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Study of the Stereoselectivity of 2-Azido-2-deoxygalactosyl Donors: Remote Protecting Group Effects and Temperature Dependency

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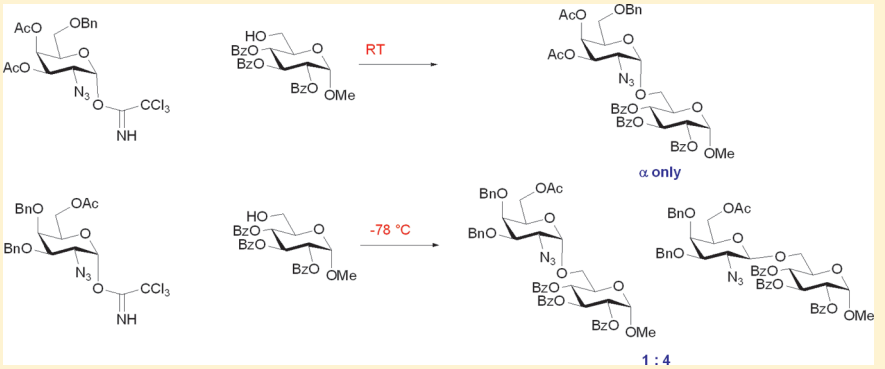
Supporting Information

ABSTRACT:



The stereoselectivity of glycosylation reactions is affected by many factors. Synthesis of 1,2-*cis* glycosidic linkages (such as α linkages in glucose and galactose like monosaccharides) is challenging due to lack of control of the stereoselectivity. Our systematic study of $GalN_3$ donors with different combination of protecting groups indicated that acetyl groups at the 3- and 4-positions are particularly important for high α-selectivity. Temperature is also recognized as a major factor in control of stereoselectivity. Mechanisms responsible for these experimental results are discussed and explored using computational methods. A remote participation model of the acetyl groups is proposed to explain the directing effects of the acetyl groups.

INTRODUCTION

Carbohydrates are important biopolymers playing pivotal roles in many cellular processes.[1] Glycomics, the comprehensive study of all glycan structures, has become an increasingly interesting research field for both life science and biomedical research.[2,3] At the same time, chemical synthesis provides one of the major means to access large quantities of carbohydrate compounds in homogeneous and structurally defined form.[4,5] However, synthesis of oligosaccharides is much more challenging than synthesis of other types of biopolymers (like peptides and nucleotides), largely due to the difficulties in controlling the stereoselectivity and regioselectivity. The control of the stereochemistry (which is not present in cases of peptide linkages and nucleotide linkages) is especially difficult because of the complexity of the contributing factors to the stereoselectivity, including the configuration of the glycosyl donor,[6−11] the structure of the leaving group,[12] the reaction conditions, the reactivity of the glycosyl acceptor,[13,14] and the protecting groups on the donor. Protecting groups, in particular, have a profound influence on the stereoselectivity of donors.[15−21] Neighboring group participation, for example, has been one of the most powerful strategies for the stereoselective synthesis of 1,2-*trans* glycosidic linkages. On the other hand, the effects of protecting groups on donors without participating neighboring groups are more difficult to control and predict. In this report, we systematically studied the influence of acetyl groups on the stereoselectivity of 2-azido-2-deoxygalactosyl ($GalN_3$) donors using both experimental and theoretical methods. $GalN_3$ donors have been widely used for the introduction of α-galactosamine ($GalNH_2$) linkages, due to the nonparticipating nature of the azido group. Even though several other methods have been reported in recent years, $GalN_3$ remains a popular choice because of the easiness of preparation and the convenience of conversion to amino group.[22,23] However, the stereoselectivity of $GalN_3$ donors is largely affected by a number of factors, including the protecting groups, acceptors, leaving groups and even reaction conditions, many of which are not well understood.[24−27] Our study on the protecting group effect and reaction temperature effect indicated that the acetyl groups and higher reaction temperature play critical roles in improving the α-selectivity of $GalN_3$ donors. The results of our study will not only help develop more efficient synthesis of α-galactosamine linkages, but will also be helpful for the development of more stereoselective glycosylations of other galactose-type monosaccharides.

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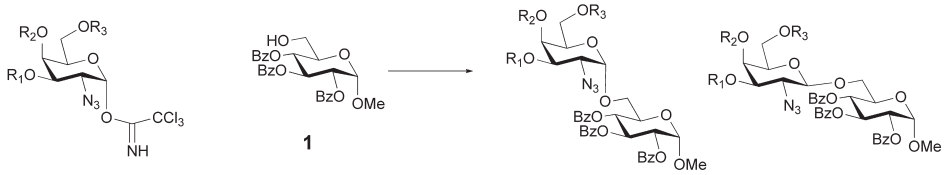
Scheme 1. Preliminary Study of the Stereoselectivity of Donor 2 and 3



2 R_1=R_2=R_3=Acetyl

	10 α	:	**10** β
-78 °C	3		1
-20 °C	5		1
0 °C	9		1
RT	11		1

3 R_1=R_2=R_3=Benzyl

	11 α	:	**11** β
-78 °C	1		3
RT	3		1

RESULTS AND DISCUSSION

To understand how the protecting groups affect the stereoselectivity of $GalN_3$ donors, especially the function of acetyl groups at the remote positions, we decided to systematically study a series of $GalN_3$ donors with different protecting group patterns. To perform this study, we selected a model reaction in which the same leaving group, same reaction conditions, and same glycosyl acceptor were used. In this way, the only factor that can change the reaction results would be the combination of the protecting groups. In this model reaction (Scheme 1), acceptor **1**[28] was used as the common glycosyl acceptor; trichloroacetimidate was used as the common leaving group; TMSOTf was used as the promoter; and room temperature and −78 °C were chosen as two representative reaction temperatures.

A. Preliminary Study of Protecting Group and Temperature Dependency of $GalN_3$ Donor Stereoselectivity. Two donors (compound **2**[29,30] and **3**, Scheme 1) were first tested at two different reaction temperatures (−78 °C and room temperature) as a preliminary study. A protecting group dependency and a reaction temperature dependency were observed in this series of experiments. Acetyl-protected donor (**2**) showed much higher α-selectivity than benzyl-protected donor (**3**). At −78 °C, donor **2** gave a 3:1 α/β mixture, whereas donor **3** afforded a 1:3 α/β mixture. At room temperature, both donors showed better α-selectivity. Donor **2** afforded an 11:1 α/β mixture, while donor **3** afforded a 3:1 α/β mixture. The preliminary study suggests that the acetyl-protected donor is more α selective than the benzyl-protected donor at both reaction temperatures. For both donors, room temperature is a more favorable reaction condition for the α product.

To further confirm the temperature dependency of the stereoselectivity, two more reactions at temperatures between −78 °C and room temperature were tested using donor **2** (scheme 1). At −20 °C, a 5:1 α/β mixture was observed; at 0 °C, a 9:1 α/β mixture was observed. It seems that the α-selectivity steadily increases as the reaction temperature increases.

Another experiment was performed to test if the increased α-selectivity was due to a thermodynamic equilibrium at higher temperature.[31,32] A 1:3 α/β mixture obtained from donor **3** at −78 °C was treated with TMSOTf under glycosylation conditions (room temperature in dichloromethane) for 30 min. The compound was then recovered and characterized with ^{1}H NMR. There was no observable change in the anomer ratio, which rules out the possibility of TMSOTf induced equilibrium under this condition and indicates that the change of product distribution is more likely due to kinetic reasons.

B. Proposed Mechanism. To explain this apparent protecting group and temperature dependence of the stereoselectivity, we considered the mechanism of the glycosylation reactions. Even though glycosylation reactions have been extensively studied, the exact mechanism is still not well understood. Oxocarbenium ions, glycosyl triflates, ion pairs, or other structures have been proposed as the key intermediates in determining the stereochemical outcome. A recent review by Demchenko et al. provides a comprehensive overview of the mechanism of glycosylation reactions.[33] On the basis of the analysis of our reaction system, we propose two possible reaction pathways that may help explain the observed experimental results (Scheme 2). Upon activation with a promoter (TMSOTf), the donors are expected to form glycosyl triflate intermediates, which can then form contact ion pairs (CIP), solution-separated ion pairs (SSIP), or free oxocarbenium ions, depending on the reaction conditions and the nature of the donor. Any of these intermediates can react with the acceptor to afford the disaccharide product. Even though we have no direct evidence to identify the true reaction intermediate involved in our reactions, we envision that different intermediates will proceed in different processes to give different stereoisomers. In the case of glycosyl triflate or contact ion pair intermediates, an S_N2-like process that causes inversion of the anomeric center should be a more favorable process, although a process that causes retention of the stereochemistry has also proven possible in theoretical study.[34] In the case of solvent-separated ion pair or free oxocarbenium ion intermediate, an S_N1-like process may be more favorable and the stereochemical outcome may be determined by the stereoelectronic factors of the oxocarbenium ion. The overall stereochemical outcome of the glycosylation reaction could therefore be determined by the reaction pathway and the conformation and configuration of the reaction intermediates. As to the S_N2 pathway, α-glycosyl triflates, which are more stable due to the anomeric effect, are expected to be dominant, as are the α-contact ion pairs. This

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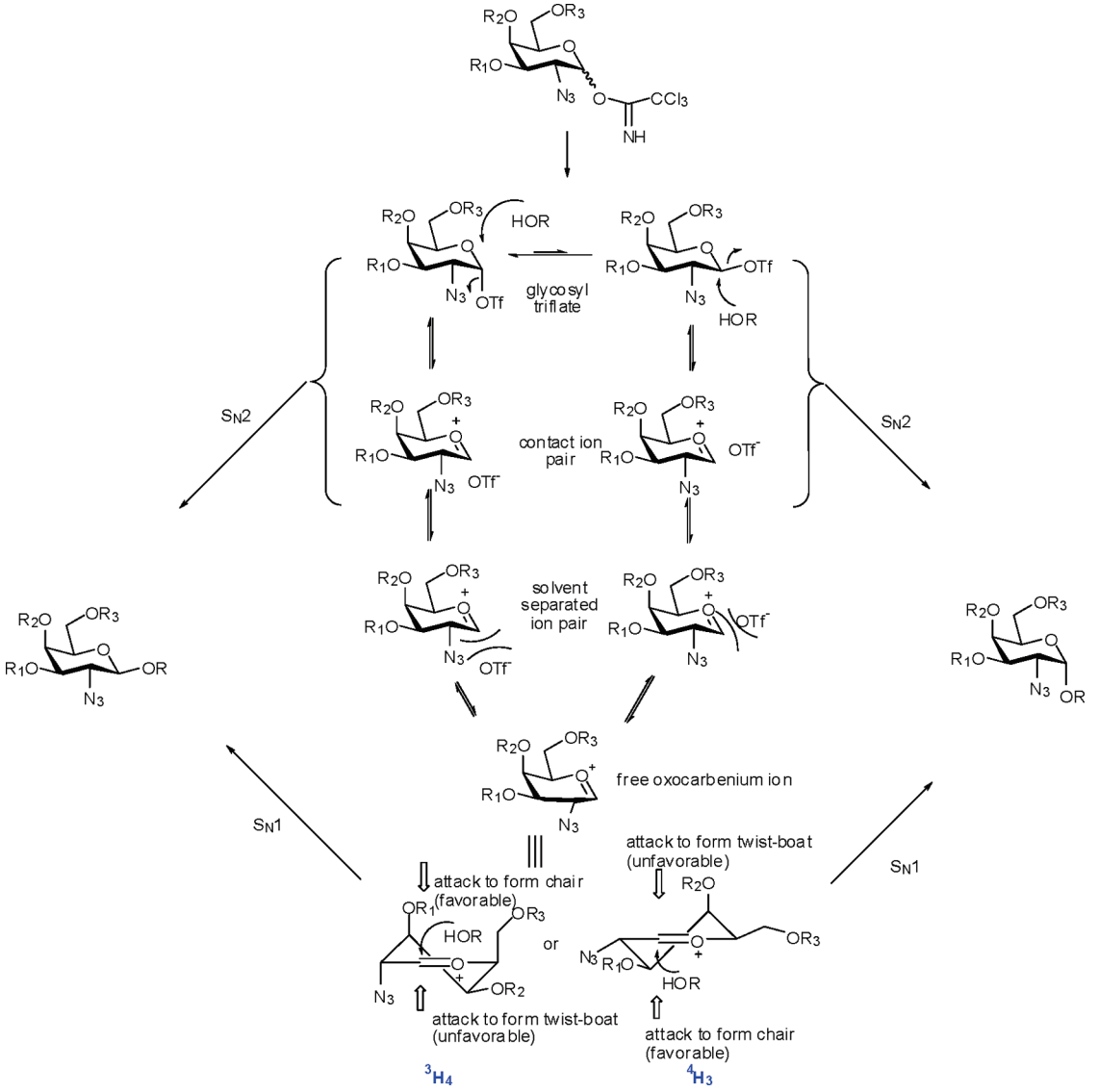
Scheme 2. Proposed Mechanism of Glycosylation Reaction



suggests that the β glycosides would be the major products through the S_N2 pathway due to the "Walden inversion". In the S_N1 pathway, the stereochemical control is much more complicated. Theoretical studies suggest that the stereoselectivity may arise from the preferred conformation of the oxocarbenium ions, which include half chairs, envelope, boat, and twist-boat conformations. For example, Woerpel and co-workers suggested that when oxocarbenium ions are in the half-chair conformation, the nucleophile will approach along a pseudoaxial trajectory with a facial selectivity which allows the formation of the lower energy chair product instead of a twist-boat product formed when the nucleophile approaches from the opposite side.[7] Therefore, the oxocarbenium ions in $^3H_4$ conformation will prefer nucleophilic attack from the top face to afford β products, whereas the oxocarbenium ions in $^4H_3$ conformation will afford α products. Even though further evidence is necessary to prove this hypothesis, it has been used to explain some stereochemistry observations successfully. For example, Dinkelaar and coworks also used this model to explain the stereoselectivity of a series of glycosyl donors in their experiments.[6] Since Whitfield reported that $^4H_3$ conformation of galactose oxocarbenium ion is more stable than $^3H_4$ in his computational study, we anticipate the α products to be the preferred product of the S_N1 pathway of $GalN_3$ donors, which have similar configuration to galactose.[35]

A computational study of the oxocarbenium ions of $GalN_3$ donors was performed to investigate the relative stability of these possible intermediates. Our results indicated that for both donors **2** and **3**, the $^4H_3$ conformation of the corresponding oxocarbenium ions is more stable than $^3H_4$, by 11.0 and 14.2 kJ/mol, respectively (Figure 1). This suggests that the oxocarbenium ion intermediates prefer $^4H_3$ conformation and thus favor the formation of α products. On the basis of this analysis, if the reaction takes the S_N1 pathway, α glycosides would be the preferred product.

This mechanistic analysis also explains the temperature dependency of the stereoselectivity. Since the glycosyl triflates have been reported to decompose at higher temperature, the S_N1 process is expected to be the preferred reaction pathway at higher

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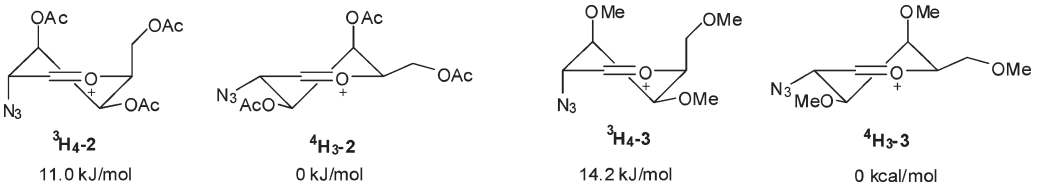
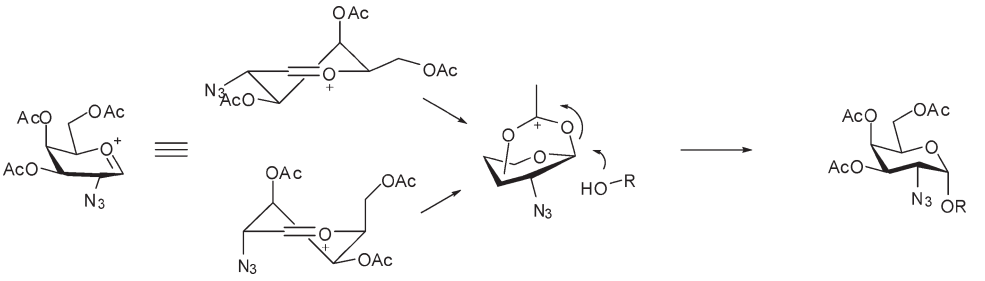


Figure 1. Relative stability of different conformations of oxocarbenium ions derived from donor **2** and **3** determined by computational study.

Scheme 3. Proposed Remote Participation of Acetyl Groups



reaction temperatures to afford more α product. The temperature dependency may also suggest that the two competing mechanisms have significantly different $\Delta S^{\ddagger}$ for the TSs. This is consistent with the proposed S_N1 vs S_N2 competing mechanism, because S_N1 mechanism should have higher $\Delta S^{\ddagger}$ than S_N2. However, we cannot explain the protecting group dependency of the stereoselectivity. When the donor is more disarmed (i.e., triacetyl protected), the glycosyl triflates are expected to have higher stability and the S_N2 process is more likely than with the armed donors, which means that more *β* product is expected from disarmed donors (donor **2**), which is opposite to our observation.[15]

To explain this apparent controversy, a modified mechanism is proposed (Scheme 3). The carbonyl oxygen of the acetyl groups of donor **2** may be able to interact with the anomeric carbon of the oxocarbenium ion and form a remote participating intermediate. This remote participation may not only stabilize the oxocarbenium ion, but also force the acceptor to attack from the "α" face, because the participating acetyl groups would have blocked the "*β*" face. Our hypothesis is that the participation of the acetyl groups compensates the unfavorable disarming effect and promotes the formation of α product. Participation of nonneighboring acetyl groups has been suggested to be responsible for unusual stereoselectivity in several literature reports.[36,37] For example, mannosyl donors with acetyl group at 3-position afford more α mannoside than the donor with a 3-*O*-benzyl group.[38−40] 4-*O*-Ester groups have been shown to improve α selectivity in galactose, fucose and *β* selectivity in glucose and mannose, which may also be attributed to possible participation.[18,20,41] However, there are also reports that do not support this type of participation. Some recent work from Crich's group showed lack of participation of 3-*O*-acetyl in a benzylidene-protected mannosyl donor.[42] Crich's work also excluded the possibility of participation of 4-*O*-ester of mannosyl donor, 6-*O*-ester of glucosyl donor and 4-*O*-ester of galactosyl donor but indicated the possibility of participation of the axial ester at O-3 of allose.

A series of calculations were carried out to test our hypothesis. Three potential participating intermediates **P3-2** (**P3-2** represents participation of 3-acetyl group in oxocarbenium ion derived from donor **2**, the same rules are used for other acetyl participation intermediates), **P4-2**, and **P6-2** were optimized and their energy calculated using quantum mechanical methods (Figure 2). All three intermediates were found to be significantly more stable than the oxocarbenium ion. Intermediate **P3-2** takes a chair conformation close to $^1C_4$ and is 37.9 kJ/mol more stable than the nonparticipating $^4H_3$-**2** oxocarbenium ion. Intermediate **P4-2** takes a twist-boat conformation $^1S_5$ and is 41.5 kJ/mol more stable than $^4H_3$-**2**. Intermediate **P6-2** takes a chair conformation close to $^1C_4$ and is 20.2 kJ/mol more stable than $^4H_3$-**2**. These results indicate that the participation of any of the three acetyl groups is thermodynamically favorable and dramatically stabilizes the oxocarbenium ion.

C. Further Study of the Protecting Group Effects. To determine which acetyl group(s) is involved in this participating process, we decided to study a series of donors with various combination of protecting groups (Figure 3, compounds **4**−**9**). Compounds **4**, **5**, and **6** are trichloroacetimidate donors with only one acetyl group, each at the 3-, 4-, or 6-position, respectively. Compounds **7**, **8** and **9** are donors with two acetyl groups at different positions.

All six donors were prepared (see the Experimental Section for their synthesis) and tested in glycosylation reactions with acceptor **1** at both −78 °C and room temperature (Table 1). Donor **4** showed 1.7:1 (entry 3) α selectivity at −78 °C and 6:1 (entry 3) at room temperature. The α-selectivity is better than donor **3**, at both temperatures, but not as good as donor **2**. Donor **5** gave a 1:1 α/*β* ratio at −78 °C and 6:1 (entry 4) at room temperature, which is also better than donor **3** but not as good as donor **2**. Donor **6**, which has acetyl group at 6-position, however, showed only 1:5 α-selectivity at −78 °C and 1.5:1 (entry 5) at room temperature, which is actually worse than donor **3**. These results suggest that acetyl group at 3- or 4-position improves the α-selectivity, whereas acetyl group at 6-position decreases the α-selectivity. At the same time, similar temperature dependency of the α-selectivity was observed.

For the donors with two acetyl groups, donor **7**, which has acetyl at the 3- and 4-positions, showed 1.5:1 α-selectivity

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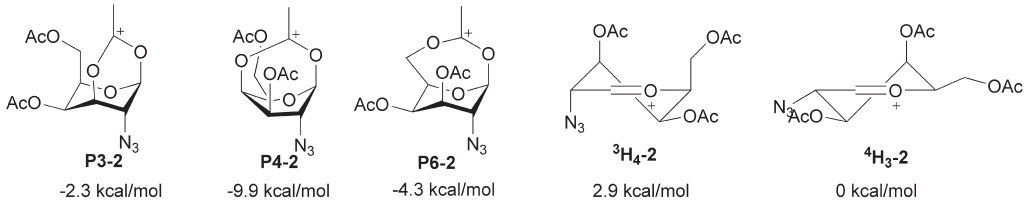


Figure 2. Computational results of participating intermediates compared with oxocarbenium ions.

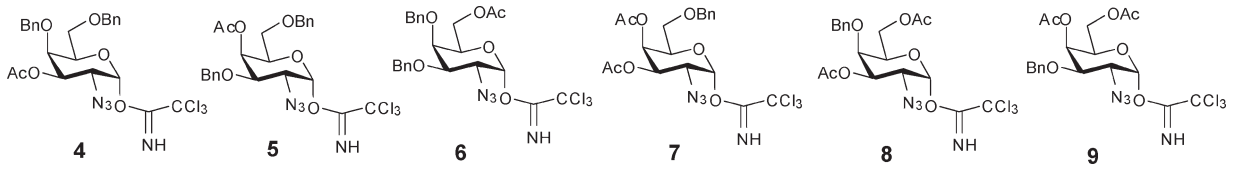
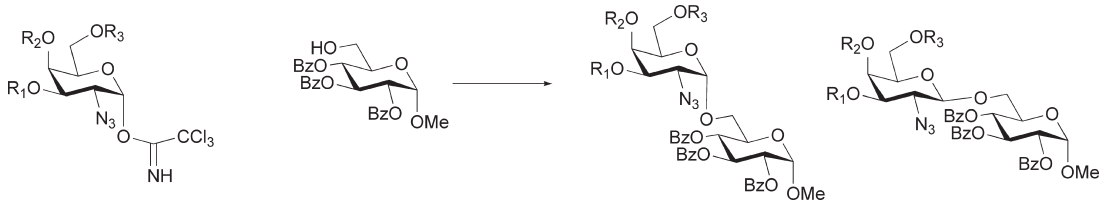


Figure 3. Donors with different protecting group patterns.

Table 1. Glycosylation Results



					at −78 °C		at rt	
entry	donor	R1	R2	R3	product (yield, %)	α:β ratio	yield (%)	α:β ratio
1	**2**	Ac	Ac	Ac	**10** (71)	3:1	75	11:1
2	**3**	Bn	Bn	Bn	**11** (74)	1:3	66	3:1
3	**4**	Ac	Bn	Bn	**12** (81)	1.7:1	66	6:1
4	**5**	Bn	Ac	Bn	**13** (51)	1:1.1	53	6:1
5	**6**	Bn	Bn	Ac	**14** (52)	1:5	75	1.5:1
6	**7**	Ac	Ac	Bn	**15** (67)	1.5:1	50	α only[a]
7	**8**	Ac	Bn	Ac	**16** (83)	1:1.1	89	4:1
8	**9**	Bn	Ac	Ac	**17** (82)	1.4:1	81	5:1

[a] No observable signals of β-anomer in ^{1}H NMR of the product; a significant amount of acceptor (30%) was recovered from the reaction.

at −78 °C and exclusive α-selectivity at room temperature (entry 6). The selectivity at room temperature is even better than donor **2**. On the other hand, donor **8**, which has acetyl at 3- and 6-positions, afforded a 1:1 α/β ratio at −78 °C and 4:1 α/β ratio at room temperature (entry 7). Donor **9**, which has acetyl groups at the 4- and 6-positions, showed 1.1:1 α-selectivity at −78 °C and 5:1 at room temperature (entry 8). The results suggest that the influence of acetyl groups at 3- and 4-positions is not only favorable for α-selectivity but also cumulative when present at the same time. The acetyl group at the 6-position, on the other hand, has little influence when it is present with acetyl groups at other positions. The temperature dependency of the α-selectivity is still the same: much higher α-selectivity is obtained at room temperature.

The overall experimental results suggest that the acetyl groups at the 3- and 4-positions can significantly improve the α-selectivity compared to the benzyl group. On the other hand, an acetyl group at the 6-position has only a marginal effect on the α-selectivity.

The effect of the 3-*O*-acetyl and 4-*O*-acetyl is consistent with the computational study of donor **2** (Figure 2), which supports the remote participation of acetyl groups, whereas the effect of the 6-*O*-acetyl is opposite to the expected result. To further study these donors, we calculated all corresponding oxocarbenium ions and possible participating intermediates derived from donors **4**−**9** using the same computational methods (Table 2, entry 3−8). In all cases, the $^4H_3$ conformation is consistently more stable than the $^3H_4$ conformation by 6.3−19.2 kJ/mol. Interestingly, the $^3H_4$ conformations of donor **5**−**9** are close to ^3E after optimization. At the same time, the intermediates involving the participation of acetyl group (**P3-*n***, **P4-*n*** and **P6-*n***) are all more stable than the corresponding $^4H_3$ oxocarbenium ion (**$^4H_3$-*n***). Noticeably, the energy benefits of the **P3-*n*** and **P4-*n*** intermediates (34.3−43.6 kJ/mol) are generally larger than that of the **P6-*n*** intermediates (12.4−26.0 kJ/mol). The large energy benefit value of 3- and 4-acetyl group participation can help explain the α-beneficial effect of 3-*O*-acetyl and

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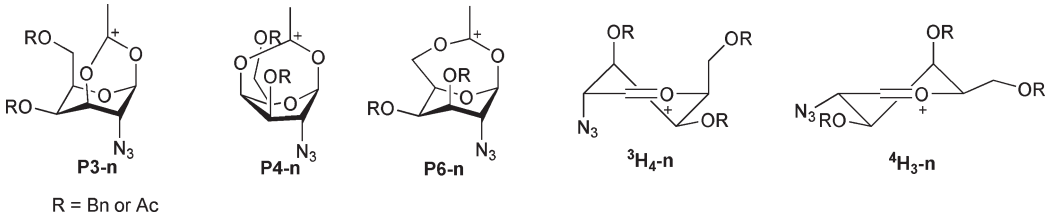
Table 2. Computational Study of the Possible Participating Structures of the Reaction Intermediates



entry	donor	3-*O*-acetyl participation (**P3-n**) (kJ/mol)	4-*O*-acetyl participation (**P4-n**) (kJ/mol)	6-*O*-acetyl participation (**P6-n**) (kJ/mol)	$^4H_3$ (^{4}**H$_3$-n**) (kJ/mol)	$^3H_4$ (^{3}**H$_4$-n**) (kJ/mol)
1	**2**	−37.9	−41.5	−20.2	0	11.0
2	**3**				0	14.2
3	**4**	−39.6			0	14.9
4	**5**		−41.3		0	19.2 (close to ^{3}E)
5	**6**			−26.0	0	11.3 (close to ^{3}E)
6	**7**	−43.6	−40.9		0	13.1 (close to ^{3}E)
7	**8**	−34.3		−12.4	0	6.3 (close to ^{3}E)
8	**9**		−40.0	−25.8	0	12.2 (close to ^{3}E)

4-*O*-acetyl groups. On the other hand, the beneficial but less substantial 6-acetyl participation may partially explain why 6-acetyl group does not favor the formation of α-product. Another explanation for the *β*-directing effect of 6-acetyl in donor **6** could be the potential H-bonding between the acceptor and the acetyl of donor in the *β* face of the oxocarbenium ion in S_N1 type mechanisms, which has been demonstrated by Whitfield et al.[43] Finally, it could also be kinetic reasons that prevent the 6-acetyl groups from participating. Whitfield studied the participation of neighboring acetyl groups (2-acetyl) using computational method and determined that the energy barriers are between 20 and 40 kJ/mol, which could be a good reference for the magnitude of the energy barrier for participation of acetyl groups.[44] In the case of 6-acetyl, the energy barrier is expected to be even higher because the participation process has to start from a higher energy conformation ($^3H_4$, Figure 2) in the first place. Computational studies to search for the transition states and determine the energy barrier of these processes using methods similar to Whitfield's are ongoing.

SUMMARY OF MECHANISM

On the basis of our current study, a possible mechanism for the stereoselectivity observed in our experiments can be summarized as follows: the stereochemical outcome is a comprehensive result of the glycosylation pathway. The S_N2 pathway is likely to be responsible for the *β*-selectivity at lower temperature and in the absence of acetyl group at the 3- and 4-positions. At room temperature, the S_N1 pathway through the oxocarbenium ion is likely to be responsible for the α-selectivity deriving from the facial selectivity of the preferred $^4H_3$ half chair conformation. The presence of acetyl group(s) at the 3- or (and) 4-position enhances the preference of the S_N1 pathway through stabilization of the oxocarbenium ion and dramatically increases the formation of α-glycosides, especially at room temperature.

CONCLUSION

Our protecting group effect study indicated that the stereoselectivity of $GalN_3$ donors is highly affected by the acetyl groups. Acetyl groups at the 3- and 4-positions can dramatically increase the α-selectivity. Higher reaction temperature can also dramatically improve the α-selectivity. Our computational study suggests that the acetyl group can stabilize the oxocarbenium ions by participating in the reaction intermediate thus increasing the α-selectivity. Our study demonstrates that protecting groups can affect the stereoselectivity of glycosyl donors in a profound way. Computational chemistry can be a useful tool to explain and predict the reaction pathway. The methodology we used in this study can also be used in understanding glycosylation reactions of other sugar types.

EXPERIMENTAL SECTION

Materials and General Methods. Unless otherwise noted, reagents and solvents were obtained from commercial suppliers and were used without further purification. TLC was performed on precoated glass plates (silica gel F_{254}). Spots were detected by visualization under UV lamp and/or by charring with *p*-anisaldehyde stain. All NMR spectra were recorded on a 360 MHz spectrometer. All ^{1}H NMR data were obtained at 360 MHz, and all ^{13}C NMR data were obtained at 90 MHz. Proton and carbon chemical shifts are reported in parts per million (ppm) using $CDCl_3$ as internal reference unless otherwise noted. Coupling constants (*J*) are reported in hertz (Hz), and multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broadened (br).

Computational Method. Computation of the oxocarbenium ion was carried out in two phases. The structure of the intermediate was built with Spartan software (Spartan'08 for Windows).[45] The structure was then subjected to a conformation distribution calculation at MMFF level to identify all low energy conformations, which include the rotamers derived from the rotation of the acetyl group around the C−O bond and different dihedral angle of exocyclic side chain (C5−C6). All of the conformations were then optimized at semiempirical (AM1) level. The optimized conformations were then reviewed to remove identical structures. The coordinates of these structures were then transferred to QCHEM (Version 3.2)[46] and further optimized using the 6-31G basis set at the HF level. The resultant structures were then visualized and classified into different categories, like $^3H_4$, $^4H_3$ and participation intermediates. The lowest energy structure in each category was

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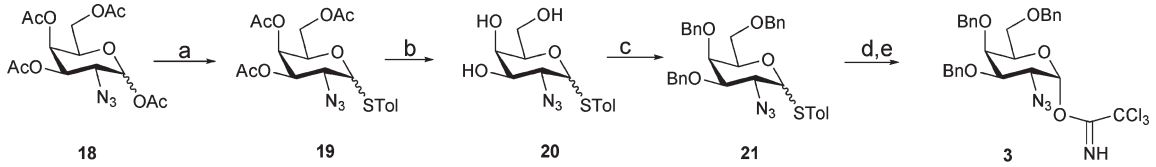
Scheme 4. Synthesis of Donor 3



a) *Para*-Thiocresol, $BF_3.ET_2O$, $CHCl_3$, 40°C 90% b) NaOMe, MeOH, Amberlite-IR 120 H^+
c) BnBr, NaH, DMF d) NBS, Acetone/H_2O (9:1) e) TCA, DBU, CH_2Cl_2

determined as the lowest energy conformation, further optimized at the B3LYP/6-31G* level, subjected to frequency calculations at the same level. No imaginary frequency was observed in the intermediates. Further single-point calculations at the B3LYP/6-31++G** level of theory for better energy estimation were also computed at B3LYP/6-31G*-optimized structures using QCHEM. All energies reported throughout refers to B3LYP/6-31++G** values. In the final structures, all nonparticipating esters have the carbonyl eclipsed with the carbohydrate carbon; it was also noticed that in most intermediates, the gt conformer of C5−C6 side chain is slightly more stable than the tg conformer (by around 0.8−4.2 kJ/mol).

General Procedure for Removal of a Nitrate Group from the Anomeric Position[47,48]**.** To a solution of the nitrate compound in dry CH_3CN were added thiophenol (3.0 equiv) and DIEA (1.0 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated under reduced pressure and the crude residue purified by flash chromatography to yield the corresponding glycosyl hemiacetal.

General Procedure for Hydrolysis of Thioglycosides to Glycosyl Hemiacetal. NBS (3 equiv) was added to a stirred solution of the thioglycoside in 10−20 mL of (9:1 v/v) acetone−water and stirred at room temperature until TLC showed disappearance of the thioglycoside and formation of a more polar compound (30 min to 1 h). Solid $NaHCO_3$ was added to neutralize the reaction and the solvents evaporated. The residue was dissolved in EtOAc and water. The organic phase was separated and washed with brine. It was dried over Na_2SO_4, concentrated, and purified by flash chromatography to give the corresponding glycosyl hemiacetal.

General Procedure for Conversion of Glycosyl Hemiacetal to Trichloroacetimidate. DBU (0.3 equiv) was added to a solution of the glycosyl hemiacetal (1.0 equiv) and trichloroacetonitrile (10.0 equiv) in dry CH_2Cl_2 at 0 °C.The reaction was stirred at 0 °C for 1 h and then at room temperature for 2 h. The crude product was evaporated and purified by flash chromatography to give the corresponding trichloroacetimidate.

*2-Azido-3,4,6-tri-O-benzyl-2-deoxy-α-D-galactopyranose-1-O-trichloroacetimidate (**3**) (Scheme 4).* The known **18**[49] (4.5 g, 0.01 mol, 1.0 equiv) and *p*-thiocresol (2.2 g, 0.02 mol, 1.5equiv) were stirred in anhydrous $CHCl_3$ (20 mL) at room temperature. The reaction mixture was cooled to 0 °C, and $BF_3 \cdot Et_2O$ (9.0 mL, 0.07 mol, 6 equiv) slowly added. The reaction was stirred at 40 °C for 3 h. It was carefully neutralized with $NaHCO_3$, and the organic layer washed with saturated NaCl, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography using EtOAc/hexanes (10−50%) to give **19** (4.7 g, 90% yield) as a 1:1 α/β mixture: R_f = 0.6 (1:1 hexanes/EtOAc); ^{1}H NMR (360 MHz, $CDCl_3$,) 2.01 (s, 3H) 2.04 (s, 3H), 2.05 (s, 3H), 2.07 (s, 3H), 2.09 (s, 3H), 2.16 (s, 3H), 2.34 (s, 3H), 2.37 (s, 3H), 3.64 (t, *J* = 10.0 Hz, 1H), 3.87 (dt, *J* = 1.0, 6.5 Hz,1H), 4.07−4.12 (m, 3H), 4.16 (dd, *J* = 6.5, 11.0 Hz, 1H), 4.30 (dd, *J* = 5.5, 11.0 Hz, 1H), 4.48 (d, *J* = 10.0 Hz, 1H), 4.78 (t, *J* = 6.5 Hz, 1H), 4.86 (dd, *J* = 3.0, 10.0 Hz, 1H), 5.18 (dd, *J* = 3.5, 11.0 Hz, 1H), 5.35 (dd, *J* = 1.0, 3.5 Hz, 1H), 5.48 (dd, *J* = 1.0, 3.0 Hz, 1H), 5.62 (d, *J* = 5.5 Hz, 1H), 7.12−7.19 (m, 4H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H).[50]

A 4.6 g (0.01 mol) portion of **19** in MeOH (20 mL) was treated with NaOMe (0.11 g, 2.13 mmol, 0.1 equiv) and stirred at room temperature for 30 min. Amberlite resin IR-120 H^+ (2 g) was added to neutralize the reaction. The resin was filtered, and the filtrate was concentrated to give **20** in quantitative yield: R_f = 0.5 (1:9 MeOH/CH_2Cl_2). To a solution of **20** (0.52 g, 1.67 mmol) and BnBr (1.2 mL, 10 mmol) in anhydrous DMF (10 mL) was added NaH (60% in mineral oil, 0.24 g, 10 mmol) slowly at 0 °C. The reaction was warmed to room temperature and stirred for 4 h. It was quenched with water (20 mL) and extracted with dichloromethane (3 × 10 mL). The organic layer was washed with water (3 × 10 mL) and brine (2 × 10 mL). It was dried, concentrated, and purified by flash chromatography using EtOAc/hexanes (0−20%) to give **21** (0.7 g, 72%) as a (1:1) α/β mixture: ^{1}H NMR (360 MHz, $CDCl_3$) (β isomer) 2.29 (s, 3H), 3.40 (dd, *J* = 2.7, 9.8 Hz, 1H), 3.55 (dt, *J* = 0.6, 6.7 Hz, 1H), 3.62 (s, 1H), 3.63 (d, *J* = 6.7 Hz, 1H), 3.79 (t, *J* = 9.9 Hz, 1H), 3.93 (d, *J* = 2.2 Hz, 1H), 4.33 (d, *J* = 10.1 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.51 (d, *J* = 11.4 Hz, 1H), 4.65 (d, *J* = 11.6 Hz, 1H), 4.71 (d, *J* = 11.6 Hz, 1H), 4.86 (d, *J* = 11.4 Hz, 1H), 7.00 (dd, *J* = 0.6, 8.4 Hz, 2H), 7.19−7.39 (m, 15H), 7.46 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 21.1, 61.3, 68.4, 72.0, 72.3, 73.5, 74.3, 77.2, 82.4, 86.5, 127.4, 127.6, 127.8, 127.9, 128.0, 128.1, 128.4, 128.5, 129.6, 133.3, 137.4, 137.7, 138.0, 138.4; (α isomer) ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.53 (dd, *J* = 6.1, 9.4 Hz, 1H), 3.61 (dd, *J* = 6.9, 9.4 Hz, 1H), 3.78 (dd, *J* = 2.7, 10.6 Hz, 1H), 4.04 (d, *J* = 1.6 Hz, 1H), 4.39−4.46 (m, 3H), 4.49 (t, *J* = 6.5 Hz, 1H), 4.54 (d, *J* = 11.3 Hz, 1H), 4.75 (s, 2H), 4.89 (d, *J* = 11.3 Hz, 1H), 5.53 (d, *J* = 5.4 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 2H), 7.23 −7.43 (m, 17H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 21.1, 60.4, 68.6, 70.4, 72.4, 73.4, 74.8, 79.1, 87.9, 127.6, 127.7, 127.8, 127.96, 128.0, 128.3, 128.4, 128.5, 129.5, 129.7, 132.8, 137.4, 137.8, 137.9, 138.2[50]

Compound **21** was hydrolyzed as per the general described procedure to give the known glycosyl hemiacetal[29] in 67% yield. The corresponding α-trichloroacetimidate **3**[29] was obtained in 75% yield: R_f = 0.55 (1:3 EtOAc/hexane); ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.61 (dd, *J* = 5.1, 9.0 Hz, 1H), 3.72 (t, *J* = 8.1 Hz, 1H), 4.09 (dd, *J* = 3.0, 10.7 Hz, 1H), 4.18−4.28 (m, 3H), 4.48, 4.53 (2d, *J* = 12.0 Hz, each 1H), 4.63, 4.97 (2d, *J* = 10.7 Hz, each 1H), 4.75, 4.84 (d, *J* = 11.1 Hz, each 1H), 6.44 (d, *J* = 3.4 Hz, 1H), 7.28 −7.50 (m, 15H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 59.1, 67.9, 72.1, 72.7, 73.5, 74.9, 77.4, 90.9, 95.4, 127.7−128.5, 137.1, 137.6, 138.1, 160.7.

*3-O-Acetyl-2-azido-4,6-di-O-benzyl-2-deoxy-α-D-galactopyranose-1-O-trichloroacetimidate (**4**) (Scheme 5)*[51]. A stirred solution of the known triol[52] (1.0 g, 6.8 mmol) in anhydrous DMF (10 mL) under nitrogen at 0 °C was treated with of NaH (60% in mineral oil, 600 mg, 15.05 mmol, 2.2 equiv). After 2 h at 0 °C, the mixture was treated dropwise and rapidly with BnBr (1.8 mL, 15.05 mmol, 2.2 equiv) and then allowed to stand for 3 h at 0 °C. The mixture solidified and was thawed out, diluted with dichloromethane (30 mL), and washed with water (20 mL). The aqueous phase was back-extracted with (3 × 10 mL)

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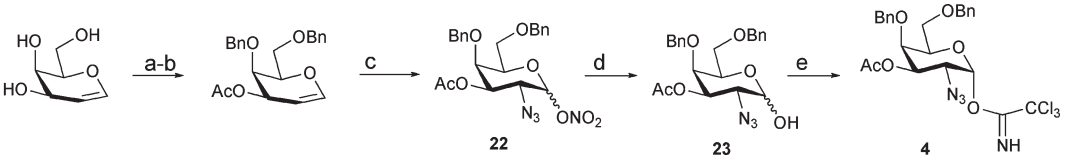
Scheme 5. Synthesis of Donor 4



a) NaH, BnBr, DMF, 0°C, 25% b) Ac_2O, Pyr, 90% c) CAN, NaN_3, CH_3CN, -15°C, 30% , **22**
d) PhSH, DIPEA, CH_3CN, 80%, **23** e) TCA, DBU, CH_2Cl_2, 68%, **4**

of dichloromethane, and all the organic fractions were combined, washed with brine (30 mL), and dried over anhydrous Na_2SO_4. The fraction was concentrated and purified by flash chromatography (0−30% EtOAc/hexanes). The main fraction contained 4,6-*O*-dibenzylated product (30%),[52] which crystallized out on cooling, 26% of the perbenzylated product, 15% of another dibenzylated product with recovery of 30% of starting material. The NMR data was comparable to literature data: TLC R_f = 0.4 (3:1 hexanes/EtOAc); ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.42 (d, J = 9.4 Hz, 1H), 3.65 (dd, J = 5.6, 11.0 Hz, 1H) 3.81 (dd, J = 6.4, 10.3 Hz, 1H), 3.91 (m, 1H), 4.20 (m, 1H), 4.33 (m, 1H), 4.35 (m, 1H, H-3), 4.49, 4.58 (2d, J = 12.4 Hz, each 1H), 4.68, 4.74 (2d, J = 11.6 Hz, each 1H), 4.76 (dddd, J = 1.0 Hz, 1H), 6.37 (dd, J = 1.3, 6.4 Hz, 1H), 7.27- 7.52 (m, 10H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 62.8, 68.1, 73.1, 73.4, 74.2, 75.1, 102.8, 127.8 − 128.5, 137.7, 144.2.

A solution of **4,6-di-*O*-benzyl-D-galactal** (800 mg, 2.45 mmol) in anhydrous pyridine (10 mL) and acetic anhydride (5.0 mmol) was stirred at room temperature for 2 h. The mixture was concentrated in vacuo, and the residue was purified by flash chromatography (25% EtOAc/hexanes) to yield **3-*O*-acetyl-4,6-di-*O*-benzyl-D-galactal** (810 mg, 90% yield) as a colorless syrup: the NMR data were comparable to literature data; TLC R_f = 0.45 (4:1 hexanes/EtOAc); ^{1}H NMR (360 MHz, $CDCl_3$) δ = 2.02 (s, 3H), 3.62 (dd, J = 5.4, 10.3 Hz, 1H), 3.76 (dd, J = 7.4, 10.3 Hz, 1H), 4.00−4.03 (m, 1H), 4.22−4.27 (m, 1H), 4.42−4.55 (m, 2H), 4.70−4.75 (m, 2H), 5.44−5.48 (m, 1H), 6.43 (dd, J = 1.4, 6.2 Hz, 1H), 7.24−7.36 (m, 10H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 21.1, 65.4, 67.8, 70.7, 73.4, 73.5, 75.5, 98.5, 127.7−128.4, 137.8, 137.9, 145.6, 170.7.

3-*O*-Acetyl-4,6-di-*O*-benzyl-D-galactal (1.5 g, 4.32 mmol) was dissolved in CH_3CN (50 mL) and cooled to −15 °C. CAN (7.0 g, 12.95 mmol, 3 equiv) and NaN_3 (0.4 g, 6.47 mmol, 1.5 equiv) were added, and mixture was stirred vigorously using a mechanical stirrer overnight. The reaction mixture was diluted with ice cold Et_2O (50 mL), washed with water (2 × 40 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude residue was purified by flash chromatography (0−20% EtOAc/hexanes) to afford the azido-nitrate product **22** (a 4:1 α/β mixture, 0.6 g, 30% yield) as a colorless oil: ^{1}H NMR (360 MHz, $CDCl_3$, selected peaks) δ 4.00 (dd, J = 8.8, 11.0 Hz, 1H), 4.07 (app d, J = 2.9 Hz, 1H), 4.18 (app d, J = 2.9 Hz, 1H), 4.29 (dd, J = 4.2, 11.3 Hz, 1H), 4.86 (dd, J = 3.0, 11.0 Hz, 1H), 5.19 (dd, J = 2.9, 11.3 Hz, 1H), 5.54 (d, J = 8.8 Hz, 1H), 6.30 (d, J = 4.1 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 20.7, 56.4, 67.2, 71.2, 71.9, 73.5, 73.7, 75.4, 97.6, 127.8−128.5, 137.4, 137.5, 170.1.

To a solution of **22** (0.4 g, 0.88 mmol) in CH_3CN (10 mL) were added thiophenol (0.27 mL, 2.63 mmol) and DIPEA (0.15 mL, 0.88 mmol) at 0 °C. After 1 h, the reaction mixture was concentrated in vacuo, and the crude residue was purified by flash chromatography (15−60% EtOAc/hexanes) to give compound **23** as α/β mixture (0.3 g, α:β = 2:1, 80% yield): ^{1}H NMR (360 MHz, $CDCl_3$, selected peaks) δ 2.05 (s, 3H), 3.07 (br s, 1H), 3.92 (dd, J = 3.5, 11.1 Hz, 1H), 3.94 (app d, J = 3.3 Hz, 1H), 4.06 (app d, J = 2.3 Hz, 1H), 4.74 (dd, J = 3.1, 10.8 Hz, 1H), 5.32 (dd, J = 2.9, 11.0 Hz, 1H), 5.38 (d, J = 3.4 Hz, 1H).

DBU (0.2 mmol, 30 μL) was added to a solution of **23** (0.29 g, 0.68 mmol) and trichloroacetonitrile (0.7 mL, 6.8 mmol) in anhydrous dichloromethane (10 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h and then at room temperature for 2 h. It was evaporated and purified by flash chromatography (5−20% EtOAc/hexanes) to give compound **4** (0.27 g, 68% yield): R_f = 0.55 (1:4 EtOAc/hexanes); ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.09 (s, 3H), 3.57 − 3.63 (m, 1H), 3.67 (m, 1H), 4.20−4.27 (2H, m), 4.31 (m, 1H), 4.40−4.75 (m, 4H), 5.36 (dd, J = 3.0, 10.7 Hz, 1H), 6.48 (d, J = 3.8 Hz, 1H), 7.24−7.43 (m, 10H), 8.74 (s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 20.7, 57.4, 67.4, 71.3, 71.4, 73.3, 73.9, 75.2, 90.8, 95.0, 127.7−128.4, 137.5, 137. 6, 160.7, 170.0; HRMS (ESI-TOF) [MH^+] calcd for $C_{24}H_{26}Cl_3N_4O_6$ 571.0912, found 571.0917.

*4-O-Acetyl-2-azido-3,6-di-O-benzyl-2-deoxy-α-D-galactopyranose-1-O-trichloroacetimidate (**5**) (Scheme 6).* To a solution of the known **24**[54,55] (0.72 g, 1.8 mmol) and BnBr (0.5 mL, 3.6 mmol, 2 equiv) in anhydrous DMF (10 mL) was added NaH (60% in mineral oil, 0.1 g, 3.6 mmol, 2 equiv) slowly at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 4 h. Aqueous workup was followed as previously described. The mixture was purified by flash chromatography (5−20% EtOAc/hexanes) to give **25** as a white powder (0.80 g, 91% yield): R_f = 0.4 (1:3 EtOAc/hexane); ^{1}H NMR (360 MHz, $CDCl_3$) (β isomer) δ 2.30 (s, 3H), 3.36 (m, 1H), 3.43 (dd, J = 3.8, 9.4 Hz, 1H), 3.71 (t, J = 10.3 Hz, 1H), 3.95 (dd, J = 1.7, 12.4 Hz, 1H), 4.07 (m, 1H), 4.29−4.36 (m, 2H), 4.67 (s, 2H), 5.42 (s, 1H), 7.03 (d, J = 8.5 Hz, 2H), 7.25−7.45 (m, 10H), 7.59 (d, J = 9.0 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 21.1, 59.4, 69.3, 69.7, 71.5, 72.0, 79.5, 85.0, 101.0, 125.9−129.8, 134.7, 137.4, 137.6, 138.5.

To a solution of the **25** (0.6 g, 1.2 mmol), powdered molecular sieves (0.6 g), and $NaBH_3CN$ (0.68 g, 10.4 mmol, 9 equiv) in anhydrous THF (15 mL) was added 4 N HCl−dioxane (4.0 mL, 16 mmol, 14 equiv) dropwise at 0 °C under N_2 atmosphere, and the mixture was stirred at 0 °C for 2 h. It was diluted with EtOAc (20 mL) and filtered through Celite. The filtrate was washed with satd $NaHCO_3$ (2 × 10 mL) and brine (10 mL), dried over Na_2SO_4, and purified by flash column chromatography (5−20%, EtOAc/hexanes to give **26** (0.5 g, 80% yield). Compound **26** (0.35 g, 0.7 mmol) was dissolved in dichloromethane (5 mL), and Et_3N (0.2 mL, 1.4 mmol, 2 equiv) followed by Ac_2O (0.14 mL, 1.4 mmol, 2 equiv) were added. The reaction was stirred at room temperature for 30 min, solvent was removed in vacuo, and the resulting residue was purified by flash chromatography (5−20% EtOAc/hexanes) to give **27** (0.38 g, 96% yield). Thioglycoside hydrolysis of **27** was carried out following the general procedure as outlined to give the glycosyl hemiacetal:[56] R_f = 0.36 (1:2 EtOAc/hexanes); ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.08 (s, 3H), 3.36 (dd, J_2= 3.2, 10.4 Hz 1H), 3.67 (dd, J = 3.6, 10.4 Hz, 1H), 3.97 (dd, J = 3.6, 10.4 Hz, 1H), 4.33 (m, J = 1.0, 5.5 Hz, 1H), 4.48 (dd, J = 4.0, 7.8 Hz, 1H), 5.32 (t, J = 3.6 Hz, 1H), 5.48 (dd, J = 0.8, 3.2 Hz, 1H), 5.57 (dd, J = 1.0, 3.0 Hz, 1H), 7.30 (m, 10H). The resulting hemiacetal was converted to the α-trichloroacetimidate **5**[56] (80% yield over two steps): R_f = 0.55 (1:3 EtOAc/hexanes),^{1}H NMR (360 MHz, $CDCl_3$) δ 2.07 (s, 3H), 3.47 (dd, J = 7.2, 12.0 Hz, 1H), 3.55 (dd, J = 5.50, 12.0 Hz, 1H), 3.82 (dd, J = 3.60,

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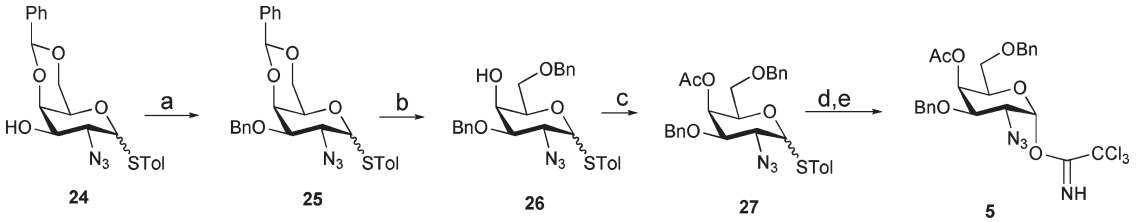
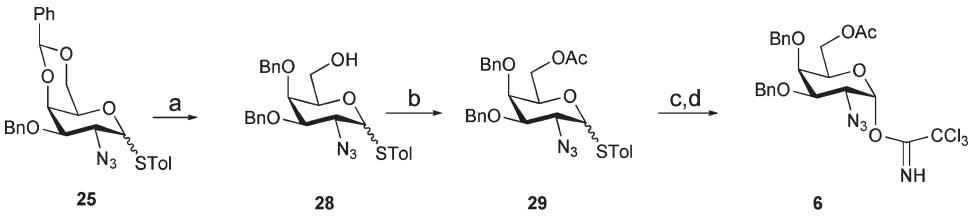
Scheme 6. Synthesis of Donor 5



a) NaH, BnBr, DMF, 91% b) $NaBH_3CN$, HCl, 80% c) Ac_2O, Et_3N, DMAP, CH_2Cl_2,, 97% d) NBS, Acetone:H_2O (9:1), 75% e) TCA, DBU, CH_2Cl_2, 86%

Scheme 7. Synthesis of Donor 6



a) BH_3.THF, TMSOTf, CH_2Cl_2, rt, 80% b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 86% c) NBS, Acetone:H_2O (9:1), 81% d) TCA, DBU, CH_2Cl_2, 60%

10.4 Hz, 1H), 4.06 (dd, $J_{2,3}$ = 3.0, 10.6 Hz, 1H), 4.30 (m, 1H), 5.78 (dd, J = 1.0, 3.0 Hz, 1H), 6.40 (d, J = 3.60 Hz, 1H), 7.30 (m, 10H) 8.69 (s, 1H).

*6-O-Acetyl-2-azido-3−4-di-O-benzyl-2-deoxy-α-D-galactopyranose-1-O-trichloroacetimidate (**6**) (Scheme 7).* To a solution of **25** (0.45 g, 0.9 mmol) in anhydrous dichloromethane (10 mL) were added a solution of BH_3.THF (1M, 1.8 mL, 1.8 mmol, 2 equiv) and TMSOTf (17 μL, 0.1 mmol, 0.1 equiv), and the mixture was stirred under N_2 at room temperature for 3 h. Et_3N (3 drops) was added followed by careful addition of MeOH (5 mL) until H_2 evolution ceased. It was concentrated, and the residue coevaporated with MeOH. The residue was purified by flash column chromatography (0−35%, EtOAc/hexanes) to give **28** (0.36 g, 80% yield). Compound **28** (0.35 g, 0.7 mmol) was dissolved in CH_2Cl_2 (5 mL), and Et_3N (0.2 mL, 1.4 mmol, 2 equiv) followed by Ac_2O (0.14 mL, 1.4 mmol, 2 equiv) were added. The reaction was stirred at room temperature for 30 min. The solvent was removed in vacuo, and the resulting residue was purified by flash chromatography (0−25%, EtOAc/hexanes) to give **29** (0.33 g, 86% yield). Thioglycoside hydrolysis of compound **29** was carried out following the general procedure to give the hemiacetal which was converted to the α-trichloroacetimidate **6** (66% yield over two steps): R_f = 0.55 (1:3 EtOAc/hexanes), $[\alpha]_D$ = 9.1 (c = 1.00 in $CHCl_3$); IR (thin film, CH_2Cl_2) 2117, 1734, 1422, 896 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.97 (s, 3H), 3.99−4.26 (m, 6H), 4.61, 4.96 (2d, J = 11.4 Hz, each 1H) 4.78, 4.84 (2d, J = 11.6 Hz, each 1H), 6.45 (d, J = 3.4 Hz, 1H), 7.29−7.48 (m, 10H), 8.72 (s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 20.7, 59.1, 63.0, 71.4, 72.4, 72.5, 74.6, 77.3, 90.9, 95.1, 127.7−128.8, 137.0, 137.5, 160.6, 170.5; HRMS (ESI-TOF) [MNa^+] calcd for $C_{24}H_{25}Cl_3N_4O_6Na$ 593.0732, found 593.0727.

*3,4-Di-O-acetyl-2-azido-6-O-benzyl-2-deoxy-α-D-galactopyranose-1-O-trichloroacetimidate (**7**) (Scheme 8).* To a solution of **20** (0.8 g, 2.56 mmol) in 2,2-dimethoxypropane (20 mL) was added CSA (catalytic amount), the mixture was stirred at room temperature for 24 h under N_2, Et_3N (0.5 mL) was then added, and the mixture was stirred for 15 min. It was concentrated and coevaporated with toluene to remove traces of Et_3N. A solution of the crude product in MeOH/H_2O (20 mL, 10:1) was boiled under reflux until TLC (1:1 hexanes/EtOAc) showed complete disappearance of the starting material. It was coevaporated with toluene and purified by flash chromatography (10−50% EtOAc/hexanes) to give 3,4-*O*-isopropylidene acetal **30** (0.72 g, 80% yield). To a stirred solution of **30** (0.4 g, 1.14 mmol) and BnBr (0.3 mL, 2.28 mmol, 2 equiv) in anhydrous DMF (10 mL) at 0 °C was slowly added NaH (60% in mineral oil, 0.06 g, 2.28 mmol, 2 equiv). The reaction was warmed to room temperature and stirred for 4 h. It was quenched with MeOH (15 mL) and extracted with dichloromethane (3 × 10 mL). The organic layer was washed with water (3 × 10 mL) and brine (2 × 10 mL). It was dried, concentrated, and purified by flash chromatography (0−10% EtOAc/hexanes) to give 6-OBn derivative **31** (0.31 g, 62% yield). Compound **31** (0.3 g, 0.7 mmol) was dissolved in TFA/H_2O (10 mL, 9:1) and stirred at room temperature for 10 min. It was coevaporated with toluene to give the 3,4-diol derivative (0.28 g, 98% yield), which was dissolved in dichloromethane (5 mL) and treated with Et_3N (0.2 mL, 1.39 mmol, 2 equiv), Ac_2O (0.13 mL 1.39 mmol, 2 equiv), and DMAP (catalytic amount). After 30 min, it was concentrated and purified by flash chromatography (0−30% EtOAc/hexanes) to give the 3,4-di-*O*-acetyl derivative **32** (0.32 g, 94% yield). Thioglycoside hydrolysis of **32** was carried following the general procedure to give the hemiacetal which was converted to the α-trichloroacetimidate **7** (80% yield over two steps): R_f = 0.4 (1:4 EtOAc/hexanes); $[\alpha]_D$ = 81.3 (c = 1.00 in $CHCl_3$); IR (thin film, CH_2Cl_2) 2116, 1755, 1677, 1234, 1037 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.07 (s, 3H), 3.41 − 3.55 (m, 2H), 4.00 (dd, J = 3.4, 10.0 Hz, 1H), 4.36 (m, H), 4.37, 4.52 (2d, J = 12.0 Hz, each 1H), 5.39 (dd, J = 3.0, 10.0 Hz, 1H), 5.62 (m, 1H), 6.48 (d, J = 3.4 Hz, 1H), 7.20 − 7.38 (m, 5H), 8.76 (s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 20.5, 20.6, 57.2, 67.0, 67.3, 68.8, 70.1, 73.3, 90.7, 94.6, 127.8, 128.4, 137.3, 160.7, 169.6, 169.8; HRMS (ESI-TOF) [MNa^+] calcd for $C_{19}H_{21}Cl_3N_4O_7Na$ 545.0368, found 545.0357.

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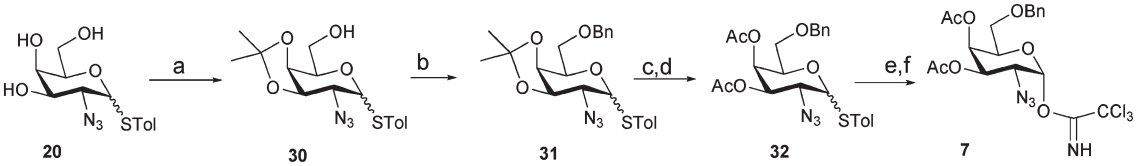
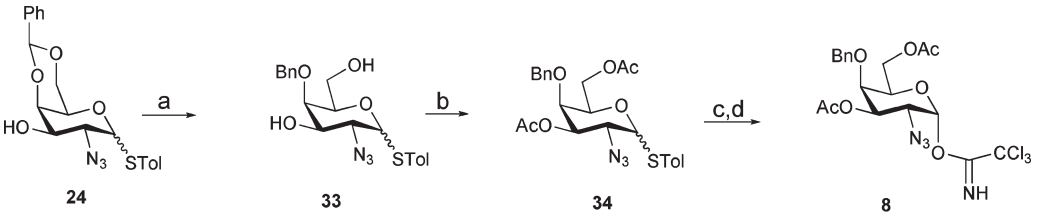
Scheme 8. Synthesis of Donor 7



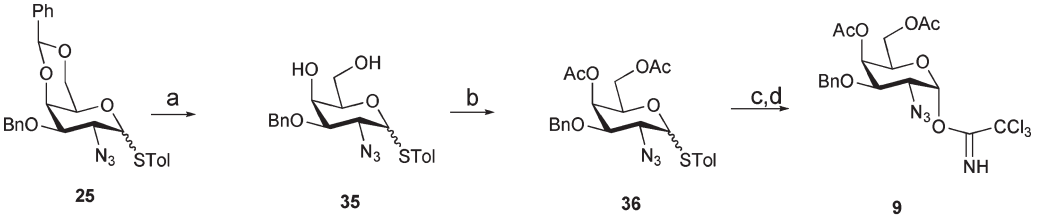
a) $Me_2C(OMe)_2$, CSA, then MeOH in H_2O under reflux, 80% b) BnBr,NaH, DMF, 62% c) TFA:H_2O (9:1), 98%
d) Ac_2O, Et_3N, DMAP CH_2Cl_2, 94% e) NBS, Acetone:H_2O (9:1), 83% f) TCA, DBU, CH_2Cl_2, 77%

Scheme 9. Synthesis of Donor 8



a) BH_3·THF, TMSOTf, CH_2Cl_2, rt, 86% b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 80%
c) NBS, Acetone:H_2O (9:1), 81% d) TCA, DBU, CH_2Cl_2, 66%

Scheme 10. Synthesis of Donor 9



a) CSA, MeOH, 90% b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 97%
c) NBS, Acetone:H_2O (9:1), 93% d) TCA, DBU, CH_2Cl_2, 76%

*3,6-Di-O-acetyl-2-azido-4-O-benzyl-2-deoxy -α-D-galactopyranose-1-O -trichloroacetimidate (**8**) (Scheme 9).* To a solution of **24** (0.6 g, 1.48 mmol) in anhydrous dichloromethane (8 mL)were added a BH_3·THF solution (1M, 3.0 mL, 2.95 mmol, 2 equiv) and TMSOTf (27 μL, 0.18 mmol, 1.2 equiv), and the mixture was stirred under N_2 at room temperature for 3 h. Et_3N (3 drops) was added followed by careful addition of MeOH (5 mL) until H_2 evolution ceased. It was concentrated, and the residue was coevaporated with MeOH. The residue was purified by flash column chromatography (10−50% EtOAc/hexanes) to give the 4-OBn derivative **33** (0.51 g, 86% yield). Compound **33** (0.50 g, 1.25 mmol) was dissolved in dichloromethane (8 mL), and Et_3N (0.7 mL, 5.0 mmol, 4 equiv) followed by Ac_2O (0.5 mL, 5.0 mmol, 4 equiv) were added together with DMAP (catalytic amount). The reaction was stirred at room temperature for 30 min. The solvent was removed in vacuo, and the resulting residue was purified by flash chromatography (0−30% EtOAc/hexanes) to give the 3,6-di-OAc derivative **34** (0.36 g, 80% yield). Thioglycoside hydrolysis of **34** was carried out following the general procedure outlined above to give the hemiacetal which was converted to the α-trichloroacetimidate **8** (74% yield over two steps): R_f = 0.5 (1:3 EtOAc/hexanes); $[\alpha]_D$ = 171.8 (*c* = 1.00 in $CHCl_3$); IR (thin film, CH_2Cl_2) 2116, 1747, 1675, 1370, 1228, 1028 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.98 (s, 3H), 2.13 (s, 3H), 4.05−4.28 (m, 5H), 4.56 (d, *J* = 11.1 Hz, 1H), 4.71 (d, *J* = 11.5, 1H), 5.32 (dd, *J* = 3.0, 11.4 Hz, 1H), 6.48 (d, *J* = 3.4 Hz, 1H), 7.29−7.40 (m, 5H), 8.76 (s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 20.6, 20.8, 57.2, 62.1, 70.6, 71.5, 73.6, 75.3, 90.7, 94.7, 128.1, 128.2, 128.5, 137.0, 160.6, 170.0, 170.1; HRMS (ESI-TOF) [MNa^+] calcd for $C_{19}H_{21}Cl_3N_4O_7Na$ 545.0368, found 545.0343.

*4,6-Di-O-acetyl-2-azido-3-O-benzyl-2-deoxy-α-D-galactopyranose-1-O-trichloroacetimidate (**9**) (Scheme 10).* CSA (catalytic amount) was added to **25** (0.4 g, 0.82 mmol) in MeOH (8 mL). The reaction was stirred at room temperature for 2 h. It was quenched with Et_3N (3 drops) and concentrated. Flash chromatography purification (20−50%, EtOAc/hexanes) gave the 4,6-diol **35** (0.6 g, 90% yield). Acetylation, thioglycoside hydrolysis, and conversion to the trichloroacetimidate were carried out following the general procedures outlined above afford compound **9** (87% yield over three steps): R_f = 0.45 (1:3 EtOAc/hexanes); $[\alpha]_D$ = 114.6 (*c* = 1.00 in $CHCl_3$); IR (thin film, CH_2Cl_2): 2116, 1747, 1677, 1225, 1064 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.14 (s, 3H), 3.95 (dd, *J* = 3.4, 10.2 Hz, 1H), 4.02−4.09 (m, 2H), 4.21 (dd, *J* = 6.0, 11.2 Hz, 1H), 4.35 (t, *J* = 6.4 Hz, 1H), 4.53, 4.81 (2d, *J* = 10.7 Hz, each 1H), 5.70 (m, 1H), 6.44 (d, *J* = 3.4 Hz, 1H), 7.27−7.42 (m, 5H), 8.75 (s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 20.6, 20.7, 58.5, 61.8, 65.6, 69.5, 71.8, 74.1, 90.7, 94.7, 127.9−128.6,

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Table 3. Determination of α:β Ratios: Diagnostic Protons

	diagnostic protons	
compd	δ_α (ppm)	δ_β (ppm)
10	5.05 (d, J = 3.4 Hz, 1H, H-1')	4.47 (d, J = 7.7 Hz, 1H, H-1')
11	5.66 (t, J = 9.8 Hz, 1H, H-4)	5.49 (t, J = 9.8 Hz, 1H, H-4)
12	5.56 (t, J = 9.8 Hz, 1H, H-4)	5.49 (t, J = 9.8 Hz, 1H, H-4)
13	5.64 (t, J = 9.8 Hz, 1H, H-4)	5.52 (t, J = 9.8 Hz, 1H, H-4)
14	5.65 (t, J = 9.8 Hz, 1H, H-4)	5.47 (t, J = 9.8 Hz, 1H, H-4)
15	5.77 (t, J = 9.8 Hz, 1H, H-4)	5.66 (t, J = 9.8 Hz, 1H, H-4)
16	5.04 (d, J = 3.8 Hz, 1H, H-1')	4.42 (d, J = 8.1 Hz, 1H, H-1')
17	4.98 (d, J = 3.4 Hz, 1H, H-1')	4.35 (d, J = 8.1 Hz, 1H, H-1')

136.5, 160.5, 170.0, 170.3; HRMS (ESI-TOF) [MNa^+] calcd for $C_{19}H_{21}Cl_3N_4O_7Na$ 545.0368, found 545.0352.

General Glycosylation Procedure at −78 °C. A solution of the acceptor (1.0 equiv), donor (1.2 equiv), and activated molecular sieves (50 mg/mL solvent) in anhydrous dichloromethane (5.0 mL/mmol donor) was stirred at room temperature for 0.5 h. The reaction was cooled to −78 °C, and TMSOTf (0.15 equiv) was added followed by stirring the solution at −78 °C for 15 min and then warming to room temperature for 15 min. It was quenched by addition of Et_3N, concentrated, and purified using flash column chromatography to give the products.

General Glycosylation Procedure at Room Temperature. A solution of the acceptor (1.0 equiv), donor (1.2 equiv), and activated molecular sieves (50 mg/mL solvent) in anhydrous dichloromethane (5.0 mL/mmol donor) was stirred at room temperature for 0.5 h. TMSOTf (0.15 equiv) was added followed by stirring the solution at room temperature until the reaction was complete as monitored by TLC. It was quenched by addition of Et_3N, concentrated, and purified using flash column chromatography to give the products. The α and β anomers in the product have generally very close R_f values and are very difficult to separate. Our general practice is to identify the fractions using TLC and combine the fractions containing either anomers. In this way, the product collected contains both α and β anomers and was then analyzed by ^1H NMR to determine the ratio.

Determination of α/β Product Ratio. The determination of the α and β anomers is a very complicated process because the anomers are often inseparable mixtures. 2D NMR (HSQC) was used to identify the anomeric protons of the nonreducing end (H-1′) in the ^1H NMR and determination of the stereochemistry was based on the coupling constant. The ratio of the anomers could then be determined on the basis of the integration. This method was used in the determination of disaccharides **10**, **16**, and **17** (Table 3). This method cannot be used for other disaccharides because the β anomeric proton overlaps with other protons. The H-4 proton of the reducing end sugar was used to determine the α/β ratio of disaccharides **12**−**15** (Table 3). All ^1H NMR experiments were performed in $CDCl_3$ (except compound **15**, which was in CD_3OD due to poor solubility in $CDCl_3$) at 360 MHz at 25 °C. ^1H NMR and ^{13}C NMR spectra of all disaccharide products from both −78 °C and room temperature reactions are included in the Supporting Information, as well as the HSQC 2D spectra.

■ ASSOCIATED CONTENT

Supporting Information. Selected ^1H and ^{13}C NMR and HSQC spectra. Cartesian coordinates and absolute energy of all intermediates in Table 2. These materials are available free of charge via the Internet at http://pubs.acs.org.

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