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Mechanistic Study of Glycosylation Using a Prop-1-enyl Donor

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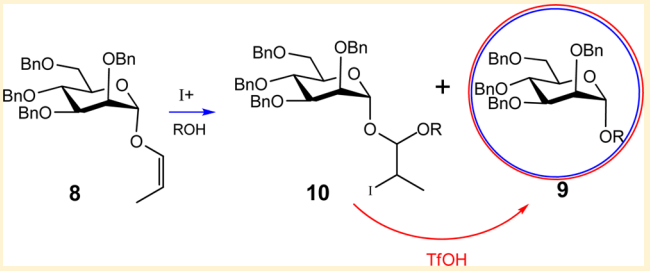
Supporting Information

ABSTRACT: Studies have been conducted to elucidate the mechanism of glycosylation reactions using a prop-1-enyl donor isomerized directly from an allyl glycoside. The reactions promoted by NIS/TfOH can take place in high yields in acetonitrile at room temperature. Activation of the anomeric prop-1-enyl group often leads to both the desired glycoside (e.g., **9**) and the addition-reaction product (e.g., the anomeric mixed acetal **10**). TfOH perhaps has a dual role in the reaction: i.e., (a) producing IOTf in situ to activate the prop-1-enyl group and (b) catalyzing the transformation from the addition-reaction product to the desired glycoside (e.g., from **10** to **9**). The latter process involves multiple competing pathways.

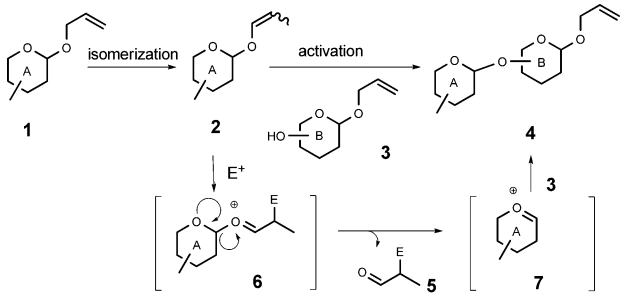


INTRODUCTION

Organic synthesis is a key force in providing structurally well-defined carbohydrates for both basic and applied research in the fields of glycobiology, biochemistry, immunology, and related biomedical sciences. Despite significant progress, efficient synthesis of complex carbohydrates remains a challenging task. Improving the overall synthetic efficiency requires step-economical synthetic approaches that comprise simple, facile, and cost-effective glycosylation methods. An ideal glycosylation method should minimize the number of steps in anomeric manipulation and intermediate purification.

We have recently demonstrated that, in a one-pot fashion (Scheme 1), the allyl glycoside **1** can be first isomerized to its corresponding prop-1-enyl glycoside **2** followed by chemoselective activation of the anomeric enol ether moiety of **2** in the presence of the allyl glycosyl acceptor **3** with a proper electrophile (E^+).[1,2] The new allyl glycoside **4** is generated along with the α-substituted propanal **5**. We postulated that the reaction passes through the reactive intermediates **6** and **7** sequentially.

Scheme 1. Glycosylation with Allyl Glycosyl Building Blocks



This approach has some salient advantages. For example, prop-1-enyl glycosides can be directly isomerized from widely used allyl glycosides without time-consuming anomeric group replacement and intermediate purification by column chromatography, a variety of facile and highly effective methods are available for allyl to prop-1-enyl isomerization,[3] and allyl glycosides can be conveniently prepared. This approach should significantly advance the latent-active strategy of iterative oligosaccharide synthesis.[4,2e,f,5] The latent-active strategy does not require building block reactivity tuning through extensive protecting group manipulation, as is mandatory for the armed/disarmed approach employing thio or *n*-pentenyl building blocks.[5−8]

We first demonstrated that prop-1-enyl xylosides underwent glycosidic bond formation in high yields upon activation with a stoichiometric amount of *N*-iodosuccinimide (NIS) in acetonitrile at room temperature.[1a] While these preliminary results were encouraging, the initial protocol utilizing only NIS as the activator had limitations. For instance, under the same conditions, perbenzylated prop-1-enyl glucosyl donors produced the desired disaccharides in only moderate yields (62−68%). Moreover, activation of prop-1-enyl mannosides and rhamnosides or disarmed prop-1-enyl glycosides with sole NIS resulted in a significant amount of byproducts originating from NIS-promoted addition of the acceptor to the C=C bond of the anomeric enol ether moiety. To overcome these limitations, it was imperative to use a catalytic amount of triflic acid (TfOH) with NIS.[1b] The NIS/TfOH combination (or NIS with other Lewis acids) has been frequently used in activating the anomeric pentenyl or sulfide group of disarmed donors.[9] It

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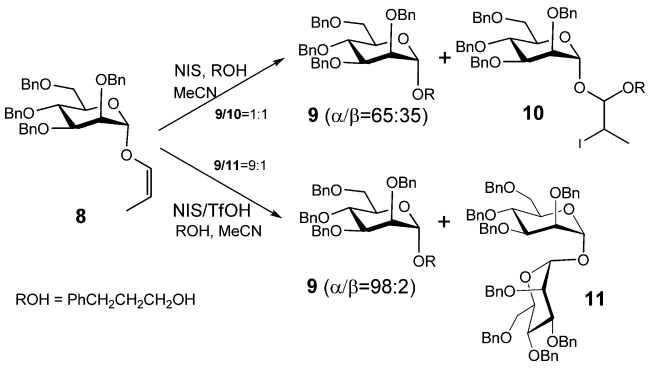
was rationalized that the highly reactive IOTf was generated in situ from NIS/TfOH, which activated, for example, the otherwise unreactive C=C bond of the anomeric pent-1-enyl group. Although activation of the anomeric prop-1-enyl group also starts from electrophilic activation of the C=C bond (e.g., from **2** to **6** in Scheme 1), our results reveal that TfOH may not only play its role by forming IOTf.

RESULTS AND DISCUSSION

Alternative Pathways. In this paper, we focused on elucidating the mechanism by using the perbenzylated propenyl mannoside donor **8** (Scheme 2). We observed that treating the

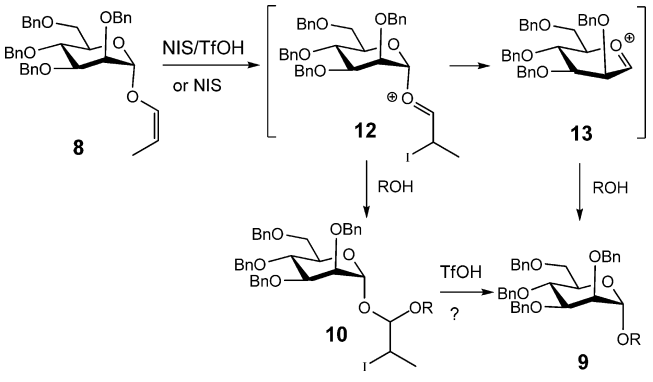
Scheme 2. Glycosylation with Allyl Glycosyl Building Blocks



mannoside **8** (0.046 M in acetonitrile) with NIS in the presence of the acceptor 3-phenyl-1-propanol at room temperature for 20 min led to a mixture of the 3-phenylpropyl mannoside **9** (α/β = 65/35) and the anomeric mixed acetal **10** in a ~1/1 ratio of **9**/**10** on the basis of ^{1}H NMR analysis.[10] This result, along with our earlier results on xylosides and glucosides,[1a] indicates that the originally proposed mechanism in Scheme 1 should operate in producing the desired glycosylation product when an acid catalyst such as TfOH is absent. However, under the same conditions, activation of **8** with premixed NIS/TfOH led to a clean reaction to produce the mannoside **9** (α/β = 98/2) and the dimeric mannoside **11** in a 9/1 yield ratio. This improved production of the mannoside **9** and the absence of **10** in the reaction products suggest alternative pathways to **9** under the acidic reaction conditions.

We postulate that, with either NIS or NIS/TfOH as the activator, the cationic intermediate **12** is generated (Scheme 3). It proceeds to the oxocarbenium **13** and leads to the glycosylation product **9**. The anomeric mixed acetal product

Scheme 3. Mechanism of Glycosylation with Donor 8

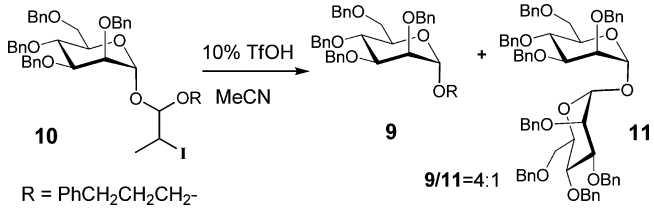


10 observed only in the case of activation with sole NIS is probably from the reaction of the intermediate **12** and the acceptor alcohol. One rationale for the absence of the mixed acetal **10** in the products of the NIS/TfOH-promoted reaction could be that the byproduct **10** is probably also produced from the same intermediate **12** but it is converted to the desired glycosylation product **9** by TfOH. The different **9*α***/**9*β*** ratios with different activators can be attributed to acid-promoted anomeric epimerization favoring the more stable **9*α***.[1b]

Although mixed acetals (at 2-O) have been utilized in intramolecular aglycon delivery (IAD) for 1,2-cis stereocontrol,[11] there are few reports on the chemistry of anomeric mixed acetals in the literature. Chenault and co-workers demonstrated that both α and β anomers of isopropenyl D-glucopyranoside generated the corresponding glucosyl methyl acetonides upon treatment with DCl (1 mM) in methanol-d_4. These compounds were stable under acidic conditions, and methyl glucopyranosides were not observed in these reactions.[12] In other reports, anomeric mixed acetals were converted to the corresponding hemiacetals upon acidic treatment.[13] This chemistry was utilized in tumor-selective activation of cytocidal drugs to release various cytotoxic aldehydes in a proton-mediated hydrolysis process.[14] However, conversion of a C-1 mixed acetal such as **10** to a new glycoside such as **9** upon acid treatment has not yet been reported.

Acid-Promoted Glycosylation Reaction of Anomeric Mixed Acetals. Our experiment proved that the anomeric mixed acetal **10** could indeed be converted to the mannoside **9** (Scheme 4). Thus, the reaction of the anomeric mixed acetal **10**

Scheme 4. Glycosylation of Anomeric Mixed Acetals



with 10 mol % of TfOH in MeCN was complete in 20 min. Inspection of the crude reaction mixture by ^{1}H NMR spectroscopy revealed that the product yield ratio of **9**/**11** was about 4/1. A control experiment showed that the dimer **11** did not produce a detectable amount of **9** upon treatment with 10 mol % of TfOH in the presence of 4 equiv of 3-phenyl-1-propanol in acetonitrile. Interestingly, the same reaction of **10** was complete in 27 min in toluene with a **9**/**11** yield ratio of 55/46, consistent with the isolated yields of **9** (50%) and **11** (44%).

To rationalize the reaction observations in acetonitrile, we hypothesize that the mixed acetal **10** is probably in equilibrium with the oxocarbenium intermediate **12** and the alcohol ROH under the reaction conditions (Scheme 5). The intermediate **12** can break down to the aldehyde **5** and the oxocarbenium **13** (Scheme 5, pathway I). In the presence of the alcohol ROH, the desired mannoside **9** thus forms. Alternatively, in pathway II, the indicated glycosidic bond would break in a Fischer glycosylation fashion, leading to the oxocarbenium **13** and the hemiacetal **14**. The latter would undergo fragmentation to produce the aldehyde **5** and the alcohol ROH. Combination of **13** and ROH would also lead to the desired mannoside **9**. This pathway perhaps involves mixed S_N1 and S_Ni mechanisms

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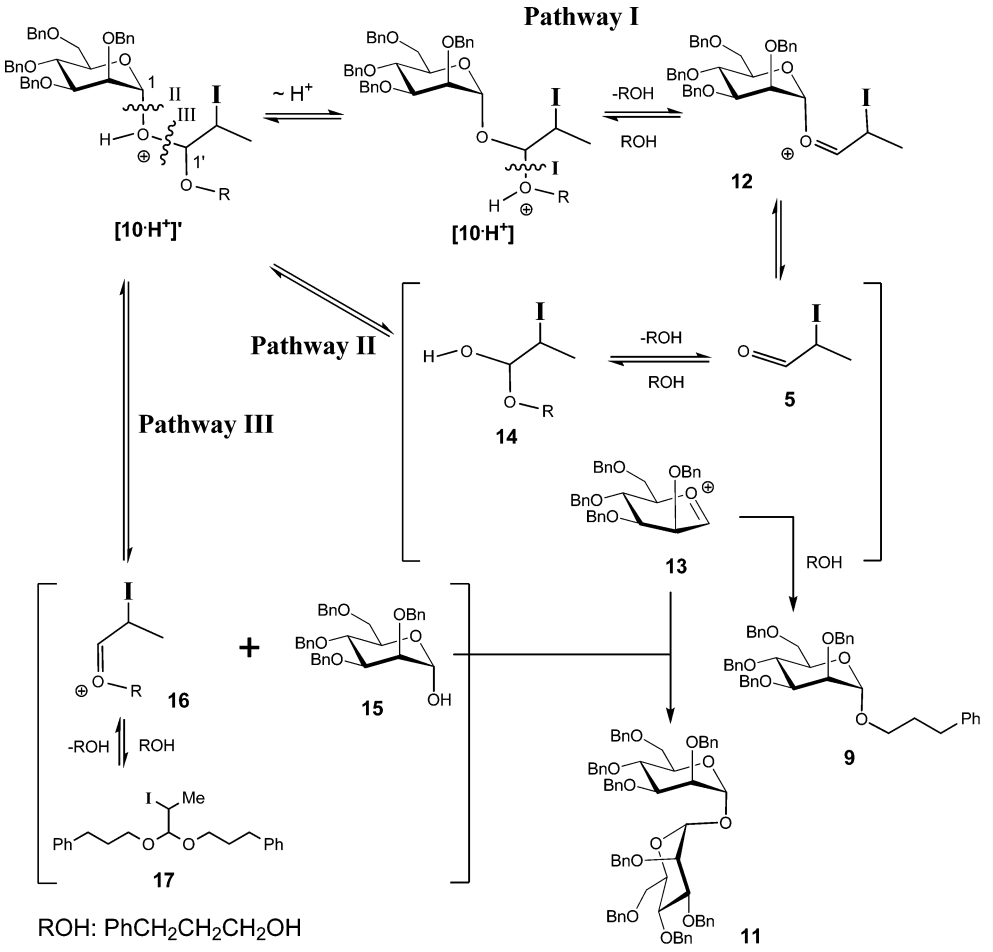
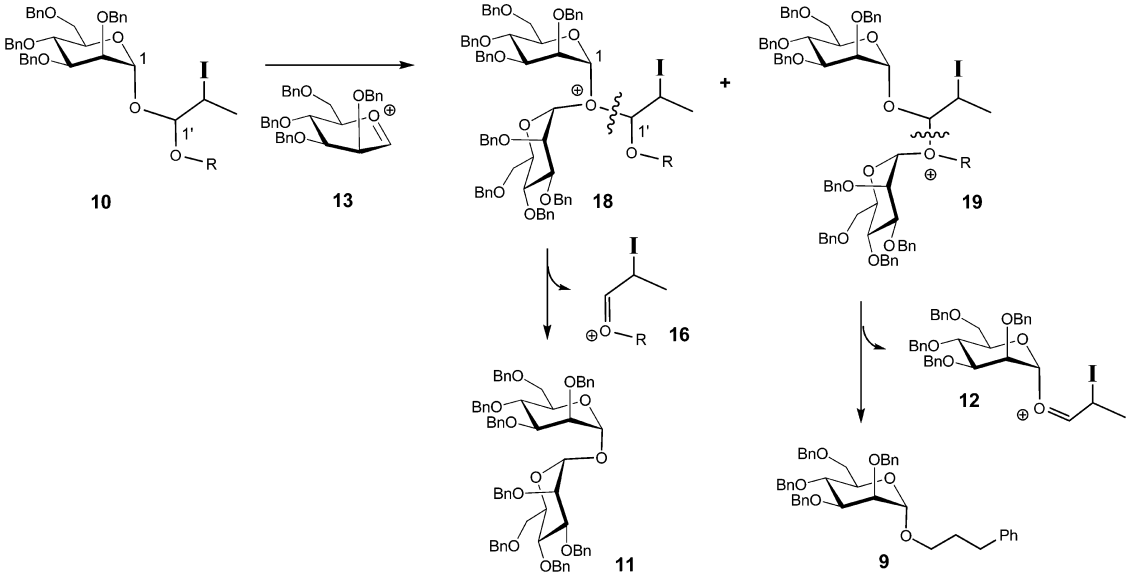
Scheme 5. Proposed Mechanism of Glycosylation with Anomeric Mixed Acetals



Scheme 6. Aglycon Transfer Mechanism



differing only in the source of ROH. Pathways I and II are indistinguishable on the basis of product analysis. However, in pathway III, cleavage of the indicated C−O should result in a different set of intermediates, the hemiacetal **15** and the oxocarbenium **16**. In the presence of the alcohol ROH (from other pathways) the acetal **17** would form while the intermediate oxocarbenium **13** and the hemiacetal **15** would combine to produce the dimeric mannoside **11**. These pathways probably coexist. Between pathways II and III, the product population in the mannoside case (i.e., a 4/1 yield ratio of **9**/**11** shown in Scheme 4) suggests that the pathway II predominated. One rationale could be that the activated

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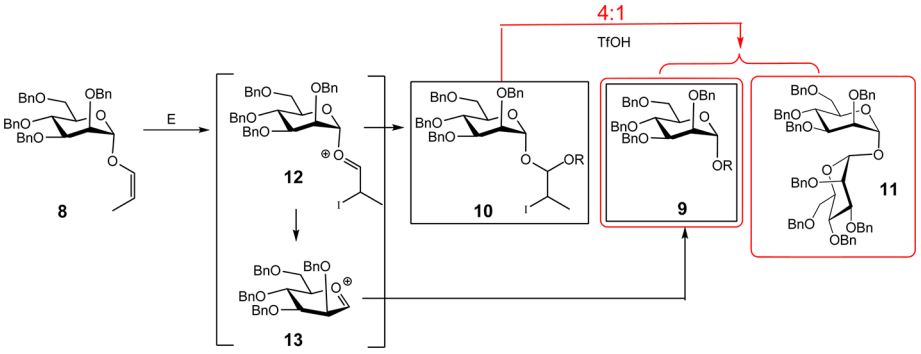
Scheme 7. Activation of 8 with Different Intervals between Adding NIS and TfOH



anomeric oxygen in $[\mathbf{10}\cdot H^+]'$ was already properly aligned in the antiperiplanar position with respect to the nonbonding electron pair of the pyranose oxygen, facilitating the anomeric bond cleavage for the formation of the oxocarbenium intermediate **13**.[15] On the other hand, for pathway III, the breaking C1′−O bond and the nonbonding electron pair on the geminal oxygen were not always properly aligned for elimination. As a result, cleaving the C1′−O bond would either take place in an S_N1 fashion without much assistance from the geminal oxygen or have to rotate the C1′−OR bond to the properly aligned antiperiplanar position first. Either way would slow down the reaction. Production of the dimer **11** at a constant ratio in repeated runs using different batches of properly dried reagent and solvent ruled out the possibility that its formation was due to traces of adventitious water.

In addition to what is illustrated in Scheme 5, the oxocarbenium **13** might initiate aglycon transfer by attaching to the oxygen of the mixed acetal moiety, where the proton attaches in $[\mathbf{10}\cdot H^+]$ and $[\mathbf{10}\cdot H^+]'$, leading to direct formation of **9** and **11**, respectively (Scheme 6).[16] In fact, repeating the reaction in Scheme 4 in the presence of 1 equiv of the acceptor ROH led to improved production of **9**, with a 96/4 yield ratio of **9**/**11**, suggesting that increasing the concentration of the acceptor improved its trapping of the oxocarbenium intermediate **13** and diminished production of **11** from the possible aglycon transfer pathway. Otherwise, we would expect more hemiacetal **15** left unreacted if **9** and **11** were only formed through competition between the acceptor and the hemiacetal **15** for the oxocarbenium **13** (Scheme 5).

More Mechanistic Studies. The current experimental data support that transformation from **10** to **9** is viable in the presence of TfOH (Schemes 5 and 6),[17] which could explain the difference in reaction outcomes between using NIS or NIS/TfOH as the activator.

For more mechanistic insights, we conducted another set of experiments (Scheme 7). Thus, we first treated the prop-1-enyl mannoside donor **8** and the acceptor 3-phenylpropanol with a premixed MeCN solution of NIS and 10 mol % of TfOH for 20 min at room temperature. The glycoside **9** and the dimeric mannoside **11** were obtained in a 9/1 yield ratio on the basis of ^{1}H NMR analysis. In the second run, the donor and the acceptor were first treated with NIS only. In 10 min, conversion of the prop-1-enyl mannoside **8** reached 77%, and the mannoside **9** (α/β = 66/34) and the mixed acetal **10** were obtained with a ∼1/1 ratio. Treatment of this mixture with TfOH (10 mol %) for 20 min resulted in a reaction mixture with a product distribution identical with that in the first run activated by premixed NIS/TfOH. In the third run, the donor and the acceptor were treated with NIS alone for 23 min. The donor was completely consumed, and a mixture of the mannoside **9** (α/β = 65/35) and the mixed acetal **10** was obtained with the same **9**/**10** ratio as in the second run prior to the acid treatment. This reaction mixture was then treated with TfOH (10 mol %) for 20 min, and again, an product distribution identical with that in the previous two runs was obtained.

The appearance of the dimeric mannoside **11** in the product mixtures in all three runs indicates involvement of the mixed acetal intermediate **10** as an intermediate even in the first run, for it is a characteristic byproduct from **10** upon its treatment with TfOH, as shown in Scheme 4. It is noteworthy that the yield ratio of **9**/**11** from these three runs was different from that of the glycosylation of the mixed acetal **10** (Scheme 4), i.e., 9/1 versus 4/1. This discrepancy in the product yield ratio rules out a mechanistic scenario where the mannoside product **9** forms exclusively through the intermediacy of the mixed acetal **10**, confirming that multiple pathways must operate simultaneously.

The constant 9/1 yield ratio of **9**/**11** in the three runs also suggests that the same ratio of **10**/**9** was probably produced upon activation regardless of the activator (i.e., NIS or NIS/TfOH). As a result, subsequent reactions of the mixed acetal **10** in different runs would lead to the same ratio of **9**/**11**. In fact, the **9**/**11** yield ratios observed in the reaction of **10** (i.e., 4/1) (Scheme 4) and that of the prop-1-enyl mannoside (i.e., 9/1) are in agreement with the observation that a mixture of **9** and **10** (∼1/1) was produced upon activation of **8** prior to treatment of TfOH in the second and third runs.

In the first run, IOTf was probably produced and was mainly responsible for the activation of the prop-1-enyl mannoside donor. It has been previously demonstrated that glycosylation reactions of prop-1-enyl donors promoted by NIS/TfOH typically finish within 1 min.[1] Since it took about 20 min for NIS alone to completely consume all the donors, NIS/TfOH probably produced the more reactive iodonium species (i.e., IOTf) to convert the prop-1-enyl donors to various intermediates much more efficiently in the first run and also in the second run after TfOH was introduced.[18] Thus, in those runs, TfOH in the NIS/TfOH combination has a dual role: i.e., to produce the more reactive activator IOTf in situ to activate

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the C=C bond of the anomeric enol ether moiety and to promote the conversion of the mixed acetal intermediate **10** to the mannoside product **9**. The experimental results suggest the former process is probably much faster than the latter. Otherwise, the reaction of the mixed acetal **10** would take place in the presence of the acceptor, which would lead to a smaller amount of the dimer **11** (vide supra) and, as a result, would change the overall ratio of **9**/**11**.

In summary, on the basis of the results of this work and our earlier results,[1] we propose a plausible general mechanism for the glycosylation reaction with prop-1-enyl donors activated by NIS or NIS/TfOH. Thus, upon activation with NIS or NIS/TfOH, the oxocarbenium intermediate **6** forms (Scheme 2). It would produce the glycoside **4** and also the addition-reaction products. Formation of the latter is affected by the nature of the donor. On one hand, formation of the addition-reaction products is negligible for reactive donors such as a perbenzylated prop-1-enyl xyloside, and high yields of desired product were obtained even with NIS alone as the activator. On the other hand, for prop-1-enyl mannosides and rhamnosides or disarmed prop-1-enyl glycosides, fragmentation of **6** to the oxocarbenium **7** becomes slower, and more of the addition-reaction products thus form. In the presence of TfOH, the addition-reaction products can be converted to the desired new glycoside **4**, accompanied by a characteristic minor dimer of the donor. TfOH in the NIS/TfOH combination has a dual role: it can generate IOTf with NIS to accelerate activation of the anomeric enol ether group and it is also imperative in promoting subsequent conversion of the addition-reaction products to the final glycosylation product **4**.

EXPERIMENTAL SECTION

General Considerations. Organic solutions were concentrated by rotary evaporation at ca. 12 Torr. Flash column chromatography was performed employing 230−400 mesh silica gel. Thin-layer chromatography was performed using glass plates precoated to a depth of 0.25 mm with 230−400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Infrared (IR) data are presented as frequency of absorption (cm^{-1}). Proton and carbon-13 nuclear magnetic resonance (^1H NMR or ^{13}C NMR) spectra were recorded on 300, 400, and 700 MHz NMR spectrometers. Chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances), coupling constant in hertz (Hz), integration.

Materials. Tetrahydrofuran was distilled from appropriate drying reagents under a nitrogen atmosphere at 760 Torr. Other chemicals were obtained from commercial vendors and used without further purification.

Preparation of the Mannoside Mixed Acetal 10. Potassium *tert*-butoxide (0.425 g, 3.78 mmol) was added to allyl 2,3,4,6-tetra-*O*-benzyl-D-mannoside (1.0 g, 1.72 mmol) in 6.4 mL of DMSO, and the reaction mixture was stirred at room temperature until the reaction was complete. The reaction was worked up with ethyl acetate and water. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to provide prop-1-enyl 2,3,4,6-tetra-*O*-benzyl-D-mannoside (0.92 g, 92%) as a waxy solid. To a stirred solution of the prop-1-enyl mannoside (200 mg, 0.34 mmol) and 3-phenylpropan-1-ol (135 μL, 1.03 mmol) in toluene (1.0 mL) was added *N*-iodosuccinimide (93 mg, 0.41 mmol) at room temperature. After 45 min, the mixture was concentrated for flash column chromatography (petroleum ether/ethyl acetate = 10/1, R_f = 0.39) to afford the mannoside acetal **10** (269 mg, 93%) as a mixture of diastereomers. For the diastereomer of **10** with lower polarity: ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.08 (m, 25H), 4.98 (d, J = 1.8 Hz, 1H), 4.90 (d, J = 10.8 Hz, 1H), 4.76 (d, J = 12.4 Hz, 1H), 4.72−4.56 (m, 4H), 4.55−4.36 (m, 3H), 4.06−3.83 (m, 5H), 3.74−3.59 (m, 3H), 3.40 (dt, J = 9.4, 6.4 Hz, 1H), 2.71−2.49 (m, 2H), 1.86−1.66 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ141.8, 138.5, 138.4, 138.3, 138.2, 128.41, 128.36, 128.31, 128.26, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 125.8, 106.1, 98.1, 79.4, 75.0, 74.7, 74.5, 73.3, 72.7, 72.6, 72.3, 69.3, 68.2, 32.1, 31.1, 27.8, 21.2; IR (neat) 3028, 2925, 2866, 1493, 1454, 1097, 1028, 739, 700; HRMS (ESI) m/e calcd for $C_{46}H_{51}IO_7Na$ 865.2577, found 865.2568. For the diastereomer of **10** with higher polarity: ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.13 (m, 25H), 5.11 (d, J = 1.9 Hz, 1H), 4.87 (d, J = 10.9 Hz, 1H), 4.78 (d, J = 12.4 Hz, 1H), 4.72−4.61 (m, 4H), 4.51 (dd, J = 11.5, 3.7 Hz, 2H), 4.33 (d, J = 3.9 Hz, 1H), 4.09 (qd, J = 6.9, 3.9 Hz, 1H), 4.04−3.86 (m, 3H), 3.81−3.66 (m, 3H), 3.54 (dt, J = 9.2, 6.2 Hz, 1H), 3.36 (dt, J = 9.2, 6.4 Hz, 1H), 2.66 (dd, J = 8.6, 6.8 Hz, 2H), 1.95−1.73 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 138.5, 138.4, 138.3, 128.5, 128.4, 128.3, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 125.9, 102.2, 95.7, 79.9, 75.1, 75.0, 74.8, 73.3, 73.0, 72.6, 69.3, 68.1, 32.2, 31.3, 27.1, 22.4; IR (neat) 3028, 2917, 2865, 1496, 1454, 1097, 1027, 737, 698; HRMS (ESI) m/e calcd for $C_{46}H_{51}IO_7Na$ 865.2577, found 865.2577.

Glycosylation of 10 in MeCN. To a stirred solution of the acetal **10** (75 mg, 0.089 mmol) in CH_3CN (1.7 mL) was added TfOH (0.8 μL, 8.9 μmol) at room temperature. After 20 min, the reaction mxture was quenched with triethylamine and concentrated for ^1H NMR. The ^1H NMR analysis indicated that the yields of **9**, **11**, and **17** were 79% (α/β = 96:4), 20%, and 12%, respectively. The yields were determined by comparing the intergration of characteristic peaks from **9** and **11** with internal standards. For **17**, R_f = 0.39 (petroleum ether/ethyl acetate = 10/1): ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.12 (m, 10H), 4.38 (d, J = 5.5 Hz, 1H), 4.17 (qd, J = 7.0, 5.4 Hz, 1H), 3.73−3.42 (m, 4H), 2.78−2.66 (m, 4H), 2.00−1.84 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 128.5, 128.4, 125.8, 105.6, 67.0, 66.8, 32.3, 31.3, 26.8, 22.5; IR (neat) 3026, 2926, 1603, 1496, 1454, 1106, 1042, 747, 699; HRMS (ESI) m/e calcd for $C_{21}H_{27}IO_2Na$ 461.0953, found 461.0946.

Control Experiment. A mixture of dimeric mannoside **11** (33 mg, 0.031 mmol), 3-phenylpropan-1-ol (16.7 μL, 0.124 mmol), and TfOH (0.27 μL, 0.0031 mmol) in toluene (0.31 mL) was stirred at room temperature for 20 h. TLC and ^1H NMR analyses showed no sign of decomposition of **11**.

Glycosylation of 10 in Toluene. To a stirred solution of acetal **10** (68.8 mg, 0.08 mmol) in toluene (1.0 mL) was added TfOH (0.7 μL, 8 μmol) at room temperature. After 27 min, the reaction mixture was quenched with triethylamine and concentrated for ^1H NMR. The ^1H NMR analysis indicated that the yields of **9**, **11**, and **17** were 55% (α/β = 88/12), 45%, and 26%, respectively. Flash column chromatograhpy (petroleum ether/ethyl acetate = 8/1) afforded the **9** (27 mg, 50% (α/β = 88:12)), **11** (19.3 mg, 44%), and **17** (7.7 mg, 22%) as clear oils.

Role of TfOH in Glycosylation of Prop-1-enyl Donors Activated by NIS/TfOH. *Run 1 (with Premixed NIS/TfOH).* To a stirred solution of **8** (52 mg, 0.09 mmol) and 3-phenylpropan-1-ol (12.2 μL, 0.09 mmol) in CH_3CN (1.0 mL) was added a solution of NIS (21.5 mg, 0.096 mmol) and TfOH (0.8 μL, 0.009 mmol) premixed in CH_3CN (0.7 mL) at room temperature. After 20 min, the reaction mixture was quenched with Et_3N and concentrated. The ^1H NMR analysis of the crude reaction mixture indicated that the yields of **9** and **11** were 90% (α/β = 98/2) and 10%, respectively.

Run 2. To a stirred solution of **8** (52 mg, 0.09 mmol) and 3-phenylpropan-1-ol (12.2 μL, 0.09 mmol) in CH_3CN (1.7 mL) was added NIS (21.8 mg, 0.097 mmol) at room temperature. After 10 min, TfOH (0.8 μL, 0.009 mmol) was added and the mixture was stirred for 20 min. The reaction mixture was then quenched with Et_3N and concentrated. The ^1H NMR analysis of the crude reaction mixture indicated that the yields of **9** and **11** were 90% (α/β = 98/2) and 10%, respectively. In a parallel run, to a stirred solution of **8** (45.2 mg, 0.078 mmol) and 3-phenylpropan-1-ol (10.5 μL, 0.078 mmol) in CH_3CN (1.7 mL) was added NIS (19.0 mg, 0.084 mmol, 1.08 equiv) at room temperature. After 10 min, the reaction mixture was quenched with a saturated aqueous solution of Na_2SO_3. The crude ^1H NMR indicated

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that 23% of **8** was left and the yield ratio of **9** (α/β = 66/34) to **10** was 47/53.

Run 3. To a stirred solution of **8** (46.7 mg, 0.08 mmol) and 3-phenylpropan-1-ol (10.9 μL, 0.08 mmol) in CH_3CN (1.7 mL) was added NIS (18.4 mg, 0.082 mmol) at room temperature. After 23 min, TfOH (0.71 μL, 0.008 mmol) was added and the resulting mixture stirred for 20 min. The reaction mixture was then quenched with Et_3N and concentrated. The ^{1}H NMR analysis of the crude reaction mixture indicated that the yields of **9** and **11** were 90% (α/β = 98/2) and 10%, respectively. In a parallel run, to a stirred solution of **8** (45.2 mg, 0.078 mmol) and 3-phenylpropan-1-ol (10.5 μL, 0.078 mmol) in CH_3CN (1.7 mL) was added NIS (19.0 mg, 0.084 mmol, 1. 08 equiv) at room temperature. After 20 min, the reaction mixture was quenched and the ^{1}H NMR indicated that the yield ratio of **9** (α/β = 65/35) to **10** was 44/55.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving NMR spectra of **8**, **9α**, **9β**, **10**, **11**, **15**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to the memory of Professor Howard E. Zimmerman.

■ REFERENCES

(1) (a) Wang, P.; Haldar, P.; Wang, Y.; Hu, H. *J. Org. Chem.* **2007**, *72*, 5870. (b) Wang, Y.; Zhang, X.; Wang, P. *Org. Biomol. Chem.* **2010**, *8*, 4322. (c) Wang, Y.; Liang, X.; Wang, P. *Tetrahedron Lett.* **2011**, *52*, 3912.

(2) Various vinyl glycosylide donors have been explored for glycosidic bond construction: (a) Marra, A.; Esnault, J.; Veyrieres, A.; Sinaÿ, P. *J. Am. Chem. Soc.* **1992**, *114*, 6354. (b) Vankar, Y. D.; Vankar, P. S.; Behrendt, M.; Schmidt, R. R. *Tetrahedron* **1991**, *47*, 9985. (c) Chenault, H. K.; Castro, A. *Tetrahedron Lett.* **1994**, *35*, 9145. (d) Chenault, H. K.; Castro, A.; Chafin, L. F.; Yang, J. *J. Org. Chem.* **1996**, *61*, 5024. (e) Boons, G.-J.; Isles, S. *Tetrahedron Lett.* **1994**, *35*, 3593. (f) Boons, G.-J.; Isles, S. *J. Org. Chem.* **1996**, *61*, 4262.

(3) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley-Interscience: New York, 1999. (b) Baudry, D.; Ephritikhine, M.; Felkin, H. J. *Chem. Commun.* **1978**, 694.

(4) (a) Cao, S.; Hernandez-Mateo, F.; Roy, R. *J. Carbohydr. Chem.* **1998**, *17*, 609. (b) Roy, R.; Andersson, F. O.; Letellier, M. *Tetrahedron Lett.* **1992**, *33*, 6053.

(5) Hasty, S. J.; Kleine, M. A.; Demchenko, A. V. *Angew. Chem., Int. Ed.* **2011**, *50*, 4197.

(6) (a) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583. (b) Ferrier, R. J.; Hay, R. W.; Vethaviyasar, N. *Carbohydr. Res.* **1973**, *27*, 55.

(7) (a) Fraser-Reid, B.; Konradsson, P.; Mootoo, D. R.; Udodong, U. *Chem. Commun.* **1988**, 823. (b) Mootoo, D. R.; Date, V.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 2662. (c) Konradsson, P.; Mootoo, D. R.; McDevitt, R. E.; Fraser-Reid, B. *Chem. Commun.* **1990**, 270. (d) Fraser-Reid, B.; Wu, Z.; Udodong, U.; Ottosson, H. *J. Org. Chem.* **1990**, *55*, 6068. (e) Mehta, S.; Pinto, B. M. *J. Org. Chem.* **1993**, *58*, 3269. (f) Ley, S. V.; Priepke, H. W. M. *Angew. Chem., Int. Ed.* **1994**, *33*, 2292. (g) Baeschlin, D. K.; Chaperon, A. R.; Charbonneau, V.; Green, L. G.; Ley, S. V.; Lücking, U.; Walther, E. *Angew. Chem., Int. Ed.* **1998**, *37*, 3423. (h) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734. (i) Ye, X.-S.; Wong, C.-H. *J. Org. Chem.* **2000**, *65*, 2410. (j) Huang, L.; Wang, Z.; Huang, X. *Chem. Commun.* **2004**, 1960.

(8) To simplify building block preparation and thus to improve synthetic efficiency, preactivation of thioglycosides has recently emerged as an appealing approach. See: (a) Yamago, S.; Yamada, T.; Maruyama, T.; Yoshida, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2145. (b) Huang, X.; Huang, L.; Wang, H.; Ye, X.-S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5221. (c) Codee, J.; van den Bos, L.; Litjens, R.; Overkleeft, H.; van Boeckel, C.; van Boom, J.; van der Marel, G. *Tetrahedron* **2004**, *60*, 1057.

(9) (a) Zhong, W.; Boons, G.-J. In *Handbook of Chemical Glycosylation*; Demchenko, A., Ed.; Wiley-VCH: Weinheim, Germany, 2008; pp 261−302. (b) Fraser-Reid, B.; Lopez, J. C. In *Handbook of Chemical Glycosylation*; Demchenko, A., Ed.; Wiley-VCH: Weinheim, Germany, 2008; pp 381−415.

(10) The anomeric mixed acetal **10** formed exclusively when the alcohol was used as the solvent or in dichloromethane, benzene, or toluene with a stoichiometric amount of the alcohol when only NIS was used as the activator.

(11) Fairbanks, A. *Synlett* **2003**, 1945 and references cited therein.

(12) Chenault, H. K.; Chafin, L. F. *J. Org. Chem.* **1994**, *59*, 6167.

(13) (a) Koto, S.; Inada, S.; Narita, T.; Morishima, N.; Zen, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3665. (b) Chenault, H. K.; Castro, A.; Chafin, L. F.; Yang, J. *J. Org. Chem.* **1996**, *61*, 5024.

(14) Tietze, L. F.; Feuerstein, T. *Curr. Pharm. Design* **2003**, *9*, 2155 and references cited therein.

(15) In a control experiment, the reaction of the β glucoside counterpart of **10** under the same reaction conditions was less clean with a lower yield of the corresponding 3-phenylpropyl glucoside product.

(16) Li, Z.; Gildersleeve, J. *J. Am. Chem. Soc.* **2006**, *128*, 11612.

(17) A transformation similar to that from **10** to **9** was also confirmed with perbenzylated rhamnosides, glucosides, and xylosides. The transformation of the corresponding anomeric mixed acetal can be carried out not only in acetonitrile but also in DCM, THF, and even hexane or toluene. A variety of acids proved to be effective in promoting the reaction. For instance, with the anomeric mixed acetal of rhamnoside in DCM, a catalytic amount of $Yb(OTf)_3$, $BF_3{\cdot}OEt_2$, $Cu(OTf)_2$, $SbCl_5$, $SnCl_4$, or TMSOTf can promote the reaction. The reaction could be carried out over a broad temperature range (i.e., 0−60 °C) without affecting the product yields significantly.

(18) Glycosylation of **8** promoted only by a catalytic amount of TfOH (10 mol %) proved to be feasible, but it was less clean and slower than the same reaction promoted by NIS/TfOH. This observation suggested that promoting the formation of an oxocarbenium intermediate such as **12** from **8** by TfOH only might not play a significant role in the reactions using NIS/TfOH, although it is known in the literature that various vinyl glycosylide donors can be activated by Lewis acids such as TMSOTf for glycosidic bond construction.[2]