates ***d*$_{21}$-8** and ***d*$_{21}$-9** observed at low temperature. Thus, ^1H NMR analysis of ***d*$_{21}$-8** at −20 °C[27] reveals that it does not exist in a traditional $^4C_1$ chair conformation. Rather, the relatively large $^3J_{H4H5}$ (9.1 Hz) value and the relatively small $^3J_{H1H2}$ (5.5 Hz),[28] $^3J_{H2H3}$ (3.2 Hz), and $^3J_{H3H4}$ (2.3 Hz) values are consistent with a twist-boat conformation (***d*$_{21}$-8**), in which the C2-sulfonium group adopts a pseudoequatorial orientation.[29] In the subsequent stage of the oxidation reaction, addition of MeOH (1 equiv) and Et_3N (3 equiv) to ***d*$_{21}$-8** generates the putative glycosyl sulfurane intermediate ***d*$_{21}$-9**. Low-temperature ^1H NMR analysis (−20 °C) of ***d*$_{21}$-9** reveals a $^3J_{HH}$ coupling pattern distinct from that of ***d*$_{21}$-8**. The relatively large values of $^3J_{H3H4}$ (9.1 Hz; axial-axial) and $^3J_{H4H5}$ (9.1 Hz; axial-axial), the relatively small values of $^3J_{H1H2}$ (<1 Hz; equatorial-equatorial) and $^3J_{H2H3}$ (4.1 Hz; equatorial-axial), and the large value of $^1J_{C1H1}$ (171 Hz; C1−H1 equatorial) are indicative of ***d*$_{21}$-9** being an α-mannopyranosyl-like substrate in a $^4C_1$ chair conformation. These data, in conjunction with the previous ^{18}O-labeling experiments, are consistent with the intermediacy of glycosyl species such as **8** and **9** in the glycal epoxidation pathway outlined in Scheme 3.

Scheme 9 [a]



[a] Warmed to −20 °C for a short time (~6 min) to allow for acquisition of ^1H NMR data with resolved $^3J_{HH}$ values.

Scheme 10



C2-Hydroxymannosylation. The use of Ph_2SO as the sulfoxide reagent for the C2-hydroxyglucosylation leads to the stereoselective formation of C2-hydroxy-β-glucopyranosides when glucal donors are employed. We have recently reported that a complementary manifold for C2-hydroxyglycosylation to generate C2-hydroxy-α-mannopyranosides **15** (Scheme 10) from glucal donors **1** can be accessed when dibenzothiophene 5-oxide (DBTO) is employed as the sulfoxide reagent.[30] This remarkable reversal of diastereoselectivity with a seemingly subtle change in sulfoxide reagent thus allows for the direct conversion of glucal donors to mannopyranosides, a transformation that heretofore has required at least a four-step synthetic sequence.[11b]

(25) The relative intensities of the $^{13}C1$ and $^{13}C2$ resonances which exhibit ^{18}O isotope-inducted $\Delta\delta_C$ values (Figures 1ii and 2ii) all reflect the ratio of ^{18}O incorporation in the sulfoxide reagent (60% ^{18}O). Therefore, it is unlikely that the observed isotope-induced $\Delta\delta_C$ values are due to $^{13}C-^{18}OTf$ linkages arising from the $CF_3SO_2{}^{18}O^-$ counterion byproduct, as this would generate a significantly diminished $^{13}C-^{18}O$ resonance intensity compared to that observed.

(26) Koto, S.; Asami, K.; Hirooka, M.; Nagura, K.; Takizawa, M.; Yamamoto, S.; Okamoto, N.; Sato, M.; Tajima, H.; Yoshida, T.; Nonaka, N.; Sato, T.; Zen, S.; Yago, K.; Tomonaga, F. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 765−777.

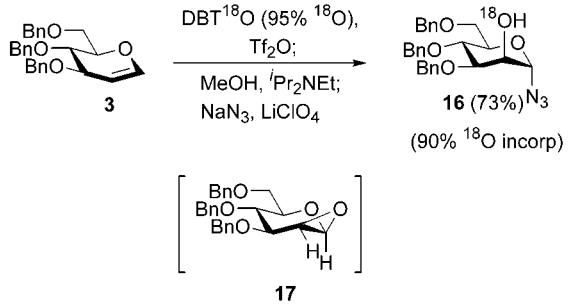
(27) Although the conversion of ***d*$_{21}$-3** to ***d*$_{21}$-8** proceeds rapidly at −78 °C, the solution of ***d*$_{21}$-8** was warmed to −20 °C for a short interval (~6 min) to aquire ^1H NMR data before recooling of the reaction to −78 °C for the next step. Warming of ***d*$_{21}$-8** to −20 °C allowed for the acquisition of ^1H NMR data with adequately resolved $^3J_{HH}$ values.

(28) The observed δ_{H2} value of 6.12 ppm is also consistent with that of α-protons in alkyldiphenylsulfonium salts. See, for example: Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5298−5307.

(29) A $^1J_{C1H1}$ value of 189 Hz was observed for **8a**. For D-pyranosides in a $^4C_1$ conformation, $^1J_{C1H1}$ values = 170 Hz are indicative of an equatorial C1−H1 linkage (α-glycoside), where the magnitude of $^1J_{C1H1}$ increases with the electron-withdrawing capacity of the anomeric substituent. However, it is worth noting that the twist-boat conformation implied by the ^1H NMR data might preclude direct correlation of $^1J_{C1H1}$ magnitudes with anomeric configuration, especially with cationic substituents on the pyranose ring. See: Duus, J. Ø.; Gotfredsen, C. H.; Bock, K. *Chem. Rev.* **2000**, *100*, 4589−4614.

(30) Kim, J.-Y.; Di Bussolo, V.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 303−306.

Scheme 11

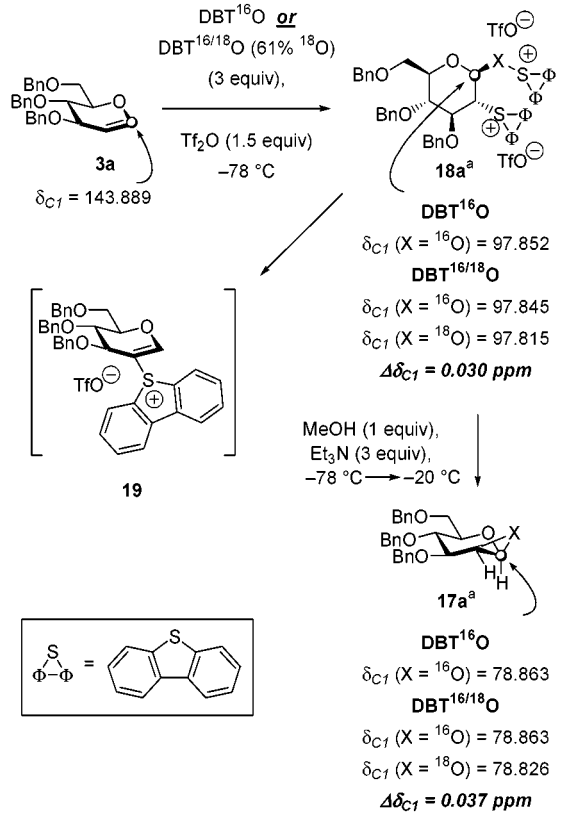


Initial mechanistic investigations into this transformation revealed that (1) excess DBTO is required for the transformation to proceed; (2) dibenzothiophene is formed as a principal byproduct of the reaction; (3) the sulfoxide oxygen atom is transferred to the C2 position of the glycal donor, as evidenced by ^{18}O-labeling of the sulfoxide reagent (Scheme 11) in the C2-hydroxyglycosylation of NaN_3 to form **16**; and (4) the β-1,2-anhydropyranoside **17** is formed as the key intermediate in the oxygen-transfer process prior to the glycosidic coupling event.[15] It is reasonable that the oxidative glycosylation with glucals employing DBTO proceeds via an oxygen-transfer pathway similar to that employing Ph_2SO. However, given the marked difference in stereochemical outcome of the two reactions (i.e., Scheme 1 vs Scheme 10), we sought to determine whether the reactions involving DBTO also involved a C1-to-C2 oxygen-transfer pathway similar to that depicted in Scheme 3.

^{13}C1-labeled tri-*O*-benzyl-D-glucal (**3a**) was treated with the reagent combination of excess DBTO (3 equiv) and Tf_2O (1.5 equiv) in CD_2Cl_2 at −78 °C (Scheme 12).[31] Monitoring of the reaction of **3a** with DBTO·Tf_2O at −78 °C by ^{13}C NMR revealed the presence of a principal intermediate, assigned as **18a** (Scheme 12). This initial intermediate is stable at −78 °C but undergoes decomposition to the C2-vinylsulfonium salt **19** upon temperature elevation above −40 °C. With the increased propensity for the DBTO-derived glycosyl intermediate **18a** to form the glycal sulfonium salt **19**, the detection of an isotope-induced $\Delta\delta_{C1}$ value when DBT$^{16/18}$O was used was particularly challenging in that resolution of $\Delta\delta_{C1}$ in **18a** was not possible at temperatures below −40 °C due to broadening of the ^{13}C1 resonances. Consequently, the reaction mixture of glucal **3a** and DBT$^{16/18}$O was activated with Tf_2O at −78 °C and then warmed to −20 °C. At this elevated temperature, the unwanted conversion of the reactive glycosyl intermediate **18a** to the C2-sulfonium glycal salt **19** was rapid; however, the ^{13}C1 resonance of **18a** could be monitored transiently at −20 °C as it diminished during the decomposition process. Under these ^{13}C NMR detection conditions, one can observe the putative glycosyl intermediate **18a**, which incorporates a ^{13}C1 resonance at δ 97.852 (Scheme 12) when unlabeled DBTO was employed in the activation (Figure 3i). When 61% ^{18}O-labeled DBT$^{16/18}$O was employed, an isotope-induced $\Delta\delta_{C1}$ of 0.030 ppm could be detected at −20 °C, indicative of the presence of a C1−O linkage within **18a** (Scheme 12, Figure 3ii).

(31) It is worth noting that the previously reported optimized reaction conditions for the conversion of glucals to C2-hydroxy-α-mannopyranosides employed 5 equiv of DBTO (Scheme 10), as these reaction conditions provide α-manno:β-gluco diastereoselectivities of at least 5:1. However, since the reactions in the current NMR studies were performed in 5-mm sample tubes at low temperature where mixing of the reagents is less efficient, only 3 equiv of DBTO was employed to ensure complete dissolution of the sulfoxide reagent at low temperatures. The use of only 3 equiv of DBTO in the NMR reactions led to erosion of the diastereoselectivity of oxygen transfer to the glycal (3:1, **17**:**5**).

Scheme 12 [a]



[a] δ_{C1} values measured at −20 °C in separate experiments.

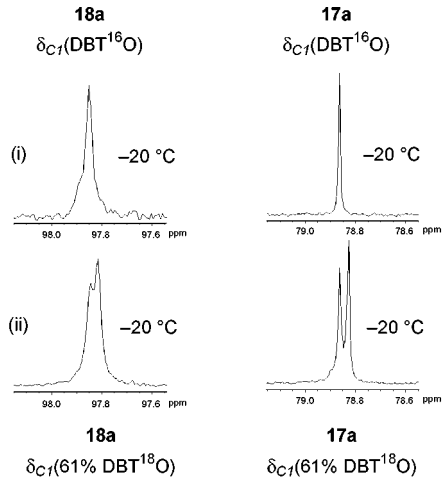
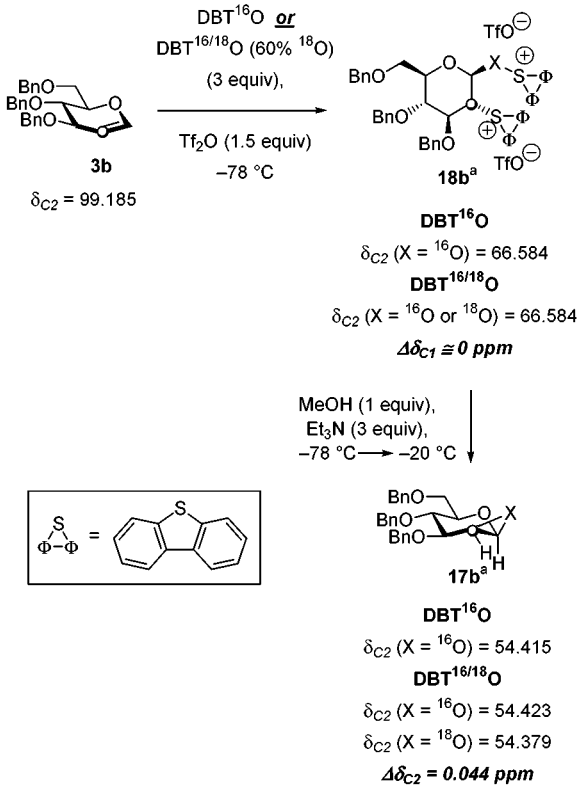


Figure 3.

The next step in the C2-hydroxymannosylation reaction, the introduction of a sacrificial nucleophile (MeOH) to initiate epoxide ring closure, was investigated by treatment of a solution of the glucal donor **3a**, DBTO, and Tf_2O in CD_2Cl_2 at −78 °C with methyl alcohol (1 equiv) and Et_3N (3 equiv) with ^{13}C NMR monitoring. Unlike the previous series of experiments with Ph_2SO, in which the putative glycosyl oxosulfurane **9** could be detected as a second glycosyl intermediate prior to oxirane formation, a similar intermediate could not be detected in the corresponding oxidation employing DBT^{16}O (Scheme 12). Unfortunately, only a complex mixture of intermediates was generated at this stage, as evidenced by multiple ^{13}C1 NMR

Scheme 13 [a]



[a] δ_{C2} values measured at −20 °C in separate experiments.

signals at low temperature upon addition of MeOH and Et_3N to **18a**. However, upon warming of the reaction mixture to −20 °C, the ^{13}C1 signals indicated formation of the β-1,2-anhydropyranoside **17a** (δ_{C1} 78.863, Scheme 12, Figure 3i) as the principal carbohydrate intermediate. When the same experiment was conducted with 61% ^{18}O-labeled DBT$^{16/18}$O, the expected $\Delta\delta_{C1}$ (0.037 ppm upfield) was detected at −20 °C for the β-1,2-anhydropyranoside **17a** (Figure 3ii). These observations establish that a glycosyl intermediate such as **18a**, incorporating a C1−O linkage, is formed prior to the β-1,2-anhydropyranoside.

The complementary experiments employing the ^{13}C2-labeled glucal **3b** were also performed to further characterize the initial activated glycosyl intermediate in this transformation (Scheme 13). Treatment of glucal **3b** with the reagent combination of 61% ^{18}O-labeled DBT$^{16/18}$O and Tf_2O as above led to the formation of the glycosyl intermediate with only a single ^{13}C2 resonance at δ 66.584 at −20 °C, indicating the absence of a ^{13}C2−$^{16/18}$O linkage (**18b**, Scheme 13, Figure 4). Following the addition of MeOH and Et_3N, two ^{13}C2 resonances were observed (δ 54.423 and δ 54.379; $\Delta\delta_{C2}$ = 0.044 ppm), consistent with the ^{13}C2−$^{16/18}$O linkage present in the β-1,2-anhydropyranoside **17b**.

These results for the DBTO-mediated C2-hydroxymannosylation are consistent with a reaction pathway involving initial transfer of the sulfoxide oxygen to the C1-position of the glucal donor, followed by oxygen migration from C1 to C2 via epoxide closure. A hypothesis consistent with the findings in Schemes 12 and 13 invokes the intermediacy of a β-glycosyl oxosulfonium intermediate **18a/b** as the activated glycosyl intermediate, incorporating an α-C2-sulfonium moiety.[32] Such an intermediate could arise from the reagent combination of DBTO and Tf_2O, assuming a sterically favored electrophilic activation of C2 from

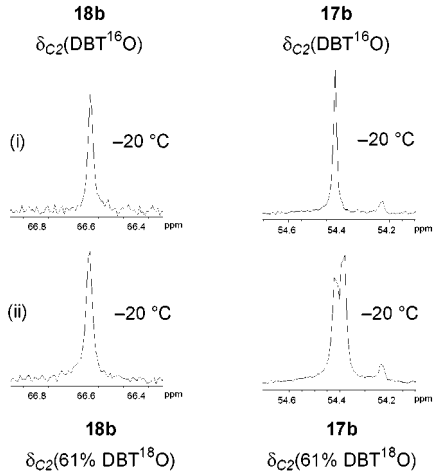


Figure 4.

the α-face,[17] followed by the addition of excess DBTO onto C1 from the β-face to provide **18**. Addition of the sacrificial nucleophile (MeOH) then serves to close the epoxide functionality with concomitant expulsion of dibenzothiophene. The C2-hydroxymannosylation process therefore appears to be analogous to that of C2-hydroxyglucosylation involving Ph_2SO, with the obvious key difference being the reversal of stereoselectivity in the oxygen transfer. While the remarkable stereochemical contrast of the two reactions (Scheme 1 versus Scheme 10) is likely the result of opposing facial selectivities in the initial sulfonium-mediated glycal activation processes, it is worth noting that the origin of the stereochemical reversal in the C2-hydroxyglycosylation reaction employing Ph_2SO versus DBTO is as yet unclear and is currently under investigation.

Conclusion

The C2-hydroxyglycosylation reaction employing the reagent combination of a diaryl sulfoxide and triflic anhydride provides a novel process for oxygen transfer to the enol ether functionality of glycal donors. Initial ^{18}O-labeling studies have established that the C2-hydroxyglucosylation process employing Ph_2SO·Tf_2O proceeds by the net transfer of the sulfoxide oxygen atom to the C2-position of the glucal, a process that also involves the in situ generation of a glucosyl-1,2-anhydropyranoside intermediate. Tracking of the C2-hydroxyglucosylation reaction by low-temperature NMR spectroscopy employing ^{13}C-labeled glycal donors and ^{18}O-labeled diphenyl sulfoxide clearly showed that formation of the intermediate α-1,2-anhydropyranoside **5** proceeds by initial formation of a glycosyl species incorporating a C1−O linkage followed by oxygen transfer to C2 by way of oxirane ring closure. Further spectroscopic characterization of the activated glycosyl species in this transformation is consistent with the intermediacy of a C2-sulfonium−C1-oxosulfonium glycosyl species **8** and a C2-sulfonium−C1-σ-sulfurane species **9** as precursors to the glucosyl-1,2-anhydropyranoside **5**. Analogous investigations into the C2-hydroxymannosylation reaction

(32) Detailed NMR structural characterization of the putative anomeric oxosulfonium intermediate **18** was, unfortunately, not possible given the lability of the intermediate at temperatures above −40 °C. At lower temperatures, proton−proton coupling constants could not be resolved; only a $^1J_{C1H1}$ coupling constant of 184 Hz could be extracted from the NMR data at −78 °C. Although this magnitude of $^1J_{C1H1}$ *may* be indicative of an equatorial C1−H1 linkage in **18a**, the absence of additional information makes it difficult to secure the structural and conformational properties of **18** beyond its C1−O connectivity.

employing DBTO·Tf_2O revealed a similar C1-to-C2 oxygen-transfer process to afford a mannosyl-1,2-anhydropyranoside intermediate **17**. These findings offer critical mechanistic insights into a new method for enol ether oxidation in the context of C2-hydroxyglycosylation.

Experimental Section

General Procedures. All reactions were performed in flame-dried modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper or rubber septa under a positive pressure of argon, unless otherwise noted. Low-temperature NMR experiments were performed in 5-mm NMR tubes (dried under a stream of N_2 gas) topped with rubber septa under a positive pressure of argon. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 30 °C at ca. 25 Torr. Flash column chromatography was performed employing 230−400-mesh silica gel. Thin-layer chromatography (analytical and preparative) was performed using glass plates precoated to a depth of 0.25 mm with 230−400-mesh silica gel impregnated with a fluorescent indicator (254 nm).

Materials. Dichloromethane, diisopropylethylamine, triethylamine, and acetonitrile were distilled from calcium hydride at 760 Torr. CD_2Cl_2 was stored over CaH_2 and vacuum transferred immediately prior to use. Methyl alcohol was distilled from Mg/I_2. ^{18}O-labeled diphenyl sulfoxide ($Ph_2S^{18}O$) and ^{18}O-labeled dibenzothiophene oxide ($DBT^{18}O$) were prepared following literature procedures.[33] Trifluoromethanesulfonic anhydride (Tf_2O) was triply distilled from phosphorous pentoxide.

Instrumentation. Infrared (IR) spectra were obtained using a Perkin-Elmer Spectrum BX spectrophotometer referenced to polystyrene standard. Data are presented as frequency of absorption (cm^{-1}). Proton and carbon-13 nuclear magnetic resonance (^1H NMR or ^{13}C NMR) spectra were recorded on Varian 500 and Varian Inova 500 NMR spectrometers; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ_H 7.26; $CHDCl_2$, δ_H 5.32; $CDCl_3$, δ_C 77.0; CD_2Cl_2, δ_C 53.8). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet and/or multiple resonances), integration, coupling constant in hertz and assignment. Melting points were recorded with a Fisher melting point apparatus and are uncorrected.

Typical Procedure for C2-Hydroxyglycosylation: *O*-Methyl [Methyl 4-*O*-acetyl-3-*O*-(*tert*-butyldimethylsilyl)-β-D-glucuronyl-(1→6)]-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside. Trifluoromethanesulfonic anhydride (25 μL, 0.15 mmol, 1.5 equiv) was added to a solution of methyl 4-*O*-acetyl-3-*O*-(*tert*-butyldimethylsilyl)-glucuronate-D-glycal (33 mg, 0.1 mmol, 1 equiv), diphenyl sulfoxide (61 mg, 0.3 mmol, 3 equiv), and 2,4,6-tri-*tert*-butylpyridine (86 mg, 0.35 mmol, 3.5 equiv) in dichloromethane (3 mL) at −78 °C. The resulting solution was stirred at −78 °C for 30 min and then at −40 °C for 1 h. Methyl alcohol (4.2 μL, 0.1 mmol, 1 equiv) and triethylamine (42 μL, 0.3 mmol, 3 equiv) were added sequentially at −40 °C. The solution was stirred at this temperature for 30 min and then at 0 °C for 1 h and at 23 °C for 1 h. A solution of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (139 mg, 0.3 mmol, 3 equiv) in dichloromethane (3 mL) was then added, and the solution was cooled to −78 °C. Zinc chloride (1.0 M in ether, 200 μL, 0.2 mmol, 2 equiv) was added, and the mixture was stirred at −78 °C for 30 min, at −40 °C for 1 h, at 0 °C for 1 h, and finally at 23 °C for 2 h. The reaction mixture was partitioned between dichloromethane (20 mL) and H_2O (20 mL), and the aqueous layer was further extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was purified by flash column chromatography (20% ethyl acetate in hexane) to afford *O*-methyl [methyl 4-*O*-acetyl-3-*O*-(*tert*-butyldimethylsilyl)-β-D-glucuronyl-(1→6)]-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (63 mg, 78%): colorless oil, R_f = 0.64 (50% ethyl acetate in hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 15H, ArH), 4.99 (d, 1H, J = 10.9 Hz, benzylic-H), 4.94 (dd, 1H, J = 9.2, 9.7 Hz), 4.90 (d, 1H, J = 10.9 Hz, benzylic-H), 4.81 (d, 1H, J = 10.5 Hz, benzylic-H), 4.79 (d, 1H, J = 12.2 Hz, benzylic-H), 4.66 (d, 1H, J = 12.4 Hz, benzylic-H), 4.59 (d, 1H, J = 10.7 Hz, benzylic-H), 4.58 (d, 1H, J = 3.4 Hz, H-1), 4.19 (d, 1H, J = 7.9 Hz, H-1′), 4.11 (dd, 1H, J = 2.4, 11.4 Hz), 3.99 (t, 1H, J = 9.2 Hz), 3.82−3.78 (m, 1H), 3.78 (d, 1H, J = 10.1 Hz), 3.70 (s, 3H, CO_2Me), 3.67−3.63 (m, 2H), 3.51 (dd, 1H, J = 3.4, 9.6 Hz), 3.48−3.44 (m, 2H), 3.37 (s, 3H, O*Me*), 2.38 (d, 1H, J = 2.6 Hz, O*H*), 2.05 (s, 3H, OCO*Me*), 0.84 (s, 9H, *t*Bu), 0.09 (s, 3H, Si*Me*), 0.053 (s, 3H, Si*Me*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.69, 167.95, 138.63, 138.21, 138.03, 128.50, 128.46, 128.42, 128.16, 128.01, 127.98, 127.81, 127.80, 127.67, 103.26, 98.04, 81.95, 79.69, 77.99, 75.78, 74.99, 74.47, 73.90, 73.37, 72.96, 71.98, 69.71, 68.94, 55.29, 52.66, 25.61, 20.85, 18.04, −4.35, −4.90; FTIR (neat film) 3486, 2930, 2362, 1750, 1454, 1372, 1297, 1232, 1030, 839 780, 737, 698 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{43}H_{58}O_{13}SiNa$ (M + Na) 833.3547, found 833.3544.

3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl azide (4).[34] To the solution of 3,4,6-tri-*O*-benzyl-D-glucal (**3**) (50 mg, 0.12 mmol, 1 equiv), diphenyl sulfoxide (73 mg, 0.36 mmol, 3 equiv), and 2,4,6-tri-*tert*-butylpyridine (104 mg, 0.42 mmol, 3.5 equiv) in dichloromethane (3.3 mL) was added trifluoromethanesulfonic anhydride (30 μL, 0.18 mmol, 1.5 equiv) at −78 °C. The resulting solution was stirred at −78 °C for 30 min, and then at −40 °C for 1 h. Methyl alcohol (4.9 μL, 0.12 mmol, 1 equiv) and triethylamine (50 μL, 0.36 mmol, 3 equiv) were added sequentially at −40 °C. The solution was stirred at this temperature for 0.5 h, at 0 °C for 0.5 h, and finally at 23 °C for 1 h. The solvent was removed under reduced pressure at 0 °C, and the residue was then dissolved in dry CH_3CN (5 mL). NaN_3 (23 mg, 0.35 mmol, 3 equiv) and $LiClO_4$ (63 mg, 0.60 mmol, 5 equiv) were added sequentially to the reaction mixture at 0 °C, and the resulting suspension was stirred at 0 °C for 30 min and then at 23 °C for 12 h. The reaction mixture was partitioned between dichloromethane (20 mL) and H_2O (20 mL), and the aqueous layer was further extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was purified by flash column chromatography (17% ethyl acetate in hexane) to afford 3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl azide (**4**) (44 mg, 77%) as a white solid (from ethyl acetate−hexane): mp 63−64 °C; R_f = 0.60 (50% ethyl acetate in hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.28 (m, 13H, ArH), 7.18−7.17 (m, 2H, ArH), 4.89 (d, 1H, J = 11.4 Hz, benzylic-H), 4.84 (d, 1H, J = 11.2 Hz, benzylic-H), 4.82 (d, 1H, J = 10.7 Hz, benzylic-H), 4.63 (d, 1H, J = 12.2 Hz, benzylic-H), 4.56 (d, 1H, J = 10.7 Hz, benzylic-H), 4.55 (d, 1H, J = 12.2 Hz, benzylic-H), 4.53 (d, 1H, J = 8.6 Hz, H-1), 3.75 (dd, 1H, J = 2.6, 11.4 Hz, H-6), 3.73 (dd, 1H, J = 3.8, 11.2 Hz, H-6), 3.67 (dd, 1H, J = 9.0, 9.6 Hz, H-4), 3.55 (t, 1H, J = 9.0 Hz, H-3), 3.54 (ddd, 1H, J = 2.4, 3.9, 9.9 Hz, H-5), 3.45 (dt, 1H, 2.6, 8.8 Hz, H-2), 2.24 (d, 1H, J = 2.6 Hz, O*H*); MS (FAB) *m*/*z* (relative intensity, %) 498.2 (M + Na, 27), 472.3 (16), 177.1 (100); HRMS (FAB) *m*/*z* calcd for $C_{27}H_{29}N_3O_5Na$ (M + Na) 498.2007, found 498.2005.

^{13}C NMR Detection and Characterization of 8, 9, and 5. To a solution of $Ph_2S^{16/18}O$ (15 mg, 0.072 mmol, 3 equiv), 2,4,6-tri-*tert*-butylpyridine (3 mg, 0.013 mmol, 0.5 equiv), and 3,4,6-tri-*O*-benzyl-D-glucal (**3a** or **3b**) (10 mg, 0.024 mmol, 1 equiv) in CD_2Cl_2 (0.66 mL) in a 5-mm NMR tube was added trifluoromethanesulfonic anhydride (6 μL, 0.036 mmol, 3 equiv) at −78 °C. The reaction mixture was briefly agitated (3 × 5 s; Fisher Vortex Genie 2) and placed in the NMR probe at −78 °C and then warmed to −40 °C for the ^{13}C NMR characterization of **8a/b**. The NMR sample was ejected from the NMR probe and immediately cooled to −78 °C. To the reaction mixture was

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added methyl alcohol (1 μL, 0.012 mmol, 1 equiv) at −78 °C, and the resulting mixture in the NMR tube was briefly agitated (3 × 5 s). Triethylamine (10 μL, 0.072 mmol, 3 equiv) was then added at −78 °C, and the resulting mixture in the NMR tube was again briefly agitated (3 × 5 s). The NMR reaction mixture was placed in the NMR probe which had been recooled to −78 °C, and the reaction mixture was then warmed to −20 °C for the ^{13}C NMR characterization of **9a/b** and **5a/b**.

^{1}H NMR Characterization of d_{21}-8 and d_{21}-9. To a solution of Ph_2SO (15 mg, 0.072 mmol, 3 equiv), 2,4,6-tri-*tert*-butylpyridine (3 mg, 0.013 mmol, 0.5 equiv), and 3,4,6-tri-*O*-d_7-benzyl-D-glucal (***d*$_{21}$-3**) (10.5 mg, 0.024 mmol, 1 equiv) in CD_2Cl_2 (0.66 mL) in a 5-mm NMR tube was added trifluoromethanesulfonic anhydride (6 μL, 0.036 mmol, 3 equiv) at −78 °C. The reaction mixture in the NMR tube was briefly agitated (3 × 5 s; Fisher Vortex Genie 2) and placed in the NMR probe at −40 °C and then warmed to −20 °C for the ^{1}H NMR characterization of ***d*$_{21}$-8**. The NMR sample was ejected from the NMR probe and immediately cooled to −78 °C. To the reaction mixture was added methyl alcohol (1 μL, 0.012 mmol, 1 equiv) at −78 °C, and the resulting mixture was briefly agitated (3 × 5 s). Triethylamine (10 μL, 0.072 mmol, 3 equiv) was then added at −78 °C, and the resulting mixture in the NMR tube was again briefly agitated (3 × 5 s). The NMR reaction mixture was placed in the NMR probe which had been recooled to −40 °C, and the reaction mixture was then warmed to −20 °C for the ^{1}H NMR characterization of ***d*$_{21}$-9**. ***d*$_{21}$-8**: ^{1}H NMR (500 MHz, CD_2Cl_2, −20 °C) δ 6.96 (d, 1H, J = 5.5 Hz, H-1), 6.12 (dd, 1H, J = 3.2, 5.9 Hz, H-2), 3.97 (dd, 1H, J = 2.3, 9.1 Hz, H-4), 3.81 (br d, 1H, J = 8.8 Hz, H-5), 3.68 (br s, 1H, H-3), 3.22 (dd, 1H, J = 3.4, 11.3 Hz, H-6), 2.46 (br d, 1H, J = 10.7 Hz, H-6). ***d*$_{21}$-9**: ^{1}H NMR (500 MHz, CD_2Cl_2, −20 °C) δ 5.55−5.54 (br m, 1H, H-2), 4.96 (br s, 1H, H-1), 4.61 (dd, 1H, J = 4.1, 8.8 Hz, H-3), 4.33 (t, 1H, J = 9.1 Hz, H-4), 4.08 (br dt, 1H, J = 9.7, 2.3 Hz, H-5), 3.81 (dd, 1H, J = 3.3, 10.5 Hz, H-6), 3.61 (br dd, 1H, J = 2.0, 10.8 Hz, H-6).

^{13}C NMR Detection and Characterization of 18a/b. To a solution of DBT$^{16/18}$O (14 mg, 0.072 mmol, 3 equiv), 2,4,6-tri-*tert*-butylpyridine (3 mg, 0.013 mmol, 0.5 equiv), and 3,4,6-tri-*O*-benzyl-D-glucal (**3a**, **3b**) (10 mg, 0.024 mmol, 1 equiv) in CD_2Cl_2 (0.66 mL) in a 5-mm NMR tube was added trifluoromethanesulfonic anhydride (6 μL, 0.036 mmol, 3 equiv) at −78 °C. The reaction mixture in the NMR tube was briefly agitated (3 × 5 s; Fisher Vortex Genie 2) and placed in the NMR probe at −78 °C and then warmed to −20 °C for the ^{13}C NMR characterization of **18a/b**.

^{13}C NMR Characterization of 17a/b. To a solution of DBT$^{16/18}$O (14 mg, 0.072 mmol, 3 equiv), 2,4,6-tri-*tert*-butylpyridine (3 mg, 0.013 mmol, 0.5 equiv), and 3,4,6-tri-*O*-benzyl-D-glucal (**3a**, **3b**) (10 mg, 0.024 mmol, 1 equiv) in CD_2Cl_2 (0.66 mL) in a 5-mm NMR tube was added trifluoromethanesulfonic anhydride (6 μL, 0.036 mmol, 3 equiv) at −78 °C. The reaction mixture in the NMR tube was briefly agitated (3 × 5 s; Fisher Vortex Genie 2) and placed in the NMR probe at −78 °C. After confirmation of the generation of **18a/b** at −78 °C by ^{13}C NMR, the NMR sample was ejected from the NMR probe and immediately cooled at −78 °C. To the reaction mixture was added methyl alcohol (1 μL, 0.012 mmol, 1 equiv) at −78 °C, and the resulting mixture was briefly agitated (3 × 5 s). Triethylamine (10 μL, 0.072 mmol, 3 equiv) was then added at −78 °C, and the resulting mixture in the NMR tube was again briefly agitated (3 × 5 s). The NMR reaction mixture was placed in the NMR probe at −78 °C, and the reaction mixture was then warmed to −20 °C for the ^{13}C NMR characterization of **17a/b**.

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Supporting Information Available: Analytical spectral data for the C(2)-hydroxyglycoconjugates and preparative procedures for the ^{13}C- and d-labeled glucal donors (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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