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C2-Amidoglycosylation. Scope and Mechanism of Nitrogen Transfer

Jing Liu and David Y. Gin*

Contribution from the Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801

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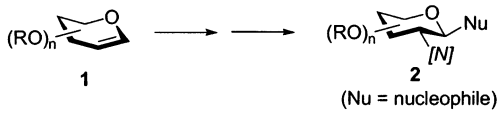
Abstract: A one-pot *C2*-amidoglycosylation reaction for the synthesis of 2-*N*-acyl-2-deoxy-β-pyranosides from glycals is described. Glycal donors activated by the reagent combination of thianthrene-5-oxide (**11**) and Tf_2O, followed by treatment with an amide nucleophile and a glycosyl acceptor, lead to the formation of various *C2*-amidoglycoconjugates. Both the *C2*-nitrogen transfer and the glycosidic bond formation proceed stereoselectively, allowing for the introduction of both natural and nonnatural amide functionalities at *C2* with concomitant anomeric bond formation in a one-pot procedure. Tracking of the reaction by low-temperature NMR spectroscopy employing ^{15}N- and ^{18}O-isotope labels suggests a mechanism involving the formation of the *C2*-sulfonium glycosyl imidate **39** as well as oxazoline **37** as key intermediates in this novel oxidative glycosylation process.

Introduction

C2-Azaglycosides are ubiquitous building blocks in biologically important glycoconjugates including glycoproteins, peptidoglycans, glycolipids, and glycosaminoglycans. These glycoconjugates are involved in critical biological functions[1] such as cell communication, cell adhesion, inflammatory response, and immune response. However, access to significant quantities of structurally well-defined, homogeneous complex oligosaccharides for glycobiological exploration has relied on chemical[2] or chemoenzymatic syntheses[3] because the biosynthesis of complex carbohydrates is not under direct transcriptional control. In this context, the synthetic incorporation of *C2*-azaglycosyl residues in the preparation of oligosaccharides and glycoconjugates is particularly challenging in that selective *C2*-*N*-functionalization as well as glycosidic bond formation with appropriate glycosyl acceptors are required for carbohydrate assembly.[4]

Glycal donors[5] are often employed as versatile starting materials in the synthesis of *C2*-azaglycosides by way of *C2*-*N*-functionalization accompanied by glycosidic bond formation. Over the last few decades, a variety of methods have been developed for the nitrogen ([*N*]) transfer to glycals (**1** → **2**, Scheme 1). In this context, numerous *N*-functionalities have been introduced at the *C2*-position including oxidized precursors to amines, such as azide,[6] hydrazine,[7] triazene,[8] or the nitro group,[9]

Scheme 1



as well as protected amino-functionalities such as amides,[10] carbamates,[11] sulfonamides,[12] or phosphoramides.[13] However, the majority of naturally occurring *C2*-azasugars are *N*-acetylated, and this highlights the importance of this class of carbohydrate residue in glycoconjugate synthesis. While all of the above-mentioned methods constitute efficient syntheses of *C2*-azasugars, the direct installation of the naturally occurring *C2*-acetamido group onto glycal donors in conjunction with glycosidic coupling remains a challenge (Scheme 1; **1** → **2**, [*N*] = AcNH). To date, the only report on the direct transfer of the native acetamido group to the *C2*-position of glycals employs a Cr(II)-mediated *N*-chloroacetamide addition to glycals,[11e] proceeding with modest yields. As a result, the preparation of *C2*-acetamidoglycosides from glycal donors typically requires multistep syntheses involving the distinct transformations of

* To whom correspondence should be addressed. E-mail: gin@scs.uiuc.edu.

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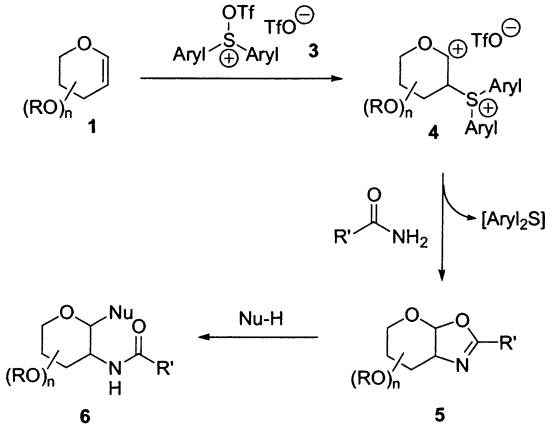
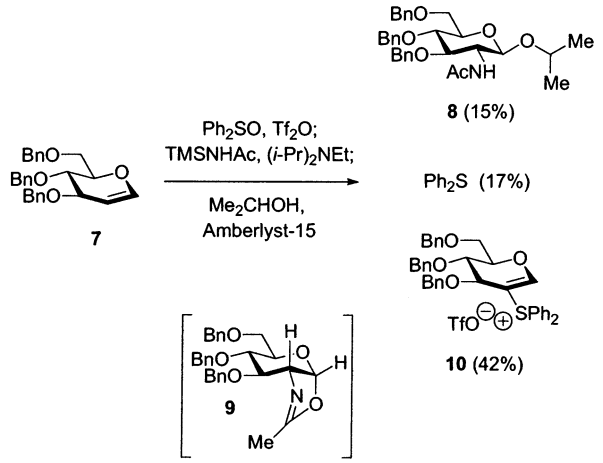
Scheme 2



Scheme 3



nitrogen transfer, glycosylation, and finally manipulation of the nitrogen protective group.

Recently, we have established a novel glycal activation method employing the reagent combination of a diaryl sulfoxide and triflic anhydride. Several glycosylation protocols have since been developed with this reagent combination,[14] including the *C2*-acetamidoglycosylation of glycals.[15] In this method, glycal activation, nitrogen transfer to *C2*, glycosidic bond formation, as well as installation of the native *N*-acetyl functionality are all accomplished in one reaction vessel with good yield and excellent diastereoselectivity. Here we report the development of this methodology, establishment of the reaction scope, as well as studies toward elucidating the mechanism of the *C2*-amidoglycosylation process.

Results and Discussion

***C2*-Amidoglycosylation.** We have established that sulfonium reagents, generated in situ from the combination of a diaryl sulfoxide and triflic anhydride,[16] can activate a variety of carbohydrate donors for glycosidic bond formation. With this reagent combination, glycosyl hemiacetals can function as effective donors for dehydrative glycosylation,[17] a process amenable to the construction of a variety of glycoconjugates. More recently, the use of this reagent combination has also been applied to the electrophilic activation of glycal donors, resulting in an oxidative *C2*-hydroxyglycosylation,[14] in which a hydroxyl functionality is stereoselectively installed at the *C2*-position of glycal with concomitant glycosylation of a nucleophilic acceptor.

On the basis of the established utility of these sulfonium triflate reagents as electrophilic oxidants, a new method for the synthesis of *C2*-azaglycosides was explored, in which an appropriate *N*-functionality is installed at the *C2*-position of glycals (Scheme 2). It was envisioned that a sulfonium triflate species **3**, generated in situ from a diaryl sulfoxide and triflic anhydride, would activate the enol ether functionality of glycal **1** at *C2*, affording a pyranosyl intermediate **4** that incorporates a sulfonium moiety at *C2*, as well as an oxocarbenium functionality at *C1*. Introduction of a suitable *N*-nucleophile at *C2* (with expulsion of $Aryl_2S$) in conjunction with an appropriate glycosyl acceptor (NuH) at *C1* would result in a *C2*-azaglycosylation reaction in which nitrogen transfer to *C2*, as well as anomeric bond formation, are accomplished. In this context, amide substrates ($R'CONH_2$) would be suitable *N*-nucleophiles as they possess two nucleophilic sites (*O*- and *N*-) that could substitute at both *C1* and *C2* of the putative activated glycosyl intermediate **4**. Ideally, regiospecific nitrogen transfer to *C2* and *O*-substitution at *C1* would result in the formation of oxazoline **5**, an intermediate known to function as a glycosyl donor for anomeric bond formation.[18] Moreover, the successful use of amide nucleophiles ($R'CONH_2$) has the potential to accomplish the direct transfer of an acetamido group to glycals and provide the native *C2*-acetamidoglycoconjugates **6** ($R' = Me$) without the need for additional protective group exchanges or *C2*-functional group interconversions.

Initial explorations to establish the method focused on the use of diphenyl sulfoxide and triflic anhydride as the glycal oxidant. For example, tri-*O*-benzyl-D-glucal (**7**, Scheme 3) was activated with this reagent combination at −78 °C, followed by introduction of *N*-(TMS)acetamide as the nitrogen transfer reagent and Hünig's base as a TMSOTf scavenger. The reaction was warmed to 23 °C, and the glycosyl acceptor 2-propanol and an acid promoter, Amberlyst-15, were added. Isopropyl 2-*N*-acetylamino-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**8**) was isolated in 15% yield (Scheme 3), thus demonstrating the feasibility of a one-pot *C2*-acetamidoglycosylation reaction with glycal donors. Although the desired *C2*-acetamidoglycoside **8** was obtained in only modest yield, several key observations offer insight into the reaction pathway, and thus present avenues for reaction optimization. First, the bicyclic oxazoline intermediate **9** (Scheme 3) could be detected and isolated in 18% yield prior to the addition of the glycosyl acceptor. This is consistent with the proposed pathway in Scheme 2 in which regioselective *C2*−*N* and *C1*−*O* bond formations occur to generate oxazoline **5** as an in situ glycosyl donor. Second, diphenyl sulfide (17%) was isolated as a byproduct of the reaction, which is consistent with nitrogen transfer to the *C2*-position by the expulsion of

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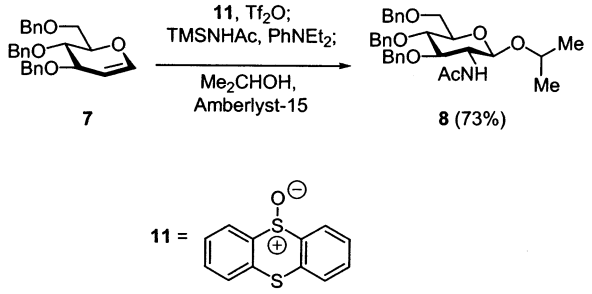
Scheme 4



sulfide from **4**. Finally, the major carbohydrate byproduct of the reaction was found to be the *C2*-vinyl sulfonium triflate **10** (42%), likely formed via the elimination of the *H2*-proton in the putative *C2*-sulfonium glycosyl intermediate **4** (Scheme 2).

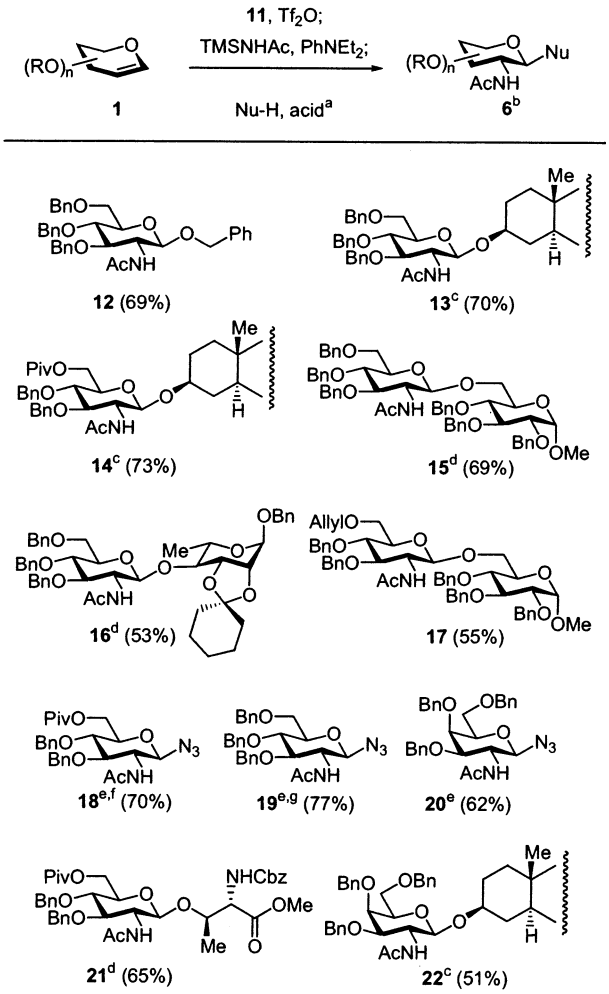
To further develop this *C2*-amidoglycosylation reaction for generalized carbohydrate synthesis, optimization of the reaction focused on minimizing the presumed *H2*-elimination pathway that produces **10**. To this end, a variety of diaryl sulfoxide reagents were screened to generate a putative *C2*-sulfonium intermediate **4** (Scheme 2) with attenuated *H2*-acidity. Thianthrene-5-oxide (**11**, Scheme 4), easily prepared from the oxidation of commercially available thianthrene, was found to provide an enhanced yield of the *C2*-amidoglycoside **8**, presumably a result of the ability of the remote sulfur atom in **11** to stabilize the *C2*-sulfonium and *C1*-oxocarbenium functionalities in **4** (vide infra). The aim of minimizing the formation of the vinyl sulfonium byproduct **10** also led to the screening of a series of tertiary amines, including several trialkylamines, pyridines, and anilines, to find the appropriate reagent to serve as an effective yet mild proton and trimethylsilyl scavenger in the *N*-transfer process. Of these, *N*,*N*-diethylaniline, an effective acid scavenger, was found to give optimal yields of the *C2*-acetamidoglycoside **8** (73%) from tri-*O*-benzyl-D-glucal (**7**), when **11** was employed as the sulfoxide reagent (Scheme 4).[19]

Using this reaction protocol, we applied the *C2*-acetamidoglycosylation reaction to the synthesis of a wide variety of *C2*-acetamidoglycosides (**12**−**22**, Chart 1), in which glycal activation, transfer of the native *N*-acetylamino functionality, and glycosidic bond formation are all accomplished in a one-pot procedure. The acetamidoglycosylation reaction is compatible with glycal substrates bearing a variety of protective groups, including alkyl ethers, silyl ethers, and esters. A wide variety of glycosyl acceptors can be glycosylated, including simple primary and secondary alcohols (**12**−**14**, **22**), primary and secondary hydroxyls within carbohydrates (**15**−**17**), as well as hydroxyl functionalities on selectively protected α-amino acids (**21**). Nitrogen nucleophiles such as azide are also glycosylated to generate glycosyl azides (**18**−**20**), although a solvent exchange from CH_2Cl_2 to DMF is required in the oxazoline ring-opening stage of the transformation to ensure adequate solubility of NaN_3.[20] It is worth noting that the glycal enol ether functionality can be selectively activated with the reagent combination of **11**·Tf_2O in the presence of simple alkenes, as demonstrated in the reaction with 6-*O*-allyl-3,4-di-*O*-benzy-α--D-glucal to afford

(19) Acetamidoglycosylation with **7** employing Ph_2SO instead of **11** under otherwise identical conditions afforded **8** in 41% yield.

(20) The minor α-manno diastereomers of **18** and **19** were also detected, but the reactions are highly selective for the *β*-gluco isomer. The minor quantities of α-manno diastereomers of the other glycoconjugates in Chart 1 could not be readily isolated and characterized because of their exceedingly small quantities.

Chart 1.[a]

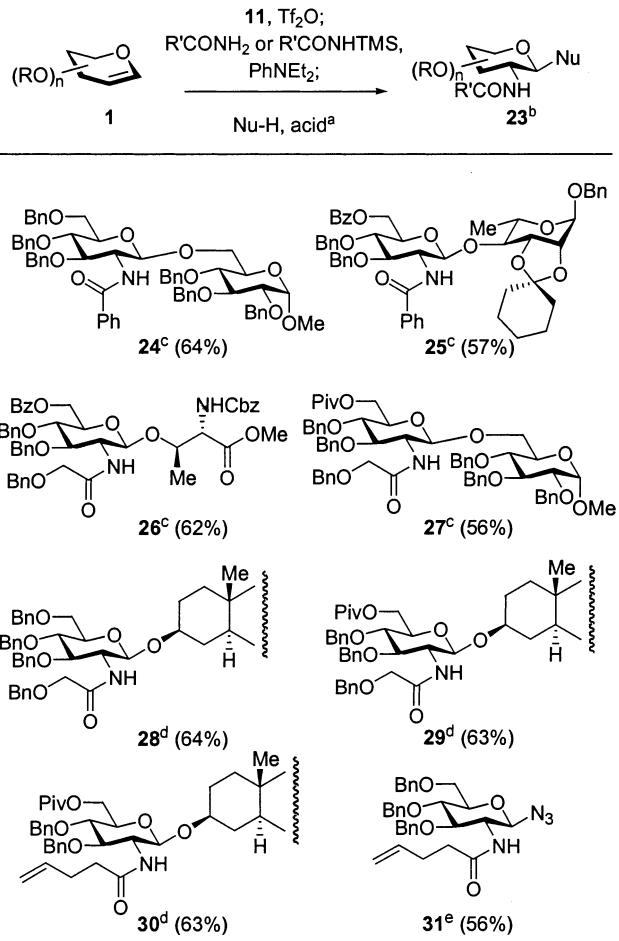


[a] Key: (a) Amberlyst-15 employed as the acid promoter unless otherwise stated; (b) amounts of reagents employed: **11**, 2 equiv; Tf_2O, 2 equiv; TMSNHAc, 3 equiv; $PhNEt_2$, 4 equiv; NuH, 3 equiv; acid, 2 equiv; (c) glycosyl acceptor = (+)-3-dihydrocholesterol; (d) camphorsulfonic acid employed as acid promoter; (e) glycosyl acceptor = NaN_3; glycosylation carried out in DMF with $Cu(OTf)_2$ as the acid promoter; (f) dr = 6:1 (*β*-gluco:α-manno diastereomers); (g) dr = 12:1 (*β*-gluco:α-manno diastereomers).

17. In addition, galactal donors such as tri-*O*-benzyl-D-galactal provide the corresponding *C2*-acetamidogalactopyranosides (**20**, **22**). In all of the *C2*-acetamidoglycosylation reactions, the *C2*-aza-glycoconjugates are derived from acid-mediated ring opening of a bicyclic oxazoline intermediate such as **5**. These substrates have been established as glycosyl donors in the presence of strongly acidic media.[18] However, in the context of developing the *C2*-amidoglycosylation reaction, we have found that sulfonic acids (i.e., Amberlyst-15, camphorsulfonic acid) in dichloromethane, or $Cu(OTf)_2$ in DMF, can function as relatively mild acid promoters for glycosylations with oxazoline donors.

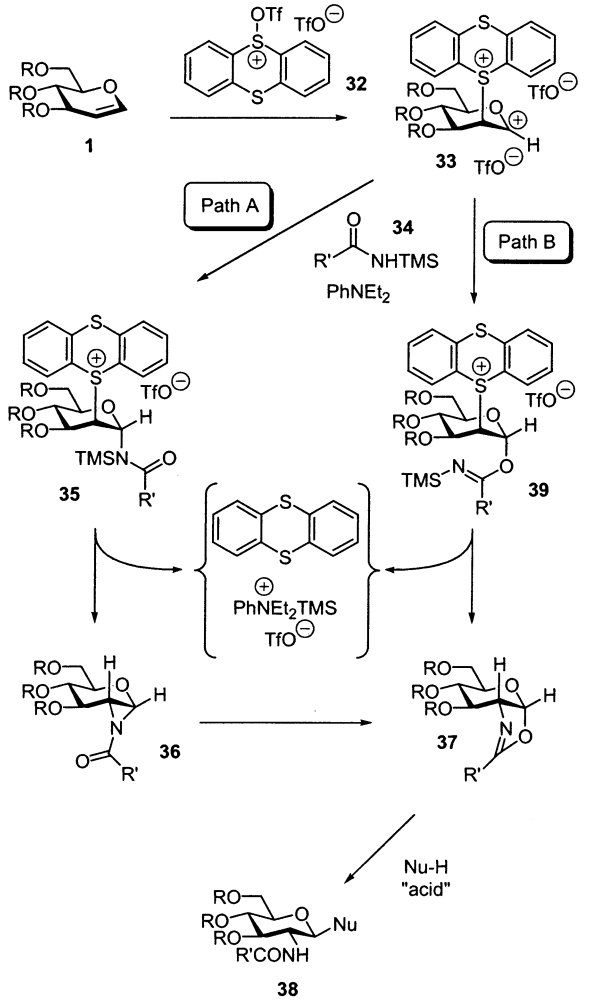
The installation of the native acetamido functionality in the *C2*-azaglycosylation reaction provides direct access to the most abundant form of *C2*-azasugars. The versatility of this novel nitrogen transfer reaction can be extended to *C2*-azaglycosides bearing different *C2*-amido functionalities (Chart 2). For example, *N*-(TMS)benzamide can be employed as the initial *N*-nucleophile to afford *C2*-benzamidoglycosides (**24**, **25**). In addition, nonsilylated amides such as 2-benzyloxyacetamide can

Chart 2.[a]



[a] Key: (a) Amberlyst-15 employed as the acid promoter unless otherwise stated; (b) amounts of reagents employed: **11**, 2 equiv; Tf_2O, 2 equiv; amide, 2−3 equiv; $PhNEt_2$, 4 equiv; NuH, 1.5−2 equiv; acid, 2 equiv; (c) camphorsulfonic acid employed as acid promoter; (d) glycosyl acceptor = (+)-3-dihydrocholesterol; (e) glycosyl acceptor = NaN_3; glycosylation carried out in DMF with $Cu(OTf)_2$ as the acid promoter.

Scheme 5



be used as the nitrogen transfer agent to install the biologically relevant *N*-glycolamido substituent at *C2* with concomitant formation of the glycosidic bond (**26**−**29**).[21] Finally, the use of pent-4-enamide as the initial *N*-nucleophile provides the *C2*-*N*-pentenoylglycosides **30** and **31**, whose *C2*-amido functionality can be deprotected to expose the *C2*-amino functionality.[22]

Probing the Mechanism of Nitrogen Transfer. The reaction pathway proposed for *N*-transfer in the *C2*-amidoglycosylation reaction involves glycal activation, oxazoline formation, and glycosylation (Scheme 5). In this process, the combination of Tf_2O and thianthrene-5-oxide (**11**) is likely to generate thianthrene bis(triflate) (**32**) in situ.[23] Electrophilic activation of the glucal donor **1** at *C2* generates the *C1*-oxocarbenium-*C2*-sulfonium intermediate **33**. Nitrogen transfer can then proceed via introduction of an unprotected or *N*-silylated amide **34** and the acid/TMS scavenger $PhNEt_2$, leading to initial *N*-glycosylation by **33** (Path A) to form the glycosyl amide intermediate **35**. Subsequent intramolecular displacement of thianthrene from *C2* by the amide nitrogen in **35** with concomitant *N*-desilylation generates the glycosyl *N*-acylaziridine **36**, which then undergoes rearrangement[24] to afford the observed oxazoline **37**. Finally, acid-mediated ring opening with the appropriate nucleophilic acceptor (Nu−H) yields the *C2*-amidoglycoside **38**. In an alternate pathway for *N*-transfer to *C2* (Path B), initial *O*-addition of the amide nucleophile **34** to *C1* of the oxocarbenium species **33** would generate the α-glycosyl imidate **39**. Subsequent intramolecular displacement of thianthrene from *C2* by the imidate nitrogen directly affords the observed oxazoline **37**, the precursor to the *C2*-amidoglycoside product **38**.

Several initial observations are consistent with the reaction pathways outlined in Scheme 5. First, the oxazoline intermediates **9**, **40**−**42** (Chart 3) can be isolated in good yields if the *C2*-amidoglycosylation process is intercepted immediately prior

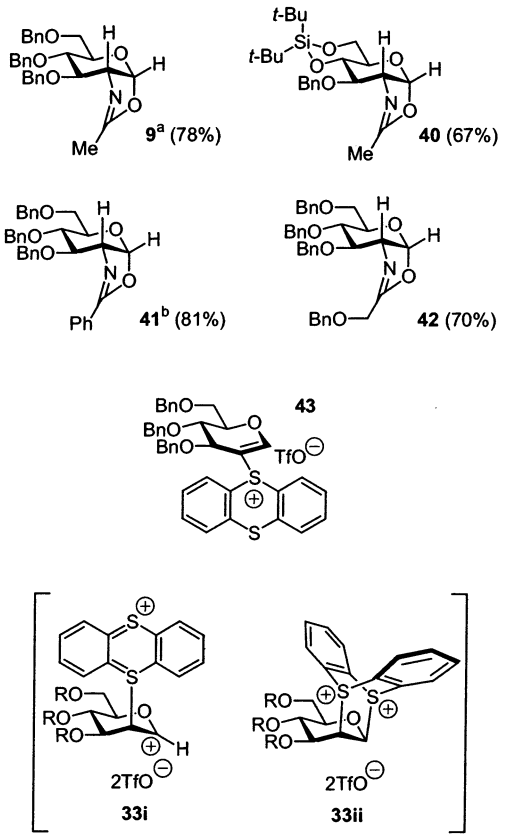
(21) The use of nonsilylated amides to form **26**−**31** suggests that the principal role of the TMS group in *N*-(TMS)acetamide and *N*-(TMS)benzamide is to enhance the solubility of these amide reagents.

(22) Madsen, R.; Roberts, C.; Fraser-Reid, B. *J. Org. Chem.* **1995**, *60*, 7920−7926.

(23) While it is reasonable that the combination of **11** and Tf_2O would generate the sulfonium triflate species **32**, our current investigations do not exclude the possibility of this species existing/reacting as the *σ*-sulfurane, the thianthrene sulfur dication, or the thianthrene radical cation. For the preparation and reactions of sulfonium triflate: (a) Hendrickson, J. B.; Schwartzman, S. M. *Tetrahedron Lett.* **1975**, *16*, 273−276. (b) Nenajdenko, V. G.; Vertelezkij, P. V.; Gridnev, I. D.; Shevchenko, N. E.; Balenkova, E. S. *Tetrahedron* **1997**, *53*, 8173−8180. *σ*-Sulfurane: (c) Martin, J. C.; Perozzi, E. F. *Science* **1976**, *191*, 154−159. Thianthrene dication and thianthrene radical cation: (d) Shine, H. J.; Bandlish, B. K.; Mani, S. R.; Padilla, A. G. *J. Org. Chem.* **1979**, *44*, 915−917. (e) Shine, H. J.; Bae, D. H.; Mansurul Hoque, A. K. M.; Kajstura, A.; Lee, W. K.; Shaw, R. W.; Soroka, M.; Engel, P. S.; Keys, D. E. *Phosphorus Sulfur Relat. Elem.* **1985**, *23*, 111−141. (f) Lee, W. K.; Liu, B.; Park, C. W.; Shine, H. J.; Guzman-Jimenez, I. Y.; Whitmire, K. H. *J. Org. Chem.* **1999**, *64*, 9206−9210.

(24) Nishiguchi, T.; Tochio, H.; Nabeya, A.; Iwakura, Y. *J. Am. Chem. Soc.* **1969**, *91*, 5835−5841.

Chart 3.[a]



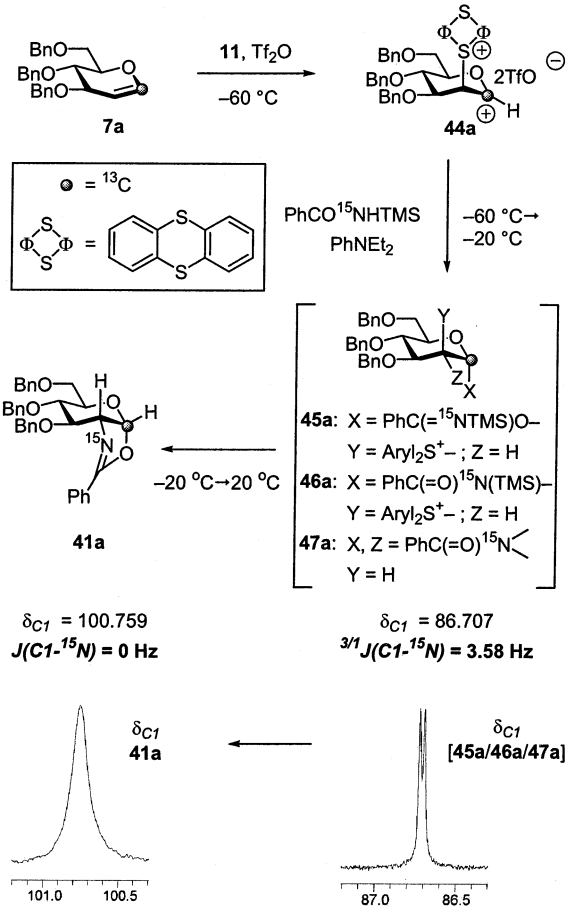
[a] Key: (a) dr = 14:1 (gluco:manno diastereomers); (b) dr = 17:1 (gluco:manno diastereomers).

to the introduction of the nucleophilic acceptor. Second, the *C2*-thianthrene sulfonium glycal **43** is isolated as a minor byproduct (<15%) in glycosylations where **7** serves as the glycal donor. Formation of **43** is likely a result of the unproductive elimination of *H2* from the putative *C2*-sulfonium species **33**, a pathway that is notably lessened with the use of thianthrene-5-oxide as the sulfoxide reagent as opposed to Ph_2SO (Scheme 3). The advantageous use of thianthrene-5-oxide in this capacity is presumably a result of added stabilization of a putative *C2*-sulfonium intermediate such as **33**. For example, the distal sulfur atom in the *C2*-sulfonium moiety in **33** can be envisioned to participate in attenuating the *H2*-acidity of **33**, either by resonance stabilization (**33i**) of the *C2*-sulfur cation or by direct participation in the stabilization of the *C1*-oxocarbenium functionality (**33ii**).

On the basis of these initial observations, the formation of oxazoline **37** from **1** is consistent with nucleophilic attack by the amide nucleophile at *C1* and *C2* of an activated glycosyl intermediate such as **33**, resulting in displacement of thianthrene as depicted in Scheme 5. However, the mechanism of *N*-transfer to *C2* remains unclear, as it can proceed either via the glycosyl amide and aziridine intermediates (**33** → **35** → **36** → **37**, Path A) or via a *C2*-sulfonium glycosyl imidate intermediate (**33** → **39** → **37**, Path B).

Detection and Characterization of Reactive Glycosyl Intermediates. A key difference in these two pathways (A vs B, Scheme 5) is the sequence of heteroatom transfer to both *C1* and *C2* of the glycal donor. In Path A, a *C1*−*N* linkage is formed prior to oxazoline formation; in Path B, a *C1*−*O* linkage is formed prior to oxazoline formation. To distinguish between

Scheme 6

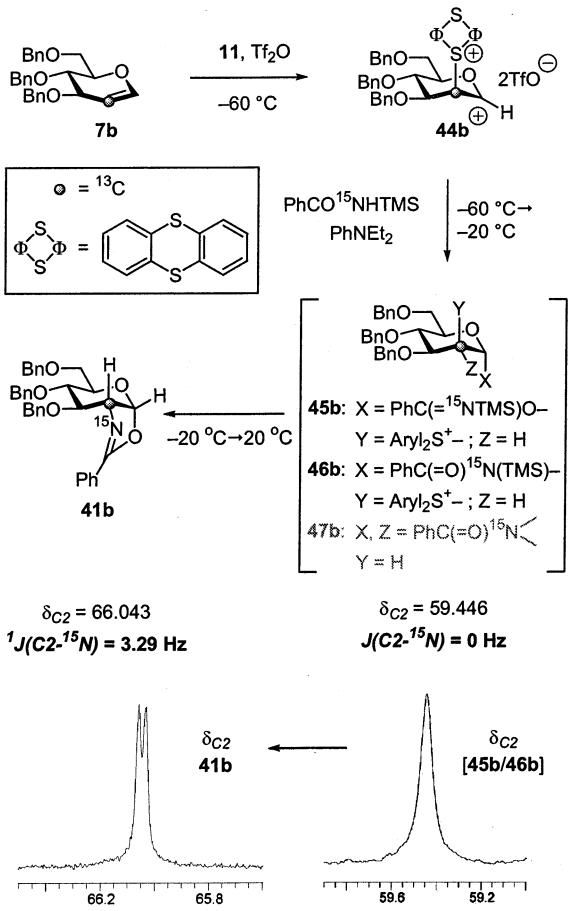


the two possible pathways, efforts focused on the identification of key intermediates such as [**35**/**36**/**39**] and determination of their *C1*/*C2*-heteroatom connectivity. To this end, both the $^{13}C1$- and the $^{13}C2$-labeled tri-*O*-benzyl-D-glucals (**7a**/**b**) were prepared[25] and employed as glycosyl donors in the *C2*-amidoglycosylation using ^{15}N-labeled *N*-(TMS)benzamide as the amide nucleophile (Schemes 6 and 7).

In the first series of low-temperature NMR experiments (Scheme 6), $^{13}C1$-labeled tri-*O*-benzyl-D-glucal (**7a**) was treated with thianthrene-5-oxide (**11**, 2 equiv) and Tf_2O (2 equiv) at −60 °C. Unfortunately, ^{13}C NMR detection of a carbohydrate species such as **44a** at this temperature was not possible owing to the presence of several distinct $^{13}C1$-resonances indicating a complex mixture of intermediates. However, upon introduction of ^{15}N-labeled *N*-(TMS)benzamide (99% ^{15}N-incorporation) with *N*,*N*-diethylaniline and warming to −20 °C, a principal carbohydrate species (tentatively assigned as either the imidate **45a**, the amide **46a**, or the aziridine **47a**) was detected, characterized by its $^{13}C1$-resonance (δ = 86.707 ppm), existing as a doublet with a $^{15}N-^{13}C$ coupling value of 3.58 Hz. Upon warming of the reaction to 20 °C, formation of the oxazoline **41a** was observed, revealing only a singlet $^{13}C1$-resonance at δ 100.759 ppm. The presence of a ^{13}C coupling constant in the intermediate [**45a**/**46a**/**47a**] suggests a structure that incorporates a $^{13}C1-^{15}N$ linkage such as that in the glycosyl amide **46a** or aziridine **47a**. However, it is worth noting that the presence of the $J_{13C-15N}$ coupling constant does not preclude the possibility of the

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

Scheme 7



glycosyl imidate structure **45a**, in which a three-bond coupling ($^3J_{13C-15N} = 3.58$ Hz) could give rise to the observed doublet resonance. Indeed, three-bond $^{15}N-^{13}C$ couplings of comparable magnitude in imidate functionalities are not uncommon,[26] wherein the magnitude of the coupling depends on orientation of the nitrogen lone pair as well as on the conformation of the substrate in question.[27]

Although this $^{13}C1$ NMR data does not allow for clear distinction between the structures of **45**, **46**, and **47** as the initial intermediate prior to oxazoline formation, further information on its identity was obtained by performing an analogous ^{13}C NMR experiment with $^{13}C2$-labeled tri-*O*-benzyl-D-glucal (**7b**, Scheme 7). Activation of **7b** with **11**·Tf_2O followed by introduction of ^{15}N-(TMS)benzamide led to the formation of an intermediate with a singlet $^{13}C2$-resonance (δ 59.446 ppm), prior to its conversion to the oxazoline **41b** (δ_{C2} 66.043 ppm, d, $J = 3.29$ Hz) upon warming to 20 °C. The lack of $^{13}C-^{15}N$ coupling in the *C2* resonance of the intermediate in question indicates the absence of a $^{13}C2-^{15}N$ linkage, thereby disqualifying aziridine **47b** as a viable structure for this species.

On the basis of the previous ^{13}C NMR investigation with ^{15}N-(TMS)benzamide, the glycosyl imidate **45** and the glycosyl amide **46** emerge as possible structures for the initial glycosyl intermediate generated prior to oxazoline formation. Efforts then focused on the determination of *C1*−*O* connectivity in the intermediate in question to distinguish between the structures **45** and **46**. It is known that an ^{18}O atom directly bound to carbon induces a small but significant (0.01−0.05 ppm) upfield shift in the ^{13}C NMR signal relative to that of the ^{16}O isotopomer. This ^{18}O-induced isotopic shift in ^{13}C NMR was first predicted by Jameson[28] and later confirmed experimentally by Van Etten,[29] Vederas,[30] and Darensbourg.[31] The technique has frequently been used in kinetic studies as a continuous, nondestructive assay method[32] and has been employed to identify the point of *C*−*O* bond cleavage in a series of hydrolysis reactions.[33]

To secure the presence/absence of a *C1*−*O* linkage in **45**/**46**, the activation of $^{13}C1$-tri-*O*-benzyl-D-glucal (**7a**) with **11**·Tf_2O, followed by introduction of ^{18}O enriched *N*-(TMS)-benzamide (47% ^{18}O), was carried out (Scheme 8), monitored by ^{13}C NMR, and compared to the data obtained in the analogous reaction with unlabeled *N*-(TMS)benzamide. When 47% ^{18}O-labeled *N*-(TMS)benzamide was introduced to the activated glycosyl species **44a**, detection of the $^{13}C1$ signal of the resulting intermediate in question revealed a species with two $^{13}C1$-resonances (δ 86.726 ppm and δ 86.702 ppm) in approximately a 53:47 ratio (Scheme 8), as opposed to the appearance of only a single resonance when unlabeled *N*-(TMS)-benzamide is employed. The upfield chemical shift perturbation ($\Delta\delta = 0.024$ ppm) of $^{13}C1$ in this intermediate upon introduction of ^{18}O-enriched *N*-(TMS)benzamide is indicative of a *C1*−*O* linkage, consistent with a glycosyl imidate structure **45a** instead of the glycosyl amide structure **46a**.[34] When the putative intermediate **45a** was allowed to warm to 20 °C to form oxazoline **41a**, a similar $^{13}C1-^{18}O$ chemical shift perturbation ($\delta_{C1(^{16}O)}$ 100.740 ppm, $\delta_{C1(^{18}O)}$ 100.710 ppm, $\Delta\delta = 0.030$ ppm) was also observed as expected in the oxazoline **41a**.

The analogous ^{18}O-labeling experiment was subsequently performed with $^{13}C2$-labeled tri-*O*-benzyl-D-glucal (**7b**, Scheme 9). The reaction of **7b** with **11**·Tf_2O and ^{18}O-enriched *N*-(TMS)-benzamide (47% ^{18}O) revealed no ^{18}O-induced isotopic $^{13}C2$-shift perturbation in either the putative imidate intermediate **45b** or the oxazoline product **41b**. This result is again consistent with a nitrogen-transfer process originally outlined in Path B, Scheme 5.

Having established the intermediacy of the glycosyl imidate **45** as a precursor to oxazoline formation and the likelihood of the *N*-transfer process proceeding according to Path B, Scheme 5, it is crucial to establish the stereochemical configuration of imidate **45** for the determination of facial selectivity in the initial activation of glycal with **11**·Tf_2O. Direct observation of the

(26) Levy, G. C.; Lichter, R. L. *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*; Wiley & Sons: New York, 1979; Chapter 4. For example, in ^{15}N-labeled methyl benzimidate, a three-bond $^{15}N-^{13}C$ coupling ($^3J_{C-N} = 1.9$ Hz) between the nitrogen and methyl carbon is observed.
(27) Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy: High-Resolution Methods and Applications in Organic Chemistry and Biochemistry*, 3rd ed.; VCH publishers: New York, 1987; pp 155−160.
(28) Jameson, C. J. *J. Chem. Phys.* **1977**, *66*, 4983−4988.
(29) Risley, J. M.; Van Etten, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 252−253.
(30) Vederas, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 374−376.
(31) Darensbourg, D. J. *J. Organomet. Chem.* **1979**, *174*, C70−C76.
(32) (a) Mega, T. L.; Cortes, S.; Van Etten, R. L. *J. Org. Chem.* **1990**, *55*, 522−528. (b) Cortes, S. J.; Mega, T. L.; Van Etten, R. L. *J. Org. Chem.* **1991**, *56*, 943−947. (c) Risley, J. M.; Van Etten, R. L.; Uncuta, C.; Balaban, A. T. *J. Am. Chem. Soc.* **1984**, *106*, 7836−7840. (d) Risley, J. M.; Van Etten, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 4389−4392.
(33) (a) Mega, T. L.; Van Etten, R. L. *J. Am. Chem. Soc.* **1988**, *110*, 6372−6376. (b) Risley, J. M.; Kuo, F.; Van Etten, R. L. *J. Am. Chem. Soc.* **1983**, *105*, 1647−1652. (c) Parente, J. E.; Risley, J. M.; Van Etten, R. L. *J. Am. Chem. Soc.* **1984**, *106*, 8156−8161. (d) Dessinges, A.; Castillon, S.; Olesker, A.; Thang, T. T.; Lukacs, G. *J. Am. Chem. Soc.* **1984**, *106*, 450−451.
(34) The ^{18}O isotope shifts at the β-carbon and γ-carbon have also been reported, although magnitudes are much smaller (<0.01 ppm). (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.

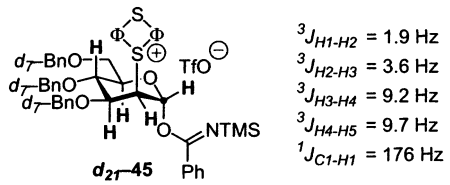
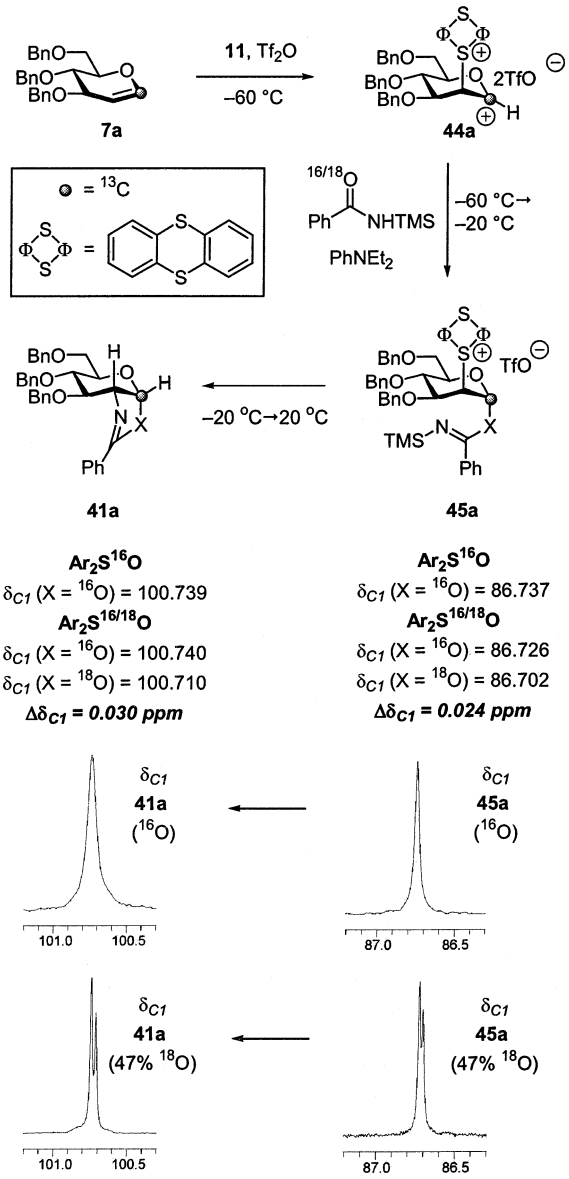


Figure 1. $^3J_{HH}$ and $^1J_{CH}$ values for ***d*$_{21}$-45**.

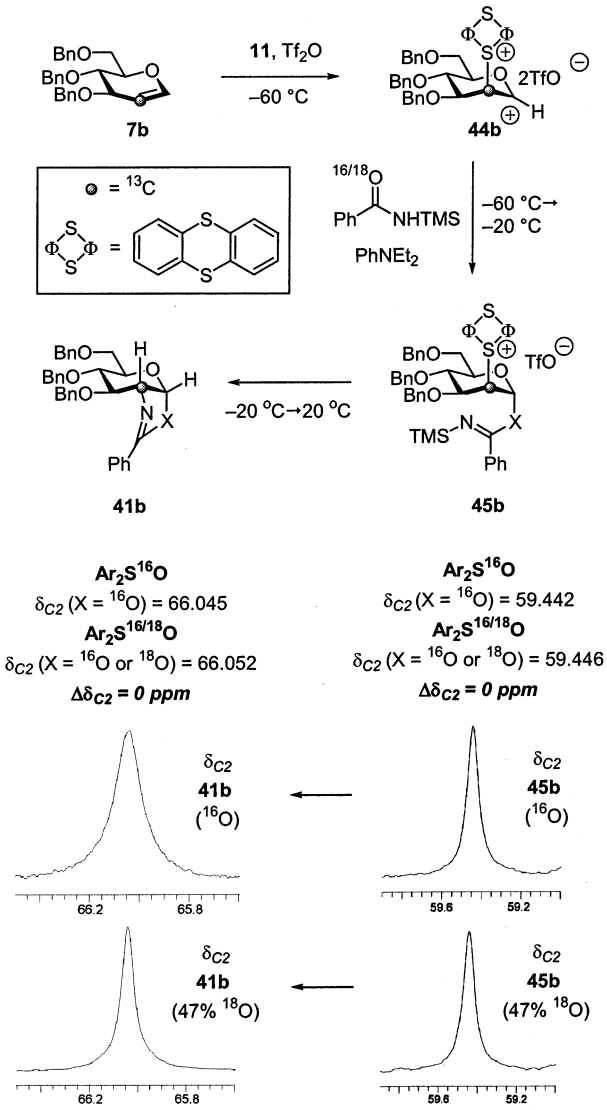
Scheme 8



$^3J_{H-H}$ coupling constants in the pyranoside ring of imidate **45** at low temperature was not possible because of their resonances overlapping with those of benzylic protons in the ^{1}H NMR data, rendering most of the $^3J_{H-H}$ coupling constants unresolvable. Therefore, tri-*O*-d_7-benzyl-D-glucal (***d*$_{21}$-7**) was prepared and used to generate imidate ***d*$_{21}$-45** (Figure 1) so that all of the pyranoside protons could be discerned by ^{1}H NMR at −20 °C.[35]

The reaction of ***d*$_{21}$-7** to form ***d*$_{21}$-45** at −20 °C according to the above-mentioned protocol allowed for the observation of relatively large coupling constants (Figure 1) between *H5* and

Scheme 9



H4 ($^3J_{H5-H4}$ = 9.7 Hz) as well as *H4* and *H3* ($^3J_{H4-H3}$ = 9.2 Hz), which are consistent with *H3*, *H4*, and *H5* existing in mutually trans-axial orientations. The relatively small coupling constant between *H3* and *H2* ($^3J_{H3-H2}$ = 3.6 Hz) is consistent with an axial−equatorial coupling magnitude, suggesting an equatorial orientation of *H2*. Although *H1* is a broad singlet in the ^{1}H NMR spectrum at −20 °C, the multiplet pattern of *H2* (dd) as well as *^{1}H*-homodecoupling and *^{1}H*-COSY data reveal a small coupling between *H1* and *H2* ($^3J_{H2-H1}$ = 1.9 Hz), consistent with diequatorial orientation of both *H1* and *H2*. The orientation of *H1* was further supported by the relatively large anomeric *^{1}H−^{13}C* coupling constant ($^1J_{C1-H1}$ = 176 Hz), consistent with an equatorial anomeric proton of a pyranoside species in a $^4C_1$ conformation.[36] On the basis of these data, it is likely that the structure of imidate **45** incorporates substituents at *C3*, *C4*, and *C5* in equatorial positions, with both the imidate and the sulfonium substituents at *C1* and *C2*, respectively, in axial orientations, a structure consistent with initial axial (β) approach of **11**·Tf_2O onto the glycal donor (i.e., **1** → **33**, Scheme 5).

(35) The assignment of proton signals and coupling constants was confirmed by both *^{1}H*-COSY and *^{1}H*-homodecoupling experiments.

(36) Duus, J. Ø.; Gotfredsen, C. H.; Bock, K. *Chem. Rev.* **2000**, *100*, 4589−4614.

Taken collectively, all of the ^{13}C and ^{1}H NMR data thus obtained are consistent with the reaction outlined in Scheme 5, Path B for *C2*-amidoglycosylation, a process that involves: (1) activation of the glycal donor by the **11**·Tf_2O from the top (β) face to give *C2*-sulfonium intermediate **33**; (2) nucleophilic attack of the amide oxygen at the *C1* position of **33** to afford *C2*-sulfonium glycosyl imidate **39**; (3) intramolecular displacement of thianthrene from *C2* by imidate nitrogen at the *C2*-position to provide oxazoline **37**; and (4) oxazoline ring opening by glycosyl acceptor under acidic conditions to yield the final 2-*N*-acylamino-2-deoxy-β-pyranoside **38**.

Conclusion

A one-pot *C2*-amidoglycosylation reaction for the synthesis of 2-*N*-acylamino-2-deoxy-β-pyranosides from glycals was developed. Both the *C2*-nitrogen transfer and the glycosidic bond formation proceed stereoselectively, allowing for the introduction of both natural and nonnatural amide functionalities at *C2* with concomitant anomeric bond formation in a one-pot procedure. Tracking of the reaction by low-temperature NMR spectroscopy employing ^{15}N- and ^{18}O-isotope labels suggests a mechanism involving the formation of the *C2*-sulfonium glycosyl imidate **39** as well as oxazoline **37** as key intermediates in this oxidative glycosylation with glycals. These studies provide critical insights into the pathway of nitrogen transfer and should facilitate the development of this method for the nitrogen transfer to electron-rich olefins in general.

Experimental Section

Typical Procedure for *C2*-Amidoglycosylation. Method (A): (+)-3-Dihydrocholesterol 3,4-Di-*O*-benzyl-2-*N*-acetylamino-2-deoxy-6-*O*-dimethylpropanoyl-β-D-glucopyranoside (14). Trifluoromethanesulfonic anhydride (28 μL, 0.17 mmol, 2.0 equiv) was added to a solution of 3,4-di-*O*-benzyl-6-*O*-dimethylpropanoyl-D-glucal (34 mg, 0.083 mmol, 1.0 equiv) and thianthrene-5-oxide (38.5 mg, 0.17 mmol, 2.0 equiv) in a mixture of chloroform and dichloromethane (2.4 mL; 3:1 v/v) at −78 °C. The reaction mixture was stirred at this temperature for 11 min, then *N*,*N*-diethylaniline (53 μL, 0.33 mmol, 4.0 equiv) was added, followed by *N*-(TMS)acetamide (33 mg, 0.25 mmol, 3.0 equiv). The mixture was immediately warmed to 23 °C and stirred at this temperature for 30 min. A solution of (+)-3-dihydrocholesterol (97 mg, 0.25 mmol, 3.0 equiv) in 1.0 mL of dichloromethane was added via cannula. Amberlyst-15 acidic resin (66 mg) was then added, and the reaction was stirred for 30 h. The mixture was filtered and concentrated under vacuum, and the residue was purified by silica gel flash column chromatography (4:1 hexane/ethyl acetate) to afford the product (52 mg, 73% yield) as a white solid (mp 207−208 °C). R_f = 0.12 (4:1 hexane/ethyl acetate). $[\alpha]_D^{25} = +45.4$ (c = 0.65, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.35−7.28 (m, 10H), 5.59 (d, 1H, J = 7.5 Hz), 5.02 (d, 1H, J = 7.8 Hz), 4.83 (d, 1H, J = 10.0 Hz), 4.82 (d, 1H, J = 11.7 Hz), 4.66 (d, 1H, J = 11.3 Hz), 4.59 (d, 1H, J = 11.1 Hz), 4.40 (dd, 1H, J = 11.7, 2.4 Hz), 4.28 (dd, 1H, J = 9.8, 8.7 Hz), 4.14 (dd, 1H, J = 12.0, 6.6 Hz), 3.65 (ddd, 1H, J = 9.4, 6.7, 2.5 Hz), 3.53 (tt, 1H, J = 11.1, 5.0 Hz), 3.44 (t, 1H, J = 9.4 Hz), 3.16 (dt, 1H, J = 9.8, 7.8 Hz), 1.95 (dt, 1H, J = 12.6, 3.4 Hz), 1.86 (s, 3H), 1.82−1.77 (m, 2H), 1.70−1.61 (m, 2H), 1.57−1.40 (m, 5H), 1.37−0.95 (m, 20H), 1.20 (s, 9H), 0.89 (d, 3H, J = 6.5 Hz), 0.86 (d, 3H, J = 6.6 Hz), 0.85 (d, 3H, J = 6.7 Hz), 0.76 (s, 3H), 0.63 (s, 3H), 0.58 (td, 1H, J = 11.5, 4.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): 178.2, 170.5, 138.3, 137.6, 129.2, 128.6, 128.5, 128.5, 128.0, 127.9, 127.9, 127.8, 98.0, 80.2, 79.3, 79.1, 74.9, 74.7, 72.8, 63.4, 58.1, 56.4, 56.2, 54.3, 44.7, 44.3, 42.5, 40.0, 38.8, 37.0, 36.1, 35.8, 35.5, 35.4, 34.5, 32.0, 29.4, 28.7, 28.2, 28.0, 27.2, 24.2, 23.8, 23.6, 22.8, 22.5, 21.2, 18.6, 12.2, 12.0. FTIR (neat film): 3274, 2932, 2867, 1732, 1652, 1566, 1453, 1371, 1316, 1285, 1170, 1115, 1078, 1029, 985, 745, 697 cm^{-1}. HRMS $(FAB)^+$ m/z calcd for $C_{54}H_{81}NO_7Na$ $(M + Na)^+$, 878.5911; found, 878.5914.

Method (B): Benzyl *O*-(2-*N*-Acetylamino-2-deoxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-(1−4)-2,3-*O*-cyclohexylidene-α-L-rhamnopyranoside (16). Trifluoromethanesulfonic anhydride (24 μL, 0.144 mmol, 2.0 equiv) was added to a solution of 3,4,6-tri-*O*-benzyl-D-glucal (30 mg, 0.072 mmol, 1.0 equiv) and thianthrene-5-oxide (33.5 mg, 0.144 mmol, 2.0 equiv) in a mixture of chloroform and dichloromethane (2.4 mL; 3:1 v/v) at −78 °C. The reaction mixture was stirred at this temperature for 12 min, then *N*,*N*-diethylaniline (45 μL, 0.29 mmol, 4.0 equiv) was added, followed by *N*-(TMS)acetamide (28 mg, 0.22 mmol, 3.0 equiv). The mixture was immediately warmed to 23 °C and was stirred at this temperature for 40 min. A solution of benzyl 2,3-*O*-cyclohexylidene-α-L-rhamnopyranoside (72 mg, 0.22 mmol, 3.0 equiv) in 1.0 mL of dichloromethane was added via cannula. Camphorsulfonic acid (33.5 mg, 0.144 mmol, 2.0 equiv) was then added, and the reaction was stirred for 40 h. The mixture was diluted with 40 mL of dichloromethane and washed with 40 mL of saturated aqueous sodium bicarbonate solution and 40 mL of saturated aqueous sodium chloride solution. The organic layer was dried over $MgSO_4$ and concentrated, and the residue was purified by silica gel flash column chromatography (94:6 dichloromethane/ethyl acetate) to afford the product (31 mg, 53% yield) as a white solid (mp 153−154 °C). R_f = 0.07 (94:6 dichloromethane/ethyl acetate). $[\alpha]_D^{25} = -13.8$ (c = 0.55, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.38−7.27 (m, 18H), 7.25−7.23 (m, 2H), 5.52 (d, 1H, J = 8.6 Hz), 5.05 (s, 1H), 4.83 (d, 1H, J = 11.4 Hz), 4.82 (d, 1H, J = 10.9 Hz), 4.71 (d, 1H, J = 8.5 Hz), 4.69 (d, 1H, J = 11.1 Hz), 4.68 (d, 1H, J = 12.2 Hz), 4.63 (d, 1H, J = 12.2 Hz), 4.62 (d, 1H, J = 10.8 Hz), 4.56 (d, 1H, J = 12.2 Hz), 4.48 (d, 1H, J = 11.7 Hz), 4.12 (d, 1H, J = 4.9 Hz), 4.07 (dd, 1H, J = 7.4, 5.7 Hz), 3.86 (dt, 1H, J = 9.8, 8.5 Hz), 3.76 (dd, 1H, J = 11.2, 4.3 Hz), 3.73 (dd, 1H, J = 12.0, 6.2 Hz), 3.74−3.68 (m, 2H), 3.64 (dd, 1H, J = 9.9, 8.7 Hz), 3.46 (dd, 1H, J = 10.0, 7.4 Hz), 3.44 (ddd, 1H, J = 9.4, 4.2, 2.2 Hz), 1.88 (s, 3H), 1.70 (q, 1H, J = 8.3 Hz), 1.65−1.47 (m, 7H), 1.41−1.36 (m, 2H), 1.31 (d, 3H, J = 6.3 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): 170.2, 138.3, 138.2, 138.0, 137.0, 128.5, 128.4, 128.3, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 110.0, 101.7, 96.0, 82.3, 81.7, 78.2, 77.9, 75.7, 75.4, 74.8, 74.4, 73.5, 69.1, 68.8, 64.4, 55.6, 37.8, 35.6, 28.1, 24.9, 24.1, 23.6, 23.5, 17.4. FTIR (neat film): 3272, 3030, 2934, 1655, 1562, 1496, 1452, 1370, 1310, 1099, 1067, 1027, 936, 735, 697 cm^{-1}. HRMS $(FAB)^+$ m/z calcd for $C_{48}H_{57}NO_{10}Na$ $(M + Na)^+$, 830.3880; found, 830.3882.

Method (C): Azido 3,4,6-Tri-*O*-benzyl-2-*N*-acetylamino-2-deoxy-β-D-glucopyranoside (19). Trifluoromethanesulfonic anhydride (40 μL, 0.24 mmol, 2.0 equiv) was added to a solution of 3,4,6-tri-*O*-benzyl-D-glucal (50 mg, 0.12 mmol, 1.0 equiv) and thianthrene-5-oxide (56 mg, 0.24 mmol, 2.0 equiv) in a mixture of chloroform and dichloromethane (2.4 mL; 3:1 v/v) at −78 °C. The reaction mixture was stirred at this temperature for 12 min, then *N*,*N*-diethylaniline (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. The solvent was quickly removed under vacuum, and *N*,*N*-dimethylformamide (2.0 mL), sodium azide (78 mg, 1.20 mmol, 10.0 equiv), and copper(II) trifluoromethanesulfonate (87 mg, 0.24 mmol, 2.0 equiv) were added, and the reaction was stirred for 48 h. The reaction mixture was diluted with water (80 mL) and extracted four times with diethyl ether (20 mL). The combined ether extract was then washed with saturated aqueous sodium chloride solution (30 mL) and dried over sodium sulfate. The solution was filtered and concentrated under vacuum, and the residue was purified by silica gel flash column chromatography (3:1 benzene/ethyl acetate) to afford the product (44 mg, 71% yield) as a white solid (mp 168−169 °C). R_f = 0.17 (3:1 benzene/ethyl acetate). $[\alpha]_D^{25} = +6.9$ (c = 0.75, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.36−7.27 (m, 13H), 7.21−7.18 (m, 2H), 5.31 (d, 1H, J = 7.7 Hz), 4.97 (d, 1H, J = 8.9

Hz), 4.84 (d, 1H, $J = 11.7$ Hz), 4.79 (d, 1H, $J = 10.8$ Hz), 4.64 (d, 1H, $J = 12.2$ Hz), 4.62 (d, 1H, $J = 11.4$ Hz), 4.59 (d, 1H, $J = 10.9$ Hz), 4.56 (d, 1H, $J = 12.1$ Hz), 3.99 (dd, 1H, $J = 10.1$, 8.7 Hz), 3.77 (dd, 1H, $J = 11.0$, 1.3 Hz), 3.74 (dd, 1H, $J = 11.0$, 4.9 Hz), 3.68 (t, 1H, $J = 8.5$ Hz), 3.61 (dt, 1H, $J = 9.6$, 3.4 Hz), 3.40 (dt, 1H, $J = 9.4$, 8.7 Hz), 1.84 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): 170.6, 138.2, 127.9, 137.8, 128.5, 128.4, 128.4, 128.0, 127.9, 127.8, 127.8, 127.7, 87.9, 80.4, 78.1, 77.0, 74.8, 74.7, 73.5, 68.3, 56.1, 23.4. FTIR (neat film): 3261, 3088, 3031, 2915, 2870, 2113, 1651, 1556, 1496, 1452, 1375, 1319, 1247, 1113, 1087, 1072, 1027, 957, 749, 694 cm^{-1}. HRMS (FAB)$^+$ *m*/*z* calcd for $C_{29}H_{32}N_4O_5Na$ $(M + Na)^+$, 539.2270; found, 539.2271. The corresponding manno-diastereomer, azido 3,4,6-tri-*O*-benzyl-2-*N*-acetylamino-2-deoxy-α-D-mannopyranoside, was also isolated in 6% yield (4 mg).

Representative Procedures for NMR Detection of Glycosyl Intermediates. Method (A). A solution of *C1-^{13}C*-tri-*O*-benzyl-D-glucal (10.0 mg, 0.024 mmol, 1.0 equiv) and thianthrene-5-oxide (11.1 mg, 0.048 mmol, 2.0 equiv) in 0.6 mL of $CDCl_3$ was transferred via cannula to a standard 5 mm NMR tube under argon atmosphere. The reaction was cooled to −60 °C, and ^{1}H, ^{13}C NMR data were acquired. Trifluoromethanesulfonic anhydride (8.1 μL, 0.048 mmol, 2.0 equiv) was added to the reaction at −60 °C, and the contents were mixed by using a Fisher Vortex Genie 2 instrument. ^{1}H and ^{13}C NMR data were acquired at −60 °C. *N*,*N*-Diethylaniline (15.2 μL, 0.096 mmol, 4.0 equiv) was then added, briefly mixed at −60 °C, and ^{1}H, ^{13}C NMR data were acquired. A solution of *^{15}N-N*-(TMS)benzamide (14.0 mg, 0.072 mmol, 3.0 equiv) in 0.1 mL of $CDCl_3$ was then added via syringe, and the reaction was briefly mixed. ^{1}H and ^{13}C NMR data were acquired at −60 °C. The reaction was gradually warmed, and ^{1}H, ^{13}C NMR data were acquired at −45, −20, −5, and 20 °C.

Method (B). Trifluoromethanesulfonic anhydride (7.4 μL, 0.044 mmol, 2.0 equiv) was added to a solution of 3,4,6-tri-*O*-d_7-benzyl-D-glucal (9.6 mg, 0.022 mmol, 1.0 equiv) and thianthrene-5-oxide (10.2 mg, 0.044 mmol, 2.0 equiv) in 0.7 mL of $CDCl_3$ in a 10 mL conical shape Schlenk flask at −60 °C. The reaction mixture was stirred at this temperature for 10 min, then *N*,*N*-diethylaniline (14.0 μL, 0.088 mmol, 4.0 equiv) was added, followed by *N*-(TMS)benzamide (12.7 mg, 0.066 mmol, 3.0 equiv). The reaction mixture was stirred at −60 °C for 4 min and then transferred via cannula to a standard 5 mm NMR tube cooled to −45 °C under argon atmosphere. The contents were then briefly mixed at −45 °C by using a Fisher Vortex Genie 2 instrument. The reaction was gradually warmed to −20 °C, and ^{1}H, ^{1}H−COSY, and ^{1}H-homodecoupling NMR data were acquired. The reaction was then further slowly warmed to 23 °C during which ^{1}H NMR data were acquired at −15, −5, and 20 °C, respectively.

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Supporting Information Available: Experimental procedures and spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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