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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Mechanism of Glycosylation of Anomeric Sulfonium Ions

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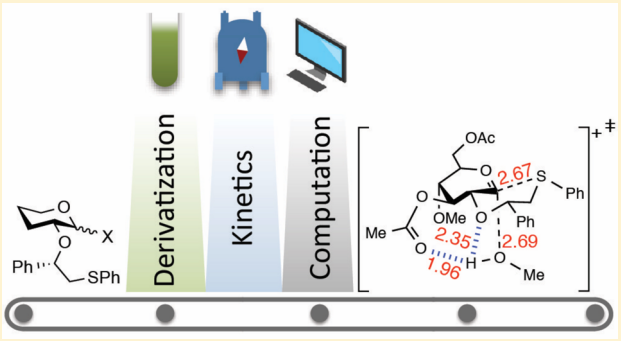
Supporting Information

ABSTRACT: Anomeric sulfonium ions are attractive glycosyl donors for the stereoselective installation of 1,2-*cis* glycosides. Although these donors are receiving increasing attention, their mechanism of glycosylation remains controversial. We have investigated the reaction mechanism of glycosylation of a donor modified at C-2 with a (1*S*)-phenyl-2-(phenylsulfanyl)ethyl chiral auxiliary. Preactivation of this donor results in the formation of a bicyclic β-sulfonium ion that after addition of an alcohol undergoes 1,2-*cis*-glycosylation. To probe the importance of the thiophenyl moiety, analogs were prepared in which this moiety was replaced by an anisoyl or benzyl moiety. Furthermore, the auxiliaries were installed as *S*- and *R*-stereoisomers. It was found that the nature of the heteroatom and chirality of the auxiliary greatly influenced the anomeric outcome and only the one containing a thiophenyl moiety and having *S*-configuration gave consistently α-anomeric products. The sulfonium ions are sufficiently stable at a temperature at which glycosylations proceed indicating that they are viable glycosylation agents. Time-course NMR experiments with the latter donor showed that the initial rates of glycosylations increase with increases in acceptor concentration and the rate curves could be fitted to a second order rate equation. Collectively, these observations support a mechanism by which a sulfonium ion intermediate is formed as a *trans*-decalin ring system that can undergo glycosylation through a bimolecular mechanism. DFT calculations have provided further insight into the reaction path of glycosylation and indicate that initially a hydrogen-bonded complex is formed between sulfonium ion and acceptor that undergoes S_N2-like glycosylation to give an α-anomeric product.



INTRODUCTION

A key step in the chemical synthesis of complex oligosaccharides of biological importance is the stereoselective installation of glycosidic linkages.[1] The introduction of 1,2-*trans*-glycosides can easily be accomplished by exploiting neighboring group participation by a 2-*O*-acyl functionality. On the other hand, the introduction of 1,2-*cis* glycosidic linkages, such as α-glucosides and α-galactosides, require glycosyl donors having a non-assisting functionality at C-2 and often these glycosylations provide mixtures of anomers. Routine complex carbohydrate synthesis will only be possible when robust methods become available for the coupling of saccharide units that give only one of the two possible anomers.[2,3]

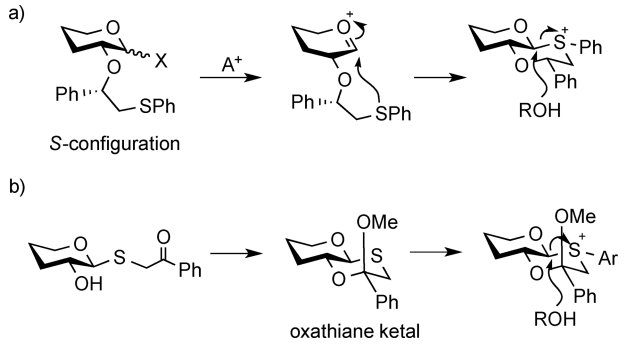
Recently, anomeric sulfonium ions have attracted considerable attention as reactive intermediates for the stereoselective installation of 1,2-*cis* glycosides.[4] This type of compound was first described by Schuerch and co-workers who treated a per-*O*-benzylated glucosyl bromide with dimethyl sulfide to give acyclic β-dimethyl-sulfonium ion.[5] Addition of methanol to the in situ formed sulfoniun ion led to the formation of the corresponding methyl glycoside as predominantly the α-anomer. It was found that anomeric sulfonium ions are more reactive than the corresponding glycosyl ammonium and phosphonium ions in reactions with alcohols. Several other reports have shown that exogenous addition of sulfides can increase anomeric selectivities of glycosylations. For example, α-anomeric selectivities of glycosylations of 2-azido-glucopyranosyl trichloroacetimidates can be enhanced by the appropriate selection of a sulfide additive and in particular the use of PhSEt and thiophene led to substantial increases in α-anomeric selectivity.[6] The corresponding intermediate β-sulfonium ion could be observed by low-temperature NMR spectroscopy and their formation is consistent with a mechanism in which the anomeric sulfonium ion is displaced by an alcohol to give an α-glycoside. A highly stable β-anomeric sulfonium ion, which could be isolated by silica gel column chromatography, was formed by the alkylation of the deactivated donor ethyl 2-*O*-benzyl-3,4,6-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside using methyl triflate. Methanolysis of this compound was completed within 15 min to give only the α-glucoside without a need for a promoter.[7]

Received: August 10, 2015
Published: February 15, 2016

DOI: 10.1021/jacs.5b08436
J. Am. Chem. Soc. 2016, 138, 3002−3011

We have introduced a stereoselective glycosylation approach based on neighboring group participation by a (*S*)-phenylthiomethylbenzyl moiety at C-2 of a glycosyl donor (Scheme 1a).[8−10] Upon formation of an oxacarbenium ion, the nucleophilic thiophenyl moiety of the C-2 functionality participates leading to the formation of an intermediate sulfonium ion. The formation of the *trans*-decalin stereoisomer is strongly favored because of the absence of unfavorable gauche interactions. The alternative *cis*-decalin system places the phenyl-substituent in an axial position inducing unfavorable steric interactions. Low temperature NMR experiments unambiguously identified a β-substituted sulfonium ion as a reaction intermediate. The addition of various sugar alcohols led to the exclusive formation of 1,2-*cis*-glycosides. The (*S*)-(phenylthiomethyl)benzyl moiety can readily be introduced by reaction of a sugar alcohol with (*S*)-(phenylthiomethyl)benzyl acetate in the presence of BF_3-OEt_2. The auxiliary can easily be converted into an acetyl ester by treatment with BF_3-OEt_2 in acetic anhydride. The attractiveness of chiral auxiliary mediated glycosylations has been shown by the solid phase synthesis of several branched oligosaccharides having only 1,2-*cis*-glucosidic linkages.[11] The methodology was extended to a latent-active iterative glycosylation strategy for the stereoselective assembly of highly branched glycogen-like glycans that had been implicated in innate immune responses.[12] Bicyclic anomeric sulfonium ions can also be formed by arylation of 1,2-oxathiane ketals, which in turn, can easily be prepared from a thioglycoside (Scheme 1b).[13]

Scheme 1. Bicyclic Sulfonium Ions Mediated Stereoselective *cis*-Glycosylations[a]



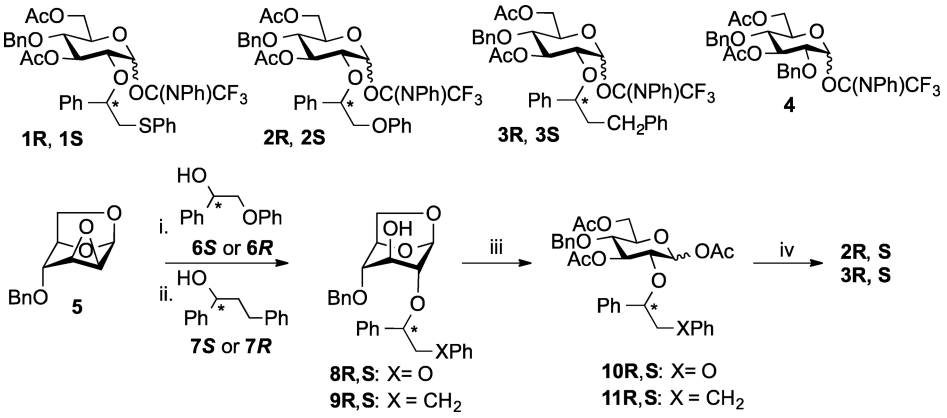
[a](a) In situ formation of bicyclic sulfonium ions by the preactivation of donors with C-2 (*S*)-auxiliary; (b) direct conversion of preformed bicyclic oxathiane ketals by arylation.

Although the formation of β-anomeric sulfonium ion intermediates supports a mechanism of glycosylation by direct nucleophilic substitution, it does not rule out alternative reactions pathways that can explain the observed stereoselectivity.[14] In this respect, NMR investigations have showed that activation of a mannosyl donor having a thioether at C-6 can readily form a 1,6-bridged sulfonium ion.[15] Subsequent glycosylations gave, however, the unexpected 1,2-*cis* linked disaccharides as the main product. This observation was rationalized by a rapid equilibrium of the sulfonium ion with the corresponding oxacarbenium ion. Although the equilibrium lies to the side of the sulfonium ion, the glycosylation is governed by Curtin−Hammett kinetic principles and proceeds through the more reactive oxacarbenium ion. The β-anomeric selectivity was rationalized by a model in which the oxacarbenium ion adopts a $^3H_4$ conformation that places all ring-substituents in electronically favorable positions. Subsequent nucleophilic attack takes place from the β-face leading to a chair conformation.[15] In another study, methylation of a bicyclic thioglycoside generated a 1,5-bridged methylsulfonium ion; however, subsequent glycosylations gave moderate stereoselectivities, and probably the reaction proceeds via an S_N1-like mechanism.[16] It has also been observed that a thiophenyl ether at a remote position (C-4) of a model tetrahydropyran acetal does not exert anomeric control in C-glycosylations.[17]

Another interesting study by Whitfield and co-workers demonstrated that a C-2 chiral nonparticipating group can exert control over the anomeric selectivity through a plausible oxacarbenium ion intermediate.[18] Thus, it is possible that the chirality of (*S*)-(phenylthiomethyl)benzyl at C-2 of donors controls the anomeric outcome of glycosylations even if it proceeds through an S_N1-like mechanism.

A proper understanding of reaction mechanisms of glycosylations is critical for the development of robust stereoselective protocols. Therefore, we report here the preparation of the trifluoroacetimidates **1R,S**, **2R,S**, and **3R,S**, which have chiral functional groups at C-2, and examined the

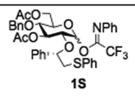
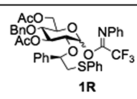
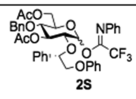
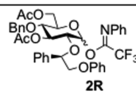
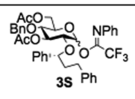
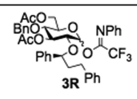
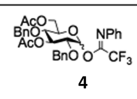
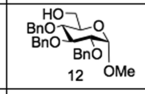
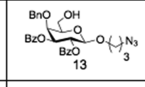
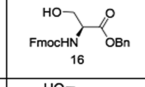
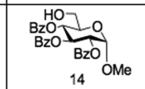
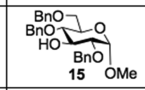
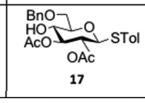
Scheme 2. Preparation of C-2 Modified Donors[a]



[a]Reagents and conditions: (i) BF_3-Et_2O, DCM, 2 h (**8R**: 48%, **8S**: 44%, **8R**: 88%, **8S**: 90%); (ii) NaH, DMF, 90 °C, 16 h (**6**: 90%, **7**: 88%); (iii) TMSOTf, Ac_2O, 0 °C, 10 min; (iv) H_2NNH_2−HOAc, DMF, 45 °C, 90 min; then CF_3C = (NPh)Cl, DBU, DCM, r.t., 10 min (2 steps, **2S**: 68%, **2R**: 73%, **3R**: 80%, **3S**: 75%).

DOI: 10.1021/jacs.5b08436
J. Am. Chem. Soc. 2016, 138, 3002−3011

Table 1. Glycosylations for Probing C-2 Participating Effects[a,b,c]

Acceptors	Donors	1	2	3	4	5	6	7
	Yield α/β	 1S	 1R	 2S	 2R	 3S	 3R	 4
a	 12	95%	85%	88%	85%	91%	76%	82%
		1:0	2:1	1:0	2:1	5:1	15:1	3:1
b	 13	63%	70%	87%	92%	100%	62%	83%
		1:0	3:1	12:1	2:1	2:1	1.5:1	3:1
c	 16	83%	90%	94%	91%	94%	98%	88%
		1:0	2:1	1:0	2.5:1	7:1	3:1	7:1
d	 14	93%	88%	100%	81%	100%	83%	74%
		1:0	3:1	1:0	4:1	1:0	10:1	10:1
e	 15	55%	69%	52%	48%	74%	61%	88%
		1:0	5:1	>15:1	>15:1	>15:1	>15:1	14:1
f	 17	56%	48%	33%	53%	44%	48%	51%
		1:0	6:1	15:1	7:1	15:1	20:1	15:1

[a]Numbering of glycosylation products (not shown) are the combination of column's Arabic number and row's alphabetic character. [b]See SI for glycosylation conditions. [c]Reaction mixtures were purified by LH-20 size exclusion column chromatography, and α/β ratio were determined by integration of key signals. The identity of the minor anomers was confirmed by 2D-gHSQCAD (gradient-selected heteronuclear single-bond correlation spectrum using matched adiabatic pulses) or 1D-TOCSY experiments. Yields were determined directly after LH-20 purification as combined yield of α/β anomers.

stereoselective outcomes of glycosylations with several glycosyl acceptors. Compound **1S** is a prototypical glycosyl donor having a (*S*)-phenylthiomethylbenzyl moiety at C-2 that upon activation will form a *trans*-decalin sulfonium ion that can react with alcohols to give α-glucosides. Compound **1R** is a stereoisomer of **1S** that has a similar thiophenyl-containing auxiliary having the (*R*)-configuration. It was anticipated that participation by this auxiliary would result in the formation of a *cis*-decalin sulfonium ion in which the C-1′ phenyl substituent is placed in an equatorial configuration. Compounds **2S** and **2R** are derived from **1S** and **1R**, respectively; however, the thiophenyl is replaced by an anisole moiety. The oxygen-containing auxiliary of **2S** and **2R** was expected to be a less efficient neighboring group participant compared to the thiophenyl-containing derivative.[19] Finally, glycosyl donors **3S** and **3R** having chiral C-2 moieties at C-2 are derived from **1S** and **1R** and cannot participate because of a lack of a heteroatom at the C-2′ position. It was found that the nature of the heteroatom of the auxiliary greatly influenced the anomeric outcome of the glycosylations and only the use of glycosyl donor **1S** gave consistently α-anomeric products. Furthermore, the sulfonium ions are sufficiently stable at temperatures at which glycosylations proceed, and thus are viable glycosylation agents. Kinetic experiments have shown that the rate of glycosylation of **1S** is dependent on the concentration of the glycosyl acceptor. DFT calculations support a reaction pathway in which a hydrogen-bonded complex is formed between acceptor and the acyl group at C-3 of the donor, which undergoes an S_N2-like glycosylation to give an α-anomeric product.

RESULTS AND DISCUSSION

Synthesis and Glycosylations of Donors Having Tunable Neighboring Participating C-2 Auxiliary. Glycosyl donors **1S** and **1R** were prepared from tri-*O*-acetyl glucal employing a procedure that made it possible to derivatize C-2 with a chiral auxiliary at a late stage of the synthesis (Scheme 2, see SI for details). The preparation of glycosyl donors **2R** and **2S** commenced from commercially available optical active styrene oxides, which were reacted with sodium phenolate or benzyl magnesium chloride to give *O*-auxiliaries **6S** and **6R** and *C*-auxiliaries **7S** and **7R**, respectively (see SI for details). Treatment of Cerny epoxide **5** with **6S** or **6R** in the presence of BF_3-Et_2O proceeded with the expected *trans*-diaxial opening to give the auxiliary modified derivatives **8R** and **8S** in acceptable yields and recovery of unreacted epoxide and auxiliary. The syntheses of *C*-analogs **9R** and **9S** failed under similar reaction conditions due to the acid sensitivity of **7S** and **7R**. Fortunately, this problem could be prevented by base-mediated opening of the epoxide, and treatment of **7S** or **7R** with NaH to form the corresponding alkoxides followed by reaction with **5** at 90 °C for 16 h gave **9R** and **9S**, respectively.[20] Acetolysis of the 1,6-bridge of compounds **8R**, **8S**, **9R**, and **9S** was carried out by the treatment with Ac_2O in the presence of catalytic amount of TMSOTf to give the corresponding acetates **10R**, **10S**, **11R**, and **11S**, which were treated with hydrazine acetate in DMF to give lactols that were converted into trifluoro *N*-phenyl imidate donors **2R**, **2S**, **3R**, and **3S** having *C*- and *O*-derived auxiliaries by treatment with trifluoro-*N*-phenylacetimidoyl chloride and DBU.[21]

Having the glycosyl donors **1R**,**S**-**3R**,**S** at hand, glycosylations with a diverse range of glycosyl acceptors, including properly protected primary sugar alcohols (**12**,[22] **13**,[25] and **14**[10]), secondary sugar alcohols (**15**[24]), properly protected serine

DOI: 10.1021/jacs.5b08436
J. Am. Chem. Soc. 2016, 138, 3002−3011

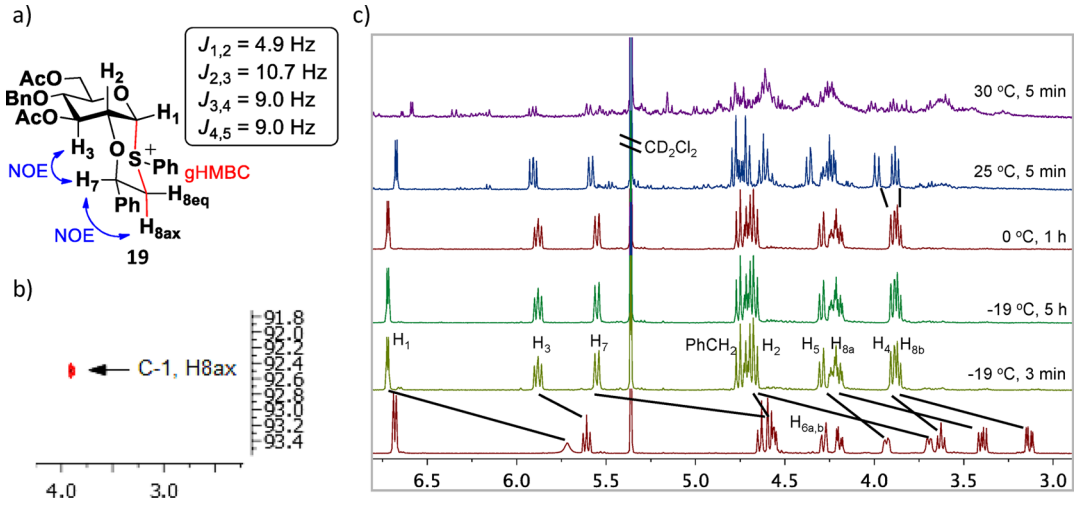


Figure 1. NMR structure and thermostability studies of *cis*-decalin sulfonium ion **19**. (a) Schematic presentation of NMR structural identification of **19**. (b) gHMBC spectrum of **19** showing C1−H8ax three bond coupling. (c) Thermostability of **19** (chemical shifts were referenced to CD_2Cl_2).

(**16**[25]), and a partially protected thioglycoside (**17**[26]), were examined and the results were compared with glycosylations using glycosyl donor **4** that has a conventional benzyl ether at C-2 (Table 1). As expected, glycosyl donor **1S**, which has a (*S*)-phenylthiomethylbenzyl auxiliary at C-2 that can form a favorable *trans*-fused sulfonium ion, gave in each glycosylation only the α-anomeric product. The use of glycosyl donor **1R**, which has a similar auxiliary with (*R*)-configuration, provided poor anomeric selectivities in each glycosylation. Interestingly, glycosyl donor **2S**, in which the sulfur atom of the auxiliary is replaced by oxygen, gave lower α-anomeric selectivities compared to the use of the parent compound **1S**. However, the chirality of the oxygen-modified auxiliary influenced the anomeric outcome of the glycosylations and in each case the (*S*)-isomer provided higher α-selectivities compared to the (*R*)-configured donor. Interestingly, the chirality of the C-2 substituent of the glycosyl donors **3S** and **3R** impacted the anomeric outcome of the glycosylations only in minor ways, and were in a similar range as for donor **4**, which has a benzyl ether at C-2.

These results demonstrate that the chirality of the C-2 substituent of the glycosyl donor influences the anomeric outcomes of the glycosylations. The most favorable outcome was achieved with the glycosyl donor **1S**, which has the greatest propensity to perform neighboring group participation by the formation of an intermediate sulfonium ion. Thus, these observations support a mechanism by which the heteroatom interacts with oxocarbenium ion and displacement is accomplished by an S_N2 like mechanism.

Mechanistic Studies. Glycosyl donor **1R**, having a (*R*)-phenylthiomethylbenzyl ether at C-2, provided poor anomeric selectivities in various glycosylations. It is possible that the C-2 substituent is unable to form a sulfonium ion, and as a result the glycosylations proceed through an oxacarbeniun-ion like transitions state, thereby providing mixtures of anomers. Alternatively, the poor anomeric selectivities may be due to the formation of a mixture of *cis*- and *trans*-fused sulfonium ions, because each species has an axial substituent making unfavorable 1,3-diaxial interactions. It is also possible that a sulfonium ion intermediate is formed as one anomer, which does not represent the reactive species. To this end, glycosyl donor **1R** was preactivated by the addition of triflic acid and the reaction was monitored by NMR spectroscopy at low temperature. The glycosyl donor was consumed within 3 min at −20 °C forming a single new compound, which was unambiguously characterized by 2D NMR experiments including gCOSY, gHSQCAD and gHMBCAD (gradient-selected heteronuclear multiple bond correlation using adiabatic pulses) as *cis*-decalin sulfonium ion **19** (Figure 1). Thus, upon activation, the anomeric proton of **1R** (δ: 5.72, broad singlet) shifted upfield (δ: 6.25, d, $J_{1,2}$ = 4.9 Hz) and the relatively small vicinal coupling constant indicated an axial orientation of the anomeric substituent. All the peaks were assigned by 1D-zTOCSY with selective irradiation of H-3 and H-7 for the ring and auxiliary protons respectively to give isolated spin systems (Figure 1c). Examination of the coupling constants of the saccharide protons indicated that no significant conformational distortion of the saccharide ring had occurred upon sulfonium ion formation. This observation is in contrast to a recently reported acyclic α-sulfonium, which adopted a distorted ring conformational and gave compromised anomeric selectivities in glycosylations.[27] A gHMBCAD experiment, which measures three bond proton-carbon couplings, showed a correlation between C-1 and H_{8eq}, demonstrating the presence of the C1−S−CH_{8eq} linkage and confirmed the formation of the decalin ring system. The *cis*-decalin configuration was further confirmed by NOESY experiment that showed spatial proximity of H-3 and H-7. These studies demonstrate that the (*R*)-configured donor can form a sulfonium ion having a *cis*-decalin configuration. The absence of anomeric selectivity in glycosylation with **19** indicates that it does not represent the reactive glycosylation intermediate.

The thermal stability of the *cis*-decalin sulfonium ion **19** was studied by raising the NMR probe temperature over a period of time. It was observed that the sulfonium ion is stable at −19 °C for at least 5 h. The compound remained intact when the temperature was raised to 0 °C and incubation was continued for 1 h. However, decomposition of **19** was observed when the temperature was raised to 25 °C. A similar stability profile was observed for the *trans*-decalin sulfonium ion arising from **1S**.

Next, we examined whether the glycosylations proceed at temperatures at which the *cis*- and *trans*- sulfonium ion have sufficient stabilities. For this purpose, the progress of the glycosylations of glycosyl donors **1S** and **1R** with glycosyl

DOI: 10.1021/jacs.5b08436
J. Am. Chem. Soc. 2016, 138, 3002−3011

acceptor **18** was examined at different temperatures. During the glycosylations, the temperature was kept constant, and aliquots were taken after 6 h and quenched by the addition of excess methanol. Sanger reagent was used as an internal standard due to its inertness under glycosylation conditions and has characteristic NMR peaks at low field that do not overlap with the carbohydrate signals. Relative percentages of conversion were obtained by comparing integrations of product peaks to the sample, which was left for another 10 h at 0 °C and was assumed to have proceeded to complete conversion (Table 2). Both sulfonium ions gave low conversions at −78 °C. The

Table 2. Conversion of 1S or 1R with Acceptor 14 at Different Temperatures after a Reaction Time of 6 h*

Temp. \ Donor / Conversion%	1S	1R
-78 °C	22	<5
-40 °C	65	40
0 °C	>90	>90

*Glycosylations were conducted with donor and acceptor concentrations adjusted to 8 mM. 1-Fluoro-2,4-dinitrobenzene was added as an internal standard. After preactivation at −78 °C, the reaction temperature was raised to the designated value.

trans-sulfonium ion arising from **1S** exhibited a somewhat higher reactivity at −40 °C as demonstrated by the larger conversion. At 0 °C, both glycosyl donors were completely converted into their glycoside products after a reaction time of 6 h. These studies show that the sulfonium ions are stable at temperatures at which glycosylations proceed with reasonable rates of reaction.

A glycosylation that proceeds through a bimolecular mechanism is expected to exhibit a rate of reaction that is dependent on the concentration of the acceptor. Therefore, glycosyl donor **1S** was preactivated with TMSOTf and the rate of glycosylation monitored by NMR in the presence of increasing concentrations of acceptor **14** (Figure 2). The glycosylation was performed at −40 °C because at this temperature the sulfoniun ion exhibits excellent stabilities and the glycosylation proceeds sufficiently slow to accurately monitor the rate of the reaction. Sanger's reagent was employed as an internal standard to precisely determine conversions at different points in time. It was observed that the initial rates of glycosylations increased with increases in acceptor concentration. Furthermore, the curves could be fitted to a second order rate equation providing a rate constant of 0.059 ± 0.031 M/s (mean ± SD). These observations support a mechanism of glycosylation by a bimolecular mechanism.

Computational Studies. The studies described above show that activation of glycosyl donor **1S** results in the formation of a *trans*-decalin sulfonium ion that does not collapse at a temperature at which a glycosylation takes place and reacts to give a glycoside when a glycosyl acceptor is added. Furthermore, we have found that the rate of glycosylation of the *trans*-decalin sulfonium ion exhibits second-order characteristics suggesting that nucleophilic attack of the alcohol at the bicyclic sulfonium ion proceeds by an S_N2-like mechanism. We have performed density functional theory (DFT) calculations to provide further insight into the reaction mechanism.

Sulfonium ion **M1**, having acetyl esters at C-3 and C-6 and a methyl ether at C-4, was selected as a model donor for the computation studies. In addition, sulfonium ion **M2** was investigated to establish the influence of the acetyl ester at C-3 on the glycosylation pathway (Figure 3). Our previous studies

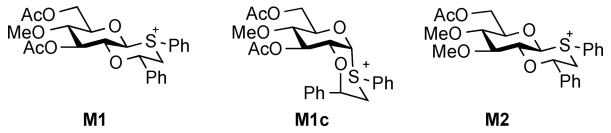


Figure 3. Model sulfonium ions used in the DFT calculations.

have shown that an ester at C-3 of a donor containing a (*S*)-phenylthiomethylbenzyl auxiliary is critical for achieving absolute α-anomeric stereoselectivity.[8,10,28] In particular, it was found that glycosylations with anomeric sulfonium ions having a benzyl ether at C-3 resulted in the formation of small quantities of the unwanted β-glycoside. We proposed that such donors are sufficiently deactivated by the electron-withdrawing protecting groups to avoid glycosylation via an oxacarbenium ion intermediate. We have performed additional glycosylations with a sulfonium ion having a methyl ether at C-3, and as expected glycosylations with acceptors **12** and **14** also gave α/β mixtures (6/1 and 10/1, respectively; for details see section 5 of SI and Scheme S2). The acceptor was simplified to methanol because α-anomeric selectivities are not dependent on the

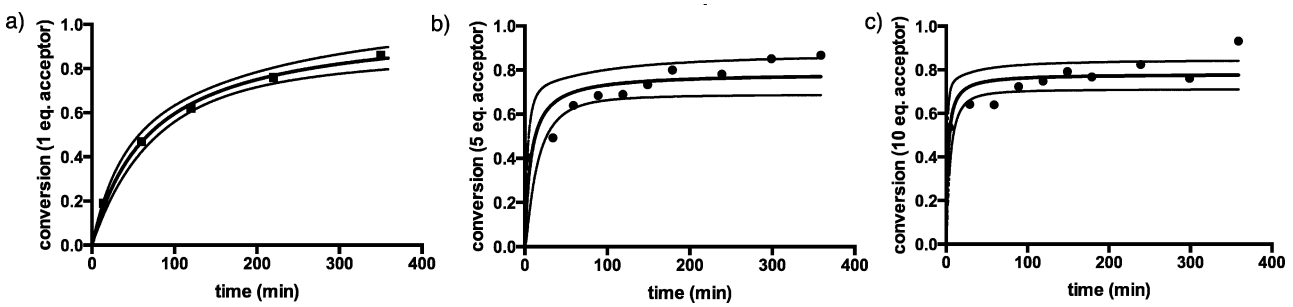


Figure 2. Kinetics (conversion vs time) of glycosylations with donor **1S** using different concentrations of acceptor **14** (a: 1 eq.; b: 5 eq.; and c: 10 eq. of **14**). The glycosyl donor was preactivated at −78 °C and the temperature was raised to −40 °C before adding the acceptor. The acceptor in DCM was precooled in a dry ice/acetone bath and quickly transferred through a double hollow needle to avoid temperature changes. Nonlinear regression analysis was based on F-test (null hypothesis: 1st order reaction; alternative hypothesis: 2nd order reaction.). In every case, Prism 6.0 denied the null hypothesis ($P > 0.05$); therefore all curves were fitted based on the second-order reaction. The experimental data fall in the 95% confidence intervals (thin lines). Details of statistic analysis are available in SI.

DOI: 10.1021/jacs.5b08436
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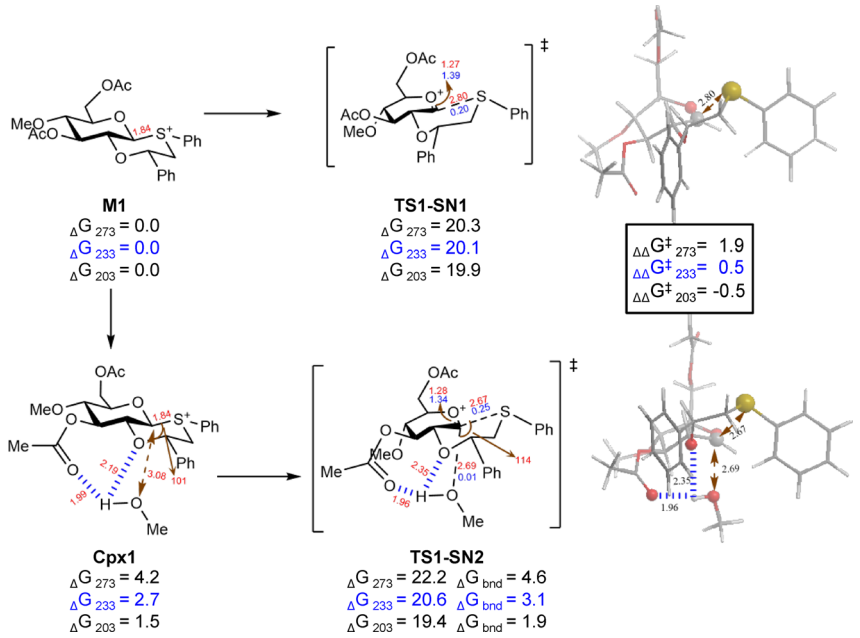
Scheme 3. Optimized Structures of S_N1 and S_N2 Transition States Associated with Sulfonium Ion M1[a]



[a]Unit: kcal/mol. The binding energy of a donor−acceptor complex is defined as the energy difference between the complex and the sum of its two components, the corresponding sulfonium ion and methanol: $\Delta G_{bnd} = \Delta G_{cpx} - \Delta G_{sulfonium} - \Delta G_{MeOH}$. The binding energy of an S_N2 transition state is defined likewise: $\Delta G_{bnd} = \Delta G_{TS} - \Delta G_{oxacarbenium} - \Delta G_{MeOH}$.

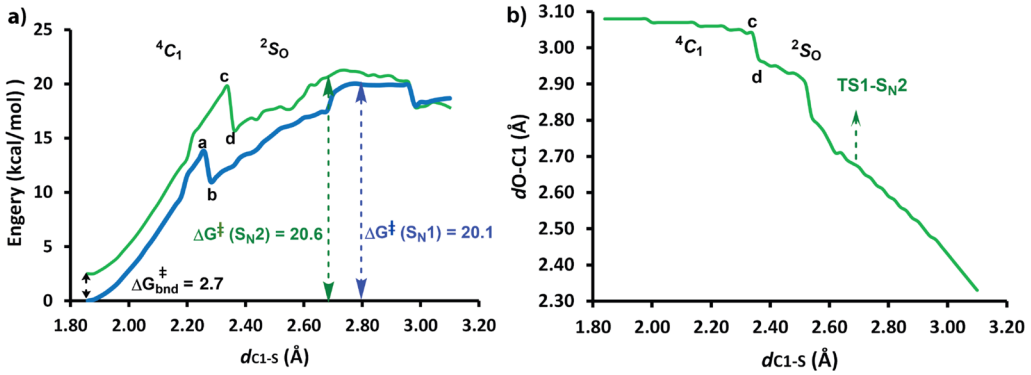


Figure 4. (a) Energy (kcal/mol)−distance (Å) plot for forced extension of C1−S bonds of sulfonium ion **M1** and sulfonium ion-methanol complex **Cpx1**; (b) d_{O-C1} (Å)−d_{C1-S} (Å) plot for forced extension of C1−S bonds of sulfonium ion−methanol complex **Cpx1**.

structure of the acceptor. Counter ions were not considered because a covalent sulfonium-triflate complex was not detected by either computation or experiments for **M1**, unlike reported complexes that have nonparticipating neutral donors.[29−33]

For each donor and donor−acceptor complex, a Low Mode search[34,35] was performed by employing the MMFF94 force field[36] in MOE[37] to generate a large number of possible conformers, which were submitted to structure optimization and frequency calculation at 233.15 K in Gaussian 09.[38] The quantum chemical level M062X/6-31G* was selected based on its accuracy for computing nonbonding interactions.[39−41] Single-point energy values were corrected and solvation was modeled at the higher M062X/6-31+G** level using the recently developed continuum SMD.[42] Transition states were confirmed by frequency calculation and IRC scans. Mayer natural bond order (NBO) analysis was performed at the same theoretical level using the NBO program 3.1 in Gaussian to reveal the structural properties of the transition states.[43−45] To study the departure of the leaving group, we employed Whitfield's approach[46] to forcibly extend the anomeric C−S bond at 0.02 Å increments without other constrains to generate a trajectory of oxacarbenium development and obtain a $\Delta G \approx d_{C1-S}$ curve.

In the absence of methanol, an S_N1 transition state was found having a ^2S_O conformation and some oxacarbenium character (B.O. $_{C1-O5}$ = 1.39) and a partial C1−S bond ($d_{c1\text{-}S}$ = 2.80 Å, B.O. = 0.20). As revealed by its imaginary vibrational mode, the dissociation of the sulfonium ion is associated with a concerted rotation of the dihedral angles C1−C2−O2−C7 and C2−O2−C7−C8. Interestingly, this transition state could not be located with the often-applied B3LYP function, which is regarded as a reliable alternative to M062X that provides computational convenience in optimizing transition state structures. The oxacarbenium ion intermediate **INT1** (see SI for structure) was found at 3.30 Å retaining the ^2S_O conformation, which has been suggested to be isoenergetic to $^4H_3$.[47]

In the presence of methanol, an S_N2 transition state was found that has considerable oxacarbenium characteristics (B.O.

DOI: 10.1021/jacs.5b08436
J. Am. Chem. Soc. 2016, 138, 3002−3011

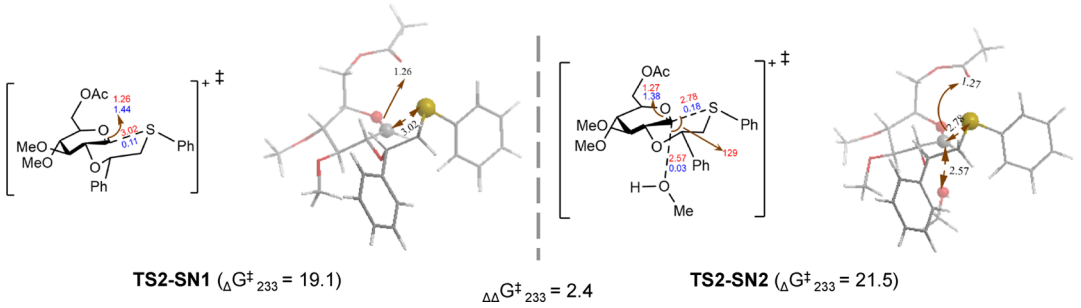


Figure 5. Optimized structures of S_N1 and S_N2 transition states associated with sulfonium ion **M2**. (Unit: kcal/mol).

$_{C1-O5}$ = 1.34) and exhibits slightly less anomeric bond cleavage ($d_{c1\text{-}S}$ = 2.67 Å, B.O. = 0.25; Scheme 3) compared to the S_N1 transition state. Despite the rather weak bonding with the anomeric carbon ($d_{c1\text{-}O}$ = 2.69 Å, B.O. = 0.01), methanol was strongly associated with the donor and favorably oriented for nucleophilic displacement due to hydrogen bond formation at O3−Ac ($d_{O3n\text{-}H}$ = 1.96 Å) and O2 (d_{O2-H} = 2.35 Å). All attempts to locate an S_N2 transition state without hydrogen bonding[18] either failed or resulted in spontaneous hydrogen bond formation during optimization. The S_N2 precursor **Cpx1** is a donor−acceptor complex that also exhibits dual hydrogen bonding ($d_{O3n\text{-}H}$ = 1.99 Å, d_{O2-H} = 2.19 Å) and orients methanol favorably for subsequent nucleophilic attack (d_{O-C1} = 3.08 Å, ∠O−C1−S= 101°). The low binding energy (2.7 kcal/mol) of this complex is likely to allow rapid equilibria between the "free" sulfonium ion **M1**, the reactive complex **Cpx1** and unreactive complexes with other binding sites. The S_N2 activation barrier (20.6 kcal/mol) is 0.5 kcal/mol higher than that of the S_N1 transition state (20.1 kcal/mol). When the calculations were performed at 203.15 K, the S_N2 barrier (19.4 kcal/mol) is 0.5 kcal/mol lower than the S_N1 barrier (19.9 kcal/mol). Thus, the computation studies indicate that the glycosylation may proceed through a mechanism in which the S_N1 as well as the S_N2 pathway plays an important role.

Forcible extension of the anomeric C−S bond of sulfonium ion **M1** (Figure 4, red curve) initially caused the dihedrals C1−C2−O2−C7 and C2−O2−C7−C8 to rotate and the free energy to steadily increase (Table S1). This process was interrupted by a sudden conformational change from $^4C_1$ (point a, $\tau_{C5-O-C1-C2}$ = −61°) to ^2S_O (point b, $\tau_{C5-O-C1-C2}$ = 11°) between 2.26 and 2.28 Å resulting in a decrease of free energy of 2.7 kcal/mol. Point a was not a transition state because no resting states could be located. After point b, the energy curve rose again and became flat at 2.70 Å without reaching an obvious maximum while the only transition state on this surface could be found at 2.80 Å as **TS1-SN1**. These observations indicate that sulfonium ion **M1** behaves similarly to peracetylated β-glucosyl halides previously reported by Whitfield and co-workers.[46,48]

Forcible extension of the anomeric C−S bond of the sulfonium ion-methanol complex **Cpx1** (Figure 4, green curve) gave an energy curve with a conformational change between points **c** (2.34 Å) and **d** (2.36 Å) accompanied by a substantial decrease in energy (4.0 kcal/mol). The only transition state, **TS1-SN2**, was found at 2.67 Å in the slightly oscillating surface. The highest point on the curve is slightly higher than the S_N2 transition state, suggesting that the anomeric bond cleavage and the addition of methanol for an S_N2 mechanism is coupled[48] (Figure 4a). A plot of distances d_{O-C1} against d_{C1-S} shows that the development of the ^2S_O oxacarbenium ion is associated with the movement of methanol toward the anomeric carbon, which is initially subtle but undergoes unevenly increase in gradient after the conformational change at d_{C1-S} = 2.34 Å. A linear relationship between d_{O-C1} and d_{C1-S} was observed with a slope of −0.86 after d_{C1-S} = 2.54 Å corresponding to gradual formation of the new glycosidic linkage. **TS1-SN2** was located at 2.67 Å and proton transfer was not observed even at the final point (d_{C1-S} = 3.10 Å, d_{O-C1} = 2.33 Å; Figure 4b).

Calculations have also revealed that the *cis*-sulfonium ion **M1c** lies 5.3 kcal/mol above the corresponding *trans*-sulfonium ion **M1** due to the unfavorable axial orientation of the C-7 phenyl group, which is in agreement with the NMR studies that showed only the presence of the β-anomeric sulfonium ion. Furthermore, the corresponding S_N1 and S_N2 transition states of **M1c** were substantially higher in energy than that for **M1** making glycosylations through **M1c** highly unlikely (for details see SI page S60).

For the model sulfonium ion **M2** (Figure 3), which has a methyl ether instead of an acetyl ester at the C-3 position, the S_N1 transition state also adopts a ^2S_O conformation but is later than **TS2-SN1** as indicated by the greater extent of anomeric bond cleavage (d_{C1-S} = 3.02 Å, B.O. = 0.11) and lower activation barrier (19.1 kcal/mol) (Figure 5). The S_N2 transition state possesses very weak donor−acceptor association (d_{O-C1} = 2.57 Å, B.O. = 0.03) lacking hydrogen bonding and corresponds to a precursor being not a donor−acceptor complex but a separated ion pair. Compared with the **TS1-SN2**, the energy barrier of **TS2-SN2** increased to 21.5 kcal/mol making the S_N1 reaction pathway substantially more favorable (Figure 5). This finding agrees with experimental results, which have demonstrated loss of facial selectivity upon replacement of an ester at the C-3 position with an ether protecting group.[10]

A previously reported computational study, dealing with the reaction mechanism of glycosylation of donors such as **1S**, attributed the α-anomeric selectivity to selective addition to an oxacarbenium ion rather than an S_N2 reaction pathway.[14] In the latter study, the glycosyl donor **1S** was simplified by having a methyl ether at C3, a hydrogen at C6 and the phenyl of the auxiliary replaced by methyl. A highly dissociated $^4H_3$ transition state was found for the S_N1 reaction mechanism and a less stable transition state for the S_N2 pathway similar to **TS2-SN2** in which the donor and the acceptor are very weakly bonded. Our results indicate that the C3-ester critically contributes to the S_N2 mechanism, and replacement by an ether protecting group will affect the pathway of reaction.

The computational data at 233 K for glycosylations of donors such as **1S** support a mechanism in which both the S_N1 and S_N2 pathway are plausible. In the case of an S_N2 mechanism, a complex is formed between an anomeric sulfonium ion intermediate and acceptor through dual hydrogen bonding

DOI: 10.1021/jacs.5b08436
J. Am. Chem. Soc. 2016, 138, 3002−3011

that undergoes glycosylation to give α-anomeric products. In the case of an S_N1 pathway, bimolecular reaction kinetics would be expected if the barrier for addition of the alcohol to the oxacarbenium ion lies above that for **TS1-SN1**. Such an assumption is reasonable because the 1.6 kcal/mol of energy difference between **TS1-SN1** and the resultant oxacarbenium intermediate **INT1** (see SI page S53) is smaller than the binding energy of **TS1-SN2** (3.1 kcal/mol). Furthermore, α-anomeric selectivity would be expected if the alcohol complexes to the already-formed oxacarbenium intermediate via hydrogen bonding prior to C−O bond formation. The oxacarbenium ion resulting from **M1** has a similar conformation as **TS1-SN2**, and thus its geometry can readily accommodate dual hydrogen bonding with the acceptor for subsequent α-anomeric attack. Others have proposed that hydrogen bonding between donor and acceptor may be important for the anomeric outcome of S_N1 glycosylations.[48,49] For example, Demchenko and co-workers have proposed that a picoloyl group at C-3 of a mannosyl donor facilitates high β-anomeric selectivities through hydrogen bonding between the nitrogen of the picoloyl moiety of the oxacarbenium ion intermediate and the hydroxyl of the acceptor.[50,51] It is also important to note that the ^2S_O conformation of the oxacarbenium ion favors nucleophilic attack from the α-face even in an uncomplexed mode of attack.[52] However, such a mode of reaction cannot rationalize the absolute anomeric selectivity observed for donors such as **M1** that have an ester protecting group at C-3. In this respect, glycosyl donors such as **M2** that have a C-3 ether protecting group, are also predicted to form an oxacarbenium ion having the ^2S_O conformation, and although such donors exhibit α-anomeric selectivity they invariably produce β-anomeric byproducts.[10]

The observation that the activation energy of the C3-*O*-acetylated **TS1-SN1** is 1.0 kcal/mol lower than that for the C-3 methylated **TS2-SN1** supports the previous proposed hypothesis that acetylation deactivates oxacarbonium ion formation thereby promoting an S_N2 like glycosylation.[10] In addition, dual hydrogen bonding between the donor and the acceptor stabilizes **TS1-SN1** by 0.9 kcal/mol and directs the acceptor favorably for nucleophilic attack from the α-face during the development of the oxacarbenium ion. The electronic and hydrogen bonding effects of the C-3 ester group combined decrease $\Delta\Delta G^{\ddagger}$ by 1.9 kcal/mol and cause the reaction to occur via a mechanism that has S_N1 and S_N2 features.

CONCLUSIONS

A detailed understanding of reaction mechanisms of glycosylations will offer opportunities to develop robust and stereoselective glycosylation protocols.[53] The studies described here support a mechanism of glycosylation of donors having a (*S*)-phenylthiomethylbenzyl ether at C-2, in which initially an anomeric sulfonium ion intermediate is formed as a *trans*-decalin system that undergoes an S_N2-like glycosylation reaction indicated by donor−acceptor complexation via hydrogen bonding leading to the selective formation of an α-glycoside. The results of glycosylations with analogs in which the thiophenyl moiety of the auxiliary was replaced by an anisoyl or benzyl moiety indicate that it is not the inherent chirality of the auxiliary that controls anomeric selectivity of glycosylations of an oxocarbenium ion intermediate. On the other hand, the chirality of the auxiliary is critical for the formation of an equatorial anomeric sulfonium ion, which places O-2 in a proper conformation for dual hydrogen bonding of the acceptor with O-2 and the carbonyl of an ester at C-3. Although the computed S_N1 and S_N2 energies are too close to make an absolute assignment to either typical S_N1 or typical S_N2, we have shown that dual hydrogen bonding stabilizes the S_N2 transition state while the C-3 ester disarming effect destabilizes the S_N1 transition state, thereby increasing the S_N2 contribution. This mode of glycosylation is supported by (i) kinetic measurements that show a bimolecular mode of reaction, (ii) the observation that auxiliaries having *S*- and *R*-configurations provide *trans*- and *cis*-decalin sulfonium ions, respectively and (iii) the experimental finding that an acetyl ester at C-3 is critical for α-anomeric selectivities. Although hydrogen bonding has previously been implicated in the stereochemical outcomes of S_N1 glycosylations,[48,49,51,54] we show that this mode of donor and acceptors complexation can also be important for in an S_N2 pathway. For the first time, experimental and computational approaches have been employed to examine the mechanism of glycosylation indicated by hydrogen-bonded donor and acceptor. It is the expectation that the mode of acceptor delivery described here can be implemented in other glycosylation protocols.

EXPERIMENTAL SECTION

General Glycosylation Procedures. *Protocol A.* A mixture of donor **1S** or **1R** (0.06 mmol) and activated molecular sieves (4 Å) in DCM (1.5 mL) was stirred for 30 min under an atmosphere of argon at room temperature. After the mixture was cooled to −70 °C, trimethylsilyl trifluoromethanesulfonate (TMSOTf) (11 μL, 0.06 mmol) was added, and the reaction mixture was allowed to warm to −20 °C over a period of 30 min. After cooling the reaction mixture to −70 °C, glycosyl acceptor (0.09 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (24 mg, 0.12 mmol) were added. The reaction mixture was allowed to warm slowly to room temperature and react for another 14 h.

Protocol B. A mixture of donor **2S,R** − **3S,R** or **4** (0.06 mmol), glycosyl acceptor (0.09 mmol), and activated molecular sieves (4 Å) in DCM (2 mL) was stirred for 30 min under an atmosphere of argon at room temperature. After the mixture was cooled to −70 °C, trimethylsilyl trifluoromethanesulfonate (TMSOTf) (11 μL, 0.06 mmol) was added. The reaction mixture was allowed to warm slowly to −40 °C and quenched until donor was consumed.

Purification. The reaction mixture was filtered through a syringe filter. The volume of the filtrate was reduced *in vacuo* and loaded directly onto a LH-20 size exclusion column. The fractions containing disaccharide were collected and the α/β ratio determined by integration of key signals in ^{1}H NMR, gHSQCAD and 1D-TOCSY.

Procedures for Kinetic Studies by NMR. In a flame-dried flask was added acceptor **14** (10 mg, 0.02 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (15 mg), DCM (0.9 mL), 1-fluoro-2,4-dinitrobenzene stock solution 100 μL (14.8 μL in 2 mL DCM), and activated molecular sieves (4 Å). In a separated flask, donor **1S** or **1R** (15 mg, 0.02 mmol) in DCM (1.5 mL) and activated molecular sieves (4 Å) were stirred for 30 min. The donor was preactivated following Protocol A and the temperature was raised to the designated value before the addition of acceptor solution. The temperature was controlled for at least 6 h. Aliquots were collected at different time intervals and quickly quenched by the addition of excess methanol. The aliquots were centrifuged to remove molecular sieves and the supernatant was transferred to another flask and dried in

DOI: 10.1021/jacs.5b08436
J. Am. Chem. Soc. 2016, 138, 3002−3011

vacuo before NMR studies. Quantitive ^{1}H NMR was conducted with 45° excitation angle, 1 s acquisition time and 5 s acquisition delay. Spectra were processed using MestreNova 7.0. Careful phase/baseline corrections were conducted before integration. The percentage of relative conversion was calculated using the following equation:

$$\text{relative conversion}\% = \frac{I'/N'}{I/N}\%$$

where I' and N' are the integrations of desired product peak and internal standard at certain point of time and I and N are the integrations of desired product peak and internal standard after overnight reaction and conversion is normalized to 1.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08436.

Full experimental procedures and characterization of prepared compounds, copies of ^{1}H and ^{13}C NMR spectra and computational methods and coordinates. (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors wish to thank Dr. John Glushka for assisting with NMR experiments and Dr. Dennis Whitfield for helpful discussions regarding the computations studies. The research was supported by the National Institute of General Medical Sciences (NIGMS) of the U.S. National Institutes of Health (R01GM065248, G.-J.B.).

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