The Synthesis of Sulfated Carbohydrates Using 2,2,2-Trichloroethoxysulfuryl Imidazolium Triflates

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Abstract

The synthesis of an entirely new class of sulfating agents in the form of 2,2,2-trichloroethoxysulfuryl-*N*-methylimidazolium triflate is reported. This reagent was shown to be highly effective for incorporating trichloroethyl (TCE) protected sulfate groups into carbohydrates. The resulting TCE-protected sulfodiester carbohydrates were stable to a wide range of conditions including protecting group manipulations, anomeric activations and coupling conditions. The TCE group could be readily removed under mild conditions that do not affect most other protecting groups commonly used in carbohydrate chemistry or glycosidic linkages. These results indicate that monosaccharides bearing TCE-protected sulfate groups can be used as building blocks for the synthesis of sulfated oligosaccharides. This route to sulfated oligosaccharides represents a significant improvement over current approaches.

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For Dad, Mum, Kristy and Julie

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List of Abbreviations

Ac	– acetate
ACN	– acetonitrile
Bn	– benzyl
Bz	– benzoyl
CAN	– cerium (iv) ammonium nitrate
DBU	– 1,8-diazabicyclo[5.4.0]undec-7-ene
DIEA	– diisopropylethylamine
DMF	– dimethylformamide
GAG	– glycosaminoglycan
Gal	– galactose
Glc	– glucose
GalNAc	– *N*-acetylgalactosamine
GlcNAc	– *N*-acetylglucosamine
Im	– imidazole
Man	– mannose
NBS	– *N*-bromosuccinimide
NIS	– *N*-iodosuccinimide
NMI	– *N*-methyl imidazole
Ph	– phenyl
Phth	– phthalimide
PIFA	– phenyliodine (III) bis(trifluoroacetate)
Py	– pyridine
PMB	– *p*-methoxy benzyl
SAR	– structure activity relationship
SL-1	– Sulfolipid 1
TBAF	– tetrabutylammonium fluoride
TCE	– trichloroethyl
TDS	– thexyldisilyl
TES	– triethylsilyl
TFA	– trifluoroacetic acid
TFE	– trifluoroethyl
THF	– tetrahydrofuran
Tol	– tolyl/toluene

Chapter 1 – Introduction

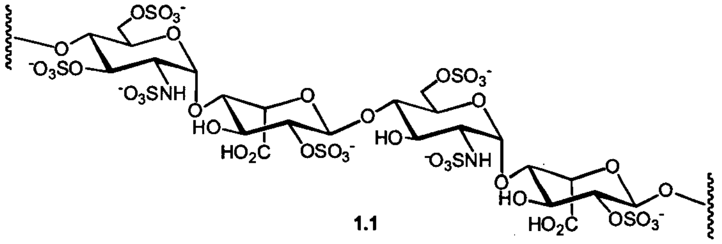
1.1 Sulfated Carbohydrates

One of the unique features of carbohydrates is the limitless number of distinct structures that can be obtained from combining individual monosaccharide building blocks. Oligosaccharides are naturally assembled with different types of linkages, at varying positions, forming straight chain or branched polymers. Further modifications such as alkylation, phosphorylation, and sulfation provide additional structural complexity to the already diverse compounds.

Sulfated oligosaccharides play important structural and functional roles in numerous biological systems. The compounds are major constituents of glycosaminoglycans (GAG), which play key roles in modulating bioactive proteins and peptides, and thus are responsible for controlling many physiological events.

The high degree of variability among biologically relevant sulfated carbohydrates is attributed to a number of factors. There is variability with respect to monosaccharides which are sulfated (*i.e.* glucose (Glc), galactose (Gal), the corresponding *N*-acetyl amines GlcNAc, GalNAc, and mannose (Man) among others); the total number of sulfate moieties, and hydroxyl(s) to which the sulfate group(s) are linked (*i.e.* 2-*O*, 3-*O*, 4-*O*, 6-*O* sulfates, and any resulting combination from multiple sulfations); and also the diverse structure of the underlying oligosaccharide moiety. An important consequence of this structural diversity is that each unique structure has the potential to be recognized by an individual receptor, making sulfated oligosaccharides ideal for carrying information in complex biological systems.

Some of the most well known sulfated carbohydrates are heparin fragments (**1.1**), shown in figure 1.1.[1] These sulfated GAGs isolated from animal tissue are the only commercially available carbohydrate based drugs, and have been clinically applied since the 1940's as an antithrombotic agents.



1.1

Figure 1.1: Typical fragment obtained from degradation of heparin

The isolation and structure elucidation of natural heparin lead to the synthesis of active analogs such as pentasaccharide **1.2**, first synthesized in over 60 steps with extremely low yield and purity, and its stabilized methyl glycoside **1.3** which is one of the heparin analogs currently used for the prevention of venous thromboembolic events after surgery.[1]

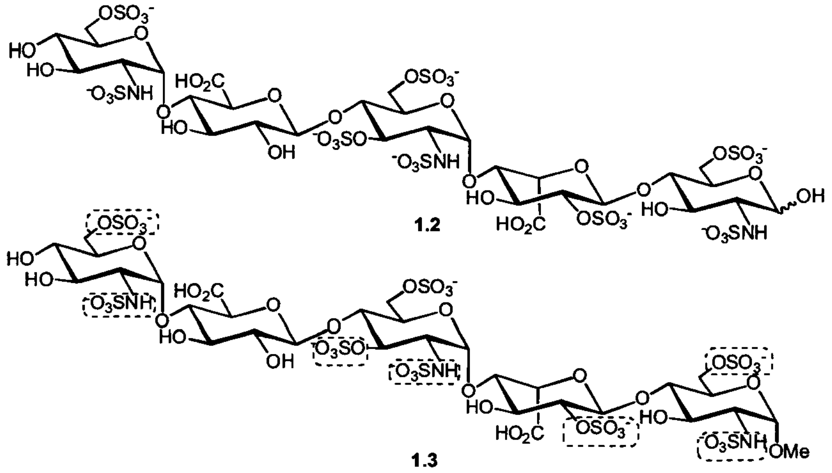


Figure 1.2: Synthetic analogs of heparin - critical sulfate groups highlighted.

Even though it still comprises many steps and only moderate yields, the synthesis of **1.3** is industrially performed on a multi-kg scale. The synthetic strategy is based on the idea of orthogonal protection, in which the positions bearing sulfate groups are esterified, whereas the hydroxyl groups in the product are masked as benzyl ether groups. The fully protected pentasaccharide is first prepared; the locations that bear the sulfates are deprotected and then *O*-sulfated. The remaining benzyl and azido groups are subjected to hydrogenolysis, and selective *N*-sulfation affords the desired pentasaccharide **1.3**. Through extensive structure-activity relationship (SAR) studies, the majority of the sulfate groups (as indicated in figure 1.2) on pentasaccharide **1.3** were determined to be essential groups, and therefore are required for biological activity.

Other more recent sulfated carbohydrates of interest include disaccharide **1.4** (figure 1.3), known as sulfolipid-1 (SL-1), which is a virulence factor in strains of *Mycobacterium tuberculosis*.[2,3] SL-1 contains a common trehalose core modified with four lipid chains, and a sulfate group at C2 of the first monomer. The sulfate group is critical for virulence.[2,3] Recently, Hsieh-Wilson and coworkers reported that tetrasaccharide **1.5**, a fragment of a chondroitin sulfate glycoaminoglycan, stimulates neuronal growth.[4] The presence of the four sulfate residues was absolutely essential for the stimulatory activity.[4] In 2004, Schroeder and co-workers isolated and identified a family of unusual sulfated nucleoside derivatives, such as **1.6** from the venom of the grass spider *Hololena curta*.[5] The neurotoxin **1.6** is a unique bisulfated glyconucleoside that was found to have an uncommon ability to effectively block kainate receptors in addition to weakly blocking calcium channels. Interestingly, these authors summarize their article by commenting on the fact that a literature search revealed very little synthetic information about these molecules, which results in very little evaluation of their biological properties. They concluded that the synthesis and subsequent biological activity studies remain important objectives for their work.[5]

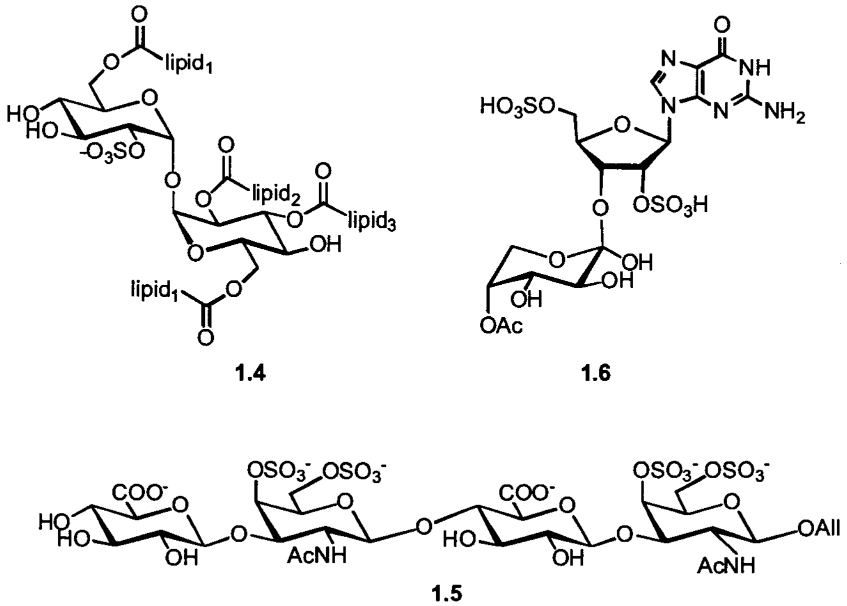
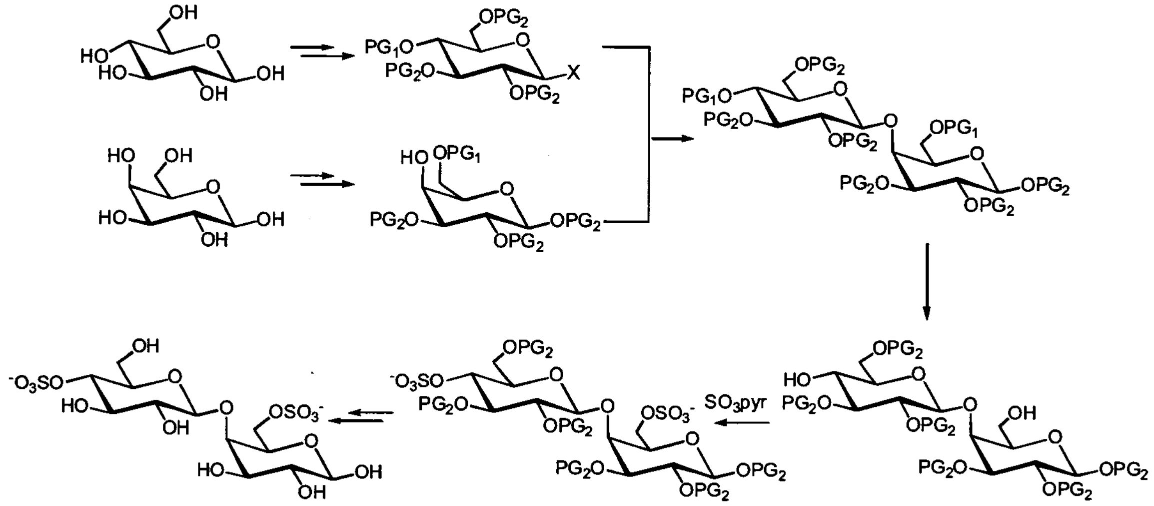


Figure 1.3: Sulfolipid-1 (1.4), Chondroitin sulfate fragment (1.5), and HF-7 (1.6)

1.2 Synthesis of Sulfated Carbohydrates

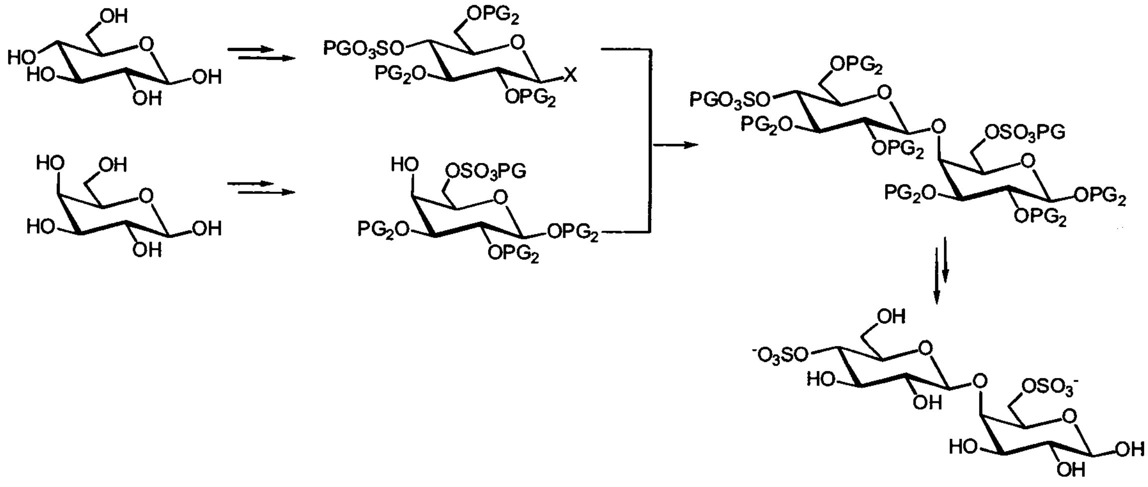
Although sulfated carbohydrates have been synthetically obtained for several decades, their synthesis still remains a considerable challenge. In the current approach, as outlined in scheme 1.1, monosaccharide or disaccharide building blocks are fully protected with the hydroxyls that will ultimately bear the sulfate groups protected in an orthogonal manner to those that will not be sulfated. After assembly of the oligosaccharide, the locations that are to be sulfated are independently deprotected, the sulfate moiety is introduced, and then all other protecting groups are removed to give the final product.



Scheme 1.1

There are several drawbacks to this method. First, intensive protecting group manipulations are required, which results in a lengthy and complex synthesis. Second, after sulfation, the resulting products are highly polar, and thus are difficult to purify and manipulate for subsequent deprotections. Finally, conventional sulfation methods such as sulfur trioxide – amine complexes can be complicated, and low yielding when multiple sulfations are necessary.

One way of getting around this problem would be to introduce the sulfate group at the monosaccharide building block stage as a protected sulfate diester (Scheme 1.2). This would reduce the required protecting group manipulations, and yield less polar compounds that are easier to manipulate. In this thesis, we introduce the 2,2,2-trichloroethyl protecting group for sulfated carbohydrates. To achieve this, we report an entirely new class of sulfating agents capable of introducing the TCE protected sulfates to monosaccharide building blocks; we also demonstrate that the TCE protected sulfates are highly tolerant to most conditions encountered in carbohydrate chemistry, yet can be easily unmasked to provide the free sulfates as desired.



Scheme 1.2

1.3 Protecting Groups for Sulfated Carbohydrates – Background

Although the idea of protecting the sulfate group during sulfocarbohydrate synthesis has been around for some time, applications of this approach have been very limited. The reason for this has to do with the number of sulfate protecting groups that are available, and the ease by which they can be incorporated into the carbohydrate building blocks, and then removed to provide the free sulfate. The limited number of protecting groups is a direct consequence of the chemical reactivity of sulfate mono- and diesters. Acid labile protecting groups cannot be used due to the well-known instability of sulfate monoesters to acid.[6] Furthermore, sulfate diesters are highly susceptible to nucleophilic attack, which can occur at either the sulfur atom or carbon atoms of the C-O-S bonds (figure 1.3).[7]

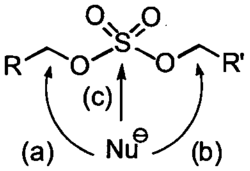


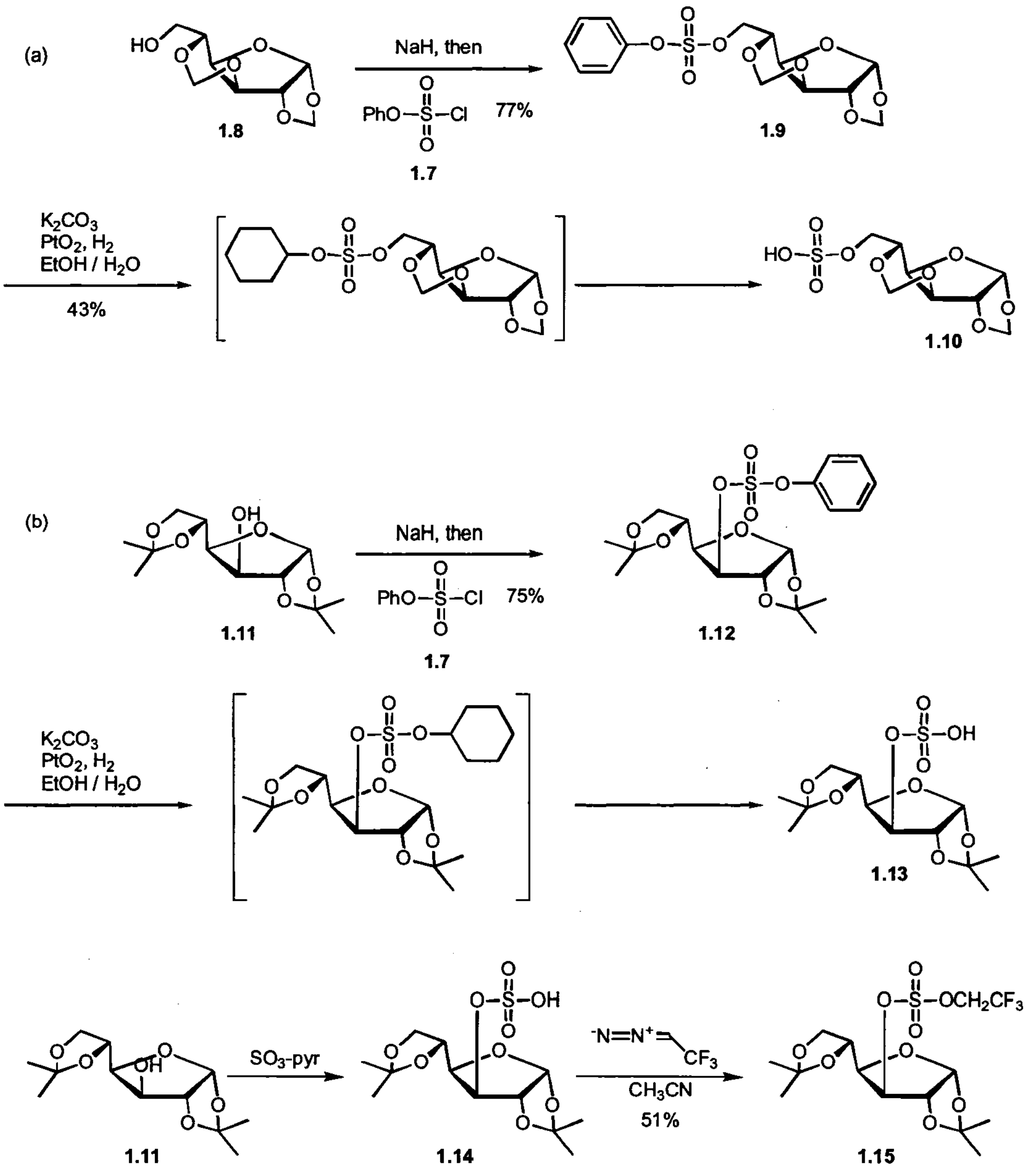
Figure 1.4: Nucleophilic attack on a sulfate ester – 3 possible routes

When R is a carbohydrate, substitution by path (a) is generally slow, especially so for the sulfate esters of secondary alcohols. The idea of protected carbohydrate sulfate diesters focuses on disfavouring attack by route (a) (figure 1.3), with the strategic design of R' in a manner which favours attack by route (b) without rendering the protecting group ineffective, as the protecting group is expected to be stable to many different chemical manipulations.

The reactivity properties of sulfate diesters eliminates the possibility of using protecting groups that are removed by hydrogenolysis or photolysis, since these are usually benzylic moieties, and so are very susceptible to nucleophilic displacement. If base labile protecting groups are used, they would have to be designed such that they are stable enough to nucleophiles while being removed under conditions that are not too harsh. In light of these difficulties, it is not surprising that, until recently, only a few protecting groups for sulfate esters have ever been reported.

1.3.1 Phenyl protected sulfocarbohydrates

Penney and Perlin were the first to propose using protected sulfated monosaccharide building blocks for the synthesis of sulfated oligosaccharides by employing phenyl protected sulfate moieties.[8] Two carbohydrates were used as model systems (scheme 1.3a,b). Phenyl chlorosulfate **1.7** was reacted with protected carbohydrates **1.8** and **1.11** to afford the corresponding phenyl sulfocarbohydrates **1.9** (scheme 1.3a) and **1.12** (scheme 1.3b). Removal of the phenyl protecting group was achieved by subjecting **1.9** and **1.12** to a solution of excess potassium carbonate and cat. platinum oxide / H_2 in ethanol-water. This resulted in hydrogenation of the phenyl ring to a cyclohexyl group, which was removed to give the desired sulfated carbohydrates **1.10** and **1.13**.

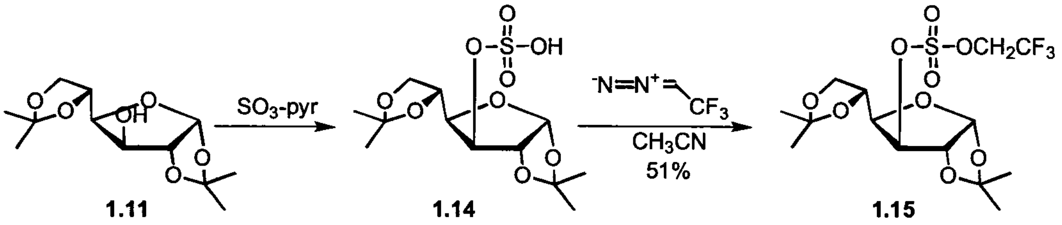


Scheme 1.3

Stability studies showed that the phenyl protecting group was stable to a number of conditions including trifluoroacetic acid (TFA) in $CHCl_3$, Ac_2O-AcOH /cat. H_2SO_4, NaOMe at room temperature, 2:1 NH_4OH-pyridine, CsF in CH_3CN, and KF / 18-C-6, but not tetrabutylammonium fluoride (TBAF) in THF or HCl.[8] Despite this method being the first approach to the synthesis of protected carbohydrate sulfate diesters, it exhibited a number of limitations. Cleavage of the sulfate diester required conditions that are not compatible with other protecting groups that are sensitive to base and hydrogenolysis. The deprotected products required tedious purifications involving anion exchange resins, and removing the phenyl protecting group was found to result in partial desulfation leading to poor yields of the desired products. Because of these limiting factors, Penney and Perlin's method was not widely applied to the synthesis of sulfated carbohydrates.

1.3.2 Trifluoroethyl protected sulfocarbohydrates

The idea of protected sulfates in carbohydrate chemistry did not resurface until sixteen years later, when Proud *et al.* offered an alternative to the phenyl group.[7] In 1997, these authors proposed the use of trihaloethyl sulfate esters, suggesting that these moieties would be stable to nucleophilic attack (as indicated in figure 1.3) for both steric and electronic reasons, and could offer versatile protection in many aspects of carbohydrate chemistry. Their initial attempts focused on the trichloroethyl (TCE) group, since it had previously been used for phosphate and carboxyl protection.[9] This appeared to be an unusual first choice, since these authors anticipated that it could be successfully removed from the protected sulfocarbohydrate without the loss of the sulfate group using Zn/AcOH, which is unlikely due to the poor stability of the sulfate monoesters to acid. Nevertheless, they never got the opportunity to test their hypothesis, since they were unable to prepare the TCE-protected sulfocarbohydrates. The authors stated that the reaction of 2,2,2-trichloroethyl chlorosulfate with carbohydrates proceeded in yields that were too low to be of use, attributing this to steric reasons. They therefore decided to examine the trifluoroethyl (TFE) group instead. Again, reacting 2,2,2-trifluoroethyl chlorosulfate with carbohydrates proceeded in poor yields. They were, however, able to develop a two step approach in which conventional sulfation methods such as sulfur trioxide / amine complexes were first used to prepare a sulfated carbohydrate such as **1.14**, which was then treated with 2,2,2-trifluorodiazoethane to give the desired TFE protected sulfocarbohydrate **1.15** (scheme 1.4).[7]



Scheme 1.4

Proud *et al.* extended the chemistry to synthesize a number of sulfated monosaccharides commonly used in the synthesis of complex carbohydrates (figure 1.5).

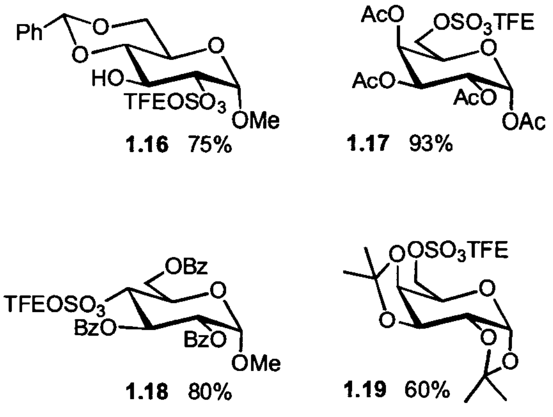
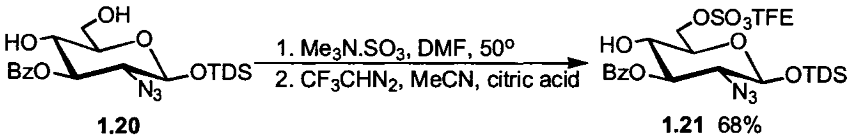


Figure 1.5: Formation of trifluoroethyl esters of carbohydrate sulfates

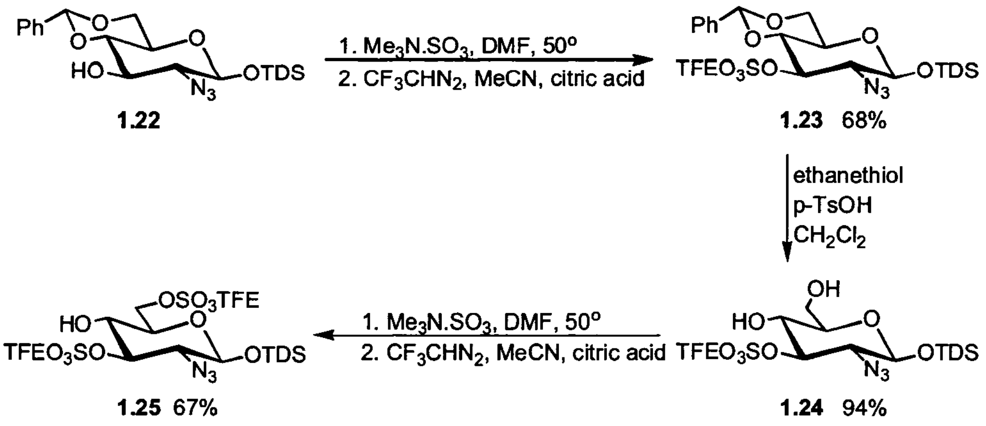
The TFE protecting group was found to be stable to a variety of conditions such as TFA in EtOH, TBAF, hydrogenation, and NaOMe in MeOH at room temperature and reflux.[7] This stability unfortunately, affected the ease with which the protecting group was removed, which required refluxing the protected carbohydrate in potassium *t*-butoxide in *t*-butanol. Deprotection yields ranged from 82-96 %. In certain cases such as **1.16** in figure 1.5, isomerization of the sulfate ester occurred during deprotection.

Despite the apparent potential that Proud *et al.*'s chemistry had for the synthesis of sulfated carbohydrates, it was another six years before it was examined in more detail. In 2003, Lindhart and coworkers published extensive studies on the use of the TFE group in the synthesis of fully differentiated hexosamine monosaccharides.[10] For example, selective 6-*O*-sulfation of carbohydrate **1.20** with sulfur trioxide-trimethyl amine followed by treatment with trifluorodiazoethane gave the TFE-protected sulfocarbohydrate **1.21** in 68% yield (scheme 1.4).



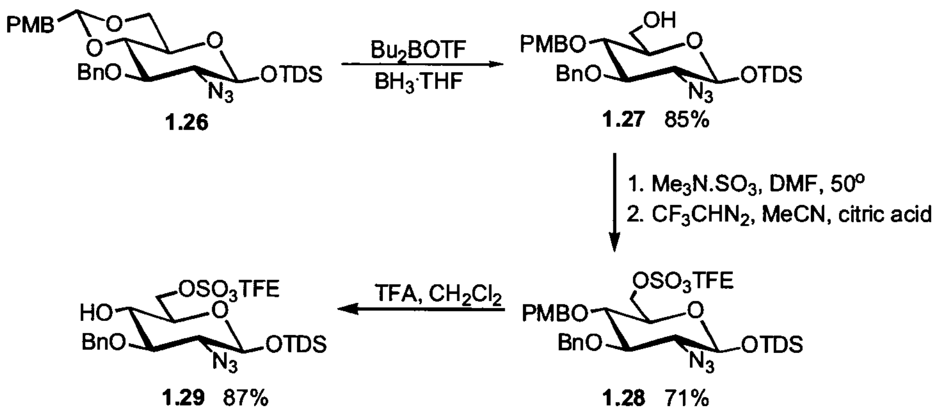
Scheme 1.5

Lindhart's group also prepared disulfo-derivative **1.25** (scheme 1.6) demonstrating that the TFE-sulfate moiety was compatible with the acidic conditions required for removing the benzylidene acetal in **1.23**, showing a greater versatility for the trifluoroethyl moiety.



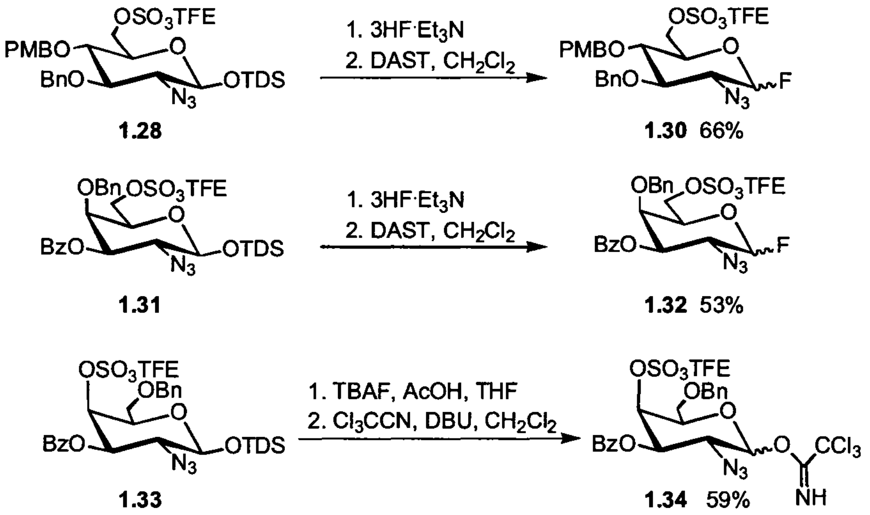
Scheme 1.6

Further monosaccharide building blocks employing *p*-methoxybenzylidene (PMB) protection at the 4,6-position of glucosamine derivative **1.26** demonstrated regioselective opening of the benzylidene ring to unmask the 6-position for sulfation. The PMB group was then selectively removed in acidic conditions to give glycosyl acceptor **1.29** (scheme 1.7).[10]



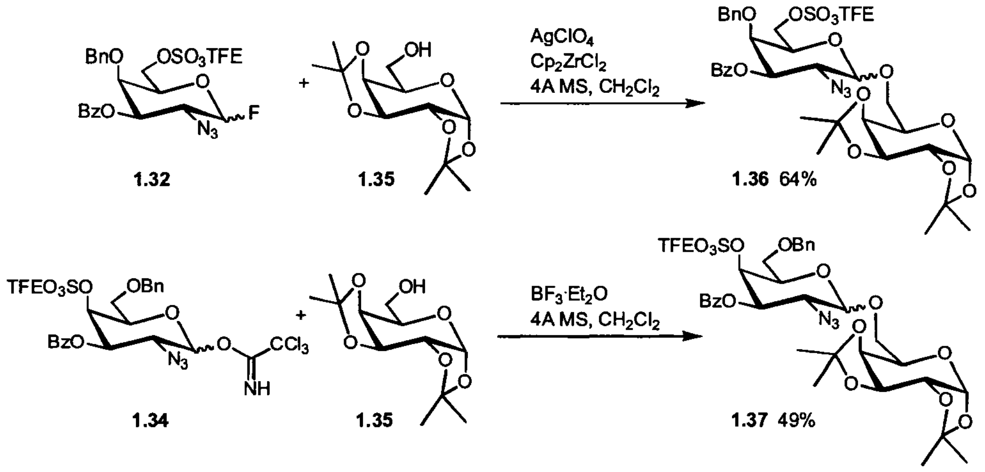
Scheme 1.7

Lindhart and coworkers then studied the preparation of activatable carbohydrates bearing the TFE sulfate moiety. Both fluoride and trichloroacetimidate species were prepared (scheme 1.8). It was reported that when present at the 6-position, the trifluoroethylsulfonate moiety acted as a good leaving group when using just TBAF to remove the anomeric thexyldisilyl (TDS) group on carbohydrate **1.28**, as 1,6-anhydro sugars were recovered as side products for the reaction (scheme 1.8). This was corrected when excess acetic acid was added to TBAF, or by applying a milder reagent such as trihydrofluoride triethylamine. It was also noted that partial loss of the sulfate protecting group was observed under the basic conditions required to prepare trichloroacetimidate **1.34** (scheme 1.8).



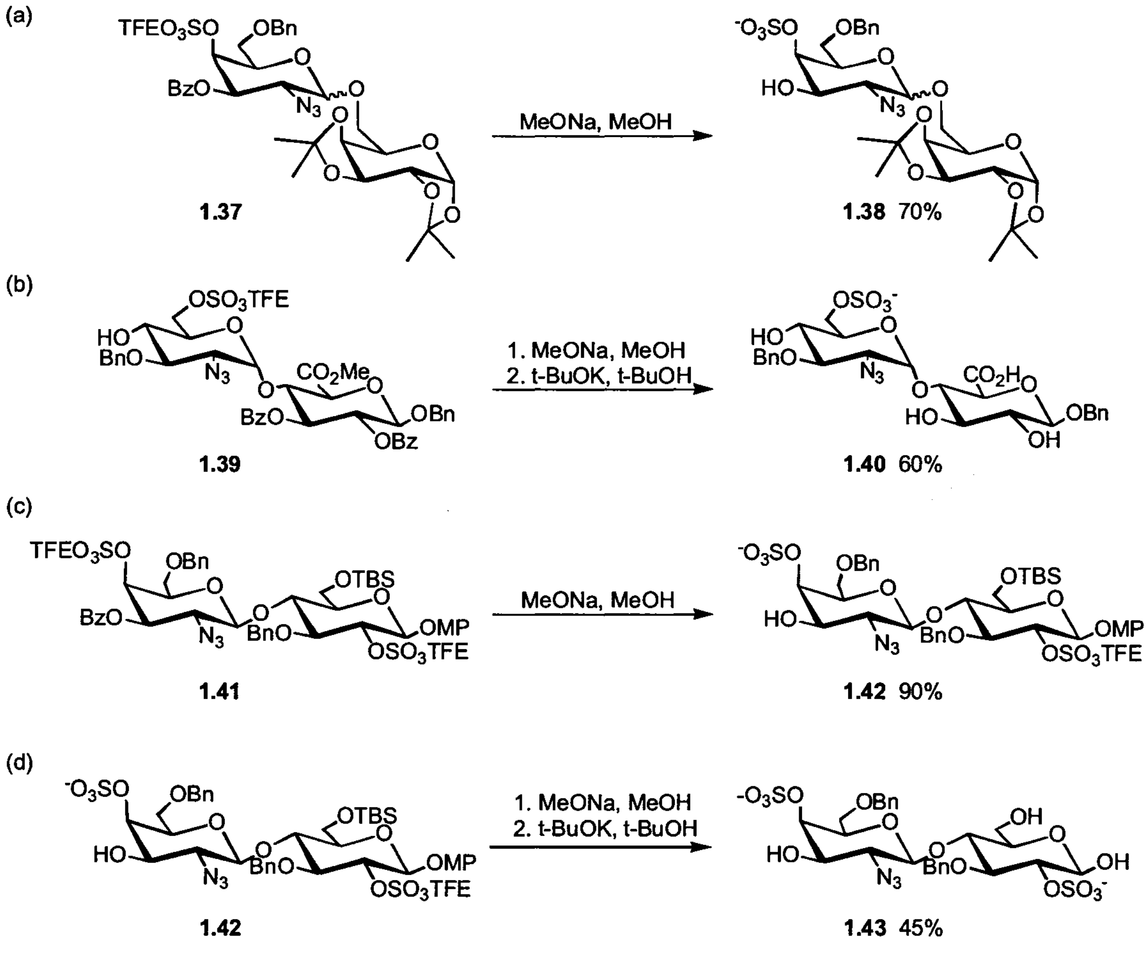
Scheme 1.8

Finally, preliminary glycosylation attempts via the coupling of α-fluoride **1.32** and α-imidate **1.34** with the 6-OH acceptor of **1.35** were reported (scheme 1.9).[10] Despite the electron-withdrawing character of the trifluoroethyl sulfonate, encouraging yields for the synthesis of **1.36** and **1.37** were reported in both cases.



Scheme 1.9

In July of 2004, a second publication from Lindhart and co-workers further described the synthesis of a variety of sulfo-protected monosaccharide donors and acceptors.[11] A wide variety of glycosylation reactions were studied, demonstrating the TFE sulfonate group was compatible with a range of activation conditions commonly used with fluoride, imidate, and sulfoxide donors. Despite the extensive TFE-sulfonate chemistry presented in the first publication, it was not until this second paper that Lindhart addressed the deprotection of the sulfate group (scheme 1.10), demonstrating that removing the TFE protecting group was quite difficult.



Scheme 1.10

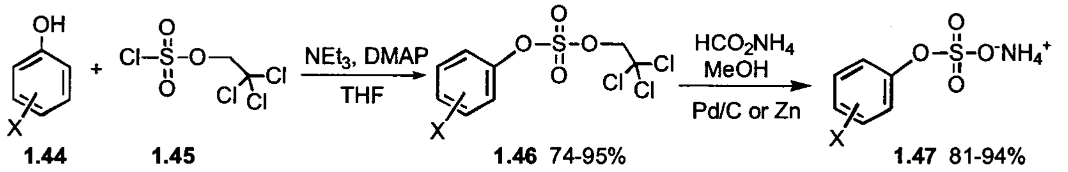
The standard conditions of *t*BuOK/*t*BuOH first reported for TFE-sulfate deprotection[7] were found to be too harsh for disaccharide **1.37** resulting in decomposition (scheme 1.10a). It was found that the TFE group could be removed using NaOMe/MeOH, conditions which Proud *et al.* reported that the TFE group was stable to,[7] affording the deprotected product **1.38** in a 70 % yield.[10,11] Deprotection of the 6-sulfate **1.39** (scheme 1.10b) presented an even greater challenge, as the *t*BuOK/*t*BuOH conditions lead to almost complete desulfation. It was found that the TFE protecting group could be removed under standard conditions only after the complete removal of the benzoyl esters in **1.39**, a method which resulted in minor loss of the sulfate group, compromising the final yield of **1.40**. Furthermore, for the 2,4-disulfo carbohydrate **1.41** (scheme 1.10c) a stepwise deprotection was required. The 4-position sulfate was removed with NaOMe/MeOH to afford **1.42**, which was then subjected to *t*BuOK/*t*BuOH to deprotect the 2-position sulfate, providing **1.43** (scheme 1.10d). Partial decomposition was also observed using this method, resulting in loss of the 6-OTBDMS and anomeric OMP protecting groups, therefore the deprotected product **1.43** was obtained in only a 45% overall yield.[11]

Although the TFE protecting group has allowed for the synthesis of protected carbohydrate sulfate diesters, and has proved to be stable to a number of synthetic conditions for complex carbohydrates, this strategy has not been widely applied to the synthesis of these compounds as the approach exhibits some strong limitations. The method relies on conventional sulfation techniques that can be unreliable. Introducing the TFE group involves the use of trifluordiazoethane, which is toxic and potentially explosive, and often proceeds in variable yields. Finally, and most significantly, removing the TFE group is difficult, and deprotection yields tend to be low when the substrate is more complex than a simple monosaccharide. While the approach is an excellent idea, alternative protecting groups and new methods for their introduction are required before this strategy becomes effective.

1.4 The 2,2,2-Trichloroethyl Protecting group for Sulfated Carbohydrates

Although the 1997 paper by Proud *et al.* focused on the TFE moiety, this was not the starting point for their research.[7] As previously stated, initial attempts involved the use of the trichloroethyl ester, a group that is used for phosphate and carboxyl protection.[9] Proud and coworkers had concluded that the TCE-sulfate moiety could not be incorporated into carbohydrates in good yields, and would not be useful for the synthesis of these compounds.[7] The TCE group has an advantage over the TFE group in that it is known to be cleaved under very mild conditions (such as Zn/AcOH). In order for this group to be used however, methodology would have to be developed for its introduction into sulfated carbohydrates in high yields without the use of toxic and explosive diazo derivatives, and a mild alternative for Zn/AcOH would have to be developed for it's removal.

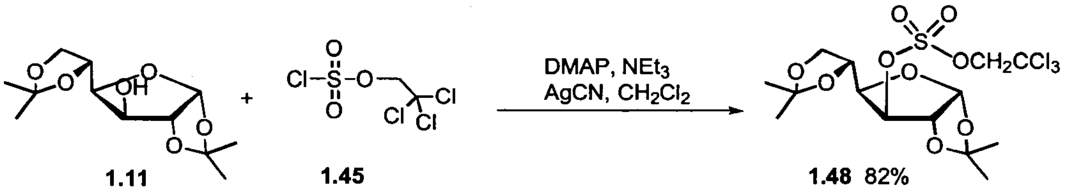
In 2004, the Taylor group reported the use of the TCE moiety as the first group for the protection of aryl sulfates.[12] They demonstrated that trichloroethyl chlorosulfate **1.45** can successfully be used to prepare protected aryl sulfates **1.46** in high yields (scheme 1.11).



Scheme 1.11

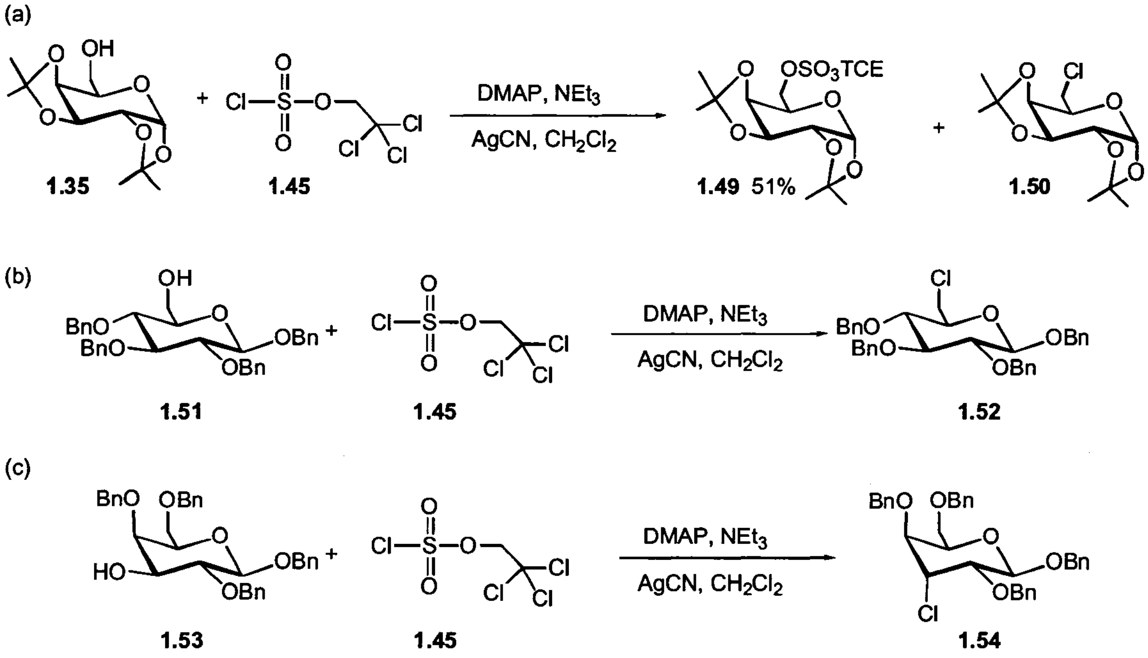
The TCE protecting group was easily removed in excellent yields under mild conditions by catalytic transfer hydrogenolysis using Pd/C and ammonium formate, or by using Zn and ammonium formate in methanol to obtain aryl sulfates **1.47**. This success prompted further investigation into the use of the TCE group for protecting alkyl sulfates, specifically carbohydrate sulfates.

The methodology reported by the Taylor group was expanded to show that TCE chlorosulfate **1.45** can be reacted with diacetone glucose **1.11** to give the sulfated **1.48** in 82% yield, according to scheme 1.12. This was an important development, since it contradicted Proud's previous conclusions that incorporation of the TCE group in high yields could not be achieved.[7]



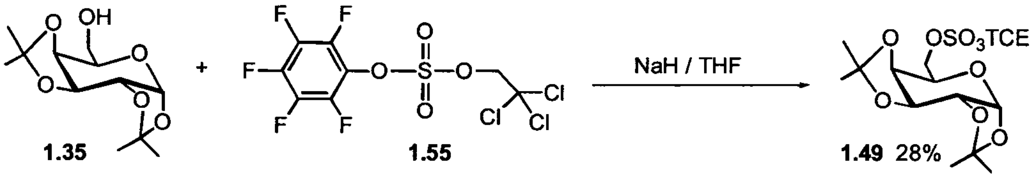
Scheme 1.12

Attempts to extend the chemistry to other carbohydrates were found to be more difficult than expected. For example, reacting 1:2,3:4-di-*O*-isopropylidene galactose **1.35** with the TCE chlorosulfate **1.45** gave carbohydrate **1.49** in only a 51% yield (scheme 1.13a). Analysis of the reaction products revealed that displacement of the TCE sulfate moiety by the liberated chloride ion to give chlorosugar **1.50** was a competing reaction. Attempts to repeat this chemistry to include benzyl protected carbohydrates **1.51** and **1.53** (scheme 1.13b,c) were less successful, as the reactions proceeded very slowly, and the chlorosugars **1.52 and 1.54** were the major products in both cases.



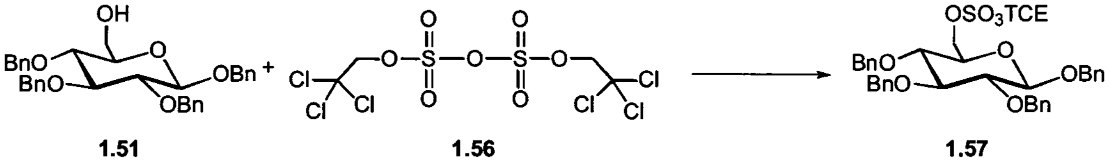
Scheme 1.13

The unexpected side reactions described in scheme 1.13 led to the investigation of alternative approaches. The chemistry was modified so that the chloride ion in sulfating reagent **40** was replaced by pentafluorphenol, with expectations that it would be an adequate leaving group, but too sterically hindered to displace the TCE-sulfate moiety. Unfortunately the new reagent **1.55** was not as reactive as expected, with the most successful outcome being a 28% yield of carbohydrate **1.49** (scheme 1.14).



Scheme 1.14

The undesired outcomes with the TCE-sulfonyl compounds **1.45** and **1.55** led to the examination of new sulfating methods. It was then proposed that reacting sulfo anhydride **1.56** with a carbohydrate such as **1.51** (scheme 1.15) should effectively incorporate the protected sulfate while avoiding the displacement reaction previously discussed. Despite literature precedent for the synthesis of similar anhydride compounds,[13] this route was abandoned due to the difficulties encountered in the preparation of anhydride **1.56**.

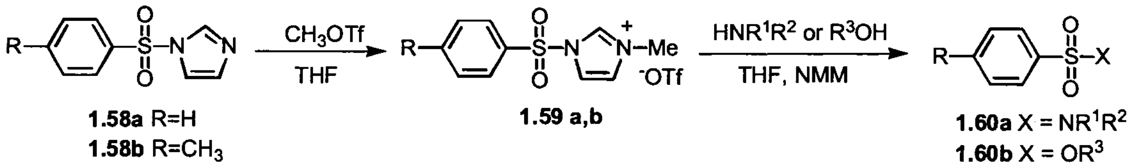


Scheme 1.15

1.5 Sulfuryl Imidazolium Salts for the Preparation of Sulfate Diesters

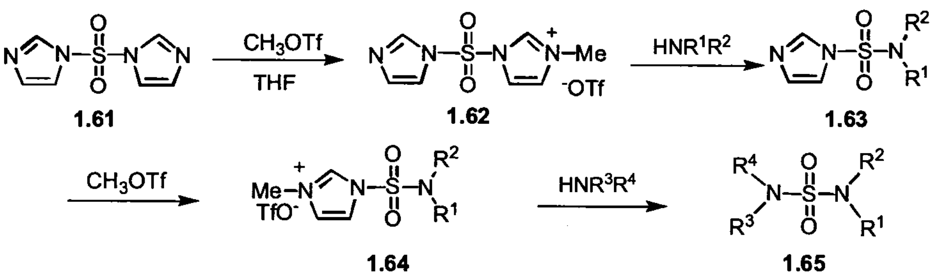
In 1992, O'Connell and Rapoport published a paper describing the use of sulfonyl imidazolium salts for preparing sulfonates and sulfonamides.[14] Traditional synthetic methods for preparing toluenesulfonyl or benzene sulfonyl derivatives employ the corresponding sulfonyl chloride or anhydride in the presence of pyridine or aqueous base. These procedures have limited effectiveness when the nucleophiles are insufficiently nucleophilic, are sterically encumbered, and when the liberated chloride ion (from the sulfonyl chloride reagent) is responsible for undesired side reactions, much like those observed during the attempted synthesis of the TCE protected carbohydrate sulfates.

O'Connell and Rapoport found that sulfonyl imidazolium salts were very reactive arylsulfonyl transfer reagents, capable of reacting with even poorly nucleophilic substrates.[14] The reagents were prepared by reacting benzenesulfonyl and toluene sulfonyl imidazolides **1.58a** and **1.58b** with methyl triflate (scheme 1.16). Reacting these species with alcohols or amines gave the corresponding sulfonates **1.60a** and sulfonamides **1.60b** in excellent yields (scheme 1.16). The released *N*-methylimidazole (NMI) is a poor nucleophile, and does not result in the formation of additional displacement products.



Scheme 1.16

In 2003, Burns and co-workers reported the sequential activation of *N*,*N*-sulfuryldiimidazole **1.61** as for the preparation of sulfonyl ureas (scheme 1.17).[15] In this method, sequential activation of each imidazole moiety using methyl triflate followed by displacement with an amine leads to the formation of unsymmetrical sulfonyl ureas such as **1.65**. During the attempts to mono-alkylate **1.61**, it was found that the resulting triflate species **1.62** could be precipitated from the reaction mixture and isolated by filtration.[15]



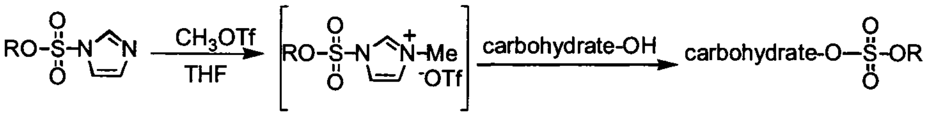
Scheme 1.17

Although sulfonyl imidazolium salts have been used to prepare sulfonates, sulfonamides and sulfonyl ureas, this approach has never been used to prepare sulfate diesters.

1.6 Project Objectives

At the outset of this project, our ultimate objective was to develop reliable methodology that would allow for efficient access to sulfated carbohydrates. With the undesired displacement reactions described in scheme 1.13 and the ineffectiveness of reagent **1.55** (scheme 1.14) it was clear that in order for this approach to be viable, an alternative sulfating agent was required.

Our first goal was to develop a highly reactive alkylsulfuryl transfer reagent that was capable of sulfating poorly reactive substrates without liberating a nucleophilic species such as a chloride ion. Based on the methodology developed by O'Connell and Rapoport, we anticipated that, if they could be prepared, alkylsulfuryl imidazolium triflate reagents (such as **1.68**) could serve as reactive sulfating agents according to scheme 1.18.



1.67 **1.68** **1.69**

Scheme 1.18

We could envision treating sulfuryl imidazole **1.67**, where R is the protecting group of choice, with methyl triflate to give imidazolium salt **1.68** from which a carbohydrate nucleophile could obtain a protected sulfate group giving the corresponding carbohydrate sulfate diester **1.69** (Scheme 1.18). If the imidazolium salt is stable, it might even be possible to isolate it and store it until needed.

Our synthetic strategy focused on the TCE protecting group expecting that it would be stable to nucleophilic attack, yet easily removed in mild conditions. Our research goals included: (1) To determine if a sulfuryl imidazolium salt of the type **1.68** can be prepared; (2) to examine the use of TCE sulfuryl imidazolium triflates in the preparation of protected carbohydrate sulfates; (3) to demonstrate the viability of the TCE protecting group by subjecting the sulfated carbohydrates to a number of conditions commonly encountered in carbohydrate chemistry; (4) to employ sulfated monosaccharide building blocks in the synthesis of more complex carbohydrates; and (5) to demonstrate that the TCE-protected sulfates can be unmasked under mild conditions to provide the desired sulfocarbohydrates.

1.7 References

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Chapter 2 – Preparation of Trichloroethoxysulfuryl Imidazolium Triflate and Synthesis of Sulfated Carbohydrates

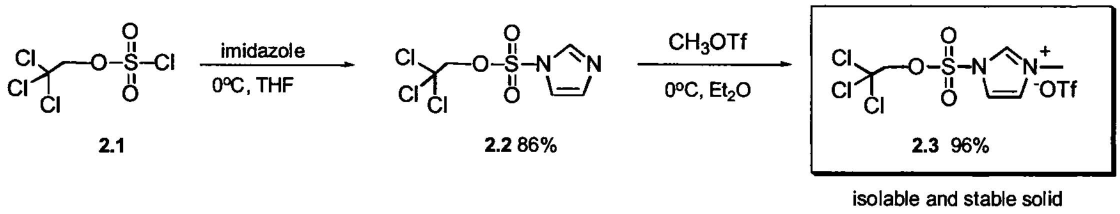
2.1 Introduction

The need for a reliable method to obtain sulfated carbohydrates is becoming more and more prevalent. Biologically relevant sulfated carbohydrates are consistently being discovered and characterized; however synthetically obtaining these compounds still remains a challenge. The idea of introducing a sulfate group as a protected sulfate diester has yet to become widely applied, due to the difficulties encountered in both incorporation and deprotection of the sulfate moieties. In this chapter, we show that the 2,2,2-trichloroethyl protected sulfates can offer a viable alternative to the previous methods, demonstrating the $TCESO_3$ group can be incorporated into carbohydrates in excellent yields, and the TCE protecting group can easily be removed to provide the desired sulfates. In doing this, we report the first synthesis of an alkoxysulfuryl imidazolium triflate species, which now represents a new class of sulfating agents.

2.2 Preparation of 2,2,2-Trichloroethoxysulfuryl Imidazolium Triflate

On the basis of the studies reported by O'Connell and Rapoport,[1] we anticipated that sulfuryl imidazolium triflates would be highly effective sulfating agents, and would be particularly useful for introducing the TCE-protected sulfate esters into carbohydrates.

Although sulfuryl imidazolium salts have never been reported, trichloroethoxysulfuryl imidazole **2.2** was easily constructed (scheme 2.1).[2] 2,2,2-Trichloroethylsulfuryl chloride **2.1** was treated with an excess of imidazole using a procedure adapted from Staab and Wendel[3] to give TCE sulfuryl imidazole **2.2** in 86% yield. Treatment of **2.2** with methyl triflate (1.0 eq.) in dry diethyl ether provided the activated imidazolium triflate species **2.3**. As this reaction progressed, **2.3** was found to precipitate out of solution, and was isolated by simple filtration in near-quantitative yields, with no further purification required. Reagent **2.3** was found to be very stable and can be stored for extended periods of time at room temperature or –20 °C with no detectable decomposition.[2]



Scheme 2.1

2.3 Synthesis of Starting Materials

A variety of carbohydrate substrates were chosen to determine the compatibility of the TCE sulfate incorporation and deprotection with many other functional groups, and are shown in figure 2.1.

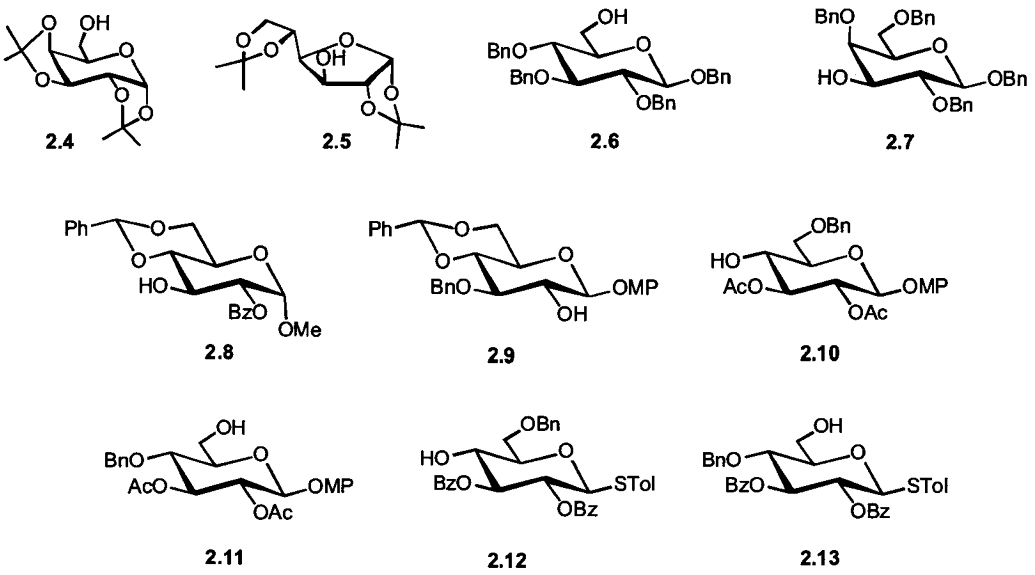


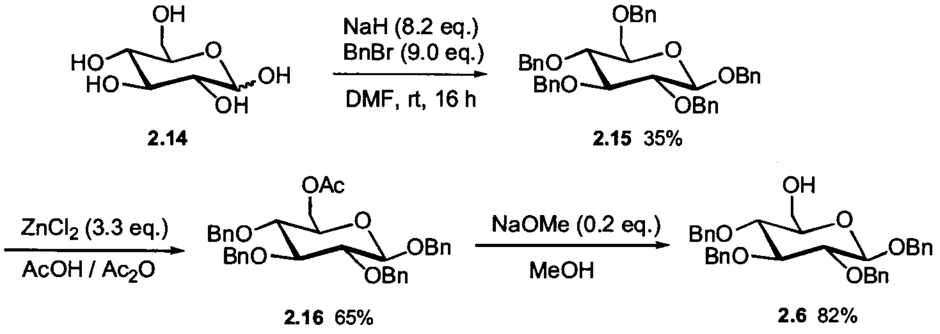
Figure 2.1: Target Monosaccharide Nucleophiles

The target nucleophile substrates were designed with a number of factors in mind: (1) that the TCE sulfate group could be incorporated at the 2-*O*, 3-*O*, 4-*O*, and 6-*O* positions, (2) a variety of commonly used protecting groups are employed, including the acetate and benzoyl groups, the benzyl and methyl ethers, as well as substituted acetals, and (3) the target TCE-protected sulfocarbohydrates should provide ready access to both glycosyl donors and acceptors. Access to functionalized glycosyl acceptors is achieved by employing a benzylidene acetal, which can easily be manipulated to provide access to 4-OH or 6-OH moieties. For access to glycosyl donors, the *p*-methoxyphenyl group was included, as it is known to be removed using cerium ammonium nitrate (CAN) to provide access to the free anomeric hydroxyl group; and thioglycosides were prepared because they are commonly used glycosyl donors, as they can be directly activated for coupling by reagents such as *N*-iodosuccinimide (NIS) with TfOH, or can easily converted to their corresponding hemiacetals to which can be converted to then other more reactive glycosyl donors.

Carbohydrate substrates **2.4** and **2.5** are commercially available, and were used as received. Wallach Lu, a previous masters student in the Taylor group, provided carbohydrate **2.7**.[4] Zena Qadoumi, an undergrad student in the Taylor laboratory, provided compound **2.9**. The target substrates that are not commercially available (compounds **2.6**, **2.8** – **2.13**) were prepared in multi-step sequences from readily available materials by applying conventional protecting group manipulations to provide the desired carbohydrates.

*2.3.1 Synthesis of per-benzylated glucose **2.6***

Preparation of **2.6** was achieved using a new approach recently described by the Taylor group, with an overall yield of 19% over 3 steps according to scheme 2.2.[5]

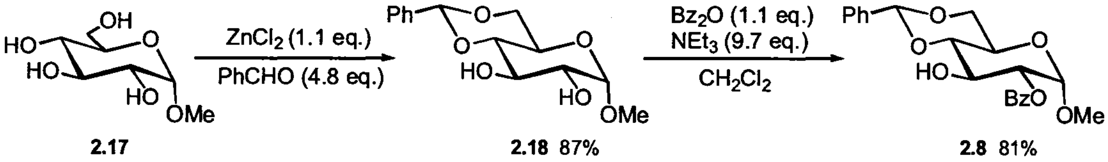


Scheme 2.2

D-glucose **2.14** in DMF was systematically treated with portions of benzyl bromide (total 9.0 eq.) and sodium hydride (total 8.2 eq.) over 6 hours to give per-*O*-benzylated glucose derivative **2.15** as a mixture of α (minor)/β (major) isomers after column chromatography. Further purification of **2.15** by recrystallization in ethyl acetate/hexanes gave the β isomer of **2.15** exclusively in 35% yield. This compound was then subjected to conditions for de-benzylation/acetylation with freshly fused $ZnCl_2$ (3.3 eq.) and AcOH/Ac_2O, to give the corresponding 6-*O*-acetate **2.16** in 65%. Transesterification of **2.16** with methanolic sodium methoxide (0.2 eq., 0.025 M) yielded carbohydrate **2.6** in 82%.

2.3.2 Synthesis of 2.8

Derivative **2.8** was synthesized over 2 steps from α-methyl-D-glucopyranoside **2.17** in an overall yield of 70%, according to scheme 2.3.

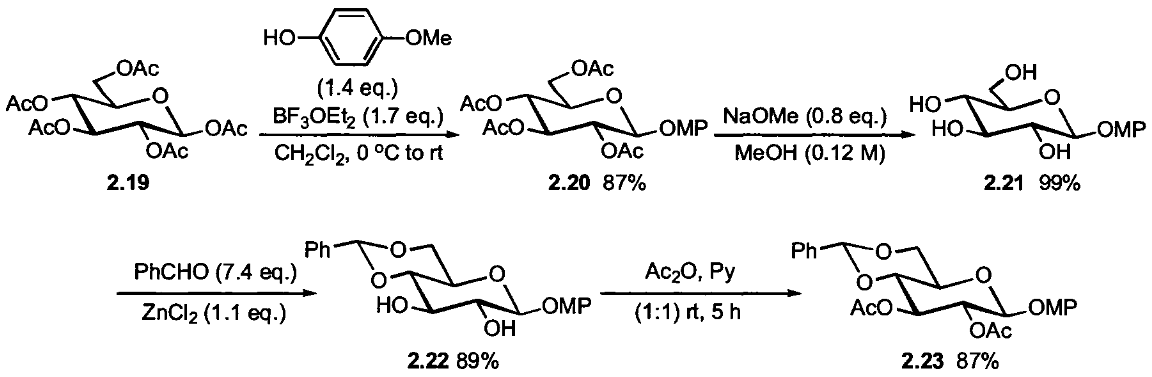


Scheme 2.3

In the first step **2.17** is suspended in an excess of benzaldehyde (4.8 eq.) in the presence of zinc chloride (1.1 eq.) for 6 h at room temperature to introduce the thermodynamic 4,6-*O*-benzylidene acetal in **2.18**, according to a procedure described by Yoza *et al.*[6] Compound **2.18** is then subjected to a regioselective 2-*O*-esterification according to a procedure established by Lu and coworkers[7] with 1.1 equivalent of benzoic anhydride and an excess of triethylamine (9.7 eq.) in dry dichloromethane, providing **2.8** in an 81% yield.

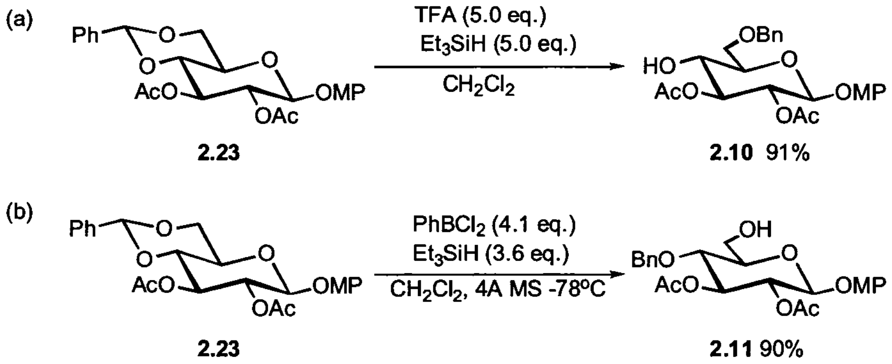
2.3.3 Synthesis of ***2.10*** *and* ***2.11***

Carbohydrates **2.10** and **2.11** are obtained from the common precursor **2.23**, which is prepared over 4 steps in an overall yield of 67% (scheme 2.4). The anomeric acetate in the commercially available per-acetylated glucose **2.19** is exchanged for a *p*-methoxyphenyl protecting group using boron trifluoride diethyl etherate (1.7 eq.) and 4-methoxyphenol (1.4 eq.) to give **2.20**. Zemplén deacetylation (0.8 eq. NaOMe), followed by introduction of the benzylidene acetal from benzaldehyde (7.5 eq.) and zinc chloride (1.1 eq.) gave intermediate **2.22,** which was then subjected to excess acetic anhydride in the presence of excess pyridine to give precursor **2.23**.



Scheme 2.4

Regioselective reductive opening of the benzylidene acetal was achieved by treating precursor **2.23** with triethylsilane (5 eq.) and TFA (5 eq.)[8] to provide the unmasked 4-OH group in **2.10** (scheme 2.5a), or by applying conditions modified and optimized from a procedure described by Sakagami and Hamana[9] in which precursor **2.23** is treated with triethylsilane (3.6 eq.) and phenyl dichloroborane (4.1 eq.) to give **2.11**, as described in scheme 2.5b.

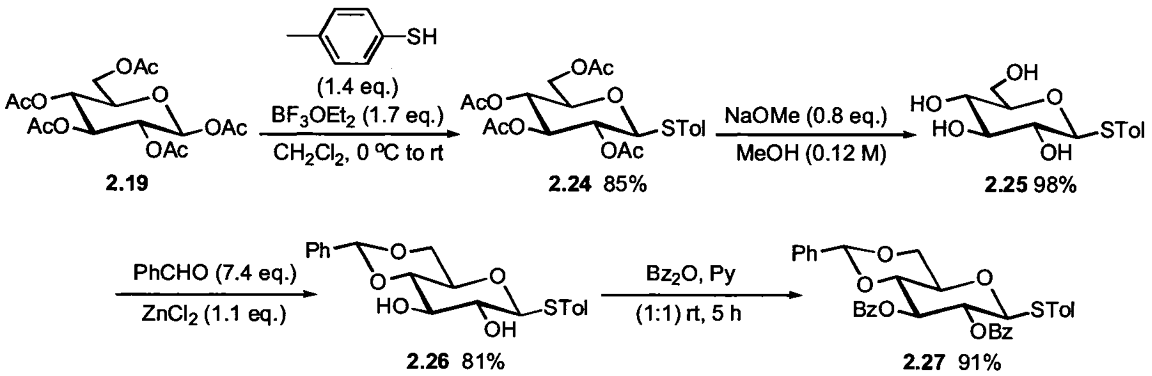


Scheme 2.5

Despite being a literature procedure, the synthesis of **2.11** required some experimentation, as the experimental conditions reported in the publication and the provided supporting information were inconsistent with regards to amounts of required acid and reducing agent for synthesis of compounds similar to **2.11**. Once the optimal reaction conditions were determined, the reaction was found to be very reliable for providing access to the free 6-OH compounds such as **2.11** in good yields. It is important to note that careful control of the reaction temperature is required, as the corresponding TES protected 6-OH is often isolated as a by-product of the reaction. Monitoring the temperature of the reaction, and quenching the reaction slowly with triethylamine and methanol upon completion by TLC can circumvent this problem.

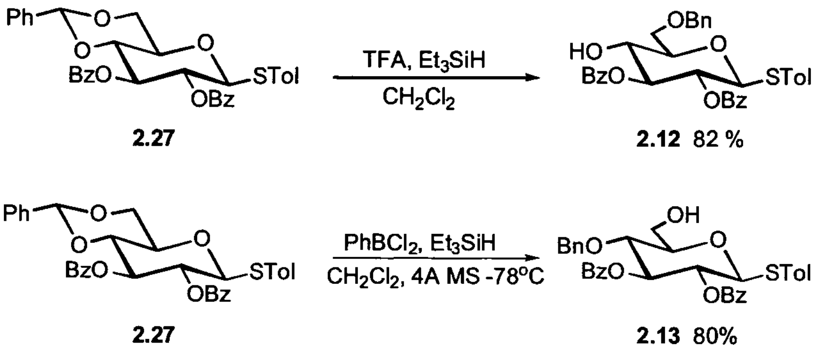
2.3.4 Synthesis of 2.12 and 213

Similar to the synthesis for the compounds described in section 2.3.3, the known compounds **2.12** and **2.13** were both obtained from precursor **2.27**, which was synthesized over 4 steps in an overall yield of 61% (scheme 2.6). The acetate anomeric protecting group in the per-acetylated glucose **2.19** was exchanged for a thiol ether using boron trifluoride diethyl etherate and 4-methylbenzene thiol to give the corresponding thioglycoside **2.24**. De-acetylation under Zemplén conditions, followed by introduction of the benzylidene acetal gave thioglycoside **2.26**, which was then subjected to benzoic anhydride in the presence of pyridine to give precursor **2.27**.



Scheme 2.6

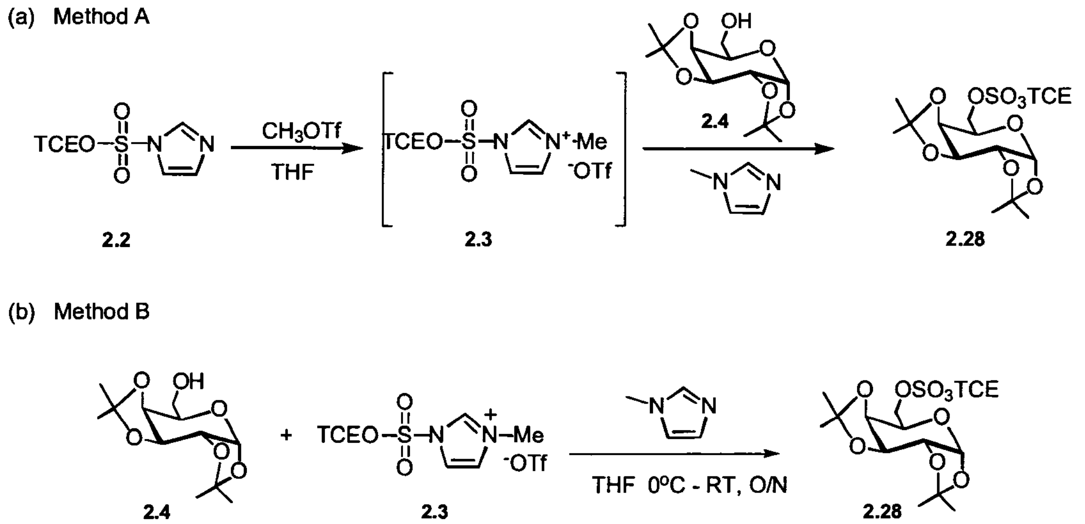
Reductive opening of the benzylidene acetal was achieved by treating **2.27** with an excess of TFA and triethylsilane to obtain the free 4-OH[8] **2.12**, or phenyl dichloroborane and triethylsilane[9] to obtain the free 6-OH in **2.13** according to scheme 2.7.



Scheme 2.7

2.4 Approaches to $TCESO_3$ Incorporation

Two approaches were first explored to investigate the viability of using the trichloroethoxysulfuryl imidazolium triflate **2.3** for the incorporation of TCE protected sulfate esters to monosaccharides (scheme 2.8a,b).



Scheme 2.8

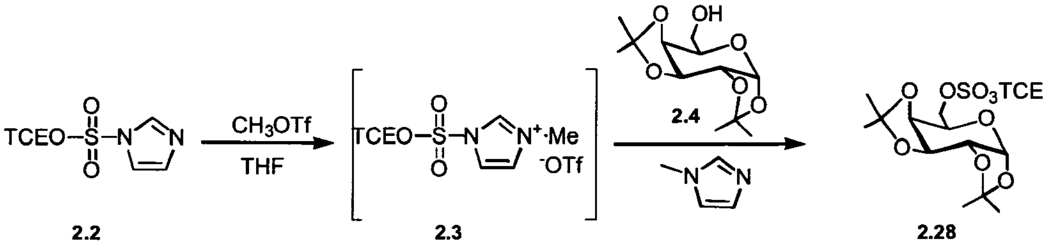
In the first approach (Method A, scheme 2.8a), trichloroethoxysulfuryl imidazole **2.2** was treated with methyl triflate to give the activated imidazolium triflate species **2.3** *in situ*. This was then treated with a solution containing a carbohydrate nucleophile such as **2.4** and NMI to give the desired sulfated carbohydrate **2.28**. In the second approach (Method B, scheme 2.8b), the isolated trichloroethoxysulfuryl imidazolium triflate **2.3** was added directly to a solution containing a carbohydrate such as **2.4** and NMI. To begin optimization studies and compare the viability of methods A and B, carbohydrates **2.4**, **2.5**, **2.6**, and **2.7** from figure 2.1 were chosen as model substrates.

2.5 Optimization of Method A – *In Situ* generation of Sulfating Agent 2.3

To determine the optimal conditions for the *in situ* generation of the sulfating agent and subsequent carbohydrate sulfation reactions, a number of reaction conditions were examined. Reactions with varied equivalents of TCE-sulfuryl imidazole **2.2**, methyl triflate, NMI, solvent, and reaction time were screened for substrates of 1:2,3:4-di-*O*-isopropylidene galactose **2.4** and diacetone glucose **2.5**.

2.5.1 Results for 1:2,3:4-di-O-isopropylidene galactose ***2.4*** *and diacetone glucose* ***2.5***

Reaction conditions for scheme 2.9 were screened and are summarized in table 2.1. Carbohydrate **2.4** was present in 1.0 eq. in each case, and the reaction was started at 0 ^{0}C and gradually warmed to room temperature.



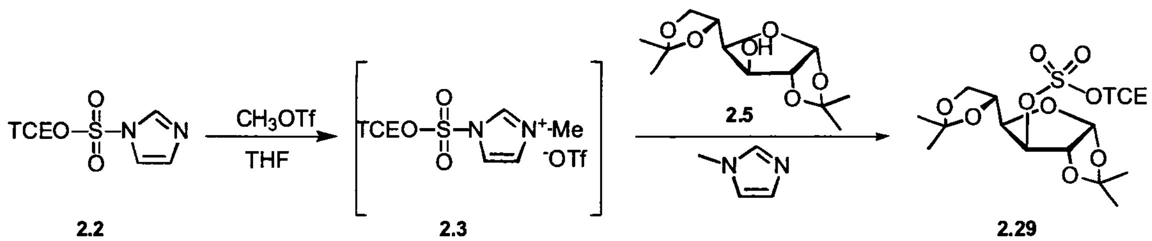
Scheme 2.9

Table 2.1: Optimization of Method A for 1:2,3:4-di-*O*-isopropylidene galactose **2.4**

Entry (#)	$TCESO_3IM$ **2.2** (eq.)	CH_3OTf (eq.)	NMI (eq.)	Solvent* [ ] M	Time (h)	Yield **2.28** (%)
1	1.0	1.0	1.5	THF (0.09M)	48	65
2	1.5	1.5	1.7	THF (0.09 M)	48	62
3	1.5	1.5	1.7	THF (0.15 M)	24	82
4	**2.2**	**2.2**	**2.2**	**THF (0.23 M)**	**24**	**85**
5	2.0	2.0	2.0	DMF (0.30 M)	24	21
6	1.1	1.3	1.3	THF (0.32 M)	24	25

* Total concentration with respect to carbohydrate **2.4**

In a similar manner, reaction conditions for scheme 2.10 were screened and are summarized in Table 2.2. Carbohydrate **2.5** was present in 1.0 eq. in each case, and the reaction was started at 0 °C and gradually warmed to room temperature.



Scheme 2.10

Table 2.2: Optimization of Method A for Diacetone Glucose **2.5**

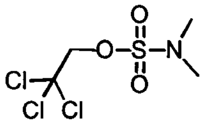
Entry (#)	TCESO$_3$IM **2.2** (eq.)	CH$_3$OTf (eq.)	NMI (eq.)	Solvent* [ ] M	Time (h)	Yield **2.29** (%)
1	1.6	1.6	1.7	THF (0.09 M)	48	70
2	2.0	2.0	2.0	THF (0.09 M)	48	79
3	2.5	2.6	2.5	THF (0.08 M)	24	82
4	**2.2**	**2.2**	**2.2**	**THF (0.23 M)**	**24**	**85**
5	2.0	2.1	2.0	DMF (0.32 M)	24	0
6	1.1	1.3	1.3	THF (0.32 M)	24	44

* Total concentration with respect to carbohydrate **2.5**

*2.5.2 Discussion for sulfation of **2.4** and **2.5** via Method A*

While studying a variety of reaction conditions, a clear correlation was noticed between the equivalents of sulfating agent, and yields of the desired product, as well as reaction concentration and final yields. The optimal reaction conditions for both carbohydrates **2.4** and **2.5** (table 2.1 entry 4; table 2.2 entry 4) were found to require 2.2 equivalents of the generated imidazolium triflate sulfating species, with at least 2.2

equivalents of NMI base, and a carbohydrate concentration of 0.23 M (carbohydrate in THF). Increasing the reaction concentration beyond 0.23 M while decreasing the equivalents of base and sulfating agent (entry 6 for tables 2.1 and 2.2) resulted in a drastic decrease in the amount of desired product owing to the poor solubility of the imidazolium triflate **2.3**. Attempts to run the reaction at 0.3 M in DMF were surprisingly unsuccessful. Analysis of the reaction by-products for the reactions with substrates **2.4** and **2.5** indicated that the DMF solvent was reacting with methyl triflate, as compound **2.30** (figure 2.2) was isolated and confirmed to be a by-product from both reactions (entry 5 for tables 2.1 and 2.2).

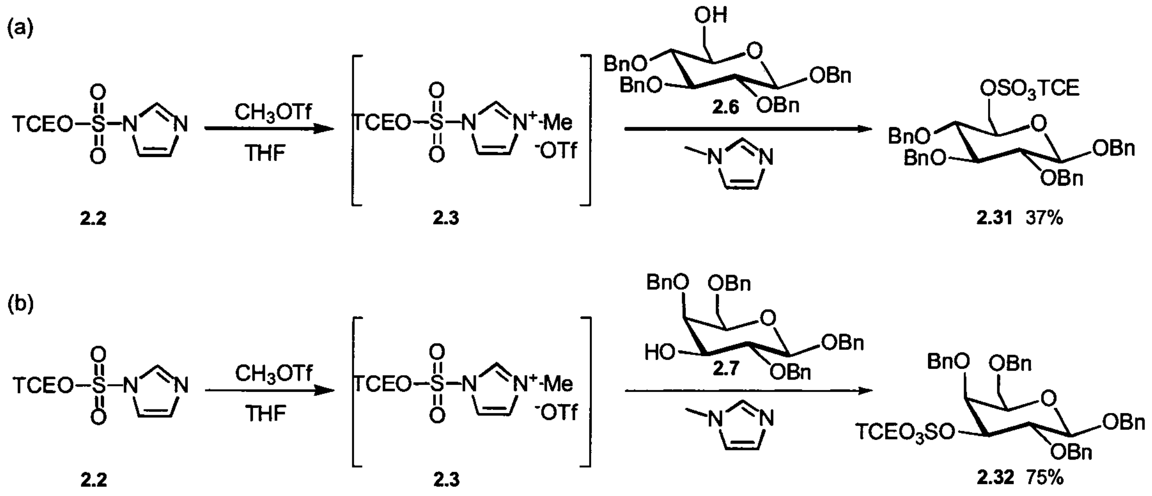


2.30

Figure 2.2: By-product isolated from reactions performed in DMF

*2.5.3 Results for per-benzylated glucose **2.6** and galactose derivative **2.7***

The optimal conditions were applied to carbohydrates **2.6** and **2.7** (scheme 2.11 a,b). The yields of these products were slightly lower, with **2.31** being isolated in a 37% yield, and **2.32** isolated in75%.



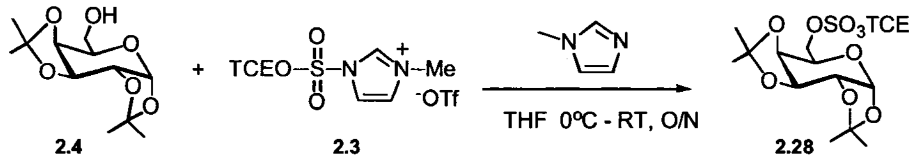
Scheme 2.11

2.6 Optimization of Method B – Direct Application of Sulfating Agent 2.3

To determine the optimal conditions for the second method for sulfating carbohydrates, the reaction conditions were again varied with respect to equivalents of TCE-sulfuryl imidazolium triflate **2.3**, NMI, solvent, and reaction time, for substrates of 1:2,3:4-di-*O*-isopropylidene galactose **2.4** and diacetone glucose **2.5**.

*2.6.1 Results for 1:2,3:4-di-O-isopropylidene galactose **2.4** and diacetone glucose **2.5***

Reaction conditions for scheme 2.12 were screened and are summarized in table 2.3. Carbohydrate **2.4** was present in 1.0 eq. in each case, and the reaction was started at 0 °C and gradually warmed to room temperature.



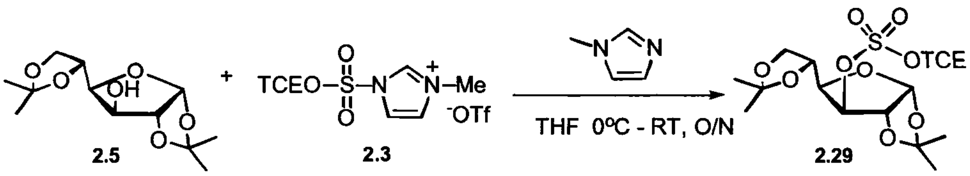
Scheme 2.12

Table 2.3: Optimization of Method B for 1:2,3:4-di-*O*-isopropylidene galactose **2.4**

Entry (#)	$TCESO_3Im^+Me$ **2.3** (eq)	NMI (eq)	Solvent* [ ] M	Time (h)	Yield **2.28** (%)
1	1.5	1.6	THF (0.09 M)	24	80
2	2.0	2.0	THF (0.09 M)	24	79
3	2.0	2.0	DMF (0.30 M)	24	88
4	**2.0**	**2.0**	**THF (0.23 M)**	**24**	**87**
5	1.3	1.3	THF (0.23 M)	24	80

* Total concentration with respect to carbohydrate **2.4**

In a similar manner, Reaction conditions for scheme 2.13 were screened and are summarized in Table 2.4. Carbohydrate **2.5** was present in 1.0 eq. in each case, and the reaction was started at 0 ^{0}C and gradually warmed to room temperature.



Scheme 2.13

Table 2.3: Optimization of Method B for Diacetone Glucose **2.6**

Entry (#)	$TCESO_3Im^+Me$ **2.3** (eq.)	NMI (eq.)	Solvent* [ ] M	Time (h)	Yield **2.29** (%)
1	1.5	1.5	THF (0.13 M)	24	24
2	2.0	2.0	THF (0.09 M)	48	79
3	2.0	2.0	DMF (0.30 M)	24	57
4	**2.0**	**2.0**	**THF (0.23 M)**	**24**	**90**
5	1.3	1.3	THF (0.23 M)	24	80

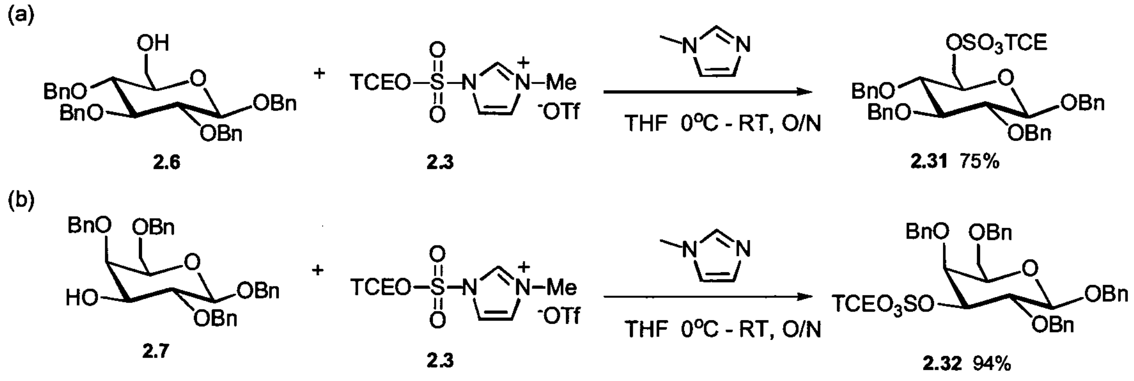
* Total concentration with respect to carbohydrate **2.5**

2.6.2 Discussion for sulfation of 2.4 and 2.5 via Method B

As was observed for the optimization of method A, a clear correlation between the equivalents of sulfating agent, and yields of the desired product, as well as reaction concentration was again observed. The optimal reaction conditions for the sulfation of both alcohols **2.4** and **2.5** via method B (entry 4 for tables 2.3 and 2.4) were found to be very similar to the most favorable conditions required for method A. The best yields obtained required 2.0 eq. of the imidazolium triflate sulfating agent **2.3**, with 2.0 equivalents of NMI base, and a reaction concentration of 0.23 M (carbohydrate to THF).

*2.6.3 Results for per-benzylated glucose **2.6** and galactose derivative **2.7***

Benzylated glucose and galactose derivatives **2.6** and **2.7** were sulfated using the same approach (scheme 2.14 a,b), to obtain **2.31** in a 75% yield at best, and **2.32** in a 94% yield. For these compounds, the reactions were run at 0.15 M instead of the optimized 0.23 M, and the reaction time was extended from 24 h to 2 d. Despite best efforts, compound **2.31** could only be isolated in a 75% yield.

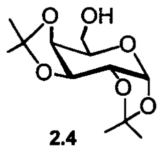
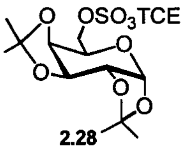
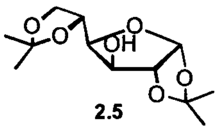
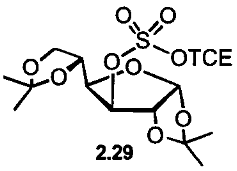
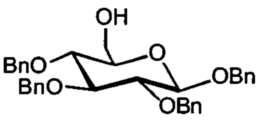
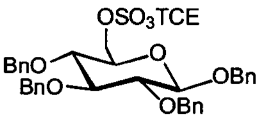
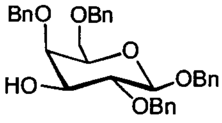
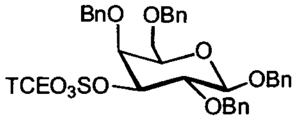


Scheme 2.14

2.7 Comparison of Sulfating Methods A and B

Table 2.5 summarizes the results obtained for the four model carbohydrates used for the comparison of sulfating methods A and B.

Table 2.5: Summary of Results for Method A and Method B

Reactant	Product	Method A (%)	Method B (%)
 **2.4**	 **2.28**	85	87
 **2.5**	 **2.29**	85	90
 **2.6**	 **2.31**	37	75
 **2.7**	 **2.32**	75	94

For the 1:2,3:4-di-*O*-isopropylidene galactose **2.4**, and diacetone glucose **2.5**, methods A and B produce comparable results, with a slight preference shown for method B. For the per-benzylated glucose **2.6** and galactose **2.7** derivatives however, there is a much stronger preference for method B, suggesting that direct application of the isolated imidazolium triflate species **2.3** is the more efficient way to obtain the desired sulfated carbohydrates.

2.8 Deprotection of TCE-protected Sulfocarbohydrates

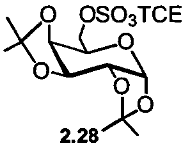
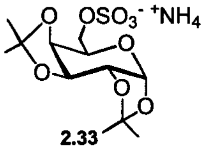
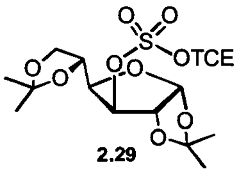
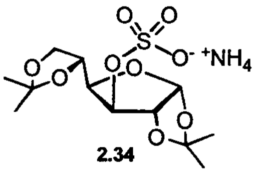
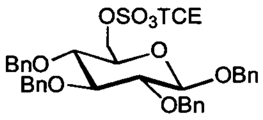
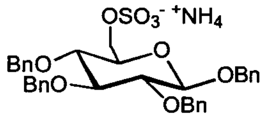
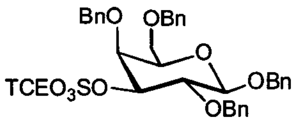
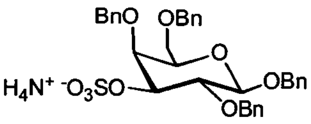
When attempting to develop and present chemistry that employs a new protecting group, it is essential to demonstrate that the group can be removed with relative ease. Fortunately, the TCE protected sulfates were easily unmasked in very mild conditions.

2.8.1 Preliminary deprotection results with Zn or Pd/C and HCO_2NH_4

Preliminary studies on the deprotection of the sulfate group in the carbohydrates in table 2.5 are summarized in table 2.6.

Two deprotection conditions were initially investigated according to the procedures outlined for the deprotection of the TCE-protected aryl sulfates.[10] The first employed catalytic transfer hydrogenolysis using Pd/C (10 weight% of 10% Pd/C) and ammonium formate (6 eq.) in MeOH while the second employed Zn (7 eq.) and ammonium formate (6 eq.) in MeOH. When the reactions were complete (by TLC), they were filtered through Celite and the crude material then rapidly passed through a small silica column using CH_2Cl_2/MeOH/NH_4OH (10:2:0.5) as eluant to remove the ammonium chloride or zinc chloride and zinc formate that is formed in the reaction as well as much of the excess ammonium formate. The pooled fractions were concentrated, the residue dissolved in water and then lyophilized to give the carbohydrate sulfates as their ammonium salts. The Zn/ammonium formate method gave the desired products in excellent yields. The Pd/ammonium formate method also gave the desired products but in yields that were significantly lower than the Zn/ammonium formate method in most cases. No loss of the sulfate group, or other functional groups was detected during the reactions using the optimized deprotection conditions. The attempted deprotection of **2.31** using modified conditions of H_2 and Pd/C, resulted not only in loss of the TCE and benzyl groups but also desulfation. It was hypothesized that HCl was formed during the reaction, which resulted in loss of the sulfate group.

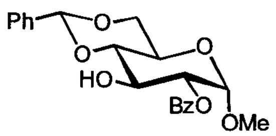
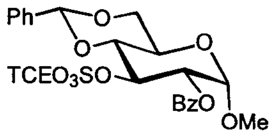
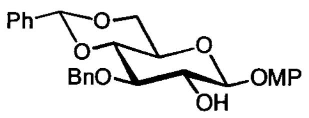
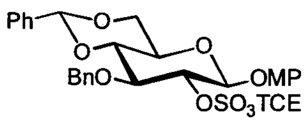
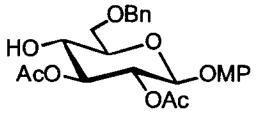
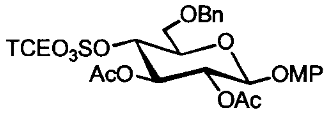
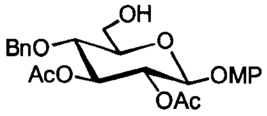
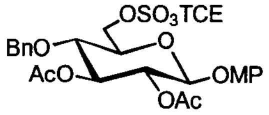
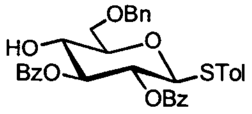
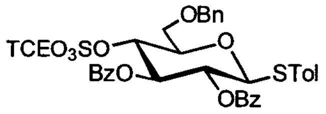
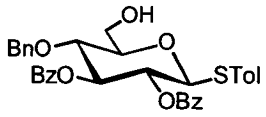
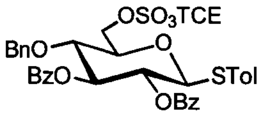
Table 2.6: Preliminary Deprotection Studies for TCE Protected Sulfates

Reactant	Product	Zn / HCO_2NH_4 (%)	Pd/C / HCO_2NH_4 (%)
 **2.28**	 **2.33**	99	62
 **2.29**	 **2.34**	94	69
 **2.31**	 **2.35**	96	80
 **2.32**	 **2.36**	94	ND

2.9 Preparation of Sulfated Carbohydrates

With the optimal conditions worked out for $TCESO_3$ incorporation and deprotection, we chose to pursue method B further and expand upon the scope of prepared TCE-protected sulfocarbohydrates. The resulting products and yields are summarized in table 2.7.

Table 2.7: Synthesis of TCE-Protected Sulfocarbohydrates

Reactant	Product	Yield (%)
 **2.8**	 **2.37**	94
 **2.9**	 **2.38**	90
 **2.10**	 **2.39**	76
 **2.11**	 **2.40**	81
 **2.12**	 **2.41**	91
 **2.13**	 **2.42**	85

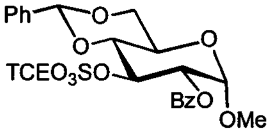
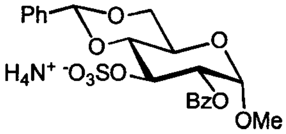
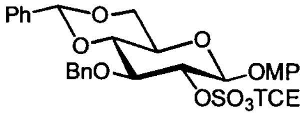
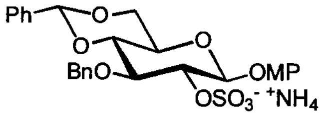
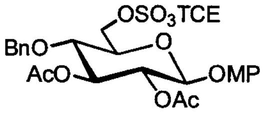
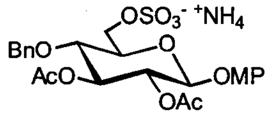
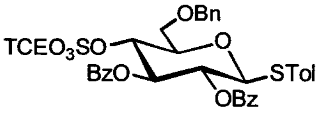
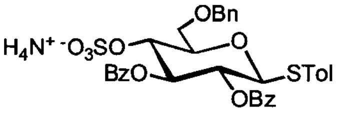
Most of the reactions were performed by adding the trichloroethoxysulfuryl imidazolium triflate **2.3** (2.0 eq.) to a solution containing the carbohydrate nucleophile (1.0 eq.), and NMI (2.5 eq.) in THF (0.23 M with respect to the carbohydrate) at 0 °C. Generally the reactions were complete in approximately 16 hours; for those that were not complete, additional aliquots of **2.3** and NMI were added portion wise until the reaction went to completion.

The sulfation reactions usually required anywhere from 2 to 5 equivalents of the imidazolium sulfating agent **2.3**, with the exception of substrates **2.9**, which required almost 12 equivalents and a reaction time of 48 h, and **2.10**, which required 6 equivalents and a reaction time of 48 hours to reach completion, affording the target **2.39** in only a 76 % yield. These substrates will be further discussed in chapter 4.

2.10 Additional Deprotection Studies

The optimized conditions of Zn (7 eq.) and HCO_2NH_4 (6 eq.) for the removal of the TCE protecting group were applied to a selection of more functionalized carbohydrates to investigate compatibility with other protecting groups. The reactions (summarized in table 2.8) proceeded very smoothly, with no detectable incompatibilities with the other functionalities present in the molecules.

Table 2.8: Zn/HCO_2NH_4 Directed TCE-Sulfate Deprotection

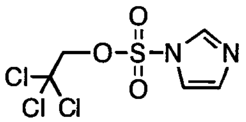
Reactant	Product	Yield (%)
 **2.37**	 **2.43**	96
 **2.38**	 **2.44**	91
 **2.40**	 **2.45**	97
 **2.41**	 **2.46**	96

2.11 Summary

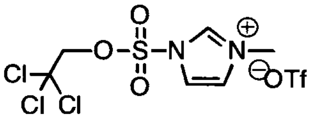
Despite lack of literature precedent for sulfuryl imidazolium salts, we found that the 2,2,2-trichloroethoxysulfuryl imidazolium triflate species **2.3** was easily prepared, and isolated in near quantitative yields by simple filtration. This reagent represents an entirely new class of sulfating agents, and has demonstrated that it is capable of sulfating a variety of acceptors, even poorly nucleophilic ones. We have incorporated the $TCESO_3$ group into a number of monosaccharide building blocks using reagent **2.3**. TCE -sulfates at the 2-*O*, 3-*O*, 4-*O*, and 6-*O*, positions were prepared in carbohydrates bearing different functionalities at the anomeric centre. We have also shown that the sulfate moieties are easily unmasked in very mild conditions providing the target sulfocarbohydrates in excellent yields.

2.12 Experimental

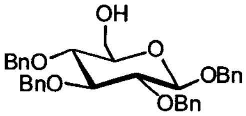
General Information: All reactions were carried out under argon with freshly distilled solvents unless otherwise noted. Tetrahydrofuran (THF) and Et_2O were distilled from sodium metal in the presence of benzophenone under argon. CH_2Cl_2 was distilled from calcium hydride under nitrogen. All commercially available reagents were obtained from Aldrich Chemical Company (Oakville, Ontario, Canada) and were used as received, with the exception of TMSOTf, which was immediately distilled into a Schlenk tube and stored under argon. Flash chromatography was performed using silica gel 60 Å (234-400 mesh) obtained from Silicycle (Laval, Quebec, Canada). ^1H, ^{19}F, ^{13}C and 2D spectra were recorded on a Bruker Avance 300 MHz or Bruker Avance 500 MHz spectrometer. Chemical shifts (δ) for ^1H NMR spectra are reported in parts per million (ppm) relative to Me_4Si (0.0 ppm) or DMSO-d_6 (2.49 ppm) and are reported as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened), integration, coupling constant in Hz, and assignment. Chemical shifts (δ) for ^{13}C spectra are reported in ppm relative to $CDCl_3$ (δ 77.0, central peak) or DMSO-d_6 (δ 39.5, central peak). Chemical shifts (δ) for ^{19}F spectra are reported in ppm relative to an external fluoroform standard (δ 0.0, $CFCl_3$). All melting points were obtained using a Fisher-Johns apparatus and are uncorrected. Electron impact mass spectra were acquired with a JEOL HX110 double focusing mass spectrometer operated at a mass resolution of ~1000 for nominal mass work and ~10,000 for elemental composition determinations. Typical source conditions were: source temp = 200 °C and electron energy of 70 eV. Ammonia was used as the CI reagent gas for positive ion CI. All samples were introduced by direct insertion. Positive and negative ion nanoelectrospray (ESI) experiments were performed with a Waters/Micromass QTOF Ultima Global mass spectrometer. Samples were infused at 1 μL/min in 1:1 CH_3CN/H_2O+0.2% formic acid for +ve ion work or 1:1 CH_3CN/H_2O for –ve ion work. Typical operating conditions were: source temp =80 °C, capillary voltage =3.5 kV, cone voltage =60-160 V and mass resolution of ~9000.



2,2,2-Trichloroethoxysulfuryl imidazole (2.2). To imidazole (21.17 g, 0.31 mol) in dry THF (50 mL) at 0 °C was added dropwise a solution of 2,2,2-trichloroethylsulfonylchloride **2.1** (20 mL, 0.15 mol) in THF (20 mL). The reaction was stirred at 0 °C for 1 h, warmed to room temperature and stirred for an additional hour. The salts were removed by suction filtration, washed with THF and the filtrate was concentrated to a yellow crude oil. Flash chromatography (33:67 EtOAc/hexanes) provided pure **2.2** as a white solid (35.9 g, 86%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.04, (s, 1H, ImH), 7.41, 7.23 (m, 2H, ImH), 4.68 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.90, 131.66, 117.97, 91.53, 80.05; Melting point 46-48 °C; HRMS (EI) *m/z* = 277.9090, $C_5H_5N_2SO_3Cl_3$ requires 277.9087.



2,2,2-trichloroethoxysulfuryl-*N*-methylimidazolium triflate (2.3).[2] To a solution of 2,2,2-trichloroethoxysulfurylimidazole **2.2** (10.6 g, 36 mmol) in Et_2O (140 mL) at 0 °C was added dropwise methyl triflate (4.6 mL, 41 mmol). The reaction was stirred for 3 h at 0 °C during which time a white precipitate formed. The desired product was isolated by suction filtration, in which the first filtrate was cooled to re-precipitate any remaining product (1x) and washed with cold Et_2O to afford **2.3** as a fluffy white solid (14.6 g, 91%). ^1H NMR (300 MHz, CD_3OD) δ 9.97, 8.34, 7.91 (3s, 3H, ImH), 5.41 (s, 2H, CH_2), 4.07 (s, 3H, CH_3); ^{13}C NMR (75 MHz, CD_3OD) δ 139.53, 125.87, 120.73, 120.43 (q, J_{CF} = 318.7 Hz, CF_3), 91.52, 82.08, 36.42; ^{19}F NMR (282 MHz, CD_3OD) δ -79.6; Melting point 146-148 °C; ESI of cation m/z = 294.9423, $C_6H_8Cl_3N_2O_3S^+$ requires 294.9635.

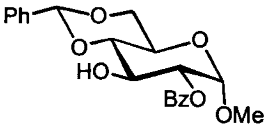


Benzyl 2,3,4-tri-*O*-benzyl-*β*-D-glucopyranoside (2.6).[5] To a suspension of D-glucose **2.14** (9.081 g, 50 mmol) in anhydrous DMF (250 mL) was added NaH (6.30 g of a 60% dispersion in mineral oil, 150 mmol) at room temperature. After 30 min, benzyl bromide (21.5 mL, 175 mmol) was added dropwise via syringe. After the first 2.5 h, repeated addition of NaH (6 g, 150 mmol) and benzyl bromide (21.5 mL, 175 mmol) after 30 minutes as described above. After another 2.5 h, NaH (4.0 g, 100 mmol) and, after 30 min, benzyl bromide (12 mL, 95 mmol) were added. The reaction was then allowed to stir for 16 hours at room temperature, at which point it was then cooled to 0 °C and carefully quenched with reagent grade methanol. Residual solvent was removed and the brown crude was dissolved in DCM, washed with H_2O, brine, and dried over $MgSO_4$. Flash chromatography (5:95 ethyl acetate/hexanes) afforded a sticky white solid that was recrystallized (ethyl acetate/hexanes) to give **2.15** as a white solid (11.0 g, 35%).

To freshly fused zinc chloride (6.1 g, 44 mmol) in AcOH/Ac_2O (v/v 1/5, 60 mL) at 0 °C was added a solution of carbohydrate **2.15** (8.5 g, 13.5 mmol) in AcOH/Ac_2O (v/v 1/5, 60 mL) dropwise via addition funnel. The solution was stirred for 3 h at room temperature, cooled to –30 °C and quenched very slowly with ice water. The desired product precipitated out of solution, was isolated by filtration and washed repeatedly with water. Recrystallization of the isolated solid (MeOH) gave **2.16** as a white crystalline product (5.1 g, 65%).

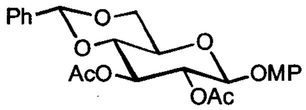
A suspension of **2.16** (4.5 g, 7.7 mmol) in 40 mL of 0.025 M NaOMe/MeOH was stirred for 24 h at room temperature. At this point, starting material still remained by TLC, thus another 20 mL of 0.025 M NaOMe/MeOH solution was added. The reaction was complete after 6 additional hours, was poured into ice water (180 mL) and stirred for 30 min. The resulting precipitate was filtered, washed with $NaHCO_3$ and water, then recrystallized (ethyl acetate/hexanes) to give **2.6** as a white solid (3.4 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (dd, 1H, $J_{OH,6} + J_{OH,6'}$ = 13.3 Hz, OH), 3.39 (ddd, $J_{5,4}$ = 9.5, $J_{5,6}$= 4.5, $J_{5,6}$'= 2.9 Hz, H5), 3.51 (dd, 1H, $J_{2,1} + J_{2,3}$ = 16.7 Hz, H2), 3.60 (dd, 1H, $J_{4,3} + J_{4,5}$ = 18.4 Hz, H4), 3.69 – 3.77 (m, 1H, H6), 3.71 (dd, 1H, $J_{3,2} + J_{3,4}$ = 17.8 Hz, H3), 3.90 (ddd, 1H, $J_{6',6}$ = 11.8, $J_{6',OH}$ = 5.6, $J_{6',5}$ = 2.6 Hz, H6'), 4.60 (d, 1H, $J_{1,2}$ = 7.8 Hz, H1), 4.64 –

5.00 (m, 8H, 4 x CH_2Ph), 7.28 – 7.41 (m, 20H, ArH). All other spectra are in agreement with literature data for this compound.[5]



Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-*β*-D-glucopyranoside (2.8).[7] To benzaldehyde (38.0 mL, 374 mmol) was added zinc chloride (11.3 g, 82.9 mmol) followed by methyl α-D-glucopyranoside **2.17** (15.0 g, 77.3 mmol). The reaction was stirred for 6 h at room temperature then poured into ice water (300 mL). The resulting precipitate was filtered and collected. The crude solid was re-precipitated from chloroform/hexanes to yield **2.18** as a white solid (19.1 g, 87%).

To precursor **2.18** (5.0 g, 1.7 mmol) in CH_2Cl_2 (50 mL) was added benzoic anhydride (5.0 g, 2.2 mmol). After 10 min, NEt_3 (2.3 mL, 16.5 mmol) was added, and the reaction was stirred for 24 h at room temperature. Upon completion, the reaction was diluted with methanol, and solvents were removed *in vacuo* to yield a clear yellow oil. Purification by flash chromatography followed by recrystallization gave pure **2.8** as white needles (5.4 g, 81%). ^1H NMR (300 MHz, $CDCl_3$) δ 2.51 (d, 1H, $J_{OH,3}$ = 3.1 Hz, OH), 3.40 (s, 3H, CH_3), 3.64 (dd, 1H, $J_{4,3} = J_{4,5}$ = 9.3 Hz, H4), 3.80 (dd, 1H, $J_{6ax,6eq} = J_{6ax,5}$ = 10.1 Hz, $H6_{ax}$), 3.92 (ddd, 1H, $J_{5,6az}$ = 10.1 Hz, $J_{5,4}$ = 9.4 Hz, $J_{5,6eq}$ = 4.7 Hz, H5), 4.31 – 4.40 (m, 2H, H3, $H6_{eq}$), 5.04 (dd, 1H, $J_{2,3}$ = 9.4 Hz, $J_{2,1}$ = 3.8 Hz, H2), 5.08 (d, 1H, J = 3.8 Hz, H1), 5.58 (s, 1H, CHPh), 7.37 – 7.58 (m, 8H, ArH), 8.08 – 8.11 (m, 2H, ArH). All other spectra are in agreement with data documented for compound 2.8.[11]

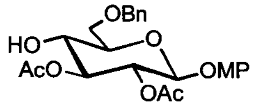


p-Methoxyphenyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranoside (2.23). To β-D-glucosepentaacetate **2.19** (40 g, 102 mmol) in CH_2Cl_2 (400 mL) at 0 °C was added 4-methoxyphenol (17.24 g, 140 mmol) followed by BF_3OEt_2 (21.2 mL, 172 mmol). The reaction was stirred for 1 h at 0 °C then removed from the ice bath and followed to completion by TLC (approx. 7 h). The reaction was poured into cold CH_2Cl_2, washed with H_2O, sat. $NaHCO_3$, H_2O, and dried over $MgSO_4$. The solvents were removed *in vacuo* and the crude solid was purified by recrystallization (EtOAc/Hexanes) to yield **2.20** as a white solid (40.1 g, 87%).

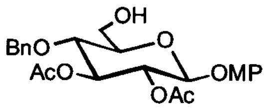
To carbohydrate **2.20** (40 g, 88.0 mmol) in MeOH (600 mL) was added Na metal (0.160 g, 7.0 mmol). The reaction was stirred for 24 h at room temperature, neutralized with Dowex 50WX8 H^+ ion exchange resin, filtered and concentrated to **2.21** as a white solid (25.0 g, 99%).

Compound **2.21** (25.0 g, 87.3 mmol) and $ZnCl_2$ (13.1 g, 96.1 mmol) were suspended in benzaldehyde (65 mL, 643 mmol) and stirred at room temperature for 5 h. The desired product precipitated out of solution after approx. 1 h, and was isolated as a white solid by filtration. The crude product was recrystallized using EtOH to provide **2.22** as a shiny white solid (29.1 g, 89%). All obtained spectra are in agreement with those reported for the known compound.[12]

Diol **2.22** (25.0 g, 66.8 mmol) was stirred in a solution of Ac_2O/pyridine (1:1 166 mL) for 5 h at room temperature. The crude product precipitated out of solution after approx. 2 h, and was recovered by vaccum filtration. Washing the crude product with hot EtOH provided **2.23** as a fine white powder (26.8 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 3.62 (ddd, 1H, $J_{5,6ax} = J_{5,4} = 9.7$ Hz, $J_{5,6eq} = 4.9$ Hz, H5), 3.78 (s, 3H, OCH_3), 3.81 (m, 2H, H4, H6$_{ax}$), 4.39 (dd, 1H, $J_{6eq,6ax} = 10.5$ Hz, $J_{6eq,5} = 4.6$ Hz, H6$_{eq}$), 5.06 (d, 1H, $J_{1,2} = 7.7$ Hz, H1), 5.25 (dd, $J_{2,3} + J_{2,1} = 16.9$ Hz, H2), 5.38 (dd, $J_{3,4} = J_{3,2} = 9.4$ Hz, H3), 5.25 (s, 1H, CHPh), 6.84 (m, 2H, ArH), 6.95 (m, 2H, ArH), 7.36 (m, 3H, ArH), 7.44 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.69, 20.79, 55.64, 66.51, 68.53, 71.77, 72.26, 78.15, 100.89, 101.57, 114.64, 118.69, 126.16, 128.26, 129.18, 136.74, 150.88, 155.83, 169.56, 170.15; Melting point 212-213 °C; HRMS (EI) m/z = 458.1585, $C_{24}H_{26}O_9$ requires 458.1577.

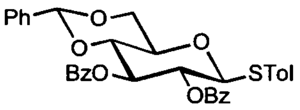


p-Methoxyphenyl 2,3-di-O-acetyl-6-O-benzyl-β-D-glucopyranoside (2.10). To the fully protected **2.23** (0.5 g, 1.09 mmol) in CH_2Cl_2 (4 mL) was added dropwise triethylsilane (0.86 mL, 5.38 mmol) followed by trifluoroacetic acid (0.42 mL, 5.40 mmol). The reaction was followed to completion by TLC, diluted with CH_2Cl_2, carefully quenched with triethylamine and concentrated to a crude syrup. Purification by flash chromatography (33: 67 EtOAc/hexanes) afforded **2.10** as a clear colourless syrup (0.46 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 3.67 (dd, $J_{5,4} = 9.6$ Hz, $J_{5,6} = 4.8$ Hz, H5), 3.79 (s, 3H, OCH_3), 3.79 – 3.88 (m, 3H, H4, H6, H6'), 4.59, 4.63 (AB, 2H, $J = 11.9$ Hz, CH_2Ph), 4.96 (d, 1H, $J_{1,2} = 7.5$ H1), 5.10 – 5.23 (m, 2H, H2, H3), 6.82 (d, 2H, J = 9.0 Hz, ArH), 6.98 (d, 2H, J = 9.0 Hz, ArH), 7.28 – 7.39 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.71, 20.85, 55.63, 69.89, 70.44, 71.32, 73.77, 74.55, 75.65, 100.24, 114.55, 118.59, 127.73, 127.88, 128.47, 137.59, 151.07, 155.60, 169.65, 171.34; HRMS (EI) m/z = 460.1734, $C_{24}H_{28}O_9$ requires 460.1733.



***p*-Methoxyphenyl 2,3-di-*O*-acetyl-4-*O*-benzyl-*β*-D-glucopyranoside (2.11).**

Carbohydrate **2.23** (0.4 g, 0.88 mmol) in CH_2Cl_2 (13 mL) and activated 4Å molecular sieves (1 g) were stirred for 1 h at room temperature. The solution was cooled to –78 °C and Et_3SiH (0.51 mL, 3.2 mmol) and $PhBCl_2$ (0.48 mL, 3.7 mmol) were added successively. The reaction was stirred at –78 °C for 1 h, quenched with NEt_3 (1 mL) and methanol (1 mL), diluted with $CHCl_3$ then warmed to room temperature. Solids were removed by filtering reaction contents through celite, the organic layer was washed with sat. $NaHCO_3$, dried over $MgSO_4$ and concentrated to a clear yellow oil. Flash chromatography (25:75 EtOAc/hexanes) provided **2.11** as a clear, colourless glassy compound (0.37 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 3.52 – 3.57 (m, 1H, OH), 3.74 – 3.77 (m, 2H, H4, H6), 3.77 (s, 3H, OCH_3), 3.94 (dd, 1H, $J_{6',6}$ = 12.3 Hz, $J_{6',OH}$ = 2.3 Hz, H6'), 4.64, 4.66 (AB, 2H, J = 11.5 Hz, CH_2Ph), 5.00 (d, 1H, $J_{1,2}$ = 7.9 Hz, H1), 5.12 (dd, 1H, $J_{2,3} + J_{2,1}$ = 17.5 Hz, H2), 5.31 (dd, 1H, $J_{3,4} = J_{3,2}$ = 9.4 Hz, H3), 6.82 (d, 2H, J = 9.5 Hz, ArH), 6.87 (d, 2H, J = 9.5 Hz, ArH), 7.26 – 7.37 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.70, 20.79, 55.64, 61.44, 71.89, 74.71, 74.88, 75.25, 75.48, 100.03, 114.65, 118.30, 128.00, 128.09, 128.56, 137.50, 150.91, 155.65, 169.71, 170.13; HRMS (EI) *m/z* = 460.1743, $C_{24}H_{28}O_9$ requires 460.1733.

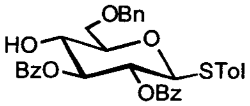


***p*-Tolyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-1-thio-ß-D-glucopyranoside (2.27)**. To *β*-D-glucose pentaacetate **2.19** (20 g, 51 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added 4-methylbenzenethiol (20 g, 175 mmol) followed by BF_3OEt_2 (20 mL, 153 mmol). The reaction was stirred for 1 h at 0 °C then removed from the ice bath and followed to completion by TLC (approx. 7 h). The reaction was poured into cold CH_2Cl_2, washed with H_2O, sat. $NaHCO_3$, H_2O, and dried over $MgSO_4$. The solvents were removed *in vacuo* and the crude solid was purified by flash chromatography (50:50 EtOAc/hexanes) to yield **2.24** as a white solid (19.8 g, 85%).

To carbohydrate **2.24** (19 g, 41.8 mmol) in MeOH (300 mL) was added Na metal (0.05 g, 2.1 mmol). The reaction was stirred for 24 h at room temperature, neutralized with Dowex 50WX8 H^+ ion exchange resin, filtered and concentrated to provide **2.25** as a white solid (11.7 g, 98%).

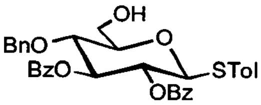
Compound **2.25** (11.0 g, 38.4 mmol) and $ZnCl_2$ (5.8 g, 42.2 mmol) were suspended in benzaldehyde (58 mL, 576 mmol) and stirred at room temperature for 8 h. The desired product **2.26** was purified by flash chromatography and isolated as a white powder (11.6 g, 81%).

Diol **2.26** (10.0 g, 26.7 mmol) was stirred in a solution of Bz_2O/pyridine (1:1 5.0 eq.) for 5 h at room temperature. The crude product precipitated out of solution after approx. 2 h, and was recovered by vaccum filtration. Washing the crude product with hot EtOH provided **2.27** as a fine white powder (14.0 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H, CH_3), 3.75 (ddd, 1H, $J_{5,6ax} = J_{5,4} = 9.6$ Hz, $J_{5,6eq} = 4.8$ Hz, H5), 3.90 (dd, $J_{4,5} = J_{4,3} = 9.5$ Hz, H4), 3.91 (dd, $J_{6ax,6eq} = J_{6ax,5} = 10.1$ Hz, H6$_{ax}$), 4.48 (dd, $J_{6eq,6ax} = 10.4$ Hz, $J_{6ax,5} = 4.7$ Hz, H6$_{eq}$), 4.98 (d, 1H, $J_{1,2} = 10.0$ Hz, H1), 5.47 (dd, 1H, $J_{2,3} + J_{2,1} = 19.1$ Hz, H2), 5.56 (s, 1H, CHPh), 5.80 (dd, $J_{3,4} = J_{3,2} = 9.4$ Hz, H3), 7.15 (d, 2H, $J = 7.9$ Hz, ArH), 7.29 – 7.58 (m, 13H, ArH), 7.93 – 7.58 (m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.09, 68.45, 70.83, 70.97, 73.23, 78.43, 87.18, 101.36, 126.00, 127.81, 128.07, 128.16, 128.28, 128.92, 129.17, 129.30, 129.67, 129.69, 129.78, 132.95, 133.18, 133.65, 136.62, 138.65, 165.06, 165.47; Melting point 210-212 °C; HRMS (EI) m/z = 581.1625 (M-H), $C_{34}H_{30}O_7S$ requires 581.1634.



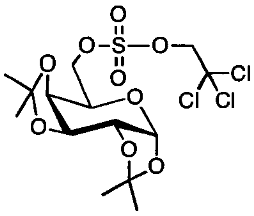
_p_-Tolyl 2,3-di-_O_-benzoyl-6-_O_-benzyl-1-thio-ß-D-glucopyranoside (2.12). To the fully protected **2.27** (0.5 g, 0.86 mmol) in CH_2Cl_2 (5 mL) was added dropwise triethylsilane (0.69 mL, 4.3 mmol) followed by trifluoroacetic acid (0.35 mL, 4.3 mmol). The reaction was followed to completion by TLC, diluted with CH_2Cl_2, carefully quenched with triethylamine and concentrated to a crude syrup. Purification by flash chromatography (33: 67 EtOAc/Hexanes) afforded **2.12** as a clear colourless syrup (0.42 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H, CH_3), 3.17 (d, 1H, $J_{OH,4} = 3.5$ Hz, OH), 3.70 (dd, 1H, $J_{5,4} = 9.4$ Hz, $J_{5,6} = 4.6$ Hz, H5), 3.86 (d, 2H, $J_{6,6'} = 4.5$ Hz, H6, H6'), 3.91 (ddd, $J_{4,5} = J_{4,3} = 9.4$ Hz, $J_{4,OH} = 3.5$ Hz, H4), 4.58, 4.61 (AB, 2H, $J = 11.9$ Hz, CH_2Ph), 4.84 (d, 1H,

$J_{1,2}$= 9.5 Hz, H1), 5.37 (dd, 1H, $J_{2,3}$ = $J_{2,1}$ = 9.4 Hz, H2),), 5.43 (dd, 1H, $J_{3,4}$ = $J_{3,2}$ = 9.4 Hz, H3), 7.04 (d, 2H, J = 8.0 Hz, ArH), 7.26 – 7.38 (m, 11H, ArH), 7.45 – 7.52 (m, 2H, ArH), 7.94 (t, 4H, J = 7.3 Hz, ArH).

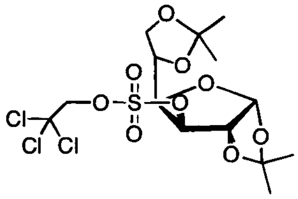


***p*-Tolyl 2,3-di-*O*-benzoyl-4-*O*-benzyl-1-thio-ß-D-glucopyranoside (2.13).** To carbohydrate **2.27** (0.15 g, 0.26 mmol) and CH_2Cl_2 (4.0 mL) were stirred over activated 4Å molecular sieves (0.4 g) for 1 h. The contents were then cooled to –78 °C and phenyldichloroborane (0.11 mL, 0.83 mmol) and triethylsilane (0.12 mL, 0.75 mmol) were added successively. The reaction was stirred for 1 h at –78 °C, then diluted with CH_2Cl_2 and quenched with NEt_3 and MeOH. The solution was filtered through celite to remove the molecular sieves, then washed with sat. $NaHCO_3$ and concentrated to a clear, colourless syurp. Purification by flash chromatography (33:67 EtOAc/hexanes) afforded **2.13** as a white foam (0.127 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H, CH_3), 3.58 – 3.63 (m, 1H, H5), 3.78 (dd, 1H, $J_{6,6'}$ = 12.2 Hz, $J_{6,OH}$ = 4.0 Hz, H6), 3.89 (dd, 1H, $J_{4,5}$ = $J_{4,3}$ = 9.5 Hz, H_4), 3.97 (dd, 1H, $J_{6',6}$ = 12.2 Hz, $J_{6',OH}$ = 2.3 Hz, H6'), 4.57 (s, 2H, CH_2Ph), 4.89 (d, 1H, $J_{1,2}$ = 10.0 Hz, H1), 5.32 (dd, 1H, $J_{2,3}$ + $J_{2,1}$ = 19.4 Hz, H2), 5.72 (dd, 1H, $J_{3,4}$ = $J_{3,2}$ = 9.4 Hz, H3), 7.09 – 7.16 (s, m, 7H, ArH), 7.34 – 7.49 (m, 8H, ArH), 7.89 – 7.96 (m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.16, 61.76, 70.91, 74.84, 75.37, 76.26, 79.55, 86.31, 127.97, 128.16, 128.36, 129.29, 129.37, 129.72, 129.79, 129.86, 133.17, 133.22, 133.44, 137.11, 138.63, 165.31, 165.68;

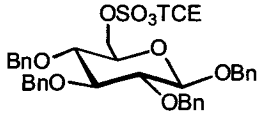
General Procedure for the Synthesis of Sulfated Carbohydrates. All sulfations commenced with the following general procedure as described for **2.5**. For reactions incomplete after 24h, additional equivalents of NMI and **2.3** (1 eq. each) were added at intervals of approximately 12 h until no starting material remained by TLC, unless otherwise described.



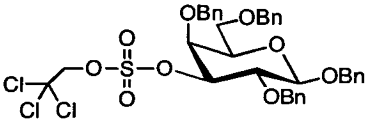
1,2:3,4-di-*O*-isopropylidene-6-*O*-trichloroethoxysulfo-*α*-D-galactopyranoside (2.28). *General Procedure*: To 1:2,3:4 di-isopropylidene galactose **2.4** (0.25 g, 0.97 mmol) in THF (4.2 mL, 0.23 M) at 0 °C was added NMI (0.19 mL, 2.39 mmol) followed by **2.3** (0.85 g, 1.92 mmol). The reaction was stirred at 0 °C, gradually warmed to room temperature, and then stirred overnight. After 24 h, the system was quenched with water and extracted with EtOAc. The combined organics were washed with sat. $NaHCO_3$, brine, and dried over $MgSO_4$ and concentrated to brown crude oil. (*Note*: work up was not performed for all products, reaction contents were instead applied directly to a silica gel column). Flash chromatography (25:75 EtOAc/hexanes) gave pure **2.28** as a white solid (0.4 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.55 (d, 1H, $J_{1,2}$ = 4.9 Hz, H1), 4.82, 4.79 (AB, 2H, J = 10.8 Hz, CH_2CCl_3), 4.76 (dd, 1H, $J_{3,2}$= 7.8, $J_{3,4}$= 2.5 Hz, H3), 4.51 (m, 2H, H6, H6'), 4.38 (dd, 1H, $J_{2,1}$ = 4.9, $J_{2,3}$= 2.5 Hz, H2), 4.26 (dd, 1H, $J_{4,3}$ = 7.8, $J_{4,5}$1.7 Hz, H4), 4.15 (m, 1H, H5), 1.56 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.35 (s, 6H, $2xCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.89 109.00, 96.00, 92.53, 79.46, 72.02, 70.50, 70.35, 70.10, 65.50, 25.90, 25.8, 24.74, 24.32; Melting Point 70-72 °C; HRMS (ESI) *m/z* = 471.0060, $C_{14}H_{22}C_{13}O_9S$ $(M+H)^+$ requires 471.0050.



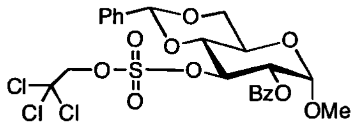
1,2:5,6-di-*O*-isopropylidene-3-*O*-trichloroethoxysulfoglucofuranoside (2.29). Prepared according to the general procedure. Carbohydrate **2.5** (0.25 g, 0.96 mmol), in THF (4.2 mL, 0.23 M), NMI (0.15 mL, 1.9mmol), **2.3** (0.85 g, 1.9 mmol). Compound **2.29** isolated as a white solid, (0.41 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (d, 1H, $J_{1,2}$ = 3.7 Hz, H1), 5.10 (1/2AB, 1H, J = 10.5 Hz, CH_2CCl_3), 5.07 (d, 1H, $J_{3,4}$ = 2.8 Hz, H3), 5.00 (d, 1H, $J_{2,1}$ = 3.7 Hz, H2), 4.81 (1/2AB, 1H, J = 10.5, CH_2CCl_3), 4.29 (m, 1H, H5), 4.18 (m, 2H, H4, H6), 4.08 (dd, 1H, $J_{6,6'}$ = 9.1, $J_{6',5}$= 3.8 Hz, H6'), 1.54, 1.46, 1.38, 1.34 (4s, 4x3H, $4xCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.67, 109.95, 104.88, 92.45, 85.29, 82.44, 79.58, 79.53, 71.54, 67.39, 26.91, 26.45, 26.05, 25.00; Melting point 100-102 °C; HRMS (ESI) *m/z* = 471.0059, $C_{14}H_{22}C_{13}O_9S$ $(M+H)^+$ requires 471.0050.



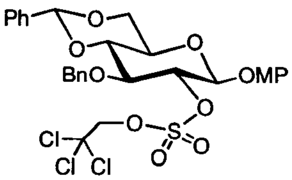
Benzyl 2,3,4-tri-*O*-benzyl-6-*O*-trichloroethoxysulfo-*β*-D-glucopyranoside (2.31). Prepared according to the general procedure. Carbohydrate **2.6** (0.251 g, 0.46 mmol), THF (3 mL, 016 M), *N*-methyl imidazole (0.11 mL, 1.4 mmol), 2,2,2-trichloroethoxysulfuryl-*N*-methylimidazolium triflate **2.3** (0.6259 g, 1.4 mmol), reaction time 2 d. Desired product **2.31** isolated as a white solid (0.261 g, 75%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.50 – 3.62 (m, 3H, H2, H4, H5), 3.70 (dd, 1H, $J_{3,4} = J_{3,2} = 8.7$ Hz, H3), 4.44 (dd, 1H, $J_{6,6'} = 10.5$, $J_{6,5}= 4.6$ Hz, H6), 4.55 – 4.60 (m, 2H, H1, H6'), 4.65 (d, 1H, $J =$ 7.1 Hz, CH$_2$Ph), 4.71 (d, 1H, $J = 5.8$ Hz, CH$_2$Ph), 4.74, 4.77 (AB, 2H, $J = 9.6$ Hz, CH$_2$CCl$_3$), 4.82 – 4.85 (m, 2H, CH$_2$Ph), 4.90 – 4.99 (m, 4H, CH$_2$Ph), 7.18 – 7.37 (m, 20H, ArH); ^{13}C NMR (75 MHz, CDCl$_3$) δ 71.39, 72.16, 72.24, 74.88, 75.02, 75.61, 76.32, 79.58, 81.92, 84.29, 92.54, 102.34, 127.68, 127.70, 127.72, 127.74, 127.89, 127.92, 128.06, 128.12, 128.13, 128.31, 128.36, 128.38, 128.43, 128.55, 136.79, 137.24, 138.01, 138.15; Melting point 111-114 °C; HRMS (ESI) *m/z* = 751.1290, $C_{36}H_{38}O_9SCl_3$ $(M+H)^+$ requires 751.1302.



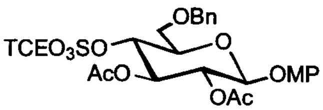
Benzyl 2,4,6-tri-*O*-benzyl-3-*O*-trichloroethoxysulfo-*β*-D-galactopyranoside (2.32). Prepared according to the general procedure. Carbohydrate **2.7** (0.5 g, 0.93 mmol), THF (6 mL, 0.16 M), NMI (0.22 mL, 2.8 mmol), **2.3** (0.86 g, 1.9 mmol), reaction time 2 d. Compound **2.32** was isolated as a white solid (0.65 g, 94%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.55-3.64 (m, 3H, H5, H6, H6'), 3.93, (dd, 1H, $J_{2,3} = 10.0$, $J_{2,1} = 7.6$ Hz, H2), 4.30 (d, 1H, $J_{4,3} = 3.0$ Hz, H4), 4.40-4.49 (m, 4H, CH$_2$CCl$_3$, CH$_2$Ph), 4.50 (d, 1H, $J_{1,2} = 7.6$ Hz, H1), 4.57 (dd, 1H, $J_{3,2} = 10.1$, $J_{3,4} = 3.1$ Hz, H3), 4.59-4.66 (m, 3H, CH$_2$Ph), 4.87 (d, 1H, $J = 11.4$ Hz, CH$_2$Ph), 4.95 (d, 1H, $J = 11.9$ Hz, CH$_2$Ph), 5.00 (d, 1H, $J = 11.0$ Hz, CH$_2$Ph), 7.25-7.37 (m, 20H, ArH); ^{13}C NMR (75 MHz, CDCl$_3$) δ 67.95, 71.04, 72.70, 73.43, 73.87, 75.09, 75.29, 76.38, 79.34, 85.65, 92.37, 102.18, 127.75, 127.81, 127.84, 127.88, 127.95, 128.01, 128.11, 128.27, 128.38, 128.41, 128.49, 136.77, 137.43, 137.51, 137.59; Melting point 52-54 °C; HRMS (ESI) *m/z* = 768.1581, $C_{36}H_{41}NO_9SCl_3$ $(M+NH_4)^+$ requires 768.1568.



Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-trichloroethoxysulfo-α-D glucopyranoside (2.37). Prepared according to the general procedure. Carbohydrate **2.8** (1.0 g, 2.6 mmol), THF (11 mL, 0.24 M), NMI (0.66 mL, 8.3 mmol), **2.3** (3.0 g, 6.76 mmol). After 24 h and 36 h, additional aliquots of NMI (0.22 mL, 2.8 mmol) and **2.3** (0.12 g, 2.7 mmol) were added at room temperature. Reaction time approx. 48 h. Flash chromatogrpahy (33:67 EtOAc/hexanes) yields product **2.37** as a white solid (1.467 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.44 (s, 3H, OCH_3), 3.86 (dd, 1H, $J_{6ax,6eq} = J_{6ax,5} =$ 10.3 Hz, $H6_{ax}$), 3.89 (dd, 1H, $J_{4.5} = J_{4,3} =$ 9.5 Hz, H4), 4.05 (ddd, 1H, $J_{5,6ax} = 9.9$, $J_{5,4} = 9.7$, $J_{5,6eq} = 4.7$ Hz, H5), 4.41 (dd, 1H, $J_{6eq,6ax} = 10.4$, $J_{6ax,5} = 4.8$ Hz, $H6_{eq}$), 4.43, 4.50 (AB, 2H, J = 11.1 Hz, CH_2CCl_3), 5.18 (dd, 1H, $J_{2,3} = 9.5$, $J_{2,1} = 3.6$ Hz, H2), 5.22 (d, 1H, $J_{1,2} = 3.6$ Hz, H1), 5.36 (dd, 1H, $J_{3,4} = J_{3,2} =$ 9.5 Hz, H3), 7.38-7.40 (m, 3H, ArH), 7.46-7.53 (m, 4H, ArH), 7.59-7.61 (m, 1H, ArH), 8.19 (d, 2H, J = 7.4 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.67, 62.27, 68.74, 71.62, 78.67, 79.64, 80.62, 94.23, 97.77, 102.59, 126.35, 128.42, 129.64, 130.19, 133.60, 136.09, 165.71; Melting point (dec.) 130-132 °C; HRMS (ESI) *m/z* = 597.0133, $C_{23}H_{23}Cl_3O_{10}S$ $(M+H)^+$ requires 597.0156.

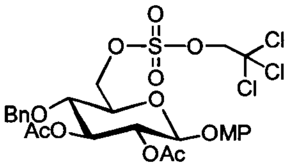


p-Methoxyphenyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-trichloroethoxysulfo-ß-D-glucospyranoside (2.38). Prepared according to the general procedure. Carbohydrate **2.9** (0.2 g, 0.43 mmol), THF (2 mL, 0.25 M), NMI (0.2 mL, 2.5 mmol), **2.3** (1.0 g, 2.25 mmol). After 24 h, additional NMI and triflate **2.3** were added (0.2 mL, 2.5 mmol, and 1.0 g, 2.25 mmol) respectively. Upon completion (48 h) the reaction contents were directly applied to a silica gel column. Flash chromatography (20:80 EtOAc/hexanes) provided **2.38** as a white solid (0.26 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.57 (ddd, 1H, $J_{5,6ax}$ = 9.7, $J_{5,4}$ = 9.5, $J_{5,6eq}$ = 5.0 Hz, H5), 3.80 (s, 3H, CH_3), 3.86 (dd, 1H, $J_{6eq,6ax}$ = $J_{6ax,5}$ = 10.4 Hz, H6$_{ax}$), 3.88 (dd, 1H, $J_{4,5}$ = $J_{4,3}$ = 9.2 Hz, H4), 3.98 (dd, 1H, $J_{3,4}$ = $J_{3,2}$ = 9.1 Hz, H3), 4.43 (dd, 1H, $J_{6eq,6ax}$ = 10.5, $J_{6eq,5}$ = 5.0 Hz, H6$_{eq}$), 4.68, 4.71 (AB, 2H, J = 11.1 Hz, CH_2CCl_3), 4.85 (m, 1H, H2), 4.87, 5.01 (AB, 2H, J = 11.2 Hz, CH_2Ph), 5.02 (d, 1H, $J_{1,2}$ = 7.8 Hz, H1), 5.61 (s, 1H, CHPh), 6.85-6.88 (m, 2H, ArH), 7.06-7.09 (m, 2H, ArH), 7.33-7.50 (m, 10H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.54, 66.19, 66.30, 74.61, 77.87, 79.86, 81.21, 83.89, 92.57, 99.89, 101.36, 114.59, 118.77, 125.88, 127.92, 128.09, 128.11, 128.25, 128.27, 128.28, 128.38, 129.13, 136.63, 137.12, 150.16, 155.99; Melting point 105-107 °C; HRMS (EI) m/z = 674.0546, $C_{29}H_{29}Cl_3O_{10}S$ requires 674.0547.

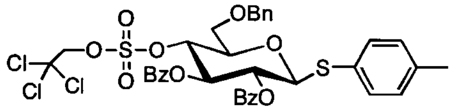


p-Methoxyphenyl 2,3-di-*O*-acetyl-6-*O*-benzyl-4-*O*-trichloroethoxysulfo-ß-D-

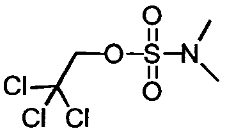
glucopyranoside (2.39). Prepared according to the general procedure. Carbohydrate **2.10** (0.376 g, 0.82 mmol), THF (4 mL, 0.26 M), NMI (0.19 mL, 2.3 mmol), **2.3** (1.0 g, 2.25 mmol). After 12 h, and 24 h, additional NMI and reagent **2.3** were added (0.19 mL, 2.3 mmol, and 0.92 g, 2.1 mmol) respectively. Upon completion (48 h) the reaction contents were directly applied to a silica gel column. Flash chromatography (20:80 EtOAc/hexanes) provided **2.39** as a clear colourless glassy compound (0.415 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.77-3.81 (m, 3H, H5, H6, H6'), 4.59, 4,62 (AB, 2H, J = 11.8 Hz, CH_2Ph), 4.68, 4.73 (AB, 2H, J = 11.1 Hz, CH_2CCl_3), 4.97 (d, 1H, $J_{1,2}$ = 7.9 Hz, H1), 5.00 (dd, 1H, $J_{4,5}$ = $J_{4,3}$ = 9.3 Hz, H4), 5.22 (dd, 1H, $J_{2,3}$ = 9.3 Hz, $J_{2,1}$ = 7.9 Hz, H2), 5.42 (dd, 1H, $J_{3,4}$ = $J_{3,2}$ = 9.3 Hz, H3), 6.78 – 6.81 (m, 2H, ArH), 6.94 – 6.97 (m, 2H, ArH), 7.26 – 7.34 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.59, 20.74, 55.63, 67.85, 71.41, 73.23, 73.81, 79.29, 80.24, 92.48, 100.16, 114.59, 118.76, 127.77, 127.82, 128.41, 137.49, 150.78, 155.85, 169.27, 170.33.



***p*-Methoxyphenyl 2,3-di-*O*-acetyl-4-*O*-benzyl-6-*O*-trichloroethoxysulfo-ß-D-glucopyranoside (2.40).** Prepared according to the general procedure. Carbohydrate **2.11** (0.81 g, 1.76 mmol), THF (8 mL, 0.22 M), NMI (0.42 mL, 5.29 mmol), **2.3** (1.9 g, 4.28 mmol). After 24 h and additional NMI (0.42 mL, 5.29 mmol) and triflate **2.3** (1.0 g, 2.25 mmol) were added at room temperature. Upon completion by TLC (approx. 36 h), reaction contents were applied directly to a silica column, and were purified by flash chromatography (33:67 EtOAc/hexanes). Product **2.40** was isolated as a white solid (0.96 g, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.04 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 3.78 (m, 5H, OCH_3, H4, H6), 4.45 (dd, 1H, $J_{5,4}$ = 10.6, $J_{5,6}$ = 3.7 Hz, H5), 4.65-4.72 (m, 5H, CH_2CCl_3, CH_2Ph, H6'), 5.02 (d, 1H, $J_{1,2}$ = 7.8 Hz, H1), 5.16 (dd, 1H, $J_{2,3}$ = 9.5, $J_{2,1}$ = 7.9 Hz, H2), 5.34 (m, 1H, H3), 6.81-6.84 (m, 2H, ArH), 6.91-6.94 (m, 2H, ArH), 7.30-7.40 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.55, 20.68, 55.55, 71.18, 71.45, 72.34, 74.52, 74.60, 74.94, 79.60, 92.28, 99.73, 114.59, 118.27, 128.04, 128.40, 128.66, 136.53, 150.53, 155.73, 169.47, 169.83; Melting point 110-112 °C; HRMS (ESI) m/z = 688.0812 $(M+NH_4)^+$ $C_{26}H_{33}NO_{12}SCl_3$ requires 688.0789.

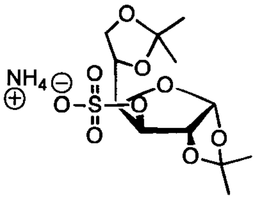


***p*-Tolyl 2,3-di-*O*-benzoyl-6-*O*-benzyl-1-thio -4-*O*-trichloroethoxysulfo -ß-D-glucopyranoside (2.41).** Prepared according to the general procedure. Carbohydrate **2.12** (0.41 g, 0.70 mmol), THF (3 mL, 0.24 M), NMI (0.17 mL, 2.1 mmol), **2.3** (1.0 g, 2.25 mmol). After 24 h and 36 h, additional aliquots of NMI (0.06 mL, 0.76 mmol) and **2.3** (0.3 g, 0.68 mmol) were added at room temperature. Upon completion by TLC (approx. 48 h), reaction contents were applied directly to a silica column, and were purified by flash chromatography (25:75 EtOAc/hexanes). Product **2.41** was isolated as a white waxy compound (5.034 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H, CH_3), 3.81-3.94 (m, 3H, H5, H6, H6'), 4.45, 4.57 (AB, 2H, J = 11.1 Hz, CH_2Ph), 4.60, 4.66 (AB, 2H, J = 11.8 Hz, CH_2CCl_3), 4.86 (d, 1H, $J_{1,2}$ = 9.9 Hz, H1), 5.14 (dd, 1H, $J_{4,5}$ = $J_{4,3}$ = 9.5 Hz, H4), 5.31 (dd, 1H, $J_{2,3}$ = $J_{2,1}$ = 9.7 Hz, H2), 5.80 (dd, 1H, $J_{3,4}$ = $J_{3,2}$ = 9.4 Hz, H3), 7.03 (d, 2H, $J = 7.9$ Hz, ArH), 7.24-7.39 (m, 11H, ArH), 7.45-7.54 (m, 2H, ArH), 7.92 (d, 4H, $J = 7.8$ Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 68.1, 70.6, 73.7, 73.8, 77.5, 79.2, 80.2, 86.1, 92.4, 127.4, 127.9, 128.0, 128.5, 128.7, 129.1, 129.9, 130.0, 130.2, 133.5, 133.7, 134.1, 137.8, 139.0; Melting point (dec.) 112-114°C; HRMS (ESI) m/z = 795.0659, $C_{36}H_{34}O_{10}S_2Cl_3$ $(M+H)^+$ requires 795.0659.

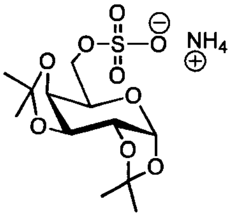


2,2,2-Trichloroethyl-*N*,*N*-dimethylsulfamate (2.30). Compound isolated as a white solid by-product from entry 5 for tables 2.1 and 2.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.61 (s, 2H, CH_2), 2.96 (s, 6H, $2xCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.7, 77.8, 93.8; LRMS m/z = 255, $C_4H_8Cl_3NO_3S$ requires 254.929.

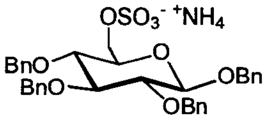
General Procedure for Deprotection of the Sulfate Moiety: All deprotections were performed with the following procedure, which is described for compound **2.34** (*note:* reaction equivalents are doubled when two trichloroethyl bearing sulfate groups are to be deprotected). The zinc used was obtained from Aldrich, and was used as received.



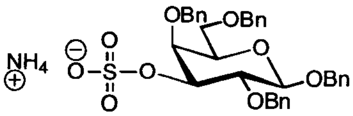
1,2:5,6-di-*O*-isopropylidene-3-*O*-sulfoglucofuranoside (2.34). *General Procedure:* To a suspension of ammonium formate (0.16 g, 2.5 mmol) in MeOH (2.5 mL, 1.0 M) was added protected carbohydrate **2.29** (0.2 g, 0.42 mmol) followed by zinc dust (0.2 g, 3.1 mmol). The reaction was stirred for 7 h at room temperature, at which point no starting material was detected using TLC. The reaction was filtered through celite, and concentrated to yield crude product. Flash chromatography (20:4:1 CH_2Cl_2/MeOH/NH_4OH) afforded a white solid, which was lyophilized (3x) from H_2O to yield **2.34** as a light white product (0.14 g, 94%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.23 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 3.91-3.96 (m, 1H, H6), 3.78-3.83 (m, 1H, H6'), 4.20-4.26 (m, 2H, H4, H5), 4.45 (d, 1H, $J_{3,4}$ = 2.7 Hz, H3), 4.76 (d, 1H, $J_{2,1}$ = 3.8 Hz, H2), 5.84 (d, 1H, $J_{1,2}$ = 3.8 Hz, H1), 7.08 (brs, 4H, NH_4); ^{13}C NMR (75 MHz, DMSO-d_6) δ 25.61, 26.42, 26.74, 26.94, 65.09, 73.03, 78.49, 79.63, 83.04, 104.73, 107.76, 111.05; HRMS (ESI) m/z = 339.0738, $C_{12}H_{19}O_9S$ requires 339.0750.



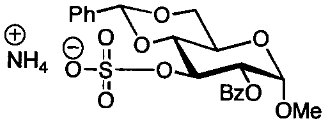
1,2:3,4-di-*O*-isopropylidene-6-*O*-sulfo-*β*-D-galactopyranoside (2.33). Prepared according to the general procedure: Carbohydrate **2.28** (0.20 g, 0.43 mmol), MeOH (2.5 mL), HCO_2NH_4 (0.16 g, 2.6 mmol), Zn (0.22 g, 3.4 mmol), reaction time 6 h. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 3.71-3.81 (m, 2H, H6, H6'), 3.94 (brdd, $J_{5,6}$ = $J_{5,6'}$ = 5.7 Hz, H5), 4.22 (brd, 1H, $J_{4,3}$ = 8.0 Hz, H4), 4.32 (dd, 1H, $J_{2,1}$ = 4.8, $J_{2,3}$ = 2.1 Hz, H2), 4.57 (dd, 1H, $J_{3,4}$ = 8.0, $J_{3,2}$ = 1.9 Hz, H3), 5.43 (d, 1H, $J_{1,2}$ = 5.0 Hz, H1), 7.09 (brs, 4H, NH_4); ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.59, 25.26, 26.15, 26.28, 65.06, 66.27, 70.13, 70.33, 70.73, 95.94, 108.15, 108.56; HRMS (ESI) m/z = 339.0754, $C_{12}H_{19}O_9S$ requires 339.0750.



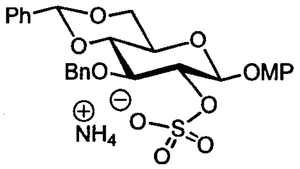
Benzyl 2,3,4-tri-*O*-benzyl-6-*O*-sulfo-*β*-D-glucopyranoside (2.35). Prepared according to the general procedure: Carbohydrate **2.31** (0.32 g, 0.42 mmol), MeOH (3.0 mL), HCO_2NH_4 (0.16 g, 2.5 mmol), Zn (0.20 g, 3.1 mmol), reaction time 24 h. Product **2.35** recovered as a light white solid (0.26 g, 96%). ^1H NMR (300 MHz, DMSO-d_6) δ 3.34 (dd, 1H, $J_{2,3} = J_{1,2}$ = 8.4 Hz, H2), 3.45 – 3.58 (m, 2H, H4, H5), 3.62 (dd, 1H, $J_{3,4} = J_{3,2}$ = 8.8 Hz, H3), 4.04 (br-d, 2H, J = 2.5 Hz, H6, H6'), 4.60 (d, 1H, $J_{1,2}$ = 7.9 Hz, H1), 4.64 (d, 1H, J = 10.0 Hz, CH_2Ph), 4.66 (d, 1H, J = 11.3 Hz, CH_2Ph), 4.67 (d, 1H, J = 12.0 Hz, CH_2Ph), 4.74 (d, 1H, J = 12.1 Hz, CH_2Ph), 4.75 (d, 1H, J = 11.4 Hz, CH_2Ph), 4.81 (d, 1H, J = 11.3 Hz, CH_2Ph), 4.84 (d, 1H, J = 11.6 Hz, CH_2Ph), 4.88 (d, 1H, J = 10.5 Hz, CH_2Ph), 7.10 (br-s, 4H, NH_4), 7.23 – 7.41 (m, 20H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 64.75, 70.65, 73.52, 74.10, 74.14, 74.80, 77.69, 82.13, 83.99, 102.22, 127.70, 127.76, 127.87, 128.08, 128.09, 128.42, 128.44, 128.46, 128.48, 128.51, 128.52, 128.54, 128.62, 128.64, 138.03, 138.73, 138.40, 139.08; HRMS (ESI) m/z = 619.1981, $C_{34}H_{35}O_9S$ requires 619.2002.



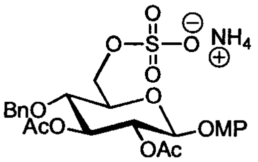
Benzyl 2,4,6-tri-*O*-benzyl-3-*O*-sulfo-*β*-D-galactopyranoside (2.36). Prepared according to the general procedure: Carbohydrate **2.32** (0.13 g, 0.18 mmol), MeOH (1.1 mL), HCO_2NH_4 (0.07 g, 1.1 mmol), Zn (0.08 g, 1.2 mmol), reaction time 8 h. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.42-3.51 (m, 3H, H2, H6, H6'), 3.73 (dd, 1H, $J_{5,6} = J_{5,6'} = 6.2$ Hz, H5), 4.21 (d, 1H, $J_{4,3} = 2.6$ Hz, H4), 4.34 (dd, 1H, $J_{3,2} = 9.8$, $J_{3,4} = 2.9$ Hz, H3), 4.43, 4.46 (AB, 2H, $J = 12.2$ Hz, CH_2Ph), 4.52 (d, 1H, $J = 11.5$ Hz, CH_2Ph), 4.56 (d, 1H, $J_{1,2} = 7.9$ Hz, H1), 4.58 (d, 1H, $J = 12.6$ Hz, CH_2Ph), 4.67 (d, 1H, $J = 11.5$ Hz, CH_2Ph), 4.78 (d, 1H, $J = 12.3$ Hz, CH_2Ph), 4.80 (d, 1H, $J = 11.5$ Hz, CH_2Ph), 4.97 (d, 1H, $J = 11.4$ Hz, CH_2Ph), 7.08 (brs, 4H, NH_4), 7.22-7.39 (m, 20H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 68.83, 70.31, 72.60, 72.60, 73.71, 74.20, 74.53, 77.85, 78.70, 102.05, 127.36, 127.60, 127.74, 127.78, 127.82, 127.99, 128.17, 128.38, 128.49, 128.59, 138.28, 138.58, 139.51, 139.56; HRMS (ESI) *m/z* = 619.1982, $C_{34}H_{35}O_9S$ requires 619.2002.



Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-sulfo-α-D-glucopyranoside (2.43). Prepared according to the general procedure: Carbohydrate **2.37** (0.2 g, 0.33 mmol), MeOH (2.0 mL), HCO_2NH_4 (0.13 g, 2.06 mmol), Zn (0.15 g, 2.29 mmol), reaction time 6h. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.31 (s, 3H, CH_3), 3.70-3.85 (m, 3H, H4, H5, $H6_{ax}$), 4.25 (dd, 1H, $J_{6eq,6ax} = 9.5$, $J_{6eq,5} = 3.6$ Hz, $H6_{eq}$), 4.78 (brdd, $J_{3,4} = J_{3,2} = 9.3$ Hz, H3), 4.90 (dd, 1H, $J_{2,3} = 9.8$, $J_{2,1} = 3.6$ Hz, H2), 5.04 (d, 1H, $J_{1,2} = 3.5$ Hz, H1), 5.64 (s, 1H, CHPh), 7.09 (s, 4H, NH_4), 7.36-7.38 (m, 3H, ArH), 7.47-7.52 (m, 4H, ArH), 7.62-7.68 (m, 1H, ArH), 8.14 (d, 2H, $J = 7.5$ Hz, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.11, 63.01, 68.18, 72.88, 73.04, 79.36, 97.66, 100.55, 126.64, 128.22, 128.67, 128.94, 130.08, 130.43, 133.54, 138.08, 166.13; HRMS (ESI) m/z = 465.0837, $C_{21}H_{21}O_{10}S$ requires 465.0855.

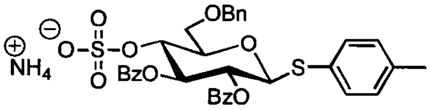


***p*-Methoxyphenyl 3-*O*-benzyl-4,6-O-benzylidene-2-*O*-sulfo-ß-D-glucospyranoside (2.44).** Prepared according to the general procedure: Carbohydrate **2.38** (0.20 g, 0.30 mmol), MeOH (1.8 mL), HCO_2NH_4 (0.11 g, 1.8 mmol), Zn (0.16 g, 2.45 mmol), reaction time 5 h. ^1H NMR (300 MHz, DMSO-d_6) δ 3.61-3.68 (m, 2H, H5, H6_{ax}), 3.72 (s, 3H, CH_3), 3.85 (dd, 1H, $J_{3,2}$ = 8.5, $J_{3,4}$ = 4.0 Hz, H3), 4.11-4.17 (m, 1H, H4), 4.23-4.25 (m, 1H, H6_{eq}), 4.51 (dd, 1H, $J_{2,3}$ = $J_{2,1}$ = 4.3 Hz, H2), 4.70, 4.90 (AB, 2H, J = 12.2 Hz, CH_2Ph), 5.40 (d, 1H, $J_{1,2}$ = 4.6 Hz, H1), 5.70 (s, 1H, CHPh), 6.88 (d, 2H, J = 9.1 Hz, ArH), 7.02 (d, 2H, J = 9.0 Hz, ArH), 7.09 (brs, 4H, NH_4), 7.23-7.33 (m, 3H, ArH), 7.38-7.41 (m, 7H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.70, 65.11, 68.81, 71.59, 77.13, 79.14, 79.76, 99.98, 100.59, 114.83, 118.96, 126.43, 127.53, 128.02, 128.31, 128.40, 129.11, 138.03, 139.14, 150.98, 155.00; HRMS (ESI) m/z = 543.1305, $C_{27}H_{27}O_{10}S$ requires 543.1325.



***p*-Methoxyphenyl 2,3-di-*O*-acetyl-4-*O*-benzyl-6-*O*-sulfo-β-D-glucopyranoside (2.45).**

Prepared according to the general procedure: Carbohydrate **2.40** (0.16 g, 0.24 mmol), MeOH (1.4 mL), HCO_2NH_4 (0.09 g, 1.42 mmol), Zn (0.12 g, 1.84 mmol), reaction time 5 h. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.95 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 3.66 (dd, 1H, $J_{4,5} = J_{4,3} = 9.6$ Hz, H4), 3.71 (s, 3H, OCH_3), 3.91 (brd, 1H, $J_{5,4} = 9.7$ Hz, H5), 4.03 (brs, 2H, H6, H6'), 4.52, 4.71 (AB, 2H, $J = 10.8$ Hz, CH_2Ph), 4.88 (dd, 1H, $J_{2,3} = 9.7$, $J_{2,1} = 8.1$ Hz, H2), 5.28 (d, 1H, $J_{1,2} = 8.0$ Hz, H1), 5.28 (dd, 1H, $J_{3,4} = J_{4,3} = 9.6$ Hz, H3), 6.87 (d, 2H, $J = 9.2$ Hz, ArH), 6.96 (d, 2H, $J = 9.1$ Hz, ArH), 7.09 (brs, 4H, NH_4), 7.27-7.37 (m, 5H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.75, 20.87, 55.73, 64,41, 71.81, 73.44, 73.80, 74.08, 75.35, 98.75, 114.95, 118.27, 128.04, 128.53, 128.66, 138.31, 150.95, 155.25, 169.54, 169.92; HRMS (ESI) *m/z* = 539.1205, $C_{24}H_{27}O_{12}S$ requires 539.1223.



***p*-Tolyl 2,3-di-*O*-benzoyl-6-*O*-benzyl-4-*O*-sulfo-1-thio-ß-D-glucopyranoside (2.46).**

Prepared according to the general procedure: Carbohydrate **2.41** (0.11 g, 0.14 mmol), MeOH (1.0 mL), HCO_2NH_4 (0.06 g, 0.95 mmol), Zn (0.09 g, 1.3 mmol), reaction time 4 h. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.57 (dd, 1H, $J_{6,6'} = 11.5$, $J_{6,5} = 8.0$ Hz, H6), 4.01 (brdd, $J_{5,6} = J_{5,4} = 8.8$ Hz, H5), 4.11 (brd, $J_{6',6} = 11.5$ Hz, H6'), 4.25 (dd, 1H, $J_{4,5} = J_{4,3} = 9.6$ Hz, H4), 4.52 (s, 2H, CH_2Ph), 5.11 (dd, 1H, $J_{2,3} = J_{2,1} = 9.7$ Hz, H2), 5.39 (d, 1H, $J_{1,2} = 9.9$ Hz, H1), 5.65 (dd, 1H, $J_{3,4} = J_{3,2} = 9.3$ Hz, H3), 7.02 (d, 2H, $J = 8.0$ Hz, ArH), 7.08 (brs, 4H, NH_4), 7.27-7.41 (m, 9H, ArH), 7.47-7.66 (m, 4H, ArH), 7.80-7.87 (m, 4H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.96, 70.62, 71.44, 72.58, 72.80, 74.89, 78.62, 83.81, 127.64, 127.80, 128.48, 129.10, 129.13, 129.23, 129.57, 129.75, 129.92, 130.37, 131.66, 137.41, 139.08, 164.99, 165.63; HRMS (ESI) *m/z* = 663.1337, $C_{34}H_{31}O_{10}S_2$ requires 663.1359.

2.12 References

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Chapter 3 – Stability of 2,2,2-TCE Protected Sulfates Towards Protecting Group Manipulations, Anomeric Activations, and Disaccharide Synthesis

3.1 Introduction

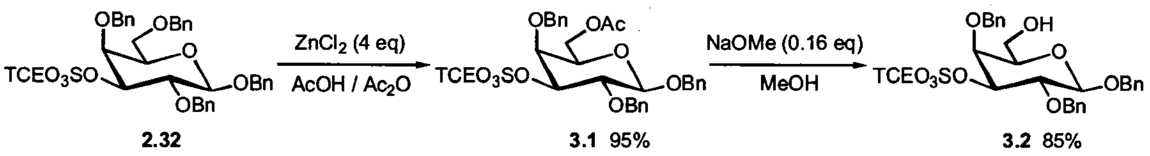
In order for the TCE protected sulfate methodology to be applied to carbohydrate chemistry, it is essential to show that the TCE sulfates are stable to conditions commonly encountered in the synthesis of higher order oligosaccharides. The $TCESO_3$ group should remain intact during routine protecting group manipulations, as this is one of the major components in the synthesis of complex carbohydrates. The protected sulfates must also tolerate conditions for anomeric activation, and while surviving conditions required for the coupling of monosaccharides, which often involve nucleophilic acceptors as well as strong promoters. This chapter demonstrates that, for the most part, the TCE protected sulfates are stable to many conditions commonly encountered in carbohydrate chemistry, indicating that the TCE-protected sulfates offer a viable approach towards the synthesis of sulfated carbohydrates.

3.2 Protecting Group Manipulations

Because the $TCESO_3$ group will be incorporated at the beginning of a multi-step sequence, it must be stable to the manipulation of other protecting groups found in the molecule. To investigate their stability, the TCE sulfates were subjected to a variety of conditions commonly encountered in carbohydrate chemistry.

3.2.1 *Introduction and selective removal of acetate protecting groups*

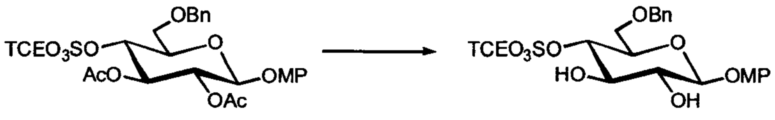
The perbenzylated 3-TCE protected sulfogalactose derivative **2.32** was subjected to selective de-benzylation, acetylation conditions using 4.0 eq. of freshly fused zinc chloride and a solution of acetic anhydride/acetic acid as described by Lu *et al.*,[1] to provide the corresponding 6-OAc sulfogalactose derivative **3.1** as shown in scheme 3.1.



Scheme 3.1

The acetate group in **3.1** was easily removed under Zemplén conditions to provide the 6-OH group in **3.2**. The $TCESO_3$ group remained stable for both the debenzylation/acetylation, and transesterification reactions as no other carbohydrate based products were identified during these reactions.

Unfortunately, the ease with which acetate protecting groups were removed under Zemplén conditions could not be extended successfully to other carbohydrates. Attempts to deacetylate **2.39** (scheme 3.2), which bears acetylated 2° hydroxyl groups were more challenging. The results of our attempts to achieve this in the presence of the 4-$TCESO_3$ group are summarized in table 3.1.



2.39 **3.3**

Scheme 3.2

Table 3.1: Selective Deacetylation Reactions of Carbohydrate **2.39**

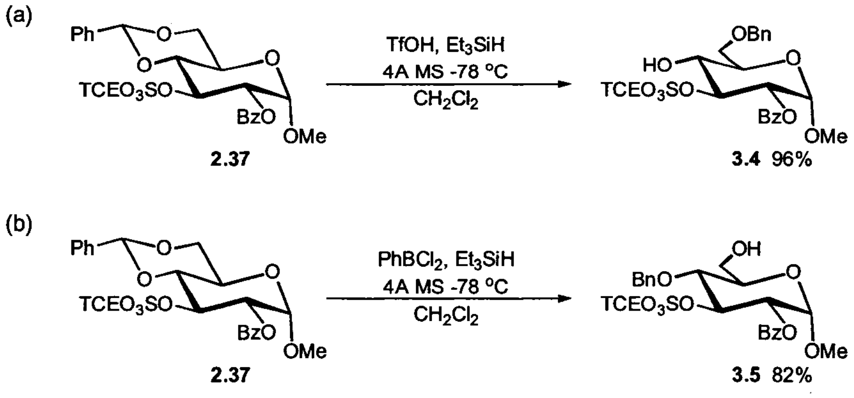
Entry	Method	Equivalents	Result
1	NaOMe/MeOH	0.7	Lost TCESO$_3$ and OAc groups
2	NaOMe/MeOH	0.2	Lost TCESO$_3$ and OAc groups
3	K_2CO_3/MeOH	0.5	Lost TCESO$_3$ and OAc groups
4	TFA/MeOH	2.0	No Reaction
5	HCl (g)	Sat.	Complex mixture by TLC
6	HCl (g)	Sat.	Product in Crude NMR
7	HCl (g)/MeOH	Sat.	30 % (approx.) and starting material
8	HCl (g)/MeOH	Sat.	70 %
9	**CH_3COCl/MeOH**	**3 M**	**84 %**

Unfortunately, the 2- and 3- position acetate protecting groups in **2.39** could not be selectively removed in the presence of the TCE-protected sulfate under basic conditions, as loss of both the OAc and TCE protecting groups was observed for entries 1, 2, and 3 in table 3.2. After some experimentation, selective de-acetylation was achieved using acidic conditions (entry 9, table 3.2). Attempts to remove the acetate groups with TFA were not successful, as no reaction was observed. More promising results were observed for the initial reactions with HCl saturated methanol (entries 5 to 8). For entries 5 and 6, HCl gas was generated from HCl (aq) and $CaCl_2$ then bubbled through a solution of carbohydrate **2.39** in methanol. This method resulted in a complicated mixture of products. For entries 7 and 8, pre-acidified methanol was added directly to carbohydrate **2.39**, and this method allowed for isolation of desired the 2,3-diol **3.3** in a 70% yield. Altering the method again, carbohydrate **2.39** was stirred in HCl saturated methanol (approx 3.0 M), which was first prepared by the dropwise addition of acetyl chloride to methanol at 0 °C. This approach provided the desired diol **3.3** in an 84% yield (entry 9, table 3.2), and was the most reliable method of those attempted.

3.2.2 Manipulations of the benzylidene acetal

As previously described in chapter 2, 4,6-*O*-benzylidene acetals are easily prepared using benzaldehyde and zinc chloride, and are key protecting groups in carbohydrate chemistry as they protect two hydroxyl groups with high regioselectivity. Once introduced into a monosaccharide building block, they are stable to most transformations used in carbohydrate synthesis, but can easily be manipulated or removed to provide highly functionalized glycosyl acceptors.

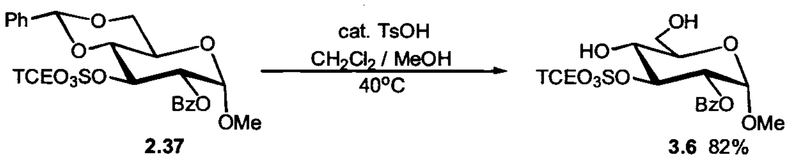
Because these acetals and their derivatives are so widely applied, the stability of the $TCESO_3$ group was investigated over a selection of benzylidene acetal manipulations including regioselective ring opening (scheme 3.4 a,b) and complete removal (scheme 3.5).



Scheme 3.3

The TCESO$_3$ group was tolerant of the conditions required for the regioselective reductive opening of the benzylidene acetal. Sulfated carbohydrate **2.37** was treated with triflic acid (3.4 eq.) and triethylsilane (3.0 eq.) in dry dichloromethane with molecular sieves to provide the ring open 4-OH product **3.4** in excellent yields. In contrast, **2.37** was subjected to phenyl dichloroborane (3.5 eq.) and triethylsilane (3.0 eq.) to provide the free 6-OH **3.5** in good to excellent yields. No detectable loss of the TCESO$_3$ group was observed in either of these reactions.

The benzylidene acetal in **2.37** was also removed under acidic conditions providing the corresponding 4,6-diol. For this reaction, carbohydrate **2.37** was suspended in a dichloromethane/methanol (1:2) solution and heated at 40 °C until most of the starting material had dissolved. Catalytic *p*-toluenesulfonic acid was added to the solution and the reaction was stirred overnight at 40 °C to provide diol **3.6** in an 82 %.



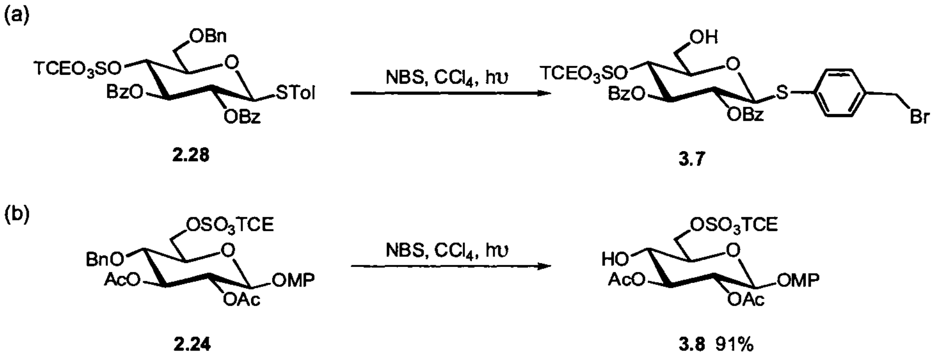
Scheme 3.4

3.2.3 Selective debenzylation reactions

Difficulties were initially encountered when attempting to selectively cleave a benzyl ether in the presence of the TCE protected sulfate in **2.41** using hydrogenolysis, as the TCE protecting group is known to be removed under the standard hydrogenolysis (palladium and hydrogen) conditons.[2]

Photochemically initiated debenzylation was first documented by Binkley and Hehemann in 1990[3] and developed further by Riley and Grindley in 2001.[4] In this approach, sterically hindered benzyl ethers that could not be removed by hydrogenolysis, or those that proceeded very slowly were readily removed by applying *N*-bromosuccinimide (NBS) and light in the presence of aqueous calcium carbonate. It was found that these conditions were compatible with the presence of the TCE-protected sulfate groups, and the method could be applied to circumvent the problems that were initially observed with the hydrogenolysis reactions.

The method was initially attempted with thioglycoside **2.41** (scheme 3.5a). The benzyl group was selectively removed while the TCE-sulfate remained intact, however not surprisingly, the benzyllic methyl group in the thiotolyl anomeric function was brominated, giving product **3.7** exclusively. Applying the same conditions for carbohydrate **2.40** resulted in selective 4-*O*-debenzylation to give easy access the corresponding alcohol **3.8** (scheme 3.5b) in a 91% isolated yield.



Scheme 3.5

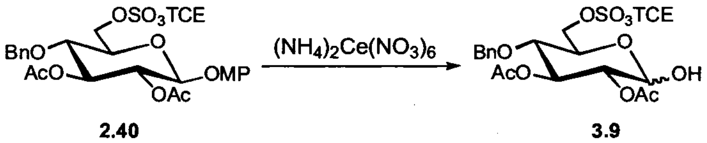
3.3 Preparation of Free Anomeric Hemiacetals

To demonstrate the viability of the TCE-protected sulfocarbohydrates in the synthesis of higher order oligosaccharides, activated carbohydrate donors bearing the $TCESO_3$ group were prepared. In the chosen approach, fully protected carbohydrates bearing the protected sulfates were first converted to their corresponding hemiacetals by removing the anomeric protecting group. Carbohydrates bearing *p*-methoxyphenyl and thiotolyl anomeric protecting groups provided access to the anomeric hydroxyl group as described below.

3.3.1 Anomeric hemiacetals from p-methoxyphenyl glycosides

The initial approach to compounds possessing both a TCE protected sulfate and a an free anomeric hydroxyl group involved carbohydrates bearing an OMP protecting group at the anomeric position. It was anticipated that oxidative removal of the *p*-methoxyphenyl glycoside with cerium (IV) ammonium nitrate (CAN), according to a procedure outlined by Karst and Jacquinet,[5] would provide ready access to the anomeric hemiacetal. In their approach, CAN (5.0 eq.) was added to a solution of the reacting glycoside in a toluene-acetonitrile-water solution, with a reaction time of 20 minutes.

Extending this procedure to *p*-methoxyphenyl glycosides **2.39** and **240** did not proceed as expected. Initial attempts for obtaining the hemiacetal **3.9** from **2.40** (scheme 3.6) resulted in very complex mixtures that did not yield any desired product after purification by flash chromatography (table 3.2, entries 1, 2).



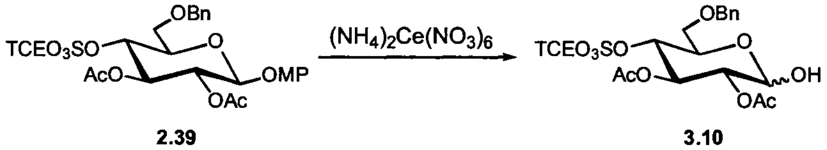
Scheme 3.6

Table 3.2: Oxidative cleavage of *p*-methoxyphenyl glycosides with **2.40**

Entry	Solvent	Conditions	Results
1	Tol/ACN/H_2O	5 eq. CAN, RT, 15 min	complex mixture
2	Tol/ACN /H_2O	5 eq. CAN, 0 °C, 15 min	complex mixture
3	**ACN/pH 7 buffer**	**5 eq. CAN, RT, 15 min**	**66% impure**

It was then postulated that the very acidic reaction conditions that result from the oxidative CAN reaction were too harsh for product **3.9**, so the reaction conditions were modified such that acetonitrile served as the only organic solvent, and the water was replaced with pH 7 phosphate buffer. These modifications drastically changed the outcome of the reaction, allowing for compound **3.9** to be isolated in a 69% yield. While the obtained proton and carbon NMR spectra confirmed the presence of the product with no impurities, compound **3.9** was isolated as a yellow-orange product, presumably contaminated with CAN or related by-products. Despite observing a distinct separation between the product spot and the yellow contaminant by TLC, completely removing the coloured contaminant from the product was very difficult, and was never completely achieved.

The conditions that allowed for the formation and isolation of product **3.9** were applied to glycoside **2.39** to provide access to hemiacetal **3.10** (scheme 3.7). Promising results were initially obtained with the new conditions (table 3.3, entry 1), however further studies were performed to increase the yield of the reaction, as described in table 3.3. All reactions were performed in acetonitrile / pH 7 buffer solution.



Scheme 3.7

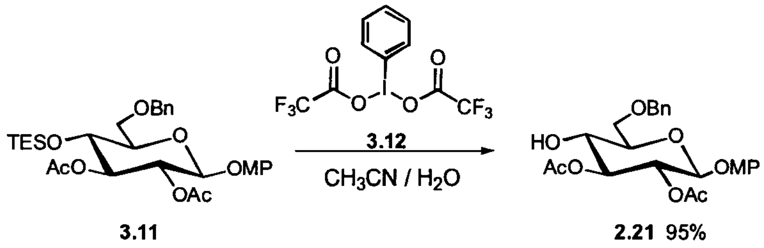
Table 3.3: Oxidative cleavage of *p*-methoxyphenyl glycosides with **2.39**

Entry	CAN (eq.)	Temp. (°C)	Time	Results
1	5 eq.	RT	15 min	50% impure
2	5.eq.	0 °C	15 min	79% impure
3	1 eq. then 2 eq.	0 °C	30 min, then 15 min	85% slight impurity
4	**1 eq. then 2 eq**	0 °C	**1h, then 15 min**	**88% (>95% pure)**

The conditions in which 5 eq. of CAN was added directly to a solution of glycoside **2.39** in an acetonitrile/pH 7 phosphate buffer solution (1.5:1, v/v) gave **3.10** in approximately 50% yield. Cooling the reaction to 0 °C increased the yield to a 79%;

however the optimal conditions were determined to be a portion wise addition of CAN, where the first equivalent was added to a solution of glycoside **2.39** in the CH_3CN/buffer solution, and 2 additional equivalents were added after 1 h. As was the case with product **3.9**, anomeric hemiacetal **3.10** was also contaminated with CAN or CAN-related contaminants, as this product was also isolated as a yellow-orange syrupy compound. After much deliberation, it was determined that the optimal purification conditions required isolation of the impure product by flash chromatography eluting 33:67 EtOAc/hexanes, followed by a short gravity column using 85:15 benzene/EtOAc. These reaction conditions and purifications allowed for hemiacetal **3.10** to be reliably obtained in good yield with acceptable purity, providing access to a compound that can easily be converted to an activated glycosyl donor.

While optimizing the conditions for the CAN mediated oxidative cleavage of the OMP glycoside, it was proposed that phenyliodine (III) bis(trifluoroacetate) (PIFA) **3.12** might serve as an alternative oxidizing agent, since the reagent is useful for the phenolic oxidative transformation such as the conversion of *p*-alkoxy phenols to 1,4-benzoquinones. [6] Glycoside **3.11** was used as a model system for the oxidative removal of the OMP group using PIFA in the place of CAN as depicted in scheme 3.8. Surprisingly, the *p*-methoxyphenyl function remained intact, while complete loss of the 4-*O*-TES protecting group was observed, providing compound **2.10** in a 95% yield. This reagent was not further pursued, however the PIFA directed removal of silyl protecting groups will be investigated in the future.

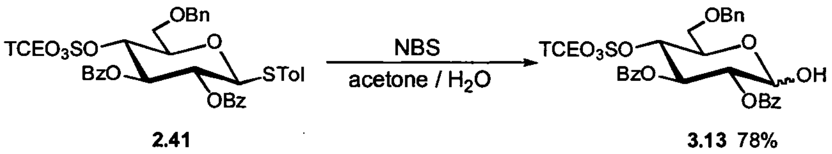


Scheme 3.8

3.3.2 Anomeric hemiacetals from thioglycosides

Thioglycosides from readily available thiols. The anomeric thio function is stable towards a range of reaction conditions encountered in carbohydrate manipulations, but can easily be activated by electrophiles to give access to a range of activated glycosylating agents or their corresponding hemiacetals.

Thioglycoside **2.41** served as a reliable precursor to hemiacetal **3.13** through the application of more favourable reaction conditions, and simplified purification compared to the CAN mediated oxidative cleavages. In this approach, **2.41** was subjected to NBS in an acetone/water solution to give hemiacetal **3.13** in a 78% yield, (scheme 3.9). No further optimization studies were conducted with this compound.



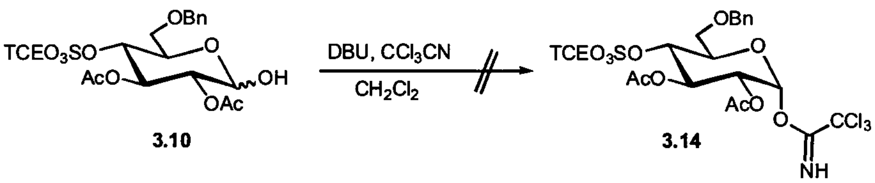
Scheme 3.9

3.4 Preparation of Anomeric Imidates

N-methylacetimidate glycosidic donors were first introduced by Sinay as an alternative to the classic Koenigs-Knorr approach for the synthesis of 1,2-*cis* linked disaccharides with high yields and excellent stereoselectivity.[7,8] This approach was further developed by Schmidt and co-workers, who discovered that trichloroacetimidoyl derivatives were even more potent glycosyl donors than their corresponding *N*-methyl counterparts.[9,10] The trichloroacetimidate approach to the synthesis of 1,2-*cis* and 1,2-*trans* disaccharides has been extensively studied, and now is one of the most widely applied glycosylation protocols.

3.4.1 Preparation of trichloroacetimidate glycosyl donors

Alcohols are known to undergo reversible base catalyzed addition to electron deficient nitriles, such as trichloroacetonitrile, providing *O*-alkyl trichloroacetimidates.[9] Standard literature conditions for the synthesis of trichloroacetimidate donors were applied to carbohydrate **3.10** anticipating that the corresponding imidate donor **3.14** would be readily obtained according to scheme 3.10.



Scheme 3.10

Hemiacetal **3.10** in CH_2Cl_2 was treated with 0.5 eq. of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 16 eq. of trichloroacetonitrile. The reaction was followed by TLC, and appeared to proceed smoothly. The crude product was purified on a short silica gel column to yield a white foam. The proton NMR obtained for the major product however did not correspond to trichloroacetimidate **3.14** (scheme 3.11a). Figure 3.1 depicts the proton spectra obtained for the major product.

It was immediately observed that the desired trichloroacetimidate **3.14** was not obtained, as there was no corresponding –NH signal, which was expected around 8-9 ppm. From the anomeric region, the AB pattern at 4.56 ppm, and the peaks at 2.08 ppm, it was confirmed that both the benzyl and acetate protecting groups remained intact. The characteristic AB pattern that results from the CH_2CCl_3 protecting group was not observed, indicating loss of the TCE-sulfate group. One of the most striking features of the spectrum however, was the absence of complex splitting patterns associated with carbohydrate ring protons. As expected, and confirmed using the HMQC spectrum, it was clear that the H1 proton was the doublet (J= 2.1 Hz) found at 5.75 ppm, and the ABX pattern at 3.41 ppm corresponded to H6, H6'. The X pattern corresponding to the ABX for H6, H6' was assumed to be for proton H5, which was confirmed by a strong cross peak in the COSY spectrum. Following the cross peaks for H1 with the COSY, it was deduced that H2 was the broadened singlet at 4.73 Hz. The 2 remaining singlets at 4.60 and 4.77 ppm, therefore corresponded to H3 and H4. Combining this information, it was concluded that the carbohydrate ring must be strongly distorted from the conventional chair formation, such that the dihedral angles between H2 and H3, H3 and H4, as well as H4 and H5 must be as close as possible to 90°. With this in mind, it was concluded that the 4-*O*-TCESO$_3$ group must have acted as a leaving group under these conditions, providing the 1,4-anhydro sugar **3.15** (scheme 3.11b). The obtained spectra correspond very closely to experimental data reported by Seeberger and co-workers, for a similar 1,4-anhydro sugar that contains 2,3-OBz groups in place of the 2,3-OAc groups in compound **3.15**.[11] This by-product was also supported by mass spectrometric analysis.

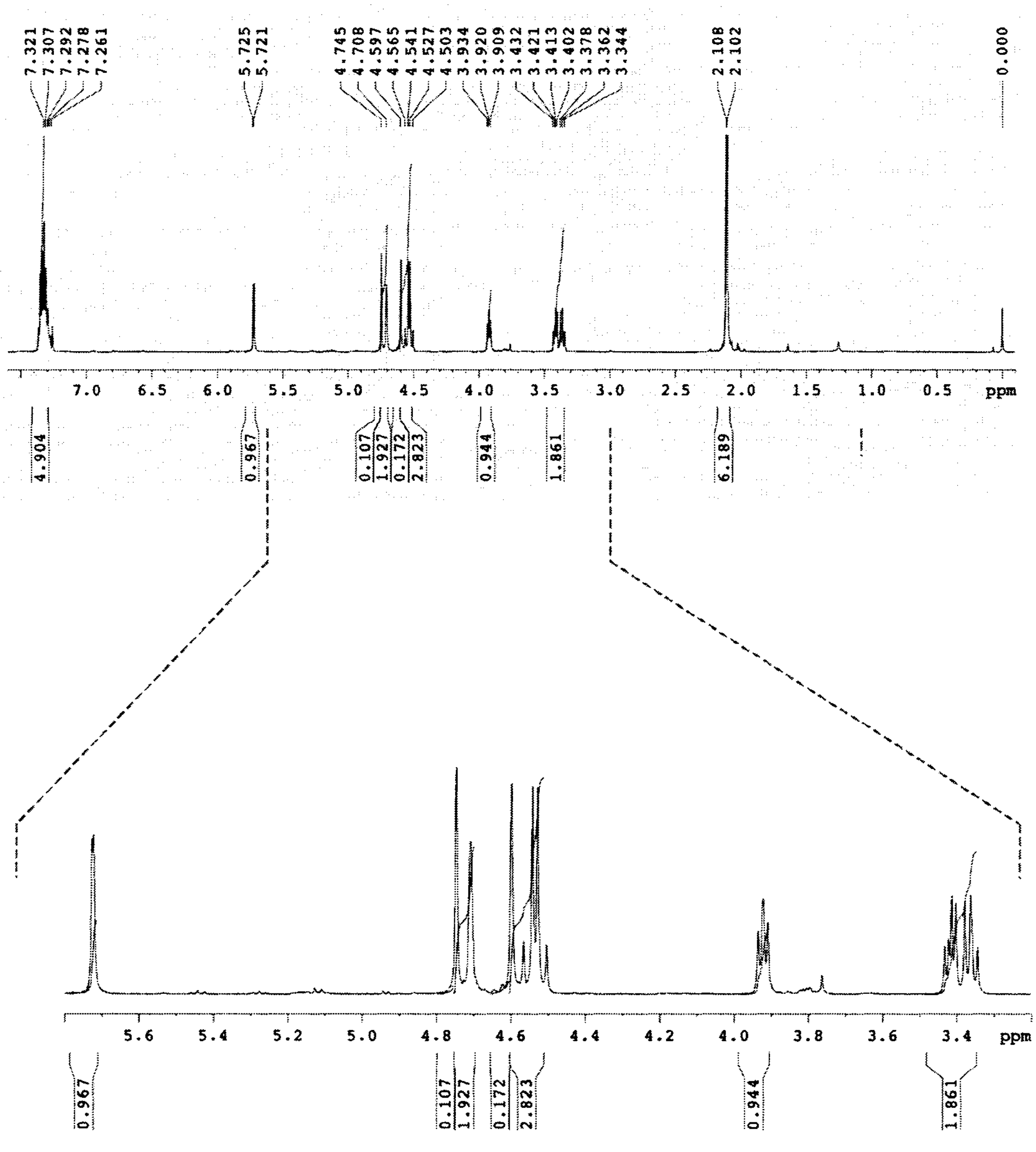
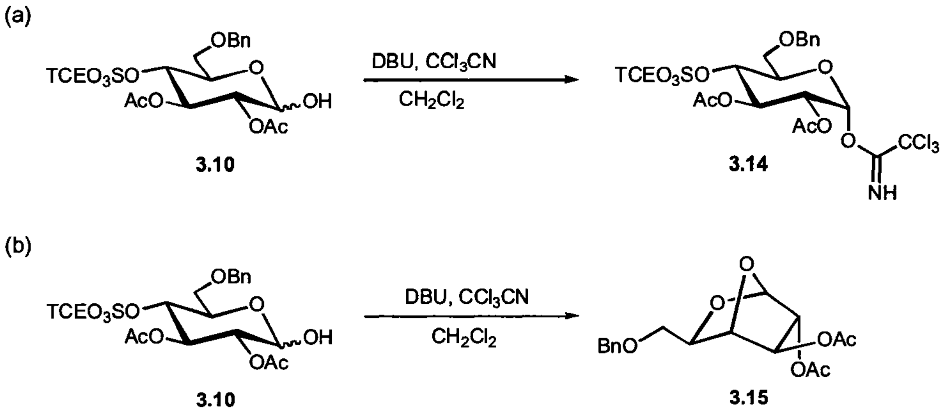


Figure 3.1: ^{1}H Spectrum for by product **3.15**



Scheme 3.11

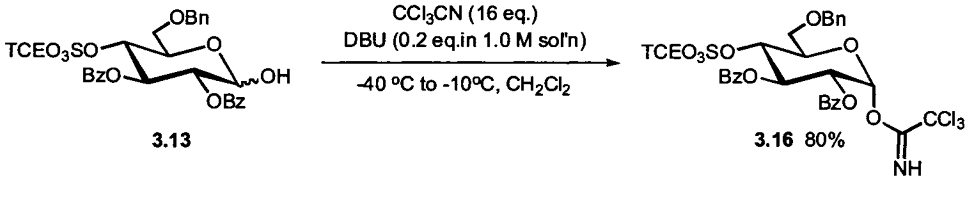
The preparation of trichloroacetimidate **3.14** was explored in further detail by modifying the base and reaction conditions. In an attempt to decrease or eliminate the amount of by-product used, the reaction conditions were changed from room temperature to 0 °C and –10°C (table 3.4, entries 1 and 2). In both cases, anhydro sugar **3.15** was the major product, however target imidate **3.14** was observed when the reaction was run at –10°C. Changing the base from DBU to triethylamine, Hunig's base, or sodium hydride was unsuccessful (entries 3,4, and 5, table 3.4). Both the product **3.14** and by-product **3.15** were observed when Cs_2CO_3 was employed at room temperature and at 0 °C. It was then discovered that performing the reaction at low temperatures while adding DBU as a dilute solution in CH_2Cl_2 allowed for the preparation of imidate **3.14** in good yields (Table 3.4, entries 9-11). The optimized conditions (table 3.4, entry 10) required a significant increase in reaction time compared to literature procedures, however under these conditions, the reaction was reliably repeated and extended to other $TCESO_3$ bearing carbohydrates, with no loss of the TCE group or formation of the 1,4-anhydro sugars.

Table 3.4: Preparation of trichloroacetimidoyl donor **3.14**

Entry	Base (eq.)	Conditions	Results
1	DBU (0.5)	0 °C, 20 min	**3.15** exclusively
2	DBU (0.4)	-10 °C, 1 h	**3.15** major, **3.14** minor
3	NEt$_3$ (0.4)	-10 °C – RT, O/N	No reaction
4	DIEA (0.4)	-10 °C – RT, O/N	No reaction
5	NaH (1.0)	0 °C, 1h	complex mixture
6	DBU (0.2)	-78 °C to –10 °C 6h	70% **3.14** and **3.15** minor
7	Cs$_2$CO$_3$ (0.4)	RT, followed by TLC	**3.15** major, **3.14** minor
8	Cs$_2$CO$_3$ (0.4)	0 °C, followed by TLC	**3.15** major, **3.14** minor
9	DBU (0.2)*	-20 °C, ~4h	85% **3.14**
10	**DBU (0.2)***	**-35 °C to –1 0°C, ~5h**	**92% 3.14**
11	DBU (0.1)*	-35 °C to –10 °C, ~5-6h	90% **3.14**

* DBU added as a1.0 M solution in dry CH$_2$Cl$_2$

The optimized reaction conditions were then used for the preparation of trichloroacetimidate **3.16** from hemiacetal **3.13** as depicted in scheme 3.12.



Scheme 3.12

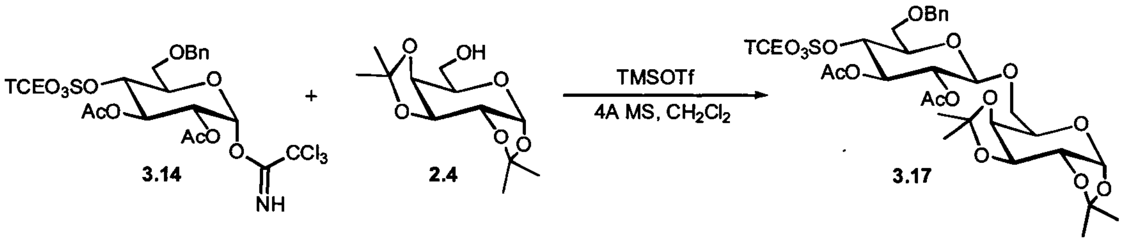
3.5 Glycosylation Reactions

In 1982, Hans Paulsen stated: "*Although we have now learned to synthesize oligosaccharides, it should be emphasized that each oligosaccharide synthesis remains an independent problem, whose resolution requires considerable systematic research and a good deal of know how. There are no universal reaction conditions for oligosaccharide synthesis.*" [12]

Theoretically, the formation of a glycosidic bond should be simple to execute. Combining a donor bearing a good leaving group, and an acceptor with a free hydroxyl group should ultimately result in simple nucleophilic substitution to give a coupled product. Unfortunately, as we quickly learned, many extenuating factors complicate oligosaccharide synthesis, and Paulsen's conclusions still stand, 25 years later.

*3.5.1 Glycosylation with sulfated imidate donor **3.14***

In order to demonstrate that the TCE-protected sulfates were tolerant to the activation and coupling conditions required for disaccharide synthesis, initial glycosylation attempts employed sulfated imidate donor **3.14**, and di-*O*-isopropylidene galactose **2.4** as the nucleophilic acceptor. Various conditions were scanned for the synthesis of disaccharide **3.17** as described in scheme 3.13, with results summarized in table 3.5.



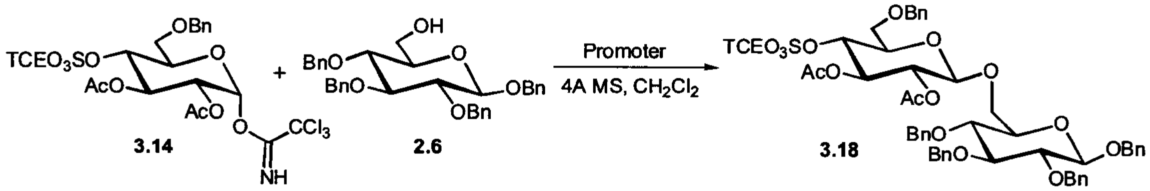
Scheme 3.13

Table 3.5: Conditions for coupling of **3.14** and **2.4**

Entry	Donor **3.14** (eq.)	Acceptor **2.4** (eq.)	TMSOTf (eq.)*	Temperature (°C)	Results
1	3.3	1.0	0.13	r.t.	degradation of donor
2	1.3	1.0	0.44	-40 to -10	degradation of donor
3	2.0	1.0	0.32	-40 to -10	32 % (3 columns)
4	2.0	1.0	0.32	-40 to -10	52%

*With respect to acceptor. Added as 1.0 M solution in CH_2Cl_2

Results for the glycosylation of **2.4** with imidate donor **3.14** under TMSOTf catalyzed conditions were somewhat disappointing. For the first glycosylation attempt, (table 3.5, entry 1) imidate donor **3.14** was added to a solution containing acceptor **2.4** and TMSOTf promoter in the presence of activated 4Å molecular sieves and CH_2Cl_2. Under these conditions, imidate donor **3.14** was found to degrade to unidentified products, while the unreacted acceptor was recovered. The reaction conditions were then modified (table 3.5, entry 2) such that the TMSOTf promoter was added as a 1.0 M solution to a mixture of donor **3.14** and acceptor **2.4** in the presence of activated 4 Å molecular sieves at low temperature (-40 °C). The reaction was followed by TLC, and allowed to gradually warm to –10 °C over several hours. Again, no glycosylation was achieved, as donor **3.14** readily degraded to unidentified products, while acceptor **2.4** remained intact. To ensure that trace amounts of moisture were not hindering the glycosylation reaction, donor **3.14** and acceptor **2.4** were then combined and co-evaporated with toluene (3 x) and left under vacuum for 12 hours. The compounds were then dissolved in dry CH_2Cl_2 and stirred over activated 4Å molecular sieves for several hours, before being cooled to –40 °C and treated with TMSOTf (0.16 eq. as 1.0 M solution). After 1 h, a new spot appeared by TLC (among others), and the reaction was monitored until complete disappearance of donor **3.14** was observed. After several purifications by flash chromatography, target disaccharide **3.17** was obtained in 32 % (table 3.5, entry 3). The somewhat successful reaction and purification conditions were then attempted again (table 3.5, entry 4) to afford **3.17** in a 52% yield. Despite a number of varied reaction conditions, each of the above reactions resulted in a significant number of unidentified carbohydrate based by products. While it was observed that the donor **3.14** easily degraded under certain conditions, it is suspected that this was not a direct result of the presence of the TCE-protected sulfate group, but a consequence of the highly reactive, somewhat unstable imidoyl anomeric centre. Another complicating factor involves the generation of triflic acid under these reaction conditions, which can potentially lead to partial degradation of the isopropylidene protecting groups in acceptor **2.4**. To eliminate this variable, the glycosyl acceptor was changed to the perbenzylated glucose derivative **2.6** (scheme 3.14), with expectations that the free 6-OH would serve as an efficient nucleophile, without the previous mentioned sensitivity to the generated triflic acid.



Scheme 3.14

Once again, the coupling conditions were varied with respect to ratio of donor to acceptor, type of promoter and equivalents applied, as well as temperature and time. The results are summarized in table 3.6. Despite several modifications to the reaction conditions, disaccharide **3.18** was obtained in only moderate yields.

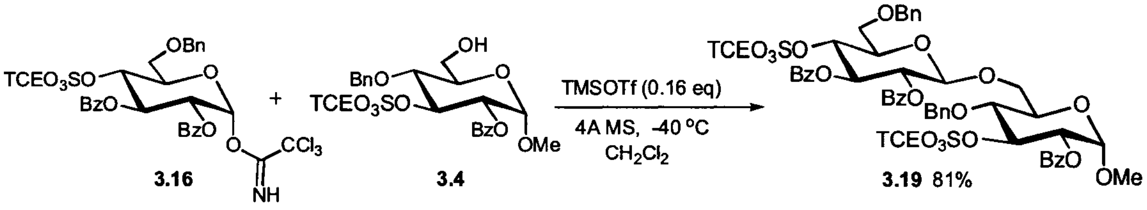
Table 3.6: Conditions for coupling of **3.14** and **2.6**

Entry	Donor **3.14** (eq.)	Acceptor **2.6** (eq.)	Promoter (eq.)*	Temperature (°C), time (h)	Results
1	2.0	1.0	TMSOTf (1.0)	0 to r.t., 16 h	51 %
2	1.4	1.0	TMSOTf (0.4)	-40 to r.t., 16 h	50 %
3	1.4	1.0	TMSOTf (1.0)	-40 to r.t., 16 h	51 %
4	1.4	1.0	TMSOTf (1.0)	0 to r.t., 5 h	48 %
5	2.0	1.0	$Sn(OTf)_2$ (1.0)	0 to r.t., 3 h	50 %

*With respect to acceptor. TMSOTf added as 1.0 M solution in CH_2Cl_2

*3.5.2 Synthesis and deprotection of disulfated disaccharide **3.19***

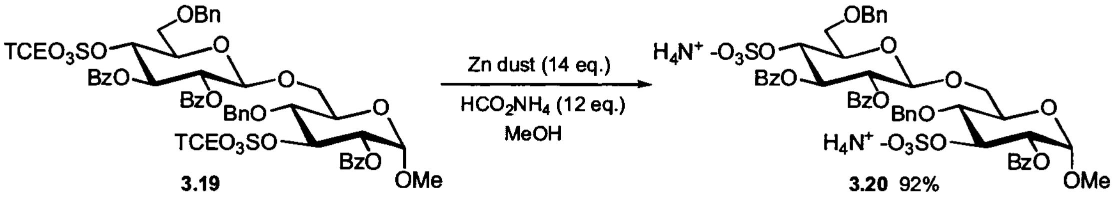
To demonstrate that the TCE-protected monosaccharide sulfates could serve as both a donor and an acceptor under the required coupling conditions, disulfated disaccharide **3.19** was prepared according to scheme 3.15.



Scheme 3.15

For this coupling reaction, donor **3.16** and acceptor **3.4** were first dissolved in CH_2Cl_2 and stirred over activated 4Å MS, then TMSOTf was slowly added as a 1.0 M solution in dry CH_2Cl_2 at –40 °C. After 30 min, there was no remaining acceptor by TLC, and the reaction was determined to be complete. A 2-step purification procedure was required, which involved first isolating the major product using flash chromatography then subjected the isolated material to a short gravity column to remove the 2,2,2-trichloroacetamide by-product. This afforded the *β*-linked target disaccharide **3.19** in a respectable 81% yield.

The disulfated disaccharide **3.19** was then subjected to zinc and ammonium formate in methanol to remove the TCE protecting group. Fortunately, the di-deprotection reaction proceeded very smoothly to afford the free sulfate groups in **3.20** as described in scheme 3.16.



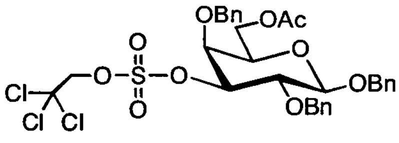
Scheme 3.16

3.6 Summary

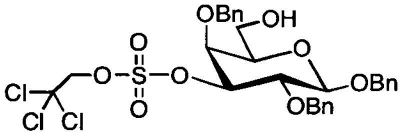
To demonstrate that early incorporation of TCE-protected sulfates presents a potential approach for the step-wise synthesis of sulfated oligosaccharides, TCE-protected sulfomonosaccharides were subjected to a variety of conditions encountered in carbohydrate chemistry. We have demonstrated that the TCE protected sulfates are stable to a number of protecting group manipulations, including de-benzylation, de-acetylation, manipulations and cleavage of benzylidene acetals, as well as removal of common anomeric protecting groups to provide free hemiacetals. We have also shown that the TCE-sulfates are stable to anomeric activation via imidate preparation. We were able to show that sulfated donors and acceptors can be combined in the preparation of disulfated disaccharides, and continued to show that the two TCE-sulfates can be easily deprotected in excellent yields. This chapter not only demonstrates that the TCE-sulfates are stable routine protecting group manipulations and glycosylation chemistry, but also that the sulfate deprotection conditions are mild enough that newly formed glycosyl linkages and other functionalities in the molecules are not affected, an important feature for multi-step synthetic sequences.

3.7 Experimental

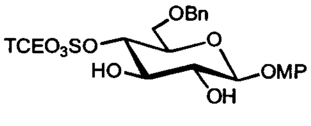
For general information, refer to chapter 2, page 49.



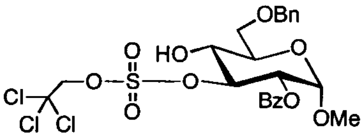
Benzyl 6-*O*-acetyl-2,4-di-*O*-benzyl-3-*O*-trichloroethoxysulfo-β-D-galactopyranoside (3.1). A solution of AcOH:Ac_2O (3 mL, 1:5 v/v) was added to freshly fused $ZnCl_2$ (0.67 g, 4.9 mmol) with stirring. After 1.5 h, carbohydrate **2.32** (1.0 g, 1.3 mmol) in AcOH:Ac_2O solution (8 mL, 1:5 v/v) was added slowly via syringe. After 3 h, no starting material remained by TLC. The reaction was cooled to 0 °C and slowly quenched with ice. The product was extracted with EtOAc, washed with sat. $NaHCO_3$ and condensed to a clear, colourless oil. Flash chromatography (25:75 EtOAc/hexanes) afforded **3.1** as a clear, colourless oil (0.89 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.03 (s, 3H, CH_3), 3.63 (dd, 1H, $J_{5,6} = J_{5,6'} = 6.6$ Hz, H5), 3.98 (dd, 1H, $J_{2,3} = 9.9$, $J_{2,1} = 7.6$ Hz, H2), 4.04 (dd, 1H, $J_{6,6'} = 11.1$, $J_{6,5} = 6.2$ Hz, H6), 4.25 (d, 1H, $J_{4,3} = 2.9$ Hz, H4), 4.31 (dd, 1H, $J_{6',6} = 11.1$, $J_{6',5} = 6.2$ Hz, H6'), 4.50 (brs, 2H, CH_2CCl_3), 4.52 (d, 1H, $J_{1,2} = 7.7$ Hz, H1), 4.60 (dd, 1H, $J_{3,2} = 9.9$, $J_{3,4} = 2.9$ Hz, H3), 4.65 (d, 1H, $J = 11.0$ Hz, CH_2Ph), 4.67 (d, 1H, $J = 11.3$ Hz, CH_2Ph), 4.68 (d, 1H, $J = 11.8$ Hz, CH_2Ph), 4.96 (d, 1H, $J = 11.5$ Hz, CH_2Ph), 4.97 (d, 1H, $J = 11.8$ Hz, CH_2Ph), 5.06 (d, 1H, $J = 11.0$ Hz, CH_2Ph), 7.28-7.41 (m, 15H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.63, 61.86, 71.00, 71.27, 73.01, 75.14, 75.15, 76.20, 79.44, 85.41, 92.28, 101.96, 127.96, 127.99, 128.06, 128.09, 128.39, 128.50, 128.55, 136.54, 136.96, 137.31, 170.20; HRMS (ESI) m/z = 720.1215, $C_{31}H_{37}Cl_3NO_{10}S$ $(M+NH_4)^+$ requires 720.1204.



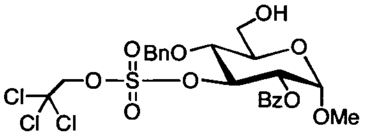
Benzyl 2,4-di-*O*-benzyl-3-*O*-trichloroethoxysulfo-*β*-D-galactose (3.2). Carbohydrate **3.1** (0.19 g, 0.27 mmol) was subjected to a 0.025 M solution of NaOMe in MeOH (1.7 mL). After 3 h, no starting material was detected by TLC. Residual solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate, washed with water, sat. $NaHCO_3$ and brine, and condensed to a clear, colourless oil. Flash chromatography (25:75 EtOAc/hexanes) provided product **3.2** as a white foam (0.15 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.44-3.53 (m, 2H, H5, H6), 3.72-3.80 (m, 1H, H6'), 3.98 (dd, 1H, $J_{2,3}$ = 10.1, $J_{2,1}$ = 7.6 Hz, H2), 4.26 (d, 1H, $J_{4,3}$ = 3.0 Hz, H4), 4.50 (s, 2H, CH_2CCl_3), 4.55 (d, 1H, $J_{1,2}$ = 7.6 Hz, H1), 4.61 (dd, 1H, $J_{3,2}$ = 10.1, $J_{3,4}$ = 3.1 Hz, H3), 4.66 (d, 1H, J = 11.9 Hz, CH_2Ph), 4.67 (d, 1H, J = 11.0 Hz, CH_2Ph), 4.71 (d, 1H, J = 11.8 Hz, CH_2Ph), 4.95 (d, 1H, J = 11.7 Hz, CH_2Ph), 4.96 (d, 1H, J = 11.9 Hz, CH_2Ph), 5.07 (d, 1H, J = 11.0 Hz, CH_2Ph), 7.28-7.44 (m, 15H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.17, 71.32, 72.63, 73.88, 74.86, 75.16, 76.39, 77.46, 85.60, 92.29, 102.37, 127.95, 127.99, 128.01, 128.06, 128.30, 128.39, 128.49, 128.51, 128.53, 128.67, 128.80, 136.71, 137.03, 137.34; HRMS (ESI) m/z = 661.0857, $C_{29}H_{31}Cl_3O_9S$ $(M+H)^+$ requires 661.0833.



***p*-Methoxyphenyl 6-*O*-benzyl-4-*O*-trichloroethoxysulfo-ß-D-glucopyranoside (3.3).** Acidic methanol (3 M) was first prepared by the slow addition of acetyl chloride to reagent grade methanol at 0 °C. Compound **2.39** (0.125 g, 0.18 mmol) was stirred in the acidic methanol (2 mL) for 5 h, until the reaction was determined complete by TLC. The crude was condensed, and purified by flash chromatography (50:30 EtOAc/hexanes) to provide **3.3** as a clear, colourless glassy compound (91.9 mg, 84 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.27 (br-s, 1H, OH), 3.40 (br-s, 1H, OH), 3.73-3.77 (m, 3H, H5, H6, H2), 3.79 (s, 3H, OCH_3), 3.90 (dd, 2H, $J_{6,6' \text{ and } 3,4} = J_{6',5 \text{ and } 3,2}$= 9.1 Hz, H6', H3), 4.59 – 4.63 (AB, 2H, J = 11.6 Hz, CH_2Ph), 4.77 (d, 1H, $J_{1,2}$ = 7.8 Hz, H1), 4.80 (dd, 1H, $J_{4,5} = J_{4,3}$ = 9.3 Hz, H4), 4.89, 4.91 (AB, 2H, J = 11.0 Hz, CH_2CCl_3), 6.82 (d, 2H, J = 9.0 Hz, ArH), 7.04 (d, 2H, J = 9.0 Hz, ArH), 7.29 – 7.36 (m, 5H, ArH); ^{13}C NMR (125MHz, $CDCl_3$) δ 55.66, 68.22, 73.73, 73.84, 73.95, 80.12, 81.68, 92.75, 101.57, 114.65, 118.67, 127.80, 127.89, 1128.40, 137.69, 150.79, 155.75;

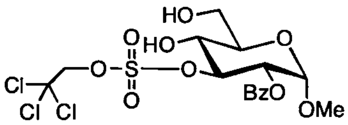


Methyl 2-*O*-benzoyl-6-*O*-benzyl-3-*O*-trichloroethoxysulfo-α-D-glucopyranoside (3.4). Carbohydrate **2.37** (0.50 g, 0.86 mmol) in CH_2Cl_2 (11 mL, 0.08 M) and activated 4Å molecular sieves (1.2 g) were stirred for 1 h at room temperature. The solution was cooled to –78 °C and Et_3SiH (0.41 mL, 2.6 mmol) and TfOH (0.26 mL, 2.9 mmol) were added successively. The reaction was stirred at –78 °C for 1 h, quenched with NEt_3 (1 mL) and methanol (1 mL), diluted with $CHCl_3$ then warmed to room temperature. Solids were removed by filtering reaction contents through Celite, the organic layer was washed with sat. $NaHCO_3$, dried over $MgSO_4$ and condensed to a clear yellow oil. Flash chromatography (25:75 EtOAc/ hexanes) provided a **3.4** as a clear colourless glassy compound (0.48 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.13-3.16 (brs, 1H, OH), 3.40 (s, 3H, OCH_3), 3.41-3.79 (m, 1H, H6), 3.85-3.92 (m, 2H, H5, H6'), 4.02 (brdd, 1H, $J_{4,5\,4,3}$ = 9.0 Hz, H4), 4.63, 4.76 (AB, 2H, J = 12.0 Hz, CH_2Ph), 4.73, 4.75 (AB, 2H, J = 11.0 Hz, CH_2CCl_3), 5.09-5.13 (m, 2H, H1, H2), 5.26 (dd, 1H, $J_{3,4} = J_{3,2}$ = 9.2 Hz, H3), 7.36-7.61 (m, 8H, ArH), 8.16 (dd, 2H, J = 8.4, 1.3 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.50, 68.83, 69.70, 70.74, 70.90, 73.82, 79.77, 85.83, 92.48, 96.91, 127.77, 128.05, 128.46, 128.53, 128.74, 130.09, 133.55, 137.11; HRMS (ESI) m/z = 599.0302, $C_{23}H_{26}Cl_3O_{10}S$ $(M+H)^+$ requires 599.0132.

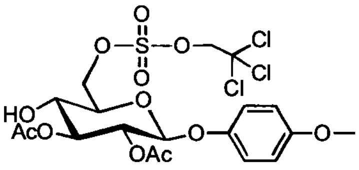


Methyl 2-*O*-benzoyl-4-*O*-benzyl-3-*O*-trichloroethoxysulfo-α-D-glucopyranoside (3.5). Carbohydrate **2.37** (0.60 g, 1.0 mmol) in CH_2Cl_2 (20 mL, 0.05 M) and activated 4Å molecular sieves (2 g) were stirred for 1 h at room temperature. The solution was cooled to –78 °C and Et_3SiH (0.50 mL, 3.0 mmol) and $PhBCl_2$ (0.46 mL, 3.5 mmol) were added successively. The reaction was stirred at –78 °C for 1 h, quenched with NEt_3 (1 mL) and methanol (1 mL), diluted with $CHCl_3$ then warmed to room temperature. Solids were removed by filtering reaction contents through celite, the organic layer was washed with sat. $NaHCO_3$, dried over $MgSO_4$ and condensed to a clear yellow oil. Flash chromatography (25:75 EtOAc/hexanes) provided a **3.5** as a white foam (0.52 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.38 (s, 3H, CH_3), 3.85 (m, 4H, H4, H5, H6, H6'), 4.53, 4.63 (AB, 2H, J = 11.1 Hz, CH_2CCl_3), 4.70, 4.99 (AB, 2H, J = 10.7 Hz, CH_2Ph), 5.12 (d, 1H, $J_{1,2}$ = 3.6 Hz, H1), 5.14 (dd, 1H, $J_{2,3}$ = 9.7, $J_{2,1}$ = 3.6 Hz, H2), 5.45 (dd, 1H, $J_{3,4} = J_{3,2} =$

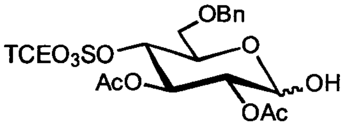
9.3 Hz, H3), 7.31-7.50 (m, 7H, ArH), 7.58-7.63 (m, 1H, ArH), 8.16-8.19 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.38, 60.91, 70.63, 71.36, 74.99, 75.02, 79.82, 85.53, 92.34, 96.87, 128.13, 128.19, 128.48, 128.72, 133.62, 136.92, 165.74; HRMS (ESI) m/z = 616.0588, $C_{23}H_{29}Cl_3NO_{10}S$ $(M+NH_4)^+$ requires 616.0578.



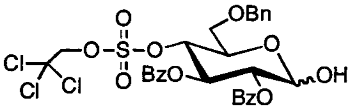
Methyl 2-*O*-benzoyl-3-*O*-trichloroethoxysulfo-α-D-glucopyranoside (3.6). A round bottom flask containing a suspension of carbohydrate **2.37** (0.30 g, 0.50 mmol) in 1:2 CH_2Cl_2/MeOH (2.4 mL, 4.8 mL) was equipped with a reflux condenser and placed in an oil bath at 40 °C. The suspension was stirred until all starting material had dissolved then pTSA (9.0 mg, 0.05 mmol) was added. The temperature was increased to 45 °C and the reaction was stirred overnight (approximately 16 hours) until no starting material remained by TLC. The reaction was neutralized with NEt_3 and condensed to a yellow oil. Flash chromatography (60:40 EtOAc/hexanes) provided a white foam (0.24 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.14 (s, 3H, CH_3), 3.78-3.84 (m, 1H, H5), 3.97 (brd, J = 3.3 Hz, 2H, H6, H6'), 4.06 (dd, 1H, $J_{4,5} = J_{4,3}$ = 9.3 Hz, H4), 4.63, 4.71 (AB, 2H, J = 10.9 Hz, CH_2CCl_3), 5.09-5.15 (m, 2H, H1, H2), 5.30 (dd, 1H, $J_{3,4} = J_{3,2}$ = 9.1 Hz, H3), 7.46 (t, 2H, J = 7.5 Hz, ArH), 7.61 (t, 1H, J = 7.4 Hz, ArH), 8.15 (d, 2H, J = 7.1 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.51, 61.68, 68.96, 70.56, 70.90, 79.81, 85.73, 92.32, 96.96, 128.52, 128.65, 130.07, 133.66, 165.68; HRMS (ESI) m/z = 508.9852, $C_{16}H_{20}Cl_3O_{10}S$ $(M+H)^+$ requires 508.9843.



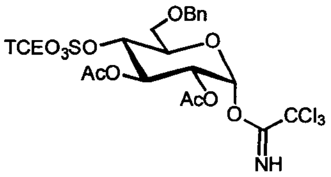
p-Methoxyphenyl 2,3-di-O-acetyl-6-O-trichloroethoxysulfo-ß-D-glucopyranoside 3.8: To carbohydrate **2.40** (0.220 g, 0.28 mmol) in CCl_4/H_2O (1.5:1, 24.5 mL) was added NBS (0.157 g, 0.88 mmol) and $CaCO_3$ (0.149 g, 1.5 mmol). The system was purged with argon for 15 minutes and the reaction was irradiated with a 250 W incandescent light for 1 h while being monitored by TLC. Upon completion, the reaction was poured into ice water (50 mL) and extracted with $CHCl_3$. Combined organic layers were dried over $MgSO_4$ and concentrated to crude residue. Flash chromatography (50:50 EtOAc/hexanes) provided **3.8** as a white foam (0.173 g, 91%). ^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.09 (d, 1H, $J_{OH,4}$ = 4.3 Hz, OH), 3.78 (s, 3H, OCH_3), 3.78-3.87 (m, 2H, H4, H5), 4.61 (dd, 1H, $J_{6,6'}$ = 10.9 Hz, $J_{6,5}$ = 4.5 Hz, H6), 4.67 (s, 2H, CH_2), 4.70 (dd, 1H, $J_{6',6}$= $J_{6',5}$ = 10.5 Hz, H6'), 5.02 (d, 1H, $J_{1,2}$ = 7.7 Hz, H1), 5.10 (brdd, 1H, $J_{3,4}$ = $J_{3,2}$ = 8.7 Hz, H3), 5.20 (brdd, 1H, $J_{2,3}$ = $J_{2,1}$ = 8.6 Hz, H2), 6.03 (d, 2H, J = 9.1 Hz, ArH), 6.94 (d, 2H, J = 9.1 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.55, 20.71, 55.57, 68.40, 70.69, 71.55, 73.20, 75.81, 79.60, 92.27, 99.82, 114.60, 118.24, 150.55, 155.73, 169.33, 171.82; HRMS (ESI) m/z = 598.0320 $(M+NH_4)^+$ $C_{19}H_{27}NO_{12}SCl_3$ requires 598.0314.



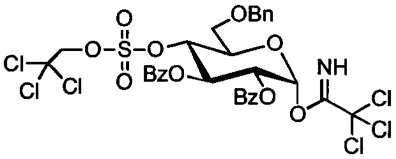
2,3-di-*O*-acetyl-6-*O*-benzyl-4-*O*-trichloroethoxysulfo-D-glucopyranose (3.10). To fully protected **2.39** (0.24 g, 0.35 mmol) in a CH_3CN/pH 7 phosphate buffer solution (1:1.5, 8 mL) at 0 °C was added CAN (0.1945 g, 0.35 mmol). The reaction was stirred for 30 minutes, then additional CAN (0.5835 g, 1.06 mmol) was added. The reaction was stirred for 15 minutes, then poured into ice water. The desired product was extracted with ethyl acetate, the combined organics were washed with sat. $NaHCO_3$ and concentrated to a crude orange oil. Purification by flash chromatography (33:67 EtOAc/hexanes) followed by a short gravity column (85:15 PhH/EtOAc) afforded hemiacetal **3.10**, a clear, slight yellow glassy compound, (0.18 g, 88%). ^1H NMR (300 MHz, $CDCl_3$) δ 2.06 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 3.50 (brs, 1H, OH), 3.77 (d, 2H, J = 2.9 Hz, H6, H6'), 4.25 - 4.31 (m, 1H, H5), 4.58, 4.64 (AB, 2H, J = 11.8 Hz, CH_2Ph), 4.69, 4.75 (AB, 2H, J = 11.1 Hz, CH_2CCl_3), 4.87 (dd, 1H, $J_{2,3}$ = 9.2, $J_{2,1}$ = 3.6 Hz, H2), 4.95 (dd, 1H, $J_{4,5} = J_{4,3}$ = 9.6 Hz, H4), 5.45 (brs, 1H, H1), 5.69 (dd, 1H, $J_{3,4} = J_{3,2}$ = 9.6 Hz, H3), 7.28-7.38 (m, 5H, ArH);



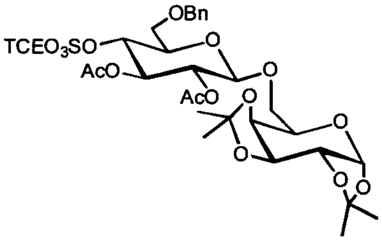
2,3-di-*O*-benzoyl-6-*O*-benzyl-4-*O*-trichloroethoxysulfo-D-glucopyranose (3.13). To carbohydrate **2.41** (0.2 g 0.25 mmol) in acetone/H_2O (9:1, 5.1mL) at 0 °C was added NBS (0.18 g, 1.0 mmol). The reaction was stirred for 20 min at 0 °C, at which point no starting material was detected by TLC. Solvents were evaporated at room temperature *in vacuo* until turbidity developed. The remaining residue was dissolved in EtOAc, washed with H_2O, sat. $NaHCO_3$ and brine, dried over $MgSO_4$ and condensed to a clear, colourless oil. Flash chromatography (33:67 EtOAc/hexanes) provided **3.13** as a white foam (0.13 g, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (brs, 1H, OH), 3.84 (d, 2H, J = 3.0 Hz, H6, H6'), 4.40-4.46 (m, 1H, H5), 4.37, 4.79 (AB, 2H, J = 14.1 Hz, CH_2CCl_3), 4.61, 4.68 (AB, 2H, J = 11.4 Hz, CH_2Ph), 5.20 (dd, 1H, $J_{2,3}$ = 10.2, $J_{2,1}$ = 3.6 Hz, H2), 5.24 (dd, 1H, $J_{4,5}$ = $J_{4,3}$ = 9.7 Hz, H4), 5.70 (brs, 1H, H1), 6.19 (dd, 1H, $J_{3,4}$ = $J_{3,2}$ = 9.8 Hz, H3), 7.33-7.55 (m, 9H, ArH), 7.97 (d, 2H, J = 7.2 Hz, ArH), 8.04 (d, 2H, J = 7.2 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.62, 68.02, 69.51, 72.02, 73.76, 73.83, 79.51, 79.99, 89.99, 92.23, 127.85, 128.03, 128.36, 128.61, 128.5, 128.80, 129.85, 129.92, 133.44, 137.20, 165.53, 165.79; HRMS (ESI) m/z = 689.0443, $C_{29}H_{28}Cl_3O_{11}S$ $(M+H)^+$ requires 689.0418.



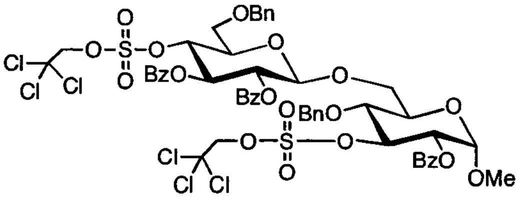
2,3-di-*O*-acetyl-6-*O*-benzyl-4-*O*-trichloroethoxysulfo-*α*-D-glucopyranosyl trichloracetimidate (3.14). To carbohydrate **3.10** (0.3792 g, 0.670 mmol) in CH_2Cl_2 (3.8 mL) at –35 °C was added trichloroacetonitrile (1.1 mL, 10.9 mmol), followed by DBU (0.134 mL of 1.0 M solution in CH_2Cl_2, 0.134 mmol). The reaction was stirred for approximately 5 hours then condensed to a brown crude oil. Purification by flash chromatography (33:67 EtOAc/hexanes) afforded **3.14** as a white foam (0.440 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.03 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 3.81 (s, 2H, H6, H6'), 4.21 (br-d, 1H, $J_{5,4}$ = 10.0 Hz, H5), 4.57, 4.66 (AB, 2H, J = 11.7 Hz, CH_2Ph), 4.72, 4.78 (AB, 2H, J = 11.1 Hz, CH_2CCl_3), 5.13 (dd, 1H, $J_{2,3}$ = 9.9 Hz, $J_{2,1}$ = 3.5 Hz, H2), 5.18 (dd, 1H, $J_{4,5}$ = $J_{4,3}$ = 9.8 Hz, H4), 5.75 (dd, 1H, $J_{3,4}$ = $J_{3,2}$ = 9.8 Hz, H3), 6.59 (d, 1H, $J_{1,2}$ = 3.4 Hz, H1), 7.33 (m, 5H, ArH), 8.72 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.26, 20.73, 66.89, 68.93, 69.70, 70.84, 73.72, 78.57, 80.25, 90.51, 92.45, 92.65, 127.78, 127.84, 128.34, 137.23, 160.58, 169.57, 169.96.



2,3-di-*O*-benzoyl-6-*O*-benzyl-4-*O*-trichloroethoxysulfo-α-D-glucopyranosyl trichloracetimidate (3.16). To carbohydrate **3.13** (0.4 g, 0.58 mmol) in CH_2Cl_2 (5 mL, 0.13 M) at –40 °C was added trichloroacetonitrile (0.93 mL, 9.28 mmol), followed by a slow dropwise addition of DBU (0.12 mL, 1.0 M solution in CH_2Cl_2). The reaction was stirred at –40°C for 2 h then gradually warmed to –10 °C over 1 h, at which point no starting material remained by TLC. The solvent was removed *in vacuo* at room temperature, and crude material was applied directly to a short silica gel column. Flash chromatography (25:75 EtOAc/hexanes) afforded **3.16** as a white foam (0.38 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (brs, 2H, H6, H6'), 4.37 (brd, 1H, $J_{5,4}$ = 10.0 Hz, H5), 4.55, 4.66 (AB, 2H, J = 11.1 Hz, CH_2CCl_3), 4.62, 4.72 (AB, 2H, J = 11.7 Hz, CH_2Ph), 5.49 (dd, 1H, $J_{2,3}$ = 10.1, $J_{2,1}$ = 3.6 Hz, H2), 5.49 (dd, 1H, $J_{4,5}$ = $J_{4,3}$ = 9.8 Hz, H4), 6.24 (dd, 1H, $J_{3,4}$ = $J_{3,2}$ = 9.9 Hz, H3), 6.79 (d, 1H, $J_{1,2}$ = 3.5 Hz, H1), 7.31-7.54 (m, 11H, ArH), 7.94 (d, 2H, J = 7.3 Hz, ArH), 8.05 (d, 2H, J = 7.3 Hz, ArH), 8.65 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.93, 69.53, 70.56, 71.15, 73.76, 77.34, 78.34, 80.09, 90.49, 92.19, 92.79, 127.81, 128.01, 128.24, 128.34, 128.36, 128.60, 129.79, 129.90, 129.96, 133.52, 133.57, 137.29, 160.27, 165.08, 165.61.

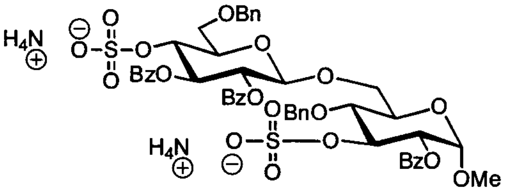


1,2:3,4-di-*O*-isopropylidene-6-*O*-(2,3-di-*O*-acetyl-6-*O*-benzyl-4-*O*-trichloroethoxysulfo-α-D-glucopyranosyl)-*α*-D-galactopyranoside (3.17): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.67 – 3.80 (m, 3H, $H5_{(I)}$, $H5_{(II)}$, $H6_{(I)}$), 3.85 (dd, 1H, $J_{6,6'}$ = 11.2 Hz, $J_{6,5}$ = 2.1 Hz, $H6_{(II)}$), 3.93 – 3.96 (m, 1H, $H6'_{(II)}$), 4.05 (dd, 1H, $J_{6',6}$ = 11.3 Hz, $J_{6',5}$ = 3.4 Hz, $H6'_{(I)}$), 4.17 (dd, 1H, $J_{4,5}$ = 7.9 Hz, $J_{4,3}$ = 1.8 Hz, $H4_{(II)}$), 4.31 (dd, 1H, $J_{2,3}$ = 5.0 Hz, $J_{2,1}$ = 2.4 Hz, $H2_{(II)}$), 4.59 (dd, 1H, $J_{3,2}$ = 7.9 Hz, $J_{3,4}$ = 2.4 Hz, $H3_{(II)}$), 4.62 – 4.66 (m, 3H, CH_2Ph, $H1_{(1)}$), 4.69 – 4.73 (AB, 2H, J = 11.1 Hz, CH_2CCl_3), 5.00 (dd, 1H, $J_{4,5} = J_{4,3}$ = 9.6 Hz, $H4_{(I)}$), 5.01 (dd, 1H, $J_{2,3} = J_{2,1}$ = 9.5 Hz, $H2_{(I)}$), 5.38 (dd, 1H, $J_{3,4} = J_{3,2}$ = 9.3 Hz, $H3_{(I)}$), 5.51 (d, 1H, $J_{1,2}$ = 5.0 Hz, $H1_{(II)}$), 7.30 – 7.40 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.61, 20.76, 24.31, 25.02, 25.93, 26.02, 67.74, 67.77, 69.43, 70.42, 70.63, 71.20, 71.28, 72.01, 72.92, 73.80, 79.62, 80.20, 92.54, 96.19, 101.19, 108.65, 109.38, 127.78, 127.83, 128.41, 137.56, 169.49, 170.30.



Methyl 6-*O*-(2,3-di-*O*-benzoyl-6-*O*-benzyl-4-*O*-trichloroethoxysulfo-ß-D-glucopyranosyl)-2-*O*-benzoyl-4-*O*-benzyl-3-*O*-trichloroethoxysulfo-α-D-glucopyranoside (3.19). Donor **3.16** (0.36 g, 0.43 mmol) and acceptor **3.4** (0.22 g, 0.36 mmol) were dissolved in CH_2Cl_2 (9.4 mL). Powdered 4Å molecular sieves were added, and the mixture was stirred at room temperature for 1.5 h. The solution was then cooled to –40 °C, stirred for an additional 30 min. TMSOTf (72 μL, 1.0 M solution in CH_2Cl_2) was added dropwise. The reaction was stirred for 30 min at –40 °C at which point no starting acceptor remained by TLC. The reaction was quenched with NEt_3 (0.1 mL), warmed to room temperature, filtered through celite and condensed to a yellow crude oil. Flash chromatography (25:75 EtOAc/hexanes) followed by gravity chromatography (80:20 PhH/EtOAc) provided the desired product **3.19** as a white foam (0.38 g, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.24 (s, 3H, OCH_3), 3.73 (dd, 1H, $J_{4,5} = J_{4,3} = 9.5$ Hz, $H4_{(II)}$), 3.81 (dd, 1H, $J_{6,6'} = 10.9$, $J_{6,5} = 4.1$ Hz, H6), 3.86-3.98 (m, 4H, $H5_{(I)}$, $H5_{(II)}$, H6, H6'), 4.20 (dd, 1H, $J_{6',6} = 10.9$, $J_{6',5} = 1.8$ Hz, H6'), 4.34, 4.59 (AB, 2H, $J = 10.7$ Hz, CH_2Ph), 4.43, 4.52 (AB, 2H, $J = 11.1$ Hz, CH_2CCl_3), 4.53, 4.63 (AB, 2H, $J = 11.1$ Hz, CH_2CCl_3), 4.68, 4.71 (AB, 2H, $J = 11.9$ Hz, CH_2Ph), 4.78 (d, 1H, $J_{1,2} = 7.8$ Hz, $H1_{(I)}$), 5.03 (d, 1H, $J_{1,2} =$

3.1 Hz, H1$_{(II)}$), 5.25 (brdd, 1H, $J_{4,5} = J_{4,3} = 9.3$ Hz, H4$_{(I)}$), 5.35 (dd, 1H, $J_{3,4} = J_{3,2} = 9.7$ Hz, H3$_{(II)}$), 5.53 (dd, 1H, $J_{2,3} = 9.6$, $J_{2,1} = 7.8$ Hz, H2$_{(I)}$), 5.87 (dd, 1H, $J_{3,4} = J_{3,2} = 9.4$ Hz, H3$_{(I)}$), 7.18 (d, 2H, $J = 5.7$ Hz, ArH), 7.27-7.61 (m, 17H, ArH), 7.93, 8.00, 8.15 (3d, 3x2H, $J = 7.2$ Hz, ArH). ^{13}C NMR (125 MHz, CDCl$_3$) δ 55.29, 67.78, 67.92, 69.40, 71.21, 71.74, 72.18, 73.45, 73.73, 74.17, 75.44, 79.43, 79.80, 80.82, 85.56, 92.29, 92.38, 96.73, 100.96, 127.78, 127.85, 128.00, 128.28, 128.44, 128.48, 128.53, 128.86, 129.72, 130.07, 130.24, 133.50, 133.63, 133.69, 136.90, 137.57, 164.80, 165.61, 165.82; HRMS (ESI) *m/z* = 1269.0546, $C_{52}H_{51}Cl_6O_{20}S_2$ (M+H)$^+$ requires 1269.0546.



Methyl 6-*O*-(2,3-di-*O*-benzoyl-6-*O*-benzyl-4-*O*-sulfo-ß-D-glucopyranosyl)-2-*O*-benzoyl-4-*O*-benzyl-3-*O*-sulfo-α-D-glucopyranoside (3.20). To disaccharide **3.19** (0.05 g, 0.039 mmol) in reagent grade MeOH (0.4 mL) was added ammonium formate (0.03 g, 0.48 mmol) followed by zinc dust (0.04 g, 0.55 mmol). The reaction was stirred for 9 h at room temperature, at which point no starting material was detected by TLC. The reaction was filtered through celite, and concentrated to crude product. Flash chromatography (20:4:1 CH$_2$Cl$_2$/MeOH/NH$_4$OH) afforded a **3.20** white solid, which was lyophilized (3 x) from H$_2$O to yield a light white product (0.038 g, 92%). ^{1}H NMR (500MHz, DMSO-*d$_6$*) δ 2.99 (s, 3H, OCH$_3$), 3.28 - 3.32 (m, 1H, H3$_{(II)}$), 3.56-3.59 (m, 3H, H6'$_{(I)}$, H4$_{(II)}$, H5$_{(II)}$), 3.65 (dd, 1H, $J_{6',6} = 10.7$ Hz, $J_{6',5} = 5.5$ Hz, H6'$_{(II)}$), 3.87 (br-dd, 1H, $J_1 = J_2 = 9.4$ Hz, H5$_{(I)}$), 4.01 (br-d, 1H, $J = 9.4$ Hz, H6$_{(II)}$), 4.06 (d, 1H, $J = 10.3$ Hz,

$CH_2PH_{(I)}$), 4.08 (d, 1H, $J_{6,6'}$ = 10.0 Hz, $H6_{(I)}$), 4.26 (dd, 1H, $J_{4,5}$ = $J_{4,3}$ = 9.5 Hz, $H4_{(I)}$), 4.52, 4.55 (AB, 2H, J = 11.9 Hz, $CH_2PH_{(I)}$), 4.68 – 4.72 (m, 2H, $H1_{(II)}$, $H2_{(II)}$), 4.85 (d, 1H, J = 10.3 Hz, $CH_2Ph_{(II)}$), 4.96 (d, 1H, $J_{1,2}$ = 8.0 Hz, $H1_{(I)}$), 5.09 (dd, 1H, $J_{2,3}$ = 9.8 Hz, $J_{2,1}$ = 8.0 Hz, $H2_{(I)}$), 5.57 (dd, 1H, $J_{3,4}$ = $J_{3,2}$ = 9.5 Hz, $H3_{(I)}$), 7.10 (br-s, 8H, NH_4), 7.14 – 7.20 (m, 7H, ArH), 7.25 – 7.38 (m, 8H, ArH), 7.43 – 7.46 (m, 2H, ArH), 7.48 – 7.52 (m, 2H, ArH), 7.57 – 7.59 (m, 1H, ArH), 7.76 – 7.80 (m, 4H, ArH), 8.07 – 8.09 (m, 1H, ArH); ^{13}C NMR (125 MHz, D_2O) δ 54.87, 67.61, 68.33, 69.00, 71.43, 71.89, 73.26, 73.37, 73.48, 74.25, 74.83, 75.43, 78.89, 96.67, 100.33, 127.81, 128.25, 128.41, 128.45, 128.57, 128.58, 128.70, 128.74, 128.79, 128.88, 129.43, 129.51, 129.90, 133.93, 134.32, 136.96, 137.40, 166.99, 167.43, 167.62; HRMS (ESI) m/z = 1006.2000, $C_{48}H_{46}O_{20}S$ requires 1006.2024.

3.8 References

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Chapter 4 – Derivatives of the 2,2,2-Trichloroethoxy-Sulfuryl Imidazolium Sulfating Agents

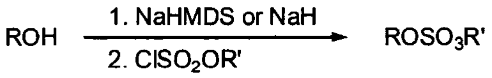
4.1 Introduction

After the method for introducing the protected sulfate group into monosaccharides had been developed, and the stability of the TCE-sulfate groups had been satisfactorily investigated, we turned our attention back to the sulfating reagent **2.3**. We began to investigate whether the chemistry could be extended to include different protecting groups other than the TCE moiety. Jenifer Hendel, an undergraduate in the Taylor lab was able to demonstrate that sulfuryl imidazolium salts could be prepared bearing both the phenyl, and trifluoroethyl (TFE) groups, and used to introduce the corresponding phenyl and TFE protected sulfates into monosaccharide building blocks. Our next step was to determine if sulfates with other protecting groups could be incorporated into carbohydrates via sulfuryl imidazolium salts. We also set out to modify the imidazole moiety in reagent **2.3**, anticipating that the reactivity and/or stability of the sulfating agents could be tuned based on substitution on the imidazole ring.

4.2 Neopentyl and Isobutyl Protection for Sulfate Monoesters

Just as we submitted our preliminary results for publication, Simpson and Widlanski published an article describing a comprehensive approach to the synthesis of sulfate esters.[1] Noting that there is no broadly useful method for the introduction of a protected sulfate monoester in the synthesis of complex molecules, the authors sought methodology, much like our TCE-protected sulfate chemistry which incorporated transient sulfate diesters that permit access to target sulfates. In approach, Simpson and Widlanski described the synthesis of sulfate esters employing neopentyl and isobutyl protecting groups for the protection of aromatic and aliphatic sulfate monoesters, basing their protecting group selection on the idea that the neopentyl and isobutyl groups are known to serve as good protecting groups for sulfonates.[1]

By treating an alkyl or aryl alcohol with a strong base, followed by the addition of neopentyl or isobutyl chlorosulfates **4.1** and **4.2** respectively (scheme 4.1), a selection of protected sulfate diesters was prepared, with results summarized below in table 4.1.

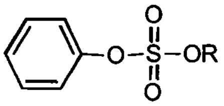
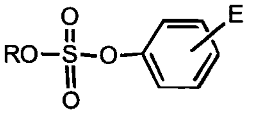
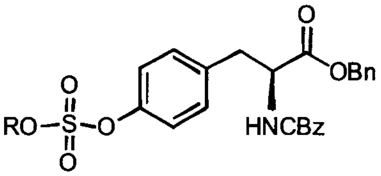
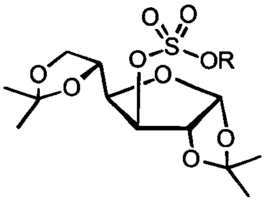
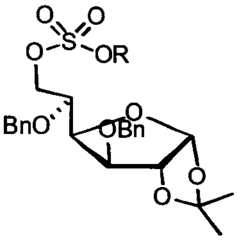


$$\mathrm{ROH}\xrightarrow[\text{2. }\mathrm{ClSO_2OR'}]{\text{1. NaHMDS or NaH}}\mathrm{ROSO_3R'}$$

Where R' = nP **4.1** or R' = iBu **4.2**

Scheme 4.1

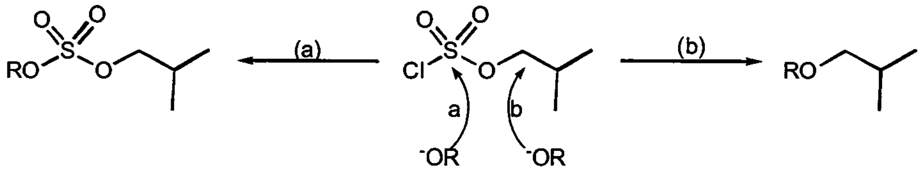
Table 4.1: Preparation of Neopentyl and Isobutyl Sulfate Diesters by Simpson and Widlanski[1]

Entry	Product*	Protecting Group*	Yield (%)
1		**4.3** R = *n*P **4.4** R = *i*Bu	95 80
2		**4.5** R = *n*P **4.6** R = *i*Bu	98 82
3		**4.7** R = *n*P	99
4		**4.8** R = *n*P **4.9** R = *i*Bu	95 95
5		**4.10** R = *i*Bu	86

* E = Estrone; *n*P = neopentyl; *i*Bu = isobutyl

The neopentyl protected sulfate monoesters were prepared by subjecting the corresponding alcohols and phenols to sodium hydride or sodium bis (trimethylsilyl)amide (NaHMDS) in THF (20% DMPU) at –75 °C, followed by treatment with a small excess of neopentyl chlorosulfate. Under these conditions, a variety of neopentyl protected sulfated monoesters including phenolic derivative **4.3**, estrone sulfate **4.5**, protected tyrosine sulfate **4.7**, as well as the sulfocarbohydrate **4.8** were readily prepared from their hydroxy substrates in excellent yields.

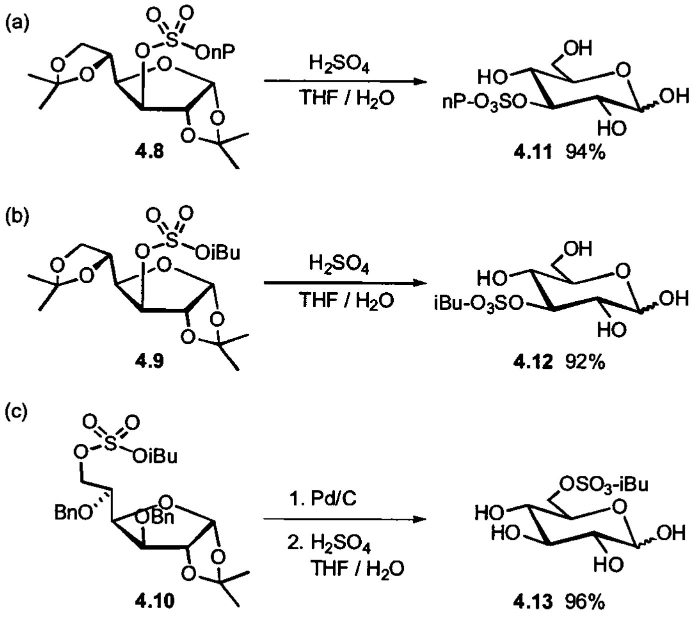
Simpson and Widlanski also examined the isobutyl group as an alternative to the neopentyl group anticipating that it would be significantly more labile as the neopentyl protecting group is known to be extremely stable.[1] To prepare the isobutyl protected sulfate monoesters, the reaction conditions required slight adjustments to eliminate isobutyl ether side products which were assumed to arise form the attack of the sodium alkoxides or phenoxides at the methylene group in isobutyl chlorosulfate (scheme 4.2, path b).



Scheme 4.2

The modifications for the introduction of the isobutyl sulfate monoesters included discontinuing the use of DMPU, lowering the reaction conditions, increasing the temperature, and using a larger excess of isobutyl chlorosulfate (5-10 eq.). Using these optimized conditions, the isobutyl protected sulfate esters of diacetone-D-glucose (product **4.9**) and its benzylated derivative (product **4.10**) were obtained in 95 % and 86 % yields respectively.[1]

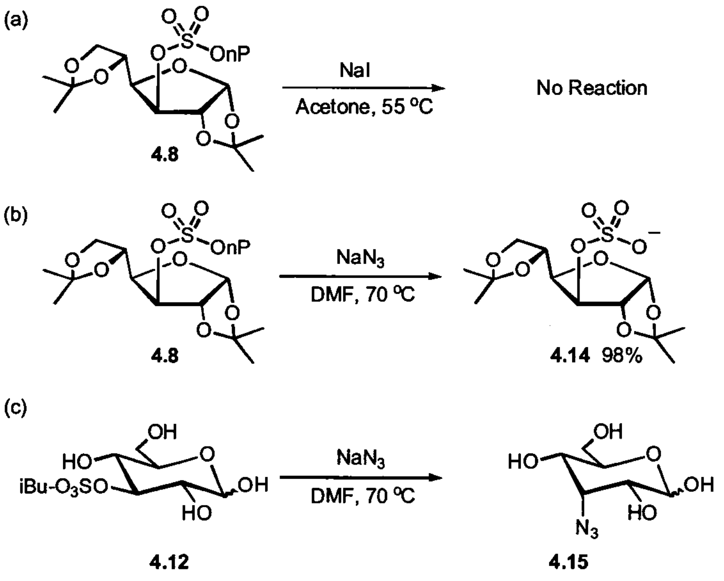
The stability of the neopentyl and isobutyl protected sulfate esters were studied using NMR assays by subjecting protected phenyl sulfates **4.3** and **4.4** to different concentrations TFA and piperidine. Both the isobutyl and neopentyl sulfate esters were found to be stable to 50% TFA, with less than 10% degradation observed after 48 h. The neopentyl sulfate ester was stable to 20% piperidine in chloroform, but the isobutyl sulfate ester was less tolerant, showing evidence of nucleophilic cleavage, even at 6% piperidine solution. From these studies, the authors concluded that both the neopentyl and isobutyl groups for sulfate esters offer viable protection in highly acidic reactions, with the isobutyl protecting group being much less effective under basic or nucleophilic conditions. While the stability of the alkyl sulfates was not investigated under the TFA or piperidine conditions, carbohydrate sulfates **4.8**, **4.9**, and **4.10** were subjected to other transformations to demonstrate the versatility of the sulfate diesters (scheme 4.3a,b,c).



Scheme 4.3

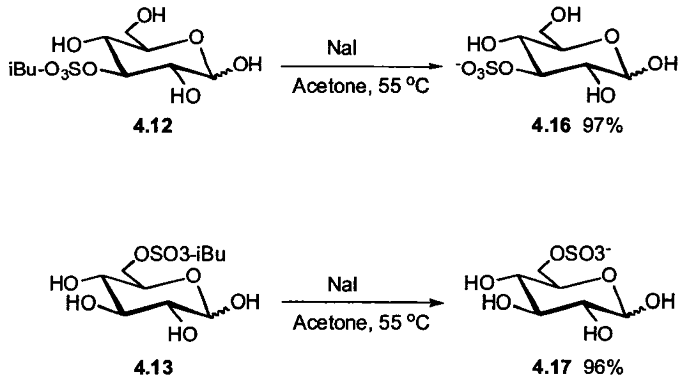
The stability of the neopentyl and isobutyl protecting groups towards hydrogenolysis and brief treatment with strong acids was demonstrated by removing the benzyl and isopropylidene groups from protected carbohydrates **4.8**, **4.9**, and **4.10** by hydrogenolysis with Pd/C and H_2, and by treatment with aqueous H_2SO_4 in THF, with yields of the deprotected hexoses ranging from 92 – 96%.

To study the deprotection conditions required to cleave the neopentyl moiety, the protected sulfate esters were reacted with a nucleophile in a polar solvent. The reaction of sodium iodide with phenyl neopentyl sulfate **4.3** yielded the desulfated phenol rather than cleavage of the neopentyl group, and did not result in any reaction with the neopentyl protected glucose sulfate **4.8** (scheme 4.4a). Other small nucleophiles such as azide and cyanide in DMF (60-70 °C) were reported to be effective for removing the neopentyl protecting group in protected aryl sulfates **4.3**, **4.5**, and **4.7**, as well as the protected sulfate of diacetone-D-glucose (scheme 4.4b) in near quantitative yields. Treating the unprotected glucopyranose neopentyl diester **4.11** with sodium azide in DMF, however, led to the displacement of the entire protected sulfate group providing 3-azido-3-deoxy D-glucose (scheme 4.4c). This result strongly suggests that the neopentyl group is not useful for the protection for sulfates of primary or secondary alcohols, as the neopentyl group cannot be removed to afford the desired sulfate monoester products.[1]



Scheme 4.4

Because nucleophilic substitution is significantly faster at isobutyl centers than at the more hindered neopentyl counterpart, a variety of nucleophiles were expected to cleave the isobutyl protecting group. The isobutyl protected sulfate esters of unprotected hexoses **4.12** and **4.13** were effectively cleaved with sodium iodide in hot acetone to provide the target sulfates **4.16** and **4.17** in excellent yields (scheme 4.5). As was the case with the neopentyl aryl sulfates, the iodide was able to displace phenoxides from the aryl alkyl sulfate esters, thus the isobutyl protecting group in sulfoestrone derivative **4.6** was cleaved using sodium thiocyanate and triethylamine in acetone at 55 °C to provide estrone sulfate in a 96 % yield.

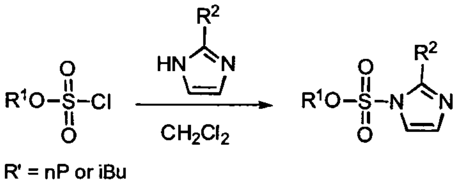


Scheme 4.5

The chemistry presented by Simpson and Widlanski does offer a unique approach for the synthesis of sulfated compounds, however, like other sulfation methods it is more successful for aryl sulfates. The neopentyl protected aryl sulfate monoesters could be highly effective for the synthesis of complex molecules but cleavage of the protecting group requires somewhat harsh conditions, to which other functionalities may not be tolerant. The isobutyl protected sulfate monoesters, designed to provide an alternative to the highly stable neopentyl counterparts, were much more sensitive to nucleophilic and basic conditions, which in turn limits their potential applications towards the synthesis of complex molecules. The authors also indicated that the isobutyl chlorosulfate approach would be effective for introducing sulfate monoesters at the last step in a synthesis. Although the method could be useful for increased yields of sulfation, it does not eliminate the unnecessary protecting group manipulations that are avoided by introducing the sulfate group at the beginning of a synthetic sequence, and therefore does not provide a significant alternative to conventional sulfation methods.

4.2.1 Synthesis of neopentyl and isobutyl imidazolium sulfating agents

To begin investigating the preparation of derivatives of reagent **2.3**, we started with the neopentyl and isobutyl protecting groups presented by Simpson and Widlanski. The neopentyl and isobutyl chlorosulfates were first prepared by reacting the corresponding alcohol with sulfuryl chloride. The chlorosulfates are easy prepared and isolated, however must be used straight away, as they are not stable for longer than 24-36 h. These compounds were then reacted with an excess of imidazole to provide the alkoxysulfuryl imidazole, as described in scheme 4.6. The initial reaction with both neopentyl (R^1) and isobutyl chlorosulfates (R^1) and imidazole (R^2 = H, scheme 4.6) to provide **4.18** and **4.22** (table 4.2, entry 1, 5) provided products which decomposed immediately upon isolation after flash chromatography.



Scheme 4.6

We then attempted to prepare the neopentyl and isobutyl sulfuryl imidazole compounds using substituted imidazoles, hoping that they would be slightly more stable. The isobutyl and neopentyl chlorosulfates were reacted with 2-methyl imidazole, 2-ethyl imidazole, and 2-isopropyl imidazole, with the results summarized in table 4.3.

Table 4.2: Synthesis of Neopentyl and Isobutyl Sulfuryl Imidazolium Derivatives

Entry	Product	R^1	R^2	Yield (%)
1	**4.18**	*i*Bu	H	unstable
2	**4.19**	*i*Bu	Me	35
3	**4.20**	*i*Bu	Et	33
4	**4.21**	*i*Bu	*i*Pr	29 (impure)
5	**4.22**	*n*Pent	H	unstable
6	**4.23**	*n*Pent	Me	86
7	**4.24**	*n*Pent	Et	94
8	**4.25**	*n*Pent	*i*Pr	58

Reacting isobutyl chlorosulfate with the 2-methyl, and 2-ethyl imidazoles provided products **4.19** and **4.20** in 35 % and 33% yields respectively (table 4.2, entries 2,3), however the reagents were not stable longer than a few hours, even when stored at –20 °C under argon or nitrogen. The neopentyl derivatives could be isolated in more respectable yields compared to their isobutyl counterparts. For instance, reacting neopentyl chlorosulfate with the 2-methyl and 2-ethyl imidazoles gave products **4.23** and **4.24** in 86 % and 94% yields (table 4.2, entries 6 and 7), however, these products were not stable and decomposed in only a few hours. Because of this, we have not pursued these reagents any further.

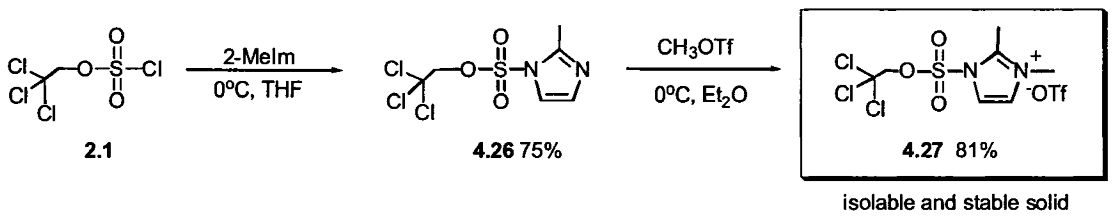
4.3 Derivatives of the Imidazole group in the Trichloroethyl Sulfating Agents

One of the limitations of the imidazolium triflate **2.3** is that sulfations performed with the reagent need to be run in THF due to the low solubility of the triflate salt in other solvents, such as dichloromethane. This is a hindering factor for the reactions involving poorly nucleophilic substrates, as these reactions tend to proceed very slowly. For example, in chapter 2, the sulfation reaction with the 4-OH substrate **2.21** proceeded very slowly, and required up to 6 equivalents of sulfating agent **2.3** to reach completion over two days. It is suspected that for the slower reactions, the trichloroethoxysulfuryl imidazolium triflate **2.3** begins to break down in THF before the sulfation occurs, thus the reaction requires additional aliquots over extended periods of time.

It was anticipated that modifying the imidazole moiety of reagent **2.3** with alkyl groups could potentially change the solubility enough such that the sulfation reactions could be performed in dichloromethane rather than THF.

*4.3.1 Trichloroethyoxysulfuryl imidazolium derivative **4.27***

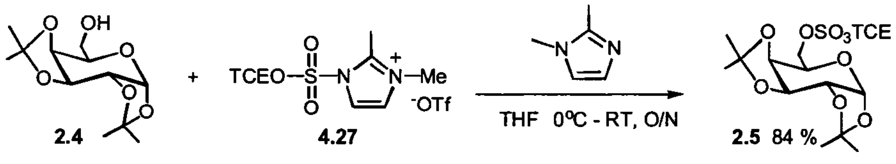
The modified imidazolium triflate **4.27** was easily prepared and isolated according to scheme 4.7. As was previously described for the synthesis of **2.3**, trichloroethoxysulfuryl chloride **2.1** was reacted with an excess of 2-methylimidazole to give the corresponding trichloroethoxysulfuryl-2-methylimidazole species **4.26** in an unoptimized 75 % yield. Compound **4.26** was then treated with methyl triflate (1.0 eq) in dry ether at 0 °C to provide the activated imidazolium salt **4.27** in 81% yield (unoptimized). Once again, this reagent precipitates out of solution and is isolated by simple filtration to provide **4.27** as a stable white solid with no further purification required.



Scheme 4.7

4.3.2 Sulfation reactions with modified reagent 4.27

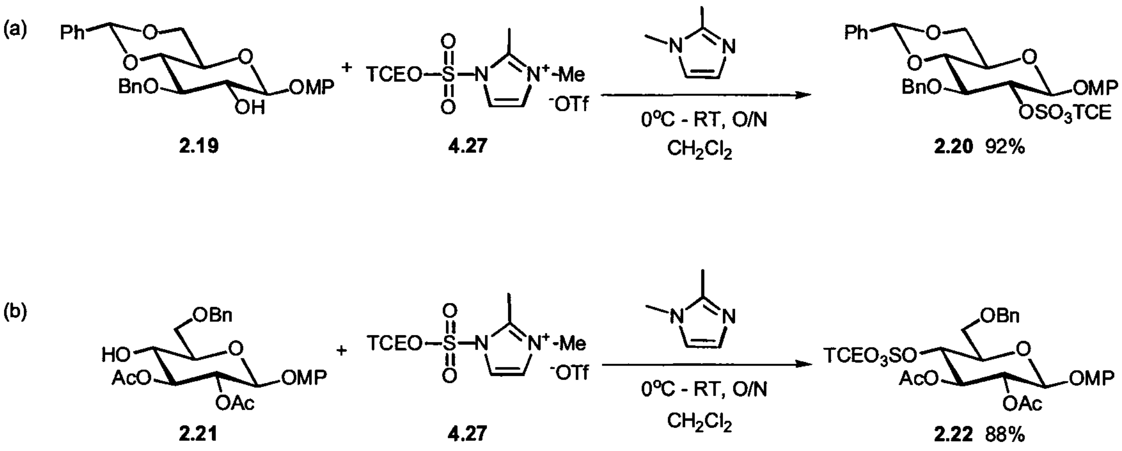
The sulfating ability of reagent **4.27** was tested using di-isopropylidene-D-galactose **2.4** as shown in scheme 4.8.



Scheme 4.8

Reacting the nucleophile **2.4** with the second generation sulfating agent **4.27** (2.0 eq.) in the presence of 1,2-dimethylimidazole (2.5 eq.) and THF provided the sulfated carbohydrate **2.5** in an 84% yield. This demonstrated that the 2-methylimidazolium triflate **4.27** had comparable sulfating ability to the original imidazolium triflate **2.3**, which performed the same reaction in an 87% yield.

As was mentioned in chapter 2, carbohydrates **2.19** and **2.21** were found to slightly more difficult to sulfate, compared to other carbohydrates studied. In both cases, a large excess of sulfating agent **2.3** and extended reaction times were required to obtain the desired products. In an attempt to improve these results, the carbohydrates were treated with the modified sulfating agent **4.27** in CH_2Cl_2 (scheme 4.9a,b).

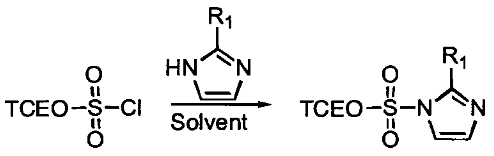


Scheme 4.9

The modified sulfating agent **4.27** appeared to be soluble and stable in CH_2Cl_2, which in turn lead to a significant decrease in the amount of required sulfating agent for both reactions. Initially, introducing the trichloroethyl protected sulfate at the 2-position in **2.19** required almost 12 equivalents of sulfating agent **2.3** to obtain **2.20** in a 90% yield after a 48 h reaction time. Using the new sulfating agent **4.27** allowed for the preparation of **2.20** in 24 hours with only 4 equivalents of sulfating agent. Similarly, introducing the TCE sulfate moiety at the 4-position of **2.21** required 48 hours and 6 equivalents of **2.3** to obtain **2.22** in a 76% yield. This was improved by modifying the solvent to CH_2Cl_2 and employing sulfating agent **4.27**, which allowed for the synthesis of **2.22** in an 88 % yield after adding 3 equivalents of reagent **4.27**. We have not yet determined if this improvement is due to the solvent change, or to the reactivity of **4.27**.

4.3.3 Other TCE-sulfuryl imidazolium derivatives

We have also begun to examine other imidazole derivatives in the preparation of the 2,2,2-trichloroethoxysulfuryl imidazolium triflate reagents, including the 2-ethyl, and 2-isopropyl imidazole groups. The results for scheme 4.10 are summarized in table 4.3.



Scheme 4.10

Table 4.3: Synthesis of Trichloroethoxysulfuryl Imidazole Derivatives

Entry	Product	R_1	Solvent	Yield (%)
1	**2.3**	H	THF	86
2	**4.26**	Me	THF	75
3	**4.28**	Et	THF	73
4	**4.28**	Et	CH_2Cl_2	75
5	**4.29**	*i*Pr	THF	74
6	**4.29**	*i*Pr	CH_2Cl_2	79

As previously described, the trichloroethoxysulfuryl imidazole compounds are prepared by reacting the corresponding $TCESO_3Cl$ with an excess of the substituted imidazole. The original reaction (for compound **2.3**) was performed in THF. Table 4.2 describes the synthesis of the imidazolium derivatives **4.26** – **4.29** in both THF and dichloromethane. The yields are very comparable for both solvents, with a slight preference shown for the reactions run in CH_2Cl_2. While the yields of the imidazolium derivatives of **2.3** are slightly lower, this area is a work in progress, and no optimization studies have been performed. When the ideal conditions for the synthesis of derivatives **4.26** – **4.29** have been worked out, these compounds will be activated with methyl triflate, and their potential as sulfating agents will be investigated.

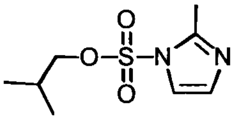
4.4 Summary

The chemistry presented in this chapter is still very much a work in progress. Attempts to extend the methodology to include neopentyl and isobutyl sulfuryl imidazole derivatives were unsuccessful due to the instability of the products, indicating that this methodology is likely limited to protecting groups which exhibit strong electron withdrawing characteristics. Further investigation is required to confirm this hypothesis.

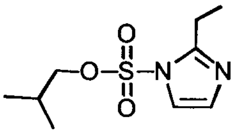
The derivatives of the trichloroethoxysulfuryl imidazole reagent **2.3**, which have been modified on the imidazole ring, have shown much more promising results. A second-generation sulfating agent, compound **4.27**, has been synthesized and applied to improve upon the limitations observed with the original compound **2.3.** Further research in this area will be reported in due course.

4.5 Experimental

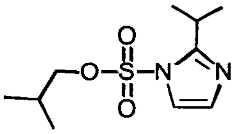
For general information, refer to chapter 2, page 49.



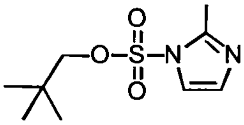
Isobutoxysulfuryl-(2-methyl)imidazole (4.19). To 2-methyl imidazole (0.657 g 8.0 mmol), in CH_2Cl_2 (1 mL) at 0 ^{0}C was added a solution of isobutyl chlorosulfate (0.5 g, 2.9 mmol) in CH_2Cl_2 (1.5 mL). The reaction was gradually warmed to room temperature, and allowed to stir for 24 h. The crude material was concentrated, then purified by flash chromatography (33:67 EtOAc/hexanes) to provide **4.19** as a clear, colourless oil (0.199g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, 6H, *J*= 6.8 Hz, 2xCH_3), 1.94 (dt, 1H, *J*= 7.5, 6.8 Hz, CH), 2.30 (s, 3H, CH_3), 3.56 (d, 2H, *J*= 7.5 Hz, CH_2), 6.73 (d, 1H, *J*= 1.3 Hz, ImH), 6.83 (d, 1H, *J*= 1.3 Hz, ImH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.1, 19.9, 29.9, 53.5, 119.6, 121.2, 126.7, 144.5. Product decomposed before HRMS was obtained.



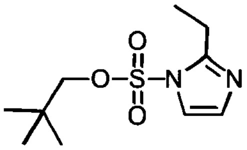
Isobutoxysulfuryl-(2-ethyl)imidazole (4.20). To 2-ethyl imidazole (0.773 g 8.0 mmol), in CH_2Cl_2 (1 mL) at 0 ^{0}C was added a solution of isobutyl chlorosulfate (0.5 g, 2.9 mmol) in CH_2Cl_2 (1.5 mL). The reaction was gradually warmed to room temperature, and allowed to stir for 24 h. The crude material was concentrated, then purified by flash chromatography (33:67 EtOAc/hexanes) to provide **4.20** as a clear colourless oil (0.220 g, 33%). Product degraded before spectrum was obtained.



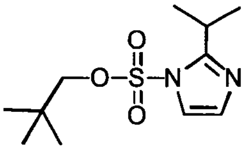
Isobutoxysulfuryl-(2-isopropyl)imidazole (4.21). To 2-isopropyl imidazole (0.885 g . 8.0 mmol), in CH_2Cl_2 (1 mL) at 0 ^{0}C was added a solution of isobutyl chlorosulfate (0.5 g, 2.9 mmol) in CH_2Cl_2 (1.5 mL). The reaction was gradually warmed to room temperature, and allowed to stir for 24 h. The crude material was concentrated, then purified by flash chromatography (33:67 EtOAc/hexanes) to provide **4.24** as a clear colourless oil (0.193 g, 29%) ^{1}H NMR (300 MHz, $CDCl_3$) – peaks listed for major product only -δ 0.89 (d, 6H, *J*= 6.7 Hz, $(CH_3)_2$iBu), 1.29 (d, 6H, *J*= 6.8 Hz, $(CH_3)_2$Im), 1.98 (dt, 1H, *J*= 7.5, 6.7 Hz, CH*i*Bu), 2.99 (sept, 1H, *J*= 6.8 Hz, CHIm), 3.62 (d, 2H, *J*= 7.5 Hz, CH_2), 6.72 (s, 1H, ImH), 6.92 (s, 1H, ImH). Product decomposed before HRMS was obtained.



Neopentoxysulfuryl-(2-methyl)imidazole (4.23): To 2-methyl imidazole (0.657 g 8.0 mmol), in CH_2Cl_2 (1 mL) at 0 ^{0}C was added a solution of neopentyl chlorosulfate (0.5 g, 2.7 mmol) in CH_2Cl_2 (1.5 mL). The reaction was gradually warmed to room temperature, and allowed to stir for 24 h. The crude material was concentrated, then purified by flash chromatography (33:67 EtOAc/hexanes) to provide **4.23** as a clear, colourless oil (0.199 g, 30%). Product degraded before spectrum was obtained.

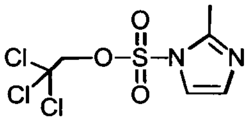


Isobutoxysulfuryl-(2-ethyl)imidazole (4.24). To 2-ethyl imidazole (0.773 g 8.0 mmol), in CH_2Cl_2 (1 mL) at 0 ^0C was added a solution of neopentyl chlorosulfate (0.5 g, 2.7 mmol) in CH_2Cl_2 (1.5 mL). The reaction was gradually warmed to room temperature, and allowed to stir for 24 h. The crude material was concentrated, then purified by flash chromatography (33:67 EtOAc/hexanes) to provide **4.24** as a clear colourless oil (0.545 g, 94%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 9H, $3xCH_3$), 1.39 (t, 3H, *J*= 7.5 Hz, CH_3), 2.98 (q, 2H, *J*= 7.5 Hz, CH_2), 3.78 (s, 2H, CH_2), 6.97 (d, 1H, *J*= 1.6 Hz, ImH), ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4, 21.5, 25.8, 83.1, 120.1, 127.5, 150.8. Product decomposed before HRMS was obtained.

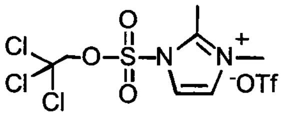


Neopentoxysulfuryl-(2-isopropyl)imidazole (4.25). To 2-isopropyl imidazole (0.885 g 8.0 mmol), in CH_2Cl_2 (1 mL) at 0 ^0C was added a solution of neopentyl chlorosulfate (0.5 g, 2.7 mmol) in CH_2Cl_2 (1.5 mL). The reaction was gradually warmed to room temperature, and allowed to stir for 24 h. The crude material was concentrated, then purified by flash chromatography (33:67 EtOAc/hexanes) to provide **4.24** as a clear colourless oil (0.404 g, 58%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 9H, $3xCH_3$), 1.36 (d, 6H, *J*= 6.8 Hz, CH_3*i*Pr), 3.50 (sept, *J*= 6.8 Hz, CH), 3.77 (s, 2H, CH_2), 6.97 (d, 1H, *J*=

1.8 Hz, ImH), 7.26 (d, 1H, *J*= 1.8 Hz, ImH). Product decomposed before HRMS was obtained.

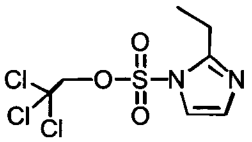


2,2,2-Trichloroethoxysulfuryl-(2-methyl)imidazole (4.26). To 2-methyl imidazole (0.493 g 6.0 mmol), in CH_2Cl_2 (1 mL) at 0 °C was added a solution of trichloroethyl chlorosulfate **2.1** (0.5 g 2.0 mmol) in CH_2Cl_2 (1.5 mL). The reaction was gradually warmed to room temperature, and allowed to stir for 24 h. The crude material was concentrated, then purified by flash chromatography (33:67 EtOAc/hexanes) to provide **4.28** as a white solid (0.464 g, 75%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68 (s, 3H, CH_3), 4.66 (s, 2H, CH_2), 6.96 (d, 1H, *J*= 1.5 Hz, ImH), 7.33 (d, 1H, *J*= 1.5 Hz, ImH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 79.9, 91.6, 120.0, 128.2, 146.4.

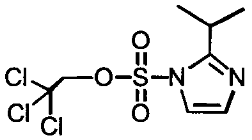


2,2,2-trichloroethoxysulfuryl-(2-methyl)-*N*-methylimidazolium triflate (4.27). To a solution of 2,2,2-trichloroethoxysulfuryl-(2-methyl)imidazole **4.26** (5.0 g, 17.0 mmol) in Et_2O (65 mL) at 0 °C was added dropwise methyl triflate (2.1 mL, 18.7 mmol). The reaction was stirred for 3 h at 0 °C during which time a white precipitate formed. The desired product was isolated by suction filtration, in which the first filtrate was cooled to re-precipitate any remaining product (1x) and washed with cold Et_2O to afford **4.27** as a fluffy white solid (6.32 g, 81%). ^{1}H NMR (300 MHz, MeOD) δ 2.96 (s, 3H, CH_3), 3.96

(s, 3H, CH_3), 5.38 , (s, 2H, CH_2), 7.77 (d, 1H, *J*= 1.6 Hz, ImH), 8.10 (d, 1H, *J*= 1.6 Hz, ImH); ^{13}C NMR (75 MHz, MeOD) δ 10.5, 35.3, 82.0, 91.6, 120.7, 123.5, 148.6.



2,2,2-Trichloroethoxysulfuryl-(2-methyl)imidazole (4.28). To 2-ethyl imidazole (0.582 g 6.0 mmol), in CH_2Cl_2 (1 mL) at 0 ^{0}C was added a solution of trichloroethyl chlorosulfate **2.1** (0.5 g 2.0 mmol) in CH_2Cl_2 (1.5 mL). The reaction was gradually warmed to room temperature, and allowed to stir for 24 h. The crude material was concentrated, then purified by flash chromatography (33:67 EtOAc/hexanes) to provide **4.28** as a white solid (0.464 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, 3H, *J*= 7.4 Hz, CH_3), 3.04 (q, 2H, *J*= 7.4 Hz, CH_2), 4.65 (s, 2H, CH_2), 7.00 (d, 1H, *J*= 1.6 Hz, ImH), 7.34 (d, 1H, *J*= 1.6 Hz, ImH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.29, 21.73, 79.98, 91.74, 119.98, 128.16, 151.29.



2,2,2-Trichloroethoxysulfuryl-(2-isopropyl)imidazole (4.28). To 2-isopropyl imidazole (0.660 g 6.0 mmol), in CH_2Cl_2 (1 mL) at 0 ^{0}C was added a solution of trichloroethyl chlorosulfate **2.1** (0.5 g 2.0 mmol) in CH_2Cl_2 (1.5 mL). The reaction was gradually warmed to room temperature, and allowed to stir for 24 h. The crude material was concentrated, then purified by flash chromatography (33:67 EtOAc/hexanes) to provide

4.28 as a white solid (0.508 g, 79%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (d, 6H, *J*= 6.8 Hz, 2xCH_3), 3.52 (sept, 1H, *J*= 6.8 Hz, CH), 4.65 (s, 2H, CH_2), 6.99 (d, 1H, *J*= 1.6 Hz, ImH), 7.29 (d, 1H, *J*= 1.6 Hz, ImH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.86, 27.55, 80.04, 91.73, 119.57, 128.11, 155.45.

4.6 References

(1) Simpson, L. S.; Widlanski, T. S. *J. Am. Chem. Soc.* **2006,** *128*, 1605-1610.

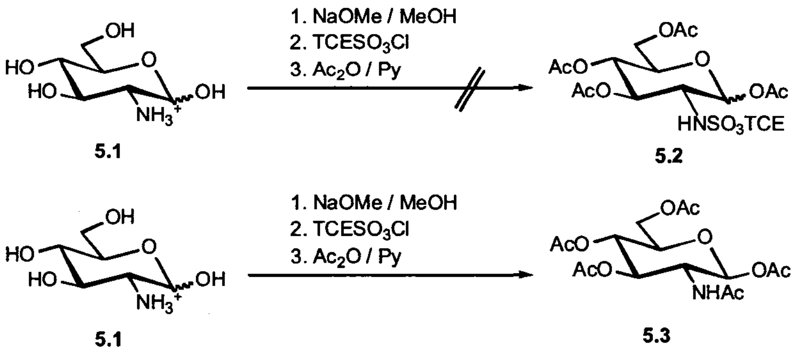
Chapter 5 – Preparation of Glucosamine Derivatives

5.1 Introduction

One of the branches of carbohydrate chemistry we felt it was very important to extend our methodology to was *N*-sulfated glucosamine derivatives, as many biologically relevant sulfated carbohydrates contain *N*-sulfate residues. The chemistry presented in this chapter is very preliminary, and requires a great deal of further investigation. Two approaches to the *N*-glucosamine sulfates were examined. The first approach involves *N*-sulfation of an unprotected glucosamine monosaccharide; the second involves the preparation of a fully protected glucosamine derivative, followed by *N*-deprotection and sulfation.

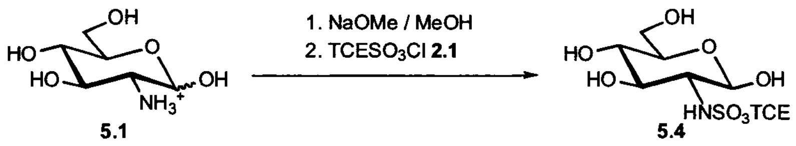
5.2 *N*-Sulfation of Unprotected Glucosamine

Expecting that the amine would be slightly more nucleophilic than the hydroxyls in glucosamine **5.1**, we had anticipated that the TCESO$_3$ group could be incorporated at the very beginning of a synthetic scheme. Glucosamine hydrochloride **5.1** was neutralized with methanolic sodium methoxide, then treated with trichloroethyl chlorosulfate **2.1**, and finally subjected to acetic anhydride and pyridine, expecting the reaction to provide the acetylated-*N*-sulfated glucosamine **5.2**. Unfortunately, the only product isolated from the reaction was the per-acetylated glucosamine **5.3** (scheme 5.1).



Scheme 5.1

Since the only product isolated from the reaction in scheme 5.1 was product **5.3**, it was not known if the $TCESO_3$ group was successfully introduced and then removed, or if *N*-sulfation even occurred at all. To determine if the *N*-sulfate was being formed, the reaction was performed according to scheme 5.2, and the products were analyzed using ^{13}C NMR. The results are summarized in table 5.1.



Scheme 5.2

Table 5.1: Unsuccessful Attempts for *N*-Sulfation with Glucosamine **5.1**

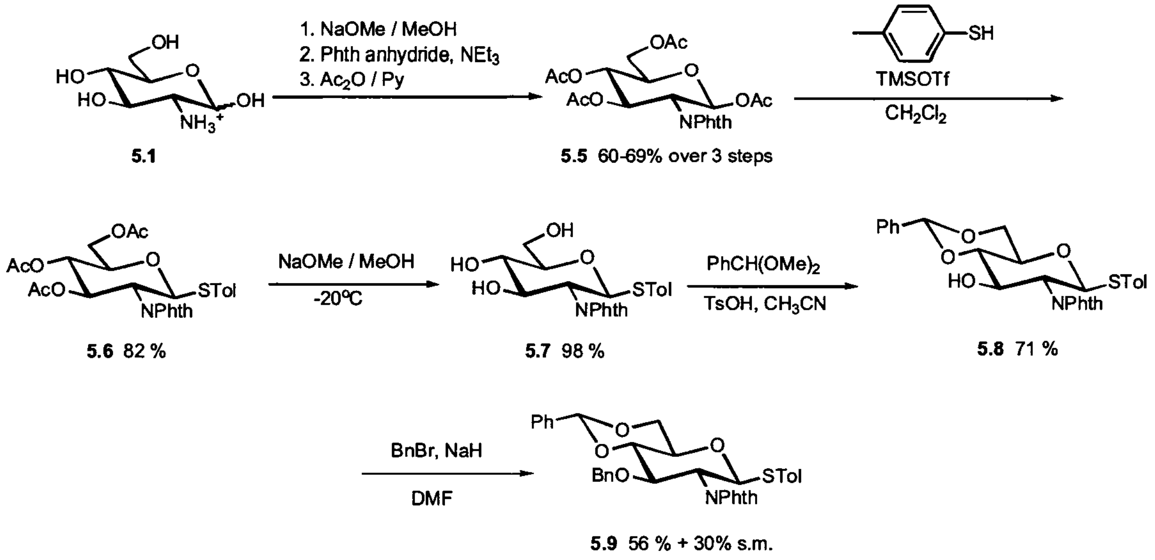
Entry	Temp. (°C)	NaOMe / Time	Conditions
1	0	1 eq. / 1h	**2.1** (0.5 eq. + 0.5 eq after 45 min)
2	0	1 eq. / 1h	**2.1** (0.5 eq.), 45 min NEt_3 (0.5 eq.) and **2.1** (0.5 eq)
3	RT	1 eq. / 1h	**2.1** (0.5 eq.), 45 min NEt_3 (0.5 eq.) and **2.1** (0.5 eq)
4	RT	2 eq. / 1h	**2.1** (0.5 eq.), 45 min NEt_3 (0.5 eq.) and **2.1** (0.5 eq
5	RT	2 eq. / 1h	**2.1** (2.0 eq.) and NEt_3 (1.0 eq.)
6	RT	1.5 eq. / 5 min	**2.3** (1.0 eq.) then **2.3** (1.0 eq.)

Unfortunately, despite a number of attempts, the $TCESO_3$ group was never successfully incorporated into glucosamine **5.1**. The reaction was also attempted using $NaCO_3$ and H_2O in place of the sodium methoxide/methanol neutralization conditions. These reactions also failed to incorporate the $TCESO_3$ group, as reagent **2.1** reacted very quickly with water, and the imidazolium salt **2.3** is not at all miscible with water. This approach will be pursued further in the near future.

5.3 *N*-Sulfation of Fully Protected Glucosamine

*5.3.1 Synthesis of orthogonally protected glucosamine **5.9***

Because of the limitations encountered when attempting to introduce the $TCESO_3$ to the unprotected glucosamine **5.1**, a second, much lengthier approach was used. In this method, the fully protected glucosamine derivative **5.9**[5] was first prepared over 7 steps, with an overall yield of 22%, according to scheme 5.3.

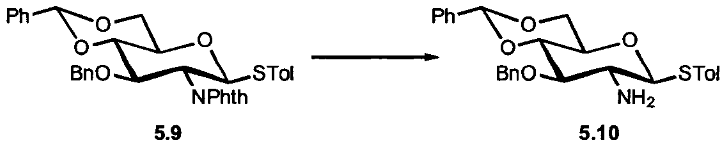


Scheme 5.3

Using a procedure described by Hernandez-Torrez and coworkers[1] which was adapted from a procedure outlined by Schmidt and coworkers,[2] **5.1** treated with NaOMe (1.0 eq.) then subjected to phthalic anhydride and triethylamine in methanol to introduce the –*N* phthalimido group. The crude product was concentrated, and then re-suspended in pyridine and subjected to an excess of acetic anhydride to provide product **5.5** in a 69% yield over 3 steps. The tetraacetate **5.5** was then converted to the thiotolyl glycoside **5.6** using TMSOTf in CH_2Cl_2. The triacetate **5.6** was subjected to deacetylation under Zemplén conditions, ensuring the reaction stays between –20 and –10 °C to prevent partial cleavage of the phthalimide group. The reaction was neutralized by adding Dowex H^+ resin, and **5.7** was isolated as a white solid. No further purification is required at this step. The benzylidene acetal was first introduced using benzaldehyde and zinc chloride, resulting in product **5.8** in a 50% yield. In an effort to increase the yield of this step, the method was changed to one reported by Ogawa and co-workers which employed

α,α-dimethoxy toluene and tosic acid in acetonitrile.[3] This approach provided **5.8** in an improved 71% yield. The final step involved benzylation of the 3-OH in **5.8** to provide the orthogonally protected glucosamine **5.9** using benzyl bromide and sodium hydride in DMF. Despite adding excess benzyl bromide and sodium hydride in portions, the reaction did not go to completion, and compound **5.9** was isolated in a 56% yield, with a 30% recovery of starting material.

Once the fully protected glucosamine **5.9** was obtained, the next step towards the *N*-sulfated compound was removing the *N*-phthalimide group. A literature procedure using hydrazine monohydrate in ethanol was first attempted to achieve the deprotection, as outlined in scheme 5.4.[4] Surprisingly, this reaction did not proceed as smoothly as expected, as the reaction resulted in a completely insoluble polymer-like material. The conditions were modified such that the solvent was changed, and hydrazine hydrate was used (table 5.2, entries 1-4), however all attempts resulted in the same insoluble product. By switching to a different literature procedure, which employs ethylenediamine in hot butanol,[5] the desired free amine **5.10** was obtained in a 91% yield (table 5.2, entry 5).



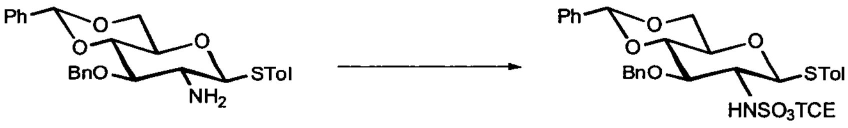
Scheme 5.4

Table 5.2: Deprotection of the NPhth in **5.9**

Entry	Base (20 eq.)	Solvent, Temperature	Results
1	$NH_2NH_2 \cdot H_2O$	EtOH, 90 °C	Insoluble ppt.
2	$NH_2NH_2 \cdot H_2O$	2:1 $EtOH/CH_2Cl_2$, 90 °C	Insoluble ppt.
3	NH_2NH_2 hydrate	2:1 $EtOH/CH_2Cl_2$, 90 °C	Insoluble ppt.
4	$H_2N(CH_2)_2NH_2$	*n*BuOH, RT	No reaction
5	$\mathbf{H_2N(CH_2)_2NH_2}$	***N*BuOH, 90 °C**	**91%**

5.3.2 N-sulfation reactions

With the free amine **5.10** fully prepared, we began to examine the preparation of the *N*-sulfate compound **5.11** as depicted in scheme 5.5. The general optimized conditions for introducing a TCE protected sulfate into a monosaccharide were first attempted (table 5.3, entry 1). For this reaction, the glucosamine derivative **5.10** was treated with NMI (2.5 eq.) and sulfating agent **2.3** in THF (0.25 M), however, the reaction surprisingly yielded a very complex mixture from which no product was isolated.



5.10 **5.11**

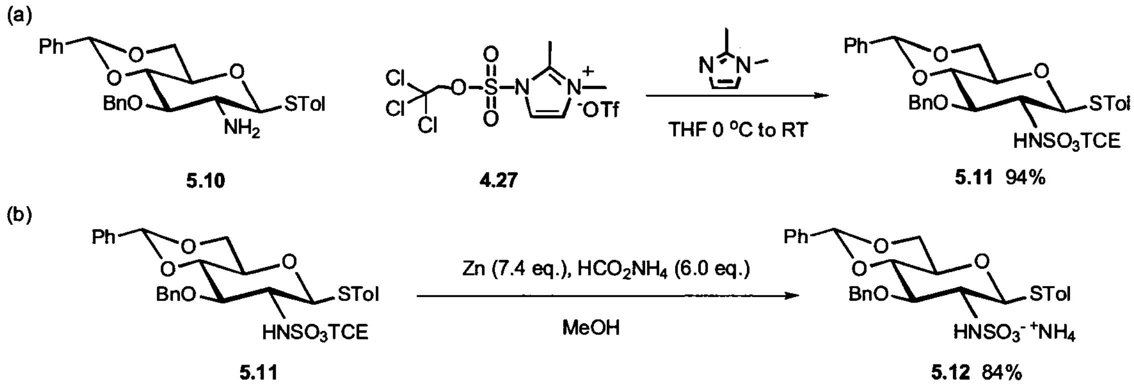
Scheme 5.5

Table 5.3: *N*-sulfation of Protected Glucosamine **5.10**

Entry	Conditions	Results
1	NMI (2.5 eq.), **2.3** (2.0 eq.), THF (0.25 M), 8 h	Complex mixture
2	NEt_3 (1.1 eq.), $TCESO_3Cl$ (1.1 eq.) CH_2Cl_2 (0.5 M), 8 h	Complex mixture
3	NMI (4 eq.), **2.3** (4.0 + 2.0 eq.), THF (0.25 M), 48hh	No desired product
4	1,2-di-MeIm (4 eq.), **4.27** (4.0 + 2.0 eq.) THF (RT), 24 h	**94%**

The reaction conditions were modified in a way that the trichloroethyl chlorosulfate **2.1** and triethylamine were used to introduce the $TCESO_3$ group instead of triflate **2.3** (table 5.3, entry 3), however, this too resulted in a very complex mixture from which no product could be detected. Returning to the sulfating agent, a larger excess of **2.3** was initially added to compound **5.10** (table 3.3, entry 3). This resulted in a slightly less complex reaction than was observed for table 5, entry 1 and the starting material, did not disappear over time. After 24 hours, additional **2.3** was added, however once again, no desired product was obtained. The last entry in table 5.3 describes the best conditions for the synthesis of the *N*-sulfated **5.11**, in which the glucosamine **5.10** is treated with sulfating agent **4.27** (4.0 eq, then 2.0 eq after 12 h) in THF. Fortunately, these conditions allowed for compound **5.11** to be isolated in a 94% yield. It is not known at this time why sulfating agent **2.3** was unable to provide compound **5.11**, where as **4.27** achieved the task fairly smoothly (scheme 5.6a), but further investigations will be performed.

The sulfated glucosamine **5.11** was then treated with our standard zinc and ammonium formate deprotection conditions to provide the unmasked *N*-sulfate **5.12** in an unoptimized 84% yield (scheme 5.6b).



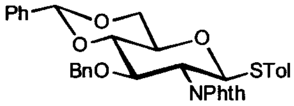
Scheme 5.6

5.4 Summary

While the research performed in this area is preliminary, we have been able to demonstrate that the sulfuryl imidazolium approach to *N*-sulfated compounds is viable. Using sulfating agent **4.27**, the TCE protected *N*-sulfate **5.11** was prepared in 2 steps from known starting carbohydrate **5.9** in a respectable yield, and the TCE group was easily removed to provide the free *N*-sulfate **5.12** with no complications.

5.5 Experimental

For general information, refer to chapter 2, page 49



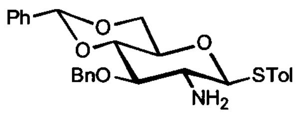
p-Tolyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-1-thio-ß-D-glucopyranoside (5.9).[6] To glucosamine hydrochloride (10.0 g, 46.4 mmol) at 0 °C was added dropwise, a solution of 1 M NaOMe (100 mL). The reaction removed from the ice bath, and was stirred with a mechanical stirrer at room temperature. Finely ground phthalic anhydride (3.8 g, 25.6 mmol) was added after 2 h, and the reaction was stirred for 45 min. A second portion of phthalic anhydride (3.8 g, 25.6 mmol) was then added along with NEt_3 (7.2 mL, 51.0 mmol) and MeOH (46 mL). The reaction was allowed to stir for 24 h, then the phthalamate was precipitated by cooling the reaction to –20 °C for 2 h. The solids were filtered and washed with cold MeOH, and allowed to dry overnight under reduced pressure. The obtained crude product was then re-dispersed in pyridine (100 mL), cooled to 0 °C and treated with Ac_2O (66 mL). The mixture was stirred at room temperature for an additional 48 hours, at which point it was slowly quenched with cold EtOH (20 mL). The crude product was concentrated, redispersed in toluene, and concentrated *in vacuo* several times for the azeotropic removal of pyridine. The obtained crude product was then dissolved in $CHCl_3$, washed with H_2O and brine, and dried over $MgSO_4$. Recrystallization (EtOAc/hexanes) provided the desired tetraacetate **5.5** as a white solid (15.2 g, 69%).

Tetraacetate **5.5** (9.3 g, 19.5 mmol) was then treated with 4-methylbenzene thiol (7.3 g, 58.7 mmol) followed by TMSOTf (4.3 mL, 23.7 mmo) in dry CH_2Cl_2. The reaction was stirred at room temperature for 8 hours, then carefully quenches with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 and the combined organics were washed with brine and dried over $MgSO_4$ and evapourated under reduced pressure. The crude product was recrystallized (EtOAc/hexanes) to give the desired thioglycoside **5.6** (8.4 g, 80%).

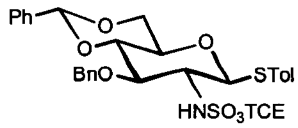
The triacetate **5.6** (7.4 g, 13.7 mmol) was dissolved in a 3:2 mixture of $MeOH/CH_2Cl_2$, cooled to –20 °C and treated with a 0.3 M solution of NaOMe/MeOH (18.5 mL). The reaction was stirred (ensuring that the temperature remained between –20 °C to –10°C) for 2 h, at which point it was warmed to 0 °C and neutralized with Dowex H^+ resin. The crude triol **5.7** (5.6 g, 98%) was concentrated by rotary evaporation, and left over night under vacuum.

A solution of triol **5.7** (5.6 g, 13.5 mmol), $\alpha\alpha$-dimethoxytoluene (6.7 mL, 44.6 mmol), and $TsOH{\cdot}H_2O$ (0.095 g, 0.5 mmol) in CH_3CN (95.2 mL) was stirred for 16 hours at room temperature then neutralized with NEt_3. The solution was concentrated under reduced pressure, and the crude oil was purified using flash chromatography to give compound **5.8** as a white solid (4.8 g, 71 %).

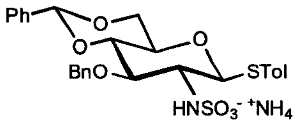
To compound **5.8** (4.8 g, 9.5 mmol) in DMF (52 mL) was added sodium hydride 0.54 g, 14.3 mmol), and the mixture was stirred for 10 minutes at room temperature. BnBr (1.2 mL, 9.8 mmol) was then added, and the reaction was allowed to stir at room temperature for 16 hours. Additional NaH (0.54g, 14.3 mmol) and BnBr (1.2 mL, 9.8 mmol) were added after 12, and 24 h intervals, however the reaction did not go to completion. Methanol was then added, and the reaction was diluted with water and extracted with EtOAc. The combined organics were concentrated to a crude oil, which was purified by flash chromatography to afford **5.9** as a white solid (3.17 g, 56%). All spectra obtained correspond with literature data for the compound.[6]



***p*-Tolyl 2-amino-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-1-thio-ß-D-glucopyranoside (5.10).** To **5.9** (1.65 g, 2.78 mmol) in *n*-butanol (132 mL) was added ethylenediamine (3.7 mL, 55.6 mmol). The reaction was heated to 90 °C and stirred for 20 h. The reaction was then concentrated *in vacuo* to dryness, and co-evaporated with toluene (3x). The crude residue was purified by flash chromatography (98:2) CH_2Cl_2/MeOH to afford **5.10** as a white foam (1.17g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75 (s, 2H, NH_2), 2.37 (s, 3H, CH_3), 2.90 (dd, 1H, $J_{2,3}= J_{2,1}=$ 9.4 Hz, H2), 3.54 (ddd, 1H, $J_{5,6ax}=J_{5,4}=$ 9.4 Hz, $J_{5,6eq}=$ 4.9 Hz, H5), 3.61 (dd, 1H, $J_{3,4}=J_{3,2}=$ 9.3 Hz, H3), 3.74 (dd, 1H, $J_{4,5}= J_{4,3}=$ 9.1 Hz, H4), 3.84 (dd, 1H, $J_{6ax,6eq} =J_{6ax,5} =$ 10.3 Hz, $H6_{ax}$), 4.41 (dd, 1H, $J_{6eq,6ax}=$ 10.4, $J_{6eq,5} =$ 4.9 Hz, $H6_{eq}$), 4.56 (d, 1H, $J_{1,2}=$ 9.9 Hz, H1), 4.72, 5.02 (AB, 2H, $J=$ 11.2 H, CH_2Ph), 5.61 (s, 1H, CHPh), 7.14 (d, 2H, $J=$ 8.0 Hz, ArH), 7.35-7.46 (m, 12H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.15, 55.36, 68.72, 70.63, 75.01, 82.15, 82.23, 89.66, 101.21, 125.96, 127.66, 127.96, 128.24, 128.28, 128.51, 128.97, 129.76, 133.58, 137.33, 138.17, 138.54; HRMS (EI) m/z = 463.1825, $C_{27}H_{29}NO_4S$ requires 463.1817.



***p*-Tolyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-1-thio-2-trichloroethoxylsulfoxyamino-ß-D-glucopyranoside (5.11).** To **5.10** (0.50 g, 1.08 mmol) in THF (5.0 mL, 0.23 M) at 0 °C was added 1,2-dimethylimidazole (0.43 g, 2.7 mmol) followed by **4.27** (2.0 g, 4.32 mmol). The reaction was stirred at 0 °C, gradually warmed to room temperature by allowing the ice bath to melt, and then stirred overnight. After 14 h, additional **4.27** (1.0 g, 2.16 mmol) was added and after 10 h the system applied directly to silica gel column. Flash chromatography (33:67 EtOAc/hexanes) gave pure **5.11** as a white solid (0.68 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H, CH_3), 3.37 (dd, 1H, $J_{2,3}$+ $J_{2,1}$= 20.1, $J_{2,NH}$= 7.1 Hz, H2), 3.52 (ddd, 1H, $J_{5,6ax}$+$J_{5,4}$= 19.4 Hz, $J_{5,6eq}$= 5.0 Hz, H5), 3.70 (dd, 1H, $J_{4,5}$=$J_{4,3}$= 9.2 Hz, H4), 3.81 (dd, 1H, $J_{6ax,6eq}$=$J_{6ax,5}$ = 10.3 Hz, H6$_{ax}$), 3.99 (dd, 1H, $J_{3,4}$= $J_{3,2}$= 9.3 Hz, H3), 4.41 (dd, 1H, $J_{6eq,6ax}$ = 10.5, $J_{6eq,5}$ = 5.0 Hz, H6$_{eq}$), 4.79, 4.83 (AB, 2H, J= 11.0 Hz, CH_2CCl_3), 4.83 (d, 1H, J= 11.0 Hz, 1/2 CH_2Ph), 4.90 (d, 1H, J= 10.4 Hz, H1), 4.95 (d, 1H, $J_{NH,2}$= 7.1 Hz, NH), 5.00 (d, 1H, J= 11.0 Hz, 1/2 CH_2Ph), 7.16 (d, 2H, J= 8.0 Hz, ArH), 7.35-7.46 (m, 12H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.20, 59.28, 68.51, 70.07, 74.07, 78.53, 78.77, 82.33, 86.42, 93.44, 101.26, 126.00, 127.21, 128.14, 128.38, 128.56, 128.59, 129.19, 129.98, 133.66, 137.01, 137.56, 138.97; HRMS (EI) m/z = 673.0513, $C_{29}H_{30}Cl_3NO_4S_2$ requires 673.0529.



p-Tolyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-2-sulfoxyamino-1-thio-ß-D-glucopyranoside (5.12). To a suspension of ammonium formate (0.083g, 1.3 mmol) in MeOH (1.3 mL, 1.0 M) was added glucosamine **5.11** (0.15 g, 0.22 mmol) followed by zinc dust (0.1 g, 1.55 mmol). The reaction was stirred for 7 h at room temperature, at which point no starting material was detected using TLC. The reaction was filtered through celite, and concentrated to crude product. Flash chromatography (20:4:1 CH_2Cl_2/MeOH/NH_4OH) afforded a white solid, which was lyophilized (3x) from water to yield **5.12** as a light white product (0.105 g, 84%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.29 (s, 3H, CH_3), 3.01 (dd, 1H, $J_{2,3}+J_{2,1}$= 17.1 Hz, H2), 3.39-3.46 (m, 1H, H5), 3.65 (dd, 1H, $J_{6ax,6eq}+J_{6ax,5}$ = 10.2 Hz, H6$_{ax}$), 3.71 (dd, $J_{4,5}+J_{4,3}$= 18.3 Hz, H4), 4.20 (dd, 1H, $J_{6eq,6ax}$= 10.2, $J_{6eq,5}$ = 5.1 Hz, H6$_{eq}$), 4.39 (dd, $J_{3,4}$ =$J_{3,2}$ = 8.5 Hz, H3), 4.74 (d, 1H, J= 11.5 Hz, 1/2 CH_2Ph), 4.97 (d, 1H, J= 11.5 Hz, 1/2 CH_2Ph), 5.59 (d, 1H, J= 9.1 Hz, H1), 5.66 (s, 1H, CHPh), 5.76 (s, 1H, NH), 7.14-7.40 (m, 18 H, 14 ArH + NH_4); ^{13}C NMR (125 MHz, DMSO-d_6) δ 21.11, 59.79, 68.52. 68.85, 73.96, 78.92, 81.74, 86.95, 100.57, 126.36, 126.45, 127.42, 128.22, 128.30, 128.53, 130.00, 131.16, 131.79, 138.29, 140.13.

5.6 References

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Chapter 6 – Conclusions and Future Work

6.1 Conclusions

We have now reported the synthesis of 2,2,2-trichloroethoxysulfuryl imidazolium triflate **2.3**. This reagent represents an entirely new class of potent sulfating agents, capable of reacting with even poorly nucleophillic substrates. We have demonstrated that reagent **2.3** and its derivatives are highly effective for the sulfation of monosaccharides through the synthesis of a number of sulfocarbohydrate building blocks.

The TCE protected sulfates are stable to many conditions encountered in carbohydrate chemistry, yet are removed under mild conditions to which most other functional groups appear to be tolerant. By analyzing the viability of this approach through protecting group manipulations, anomeric activations disaccharide synthesis, and deprotection studies, we have demonstrated that this chemistry provides a superior alternative to the current methods used to obtain sulfated carbohydrates.

For what was described as our ultimate objective, we have developed and herein reported a unique and reliable approach to the synthesis of sulfated carbohydrates. Incorporating a sulfate moiety as a protected sulfated monoester at the monosaccharide stage provides a viable alternative to conventional approaches, which are lengthy, complex and can be very low yielding. Using the developed approach, unnecessary protecting group manipulations can now be avoided, as the protected sulfate moiety can be carried through many chemical transformations.

6.2 Future Work

Despite the extensive amount of research done, this project is by no means complete. There are still a number of areas that require further investigation to demonstrate the breadth of this approach.

It is important to show that multiple sulfations can be performed at once; as well as investigating the potential for selective sulfations. Developing conditions in which one hydroxyl group can be selectively sulfated over others would further eliminate unnecessary protecting group manipulations, contributing to much shorter, concise synthetic sequences.

All of the *N*-sulfated glucosamine chemistry is very preliminary. Despite showing that the orthogonally protected glucosamine compound can be easily sulfated, we would like develop conditions under which the *N*-sulfation can occur on the un-protected, or partially protected glucosamine or galactosamine residues, again to decrease the number of steps required to obtain the target disaccharides.

The area of glycosylation still requires a great deal of attention. We have shown that the TCE-sulfates are compatible with the glycosyl imidate method for coupling, but we would like to extend the chemistry to one-pot thioglycoside acitivation and coupling conditions. We would also like to synthesize more di- and trisaccharides that exhibit biological importance.

Finally, we have only begun to investigate the derivatives of the trichloroethoxysulfuryl imidazolium triflate **2.3**. The second generation sulfating agent **4.27** has been used to improve upon the areas in which **2.3** exhibited limitations. Further modifications of the imidazole moiety and studying the resulting sulfating agents are required.

While a great deal of research is still required, we hope that this methodology will have a significant impact on the synthesis of sulfated carbohydrates. More studies on the scope of this methodology and its application to the synthesis of complex sulfated oligosaccharides are in progress, and will be reported in due course.