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Installation of Electron-Donating Protective Groups, a Strategy for Glycosylating Unreactive Thioglycosyl Acceptors using the Preactivation-Based Glycosylation Method[1]

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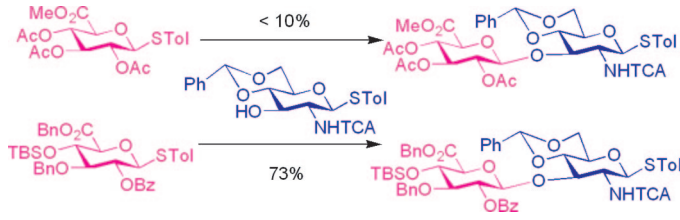

Preactivation-based chemoselective glycosylation is a powerful strategy for oligosaccharide synthesis with its successful application in assemblies of many complex oligosaccharides. However, difficulties were encountered in reactions where glycosyl donors bearing multiple electron-withdrawing groups failed to glycosylate hindered unreactive acceptors. In order to overcome this problem, it was discovered that the introduction of electron-donating protective groups onto the glycosyl donors can considerably enhance their glycosylating power, leading to productive glycosylations even with unreactive acceptors. This observation is quite general and can be extended to a wide range of glycosylation reactions, including one-pot syntheses of chondroitin and heparin trisaccharides. The structures of the reactive intermediates formed upon preactivation were determined through low-temperature NMR studies. It was found that for a donor with multiple electron-withdrawing groups, the glycosyl triflate was formed following preactivation, while the dioxalenium ion was the major intermediate with a donor bearing electron-donating protective groups. As donors were all cleanly preactivated prior to the addition of the acceptors, the observed reactivity difference between these donors was not due to selective activation encountered in the traditional armed-disarmed strategy. Rather, it was rationalized by the inherent internal energy difference between the reactive intermediates and associated oxacarbenium ion like transition states during nucleophilic attack by the acceptor.

Introduction

With the increasing recognition of the important biological functions of carbohydrates, carbohydrate synthesis is a very active research area, with many innovative methodologies developed during the past two decades.[2−5] In most glycosylation reactions, a promoter is added to a mixture of the glycosyl donor and the acceptor. The glycosyl donor is activated by the promoter, which undergoes in situ nucleophilic addition or displacement reaction with the acceptor, leading to the glycoside

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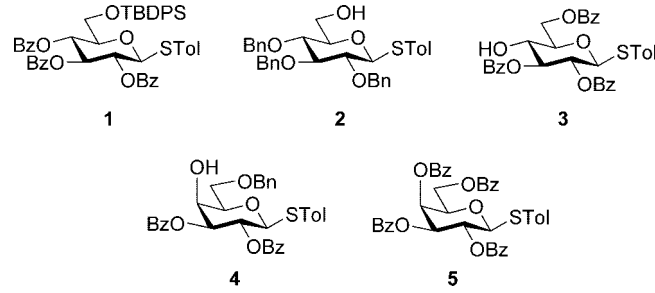
product. As an alternative, a glycosyl donor can be activated in the absence of an acceptor (preactivation).[6−18] Upon complete donor activation, the acceptor is then added to the reaction mixture, initiating glycoside formation. Using the preactivation strategy, unique stereochemical outcomes[6,9,16,17] and chemoselectivities[10−13,15] can be obtained. Boons and co-workers developed a novel α-selective glycosylation strategy,[9] where preactivation of a trichloroacetimidate donor allowed for the 2-O protective group to participate and stabilize the oxacarbenium ion from the β face. Thus, S_N2-like displacement by the acceptor gave α-glycosides highly selectively. The Crich group discovered that preactivation of a benzylidene-protected thiomannoside or mannosyl sulfoxide generated an α-mannosyl triflate,[17] which upon triflate displacement by an acceptor led to the β-mannoside stereoselectively, overcoming this long-standing challenge. Gin and co-workers reported that the preactivated hemiacetal donor could chemoselectively glycosylate a hemiacetal acceptor.[15] The glycoside product could then be directly activated using the identical condition, and glycosylation can be carried out iteratively.

Recently, we[7,8,11,19−22] and others[12,13,23] applied the preactivation scheme to the chemoselective glycosylation of a thioglycoside acceptor by a thioglycosyl donor. In this approach, the glycosyl donor is preactivated by a stoichiometric promoter. Upon complete donor activation, a thioglycosyl acceptor is added to the reaction mixture. Nucleophilic attack on the activated donor by the acceptor yields a disaccharide product containing a thioether aglycon, which can be directly activated for the next round of glycosylation without any aglycon adjustment as typically required by other selective activation strategies. With the preactivation scheme, because donor activation and addition of the acceptor are performed in two distinct steps, the anomeric reactivity of the thioglycosyl donor is independent of that of the thioglycosyl acceptor. This confers much freedom in protective group selection, greatly simplifying the overall synthetic design. This is in contrast with the traditional reactivity-based armed-disarmed chemoselective glycosylation method,[24−26] where the glycosyl donor must possess much higher anomeric reactivity (typically at least 10 times higher) than the glycosyl acceptor,[24] as the donor is activated in the presence of the acceptor.

A wide range of thioglycosyl donor and acceptor pairs have been examined using the preactivation protocol.[7,8,11,12,19−23] In many cases, the chemoselective glycosylation reactions proceeded smoothly with good yields. It is particularly noteworthy that a disarmed donor (e.g., **1**) can glycosylate an armed acceptor (e.g., **2**).[11,20] This reversal of anomeric reactivity is not possible using the reactivity-based armed-disarmed method.[24,25] The preactivation-based strategy has been successfully applied to total synthesis of a wide range of complex linear and branched oligosaccharides, including $Lewis^X$,[21] dimeric $Lewis^X$,[21] Globo-H,[20] hyaluronic acid oligosaccharides,[8] chito-oligosaccharides,[13,22] and complex type sialylated core fucosylated *N*-glycan dodecasaccharide.[7] However, difficulties were encountered in reactions of very unreactive secondary carbohydrate acceptors such as **3** and **4** with electron-poor donors **1** and **5**.[11] In this article, we will explore a strategy to overcome this problem. We will also study the intermediates generated upon preactivation to provide insights to design even better glycosylation strategies.



Results and Discussion

The reaction of donor **5** with acceptor **3** was performed by first preactivating donor **5** with the promoter system *p*-TolSCl/AgOTf[11] followed by addition of acceptor **3** and a sterically hindered base tri-*tert*-butyl pyrimidine (TTBP)[27] (Table 1, entry 1). Although no desired disaccharide was formed, complete disappearance of the donor was observed by TLC and NMR (vide infra). Analysis of the reaction mixture showed that donor **5** was converted to the expected breakdown products (the hemiacetal or the glycal) of the oxacarbenium ion corresponding to **5**, with most of the acceptor **3** recovered. This demonstrated that despite the presence of multiple electron-withdrawing benzoyl groups, the electron-poor donor **5** was activated by the powerful promoter *p*-TolSCl/AgOTf. Similar phenomena were observed in the reaction of **4** with **5** (Table 1, entry 2) or donor **1**.[11] Interestingly, reaction of perbenzylated glucose donor **8** with

TABLE 1. Glycosylation Results of Various Donor/Acceptor Pairs

Donor (1 eq) + AgOTf → (1) *p*-TolSCl, -60 °C; (2) acceptor (0.9 eq), TTBP, -60 - -20 °C → Product

entry	donor	acceptor	product	yield (%)
1	**5**	**3**	**6**	<10
2	**5**	**4**	**7**	<10
3	**8**	**3**	**9**	67
4	**8**	**4**	**10**	65
5	**11**	**4**	**12**	56 (48% β + 8% α)
6	**13**	**3**	**14**	74
7	**13**	**4**	**15**	70
8	**16**	**17**	**18**	<10
9	**13**	**17**	**19**	75
10	**20**	**21**	**22**	<10
11	**23**	**21**	**24**	73
12	**11**	**25**	**26**	65 (51% β + 14% α)

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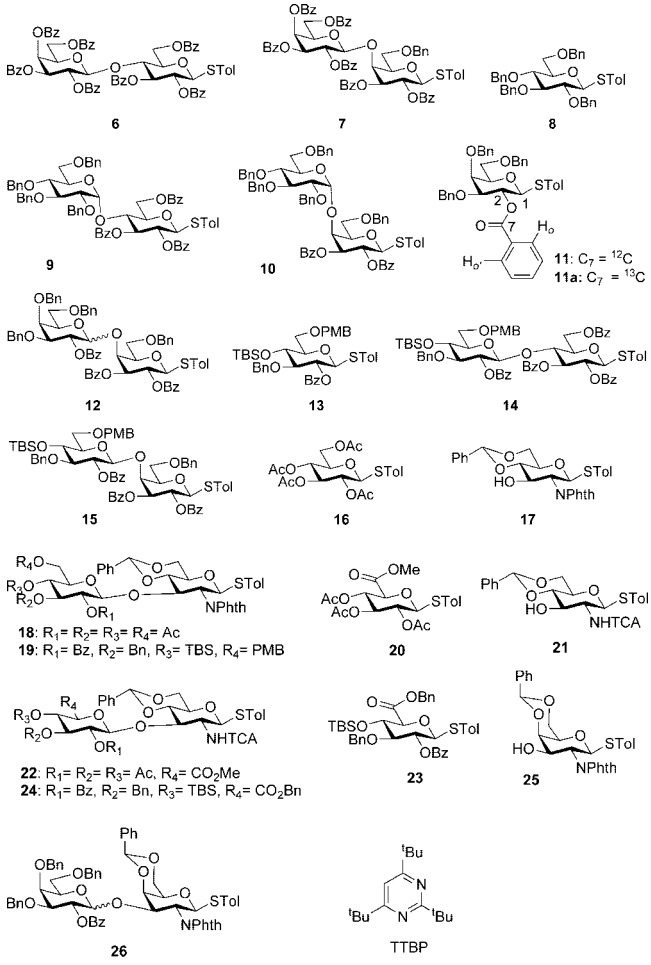
acceptors **3** and **4** gave the corresponding disaccharides **9** and **10** smoothly in good yields following the identical reaction protocol (Table 1, entries 3 and 4).[11] The contrasting outcome in these glycosylations using the same acceptor can be due to two possible factors: (1) with donor **8**, α-glycoside product is predominantly formed, whereas donor **5** would favor the *β*-product due to neighboring group participation; and (2) electronic properties of the two glycosyl donors are quite different with donor **8** bearing multiple electron-donating protective groups and donor **5** containing electron-withdrawing protective groups only. These two factors correspond to an inherent α/*β* facial selectivity at the TS for **5** and **8** (Figure 1a) or an inherently lower transition state (TS) energy in reaction coordinates of **8** versus **5** (Figure 1b).



To better differentiate the factors governing the glycosylation, donor **11**[20] was prepared, which bears multiple electron-donating groups and a participating protective group at O-2. After preactivation by *p*-TolSCl/AgOTf, donor **11** successfully glycosylated acceptor **4** producing disaccharide **12***β* in 48% yield (Table 1, entry 5), suggesting that facial selectivity is not the dominating factor for determining the donor's ability to react with **4**. The identity of the sugar is not crucial as the electron-rich glucoside donor **13**[8] also smoothly glycosylated acceptors **3** and **4** to give disaccharides **14** and **15** (Table 1, entries 6 and 7). Thus, the observed dichotomy in reaction outcome must be resulting from different electronic properties of the glycosyl donors. To glycosylate unreactive acceptors, donors containing more electron-donating groups are preferred as they inherently possess higher glycosylating activity following the reaction scheme of Figure 1b.

This observation turns out to be quite general and can be extended to a wide range of reactions, which are synthetically useful. Per-acylated thioglucoside **16** failed to react with glucosamine **17**. Replacement of its 3,4,6-tri-*O*-acetyl groups with electron-donating silyl and ether protective groups (donor **13**) renders it an effective donor to glycosylate **17**, producing disaccharide **19** (Table 1, entry 9).[8] Glucuronic acid residues exist in many naturally occurring oligosaccharides. However, due to the presence of the electron-withdrawing carboxylic acid, glucuronic acid thioglycoside derivatives have been rarely used as glycosyl donors.[28−31] Instead, thioglucosides are typically employed, which require oxidation state adjustment after the glycosylation.[28,32] It will be desirable to be able to use protected glucuronic acid derivatives directly as glycosyl donors. However, the electron-poor glucuronic acid donor **20** did not undergo glycosylation with acceptor **21** at all. This problem was solved by using its electron-rich counterpart **23**, which gave hyaluronic acid precursor disaccharide **24** in 73% yield (Table 1, entry 11). The electron-rich thiogalactoside donor **11** also glycosylated the sterically hindered acceptor **25** in good yield (Table 1, entry 12).

There are high interests in acquiring glycosaminoglycans, such as chondroitin and heparin, due to their important biological functions.[33−38] Heparin synthesis requires glycosylation of the 4-OH of a glucosamine acceptor, which is known to be notoriously unreactive.[39] A similar challenge is also present for chondroitin preparation as the 3-hydroxyl group of most galactosamine acceptors is sterically hindered. We envision that the high glycosylating power of donor **13** bestowed by the electron-donating protective groups can overcome the low reactivities of glucosamine and galactosamine acceptors. Moreover, we want to examine whether these syntheses can be performed in a one-pot fashion.

Preactivation of donor **13** by *p*-TolSCl/AgOTf at −60 °C was followed by the addition of acceptor **25** (Scheme 1a). Upon complete consumption of the acceptor, a second acceptor **27**[40] and an additional 1 equiv of the promoter *p*-TolSCl/AgOTf were added to the same reaction flask. Chondroitin precursor trisaccharide **28** was successfully produced from this three-component one-pot synthesis in 67% overall yield within just 5 h. A heparin

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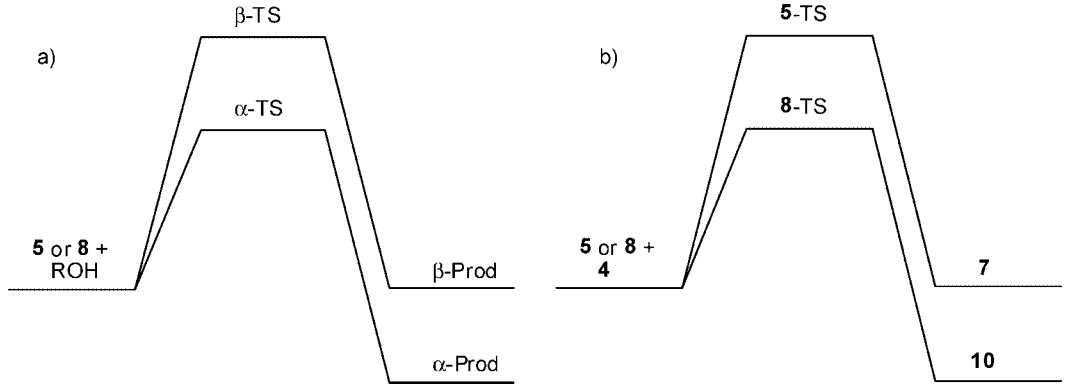


FIGURE 1. Schematic demonstrations of (a) inherent α/β facial selectivity at the TS for **5** and **8** glycosylations with an acceptor and (b) TS energy difference in reaction coordinates of donor **8** versus **5**.

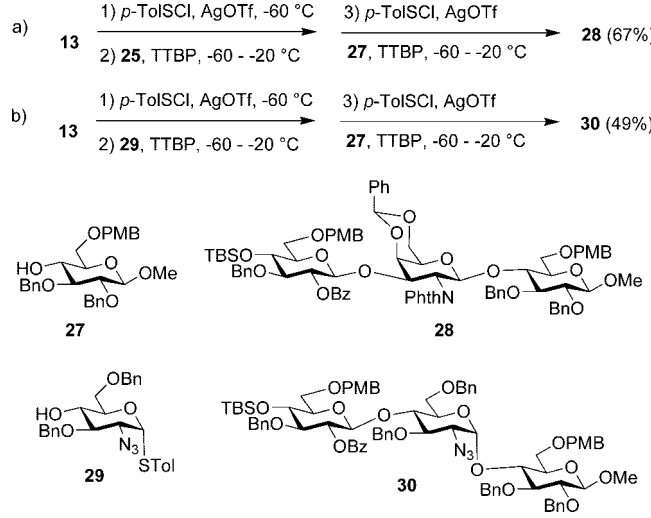
precursor trisaccharide **30** was prepared in a similar manner through sequential reactions of **13**, **29**,[41] and **27** in one pot in 49% yield (Scheme 1b).

Why do the more electron-rich donors have higher glycosylating power? To answer this question, the reactive intermediates formed following preactivation were examined. In general, it is a difficult task to thoroughly characterize the reactive intermediates due to their limited lifetime, especially when donor activation is carried out in the presence of an acceptor. With the preactivation scheme, because the activation and glycosylation are two distinct steps, it will be possible to observe the intermediates at low temperature following preactivation.

Recently, low-temperature NMR has been shown to be a powerful tool to monitor the glycosylation process.[9,14,42−47] Crich and colleagues have carried out ground-breaking work in studying the reactive intermediates of a glycosylation reaction.[47] They demonstrated that in the absence of neighboring group participation, glycosyl triflates, which have characteristic ^{1}H, ^{13}C, and ^{19}F NMR profiles, were the dominant intermediates when several thiophenyl mannosylpyranosides and thiophenyl glucosylpyranosides were preactivated by PhSOTf at low temperatures. The identification of glycosyl triflate was used to rationalize the high β-selectivity in glycosylation of benzylidene-protected mannothiopyranosides. Lowary and co-workers showed that in the activation of a furanosyl sulfoxide, although multiple intermediates existed at −60 °C, glycosyl triflate was the dominant one when the reaction was warmed up to −40 °C. This observation enabled them to modify the operations and enhance the yield and stereoselectivity of their synthesis.[14]

In our glycosylation reaction, upon addition of *p*-TolSCl to a mixture of *p*-tolylthioglycoside donor and AgOTf, *p*-TolSOTf is formed, which electrophilically attacks the anomeric sulfur atom of the donor to generate disulfonium ion **31** (step 1, Scheme 2). The disulfonium ion **31** can further evolve to several possible intermediates prior to the addition of the nucleophilic acceptor (step 2): (1) oxacarbenium ion pair **32**; (2) glycosyl triflate **33** by addition of the triflate anion to the anomeric center; (3) disulfonium ion **34** formed by equilibrating with the *p*-tolyl disulfide side product; and (4) dioxalenium ion **35** in the cases

SCHEME 1



where the donor contains an O-2 acyl participating protective group. Nucleophilic attack of the reactive intermediate(s) by the acceptor will then generate the glycoside product (step 3). Although drawn as free ion pairs, **32**, **34**, and **35** can also possibly exist as either solvent-separated ion pairs or contact ion pairs.

Because the intermediates upon activation of glycosyl donors without 2-O participating neighboring groups have been quite extensively studied,[14,17,47−49] we focused on donors containing O-2 acyl groups in this study. The preactivation of per-O-benzoylated galactose donor **5** was monitored first by NMR. No significant differences in product yields or NMR spectra were observed when the reactions were performed in CD_2Cl_2, $CDCl_3$, CD_2Cl_2/Et_2O-d_{10} (1:1), or $CDCl_3/Et_2O$-d_{10} (1:1). Therefore, all subsequent studies were performed in anhydrous $CDCl_3$. Addition of *p*-TolSCl to a mixture of donor **5** and AgOTf at −60 °C led to rapid dissipation of the characteristic yellow color of *p*-TolSCl within seconds. Inspection of the ^{1}H NMR spectrum revealed that the donor was transformed within a few minutes to one major new carbohydrate species characterized by its anomeric proton signal, a doublet at δ 6.57 ppm with $J_{1,2}$ = 3.2 Hz (Figure 2). No signals around δ 9.5 ppm due to the anomeric proton of the possible oxacarbenium ion **36** were observed.[50]

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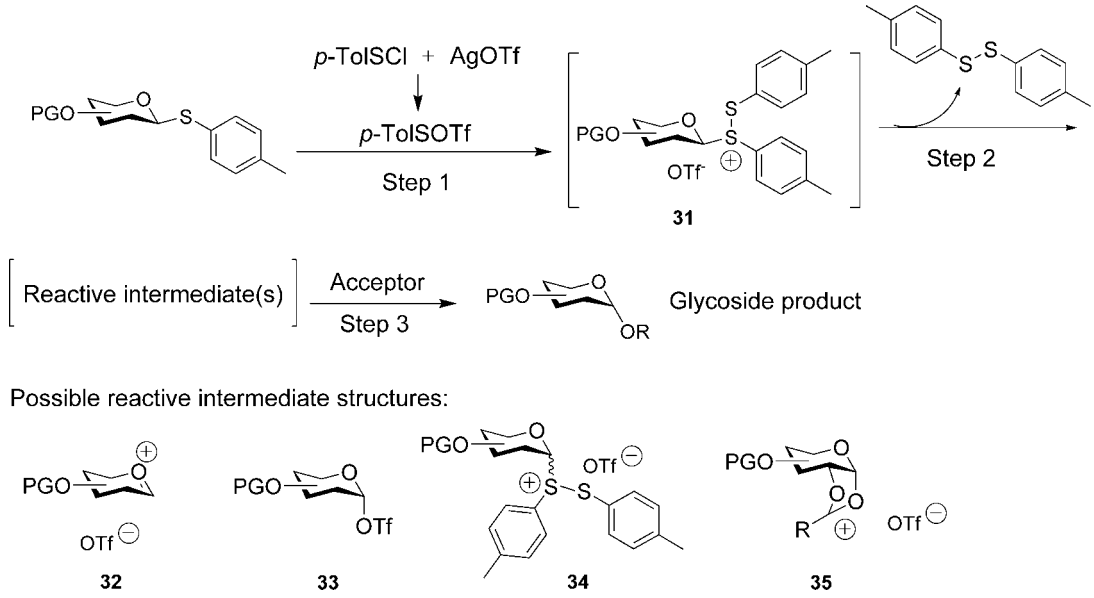
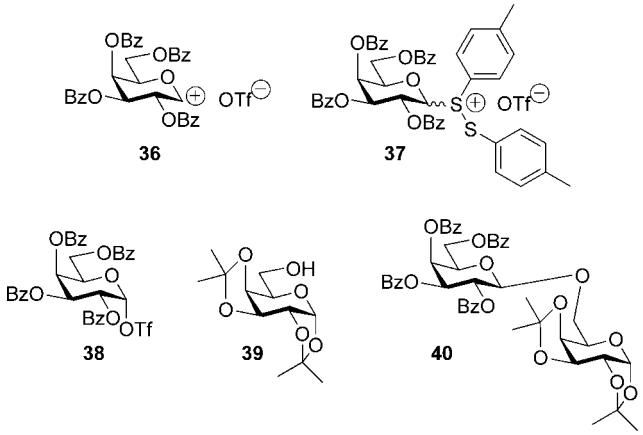
SCHEME 2



The methyl group of the *p*-tolyl moiety after preactivation appeared as a singlet in its ^{1}H NMR spectrum, which was the case for all *p*-tolyl thioglycosides examined. If the glycosyl disulfonium ion **37** were formed, the two *p*-TolS groups would have become nonequivalent, leading to two separate methyl peaks in ^{1}H NMR. This was supported by the fact that the ^{1}H NMR of dimethyl(methylthio)sulfonium triflate (DMTST) exhibits two singlets at 3.27 and 2.92 ppm with the integration ratio of 2:1.[51] Furthermore, in glycosylation of **2** by **8**, addition of exogenous *p*-tolyl disulfide to the reaction did not cause significant changes in either reaction yield or stereoselectivity (data not shown). Thus, the glycosyl disulfonium ion does not play a significant role in the thioglycoside glycosylation but rather a transient function on route to other species.



The ^{13}C NMR spectrum of the activated intermediate from donor **5** at −60 °C corroborated the clean formation of a new carbohydrate species with its anomeric carbon signal resonating at δ 104.4 ppm and four carbonyl carbon signals at δ 166.4, 165.9, 165.8, 165.5 ppm (Figure 2). The chemical shift of the anomeric carbon also excluded the possibility of oxacarbenium ion **36** as the positively charged anomeric carbon in the oxacarbenium ion was expected to appear above 210 ppm[47] through analogy with other sp^2 hybridized alkoxy carbenium ions.[50,52,53] By electrochemical oxidation, Crich, Yoshida, and co-workers generated a series of glycosyl triflates for glucosides, galactosides, and mannosides without participating neighboring groups on O-2. The anomeric protons of these glycosyl triflates appeared around 6.2 ppm and anomeric carbons around 106 ppm.[42] Our NMR data is consistent with the intermediate structure following preactivation of **5** being the α-glycosyl triflate **38**. Prior to the activation, the ^{19}F NMR spectrum showed a single peak at δ −4.2 ppm due to the triflate anion from AgOTf. The corresponding ^{19}F NMR after activation revealed two signals, δ −1.2 and δ −4.2 ppm assigned to glycosyl triflate **38** and excess AgOTf, respectively. The glycosyl triflate **38** was found to be quite stable because no significant changes were observed by NMR when the temperature was raised to −20 °C. The triflate **38** was a competent glycosyl donor with reactive acceptors as the addition of the primary galactoside acceptor **39** to the NMR tube led to the desired disaccharide **40** cleanly. Yet, adding the unreactive acceptor **3** to **38** did not produce any disaccharide **6**. This is consistent with a model that some nucleophilic push is required in order to activate anomeric triflates.

When the more electron-rich donor **11** was preactivated by *p*-TolSCl/AgOTf, one major intermediate was formed along with several minor ones. The ^{1}H NMR of activated donor **11** was considerably broader than that of activated donor **5**, presumably due to residual silver cation complexation with aromatic residues[54] possibly the benzyl protecting groups of **11** (Figure 3). A gCOSY correlation experiment showed that the anomeric proton of the major intermediate had undergone significant downfield shift from 4.98 ppm in donor **11** to 7.34 ppm, while H-2 shifted slightly to 5.77 ppm (Supporting Information, Figure S1). To better probe this intermediate by ^{13}C NMR, a ^{13}C-labeled benzoyl group was introduced onto O-2 of the galactoside (donor

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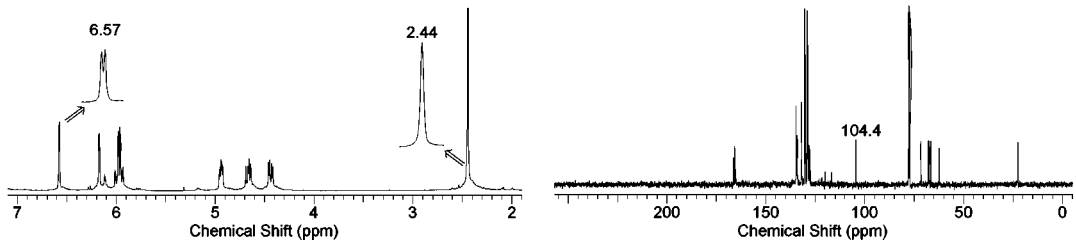


FIGURE 2. ^{1}H NMR and ^{13}C NMR spectra of the intermediate formed after preactivation of donor **5** in $CDCl_3$ at −60 °C.

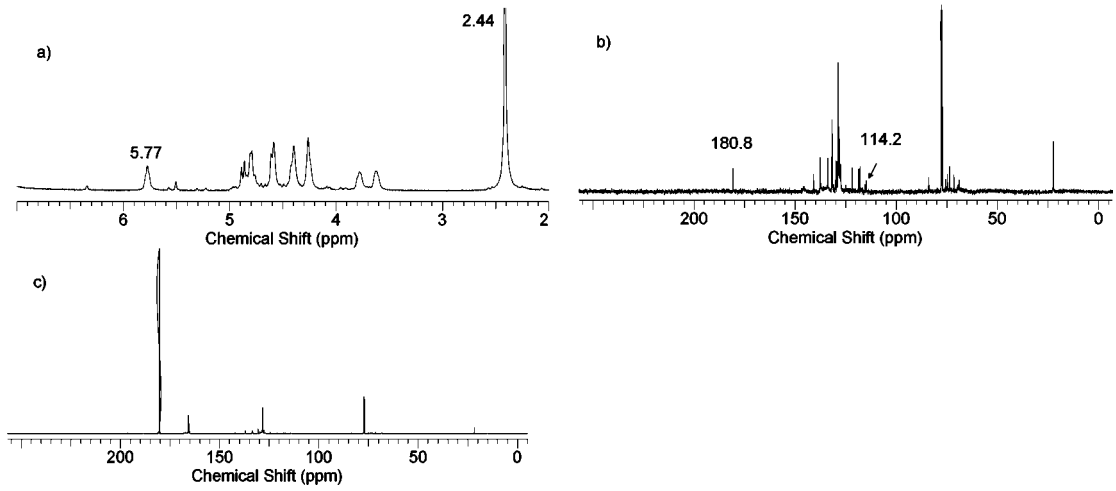
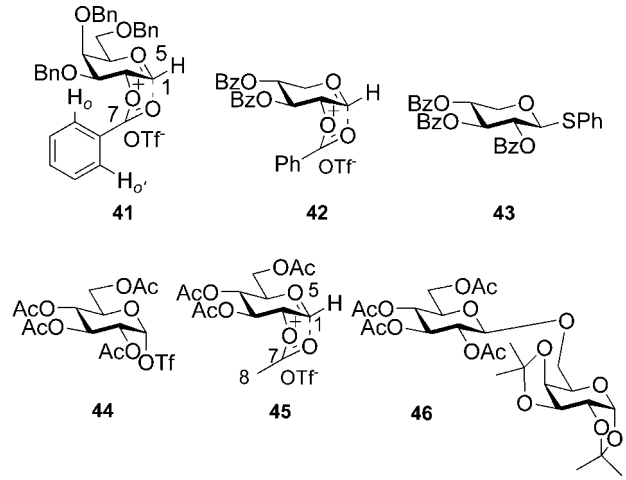


FIGURE 3. (a) ^{1}H NMR and (b) ^{13}C NMR spectra of the intermediates formed after preactivation of donor **11**; (c) ^{13}C NMR after preactivation of donor **11a** in $CDCl_3$ at −60 °C.

11a), which showed a chemical shift of 165.5 ppm by ^{13}C NMR. An HMBC spectrum of the ^{13}C labeled donor **11a** displayed correlations between the ^{13}C 165.5 ppm peak and protons at 8.02 ppm (H_o, $H_{o'}$protons of the Bz phenyl ring) and 5.66 ppm (H-2) with no correlations with the anomeric proton at 4.98 ppm (Supporting Information, Figure S2a). Upon activation, a strong new resonance at δ 180.8 ppm appeared in the ^{13}C NMR with the concomitant decrease of the resonance at δ 165.5 ppm (Figure 3c). For this new carbon signal, in addition to its HMBC correlations with ^{1}H NMR signals at 8.02 ppm (H_o, $H_{o'}$) and 5.77 ppm (H-2), a new correlation with the H-1 proton signal at 7.34 ppm was observed (Supporting Information, Figure S2b). These correlations strongly suggest the bridging dioxalenium ion **41** formed through participation by the neighboring O-2 benzoyl group. The chemical shift of 180.8 ppm for the bridging carbon in **41** was similar to the value of 180.3 ppm observed for the dioxalenium ion **42** formed from xyloside **43**.[55] The HSQC spectrum of **41** indicated that the anomeric carbon was also downfield shifted to 114.2 ppm (Supporting Information, Figure S3). The positive charge of the dioxalenium ion **41** could be distributed over O-5, C-1, O-1 and C-7, explaining the significant downfield shift of H-1, C-1 and C-7. By quantum mechanical calculation the LUMO of dioxalenium ions has been shown to be a vacant *p*-like orbital centered on C-7 in agreement with these observations.[56] Compared with the glycosyl triflate **38**, the dioxalenium ion **41** was less stable with decomposition setting in when the temperature was raised to above −30 °C.

Interestingly, preactivation of the tetra-*O*-acetyl glucose **16** converted it into two reactive intermediates in roughly 1:1 ratio



at −60 °C (Figure 4a,b). Based on the resonances at δ 6.21 ppm ($J_{1,2}$ = 2.4 Hz) and δ 104.1 ppm of the anomeric proton and carbon atoms, the first intermediate was assigned to be the α-glycosyl triflate **44**. The second intermediate has ^{13}C NMR resonances at δ 191.7, 113.3 ppm for C-7 and C-1, and ^{1}H NMR resonances at δ 7.35 and 2.82 ppm for H-1 and H-8 of the dioxalenium ion **45**. The glycosyl triflate **44** and dioxalenium ion **45** were shown to interconvert by warming the mixture to −20 °C, which led to the disappearance of **45** (Figure 4c,d) with it reappearing upon recooling to −60 °C. Addition of the primary galactoside acceptor **39** to the preactivated donor **16** at −60 °C generated disaccharide **46** in 85% yield with both the glycosyl triflate **44** and the dioxalenium ion **45** consumed at comparable rates.

Why do donors **5**, **11**, and **16** form different intermediates following preactivation? This can be explained by the fact that

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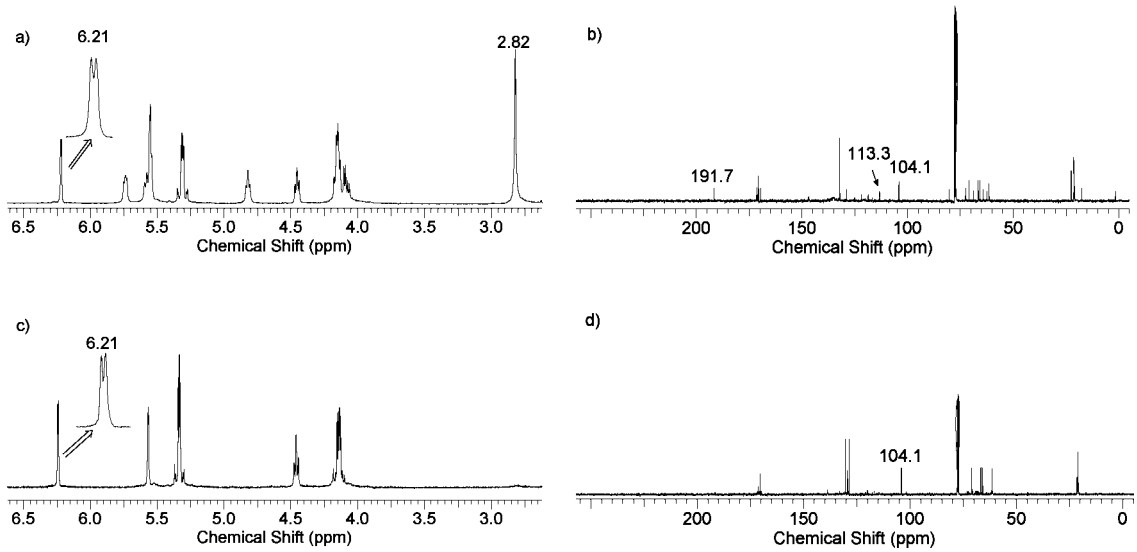

FIGURE 4. (a) ^{1}H NMR and (b) ^{13}C NMR spectra of the intermediates formed after preactivation of donor **16** in $CDCl_3$ at −60 °C; (c) ^{1}H NMR and (d) ^{13}C NMR spectra after warming to −20 °C.

SCHEME 3. Competitive Glycosylation of Acceptor 39 by a Mixture of Donors 5 and 11

there are more electron-withdrawing protecting groups (Bz is more deactivating than Ac) on the glycan ring of donors **5**, which greatly disfavor the formation of positively charged dioxalenium ions. On the other hand, the presence of multiple electron-donating benzyl groups on **41** stabilizes the positive charge sufficiently, rendering it unnecessary for the covalent attachment of the poor nucleophile triflate anion. The tetraacetyl glucoside **16** presents the intermediate case between donors **5** and **11**, leading to a mixture of glycosyl triflate and dioxalenium ion upon preactivation. Crich and co-workers reported the dioxalenium ion **42** as the major intermediate when they activated the per-benzoylated thioxyloside **43**.[55] As xylose is a pentose, it contains one fewer highly electron-withdrawing group on the sugar ring,[57,58] which is likely the reason why the dioxalenium ion **42** was formed as the major intermediate.

It is known that donor **11** is more reactive than donor **5** toward a thiophilic promoter.[24] Wong and co-workers quantified relative reactivity values of a wide range of thiotolyl donors by having two different donors competing with a limiting amount of promoter in the presence of excess acceptor. Donor **11** was found to react with a promoter about 800 times faster than donor **5**,[24] which mostly reflected the internal free energy difference between the reactants and the activated intermediate (steps 1 and 2 for the glycosylation process). In contrast, preactivation of a mixture of donors **11** and **5** completely converted both donors into reactive intermediates, thus removing the rate difference in reaction with the promoter. Upon addition of 1 equiv of galactoside **39** to a preactivated mixture of 1 equiv of donor **5** and 1 equiv of donor **11** at −60 °C, disaccharide **40** and **47** were isolated in a 1: 2.9 ratio with a combined yield of 90% based on the amount of the acceptor added, suggesting the activated intermediates from donor **11** were 2.9 times more reactive than that from donor **5** (Scheme 3). When the reactivity of the acceptor decreased, the reaction became more selective as donor **5** failed to glycosylate acceptor **4** while donor **11** gave disaccharide **12** in 56% yield. Since the glycosyl triflate **38** is more stable than the dioxalenium ion **41**, the different glycosylation outcome using donors **5** and **11** is not due to decomposition of the activated intermediate. The higher reactivity of dioxalenium ion **41** can be resulting from the lower free energy difference between **41** and the corresponding oxacarbenium ion like TS during nucleophilic attack of the acceptor (step 3) due to the higher electron density of the glycan ring and better stabilization of the TS. At the mean time, anomeric triflates may require some additional activation, which is dependent on the electron-donating potential of the protecting groups of the donor. Possible mild activators include residual Ag^{+} ions or the protonated base. In the absence of such promoters the reaction temperature needs to be raised to activate the anomeric triflates toward unreactive acceptors.

A TS connecting the dioxalenium ion derived from the reaction of methanol with 2-*O*-acetyl-3,4,6-tri-*O*-methyl-D-glucopyranosyl oxacarbenium ion has been found by quantum mechanical calculations.[59] This TS is only 12.9 kJ mol^{-1} above the complex between methanol and the dioxalenium ion and is initiated by C-2—O-2 bond rotation. The ease of C-2—O-2 bond

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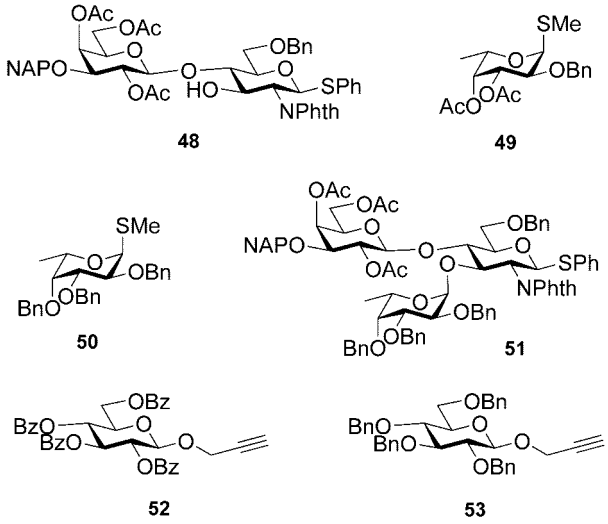
rotation is expected to depend on the protecting groups of the donor. This TS is also stabilized by intramolecular H-bonding from the hydroxylic proton to electronegative oxygens of the donor. Such H-bonding is reasonably expected to be sensitive to the steric accessibility of the hydroxyl and the electronegativity of the donor's H-bonding acceptor oxygen. It was further postulated that in the absence of intramolecular H-bonding, species like the counterions such as triflate or others such as added bases, molecular sieves, etc. could act as the proton acceptor.

Although we primarily focused on the preactivation strategy using thioglycosides, there have been reports that electron-rich glycosyl donors possessing higher glycosylation power in other glycosylation protocols and other glycosyl building blocks.[60−63] Matta and co-workers discovered that while fucosylation of the hindered disaccharide **48** failed with donor **49**, mixing the more electron-rich counterpart (donor **50**) with **48** under the in situ anomerization protocol led to trisaccharide **51** in high yield.[63] Similarly, substituting the electron-withdrawing benzoyl groups on a per-*O*-benzoylated propargyl glycoside donor (donor **52**) with benzyl groups (donor **53**) transformed the failed glycosylation with donor **52** to one with 68% yield.[62] Therefore, we propose that when a glycosylation reaction fails to yield the desired glycoside product, the installation of electron-donating protective groups onto glycosyl donors can be explored in order to enhance the glycosylation yield. However, cautions need to be taken as the more electron-rich donors become less stable after activation, and thus the usage of lower reaction temperature is preferred for this type of reactions.



Conclusions

We have investigated the intermediate structures following preactivation of several representative thioglycosyl donors bearing 2-O acyl groups by low-temperature NMR. It was found that glycosyl triflates were the major intermediates formed for donors bearing multiple electron-withdrawing groups, while with the electron-rich donors the dioxalenium ions were produced. We demonstrated that the introduction of electron-donating groups onto glycosyl donors can overcome the low reactivities of glycosyl acceptors using the preactivation protocol. This can be applied to one-pot synthesis leading to chondroitin and heparin trisaccharide precursors in high yields. It should be emphasized that the high reactivity bestowed by electron-donating groups in our study is observed in the glycosylating step, rather than in the selective donor activation step encountered in the armed-disarmed strategy. The installation of electron-donating protective groups onto glycosyl donors may be a general strategy to enhance the glycosylation yield, especially for difficult glycosylation reactions with unreactive acceptors.

Experimental Section

General Procedure for Single-Step Preactivation-Based Glycosylation. A solution of donor (0.060 mmol), AgOTf (0.18 mmol), and freshly activated molecular sieve MS 4 Å (200 mg) in diethyl ether/CH_2Cl_2 (v:v = 2:2 mL), CH_2Cl_2 (3 mL), or $CDCl_3$ (3 mL) was stirred at room temperature for 30 min and cooled to −60 °C. After 5 min, orange colored *p*-TolSCl (9.5 μL, 0.060 mmol) was added through a microsyringe. Since the reaction temperature was lower than the freezing point of *p*-TolSCl, *p*-TolSCl was added directly into the reaction mixture to prevent it from freezing on the flask wall. The characteristic yellow color of *p*-TolSCl in the reaction solution dissipated rapidly within a few seconds, indicating depletion of *p*-TolSCl. After the donor was completely consumed according to TLC analysis (less than 5 min at −60 °C), a solution of acceptor (0.054 mmol) and TTBP (1 equiv) in CH_2Cl_2 (0.2 mL) was slowly added dropwise via a syringe. The reaction mixture was warmed to −20 °C under stirring in 2 h. Then the mixture was diluted with CH_2Cl_2 (20 mL) and filtered over Celite. The Celite was further washed with CH_2Cl_2 until no organic compounds were observed in the filtrate by TLC. All CH_2Cl_2 solutions were combined and washed twice with saturated aqueous solution of $NaHCO_3$ (20 mL) and twice with water (10 mL). The organic layer was collected and dried over Na_2SO_4. After removal of the solvent, the desired disaccharide was purified from the reaction mixture via silica gel flash chromatography.

General Procedure for Monitoring Preactivation by NMR. Reactions were carried out in NMR tubes with anhydrous $CDCl_3$ at −60 °C. The donor (1.0 equiv) and AgOTf (3.0 equiv) were added to an NMR tube and dried in vacuo for 3 h. $CDCl_3$ (0.75 mL) was added slowly at −60 °C. Then the donor was preactivated by the addition of *p*-TolSCl (1.0 equiv) at −60 °C and the ^{1}H, ^{13}C, ^{19}F, and 2D NMR were acquired. Chemical shifts are downfield from tetramethylsilane for ^{1}H and ^{13}C NMR and from 1% trifluoroacetic acid in $CDCl_3$ for ^{19}F NMR.

***p*-Tolyl 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-galactopyranoside (11).** Compound **11** was synthesized following the literature procedure.[16] $[\alpha]_D^{20}$ +34.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03−6.90 (m, 24 H, CO*Ph*, S*Ph*Me, 3 CH_2*Ph*), 5.66 (t, 1 H, $J_{2,1} = J_{2,3} = 9.6$ Hz, H-2), 4.98 (d, 1 H, $J = 12.0$ Hz, C*H*HPh), 4.70 (d, 1 H, $J_{1,2} = 9.6$ Hz, H-1), 4.64−4.44 (m, 4 H, CH*H*Ph, 2 CH_2Ph), 4.03 (d, 1 H, $J_{4,5} = 3.0$ Hz, H-4), 3.70−3.65 (m, 4 H, H-3, H-5, H-6$_a$, H-6$_b$), 2.27 (s, 3 H, SPh*Me*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.5 (1 C, 1 *C*OPh), 138.7, 138.1, 137.9, 137.8, 133.2, 132.9, 130.4, 130.1, 130.0, 129.7, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.7 (CH_2*Ph*, CO*Ph*, S*Ph*Me, some signals overlapped), 87.5 (1 C, $J_{C\text{-}1,H\text{-}1} = 166.3$ Hz, C-1), 81.4, 77.9, 74.6, 73.9, 72.9, 72.0, 70.7, 69.0, (C-2∼6, 3 *C*H$_2$Ph), 21.4 (1 C, SPh*Me*). ESI-MS $[M + Na]^+$ calcd for $C_{41}H_{40}NaO_6S$ 683.2, found 683.2.

***p*-Tolyl 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-α,β-D-galactopyranosyl-(1→4)-2,3-di-*O*-benzoyl-6-*O*-benzyl-1-thio-β-D-galactopyranoside (12α and 12β).** Donor **11** (25 mg, 37.8 μmol, 1.0 equiv) and AgOTf (29.9 mg, 113.5 μmol, 3.0 equiv) were placed in an NMR tube and dried in vacuo for 3 h. $CDCl_3$ (0.75 mL) was added slowly at −60 °C. Then the donor was preactivated by the addition of

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(63) Xia, J.; Alderfer, J. L.; Locke, R. D.; Piskorz, C. F.; Matta, K. L. *J. Org. Chem.* **2003**, *68*, 2752–2759.

p-TolSCl (6.0 μL, 37.8 μmol, 1.0 equiv) at −60 °C. After ^{1}H, ^{13}C, ^{19}F, and 2D NMR were acquired at −60 °C, a solution of the acceptor **4** (20.0 mg, 34.2 μmol, 0.9 equiv) and TTBP (9.0 mg, 37.8 μmol, 1.0 equiv) in $CDCl_3$ (0.25 mL) was added to the NMR tube. The reaction mixture was gradually warmed up to rt in 3 h. The reaction mixture was quenched by Et_3N and filtered through Celite. The filtrate was concentrated and purified by flash column chromatography (toluene/hexanes/ethyl acetate = 10:10:1) to give **12α** (6.0 mg, 5.0 μmol, 8%) and **12*β*** (37.0 mg, 33 μmol, 48%). For α-isomer **12α**: $[\alpha]_D^{20}$ +44.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23−7.00 (m, 34 H, 2 CO*Ph*, S*Ph*Me, 4 CH_2*Ph*), 5.77 (t, 1 H, $J_{2,1} = J_{2,3} = 9.6$ Hz, H-2), 5.70 (dd, 1 H, $J_{2',1'} = 3.2$ Hz, $J_{2',3'} = 8.4$ Hz, H-2′), 5.24 (dd, 1 H, $J_{3,2} = 9.6$ Hz, $J_{3,4} = 2.4$ Hz, H-3), 5.20 (d, 1 H, $J_{1',2'} = 3.2$ Hz, H-1′), 4.84 (d, 1 H, $J =$ 11.2 Hz, C*H*HPh), 4.83 (d, 1 H, $J_{1,2} = 9.6$ Hz, H-1), 4.70−4.44 (m, 4 H, CH*H*Ph, CH_2Ph), 4.30−3.77 (m, 8 H, H-4, H-5, H-6$_a$,H-6$_b$, 2 CH_2Ph), 3.60−3.33 (m, 2 H, H-3′, H-6′$_a$), 3.33 (dd, 1 H, $J_{6'b,5'} = J_{6'b,6'a} = 8.8$ Hz, H-6′$_b$), 2.80 (dd, 1 H, $J_{5',6'b} = 5.2$ Hz, $J_{5',6'a} =$ 8.8 Hz, H-5′), 2.17 (s, 3 H, SPh*Me*); HRMS $[M + Na]^+$ calcd for $C_{68}H_{64}NaO_{13}S$ 1143.3965, found 1143.3972. For *β*-isomer **12*β***: $[\alpha]_D^{20}$ +57.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10−6.90 (m, 34 H, 2 CO*Ph*, S*Ph*Me, 4 CH_2*Ph*), 5.64 (dd, 1 H, $J_{2',1'} = 7.8$ Hz, $J_{2',3'} = 9.6$ Hz, H-2′), 5.48 (t, 1 H, $J_{2,1} = J_{2,3} = 9.6$ Hz, H-2), 5.38 (dd, 1 H, $J_{3,2} = 9.6$ Hz, $J_{3,4} = 2.4$ Hz, H-3), 4.98 (d, 1 H, $J =$ 11.8 Hz, C*H*HPh), 4.79 (d, 1 H, $J_{1,2} = 9.6$ Hz, H-1), 4.71 (d, 1 H, $J_{1',2'} = 7.8$ Hz, H-1′), 4.60 (d, 1 H, $J =$ 12.6 Hz, C*H*HPh), 4.57 (d, 1 H, $J =$ 12.0 Hz, C*H*HPh), 4.55 (d, 1 H, $J =$ 12.0 Hz, CH*H*Ph), 4.50 (d, 1 H, $J =$ 11.8 Hz, CH*H*Ph), 4.45−4.41 (m, 2 H, H-4, CH*H*Ph), 4.26 (s, 1 H, CH_2Ph), 3.92−3.73 (m, 3 H, H-4′, H-5, H-6$_a$, H-6$_b$), 3.55 (dd, 1 H, $J_{6'a,5'} = J_{6'a,6'b} = 8.4$ Hz, H-6′$_a$), 3.43 (dd, 1 H, $J_{3',2'} = 9.6$ Hz, $J_{3',4'} = 2.4$ Hz, H-3′), 3.32 (dd, 1 H, $J_{6'b,5'} = 5.4$ Hz, $J_{6'b,6'a} = 8.4$ Hz, H-6′$_b$), 3.26 (dd, 1 H, $J_{5',\ 6'b} = 5.4$ Hz, $J_{5',6'a} = 8.4$ Hz, H-5′), 2.21 (s, 3 H, SPh*Me*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.0, 165.8, 164.7 (3 C, 3 *C*OPh), 138.8, 138.7, 137.9, 137.9, 133.6, 133.1, 132.8, 132.7, 130.8, 130.3, 130.0, 129.9, 129.7, 129.3, 129.2, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, (CH_2*Ph*, CO*Ph*, S*Ph*Me, some signals overlapped), 101.0 (1 C, $J_{C\text{-}1,H\text{-}1} = 165.3$ Hz, C-1), 87.0 (1 C, $J_{C\text{-}1',H\text{-}1'} = 162.4$ Hz, C-1′), 80.5, 78.4, 75.7, 74.8, 73.8, 73.7, 72.8, 72.2, 72.1, 71.9, 70.0, 68.7, 68.3, (C-2−6, 4 *C*H_2Ph, some signals overlapped), 21.3 (1 C, SPh*Me*). HRMS $[M + H]^+$ calcd for $C_{68}H_{65}O_{13}S$ 1121.4146, found 1121.4130.

***p*-Tolyl 2-*O*-Benzoyl-3-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-6-*O*-*p*-methoxylbenzyl-*β*-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-1-thio-*β*-D-glucopyranoside (14).** Compound **14** (60 mg, 74%) was prepared according to the general procedure for glycosylation using donor **13** (50 mg, 69.9 μmol, 1.0 equiv) and acceptor **3** (37.7 mg, 63.0 μmol) and purified by flash column chromatography (hexanes/ethyl acetate = 4:1). $[\alpha]_D^{20}$ +61.3° (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10−6.70 (m, 33 H, 4 CO*Ph*, S*Ph*Me, CH_2*Ph*, CH_2*Ph*OMe), 5.52 (t, 1 H, $J_{2,1} = J_{2,3} = 9.6$ Hz, H-2), 5.38 (dd, 1 H, $J_{3,2} = 9.6$ Hz, $J_{3,4} = 3.0$ Hz, H-3), 5.35 (dd, 1 H, $J_{2',1'} = J_{2',3'} = 8.4$ Hz, H-2′), 4.81 (d, 1 H, $J_{1,2} = 9.6$ Hz, H-1), 4.74 (d, 1 H, $J_{1',2'} = 7.8$ Hz, H-1′), 4.72 (dd, 1 H, $J_{6a,5} = 3.0$ Hz, $J_{6a,6b} = 12.6$ Hz, H-6a), 4.69 (d, 1 H, $J =$ 11.4 Hz, C*H*HPh), 4.62 (dd, 1 H, $J_{6b,5} =$ 8.4 hz, $J_{6a,6b} = 12.6$ Hz, H-6b), 4.60 (d, 1 H, $J =$ 11.4 Hz, CH*H*Ph), 4.52 (d, 1 H, $J_{4,3} = 3.0$ Hz, H-4), 4.47 (d, 1 H, $J =$ 11.4 Hz, C*H*HPhOMe), 4.35 (d, 1 H, $J =$ 11.4 Hz, CH*H*PhOMe), 4.08 (dd, 1 H, $J_{5,6a} = 3.0$ Hz, $J_{5,6b} = 8.4$ Hz, H-5), 3.72−3.62 (m, 4 H, H-4′, CH_2PhO*Me*), 3.61 (dd, 1 H, $J_{6'a,5'} = 1.8$ Hz, $J_{6'a,6'b} = 10.2$ Hz, H-6′a), 3.53 (dd, 1 H, $J_{3',2'} = J_{3,4} = 8.4$ Hz, H-3′), 3.50 (dd, 1 H, $J_{6'b,5'} = 6.0$ Hz, $J_{6'a,6'b} = 10.2$ Hz, H-6′b), 3.33 (ddd, 1 H, $J_{5',4'} = 7.8$ Hz, $J_{5',6'a} = 1.8$ Hz, $J_{5',6'b} = 6.0$ Hz, H-5′), 2.19 (s, 3 H, SPh*Me*), 0.76 (s, 9 H, *tert*-butyl), −0.05 (s, 3 H, *Me*), −0.10 (s, 3 H, *Me*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.5, 166.0, 165.6, 164.8 (4 C, *C*OPh), 159.3, 138.1, 137.8, 133.6, 133.3, 133.2, 133.1, 132.4, 130.4, 130.2, 130.1, 130.0, 129.9, 129.8, 129.7, 129.6, 129.1, 128.7, 128.6, 128.5, 128.4, 128.3, 127.7, 127.5, 114.0, (CH_2*Ph-C*, CH_2*Ph*OMe, S*Ph*Me, some signals overlapped), 100.9 (1 C, $J_{C\text{-}1',H\text{-}1'} = 165.4$ Hz, C-1′), 87.5 (1 C, $J_{C\text{-}1,H\text{-}1} = 163.6$ Hz, C-1), 76.6, 76.5, 75.2, 74.8, 74.3, 73.3, 73.2, 71.2, 69.2, 68.5, 65.4 (12 C, C-2−6, *C*H_2Ph, *C*H_2PhOMe, some signals overlapped), 55.4 (1 C, CH_2PhO*Me*), 26.1, 21.4, 18,2 (5 C, SPh*Me*, *C*(Me)$_3$, C(*Me*)$_3$, some signals overlapped), −3.64, −4.63 (2 C, Si*Me*). ESI-MS $[M + Na]^+$ calcd for $C_{68}H_{72}O_{15}NaSSi$ 1211.4, found 1211.4. HRMS $[M + Na]^+$ calcd for $C_{68}H_{72}O_{15}NaSSi$ 1211.4259, found 1211.4252.

***p*-Tolyl 2-*O*-Benzoyl-3-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-6-*O*-*p*-methoxylbenzyl-*β*-D-glucopyranosyl-(1→4)-2,3-di-*O*-benzoyl-6-*O*-benzyl-1-thio-*β*-D-galactopyranoside (15).** Compound **15** (32 mg, 26.5 μmol, 70%) was prepared according to the general procedure for glycosylation using donor **13** (31 mg, 43.4 μmol, 1.0 equiv) and acceptor **4** (20.0 mg, 34.2 μmol, 0.9 equiv) and purified by flash column chromatography (hexanes/ethyl acetate = 4:1). $[\alpha]_D^{20}$ +69.3° (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00−6.80 (m, 33 H, 3 CO*Ph*, S*Ph*Me, 2 CH_2*Ph*, CH_2*Ph*OMe), 5.47 (dd, 1 H, $J_{2,1} = J_{2,3} = 9.6$ Hz, H-2), 5.37 (dd, 1 H, $J_{3,2} = 9.6$ Hz, $J_{3,4} = 3.0$ Hz, H-3), 5.28 (dd, 1 H, $J_{2',1'} = 7.8$ Hz, $J_{2',3'} = 8.4$ Hz, H-2′), 4.80 (d, 1 H, $J_{1,2} = 9.6$ Hz, H-1), 4.79 (d, 1 H, $J_{1',2'} =$ 7.8 Hz, H-1′), 4.66 (d, 1 H, $J =$ 10.8 Hz, C*H*HPh), 4.56 (d, 1 H, $J =$ 10.8 Hz, CH*H*Ph), 4.52 (d, 1 H, $J =$ 11.4 Hz, C*H*HPh), 4.47−4.45 (m, 2 H, CH*H*Ph, H-4), 4.41 (d, 1 H, $J =$ 12.0 Hz, C*H*HPh), 4.29 (d, 1 H, $J =$ 12.0 Hz, CH*H*Ph), 3.90−3.83 (m, 3 H, H-5, H-6$_a$,H-6$_b$), 3.75−3.71 (m, 4 H, H-4′, CH_2PhO*Me*), 3.54−3.21 (m, 4 H, H-3′, H-6′$_a$, H-6′$_b$, H-5′), 2.21 (s, 3 H, SPh*Me*), 0.77 (s, 9 H, *tert-butyl*), −0.07 (s, 3 H, *Me*), −0.12 (s, 3 H, *Me*); ^{13}C NMR(150 MHz, $CDCl_3$) δ 165.9, 165.7, 164.8 (3 C, *C*OPh), 159.4, 138.8, 138.1, 137.8, 133.3, 133.1, 132.8, 130.4, 130.2, 130.1, 129.9, 129.8, 129.3, 129.2, 128.6, 128.5, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 114.0, (CH_2*Ph-C*, CH_2*Ph*OMe, S*Ph*Me, some signals overlapped), 103.8 (1 C, $J_{C\text{-}1',H\text{-}1'} = 166.0$ Hz, C-1′), 87.2 (1 C, $J_{C\text{-}1,H\text{-}1} = 159.0$ Hz, C-1), 83.4, 78.7, 76.6, 75.6, 74.7, 74.3, 73.7, 73.2, 72.8, 71.0, 70.9, 69.1, 68.7, 68.2, 66.7 (13C, C-2∼6, 2 *C*H_2Ph, *C*H_2PhOMe, some signals overlapped), 55.5 (1 C, CH_2PhO*Me*), 26.1, 26.1, 21.3, 18,5 (5 C, SPh*Me*, *C*(Me)$_3$, C(*Me*)$_3$, some signals overlapped), −3.66, −4.67 (2 C, Si*Me*); HRMS $[M + Na]^+$ calcd for $C_{68}H_{74}O_{14}NaSSi$ 1197.4466, found 1197.4451.

***p*-Tolyl (Benzyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-*β*-D-glucopyranosyluronate)-(1→3)-4,6-*O*-benzylidene-2-(2,2,2-trichloroacetylamino)-2-deoxy-1-thio-*β*-D-glucopyranoside (24).** Compound **24** was synthesized from donor **23** and acceptor **21** in 73% yield following the general procedure of single step glycosylation and purified by flash column chromatography (hexanes/ethyl acetate = 3:1). $[\alpha]_D^{20}$ + 11.2 (*c* 1, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87−7.85 (m, 2H, aromatic), 7.52−7.49 (m, 1H, aromatic), 7.36−7.25 (m, 9H, aromatic), 7.16−7.08 (m, 6H, aromatic), 6.93−6.89 (m, 1H, aromatic), 5.30 (s, 1H, CHPh), 5.27 (d, 1H, $J_{1,2} = 10.2$ Hz, H-1), 5.17−5.10 (m, 3H, CH_2Ph, H-2′), 4.99 (d, 1H, $J_{1',2'} = 7.2$ Hz, H-1′), 4.64−4.56 (m, 2H, CH_2Ph), 4.52 (t, 1H, $J = 9.6$ Hz, H-4′), 4.29−4.26 (m, 1H, H-6a), 4.15−4.12 (m, 1H, H-4′), 3.80 (d, 1H, $J_{4',5'} = 6.0$ Hz, H-5′), 3.67−3.63 (m, 2H, H-4, H-6b), 3.52−3.47 (m, 2H, H-2, H-5), 3.27−3.25 (m, 1H, H-3′), 2.34 (s, 3H, $SPhCH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.3, 165.1, 161.5, 139.0, 137.6, 137.0, 135.0, 133.9, 133.2, 130.0, 129.8, 129.4, 129.1, 128.7, 128.6, 128.3 (x2), 128.1, 127.5, 127.4, 127.0, 126.2, 101.5, 98.8, 84.2, 81.0, 79.9, 77.3, 76.2, 74.0, 71.2, 70.5, 67.2, 57.2, 25.7, 21.2, 17.8, −4.5, −5.3; ESI-MS $[M + Na]^+$ calcd for $C_{55}H_{60}Cl_3NNaO_{12}SSi$ 1114.3, found 1114.6; HRMS $[M + Na]^+$ calcd for $C_{55}H_{60}Cl_3NNaO_{12}SSi$ 1114.2569, found 1114.2573; gHMQC (without ^{1}H decoupling): $^1J_{C1,H1} = 161.9$ Hz, $^1J_{C1',H1'} = 164.6$ Hz.

p*-Tolyl 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-*β*-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-*N*-phthalimido-1-thio-*β*-D-galactopyranoside (26).** Compound **26** was synthesized from donor **11** and acceptor **25** in 65% yield (51% *β* + 14% α) following the general procedure of single step glycosylation. $[\alpha]_D^{20}$ +33.6 (*c* 1, CH_2Cl_2); **26*β ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70−7.68 (m, 2H), 7.56−7.55 (m, 1H), 7.50−7.42 (m, 4H, aromatic), 7.36−7.16 (m, 19H, aromatic), 7.12−7.10 (m, 1H, aromatic), 7.04−6.95 (m, 6H, aromatic), 5.53−5.50 (m, 1H), 5.52 (d, 1H, $J_{1,2} = 7.8$ Hz, H-1), 5.28 (s, 1H, CHPh), 4.93 (d, 1H, $J = 12$ Hz), 4.80−4.78 (m, 1H),

4.66 (d, 1H, $J_{1',2'}$ = 8.4 Hz, H-1′), 4.62−4.56 (m, 2H), 4.50 (d, 1H, J = 12 Hz), 4.43−4.42 (m, 1H), 4.33−4.23 (m, 4H), 3.90−3.88 (m, 2H), 3.54 (s, 1H), 3.46−3.42 (m, 3H), 3.05−3.03 (m, 1H), 2.26 (s, 3H, SPhCH$_3$); ^{13}C NMR (150 MHz, CDCl$_3$) δ 168.9, 166.9, 165.3, 138.8, 138.1, 138.0, 137.6, 134.1, 133.9, 133.6, 133.0, 131.9, 131.7, 129.9, 129.8, 129.6, 128.8, 128.7, 128.5 (× 2), 128.4, 128.1 (×3), 127.9, 127.8, 127.7 (×2), 127.6, 126.8, 123.7, 122.9, 101.3, 100.4, 82.9, 80.3, 75.1, 74.4, 73.6 (×2), 73.2, 72.1, 71.7, 71.4, 70.4, 69.5, 68.2, 50.7, 21.4; ESI-MS [M + Na]$^+$ calcd for $C_{62}H_{57}NNaO_{12}S$ 1063.3, found 1063.2; HRMS [M + NH$_4$]$^+$ calcd for $C_{62}H_{61}N_2O_{12}S$ 1057.3945, found 1057.3933; gHMQC (without ^{1}H decoupling): $^1J_{C1,H1}$ = 161.1 Hz, $^1J_{C1',H1'}$ = 159.3 Hz.

Methyl 2-*O*-Benzoyl-3-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-6-*O*-*p*-methoxybenzyl-*β*-D-glucopyranosyl-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-*N*-phthalimido-*β*-D-galactopyranosyl-(1→4)-2,3-di-*O*-benzyl-6-*O*-*p*-methoxybenzyl-*β*-D-glucopyranoside (28). Compound **28** was synthesized by a three-component one-pot synthesis procedure. After the donor **13** (50 mg, 69.93 μmol) and activated molecular sieve MS 4 Å (500 mg) were stirred for 30 min at room temperature in CH_2Cl_2 (5 mL), the solution was cooled to −60 °C, followed by addition of AgOTf (54 mg, 209 μmol) in Et$_2$O (1.5 mL). The mixture was stirred for 5 min at −60 °C, and then *p*-TolSCl (11.1 μL, 69.9 μmol) was added to the solution. (See the general procedure for single-step preactivation-based glycosylation for precautions.) The mixture was vigorously stirred for 10 min, followed by addition of a solution of building block **25** (28.2 mg, 56.0 μmol) and TTBP (17.4 mg, 69.9 μmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 2 h from −60 to −20 °C and then the mixture was cooled down to −60 °C, followed by sequential addition of AgOTf (18 mg, 69.9 μmol) in Et$_2$O (1 mL), acceptor **27** (20.8 mg, 42.0 μmol), and TTBP (17.4 mg, 69.9 μmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 5 min at −60 °C and then *p*-TolSCl (8.9 μL, 56.0 μmol) was added into the solution, and the reaction mixture was stirred for 2 h from −60 to −20 °C. The reaction was quenched with Et$_3$N (50 μL), concentrated under vacuum to dryness. The resulting residue was diluted with CH_2Cl_2 (20 mL), followed by filtration. The organic phase was washed with saturated aqueous NaHCO$_3$ and H$_2$O and then dried over Na$_2$SO$_4$, filtered, and concentrated. Silica gel column chromatography (3:1:1 hexanes/ethyl acetate/CH_2Cl_2) afforded **28** as a white solid (41.2 mg, 67%). Mp 82−84 °C; $[\alpha]_D^{20}$ +30.4 (*c* 1, CH_2Cl_2); ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.50−7.34 (m, 7H. aromatic), 7.31−7.16 (m, 16H, aromatic), 7.12−7.00 (m, 8H, aromatic), 6.92−6.90 (m, 2H, aromatic), 6.83−6.79 (m, 4H, aromatic), 5.40 (s, 1H, CHPh), 5.30 (d, 1H, J = 8.4 Hz), 5.12 (t, 1H, J = 7.8 Hz), 5.02 (d, 1H, J = 11.4 Hz), 4.85 (d, 1H, J = 12 Hz), 4.76 (d, 1H, J = 11.4 Hz), 4.70 (d, 1H, J = 7.2 Hz), 4.66−4.64 (m, 1H), 4.60−4.57 (m, 2H), 4.46−4.32 (m, 5H), 4.10 (d, 1H, J = 7.8 Hz), 4.09−4.07 (m, 1H), 3.99−3.97 (m, 1H), 3.78−3.76 (m, 7H), 3.65−3.64 (m, 1H), 3.59−3.55 (m, 2H), 3.53−3.46 (m, 3H), 3.43−3.37 (m, 4H), 3.32−3.28 (m, 3H), 3.14−3.10 (m, 2H), 2.96 (s, 1H), 0.78 (s, 9H, (CH$_3$)$_3$CSi), −0.11(s, 3H, CH$_3$Si), −0.15 (s, 3H, CH$_3$Si); ^{13}C NMR (150 MHz, CDCl$_3$) δ 169.4, 167.3, 164.4, 159.5, 159.1, 139.6, 138.7, 138.3, 137.8, 133.8, 133.6, 132.7, 131.4, 131.2, 130.7, 130.2, 129.6 (×2), 129.1, 128.7, 128.4 (×2), 128.3, 128.2 (×2), 128.1, 127.7, 127.5, 127.3 (×2), 127.1, 126.7, 123.4, 122.6, 114.0, 113.7, 104.5, 101.8, 100.7, 98.5, 83.6, 83.3, 82.3, 76.5, 76.3, 76.0, 75.1, 74.9, 74.8, 74.7, 74.3, 74.1, 73.3, 72.4, 71.3, 70.0, 69.0, 68.2, 67.0, 57.1, 55.5 (×2), 52.5, 26.1, 18.1, −3.7, −4.5; HRMS [M + Na]$^+$ calcd for $C_{84}H_{93}NNaO_{20}Si$ 1486.5958, found 1486.5946; gHMQC (without ^{1}H decoupling): $^1J_{C1,H1}$ = 159.3 Hz, 162.2 Hz, 162.2 Hz.

Methyl 2-*O*-Benzoyl-3-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-6-*O*-*p*-methoxybenzyl-*β*-D-glucopyranosyl-(1→4)-2-azido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-benzyl-6-*O*-*p*-methoxybenzyl-*β*-D-glucopyranoside (30). Compound **30** was synthesized by a three-component one-pot procedure. After the donor **13** (50 mg, 69.93 μmol) and activated molecular sieve MS 4 Å (500 mg) were stirred for 30 min at room temperature in CH_2Cl_2 (5 mL), the solution was cooled to −60 °C, followed by addition of AgOTf (54 mg, 209 μmol) in Et$_2$O (1.5 mL). The mixture was stirred for 5 min at −60 °C and then *p*-TolSCl (11.1 μL, 69.9 μmol) was added into the solution. (See the general procedure for single-step preactivation-based glycosylation for precautions.) The mixture was vigorously stirred for 10 min, followed by addition of a solution of acceptor **29** (32.7 mg, 66.4 μmol) and TTBP (17.4 mg, 69.9 μmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 2 h from −60 to −20 °C, and then the mixture was cooled down to −60 °C, followed by sequential addition of AgOTf (18 mg, 69.9 μmol) in Et$_2$O (1 mL), acceptor **27** (27.7 mg, 55.9 μmol), and TTBP (17.4 mg, 69.9 μmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 5 min at −60 °C, then *p*-TolSCl (10.5 μL, 66.4 μmol) was added to the solution, and the reaction mixture was stirred for 2 h from −60 to −20 °C. The reaction was quenched with Et$_3$N (50 μL) and concentrated under vacuum to dryness. The resulting residue was diluted with CH_2Cl_2 (20 mL), followed by filtration. The organic phase was washed with saturated aqueous NaHCO$_3$ and H$_2$O and then dried over Na$_2$SO$_4$, filtered, and concentrated. Silica gel column chromatography (5:1:1 hexanes/ethyl acetate/CH_2Cl_2) afforded **30** as a gel (39.7 mg, 49%). $[\alpha]_D^{20}$ +34.3 (*c* 1, CH_2Cl_2); ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.77−7.75 (m, 2H, aromatic), 7.44−7.20 (m, 21H, aromatic), 7.12−7.06 (m, 9H, aromatic), 6.98−6.97 (m, 2H, aromatic), 6.84−6.82 (m, 2H, aromatic), 6.77−6.76 (m, 2H, aromatic), 5.66 (d, 1H, J = 4.2 Hz), 5.19 (t, 1H, J = 8.4 Hz), 5.13 (d, 1H, J = 11.4 Hz), 5.00 (d, 1H, J = 10.2 Hz), 4.89 (d, 1H, J = 11.4 Hz), 4.75−4.59 (m, 6H), 4.47−4.42 (m, 3H), 4.24 (d, 1H, J = 7.8 Hz),4.11 (d, 1H, J = 12 Hz), 4.02−3.95 (m, 3H), 3.87−3.84 (m, 1H), 3.79−3.61 (m, 9H), 3.60−3.58 (m, 1H), 3.51−3.50 (m, 4H), 3.41−3.25 (m, 8H), 3.12−3.06 (m, 2H), 3.43−3.37 (m, 4H), 3.32−3.28 (m, 3H), 3.14−3.10 (m, 2H), 2.96 (s, 1H), 0.87 (s, 9H, (CH$_3$)$_3$CSi), −0.02(s, 3H, CH$_3$Si), −0.04 (s, 3H, CH$_3$Si). ^{13}C NMR (150 MHz, CDCl$_3$) δ 164.7, 158.9, 158.8, 138.7, 138.3 (×2), 137.8, 137.7, 133.2, 130.6, 130.2, 129.5 (×2), 129.0, 128.9 (×2), 128.7, 128.4 (×2), 128.3 (×3), 128.2, 128.0 (×2), 127.7, 127.6, 127.5 (×2), 127.4, 127.3, 113.6, 113.4, 104.5, 99.7, 97.3, 84.9, 83.1, 82.6, 77.5, 76.8, 75.6, 75.1 (×2), 75.0, 74.5 (×2), 74.0, 73.7, 73.0, 72.4, 72.3, 71.3, 70.8, 69.0, 68.3, 66.8, 62.4, 57.0, 55.2 (×2), 25.9 (×2), 17.9, −3.8, −4.7; HRMS [M + Na]$^+$ calcd for $C_{83}H_{97}N_3NaO_{18}Si$ 1474.6434; obsd 1474.6414; gHMQC (without ^{1}H decoupling): $^1J_{C1',H1'}$ = 172.6 Hz, other two $^1J_{C1,H1}$ = 160.2 Hz, 162.8 Hz.

2,3,4,6-Tetra-*O*-benzoyl-α-D-galactopyranosyl Triflate (38). Compound **38** was obtained according to the general procedure. ^{1}H NMR (400 MHz, CDCl$_3$, −60 °C) δ 8.12−7.20 (m, 28 H, 4 CO*Ph*, (S*Ph*Me)$_2$), 6.57 (d, 1 H, $J_{1,2}$ = 3.2 Hz, H-1), 6.17 (d, 1 H, $J_{1,2}$ = 2.0 Hz, H-4), 6.11−5.80 (m, 2 H, H-2, H-3), 4.94 (dd, 1 H, $J_{5,6a}$ = 8.0 Hz, $J_{5,6b}$ = 5.2 Hz, H-5), 4.66 (dd, 1 H, $J_{6a,5}$ = 8.0 Hz, $J_{6a,6b}$ = 11.6 Hz, H-6a), 4.43 (dd, 1 H, $J_{6b,5}$ = 5.2 Hz, $J_{6b,6a}$ = 11.6 Hz, H-6b), 2.44 (s, 6 H, (SPh*Me*)$_2$);^{13}C NMR (100 MHz, CDCl$_3$, −60 °C) δ 166.4, 165.8, 165.8, 165.5 (4 C, *C*OPh), 134.7, 134.3, 134.2, 131.9, 130.4, 130.3, 130.2, 130.0, 129.3, 129.2, 129.0, 128.9, 128.8, 128.3, 128.2, 127.7 (CO*Ph-C*, (S*Ph*Me)$_2$, some signals overlapped), 104.4 (1 C, C-1), 71.6, 67.7, 67.4, 66.7, 62.4 (5C, C-2−6), 22.4 (2 C, (SPh*Me*)$_2$).

2,3,4,6-Tetra-*O*-benzoyl-*β*-D-galactopyranosyl-(1→6)-1,2:3,4-di-isopropylidene-α-D-galactopyranoside (40). Donor **5** (31 mg, 44.1 μmol, 1.0 equiv) and AgOTf (33.9 mg, 132.3 μmol, 3.0 equiv) were added to an NMR tube and dried in vacuo for 3 h. CDCl$_3$ (0.75 mL) was added slowly at −60 °C. Then the donor was preactivated by the addition of *p*-TolSCl (7.1 μL, 44.1 μmol, 1.0 equiv) at −60 °C and ^{1}H, ^{13}C, ^{19}F, and 2D NMR were acquired at −60 °C. This was followed by the addition of acceptor **39** (10.3 mg, 39.7 μmol, 0.9 equiv) and TTBP (11.0 mg, 44.1 μmol, 1.0 equiv) as acid scavenger in CDCl$_3$ (0.25 mL). The reaction mixture was quenched by Et$_3$N, and purified by flash column chromatograph (hexanes/ethyl acetate = 4:1) to give **40** (29.9 mg, 35.7 μmol, 90%) as a colorless syrup. $[\alpha]_D^{20}$ +37.4° (*c* 1.0, CHCl$_3$); ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.07−7.20 (m, 20 H, 4 CO*Ph*), 5.83 (d, 1 H, $J_{4',3'}$

= 3.6 Hz, H-4′), 5.80 (dd, 1 H, $J_{2',1'}$ = 7.8 Hz, $J_{2',3'}$ = 10.8 Hz, H-2′), 5.60 (dd, 1 H, $J_{3',2'}$ = 10.8 Hz, $J_{3',4'}$ = 3.6 Hz, H-3′), 5.40 (d, 1 H, $J_{1,2}$ = 3.2 Hz, H-1), 5.01 (d, 1 H, $J_{1',2'}$ = 7.8 Hz, H-1′), 4.67 (dd, 1 H, $J_{6a',5'}$ = 5.4 Hz, $J_{6a',6b'}$ = 11.4 Hz, H-6'a), 4.42−3.38 (m, 2 H, H-5′, H-6'b), 4.33 (t, 1 H, $J_{3,2} = J_{3,4}$ = 6.6 Hz, H-3), 4.20 (dd, 1 H, $J_{2,1}$ = 3.2 Hz, $J_{2,3}$ = 6.6 Hz, H-2), 4.06 (dd, 1 H, $J_{6a,5}$ = 7.2 Hz, $J_{6a,6b}$ = 10.8 Hz, H-6a), 3.95−3.70 (m, 2 H, H-5, H-6b), 1.38 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3, 165.8, 165.7, 165.5 (4 C, 4 *C*OPh), 133.8, 133.5, 133.3, 130.3, 130.2, 130.0, 129.6, 129.2, 129.0, 128.8, 128.7, 128.5, (CO*Ph-C*, some signals overlapped), 109.4 (1 C, *C*$(CH_3)_2$), 108.7 (1 C, *C*$(CH_3)_2$), 101.9 (1 C, $J_{C\text{-}1',H\text{-}1'}$ = 165.4 Hz, C-1′), 96.4 (1 C, $J_{C\text{-}1,H\text{-}1}$ = 176.1 Hz, C-1), 72.0, 71.5, 71.2, 70.7, 70.5, 69.9, 68.6, 68.4, 67.7, 62.3 (C-2−6, some signals overlapped), 26.1, 25.9, 25.1, 24.4 (4 C, 2 C(*C*H_3)$_2$); ESI-MS $[M + Na]^+$ calcd for $C_{46}H_{46}NaO_{15}$ 861.3, found 861.2; HRMS $[M + NH_4]^+$ calcd for $C_{46}H_{50}NO_{15}$ 856.3180, found 856.3162.

3,4,6-Tri-*O*-benzyl-D-galactopyranosyl Benzoxonium Ion (41). Compound **41** was obtained according to the general experimental procedure. ^{1}H NMR (400 MHz, $CDCl_3$, −60 °C) δ 8.10−7.24 (m, 29 H, H-1, 3 CH_2*Ph*, C*Ph*, (S*Ph*Me)$_2$), 5.77 (bs, 1 H, H-2), 4.89−4.67 (m, 3 H, 2 C*H*HPh, CH*H*Ph), 4.62−4.58 (m, 2 H, CH*H*Ph, H-5), 4.42−4.34 (m, 2 H, C*H*HPh, H-3), 4.30−4.20 (m, 2 H, CH*H*Ph, H-4), 3.79−3.76 (1 H, H-6a), 3.64−3.58 (1 H, H-6b), 2.44 (s, 6 H, (SPh*Me*)$_2$);^{13}C NMR (100 MHz, $CDCl_3$, −60 °C) δ 180.8 (1 C, C-7), 140.9, 137.7, 137.5, 133.9, 131.8, 131.0, 130.3, 130.0, 129.4, 128.8, 128.7, 128.5, 128.3, 128.1, 127.5, 125.0, 121.8, 118.6, 118.0 (C*Ph-C*, CH_2*Ph*, (S*Ph*Me)$_2$, some signals overlapped), 114.2 (1 C, C-1), 83.9 (1 C, C-2), 75.6, 74.8, 73.6, 71.6, 69.0 (7 C, C-3−6, *C*H_2Ph), 22.4 (1 C, (SPh*Me*)$_2$).

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl Triflate (44) and 3,4,6-Tri-*O*-acetyl-D-glucopyranosyl Acetoxonium Ion (45). The mixture of intermediates **44** and **45** was obtained following the general experimental procedure. For the mixture of **44** and **45** in 1:1 ratio: ^{1}H NMR (400 MHz, $CDCl_3$, −60 °C) δ 7.41−7.24 (m, 9 H, H-1, 2 (S*Ph*Me)$_2$), 6.21 (d, 1 H, $J_{1,2}$ = 2.4 Hz, H-1 from **44**), 5.73 (1 H, H-3 from **45**), 5.57 (3 H, H-2 from **45**, H-3 from **44**, H-4 from **45**), 5.31 (2 H, H-2 from **44**, H-4 from **44**), 4.82 (1 H, H-5 from **45**), 4.44 (1 H, H-5 from **44**), 4.14 (4 H, 2 H-6 from **44**, 2 H-6 from **45**), 2.82 (3 H, CCH_3 from **45**), 2.44 (s, 12 H, 2 (SPh*Me*)$_2$), 2.19, 2.15, 2.14, 2.09, 2.07, 2.03 (21 H, 7 COCH_3); ^{13}C NMR (100 MHz, $CDCl_3$, −60 °C) δ 191.7 (1 C, C-7 from **45**), 171.4, 171.3, 170.8, 170.8, 170.7, 170.5, 169.6 (7 C, 4 *C*OCH_3 from **44** and 3 *C*OCH_3 from **45**), 132.2, 128.8, 121.9, 118.7 ((S*Ph*Me)$_2$, some signals overlapped), 113.3 (1 C, C-1 from **45**), 104.1 (1 C, C-1 from **44**), 80.3, 72.5, 70.9, 68.9, 66.7, 66.6, 65.8, 64.2, 62.5, 61.5 (12 C, C-2∼6, some signals overlapped), 22.5, 21.4, 21,4, 21.3, 21.2, 21.0, 17.6 (9 C, 7 CO*C*H_3, *C*CH_3, (SPh*Me*)$_2$, some signals overlapped). For **44**: ^{1}H NMR (400 MHz, $CDCl_3$, −20 °C) δ 7.34−7.09 (m, 8 H, H-1, (S*Ph*Me)$_2$), 6.21 (d, 1 H, $J_{1,2}$ = 2.4 Hz, H-1), 5.57 (s, 1 H, H-3), 5.33−5.30 (m, 2 H, H-2, H-4), 4.46−4.41 (m, 1 H, H-5), 4.18−4.10 (m, 4 H, 2 H-6), 2.44 (s, 6 H, (SPh*Me*)$_2$), 2.18, 2.15, 2.14, 2.07, 2.03 (s, 12 H, 4 COCH_3); ^{13}C NMR (100 MHz, $CDCl_3$, −20 °C) δ 171.3, 170.5, 170.5,170.5 (4 C, 4 *C*OCH_3), 130.4, 129.4, 128.7, 118.7 ((S*Ph*Me)$_2$, some signals overlapped), 104.1 (1 C, C-1), 71.0, 66.8, 66.7, 65.9, 61.4 (5 C, C-2−6), 21.6, 21,3, 21.2, 21.1, 21.0 (5 C, (5 C, 5 CO*C*H_3, (SPh*Me*)$_2$).

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-diisopropylidene-α-D-galactopyranoside (46). Donor **16** (20.0 mg, 44.0 μmol, 1.0 equiv) and AgOTf (33.9 mg, 132.0 μmol, 3.0 equiv) were added to an NMR tube and dried under in vacuo for 3 h. $CDCl_3$ (0.75 mL) was added slowly at −60 °C. Then the donor was preactivated by addition of the *p*-TolSCl (7.0 μL, 44.0 μmol, 1.0 equiv) at −60 °C, and the ^{1}H, ^{13}C, ^{19}F, and 2D NMR spectra were acquired. This was followed by addition of the acceptor **39** (10.3 mg, 39.7 μmol, 0.9 equiv) and TTBP (10.9 mg, 44.0 μmol, 1.0 equiv) as acid scavenger in $CDCl_3$ (0.25 mL). After reaching −20 °C, the reaction mixture was quenched by Et_3N and purified by flash column chromatograph (hexanes/ethyl acetate = 3:1) to give **46** (20.0 mg, 33.7 μmol, 85.0%) as a white foam. $[\alpha]_D^{20}$ −50.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.47 (d, 1 H, $J_{1,2}$ = 4.8 Hz, H-1), 5.35 (d, 1 H, $J_{4,3}$ = 3.0 Hz, H-4), 5.18 (dd, 1 H, $J_{2',1'}$ = 8.4 Hz, $J_{2',3'}$ = 10.2 Hz, H-2′), 4.98 (dd, 1 H, $J_{3',2'}$ = 10.8 Hz, $J_{3',4'}$ = 3.0 Hz, H-3′), 4.57−4.54 (m, 2 H, H-1′, H-4′), 4.26 (dd, 1 H, $J_{2,1}$ = 4.8 Hz, $J_{2,3}$ = 2.4 Hz, H-2), 4.15−4.07 (m, 3 H, H-5′, H-6'a, H-6'b), 4.01 (dd, 1 H, $J_{6a,5}$ = 3.0 Hz, $J_{6a,6b}$ = 10.8 Hz, H-6a), 3.91−3.84 (m, 2 H, H-3, H-5), 3.65 (dd, 1 H, $J_{6b,5}$ = 3.0 Hz, $J_{6b,6a}$ = 10.8 Hz, H-6b), 2.11 (s, 3 H, COCH_3), 2.04 (s, 3 H, COCH_3), 2.02 (s, 3 H, COCH_3), 1.95 (s, 3 H, COCH_3), 1.45(s, 3 H, C(CH_3)$_2$), 1.42(s, 3 H, C(CH_3)$_2$), 1.29(s, 3 H, C(CH_3)$_2$), 1.29 (s, 3 H, C(CH_3)$_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 170.5, 170.4, 170.0 (4 C, 4 *C*OCH_3), 109.6, 108.9 (2 C, 2 *C*$(CH_3)_2$), 102.2 (1 C, $J_{C\text{-}1',H\text{-}1'}$ = 167.4 Hz, C-1′), 96.4 (1 C, $J_{C\text{-}1,H\text{-}1}$ = 177.6 Hz, C-1), 71.5, 71.0, 70.8, 70.7, 70.6, 69.8, 68.8, 68.1, 67.2, 61.4 (C-2−6, some signals overlapped), 26.2, 26.1, 25.3, 24.5 (4 C, 2 C(*C*H_3)$_2$), 21.0, 20.9, 20.9, 20.8 (4 C, 4 CO*C*H_3). ESI-MS $[M + Na]^+$ calcd for $C_{26}H_{38}NaO_{15}$ 613.2, found 613.3; HRMS $[M + Na]^+$ calcd for $C_{26}H_{38}NaO_{15}$ 613.2108, found 613.2114.

2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→6)-1,2:3,4-diisopropylidene-α-D-galactopyranoside (47). $[\alpha]_D^{20}$ −19.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05−7.11 (m 20 H, CO*Ph*, 3 CH_2*Ph*), 5.64 (dd, 1 H, $J_{2',1'}$ = 7.8 Hz, $J_{2',3'}$ = 10.2 Hz, H-2′), 5.37 (d, 1 H, $J_{1,2}$ = 4.8 Hz, H-1), 4.98 (d, 1 H, *J* = 12.0 Hz, C*H*HPh), 4.66−4.60 (3 H, H-1′, CH*H*Ph, C*H*HPh), 4.50−4.42 (3 H, 2 CH*H*Ph, C*H*HPh), 4.40 (dd, 1 H, $J_{6a',5'}$ = 1.8 Hz, $J_{6a',6b'}$ = 8.4 Hz, H-6a′), 4.16 (dd, 1 H, $J_{2,1}$ = 4.8 Hz, $J_{2,3}$ = 4.8 Hz, H-2), 4.10 (dd, 1 H, $J_{6b',5'}$ = 1.8 Hz, $J_{6b',6a'}$ = 8.4 Hz, H-6b′), 4.01 (d, 1 H, $J_{3',4'}$ = 2.4 Hz, H-4′), 3.96 (dd, 1 H, $J_{6a,5}$ = 4.8 Hz, $J_{6a,6b}$ = 10.8 Hz, H-6a), 3.80−3.50 (m, 6 H, H-3, H-3′, H-4, H-5, H-5′, H-6b), 1.37(s, 3 H, C(CH_3)$_2$), 1.21(s, 3 H, C(CH_3)$_2$), 1.15(s, 3 H, C(CH_3)$_2$), 1.09 (s, 3 H, C(CH_3)$_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 1165.6 (C, *C*OPh), 138.7, 138.1, 137.9, 133.0, 130.5, 130.3, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9 (CH_2*Ph-C*, CO*Ph-C*, some signals overlapped), 109.2, 108.5 (2 C, 2 *C*$(CH_3)_2$), 102.0 (1 C, $J_{C\text{-}1',H\text{-}1'}$ = 164.3 Hz, C-1′), 96.3 (1 C, $J_{C\text{-}1,H\text{-}1}$ = 175.3 Hz, C-1), 80.9, 74.7, 73.8, 72.6, 72.0, 71.9, 71.0, 70.7, 70.6, 68.7, 68.0, 67.9, 67.6 (C-2−6, some signals overlapped), 26.1, 25.8, 25.1, 24.3 (4 C, 2 C(*C*H_3)$_2$); ESI-MS $[M + Na]^+$ calcd for $C_{46}H_{52}NaO_{16}$ 819.3, found 819.4; HRMS $[M + NH_4]^+$ calcd for $C_{46}H_{56}NO_{16}$ 814.3803, found 814.3806.

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Supporting Information Available: General experimental procedures and selected ^{1}H, ^{13}C, ^{19}F, and 2D NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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