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Mechanistic Studies and Methods To Prevent Aglycon Transfer of Thioglycosides

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Abstract: Thioglycosides have been employed extensively for the synthesis of complex oligosaccharides, carbohydrate libraries, and mimetics of *O*-glycosides. While very useful, aglycon transfer is a problematic side reaction with thioglycosides. In this paper, a series of mechanistic studies are described. The aglycon transfer process is shown to affect both armed and disarmed thioglycosides, cause anomerization of the carbon−sulfur bond of a thioglycoside, and destroy the product of a glycosylation reaction. The results indicate that the aglycon transfer process can be a major problem for a wide range of thioglycosides. This side reaction is especially important to consider when carrying out complex reactions such as solid-phase glycosylations, one-pot or orthogonal multicomponent glycosylations, and construction of carbohydrate libraries. To prevent transfer, a number of modified aglycons were examined. The 2,6-dimethylphenyl (DMP) aglycon was found to effectively block transfer in a variety of model studies and glycosylation reactions. The DMP group can be installed in one step from a commercially available thiol (2,6-dimethylthiophenol) and is useable as a glycosyl donor. On the basis of these features, the DMP group is proposed as a convenient and improved aglycon for thioglycosides.

Introduction

Oligosaccharides play important roles in many biological processes such as inflammation, bacterial and viral infection, and protein folding. In addition, carbohydrates are critical components of many natural products and drugs such as erythromycin, vancomycin, and doxorubicin. Unfortunately, carbohydrates and glycosylated natural products can be particularly difficult to obtain from natural sources, especially in homogeneous form. Therefore, chemical synthesis is an important tool for gaining access to these compounds. Furthermore, synthesis allows one to obtain unnatural derivatives which can be useful for studying relationships between structure and function and improving the activity of oligosaccharides and glycosylated drugs. However, synthesis of carbohydrates remains a challenging area of organic chemistry.

Alkyl and aryl thioglycosides are extremely versatile and convenient derivatives for carbohydrate synthesis.[1,2] The sulfide group is easy to install and stable to a wide range of reaction conditions. As a result, it can be incorporated at an early stage and carried through many steps of a synthesis, a feature that permits highly convergent approaches to the synthesis of complex oligosaccharides (Scheme 1). Once a suitable building block has been made, thioglycosides can be readily activated as glycosyl donors. Alternatively, they can be converted into other types of glycosyl donors such as glycosyl halides,[3] sulfoxides,[4] and sulfones.[5] Therefore, one can test a variety of glycosylation methods and conditions via a common synthetic precursor. Not surprisingly, thioglycosides have been used frequently for the synthesis of glycosylated natural products and biologically interesting oligosaccharides,[1,2] solid-phase synthesis of oligosaccharides,[6,7] the construction of carbohydrate libraries,[8,9] and programmable and orthogonal one-pot glycosylations.[10−12] Thioglycosides are also used often as mimetics of *O*-glycosides for the development of glycosyltransferase inhibitors, ligands for lectins, and carbohydrate-based vaccines.[13,14]

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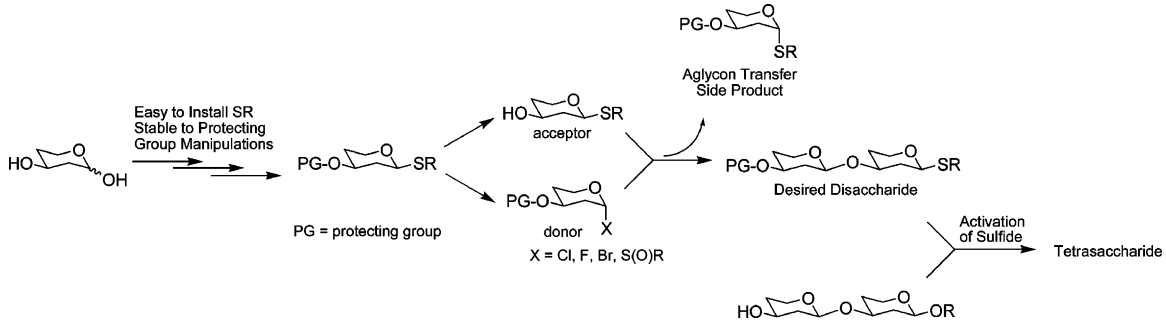
10.1021/ja063247q

Scheme 1. Thioglycosides Are Highly Versatile Carbohydrate Derivatives



While thioglycosides possess many beneficial features, aglycon transfer can be a problematic side reaction. When a glycosyl acceptor possessing a thioglycoside aglycon is reacted with a glycosyl donor, the sulfide group can be transferred from the acceptor to the donor (Scheme 1). Aglycon transfer of thioglycosides has been reported in a number of papers over the last 15 years.[15−28] It can occur with a variety of glycosyl donors using a range of reaction conditions. Unfortunately, the factors that determine whether aglycon transfer will occur for a particular donor/acceptor pair are not well understood, and even small changes to protecting groups or reaction conditions can have a dramatic effect on the outcome of a reaction. Therefore, aglycon transfer has been exceedingly difficult to predict even for experienced carbohydrate chemists. Moreover, the limited understanding of this process has also made it difficult to develop convenient, reliable, and general strategies to block aglycon transfer. Given the prevalence of thioglycosides in carbohydrate chemistry, more detailed information on the mechanism of transfer and factors that affect transfer are necessary.

In this paper, a series of experiments are described which provide new insights into the transfer process. On the basis of our studies, aglycon transfer has the potential to be a problem for nearly any thioglycoside. Consideration of aglycon transfer is especially important for solid-phase oligosaccharide synthesis, construction of carbohydrate libraries, and one-pot glycosylation reactions involving thioglycosides. Finally, a simple and efficient strategy for avoiding transfer was developed and utilized to overcome a problematic glycosylation required for the synthesis of a GalNAcα1−3Gal-linked disaccharide found on human mucins.

Results and Discussion

Our group has been developing a carbohydrate microarray as a new tool for basic and translational cancer research.[29,30] Carbohydrate microarrays contain many different carbohydrate structures immobilized on a solid support in a miniaturized fashion. The unique format is designed for high-throughput evaluation of carbohydrate−macromolecule interactions with a minimal amount of sample. One of the key challenges for the development of a carbohydrate array is obtaining a large set of structurally defined, homogeneous glycans for the array. Since the vast majority of carbohydrates are not readily accessible, our group relies heavily on organic synthesis to acquire them.

Like many other carbohydrate chemists, we employed thioglycosides as key intermediates for the syntheses of glycans. During the construction of a series of structurally related human disaccharide glycans, aglycon transfer became a serious problem. The key step for the synthesis of each disaccharide was formation of the glycosidic linkages (Scheme 2). Coupling of donor **1** with thioglycoside **2** and donor **4** with thioglycoside **5** produced disaccharides **3** and **6** in high yield. However, the related glycosylation between chloride **7** and thioglycoside **8** to form the glycosidic linkage of GalNAcα1−3Gal derivative **9** was completely unsuccessful (Scheme 2). Sulfide **10** was found to be the major side product in the reaction resulting from transfer of the thiophenyl aglycon from acceptor **8** to donor **7**. Equivalent results were obtained with imidate **4**.

The results raised several important questions. First, how did aglycon transfer occur? Second, why did it occur in one reaction and not the others? Finally, how could transfer be avoided in order to complete the synthesis of the mucin glycan?

Mechanism of Transfer and Factors Affecting the Outcome. Aglycon transfer is generally considered to proceed via activation of the glycosyl donor[31] followed by glycosylation of the sulfur atom of the thioglycoside to form sulfonium ion **11** (Scheme 3). The sulfonium ion can break down in several ways.

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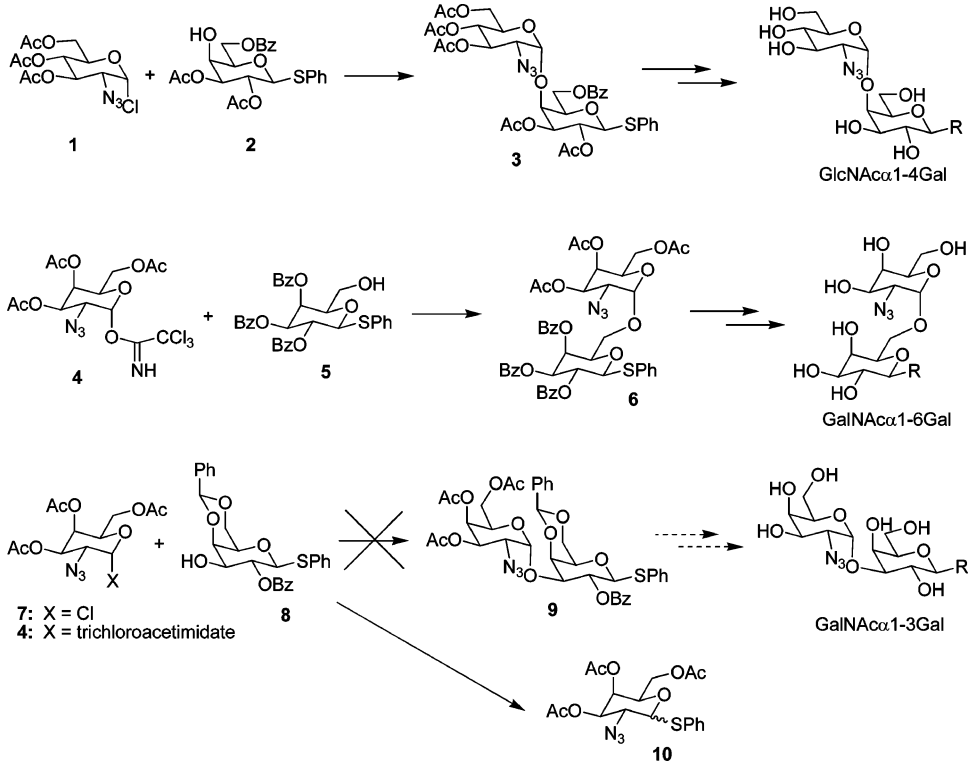
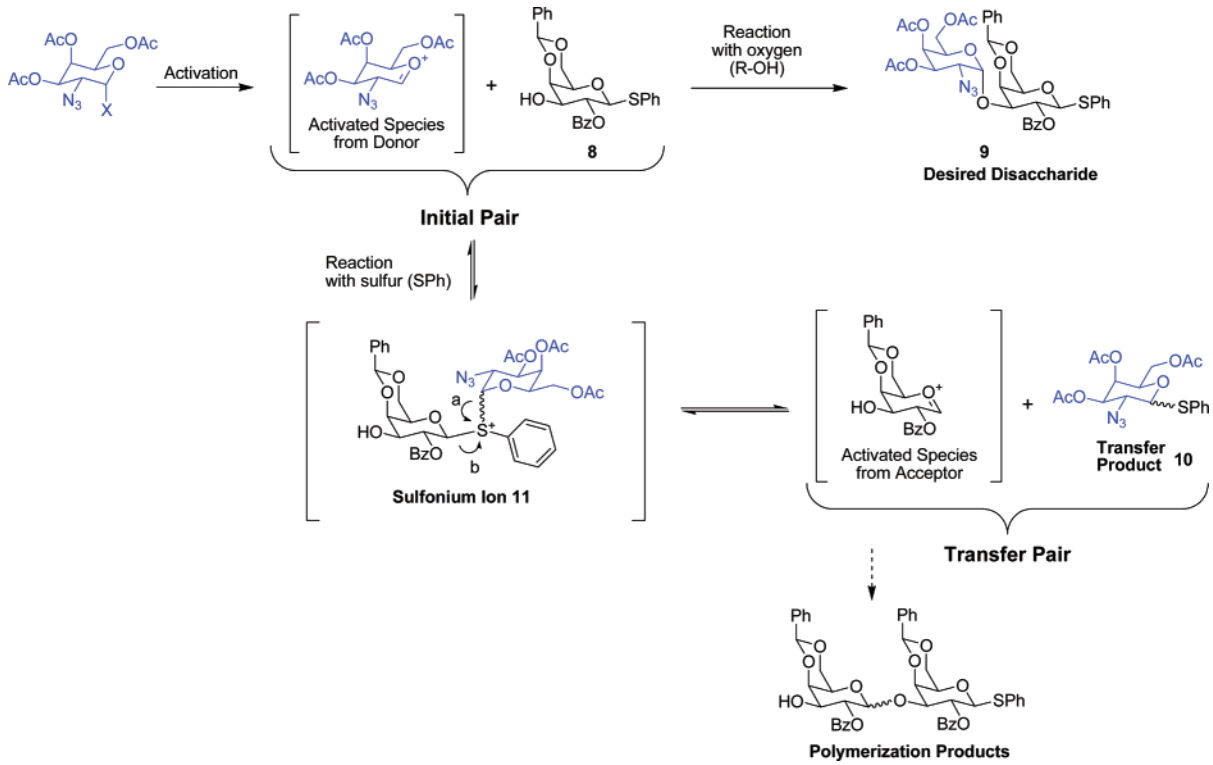
(31) For simplicity, the activated species has been represented as an oxocarbenium ion. However, other activated intermediates such as glycosyl triflates and dioxolenium ions may be present as well.

Scheme 2. Synthesis of Mucin Glycans and Aglycon Transfer



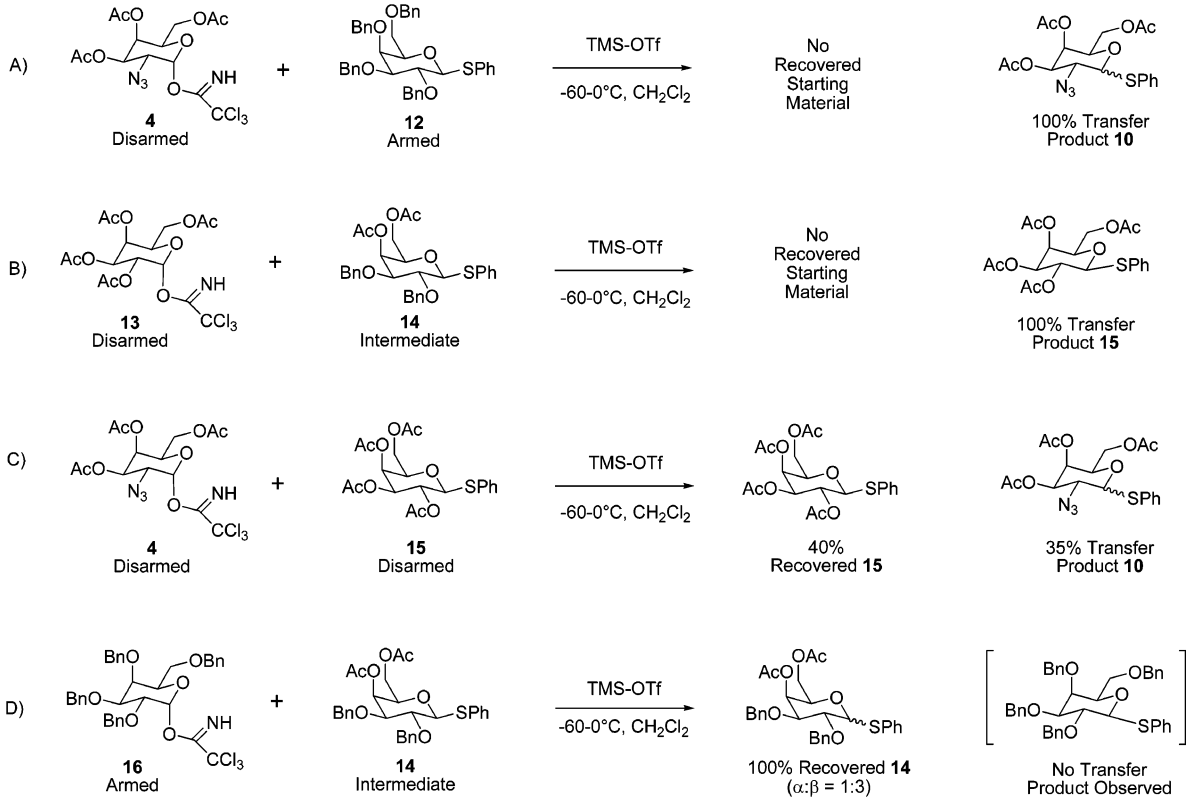
Scheme 3. Mechanism of Aglycon Transfer



Cleavage of the bond between the sulfur atom and the anomeric carbon of the glycosyl donor (arrow a) reforms the original thioglycoside and activated donor (initial reactants). Alternatively, cleavage of the bond between the sulfur atom and the anomeric carbon of the acceptor (arrow b) results in transfer of the thiophenyl aglycon group to the glycosyl donor along with formation of the oxocarbenium ion (or other activated intermediate) derived from the thioglycoside. In principle, polymerization can occur if the activated intermediate derived from the acceptor glycosylates another acceptor molecule.

On the basis of the mechanistic picture, a number of factors could play a role in determining whether transfer occurs.[32] Since the sulfide and hydroxyl compete for the activated intermediate,

Scheme 4. Model Studies on Transfer with Armed vs Disarmed Thioglycosides



one key factor is the relative reactivity of the sulfur atom and oxygen atom. The nucleophilicity of the hydroxyl can be affected by its stereochemistry (axial vs equatorial), its position on the ring, the size and electronic nature of nearby protecting groups, and hydrogen bonding. The nucleophilicity of the sulfide will be affected by the steric and electronic effects of the aglycon, the stereochemistry of the bond between the anomeric carbon and sulfur atom (axial vs equatorial), and the nearby protecting groups. The reaction conditions can also affect the competition between the sulfide and hydroxyl. For example, kinetic selectivity favoring the better nucleophile may be eroded at higher temperatures. Thus, factors that affect the activation temperature such as the solvent, activating agent, and type of glycosyl donor may affect transfer.

A second factor that can determine whether aglycon transfer will occur in a particular reaction is the electronic nature of the donor and acceptor. The electronic nature of a carbohydrate derivative is frequently described as "armed" or "disarmed".[33,34] These terms refer to the ease or difficulty of activating a sugar as a glycosyl donor. Disarmed sugars are harder to activate; they generally contain functionality that would destabilize an oxocarbenium ion such as electron-withdrawing groups (e.g., esters and azides) and/or higher degrees of oxygenation.[35] Armed sugars are easier to activate; they typically contain functionality that is less destabilizing such as ether protecting groups on the hydroxyls (e.g., *O*-benzyl, *O*-allyl, and *O*-silyl groups) and/or deoxygenated positions on the ring. All previously reported cases of aglycon transfer have involved armed thioglycoside acceptors. In fact, Yu et al. directly compared several armed and disarmed thioglycosides and found that only the armed thioglycosides suffered from transfer.[20] The authors rationalized this observation in terms of relative stabilities of oxocarbenium ions; the reaction is driven to produce the more stable oxocarbenium ion. On the basis of this hypothesis, any thioglycoside could undergo transfer as long as the oxocarbenium ion derived from the thioglycoside is more stable than the oxocarbenium ion derived from the glycosyl donor. It is important to note that activation of a glycosyl donor can produce a number of other activated intermediates such as glycosyl triflates and dioxolenium ions. Therefore, a more general phrasing of this theory is that the reaction is driven to the more stable set of activated intermediates.

The lack of observed transfer with disarmed thioglycosides could also be explained via a kinetic argument: cleavage of the C−S bond for disarmed thioglycosides may be too slow under the reaction conditions. On the basis of this rationale, highly disarmed thioglycosides would not be expected to transfer regardless of the armed/disarmed nature of the donor. If true, one could avoid transfer by using disarmed thioglycosides. However, it would be important to know how deactivated a thioglycoside must be to avoid transfer.

To distinguish between kinetic and thermodynamic explanations and probe the scope of the aglycon transfer problem, a series of model glycosylation reactions were carried out. Various armed and disarmed donors were activated in the presence of highly armed, highly disarmed, and intermediate thioglycosides

(32) While this paper focuses on other factors, it should be noted that the relative rates of decomposition of the activated intermediates and glycosylation may also affect the outcome of a reaction.
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(35) For a nice paper illustrating the effects of various protecting groups on the relative reactivities of glycosyl sulfides, see: Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734−753.

(Scheme 4). To simplify analysis of the products and eliminate competition with the hydroxyl, fully protected thioglycosides were utilized. First, the disarmed imidate **4**[36] (three disarming ester protecting groups and one disarming azide group) was activated in the presence of armed thioglycoside **12**.[37] As expected from both theories, transfer product **10**[38] was isolated in 100% yield from the reaction mixture.[39] Next, the disarmed imidate **13**[40] was reacted with thioglycoside **14** of intermediate reactivity (i.e., two disarming ester protecting groups and two ethers). Again, the transfer product (**15**) was isolated in 100% yield. Finally, disarmed imidate **4** was reacted with disarmed thioglycoside **15**.[41,42] Since the donor and thioglycoside are both highly disarmed, one might expect the oxocarbenium ions (or other intermediates) to be of similar stability. On the basis of a thermodynamic rationale, one would predict a mixture of transfer and starting material. In contrast, one would predict no transfer based on the kinetic argument since the thioglycoside is highly disarmed. In actuality, the transfer product (**10**, 35%) was isolated from the reaction along with some recovered starting material (40%). Therefore, the C−S bond of highly disarmed thioglycosides can be cleaved under standard reaction conditions. While transfer is more likely to occur with armed thioglycosides, it has the potential to occur with any thioglycoside.

One additional reaction was investigated to further probe the mechanism and scope of the aglycon transfer process. The mechanistic pathway described in Scheme 3 is a reversible process. If the carbon−sulfur bond of the thioglycoside can break and reform, the transfer process could provide a pathway to equilibrate the anomeric center of the thioglycoside. Moreover, equilibration could potentially occur even when formation of the transfer product is not energetically favored (e.g., the thioglycoside is more disarmed than the glycosyl donor). To investigate this possibility, the intermediate thioglycoside **14** was reacted with a more armed donor, **16**[43] (reaction D, Scheme 4). As expected, no transfer product was isolated from the reaction. Interestingly, the thioglycoside (**14**) was recovered as an alpha/beta mixture, indicating that anomerization had occurred. Thus, even when transfer is not energetically favored, the process can still be detrimental in a reaction by producing a mixture of products.

Product Destruction. Thioglycoside aglycons are frequently used for both solid-phase synthesis of oligosaccharides and construction of libraries of carbohydrates. When synthesizing compounds on a solid support or synthesizing large collections of compounds, product purification can be extremely difficult or completely impractical. Moreover, monitoring reaction progress can be equally challenging. Therefore, obtaining a high yield is critical. To achieve this, chemists frequently use a large excess of reagents and starting materials in order to drive reactions to completion. In addition, glycosylation reactions are repeated multiple times. Increasing the equivalents of glycosyl donor is also a common strategy for improving yields of standard solution-phase glycosylations.

On the basis of the mechanism, glycosylation on the sulfur atom of the *product* of a glycosylation reaction should also be a viable pathway in reactions. Therefore, excess equivalents of donor could destroy the product of a glycosylation reaction or cause anomerization of the carbon−sulfur bond. With excess equivalents of donor, destruction could become a problem even when glycosylation of the hydroxyl is much faster than glycosylation of the sulfur atom. To examine this possibility, acceptor **5** was reacted with either 1 or 2 equivalents of donor **4** (Scheme 2). The free hydroxyl of the acceptor is a primary alcohol and should react rapidly with activated donor. However, the donor is similar or slightly more disarmed than the acceptor. Therefore, transfer should be energetically favorable. With 1 equivalent, the reaction proceeded smoothly to form disaccharide **6** in 76% yield. However, with 2 equivalents of donor, only 25% of disaccharide **6** was isolated. Moreover, aglycon transfer product **10** was obtained in 60% yield. Thus, destruction of product by excess equivalents of donor leads to a much lower yield. While excess equivalents can drive reactions to completion, they may drive the *wrong* reaction to completion.

Preventing Aglycon Transfer. Taken together, the above experiments indicate that aglycon transfer can be a major problem with a wide range of thioglycosides. One obvious strategy to avoid this problem is to remove the thioglycoside functional group. With this approach, however, one loses all the advantageous features of thioglycosides. Therefore, synthetic strategies that minimize side reactions while retaining the advantageous features of thioglycosides would be best.

One approach to avoid transfer involves modifying the aglycon. Transfer occurs via nucleophilic attack of the sulfur atom on the activated glycosyl donor. Therefore, strategies to reduce the reactivity of the sulfur could minimize transfer. This approach has been examined by other groups, but a general and convenient alternative has not yet emerged.[19,23,24,27] One of the key challenges is reducing the reactivity of the sulfur atom sufficiently to prevent transfer but not so drastically that the thiol group becomes difficult to install and/or utilize at a later stage in a synthesis. For example, thioglycosides with a para-nitrophenyl aglycon have substantially reduced nucleophilicity but cannot be activated as glycosyl donors even under very strong activating conditions (e.g., NIS/TfOH).[44] Therefore, one must find a balance between reduced nucleophilicity and adequate reactivity. Ideally, one would also like a starting thiol that is commercially available, inexpensive, and nontoxic.

To identify a suitable aglycon group, a series of model reactions were carried out. The first model reaction involved activating disarmed donor **4** in the presence of disarmed thioglycosides **15a**−**m** (Table 1). The reaction of the parent thiophenyl aglycon produces a 1:1 mixture of transfer product and starting material. Therefore, the model system would be sensitive to even modest changes in yield of transfer product. In addition, the thioglycoside substrates for this model reaction required only a single synthetic step which allowed us to readily evaluate an assortment of aglycons. Initially, we focused on systematically varying the substituents on the phenyl ring of thiophenol. Results are summarized in Table 1. In agreement with the mechanistic analysis, electron-donating groups increased the amount of transfer while electron-withdrawing groups decreased the yield of transfer product. In fact, many of

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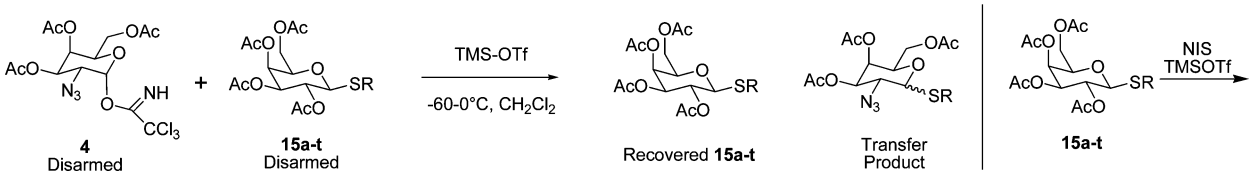
Table 1. Effects of Modified Aglycons on Transfer in Model System 1 and on the Activation Temperature of the Thioglycoside



entry	aglycon R group	recovered starting material, %	transfer product, %	thioglycoside activation temp., °C[a]
1	**15a** = Ph	40	35[b]	−45
2	**15b** = 2-FPh	50	40	
3	**15c** = 2-ClPh	90	10	
4	**15d** = 2-(CF_3)Ph	100	none	>15
5	**15e** = 3-FPh	50	20[b]	
6	**15f** = 3-ClPh	100	none	−45
7	**15g** = 3-BrPh	100	none	−50
8	**15h** = 3-MePh	50	44	
9	**15i** = 3-(CF_3)Ph	100	none	0
10	**15j** = 4-(OMe)Ph	30	70	
11	**15k** = 4-(CF_3)Ph	100	none	0
12	**15l** = 3,5-Cl_2Ph	100	none	>15
13	**15m** = 3,5-$(CF_3)_2$Ph	100	none	0
14	**15n** = 1-naphthyl	80	16	
15	**15o** = 2-naphthyl	60	40	
16	**15p** = adamantanyl (α)	100	none	−40
17	**15q** = adamantanyl (*β*)	100	none	−50
18	**15r** = 2,6-Me_2Ph (*β* DMP)	100	none	−15
19	**15s** = 2,6-Me_2Ph (α DMP)	100	none	−50
20	**15t** = 2,6-Cl_2Ph (α)	100	none	−15

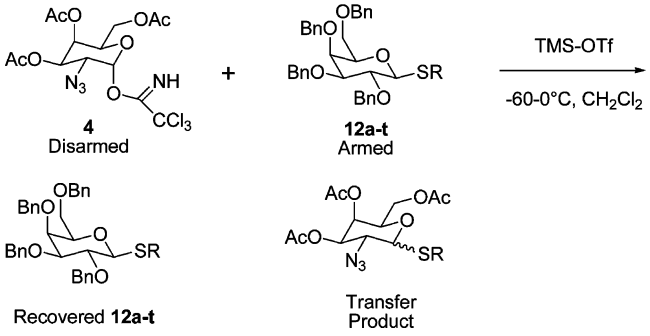
[a] In a separate experiment, compounds **15a**−**t** were cooled to −60 °C and NIS/TMSOTf was added. The reaction was slowly warmed while monitoring by TLC to determine the activation temperature. [b] A number of minor components were also observed by TLC.

the modified aglycons with electron-withdrawing groups such as 3-chlorophenyl, 3-trifluoromethyl, and 3,5-dichlorophenyl completely blocked transfer in this first model system. Modified aglycons performing well in model system 1 were also tested for activation using NIS/TMSOTf. Thioglycosides were treated with NIS and TMSOTf at −60 °C. The reaction mixture was monitored while slowly warming, and the temperature at which activation occurred was measured (Table 1).

Next, the best candidates were examined in a second, more challenging aglycon transfer system. Donor **4** was activated in the presence of perbenzylated thioglycosides **12a**, **12f**, **12i**, and **12l**. In this model system, the thioglycosides are highly armed and the donor is highly disarmed. Therefore, this represents an extreme mismatch and a highly challenging system for blocking transfer. For reference, reaction of the parent thiophenyl glycoside results in 100% transfer. The results are summarized in Table 2. None of the aglycons with electron-withdrawing groups were sufficiently deactivated to block transfer in this very difficult reaction. Moreover, many of the thioglycosides with modified aglycons required significantly higher temperatures to activate using NIH/TMSOTf. For these reasons, phenyl rings with electron-withdrawing substituents did not appear to be a viable, general solution for the aglycon transfer problem.

Glycosylation of the sulfur atom produces a sterically congested sulfonium ion (structure **11**, Scheme 3). Therefore, it was anticipated that bulky aglycons might also block transfer, even in the absence of electron-withdrawing groups. In addition, one might be able to overcome difficulties associated with activation by using small activating agents. In support of this approach, the Boons group recently reported the use of a dicyclohexylmethyl thio aglycon to block transfer.[24] We incorporated this aglycon into the perbenzylated galactose model system and evaluated its ability to prevent transfer (**12u**, Table 2). While performing better than most of the modified phenyl aglycons, transfer still occurred. In addition, the corresponding thiol starting material was not commercially available. To identify a more optimal and convenient aglycon, a variety of commercially available thiols were considered. The sterically hindered adamantyl, 1-naphthyl, 2-naphthyl, and 2,6-dimethylphenyl thiols were chosen for further evaluation.[45] Each was incorporated into galactose, evaluated in both model systems, and tested for activation (Tables 1 and 2). Happily, the 2,6-

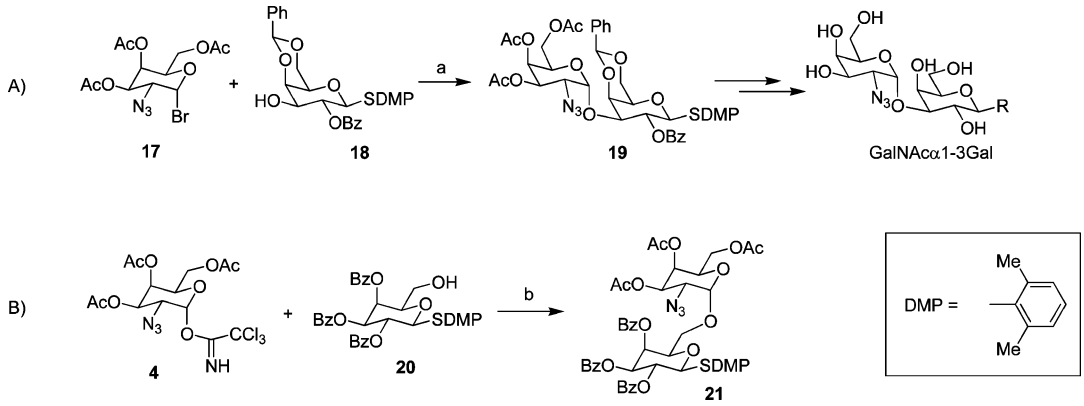
Table 2. Preventing Aglycon Transfer in a More Challenging Model System



entry	aglycon R group	recovered starting material, %	transfer product, %
1	**12a** = Ph	none	100
2	**12f** = 3-ClPh	10 (α)	77
3	**12i** = 3-(CF_3)Ph	20 (α)	67
4	**12l** = 3,5-Cl_2Ph	10 (α)	75
5	**12q** = adamantyl (*β*)	30 (1:1 α:*β*)	50
6	**12r** = 2,6-Me_2Ph (*β* DMP)	81 (*β*)	none
7	**12s** = 2,6-Me_2Ph (α DMP)	80	none
8	**12u** = CH(cHexyl)$_2$	50	15

(45) 2,6-Dimethylthiophenol was purchased from Oakwood Products, Inc. (West Columbia, SC) and is available from Aldrich (St. Louis, MO).

Scheme 5. DMP Aglycon Blocks Transfer[a]



[a] Reaction conditions: (a) AgOTf, di-*tert*-butylmethylpyridine, CH_2Cl_2, −60 to 0 °C (78% yield); (b) TMSOTf, diethylether, −20 to 0 °C (82% yield).

dimethylphenyl (DMP) aglycon completely blocked transfer in both model systems (**12r**, **12s**, **15r**, and **15s**). In addition, the DMP thioglycoside could be activated under relatively mild conditions. The 2,6-dichlorophenyl aglycon was also evaluated but found to be suboptimal.[46] On the basis of these model studies, the DMP group satisfied the initial screening criteria and appeared to be an excellent candidate as an alternative aglycon for thioglycosides.

Next, the DMP aglycon was tested in several problematic glycosylation reactions. First, the DMP aglycon was incorporate into galactose derivative **18** and coupled with donor **17**[47] in an effort to synthesize the corresponding alpha 1−3 linked disaccharide (reaction A, Scheme 5). As mentioned previously, no product was obtained in the glycosylation when a phenyl group was used as the aglycon. With the DMP aglycon, however, a 78% yield of the desired disaccharide (**19**) was obtained. It is important to note the DMP modified disaccharide could be successfully transformed into the final target glycan via the same reaction sequence and conditions previously used to convert the thiophenyl-containing disaccharides **3** and **6** into the related targets (see Supporting Information and ref 15). In a second test case, the DMP aglycon was incorporated into galactose derivative **20** and coupled with varying equivalents of donor **4** to determine if the modified aglycon could block product destruction (reaction B, Scheme 5). Even with two equivalents of donor, the disaccharide (**21**) could be obtained in 82% yield, indicating that the modified aglycon effectively prevents transfer.

Conclusions

Glycosylation reactions are one of the most challenging and unpredictable chemical transformations known. Due to both steric and electronic effects, hydroxyls found on carbohydrates are especially poor nucleophiles. As a result, most glycosylation methods are designed to produce extremely reactive intermediates such as glycosyl triflates and oxocarbenium ions. While necessary for glycosylations, the high reactivity can lead to a variety of side reactions. A better understanding of these processes and methods to prevent them are critical for advancing the field.

One side reaction that has emerged as a general problem is glycosylation of other nucleophilic groups such as amides, sulfoxides, and imidates present on the glycosyl donor and/or acceptor.[48−51] Glycosylation of the sulfur atom of a thioglycoside can also occur, and this process leads to transfer of the aglycon from the thioglycoside to the glycosyl donor. In this paper, it is shown that (a) the transfer process can occur for a wide range of thioglycosides, (b) even if the transfer product is not observed, the process can lead to anomerization of the C−S bond of the thioglycoside, and (c) excess equivalents of glycosyl donor can lead to destruction of the product of a glycosylation reaction. Taken together, the results show that the aglycon transfer process can affect a wide range of thioglycosides. This side reaction is especially important to consider when carrying out complex reactions such as solid-phase glycosylations, one-pot or orthogonal multicomponent glycosylations, and construction of carbohydrate libraries. Finally, the sterically hindered 2,6-dimethylphenyl (DMP) aglycon was found to block glycosylation of the sulfur atom and prevent aglycon transfer in a range of model reactions and glycosylation reactions. The DMP group can be easily installed using a commercially available thiol (2,6-dimethylthiophenol) and utilized as a glycosyl donor at a later stage in a synthesis. On the basis of the results, the DMP group is a convenient and improved aglycon for thioglycosides.

Experimental Section

General Methods. Unless otherwise stated, reagents were obtained from commercial suppliers and used without purification. NMR spectra were recorded on a Unity Inova 400 Fourier transform NMR spectrometer. All proton NMR data was obtained at 400 MHz, and all carbon NMR data was obtained at 100 MHz. Proton chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) unless otherwise noted. Carbon chemical shifts are reported in parts per million (ppm) downfield from TMS using $CDCl_3$ as an internal reference unless otherwise noted. Coupling constants (*J*) are reported in hertz (Hz). Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintuplet (p), multiplet (m), and broadened (br). High-resolution mass spectra were obtained on a VG ZAB (University of California, Riverside, Mass Spectrometry Facility). 2,6-Dimethylthiophenol was purchased from Oakwood Products, Inc. (West Columbia, SC)

General Procedure for Aglycon Transfer Model Reactions. Thioglycosides (0.1 mmol, 1 equiv) and glycosyl imidates (0.1 mmol,

(46) The 2,6-dichlorophenyl aglycon was harder to install, harder to activate, and generally produced lower yields.
(47) Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244−1251.
(48) Schmidt, R. R.; Toepfer, A. *Tetrahedron Lett.* **1991**, *32*, 3353−3356.
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(50) Liao, L.; Auzanneau, F. I. *Org. Lett.* **2003**, *5*, 2607−2610.
(51) Liao, L.; Auzanneau, F. I. *J. Org. Chem.* **2005**, *70*, 6265−6273.

1 equiv) were dissolved in DCM (1 mL) and stirred with molecular sieves at room temperature for 0.5 h. The reaction mixture was cooled to −78 °C (dry ice/acetone bath) for 10 min and then warmed to −60 °C. TMSOTf (2 drops) was added via syringe at −60 °C, and the reaction mixture was slowly warmed to 0 °C over 1.5 h. The temperature was monitored externally. When the temperature reached 0 °C, the reaction mixture was quenched by addition of triethylamine (0.1 mL), loaded directly onto a silica column, and purified by chromatography.

2,6-Dimethylphenyl 2,3,4,6-Tetra-*O*-acetyl-1-thio-D-galactopyranoside (15r, 15s). BF_3EtO_2 (1 mL, 1.3 equiv) was added to a mixture of galactose pentaacetate (2 g, 1 equiv) and 2,6-dimethylthiophenol[45] (700 mg, 1 equiv) in CH_2Cl_2 and toluene (1:1, 8 mL). The reaction mixture was stirred at 50 °C for 4 h and diluted with CH_2Cl_2 (10 mL). The CH_2Cl_2 solution was washed with saturated $NaHCO_3$ twice followed by brine. Solvent was evaporated, and the product was purified by chromatography (1:3 ethyl acetate/hexanes).

β product **15r** (white powder, 1.4 g, 56% yield): $R_f = 0.3$ (1:2 ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.19−7.11 (m, 3 H), 5.38 (dd, J = 3.2, 0.8 Hz, 1 H), 5.33 (t, J = 10.0 Hz, 1 H), 5.01 (dd, J = 10.0, 3.2 Hz, 1 H), 4.41 (d, J = 10.0 Hz, 1 H), 4.10 (dd, J = 11.2, 7.2 Hz, 1 H), 4.04 (dd, J = 11.2, 7.2 Hz, 1 H), 3.74 (m, 1 H), 2.54 (s, 6 H), 2.18 (s, 3 H), 2.14 (s, 3 H), 1.99 (s, 3 H), 1.97 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.2, 170.0, 169.5, 144.0, 131.2, 129.3, 128.2, 89.2, 74.1, 71.9, 67.7, 67.2, 61.5, 22.3, 20.7, 20.6, 20.51, 20.49. HRMS $[M + Na]^+$: calcd for $C_{22}H_{28}O_9NaS$ 491.1352; found 491.1369.

α product **15s** (white powder, 390 mg, 15% yield): $R_f = 0.4$ (1:2 ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.20−7.08 (m, 3 H), 5.55 (d, J = 4.8 Hz, 1 H), 5.53 (m, 1 H), 5.35 (m, 2 H), 4.77 (m, 1 H), 4.08 (m, 2 H), 2.49 (s, 6 H), 2.136 (s, 3 H), 2.135 (s, 3 H), 2.019 (s, 3 H), 2.017 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.2, 170.1, 169.8, 143.2, 130.7, 129.0, 128.4, 87.2, 68.0, 67.93, 67.87, 61.6, 22.0, 20.7, 20.6. HRMS $[M + Na]^+$: calcd for $C_{22}H_{28}O_9NaS$ 491.1352; found 491.1351.

2,6-Dimethylphenyl 4,6-*O*-Benzylidene-2-*O*-benzoyl-1-thio-β-D-galactopyranoside (18). To a solution of compound **15r** (1.4 g, 3.0 mmol) in methanol (10 mL) was added NaOMe (catalytic amount). The reaction mixture was stirred at room temperature for 2 h and quenched by adding ion-exchange resin. The resin was filtered, and the solvent was evaporated to give 2,6-dimethylphenyl 1-thio-β-galactopyranoside (900 mg, 100% yield): ^{1}H NMR (DMSO-d_6) δ 7.11−7.04 (m, 3 H), 5.11 (d, J = 5.6 Hz, 1 H), 4.82 (d, J = 5.2 Hz, 1 H), 4.45−4.40 (m, 2 H), 4.07 (d, J = 9.6 Hz, 1 H), 3.61 (m, 1 H), 3.46−3.42 (m, 1 H), 3.36−3.30 (m, 1 H), 3.25−3.20 (m, 2 H), 3.13 (t, J = 6.4 Hz, 1 H), 2.45 (s, 6 H); ^{13}C NMR (DMSO-d_6) δ 144.2, 132.7, 128.9, 128.2, 91.6, 79.1, 75.1, 70.7, 68.4, 60.6, 22.7.

2,6-Dimethylphenyl thiogalactoside (300 mg, 1.0 mmol) and camphorsulfonic acid (catalytic amount) were dissolved in acetone dimethyl acetal (25 mL) and stirred at room temperature overnight. The reaction was quenched by addition of triethylamine (1 mL), and the solvent was evaporated. The product was purified by chromatography (1:1 ethyl acetate/hexanes, 0.1% triethylamine) to yield a white solid (240 mg, 58% yield): $R_f = 0.4$ (1:1 ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.11−7.05 (m, 3 H), 4.13 (d, J = 10.4 Hz, 1 H), 4.10 (dd, J = 5.6, 2.0 Hz, 1 H), 3.97 (dd, J = 6.8, 5.2 Hz, 1 H), 3.66−3.64 (m, 1 H), 3.60−3.55 (m, 3 H), 3.13 (s, 3 H), 2.88 (d, J = 2.4 Hz, 1 H), 2.54 (s, 6 H), 1.49 (s, 3 H), 1.29 (s, 6 H), 1.27 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 143.9, 131.2, 129.1, 128.2, 110.0, 100.0, 90.9, 79.0, 75.8, 73.6, 72.8, 60.3, 48.5, 28.1, 26.2, 24.3, 24.2, 22.7.

The product (240 mg, 0.58 mmol) was dissolved in CH_2Cl_2 (5 mL), followed by addition of benzoyl chloride (140 mg, 1 mmol), triethylamine (2 mmol), and DMAP (catalytic amount). The solution was stirred at room temperature for 5 h and diluted by CH_2Cl_2. The solution was washed with 1 N HCl, saturated sodium bicarbonate, and brine. The solvent was removed, and the product was purified by chromatography (1:3 ethyl acetate/hexanes with 0.1% triethylamine) to afford a white solid (200 mg, 67% yield): $R_f = 0.7$ (1:1 ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.11−8.09 (m, 2 H), 7.60−7.56 (m, 1 H), 7.47−7.43(m, 2 H), 7.13−7.04 (m, 3 H), 5.40 (dd, J = 10.0, 7.2 Hz, 1 H), 4.43 (d, J = 10.0 Hz, 1 H), 4.30 (dd, J = 7.2, 5.6 Hz, 1 H), 4.23 (dd, J = 5.2, 2.0 Hz, 1 H), 3.76 (m, 1 H), 3.68−3.64 (m, 2 H), 3.18 (s, 3 H), 2.46 (s, 6 H), 1.65 (s, 3 H), 1.34 (s, 6 H), 1.33 (s, 3 H);^{13}C NMR ($CDCl_3$) δ 165.4, 144.0, 133.1, 132.0, 129.9, 129.7, 128.9, 128.2, 128.0, 110.5, 100.1, 88.3, 75.5, 73.8, 72.4, 60.3, 48.6, 27.7, 26.2, 24.3, 24.2, 22.5.

The product (200 mg, 0.39 mmol) was dissolved in acetic acid solution (80%, 3 mL) and heated to 70 °C for 3 h. The solvent was evaporated, and the residue was dried by azeotropic distillation using toluene. The residue was suspended in acetonitrile (10 mL) and treated with benzaldehyde dimethyl acetal (119 mg) and camphorsulfonic acid (catalytic amount). The mixture was stirred at room temperature for 4 h. The reaction was quenched by triethylamine (1 mL), and the product was purified by chromatography (1:1 ethyl acetate/hexanes, with 0.1% triethylamine) to give the desired product (**18**) as a white powder (130 mg, 68% yield for two steps): $R_f = 0.6$ (1:1 ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.11−8.09 (m, 1 H), 7.60−7.53 (m, 3 H), 7.47−7.39 (m, 5 H), 7.14−7.06 (m, 3 H), 5.53 (s, 1 H), 5.45 (t, J = 10.0 Hz, 1 H), 4.59 (d, J = 10.0 Hz, 1 H), 4.26−4.22 (m, 2 H), 3.99 (dd, J = 12.4, 1.6 Hz, 1 H), 3.85 (m, 1 H), 3.38 (m, 1 H), 2.50 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 166.1, 144.3, 137.4, 133.1, 131.2, 129.9, 129.7, 129.3, 129.0, 128.31, 128.28, 128.1, 126.4, 101.4, 87.8, 75.6, 72.9, 91.9, 69.7, 69.2, 22.5. HRMS $[M + Na]^+$: calcd for $C_{28}H_{28}O_6NaS$ 515.1504; found 515.1512.

2,6-Dimethylphenyl (3,4,6-Tri-*O*-acetyl-2-azido-2-deoxyl-α-D-galactopyranosyl)−(1→3)-4,6-*O*-benzylidene-2-*O*-benzoyl-1-thio-β-D-galactopyranoside (19). A mixture of donor 17[47] (70 mg, 1.6 mmol, 2 equiv), acceptor 18 (40 mg, 0.8 mmol, 1 equiv), and di-*tert*-butylmethylpyridine (60 mg, 1.6 mmol, 2 equiv) was dried under vacuum for 1 h and dissolved in CH_2Cl_2 (1.5 mL). Molecular sieves (100 mg) were added, and the mixture was stirred and cooled to −78 °C. AgOTf (60 mg, 1.6 mmol, 2 equiv) was added to the reaction mixture, and the mixture was allowed to warm to 0 °C over 2.5 h. The reaction was quenched with $NaHCO_3$ (1 mL), and the mixture was filtered to remove the molecular sieves. The filtrate was extracted with CH_2Cl_2 three times. The organic layers were combined and washed with brine. The solvent was removed, and the residue was purified by column chromatography to give desired product as a white solid (50 mg, 77% yield): $R_f = 0.5$, (1:1 ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.10−8.07 (m, 2 H), 7.59−7.54 (m, 3 H), 7.46−7.42 (m, 2 H), 7.39−7.33 (m, 3 H), 7.10−7.01 (m, 3 H), 5.69 (t, J = 10.0 Hz, 1 H), 5.53 (s, 1 H), 5.16−5.12 (m, 2 H), 5.06 (dd, J = 2.8, 0.8 Hz, 1 H), 4.61 (d, J = 10.4 Hz,1 H), 4.37 (d, J = 3.2 Hz, 1 H), 4.23 (dd, J = 12.4 Hz, 1.2 Hz, 1 H), 4.02−3.97 (m, 3 H), 3.80 (dd, J = 11.2, 8.0 Hz, 1 H), 3.68 (dd, J = 11.2, 8.0 Hz, 1 H), 3.50 (dd, J = 12.4, 3.6 Hz, 1 H), 3.34 (d, J = 0.8 Hz, 1 H) 2.45 (s, 6 H), 2.01 (s, 3 H), 1.95 (s, 3 H), 1.88 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.0, 169.8, 169.2, 164.9, 144.3, 137.4, 133.3, 131.3, 129.8, 129.5, 129.0, 128.9, 128.5, 128.12, 128.06, 126.2, 101.0, 95.6, 88.2, 77.1, 72.1, 69.6, 69.5, 69.3, 67.5, 67.0, 66.9, 60.7, 59.9, 22.5, 20.6, 20.50, 20.49.

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Supporting Information Available: Experimental details for the syntheses of compounds **8**, **12f**, **12i**, **12l**, **12q**, **12r**, **12s**, **14**, **15b−q**, **15t**, **20**, and **21**; ^{1}H and ^{13}C NMR spectra for compounds **12r**, **12s**, **14**, **15r**, **15s**, **18**, **19**, **20**, and **21**; complete author list for ref 8b. This material is available free of charge via the Internet at http://pubs.acs.org.

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