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Evolution of a Reagent-Controlled Strategy for β-Selective *C*-Glycoside Synthesis

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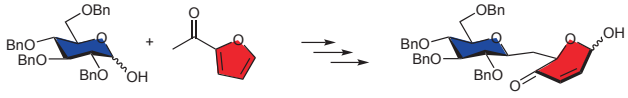

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Abstract *C*-Alkyl glycosides represent an attractive class of nonhydrolyzable carbohydrate mimetics which possess enormous potential as next-generation therapeutics. Methods for the direct stereoselective synthesis of *C*-alkyl glycosides with a broad substrate tolerance are limited, however. This is especially in the case of β-linked *C*-alkyl glycosides, where direct methods for synthesis from commonly available coupling partners remain limited. This Account describes the evolution of our laboratory's studies on glycosyl sulfonate chemistry from a method for the construction of simple β-linked 2-deoxy-sugars to a technology for the direct synthesis of β-linked acyl and homoacyl glycosides that can be elaborated into more complex structures.

Key words glycosylation, C–C-bond-forming reactions, glycoconjugates, S_N2 reactions, reactivity

1 Introduction

Many carbohydrates and glycoconjugates possess biological activities, such as immunostimulatory properties or antimicrobial activity, that render them attractive as leads for the development of new therapeutics.[1,2] In practice, however, there are many hurdles which must be overcome before the full potential of these molecules can be realized. While the difficulties associated with diastereoselective oligosaccharide synthesis are most frequently cited as one of these issues, another challenge lies in the instability of oligosaccharides towards hydrolysis and enzymatic cleavage. This has led a number of investigators to examine nonhydrolyzable carbohydrate mimetics. Among these different classes of compounds, *C*-linked glycosides, where the anomeric oxygen is replaced by a methylene unit, have been extensively investigated.[3] NMR studies have demonstrated that *C*-glycosides can adopt a number of conformations similar to their *O*-linked parent compounds.[4] Furthermore, investigations from several laboratories have shown that these molecules can bind to carbohydrate binding proteins and inhibit glycosidases.[5] In some cases, such as the immunostimulatory glycolipid KRN-7000, *C*-linked glycoconjugates have even been shown to possess superior activity to their native *O*-linked counterparts.[6]

As a consequence of their potential, a vast number of methods for the construction of *C*-linked glycosides have been developed over the past several decades.[3] Approaches to *C*-alkyl glycosides typically involve first introducing a carbon linkage possessing a handle for derivatization, followed by elaboration to the desired product. For α-linked *C*-glycosides, stereoselective synthesis can often be achieved through the use of a glycosyl radical, as first described by Giese.[7,8] In the case of β-linked *C*-alkyl glycosides synthesis often commences with the construction of *C*-acyl or homoacyl glycosides. This is typically achieved through addition to lactones followed by reduction,[9] cross-coupling of anomeric stannanes,[10] or direct displacement of a leaving group.[11] Many of these approaches rely on either the use of strongly oxidizing conditions to unmask the desired product or highly specialized protecting group patterns. In order to address these concerns, we sought a mild and direct method for β-linked *C*-glycoside synthesis where selectivity is not sensitive to the protecting group on the sugar coupling partner. Based off our own laboratory's ongoing studies on using sulfonate activation for the direct synthesis of β-linked *O*-glycosides, we began to wonder if a similar approach could be applied to *C*-glycoside synthesis. This Account describes our evolution in thinking about glycosyl sulfonate reactivity, and how it led to a S_N2 approach for the direct synthesis of *C*-acyl and homoacyl glycosides

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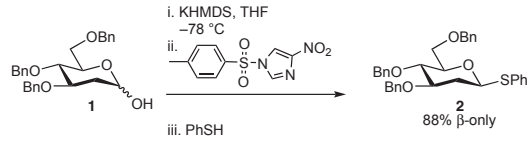
2 Glycosyl Sulfonates for Deoxy Sugar Synthesis

Our initial forays into glycosylation started over a decade ago when I began my independent career. Coming from a natural products and chemical glycobiology background, a program of developing new glycosylation reactions was as new to me as it was to my students. To be able to carve out our laboratory's niche in what is a crowded field, I looked for an unsolved problem that at the time was not attracting much attention. To this end, we began searching for methods to control selectivity in glycosylation reactions using 2-deoxy sugar donors. Our motivation for conducting this research came from the fact that deoxy sugars are important components of many bioactive natural products. At the time (and arguably still today), methods for stereoselective direct glycosylation reactions with these compounds were limited.[12] This was especially true for the synthesis of β-linked deoxy sugars, where selective methods relied on either indirect synthesis (using temporary directing groups on the glycosyl donor)[13] or *de novo* approaches.[14]

After many false starts, we began to think about the mechanism of the chemical glycosylation reaction. Specifically, while oxocarbenium cations are frequently invoked as key intermediates in chemical glycosylation reactions, evidence for their existence outside of extreme environments is extremely sparse.[15] On the other hand, several covalent intermediates, in particular glycosyl triflates, had been described for these reactions.[16] While glycosyl triflates were too reactive to reliably be used in direct stereoselective deoxy sugar oligosaccharide synthesis,[17] we began to wonder if a less reactive glycosyl sulfonate could provide β-linked products through an invertive mechanism. To this end, we settled on examining glycosyl tosylates as leaving groups in this chemistry, owing to both the availability of several tosylate sources and their ease of handling.

Having settled on α-linked glycosyl tosylates as the first target to investigate, the next challenge was to develop a method that would allow us to form these species selectively. To this end, we drew inspiration from work by Shair, who had shown that metalating deoxy sugar hemiacetals with potassium hexamethyldisilazide (KHMDS) at –78 °C in THF followed by treatment with allyl bromide resulted in the formation of α-linked allyl glycosides with extremely high levels of selectivity.[18] We reasoned that replacing the allyl bromide with an appropriate tosylate source under otherwise identical conditions would lead to the formation of an α-linked glycosyl sulfonate that could be further reacted *in situ* to afford β-linked products. This proved to be the case, and when **1** was activated with tosyl 4-nitroimidazole (Ts-4-NO_2Im) followed by treatment with thiophenol we were able to obtain the β-linked thioglycoside **2** exclusively (Scheme 1).[19] Further investigations into this chemistry revealed that less reactive alkyl thiolate and phenoxide nucleophiles were also competent coupling partners in the reaction.

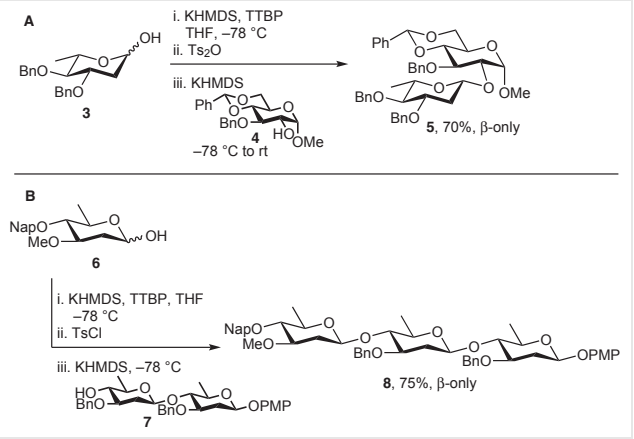


Scheme 1 Early studies from our lab demonstrating that tosylate sources could activate hemiacetals for β-selective glycosylations

To expand the utility of the reaction we turned our attention to using aliphatic alkoxides as nucleophiles, with a focus on sugar-based coupling partners. Unfortunately, all attempts to carry out these reactions with Ts-4-NO_2Im failed to provide reliable access to the desired products. To extend the scope of this chemistry, we chose to examine more reactive tosylate sources. In a sense we went to the other extreme of reactivity and investigated using tosic anhydride (Ts_2O) in the reaction. This proved to be one of those rare moments in synthesis where the first set of conditions examined worked extremely well. Indeed, with almost no optimization we were able to demonstrate that the use of this reagent permitted highly selective glycosylation reactions with aliphatic acceptors.[20] Notably, the reactions worked with both highly reactive 2,6-dideoxy sugars in addition to 2-deoxy sugars (Scheme 2A), an important obser-

Biographical Sketches

Clay S. Bennett received his BA in chemistry from Connecticut College in 1999. In 2005 he obtained his PhD studying complex natural product synthesis under the direction of Amos B. Smith III at the University of Pennsylvania. Following postdoctoral studies in carbohydrate chemistry and glycobiology with Chi-Huey Wong at the Scripps Research Institute, he started his independent career at Tufts University in 2008, where he is currently professor of chemistry. His research interests include the development of new stereoselective methods for *C*- and *O*-glycoside synthesis, their use in automated synthesis, and their application to the synthesis of antimicrobial oligosaccharides.



Scheme 2 The use of Ts_2O (A) and TsCl (B) in β-selective deoxy sugar disaccharide synthesis. TTBP = 2,4,6-tri-*tert*-butylpyrimidine; Nap = 2-naphthyl methyl; PMP = 4-methoxyphenyl.

vation considering that while the former species are commonly found in natural products, the latter are not.[21]

Having established that the new system could indeed provide access to β-linked deoxy sugars with extremely high levels of selectivity, we carried out preliminary studies on the mechanism of the reaction. Specifically, was it indeed proceeding through the intermediacy of an α-linked glycosyl tosylate? To investigate this, we used VT NMR to identify the reaction intermediates. HSQC NMR studies clearly showed that upon treatment with KHMDS and Ts_2O at –78 °C, the starting material was quantitatively converted into an α-linked glycosyl sulfonate. Furthermore, VT NMR studies demonstrated that this intermediate rapidly decomposed above –60 °C, despite being in a sealed tube under argon.

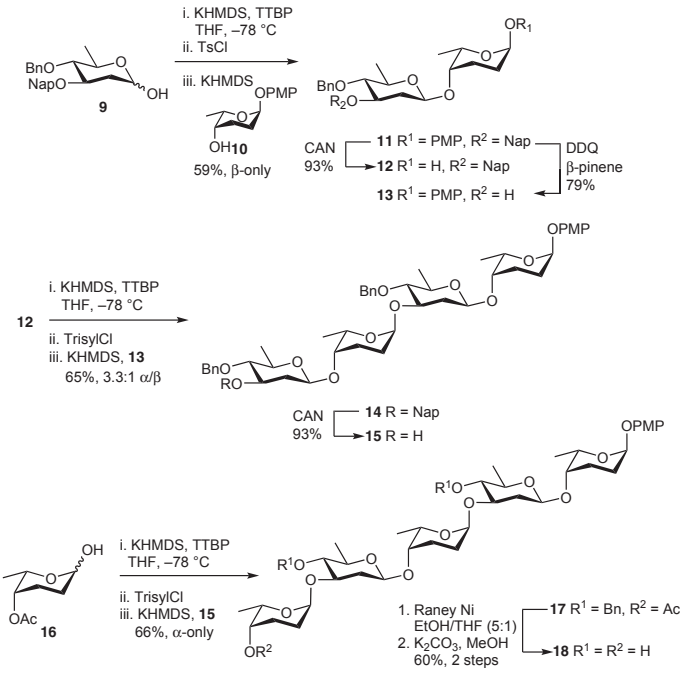
While the Ts_2O reagent had provided us with a method for deoxy sugar oligosaccharide synthesis, it was not without its faults. Specifically, the reagent is an extremely unstable solid, which led to issues with batch-to-batch reproducibility on scale-up. Furthermore, we were cognizant of the fact that the tosylate may not provide a one size fits all solution to the challenge of β-selective chemical glycosylation. This latter issue was of particular concern, considering most sulfonic anhydrides are not commercially available and difficult to cleanly synthesize. In what was almost an act of desperation we chose to look at tosyl chloride in the reaction. While this reagent is certainly more inexpensive and easier to handle than our previous promoter systems, we did have concerns that upon activation the KCl byproduct could react with the newly formed glycosyl sulfonate to form an unreactive (under our conditions) glycosyl chloride. Pleasingly this proved not to be the case, and not only did the reaction work well on test scale, but we were now able to conduct gram-scale reactions reliably. The utility of this chemistry was further demonstrated through the synthesis of the tetrasaccharide of kigamicin C and the trisaccharide from FD-594 (Scheme 2B).[22]

3 Glycosyl Sulfonates in Oligosaccharide Synthesis

With an optimized method for β-selective dehydrative glycosylation in hand, we began to explore expanding the scope and utility of the reaction. These latter studies took two tracks: 1) extend the chemistry to other less reactive donors (*vide infra*); and 2) demonstrate its utility in complex oligosaccharide synthesis. Using the chemistry in synthesis was of particular importance to us, because while the literature is full of glycosylation methods, most reports do not extend beyond preliminary scope. We reasoned that if others were to adopt this chemistry, we would need to demonstrate its utility ourselves. To this end, we selected two complex oligosaccharide targets: the hexasaccharide from landomycin A and the pentasaccharide from saquayamycin Z.

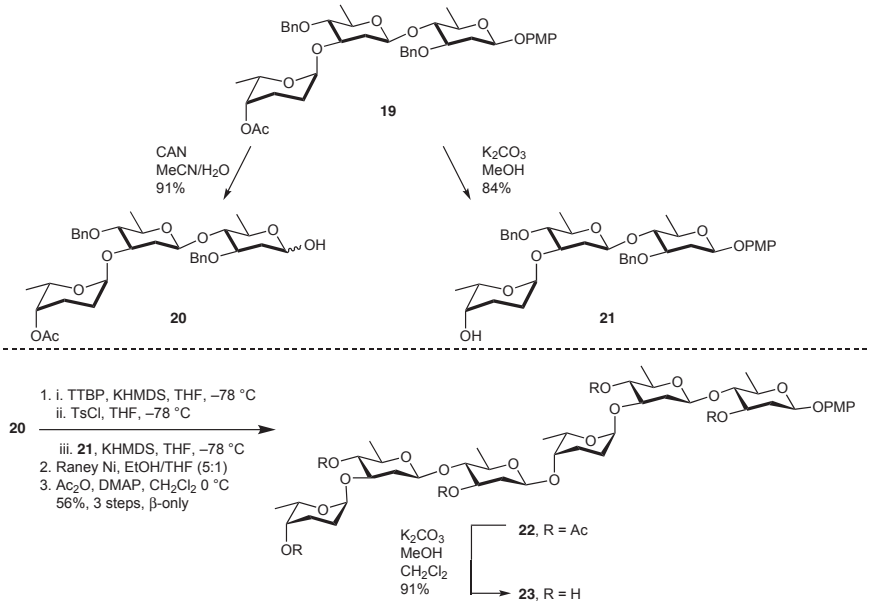
For the synthesis of the saquayamycin Z pentasaccharide, we envisioned an iterative process linking olivose residues to rhodinose residues.[23] These studies would take advantage of an observation we made while developing the TsCl chemistry that acetate-protected trideoxy sugar hemiacetals underwent α-selective glycosylation reactions when activated with triisopropylbenzenesulfonyl chloride (TrisylCl). To this end coupling olivose **9** with rhodinose acceptor **10** afforded disaccharide **11** in good yield and selectivity (Scheme 3). Compound **11** could be then converted into donor **12** and acceptor **13** though standard protecting group manipulations. Coupling of these two disaccharides proceeded in good yield, however, with attenuated selectivity. Further investigations into this chemistry revealed that the acetate at the 4-position of the rhodinose was crucial for optimal selectivity, although the origin of this control remains unclear at this time. Following removal of the terminal 2-naphthylmethyl (Nap) ether the final rhodinose was installed and the molecule subjected to global deprotection to afford the target pentasaccharide **18** in 2.5% overall yield from commercial starting materials.

In the case of landomycin, we chose to examine a more convergent approach to the target.[24] To this end we initially targeted trisaccharide **19**, which could serve as a precursor to both donor **20** and acceptor **21** required for oligosaccharide synthesis (Scheme 4). Following an iterative sequence of glycosylation and deprotection, the synthesis of **19** proceeded smoothly, as did the subsequent deprotections to provide **20** and **21**. It was at this point that we hit a wall in the synthesis. Specifically, while the coupling of **20** and **21** proceeded well as judged by crude NMR and MS analyses, all attempts to isolate the hexasaccharide resulted in decomposition! We therefore chose to remove the benzyl ethers from the crude product and install acetates in their



Scheme 3 Glycosyl sulfonate mediated synthesis of the saquayamycin Z pentasaccharide. TrisylCl = 2,4,6-triisopropylbenzenesulfonyl chloride.

place to facilitate isolation. This also proved to be easier said than done, as both hydrogenolysis and Birch reduction conditions also led to decomposition of the molecule. Finally, we chose to examine Raney Ni mediated deprotection as reported by the Yu lab.[25] Pleasingly, subjecting the crude product to these conditions followed by acetylation afforded a hexasaccharide target **22**, which was isolated as a single isomer in 56% yield over the three steps. Removal of the acetates then afforded the target **23**. In total, the hexasaccharide was produced in 8.9% overall yield, providing enough material for ongoing biological investigations. Following our demonstration of the utility of this chemistry,

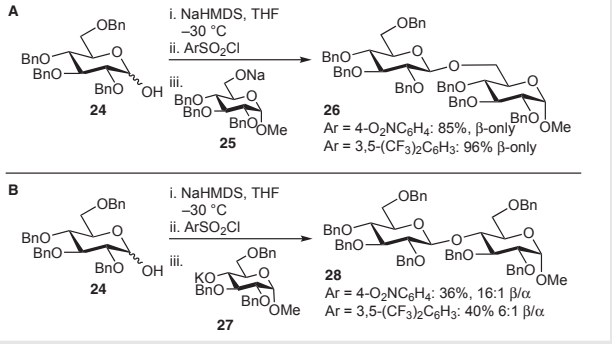


Scheme 4 Synthesis of the landomycin A hexasaccharide using sulfonate-mediated glycosylation

we were delighted to see other laboratories begin to adopt it in their own total syntheses.[26] With this success, we were eager to see if this chemistry could be used for other classes of sugar donors.

4 Matching Donor and Sulfonate Reactivity

While on the surface it might seem that this chemistry could be readily extended to activating other classes of sugars, in practice, this turned out to be much more challenging. This is because the reactivity of different sugars can vary tremendously, as demonstrated by Wong and co-workers in their relative reactivity (RRV) studies.[27] Mong and co-workers later showed that the 2-deoxy sugars which were used to develop our chemistry were approximately 500 times more reactive than perbenzylated glucose.[28] Consequently, we were aware that the tosylate may not be the optimal promoter for activating glucose, since the resulting glucosyl tosylate could be stable enough that it would only be a competent electrophile at elevated temperatures where competing S_N1-like reactions could take place. Indeed, this proved to be the case and we found it necessary to screen other sulfonyl chloride promoters in the reaction. Fortunately, this task was made easier by the fact that dozens of sulfonyl chlorides are commercially available. After extensive screening, we found two sulfonyl chlorides, 3,5-bis(trifluoromethyl)benzenesulfonyl chloride ($BTMSO_2Cl$) and 4-nitrobenzenesulfonyl chloride (nosyl chloride, NsCl), were both extremely competent promoters for the reaction between donor **24** and primary acceptor **25** (Scheme 5A).



Scheme 5 Effects of sulfonate electronics on reactions between glucose and (A) primary and (B) secondary acceptors

Further investigations into this chemistry demonstrated that these promoters worked very well with glucose, galactose, and fucose donors, provided that highly reactive primary alkoxide acceptors were used in the reaction. With less reactive sugar alkoxide nucleophiles a different picture began to arise, however. Our initial indication that something more complex was going on came with reacting glucose with the sterically and electronically deactivated alkoxide **27** (Scheme 5B) With this acceptor, the $BTMSO_2Cl$ promoter afforded the disaccharide product **28** as a 6:1 (β/α) mixture of isomers, while NsCl promoted the same reaction to give the product as a 16:1 mixture of anomers.[29]

The reason for this change in selectivity quickly became apparent when we used VT-NMR to study the stability of the sulfonate intermediates. Specifically, while the sulfonate derived from NsCl was stable above 0 °C, the sulfonate derived from $BTMSO_2Cl$ rapidly decomposed at this temperature. Hypothesizing that the observed changes in selectivity were due to a change in mechanism from S_N2 to S_N1, we carried out primary kinetic isotope effect studies on the selective reactions with primary acceptors.[30] These experiments showed that the selective reactions had a primary ^{13}C KIE of 1.03, between the extremes of S_N2 and S_N1.

To better understand the reactivity in selective reactions we turned to DFT calculations [B3LYP-D3(BJ)/6-31G*/PCM(THF)] shed further light on the situation. These calculations indicating an asynchronous, invertive transition state where the sodium counterion of the alkoxide serves as a Lewis acid to activate the sulfonate for displacement. By virtue of the electrostatic interactions between the cation and the alkoxide, the resulting pre-organized transition state sets up both coupling partners for a selective reaction (Figure 1).

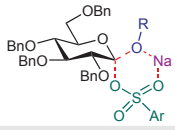
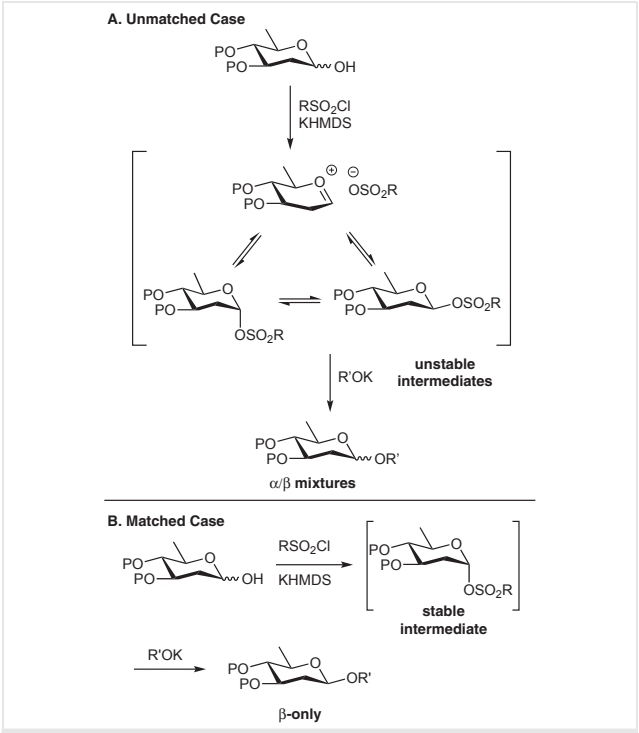


Figure 1 Transition state for S_N2-like glycosylations using glycosyl sulfonate donors. The sodium cation (purple) is responsible for both activating the sulfonate leaving group (green) and pre-organizing the transition state with the alkoxide nucleophile (blue).

Extending these observations to reactions with other sugar donors and hindered acceptors, we found that different sulfonates were necessary. For galactose the 4-bromobenzenesulfonyl chloride was the optimal promoter, while for fucose the 4-fluorobenzene sulfonyl chloride was superior. To rationalize these results, we looked at the Hammett σ constant of the substituent on each of the optimal promoters as a measure of how electron deficient they were. This revealed a trend, where there was a relationship between the relative reactivity of the donor and the electron deficiency (and by analogy the leaving group ability) of the sulfonate. From these studies we were able to put together a mechanistic proposal (Scheme 6). When the reactivity of the sulfonate leaving group is 'matched' to the reactivity of the donor, the sulfonate is stable until activated by the cation of the alkoxide for an S_N2-like reaction. Conversely, when the sulfonate and donor are not matched, ionization can occur leading to either S_N1 processes or inversion of the leaving group to the more reactive β-sulfonate which reacts through an S_N2-like process to give α-linked products. While studies to further understand this reactivity in *O*-

glycoside formation continue to be an ongoing process in our lab, we also became intrigued by the possibility that this process could be applied to other classes of nucleophiles. In particular, we were drawn to *C*-glycosides for many of the reasons outlined in section 1.



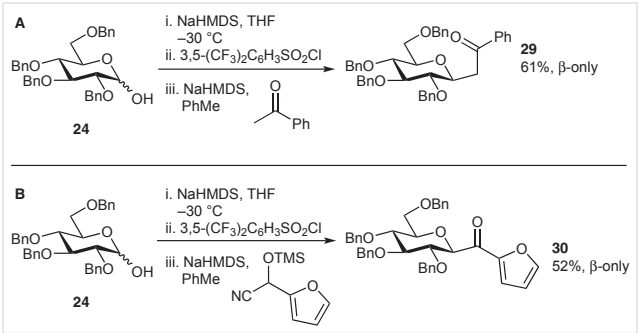
Scheme 6 Role of sulfonate/donor matching in controlling selectivity in glycosylation reactions. (A) In an unmatched case scrambling of the anomeric stereochemistry leads to nonselective reactions. (B) When the donor and sulfonate are matched selective reactions occur.

5 β-Linked *C*-Acyl and Homoacyl Glycoside Synthesis

We chose to use glucopyranoside donor **24** as the model compound for our *C*-glycoside studies owing to how well it behaved in our *O*-glycoside work. This left two questions to address. First was the choice of sulfonate leaving group. While NsCl worked better with more hindered nucleophiles, $BTMSO_2Cl$ provided higher yields with more reactive primary acceptors. In anticipation of the increased nucleophilicity of many carbon nucleophiles, we therefore decided to proceed with the latter promoter.

A second decision that we had to make was choosing the appropriate nucleophile. To this end we chose to examine both alkyl cuprates and enolates in the reaction. We choose cuprates owing to reports that they could undergo S_N2 reactions with alkyl sulfonates,[31] while enolates were explored owing to their successful use in other *C*-glycosylation reactions.[9,11] Unfortunately, all attempts to obtain a reaction with cuprates failed to provide productive reactions, instead leading to elimination. In hindsight, this should not have been too surprising considering alkyl sulfonates are chromatographically stable species, while glycosyl sulfonates typically decompose rapidly above cryogenic temperatures (*vide supra*).

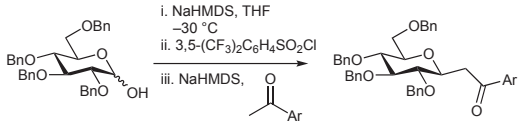
A different picture emerged when stabilized nucleophiles were used in the reaction. While aliphatic enolates proved to be unproductive in the reaction, the sodium enolate of acetophenone did produce the desired product **29** in 52% yield as a single β-anomer. The reaction also produced a significant (11%) amount of *O*-alkylation product. We attempted to suppress this reaction by using a tighter coordinating counterion, such as lithium. Unfortunately, using the lithium enolate of acetophenone in the reaction led to a reduction in yield, and no reaction was observed when LiHMDS was used to activate the hemiacetal donor. In hindsight, these results make sense based off our mechanistic studies with *O*-glycosylation. This work was carried out concurrently with those studies, however, and we did not have the information at that time.



Scheme 7 *C*-Glycosylations with enolate (A) and *O*-TMS-protected cyanohydrin nucleophiles (B)

A solution was found by moving to more nonpolar solvents to strengthen enolate oxygen-counterion interactions. In particular, toluene was found to be a superior medium to suppress *O*-alkylation without compromising the yield of the reaction (Scheme 7A). Notably, the reaction was found to be unaffected by the electronics of the aryl substituent on the enolate, and both electron-deficient and electron rich-rings provided the desired products in good yield as single diastereomers (Table 1). Heterocycles were also found to be compatible with the reaction conditions, opening the possibility for further elaboration of the products. Importantly, kinetic isotope effect studies on the reaction showed that as with the *O*-glycosylations it was indeed proceeding through an S_N2-like manifold, and not an addition/isomerization pathway.[32]

Table 1 Effect of Aromatic Electronics on the *C*-Glycosylation



Entry	Ar	Yield (%)[a]
1	4-MeC_6H_4	65
2	4-$MeOC_6H_4$	54
3	4-ClC_6H_4	62
4	4-$O_2NC_6H_4$	52
5	4-$F_3CC_6H_4$	62
6	2-furyl	60
7	2-thienyl	60

[a] β-only.

Exploring the scope of the reaction, we found that galacto-configured hemiacetals and disaccharides were also competent donors for the reaction. More importantly, we found that metalated *O*-TMS-protected cyanohydrins were also competent nucleophiles in the reaction, opening the door to a method for the direct formation of *C*-acyl glycosides (Scheme 7B). Again, both aromatic and heteroaromatic cyanohydrins were competent donors in the reaction, while aliphatic cyanohydrins did not lead to productive reactions under the current conditions.

6 Elaboration to Other Products

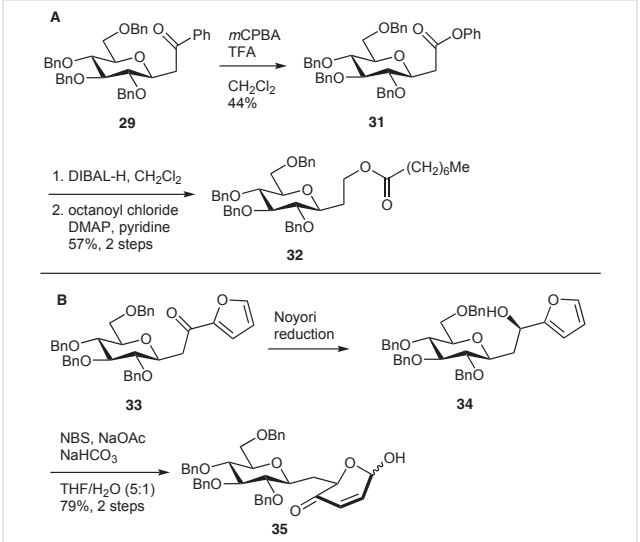
While we were very pleased to have developed a method for the direct β-specific construction of *C*-glycosides without recourse to specialized protecting group schemes, we felt the need for stabilized nucleophiles was a limitation to the reaction. Given the difficulties we had in using non-stabilized nucleophiles in the reaction, we therefore set about examining methods to elaborate the glycosylation products into more complex materials. To this end, we decided to target two classes of compounds: glycolipid and *C*-disaccharide mimetics.

We envisioned that *C*-glycolipid mimetics could be obtained through a sequence that was initiated through a Baeyer–Villiger reaction to convert **29** into the corresponding ester **31**. While this looked good on paper it was easier said than done. The use of *m*CPBA alone in the reaction failed to provide any product. After considerable experimentation, we found that the addition of TFA was necessary to drive the reaction.[33] At this point, a simple reduction/esterification sequence was performed to afford glycolipid mimetic **32** (Scheme 8A).

The synthesis of *C*-pseudodisaccharide mimetics appeared to be more challenging but was in fact much easier to execute. To this end, furan-containing glycoside **33** was subjected to Noyori transfer hydrogenation to afford chiral alcohol **34**. Following work from the O'Doherty lab,[34] **34** was subjected to an Achmatowicz rearrangement to provide **35** in 79% yield over the two steps (Scheme 8B). Since it is well established that enones such as **35** can be transformed into the corresponding sugar, this effectively represents a pseudo-*C*-linked disaccharide, albeit one with a truncated linkage between the residues. All the same, one could envision similar sequences for more native type linkages.

7 Conclusion

What had started as an effort to develop a more efficient synthesis of β-linked 2-deoxy glycosides has evolved into a much more comprehensive research program. Along the way we have expanded our program to include complex molecule synthesis, leading to some of the most efficient syntheses of deoxy sugar oligosaccharides reported to date. As we expanded this chemistry, we delved into physical organic chemistry studies in order to understand how these reactions worked. Finally, in an effort to further extend these studies, we developed *C*-glycosylation reactions, providing products that are arguably more similar to the polyketides I worked with as a graduate student than the carbohydrates upon which my own research program is built. Perhaps more importantly, we have come to realize that there is still much to learn about *C*- and *O*-glycoside synthesis, especially in cases where the sulfonate chemistry



Scheme 8 Elaboration of *C*-acyl glycosides into more complex products

does not behave as expected.[35] The students in my laboratory and myself do not view this as a negative, however. Rather, one of the greatest aspects of chemistry occurs when answering one question opens up several new lines of inquiry. Even in a field as venerable as carbohydrate chemistry, there are still many important unanswered questions before us. We look forward to seeing where our journey along the road of carbohydrate chemistry and glycoscience takes us in the future.

Conflict of Interest

The authors declare no conflict of interest.

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