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Chemical synthesis approaches to amphiphilic mimetic glycosides

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Under the supervision of Prof Gavin J Miller and Dr Timothy Miller

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Abstract

The majority of surfactants in use are derived from petroleum feedstocks. Synthetic surfactants face numerous issues including low biodegradability, ecotoxicity and bioaccumulation. Biosurfactants such as amphiphilic glycoconjugates are a promising candidate for the development of non-toxic, biodegradable, and sustainable alternatives. Due to the infant nature of the chemical space, structure function studies are required to fully unlock their potential and so the chemical synthesis of these materials is required.

Herein, the synthesis of pyranose-component modified oleyl based glycolipids is detailed. These modifications include fluorination at C6 and C4 within glucosides and glucosamine. Whilst pursuing galactose/galactosamine 2,3,6-tri-*O*/3-6-di-*O*-benzoates for regioselective heteroatom introduction, an understanding into the effect of anomeric aglycon and chalcogen on the outcome of low temperature regioselective protection was acquired.

A mild and reliable glycosylation method to access oleyl glucosides was developed and glycosidation of oleyl alcohol with α-trichloroacetimidate donors successfully yielded five target glycolipids. The effect of anomeric configuration and aglycon identity on regioselectivity for 2,3,6-tri-*O*-benzoates was also determined with α configured substrates providing complete selectivity. In the β configuration selectivity was hindered by larger and electron donating aglycons with small and electron donating aglycons favouring the 2,3,6-tri-*O*-benzoate. From these studies a number of advanced precursors were synthesised and effectively utilised to access further glycomimetics beyond glycolipids including glycosyl 1-phosphates. These materials provide an exciting series of tools to explore structure function relationships of amphiphilic oleyl glycoconjugates.

Abbreviations

Acetyl	Ac
Automated glycan assembly	AGA
Benzoyl	Bz
Benzoyl cyanide	BzCN
Bis(trimethylsilyl)amine	HMDS
Correlated Spectroscopy	COSY
Critical micelle concentration	CMC
Cyanide	CN
Cysteine	Cys
Dichloroethane	DCE
Deuterium	D_2O
Diethylaminosulfur trifluoride	DAST
Dimethylacetamide	DMA
4-Dimethylaminopyridine	DMAP
Dimethylsulfoxide	DMSO
Di-*tert*-butylsilyene	DTBS
Dithiothreitol	DTT
Electron donating	ED
Electron withdrawing	EW
1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide	EDC
Geminal	Gem
Glucose transporter 1	GLUT1
Glutathione	GSH
Glycolipid	GL
Heparan sulfate	HS
Heteronuclear single quantum coherence	HSQC
High performance liquid chromatograph	HPLC
High resolution mass spectrometry	HRMS
Human equilibrative nucleoside transporter 1	hENT1
Hydrochloric acid	HCl
Isoglobotriosylcreamide	igB3
Isopropyl alcohol	IPA
Lithium diisopropylamide	LDA
Mass-to-charge ratio	*m/z*
Megahertz	MHz
Millimolar	mM
Minutes	Mins.
N-Bromosuccinimide	NBS
Neighbouring group participation	NGP
Nucleoside analogue	NA
para-nitrophenyl	PNP
Parts per million	ppm
Partition coefficient	(*P)*
Protecting group	PG

Reactive oxygen species	ROS
Saturated	Sat.
Strong anion-exchange	SAX
tert-Butyldimethylsilyl chloride	TBSCl
Tetrabutylammonium bromide	TBAB
Tetrahydrofuran	THF
2,2,6,6-tetramethyl-1-piperidinyloxy	TEMPO
Tetra-*n*-butylammonium fluoride	TBAF
Tetra-*n*-butylammonium iodide	TBAI
Thioredoxin-1	Trx1
Toluenesulfonic acid	TsOH
Trichloroacetimidate	TCA
Trichloroisocyanuric acid	TCCA
Trifluoroacetic acid	TFA
Triisopropylsilyl chloride	TIPSCl
Trimethylsilyl	TMS
Uridine diphosphate	UDP

Publications

1. **Jack Porter,** Marcelo A. Lima, Imlirenla Pongener and Gavin J. Miller; *Synthesis of 4-thio-D-glucopyranose and interconversion to 4-thio-D-glucofuranose, Carbohydr. Res.,* **2023**, 524, 108759.

2. **Jack Porter**, Daniele Parisi, Timothy Miller, Aisling Ní Cheallaigh, Gavin J. Miller; *Chemical synthesis of amphiphilic glycoconjugates: Access to amino, fluorinated and sulfhydryl oleyl glucosides, Carbohydr. Res.,* **2023**, 530, 108854.

Chapter 1

Introduction

1.0 Introduction

1.1 Carbohydrates

Carbohydrates are one of the most abundant biomolecules in nature and account for more than 80% of all biomass on earth. From a chemical perspective carbohydrates are organic in nature. They comprise of 4 core elements, nitrogen (N), oxygen (O), carbon (C) and hydrogen (H). Their role is vast and spans many physiological and pathological processes across almost all organisms.[1,2] Carbohydrates exists within numerous categories with the most basic being monosaccharides. This class rarely occurs in nature and instead they are utilised as building blocks to form more complex structures such as polysaccharides/oligosaccharides. These polymeric carbohydrates typically comprise of thousands of repeating monomer units bound together by glycosidic bonds. Monosaccharide units can be linked at various positions and through either *cis* or *trans* linkages.

This expansive variability allows for an almost endless number of combinations and such their synthesis and characterisation can be a daunting task. Monosaccharides can be classified into various subcategories depending on their chemical composition and conformation. For example, monosaccharides possessing an aldehydic carbonyl would be classified as aldoses and those posing a ketonic carbonyl, ketoses. A further example of classification would be furanose and pyranoses. Most carbohydrates present in cyclic form as opposed to their open chain conformation (***Figure 1***). Cyclic carbohydrates with a five-membered ring are classed as furanoses and carbohydrates with six membered rings are classified as pyranoses.[3] The most common sugar in nature, glucose, exist almost entirely in the pyranose form (***Figure 1***).[4] This preference for the pyranose

tautomer can be reasoned by the reduced angular and ecliptic strain within the ring. To alleviate this strain furanose rings will typically adopt an envelope or twist conformation.[5]

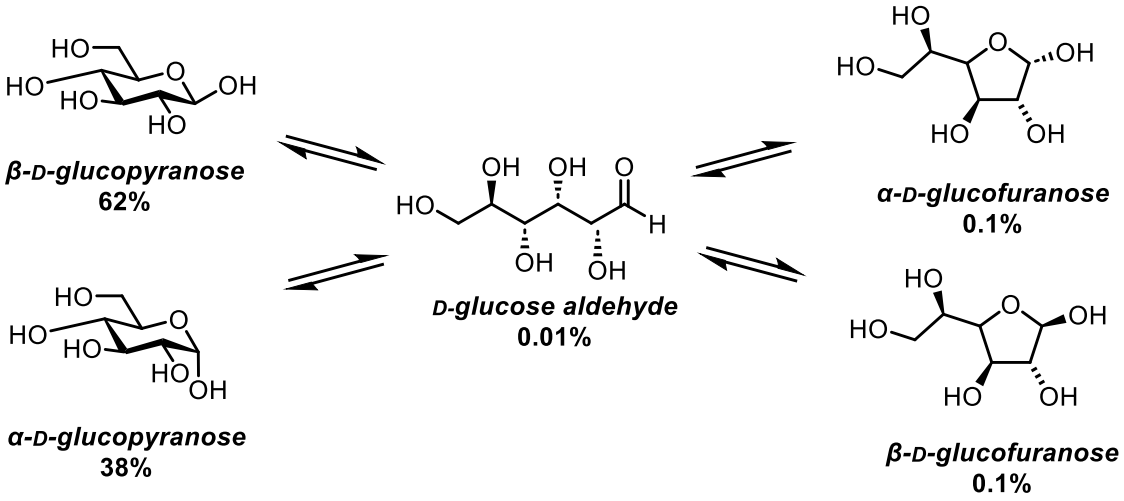


Figure 1: Anomeric equilibrium of D-glucose in aqueous solution, relative abundances at 25 °C and pH 7.[4]

The role of glycans can vary dramatically, and is directly linked to their structural properties, for example starch and cellulose; both are glucose polymers however one serves as energy storage and the other as a structural component. The difference between the two is minor with starch demonstrating α-1-4 linkages of monomers and cellulose contains β-1-4 linkages of monomers. This is a basic example of how minor modifications can result in significant implications for the inter-and intramolecular interactions. These interactions are important as they dictate final function of a carbohydrate/polysaccharide. Carbohydrates and their derivatives are known to be major components of various biological processes including metabolic events and intracellular communication. Despite decades of interest and research there is still much progress to be made in expanding libraries for defined glycans, both natural and unnatural. The process of synthesising glycans is a complex and laborious task due to their heterogenous nature. This inherent difficulty has held back progress within the area when compared

with similar fields, for example those concerned with polypeptides and nucleic acid synthesis.[6-9]

1.2 Glycolipids

Glycolipids (GLs) are a class of glycans composed of a polar headgroup connected by glycosidic linkage to a nonpolar lipid tail.[10] The headgroup can be a sole monosaccharide or an oligosaccharide in more complex examples. Those containing a single monosaccharide head group are known as cerebrosides. Further sub classes include rhamnolipids, sophorolipids, mannosylerythritol lipids, cellobiose lipids and trehalolipids.[11] GLs are ubiquitous within nature and can be found in all living organisms ranging from plants to humans.[12, 13] Such diverse biological functions have drawn interest from researchers. GLs have been established as components in mechanisms such as cell to cell communication and immune response.[14] Beyond these critical processes, they have also been proven as successful vaccine adjuvants and novel treatments for cancer.[15] The amphiphilic structure of GLs is tied directly to their role and function. When in aqueous solution GLs tend to self-aggregate and form micelles or liposomes (***Figure 2***).[16]

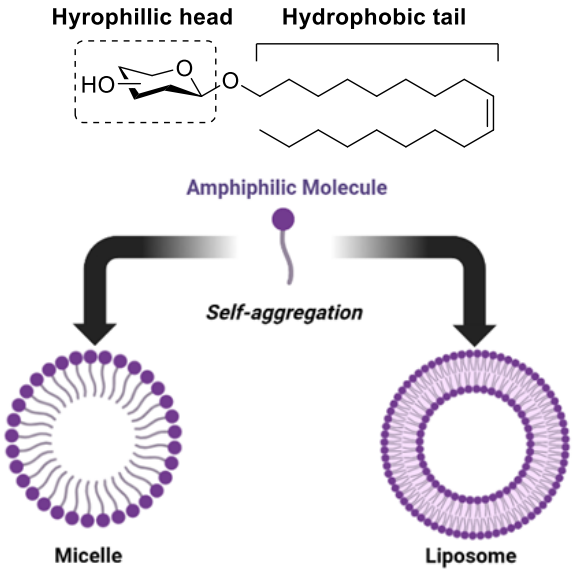


***Figure 2*:** Selected examples of aggregation type for amphiphilic molecules in aqueous media and example oleyl-glucoside GL.

Micelles can be described as colloidal particles consisting of amphiphilic molecules presenting as a spherical ball.[17] This self-aggregation is driven by hydrophobic/hydrophilic interactions with the aqueous media. The non-polar tails position themselves away from the polar media and the polar headgroup acts in a hydrophilic manner forming a 'protective' front with the solution. Liposomes are slightly different and are composed of a lipid bilayer allowing for an aqueous core separated from the bulk aqueous media. Each type of aggregation lends itself to a particular function with GLs having an array of applications.[18]

1.3 Glycolipids as surfactants

Surfactants are a pivotal part of daily life for most human beings. They are a major component in formulations for products ranging from food and drinks, drugs and cosmetics.[19] Surfactants reduce surface tension between two substances that can vary in phase and combination. Surfactants can serve multiple functions, for example emulsifiers, wetting and foaming agents. When surfactants reach their critical micelle concentration (CMC) they form micelles.[20] This can reduce surface tension between different phases making them ideal for the removal of oil from water or soil (***Figure 3***).

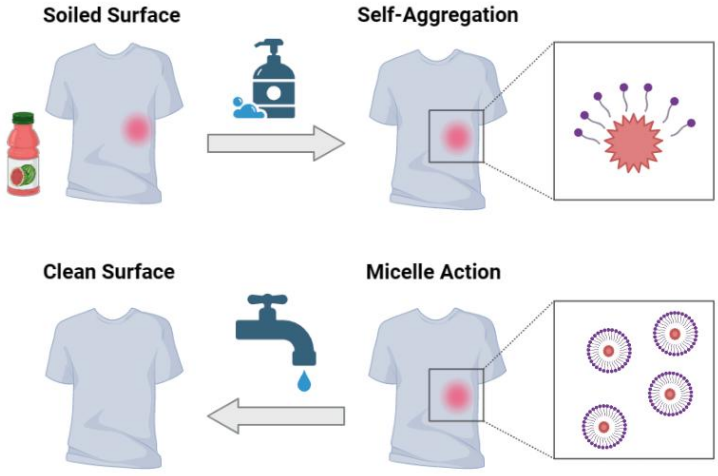


Figure 3: Surfactant action on a soiled surface demonstrating self-aggregation of amphiphilic molecules.

Most surfactants are derived from petroleum feedstocks and as the world turns away from the petrochemical industry sustainable alternatives are highly sought.[21] Current issues are not just limited to the production of modern surfactants, low biodegradability, ecotoxicity and bioaccumulation are all additional concerns. In the past safety concerns have resulted in widespread market withdrawal for certain surfactants. Nonylphenol and nonylphenol ethoxylated surfactants are a good example of such action being taken. These examples were widely restricted in the EU from 2003 having been found to produce toxic byproducts in their degradation pathway.[22, 23] There are numerous types of commonly employed surfactants. These can be classified based on their charge characteristics for example being anionic or cationic. (***Figure 4***).[25] The nature of the polar head often dictates the application of the surfactant. Anionic and non-ionic are the most common types of amphiphiles with non-ionic surfactants seeing extensive use as wetting agents and as food ingredients. Anionic surfactants can be found in detergents and shampoos.[26]

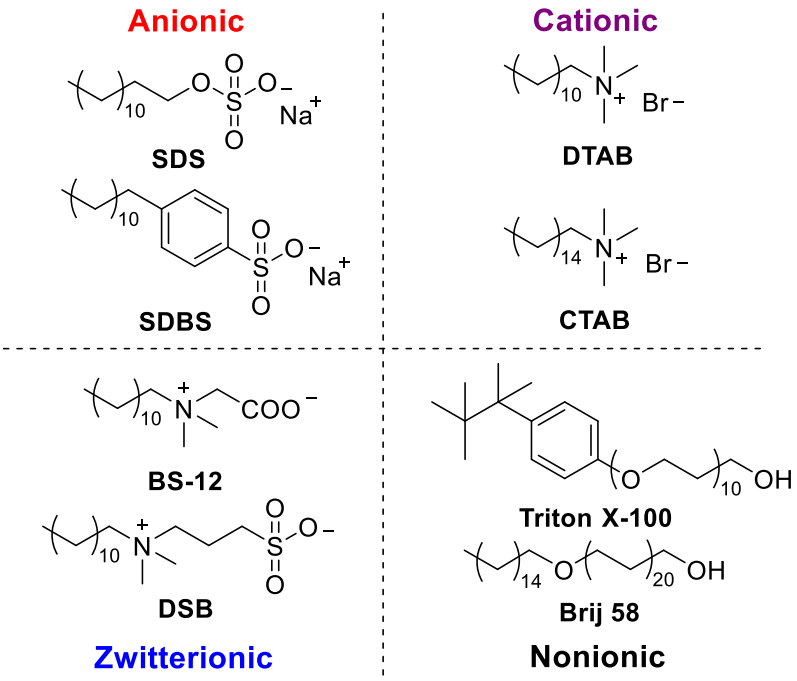


Figure 4: Common types of traditional amphiphilic surfactant molecules

In response biosurfactants have been put forward as a promising alternative to petrochemical derived surfactants. This class of amphiphilic molecules typically originate from biological sources. Biosurfactants can be classified according to their chemical components. GL surfactants are made up of one or more carbohydrates and a fatty acid chain that can vary in length and number. Lipopeptides and lipoproteins are further examples made up of cyclic peptides linked *via* a fatty acid chain.[27] Whilst solving the issues surrounding biodegradability and sustainability, the lack of current widespread adoption would suggest underlying issues. Indeed, high costs relating to purification and scaled productions are seen as commercial barriers. To be more specific, high levels of foaming during processing, lower yields and affordable raw materials are limitations to scaling production of biosurfactants in a cost-effective manner.[28] Over the last century modern surfactants have been refined to a high degree and as such they are well developed and display high levels of efficiency. Biosurfactants are commonly quoted as possessing greater efficacy over a broader range of pH and temperature compared with their synthetic equivalents.[29] The chemical space is still relatively infant and further structure function studies are required to fully unlock the full potential of biosurfactants. Some example studies have found that GL-based surfactants are more efficient in some laboratory experiments than synthetic counterparts. Being found to outcompete common synthetic surfactants such as Tween 60 and SDS demonstrating improved surface activity.[30]

1.4 Synthesis of glycolipids and glycosylation

Glycosylation is best described as a coupling reaction between a glycosyl donor and a glycosyl acceptor. The glycosyl donor is the electrophile bearing a leaving group at the anomeric position and the glycosyl acceptor is the nucleophile bearing at least one free

OH, NH or SH. As sugars bear multiple nucleophilic sites, suitable protecting group chemistry is typically required. Controlling regioselectivity and stereoselectivity in glycosidic bond formation is a difficult challenge as each time a new glycosidic linkage is formed, so is a new stereogenic centre (***Figure 5***).

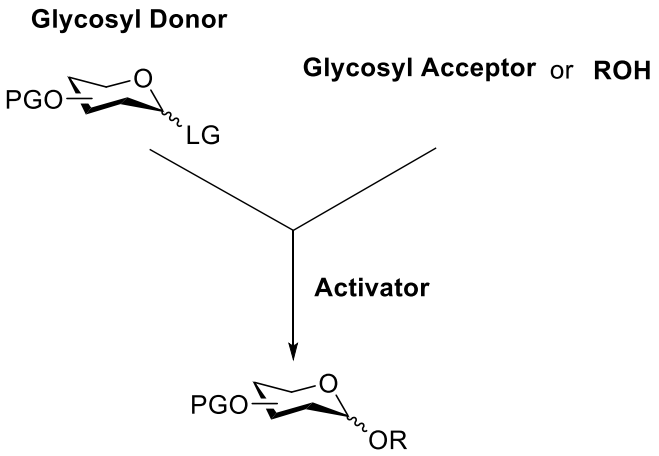
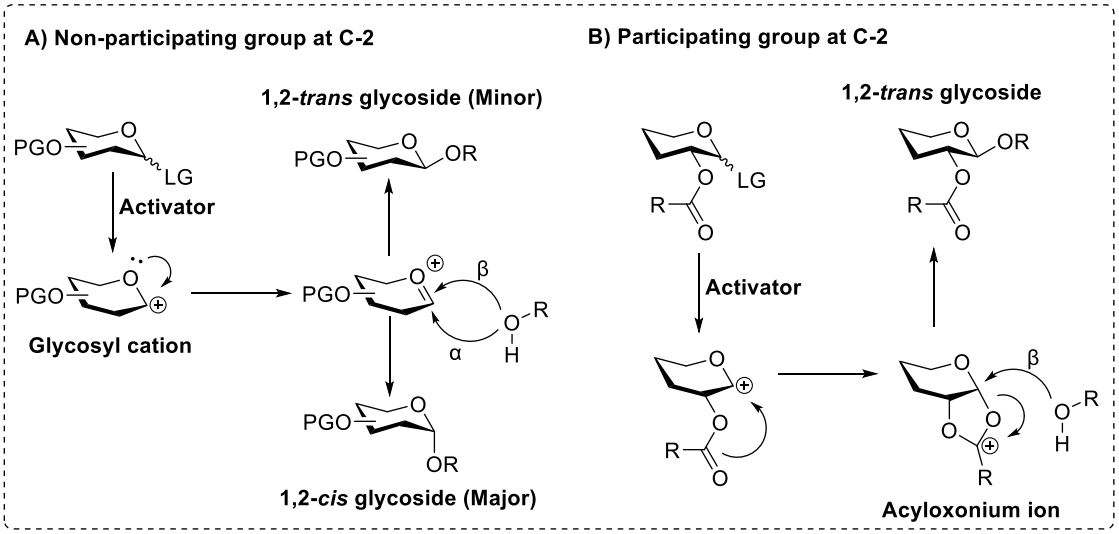


Figure 5: Outline of chemical glycosylation (PG: Protecting group, LG: Leaving group)

A key consideration when planning glycosylation reactions is the identity of the protecting group (PG) at C2. If the PG present at C2 is a participating group, then the stereoselectivity can be controlled as a result of neighbouring group participation (NGP). For example, if C2 is protected by an ester group then an acyloxonium ion can be formed; this limits the incoming nucleophile to only being able to attack from the opposite face affording the 1,2-*trans*- glycoside as the product (***Scheme 1***).[30a] However If the group is non-participating for example, such as benzyl ethers, then the oxocarbenium ion formed will not be stabilised. As a result, nucleophilic attack may happen from either the top or bottom face of the oxocarbenium. The major product in this case will be the thermodynamically favoured 1,2-*cis*-glycoside glycoside resulting from the anomeric effect, however there will still be some amount of the kinetically favoured the 1,2-*trans*- glycoside formed not allowing absolute stereoselectivity (***Scheme 1***).[30b]



Scheme 1: General glycosylation mechanism and influence by the group at C2.

The anomeric effect described in its simplest form is the tendency of an electronegative substituent at the anomeric carbon to take up an axial position.[30c] There has been a variety of different explanations put forward for the anomeric affect, two of the most widely accepted are the hyperconjugation interaction and dipole electrostatic interaction theory.[30d] The hyperconjugation explanation is based on molecular orbital interactions and suggests that hyperconjugation of the unshared electrons present on the heteroatom with the σ* orbital of the C-X bond takes place; this produces a stabilising affect favouring the axial conformation (***Figure 6***).

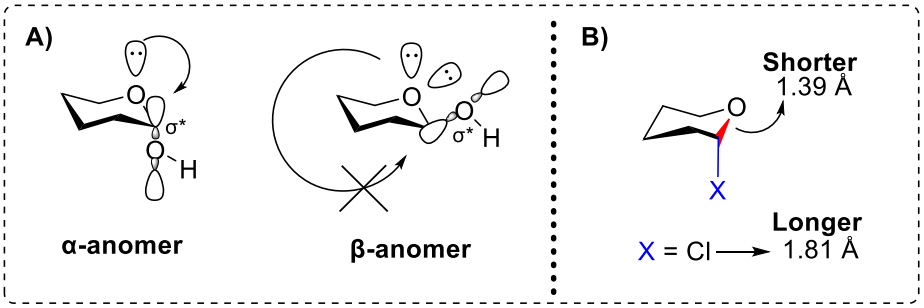


Figure 6: A) Hyperconjugation rationalisation for the anomeric effect; B) Impact of the anomeric effect on bond length.

The hyperconjugation explanation is supported by differences in observed bond lengths. It has been determined through investigation that the C1-O bond is shorter than standard, and the C1-X bond is longer than standard for a variety of anomeric functionalities.[30d] The dipole electrostatic theory put forward suggests that the energy difference between axial and equatorial conformations is the result of dipole moments. In the equatorial position the dipoles of both heteroatoms are partially aligned, leading to repulsion. Conversely in the axial position the dipoles are in opposing positions leading to a more stable conformation (***Figure 7***).

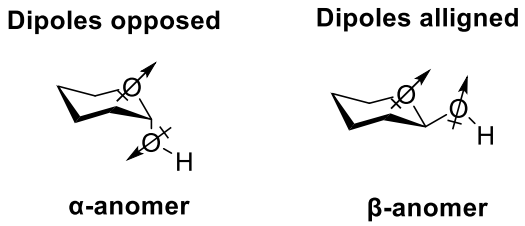
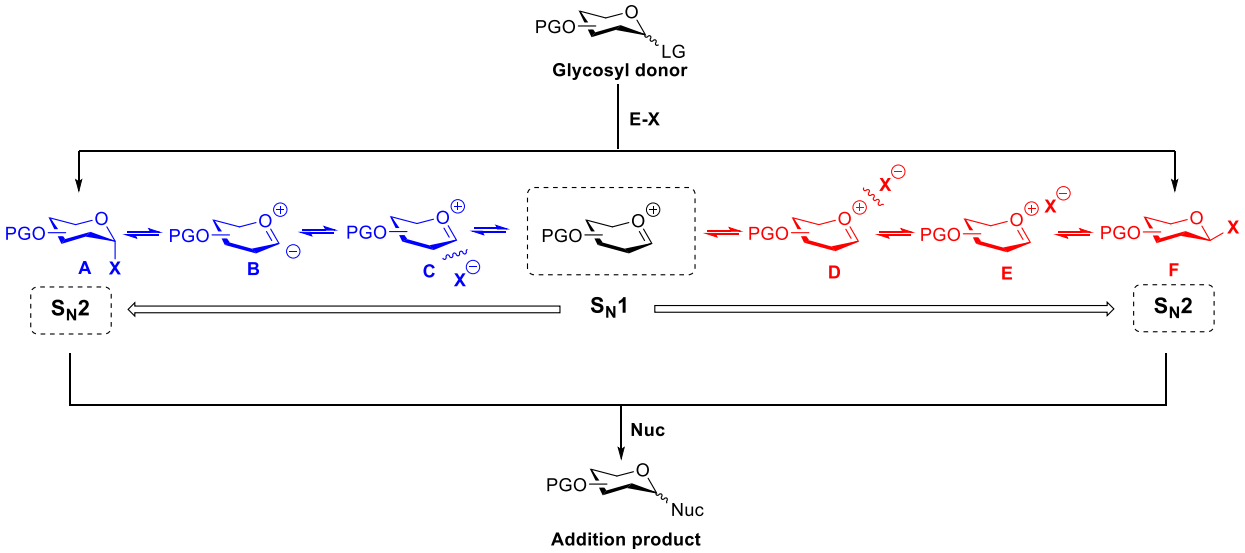


Figure 7: Dipole interactions that rationalise the electrostatic theory explanation for the anomeric effect.

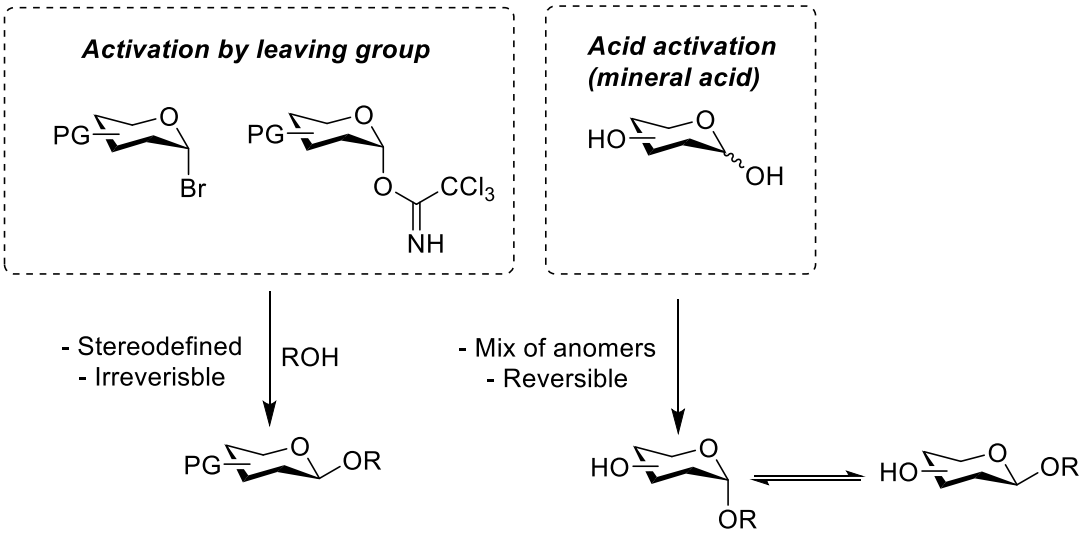
The mechanism of glycosylation is also crucial in determining the stereochemical outcome. Glycosidic linkages can be formed through either an S_N1 pathway or alternatively a S_N2 pathway, although the interplay between both is often described as a spectrum. The S_N2 route is typified as being associative in nature with reactive species resulting from glycosyl donor activation being covalent in nature. Glycosylation's proceeding *via* an S_N2 pathway see an inversion of stereochemistry at the anomeric position (***Scheme 2***). On the other end of the spectrum, the S_N1 pathway is described as dissociative involving oxocarbenium ion interactions with either solvent molecules or counter-ions. In these instances, the stereochemical outcome is variable, solvent separated ion-pairs (SSIP) have no effect on reaction outcome. Lying in-between counter-ion pair interactions (CIP) with the oxocarbenium ion are typically closer in nature, and

so they can have an influence on stereochemical outcome. Studies have revealed that weak nucleophiles are more likely to proceed *via* the S_N1 pathway, this is reversed for strong nucleophiles reacting *via* the S_N2 pathway.[30e]



Scheme 2: A guide to the potential reactive intermediates following activation of a glycosyl donor. (A) covalent α-intermediate; (B) α-CIP; (C) α-SSIP; (D) β-SSIP; (E) β-CIP; (F) covalent β-intermediate; PG, protecting group; Nuc, nucleophile; E-X, promoter system.[30f]

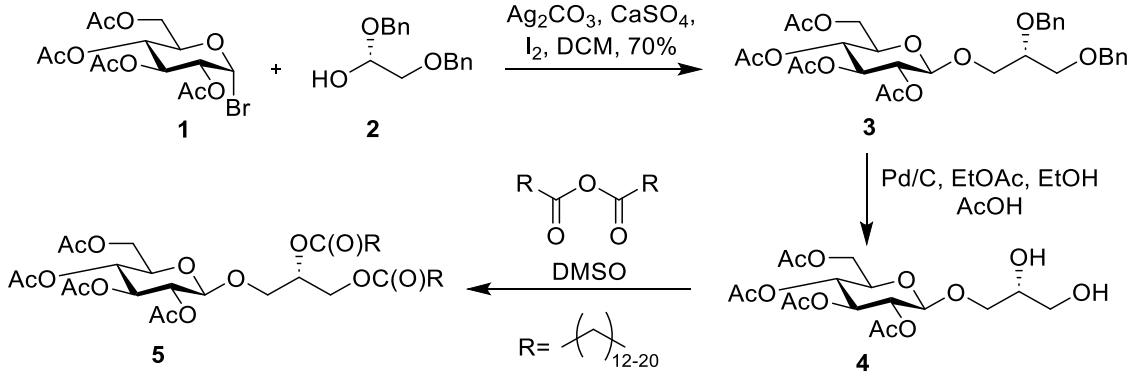
Typically, chemical glycosylation strategy can be separated into two processes. Those that deliver stereodefined products and those leading to complex oligomer equilibria, for example Fischer glycosylation.[31] This type of acid-catalysed glycosyl exchange typically generates an anomeric mix of alkyl glycosides from unprotected starting materials. Stereospecific methodologies rely on substitution of suitably activated carbohydrates for example trichloroacetimidates or glycosyl halides. Access to such structures typically requires protecting groups extending the synthetic route (***Scheme 3***).[32]



Scheme 3: Overview of glycosylation strategy for accessing long chain alkyl GLs with selected examples of donor type.

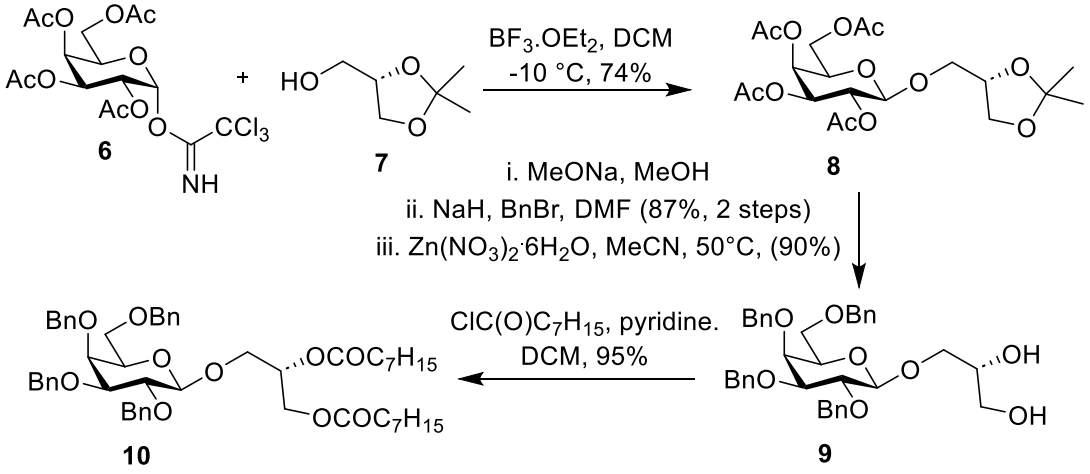
Acid-catalysed approaches benefit from short glycosylation routes, easy operation and cost effectiveness making this approach more suitable for industrial scale production.[33, 34] One example of an employed catalyst includes sulfuric acid amongst other mineral acids. Whilst being effective these cannot be recycled and are classed as hazardous. Recent advances have been made in the development of reusable solid superacid catalysts.[35] To uncover the biological role or structure function relationships for GLs defined structures are a necessity.

In this case stereospecific glycosylations are required. Relying on glycosyl bromides and the Koenigs-Knorr method of glycosylation, glycosidic linkages can be created. Mannock and co-workers previously reported the synthesis monoglucosyl diacylglycerols using the Koenigs-Knorr method for the key glycosylation step and achieving a yield of 70%.[36] From **3**, hydrogenolysis and acylation of a fatty acid grants access to varying β-glycoglycerolipids of choice (***Scheme 4***).



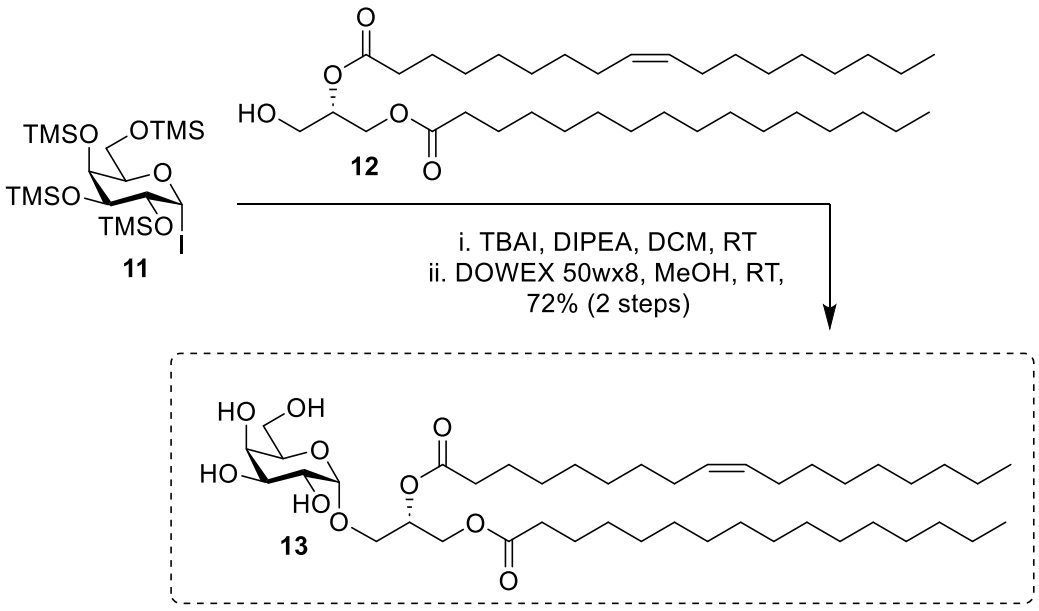
Scheme 4: Mannocks approach for the synthesis of β-glycoglycerolipids using glucosyl halide **1** as a donor (all yields not reported).[36]

TCA donors have also been employed for the synthesis of glycoglycerolipids. TCA donors can be readily synthesised from the corresponding hemi-acetal using trichloroacetonitrile and base. Anomeric configuration of the donor can be dictated by choice of base with potassium carbonate (K_2CO_3) delivering β-TCA donors and DBU providing α-TCA donors. Amara and co-workers used TCA donors to access **8** by glycosidating acetonide protected glycerol derivative **7** achieving a yield of 74%.[37] Replacement of the pyranose protecting groups (PGs) with benzyls and removal of the acetonide *via* zinc nitrate hexahydrate allowed for esterification using octanoyl chloride delivering **10** in 95% yield.



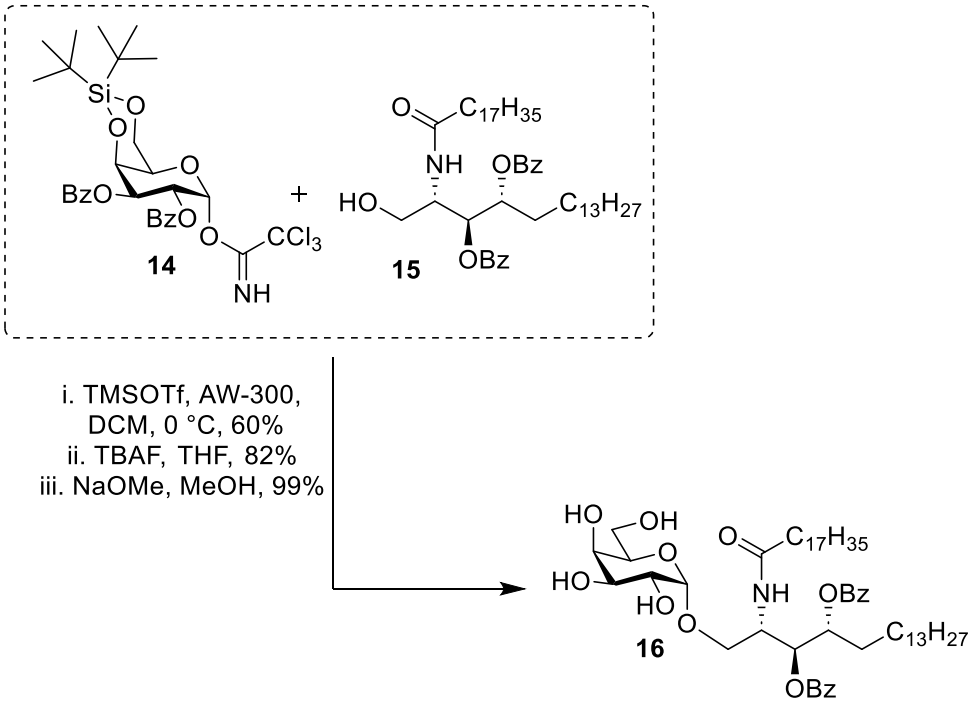
Scheme 5: Amaras approach for the synthesis of β-monogalactosyl diacylglycerol **10** using trichloroacetimidate **6**.[37]

This approach of building up the lipid moiety post glycosylation is sometimes preferred. By carrying out the key glycosylation using a simpler alcohol improved yields can be achieved.[38] This is especially the case when ester protecting groups are in use to direct the stereochemical outcome. Despite providing assured stereochemistry, esters have the disadvantage of deactivating the glycosyl donor making glycosylation more challenging. Examples in ***Scheme* 4** and **5** targeted only the β anomer, when the α configuration is desired, a different approach is typically taken. For example, utilising *O*-TMS protected glycosyl iodide **11** biologically relevant α-linked galactosyl ceramides were accessed in minimal steps with high stereoselectivity (***Scheme 6***).[39] Silyl groups provide increased donor reactivity and allow for direct glycosylation of the complete lipid moiety in high yield. *O*-TMS groups can be readily removed under mildly acidic conditions not affecting unsaturation unlike benzyl groups that require hydrogenation. Use of TBAI accelerates the glycosylation and determines α-stereoselectivity through *in situ* anomerization.[40]



Scheme 6: Kulkarni's approach for the synthesis of α-glycoglycerolipids using *O*-TMS protected glycosyl iodide **11** as a donor.[39]

Silyl groups provide increased donor reactivity and allow for direct glycosylation of the complete lipid moiety in high yield. *O*-TMS groups can be readily removed under mildly acidic conditions not affecting unsaturation unlike benzyl groups that require hydrogenation. Use of TBAI accelerates the glycosylation and determines α-stereoselectivity through *in situ* anomerization.[40] Another method previously employed for α-selective glycosylation of ceramides includes use of a di-*tert*-butylsilylene (DTBS) group. When protecting *O*-4, 6- positions of galactose this PG hinders attack from the β-face through steric effects.[41] High levels of α-selectivity can still be achieved even with a NGP benzoyl group at C2. Kimura and co-workers used this method to synthesise isoglobotriosylcreamide (igB3) achieving a reasonable yield for galacto-ceramide building block **16** (60%) with complete regioselectivity for the α-anomer in the key glycosylation step from TCA donor **14** (***Scheme 7***).[42]



Scheme 7: Kimuras synthesis of α-galactosylceramide **16** using DTBS-directed α-selective glycosylation.[42]

These highlighted examples demonstrate that the approach for the synthesis of GL's is often dictated by the properties of the target molecule. Saturation of the lipid, donor reactivity and desired stereochemistry are the most important factors to consider when developing an appropriate method for glycosylation.

1.5 Structure function relationships

When carrying out research into new materials, developing an understanding of their structure-function relationships is a key step in determining direction when designing synthetic analogues for a particular task. The structural properties of glycans can be partly attributed to a dense and complex network of intra-and intermolecular forces. The hydrogen bonds formed are a consequence of the different functionalities present on the monomeric units and their position in space. One of the issues in understanding these relationships is the difficulty in synthesising a large array of carbohydrates with different functionalities. Each glycan developed towards a library typically requires a lengthy and complex synthetic route. When carrying out structure function relationship studies a larger sample size will inevitably give a deeper understanding and makes it more likely that any correlations will be identified. Synthesising hundreds or thousands of individual glycans for analyses would take an impractical amount of time and isn't feasible, therefore sample size will always be limited. As such, a deeper consideration is required when synthesising modified carbohydrates to uncover elusive structure function relationships.[43]

Altering the functionality of glycans can be done by either modifying monosaccharides for glycan assembly into longer chains or by directly modifying pre-assembled polysaccharides. For example, a commonly employed method is carboxymethylation. This introduces a carboxymethyl group and is a known to increase the water solubility of

several polysaccharides including cellulose. Work by Dr Yang Liu utilised carboxymethylation to successfully increase the bioactivity of LEP-1b, a polysaccharide that helps mitigate chronic renal failure.[44] An elegant example of structure-property correlation development was previously reported by Martina Delbianco and co-workers.[45] This work detailed a systematic approach to hydrogen bond disruption, synthesising a range of cellulose carbohydrate materials through automated glycan assembly (AGA). These tailor-made oligosaccharides contained differentially modified motifs including deoxygenated, fluorinated and carbomethoxy monomers. (***Figure 8***). Expediting the synthesis by use of AGA allowed for a relatively large library to be assembled. Following structural analysis using techniques such as X-ray crystallography and NMR the authors uncovered trends related to the type of modification. For example, they found all unnatural analogues to possess more flexible backbones and fluorinated derivatives to be shorter overall (end-to-end distance). It is hoped that by conducting these studies in the future novel biomaterials may be engineered to best suit their purpose.

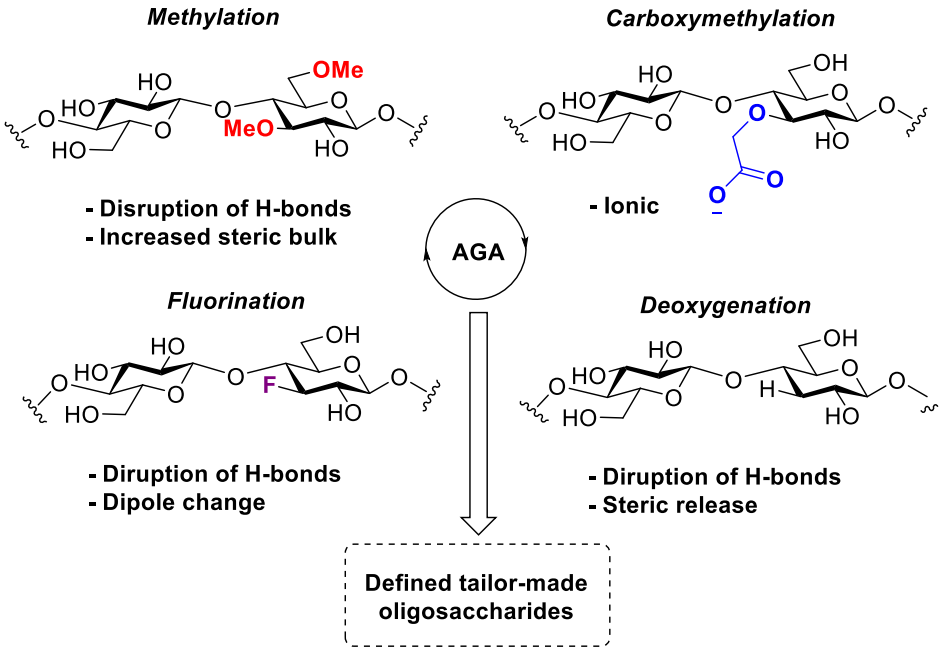


Figure 8: Systematic approach to study structure–property correlations in carbohydrate material, highlighting modifications such as fluorination and methylation for cellulose derivatives.[45]

1.6 Fluorination of Carbohydrates: influences on physical properties

Fluorine substituted carbohydrate derivatives have been explored quite extensively due to the beneficial properties this modification can provide. Fluorine is the most electronegative element and as such its introduction to a molecule can have profound effects. Whilst being considered a bio isostere of oxygen, when compared they are similar in size but a large difference in ionisation potential exists. Whilst oxygen can act as a hydrogen bond donor and acceptor fluorine can only act as an acceptor (***Figure 9***).[46] Although being capable of accepting hydrogen bonds, the high ionisation potential of the fluorine lone pairs means they are weak in this respect.

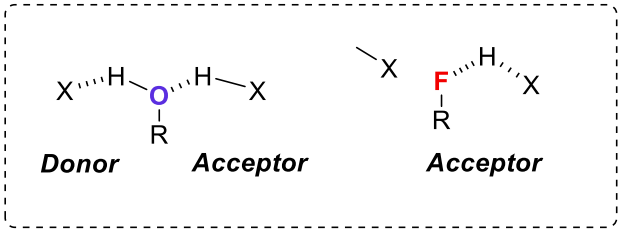


***Figure 9*:** Hydrogen bonding capability of oxygen and fluorine.

As a consequence, C-F bonds are useful for disrupting hydrogen bond networks and epitope mapping.[47] Generally, the introduction of fluorine does not have a significant impact on the conformation of a pyranose ring. Numerous deoxy fluorinated carbohydrates derivatives have been synthesised over the years with crystal structures revealing the configuration to remain $^{4}C_{1}$.[48, 49] This remains the case even for extreme examples with a hexafluorinated pyranose being previously reported and found to be in the $^{1}C_{4}$ conformation (***Figure 10***).[50]

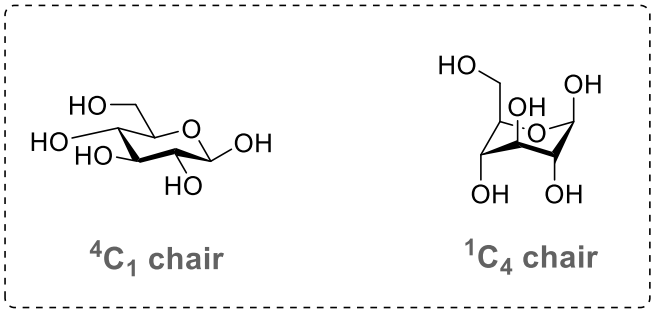


Figure 10: $^4C_1$ and $^1C_4$ chair conformations of glucose**.**

Another well-known consequence of deoxyfluorination is an increase in lipophilicity. Lipophilicity is commonly referred to as the ability of a compound to dissolve in fat, oils and lipids. Lipophilicity can be measured experimentally and given a defined value, quantified by the partition coefficient (*P)* between octanol and water.[51] Deprotected carbohydrates possess a number of hydroxyl groups and are very hydrophilic, in some circumstances increased lipophilicity serves as an advantage making deoxy fluorination an ideal modification.[51]

1.7 Thiol modification of carbohydrates

Glycomimetics that incorporate sulfur have received considerable attention. The choice of sulfur for replacement of native oxygen atoms can be attributed to a number of provided benefits. In the case of *S*-linked thiooligosaccharides a reduced susceptibility to enzyme and acid hydrolysis is observed. This makes them ideal candidates for use as tools within glycobiology offering increased catabolic stability. *S*-glycosidic linkages possess similar conformational preferences to *O*-glycosides when in solution and when complexed with a protein not affecting binding processes.[52] The C-O-C bond and C-S-C bond differ in length with the former being longer. This additional length allows for greater flexibility of the glycosidic linkage. Because of these attributes

thiooligosacharides have been put forward as promising candidates for the preparation of carbohydrate-based therapeutics.

Varela and co-workers previously reported the synthesis of *S*-linked thiodisaccharides **17** and **18** (***Figure 11***).[53] Both examples were found to inhibit *E. coli* β-galactosidase with structure **18** proving to be the most potent as a non-competitive inhibitor (K_i = 95 μM). Glycosidase inhibitors are of particular interest as they provide insight into binding and recognition events and in some instances provide therapeutic effects.

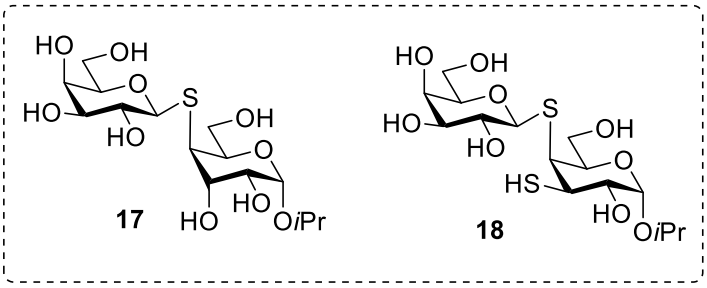


Figure 11: Structures of *S*-linked thiodisaccharides **17** and **18**.

Further work by Lindhart and co-workers reported the first *S*-linked polysaccharide heparinase inhibitor.[54] Using a chemoenzymatic approach the authors synthesised an unnatural *S*-linked heparan sulphate (HS) sequence utilising unnatural and natural UDP sugars catalysed by heparosan synthase. Interestingly the authors found the 4-SH modification served as an acceptor allowing for the polymerisation of the *S*-linked backbone. The authors found reported their *S*-linked HS sequence to be a competitive inhibitor of heparinase speculating the C-S-C bond allows for a mimicking of the transition state of HS undergoing cleavage in the active site. This was rationalised as a consequence of increased bond flexibility and or ring puckering. Heparinase overexpression is widely implicated in aggressive cancer growth and so effective inhibitors are regarded as an emerging treatment option.[55] Incorporation of a thiol moiety also allows for simple labelling/conjugation with any thiol-reactive

maleimide/iodoacetamide type compounds.[56] This allows incorporation of useful functionalities such as fluorescent dyes or biotin.[57]

1.8 Project overview and aims

The main goal of this project is accessing a range of beta linked oleyl GLs with various pyranose-component modifications in collaboration with CRODA. GLs have been put forward as promising biosurfactants however the chemical space is however relatively infant. Through the introduction of differing heteroatoms (Fluorine and Sulfur) at various positions of the pyranose ring, structure function correlations can be developed for this type of amphiphilic molecule. Hypothesising that hydrogen bond disruption and disulfide formation will result in different types of self-aggregation within aqueous media. Access to oleyl β-glucosamine derivatives would also provide an entry point for new molecular probes to study related glycolipid metabolic pathways. Through conjugation at the amine a suitable photoaffinity label could be introduced. Allowing for the capture of intracellular interactions for further analysis by HRMS and identification of protein binding partners.

Previous reports for the glycosidation of oleyl alcohol are limited and extend only to simple per-acetylated donors. As such this work aims to investigate other types of glycosyl donor including thioglycosides and trichloroacetimidates. Hoping to develop a robust methodology method to glycosidate oleyl alcohol with more exotic glycoysl donors. Regioselective introduction of heteroatoms within the pyranose component requires the development of suitable protecting group chemistry also. Efficient and optimised access to these novel materials and their precursors will provide wider applicability to the development of glycomimetic beyond GLs.

Chapter 2

Chemical Synthesis of Modified Oleyl Glucosides

2.0 Aims and Introduction

This chapter will focus on the synthesis of oleyl GLs with a range of pyranose-component modifications. These modifications include fluorination at C6 and C4 within glucosides, glucosamines, and glucuronic acid derivatives **19**-**24**. (***Figure 12***). A C4 sulfurhydryl modified glucose target **24** was also explored. Oleyl glycosides offer an interesting prospect as biosurfactants and for probing glycosphingolipid metabolism.[38] The pyranose component of oleyl glucosides allows for modification to explore different biosurfactant properties.[58] Biosurfactants offer a number of advantages when compared with traditional surfactants, being non-ionic, non-toxic, and also biodegradable.[59] As mentioned in section **1.6**, fluorination of carbohydrates can result in different structural properties and effect molecular interactions especially in the case of hydrogen bonding.[60]

Target Oleyl Glucosides

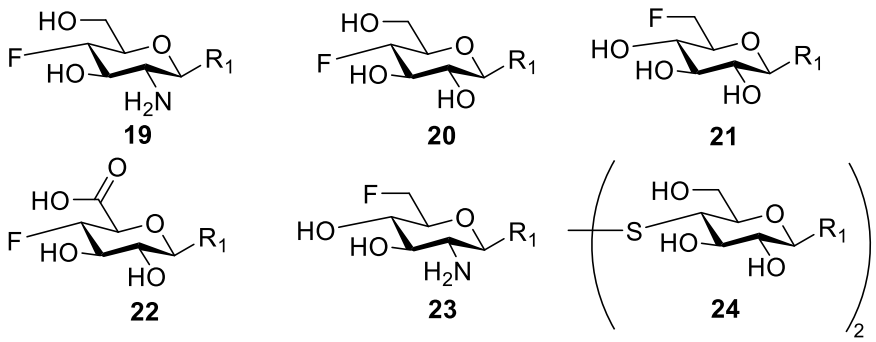


Figure 12: Target oleyl glucosides and including non-native heteroatom introduction.

As such, C4 and C6 derivatives were targeted to explore this chemical space. The sulfhydryl handle of **24** will offer the potential of further labelling/derivatisation using

maleimide type compounds.[61] In the pursuit of modified oleyl GLs a synthetic investigation was performed to establish a reliable glycosylation method to access oleyl β-glucosides.

2.1 Oleyl glycosylation method development

Fischer glycosidation of the corresponding alcohols has been previously implemented for accessing long chain alkyl glycosides.[31, 62] More recently, examples of oleyl glycoside formation *via* the free sugar using H_2SO_4-silica and $SnCl_4$ activation of the glycosyl chlorides have proven successful (***Figure 13***).[63, 64, 65]

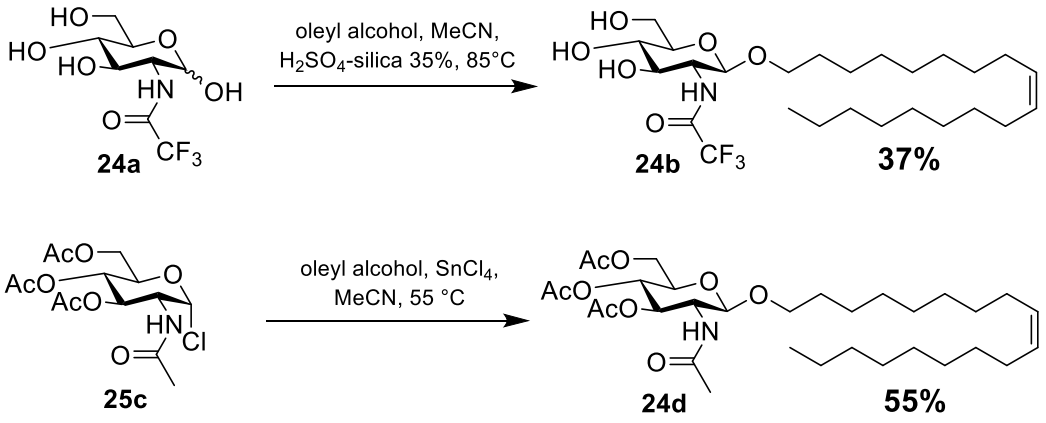
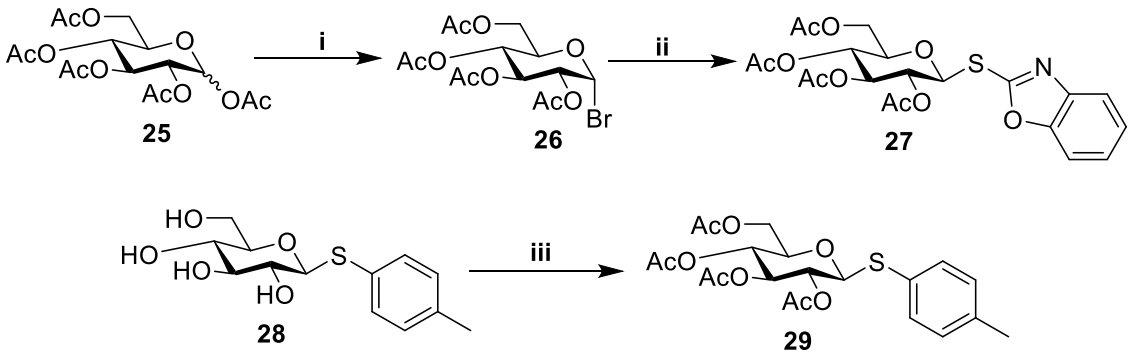


***Figure 13*:** Selected examples of oleyl glycoside synthesis using chemical methods.

With previous successes in mind, a synthetic investigation began to establish a reliable glycosylation method for accessing appropriately protected oleyl β-glucosides with the intention of extending this to non-native pyranose modified oleyl glucosides. Esters were selected as the monosaccharide protecting group due to their ability to influence the desired stereochemical outcome, ease of removal and compatibility in deprotection likely not affecting the unsaturation within the oleyl chain. Accordingly, different glucosyl anomeric leaving groups were selected and glycosidation of oleyl alcohol was explored.

2.2 Thioglycoside donors with NIS/Lewis acid activation

The initial approach centred around the use of thioglycosides; this decision was based on the ease of handling, long shelf life and mild activation conditions this class of donor offers.[66] Two thioglycoside donors were initially selected for screening: per-*O*-acetylated *p*-tolylthio (STol) donor **29** and a *S*-benzoxazolyl (SBox) counterpart **27**. Donor **27** was included to gauge the effect of donor reactivity, with the SBox donor being more reactive.[67, 68] Synthesis of the SBox donor was achieved in 2 steps, first treating per-*O*-acetylated glucose with HBr in AcOH giving the corresponding α glycosyl bromide **26**. Without intermediate purification, a thioglycosylation utilising 2-mercaptobenzoxazole provided donor **27** in 80% yield over two steps. Reaction success was supported by the appearance of aromatic chemical shifts in the ^{13}C NMR spectrum [δ_C 110.2-152.0 ppm]. To access donor **29**, acetylation of commercially available *p*-tolyl 1-thio-β-D-glucopyranoside **28** gave **29** in 91% yield (***Scheme 5***).



Scheme 8: Synthesis of per-*O*-acetylated SBox and the STol donors **27** and **29**. Reagents and conditions. i. HBr in AcOH 33%wt, DCM, 0 °C to RT, ii. 2-mercaptobenzoxale, K_2CO_3, acetone, 80% over 2 steps iii. Ac_2O, pyridine, 0 °C to RT, 91%.

With a stock of both donors in hand, Lewis acid promoted glycosidation of oleyl alcohol was attempted. Donor **29** was screened first (***Table 1***, ***entry 1***) following general procedure **A** (See section **6.2)**. The first set of activation conditions investigated involved

the use of *N*-iodosuccinimide (NIS) and various Lewis acids: TMSOTf, $Cu(OTf)_2$, AgOTf and $BF_3{\cdot}OEt_2$.

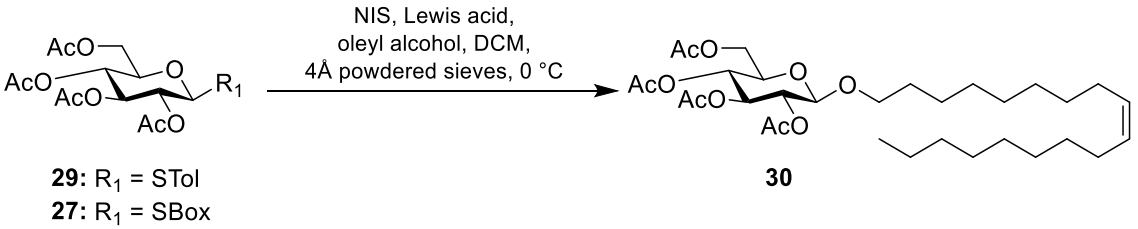


Table 1. Conditions for glycosylation of oleyl alcohol with thioglycoside donors using NIS/Lewis acid activation [A]

Entry	Donor	Lewis acid [1 equiv.]	Pre-activation [mins] [B]	NIS [equiv.]	Yield **30** [%] [C]
1	**29**	TMSOTf	n/a	1.5	n/a
2	**29**	$Cu(OTf)_2$	n/a	1.5	n/a
3	**29**	AgOTf	n/a	1.5	n/a
4	**29**	$BF_3{\cdot}OEt_2$	n/a	1.5	11
5	**29**	$BF_3{\cdot}OEt_2$	10	1.0	18
6	**27**	$BF_3{\cdot}OEt_2$	10	1.0	22

[A] For reaction conditions see general procedures **A** and **B**, [B] Time allowed to pass after until addition of oleyl alcohol following the Lewis acid, [C] Isolated yields of pure products after column chromatography.

The only entry using STol donor **29** to successfully deliver target alkyl glycoside **30** made use of $BF_3{\cdot}OEt_2$, albeit in low yield (***Table 1***, ***entry 4***). TLC analysis of these initial glycosylations provided useful insight. The appearance of multiple new spots possessing higher R_f values and consumption of oleyl alcohol pointed towards acceptor-based side reactions. ^{1}H NMR analysis of the isolated materials revealed only chemical shifts in the aliphatic region between δ 0.78 – 3.09 ppm; the lack of any other prominent chemical

shifts supports that the side reactions being observed were oleyl based. One possible explanation is undesired iodonium ion formation across the double bond in oleyl alcohol, followed by either inter or intramolecular nucleophilic attack by the alcohol.

In an effort to reduce these suspected oleyl-based side reactions, two modifications were implemented. First an approach of pre-activation was put into practice. Secondly, the equivalents of NIS were reduced from 1.5 to 1.0. When the glycosylation was carried out with pre-activation, donor **29** yielded 18% of target GL **30** (***Table* 1**, ***entry 5***). Again, starting material remained, suggesting reformation of the donor was occurring due to a combination of low donor and acceptor reactivity.[69] When pre-activation was applied to donor **27** there was a slight increase in yield, up to 22% (***Table 1***, ***entry 6***). As these combined modifications had limited effect in increasing yield or limiting side product formation a different method was investigated.

2.3 Thioglycoside donors and Tf_2O/sulfoxide activation

The next method to be implemented was first presented in 1989 by Kahne.[70] This work made use of triflic anhydride (Tf_2O), a glycosyl sulfoxide and 2,4,6-tri-*tert*-butylpyrimidine (TTBP) acting as an acid scavenger. This method avoided use of NIS and typically offered higher yields for unreactive donors, helping combat two of the issues encountered previously. The first donor to be screened was 2**9** (***Table 2***, ***entry 1***) following general procedure **C** (See section **6.2**). When subjected to glycosylation conditions, none of the desired product was observed by TLC analysis and consumption of oleyl alcohol was again noticed. ***Table 2 entry 2*** saw limited conversion to the target GL **30** achieving a yield of 16%. One notable observation was a decrease in the number of TLC components when compared with NIS/Lewis acid activation conditions. Despite

the TLC plate showing less components, consumption of oleyl alcohol was an ever-present issue.

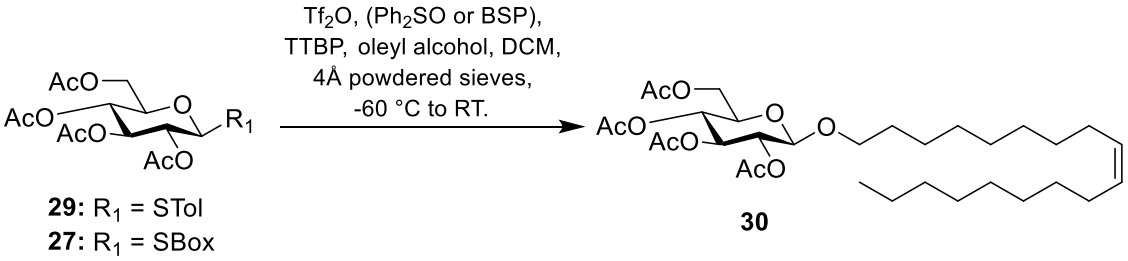


Table 2. Conditions for glycosylation of oleyl alcohol with thioglycoside donors, using Tf_2O/sulfoxide activation conditions.[A]

Entry	Donor	TTBP [equiv.]	Yield: 30 [%][B]
1	29	3.0	n/a
2	27	3.0	16
3	29	n/a	n/a
4	27	n/a	18

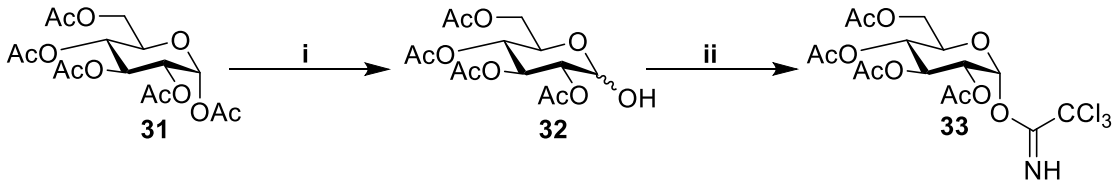
[A] For full reaction conditions see general procedure **C**, [B] Isolated yields of pure products after column chromatography.

It was suspected TTBP was driving rapid consumption of the alcohol acceptor after noticing a colour change prior to Tf_2O addition. They were deduced as being oleyl based on their low polarity running off the plate in neat hexane. A control experiment was performed without TTBP and after 1 hr of stirring, TLC analysis revealed only minor consumption of the acceptor with the majority remaining unreacted. TTBP (3.0 equivs,) was added and after 10 mins further analysis by TLC revealed full consumption of the alcohol acceptor. It is plausible to suggest the rapid consumption of the acceptor limited

opportunity for glycosylation and thus the achievable yield. A further experiment was performed, where both donors were subjected to glycosylation conditions **C** (See section **6.2**) without the inclusion of TTBP. In each case, a similar outcome was realised and only a slight increase in yield was observed for donor **27** (***Table 2, entry 4***). With yields remaining unsatisfactory utilising thioglycosides, a different donor was explored.

2.4 Trichloroacetimidate donors with TMSOTf/ PV- TSEAC activation

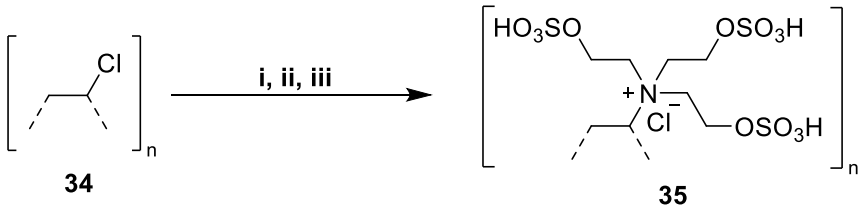
First presented by Schmidt, TCA donors are a more reactive class of donor than their thioglycoside counterparts.[71] Whilst offering more reactivity, TCA donors lack the stability of thioglycosides and their handling can be problematic, with hydrolysis occurring relatively readily. TCA donors can be synthesised from glycosyl hemi-acetals. Starting from *per*-acetylated glucose **31** selective cleavage of the anomeric acetate using benzylamine delivered hemiacetal **32** (α/β, 0.6:1) in 78% yield. The corresponding TCA donor was prepared through treatment with trichloroacetonitrile and DBU to afford α configured donor **33** (d, $^{3}J_{H1\text{-}H2}$ = 3.6 Hz), (***Scheme 9***).



***Scheme 9*:** Synthesis of trichloroacetimidate donor **33**. Reagents and conditions. i. benzylamine, DMF, DCM, 60 °C, 78%; ii. trichloroacetonitrile, DBU, MeCN, RT, 79%.

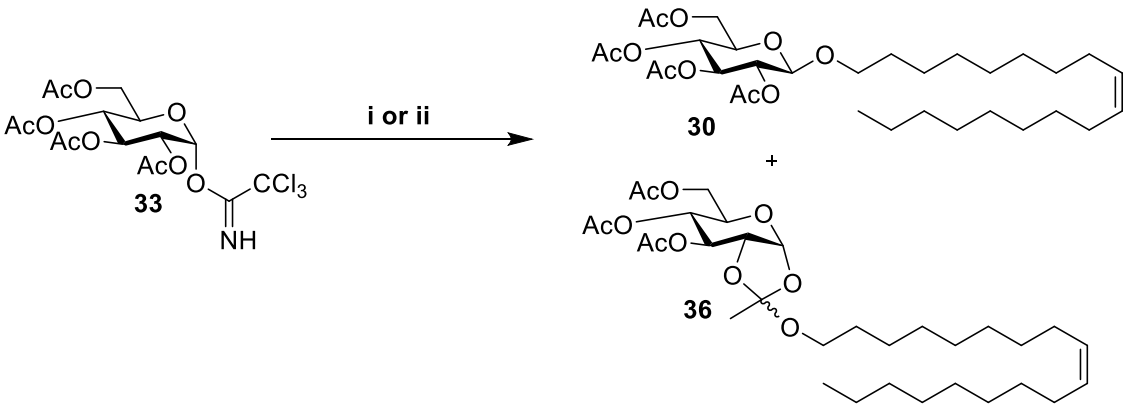
TCA donors are commonly activated by a range of Lewis acids. Alternatively, work presented by Kim and co-workers made use of polyvinyl bound trisulfonate ethylamine chloride (PV-TSEAC) acting as a Brønsted acid catalyst.[72] One benefit of PV- TSEAC is

reusability. To obtain PV-TSEAC a three-step synthesis was required starting from polyvinyl chloride (PVC) (***Scheme 10***). With the acid catalyst PV-TSEAC in hand, the glycosidation of oleyl alcohol with TCA donor **33** was attempted following general procedure **D** (See section **6.2**). In Kim's original work, 15% wt. of catalyst was selected for solventless reactions. Here it was found when carrying out small scale reactions (1 mmol), the required amount of oleyl alcohol to maintain good reaction mixing also made purification more challenging.



34 **35**

Scheme 10: Synthesis of PVC-TSEAC **35**. Reagents and conditions; i. diethanolamine, MeCN, 80 °C; ii. chloroethanol, MeCN, 80 °C; iii. chlorosulfonic acid, RT, 62% (3 steps).



Scheme 11: Glycosylation of oleyl alcohol with TCA donor **33** using TMSOTf/PV-TSEAC activation conditions. Reagents and conditions. i. oleyl alcohol, PV-TSEAC, 60 °C, toluene, 73%; ii. oleyl alcohol, TMSOTf, DCM, 0 °C, Et_3N, 55%.

Heavy streaking and a marginal R_f difference on TLC between the alcohol acceptor and desired alkyl glycoside meant multiple columns were necessary to isolate **30** in suitable purity. To this end, a solvent was introduced, and glycosylation performed varying the amount of PV-TSEAC between 5-30%wt. had differing effects on reaction outcome.

Table 3, entry 1 saw mostly SM recovered with minor amounts of both the orthoester **36** and alkyl glycoside **30** being formed. Increasing the amount of catalyst resulted in a significant increase in yield with the desired GL being heavily favoured over the orthoester (***Table 3, entry 2***). Further increasing the amount of catalyst altered this preference towards the orthoester **36** (***Table 3, entry 3***). Next, TMSOTf was screened as an activator. When carrying out the glycosylation with 0.1 equiv., the major component isolated was hemi-acetal and a small amount of **33** (***Table 3, entry 4***). A small amount of **30** was also isolated achieving a yield of 5%. Increasing the equivalents to 0.5 (***Table 3, entry 5***) saw a large increase in yield (to 49%), with a small amount of the orthoester side product also formed in a ratio of 8:2 (**30**/**36**).

Table 3. Conditions for glycosylation of oleyl alcohol with TCA donor **33**, using TMSOTf/PV-TSEAC activation conditions. [A]

Entry	Activator	[%wt.] or equiv.	Solvent	Product ratio (30:36)[B]	Yield of 30%[C]
1	PV-TSEAC	5%	Toluene	1:1	8
2	PV-TSEAC	15%	Toluene	9:1	73
3	PV-TSEAC	30%	Toluene	3:7	21
4	TMSOTf	0.1	DCM	1:0	5
5	TMSOTf	0.5	DCM	8:2	49
6	TMSOTf	1.0	DCM	8:2	55

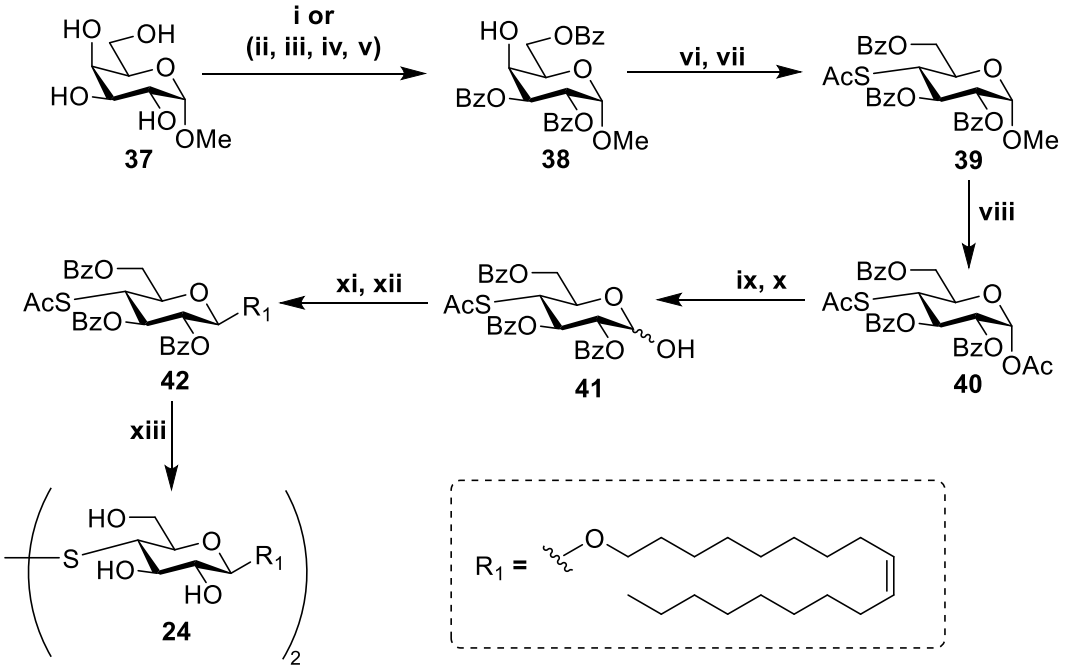
[A] For reactions conditions see general procedure **D**, [B][C] Isolated amounts of pure products after column chromatography.

The final entry (***Table 3, entry 6***) relied on a stoichiometric amount of activator with respect to the starting material, achieving the highest yield, delivering **30** in 55% yield. Notably the ratio of product to the orthoester side product remained the same.

2.5 Synthesis of di(oleyl 4-thio-β-D-glucopyranoside)-4-4'-disulfide 24

Although PV-TSEAC activation of **33** provided the highest yield for the synthesis of **30** it was decided to proceed using TMSOTf activation. This decision was based on the operational simplicity offered, with handling of the solid catalyst being more difficult. Having developed a working method for the glycosidation of oleyl alcohol the next step was application to pyranose modified derivatives. Starting with the synthesis of di (oleyl 4-thio-β-D-glucopyranoside)-4-4'-disulfide **24**. Beginning from commercially available methyl α-D-galactospyranoside **37** $Cu(OTf)_2$ promoted regioselective 4,6-*O*-benzylidene acetal formation enabled successive benzoyl protection of the remaining C2- and C3-hydroxyl groups in 85% yield (2 steps) (***Scheme 12***). Following aqueous AcOH-mediated hydrolysis of the benzylidene acetal, a final C6-benzoyl protection successfully delivered tri-*O*-benzoyl glycoside **38**.

Alternatively, a one-step procedure was performed using low temperature regioselective benzoylation to access **20** in 64% yield.[73] From **38** a two-step synthesis was carried out to install a thioacetate moiety at the 4-OH (***Scheme 12***). First, triflic anhydride (Tf_2O) was added to tri-*O*-benzoate **38** with stirring at 0 °C to successfully furnish the desired C-4 triflate. After completing an aqueous workup, a crude aliquot was subjected to ^{19}F NMR analysis, revealing a chemical shift at δ 74.2 ppm, matching previous reports.[74] Proceeding without purification, an S_N2 inversion with potassium thioacetate was performed. Appearance of a new singlet [δ 2.21 ppm] in the ^1H NMR spectrum, representing the thioactetal moiety confirmed reaction success, delivering **39** in 89% yield over 2 steps.



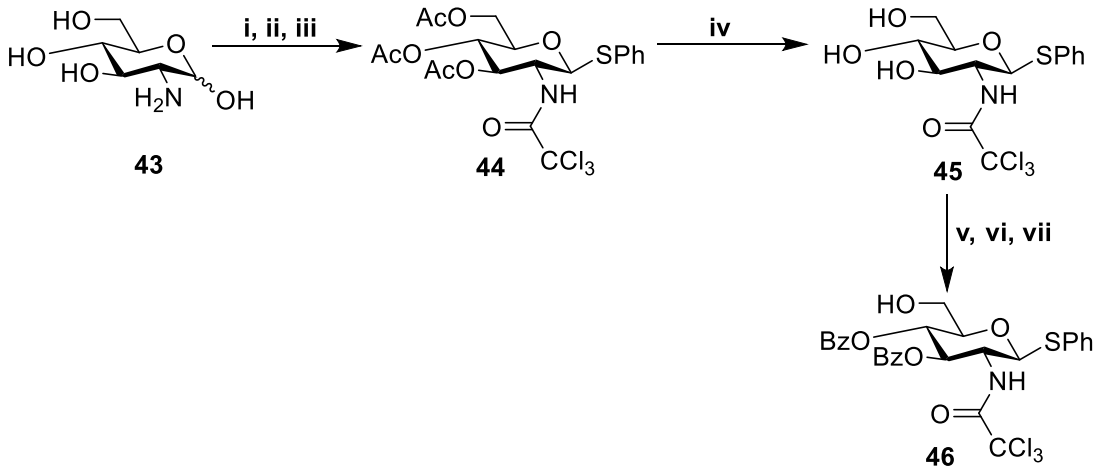
***Scheme 12*:** Synthesis of di (oleyl 4-thio-β-D-glucopyranoside)-4-4'-disulfide **24**. Reagents and conditions. i. BzCl, pyridine, DCM, -40 °C, 64%; ii. $Cu(OTf)_2$, $PhCH(OMe)_2$, MeCN, RT; iii. BzCl, pyridine, RT, 85% (2 steps); iv. AcOH, H_2O, RT; v. BzCl, pyridine, RT, 81% (2 steps); vi. Tf_2O, DCM, 0 °C to RT; vii. KSAc, pyridine, RT, 89% (2 steps); viii. Ac_2O, AcOH, H_2SO_4, RT, 66%; ix. $TiBr_4$, DCM, RT; x. Ag_2CO_3, acetone, H_2O, RT, 75% (2 steps); xi. Cl_3CCN, DBU, DCM, RT; xii. oleyl alcohol, TMSOTf, DCM, 0 °C, 37% (2 steps); xiii. NaOMe, MeOH, RT, 67%.

Methyl glycoside **39** next underwent conversion into an anomeric acetate using acetolysis. This was followed by conversion to the anomeric bromide by use of $TiBr_4$. Hydrolysis of the glycosyl bromide using Ag_2CO_3 in acetone/H_2O delivered the hemi-acetal, based on work presented by Rice and co-workers.[75] This transformation successfully delivered **41** in 75% over 2 steps from the anomeric acetate **40**. With the desired hemi-acetal in hand, glycosidation of oleyl alcohol *via* the α-trichloroacetimidate successfully installed the lipid moiety to deliver oleyl glycoside **42** in 37% yield (2 steps). A final deacetylation using Zemplén conditions furnished target alkyl glycoside **24** in 67% yield. The free sulfhydryl compound rapidly oxidised to disulfide **24**, as confirmed by HRMS [Found: $(M-H)^-$ 889.5887 $C_{48}H_{89}O_{10}S_2$ requires M^- 889.5903]. In summary the

previously developed methodology for glycosylation was successfully extended to access 4-thio derivative **24** on multi-milligram scale. The observed yield for the critical glycosylation was lower than the acetylated donor **33** previously examined (35% vs 55%).

2.6 Towards oleyl 6-deoxy-fluoro-β-D-glucosaminopyranoside 23

Progressing onto fluorinated derivatives, oleyl 6-deoxy-fluoro-β-D-glucosaminopyranoside **23** was targeted. A synthetic plan was devised starting from D-glucosamine **43**. The first step saw protection of the free amine by use of a trichloroacetamide protecting group. Acetylation of the free hydroxyl groups followed by glycosylation utilising thiophenol and TMSOTf successfully delivered thioglycoside **44** in 67% over 3 steps [$^3J_{H1\text{-}H2}$ = 10.4 Hz]. Following deacetylation, thioglycoside **45** was treated with TIPSCl and imidazole in pyridine to yield the corresponding 6-*O*-TIPS protected glycoside. Protection of 3/4-OH followed by addition of BzCl to the same pot and subsequent TIPS deprotection using TFA in THF/H_2O uncovered free 6-OH and delivered **46** in 55% over 3 steps (***Scheme 13***).



***Scheme 13*:** Synthesis of **46**. Reagents and conditions. i. trichloroacetyl chloride, MeOH, 0 °C to RT; ii. Ac_2O, pyridine, 0 °C to RT; iii. PhSH, TMSOTf, DCM, RT, 67% (3 steps);

iv. NaOMe, MeOH, RT, 95%; v. TIPSCl, imidazole, RT; vi. BzCl, RT; vii. TFA/THF/H_2O, RT, 55% (3 steps).

Two chemical shifts [δ_c 166.67 (C=O), 165.86 (C=O) ppm] displayed cross peaks to H-3 and H-4 corresponding with expected structure of **46** (***Figure 14***). Site selective fluorination at 6-OH was carried out next using DAST. After stirring overnight TLC analysis of the reaction mixture revealed several products.

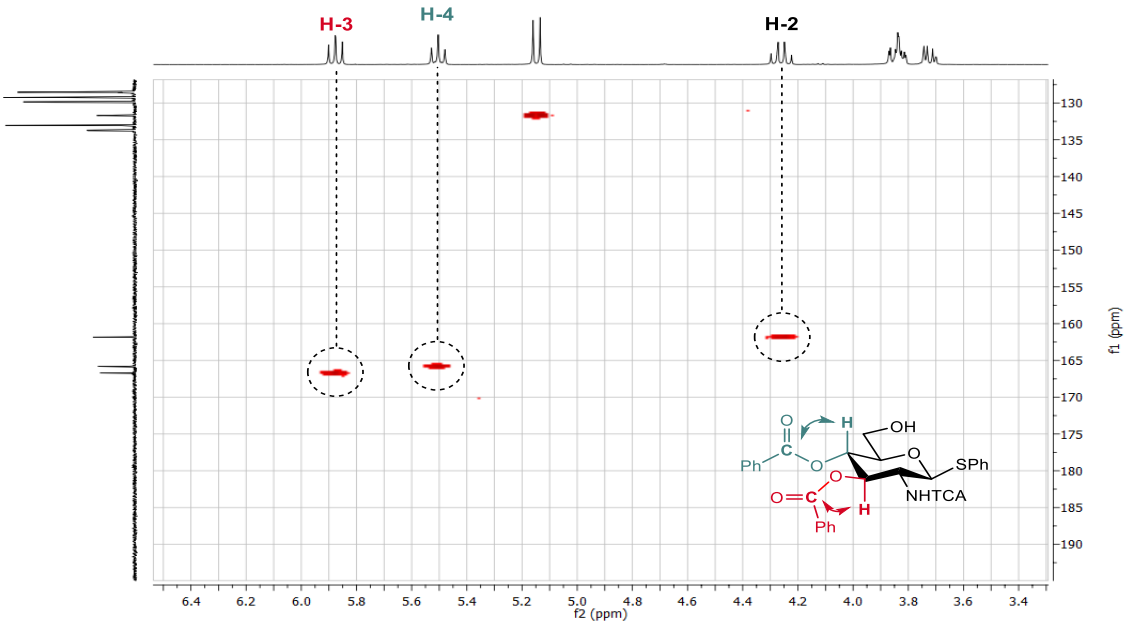
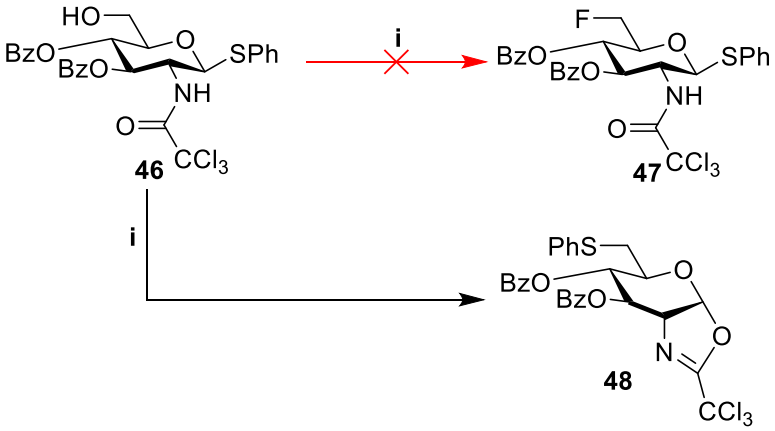


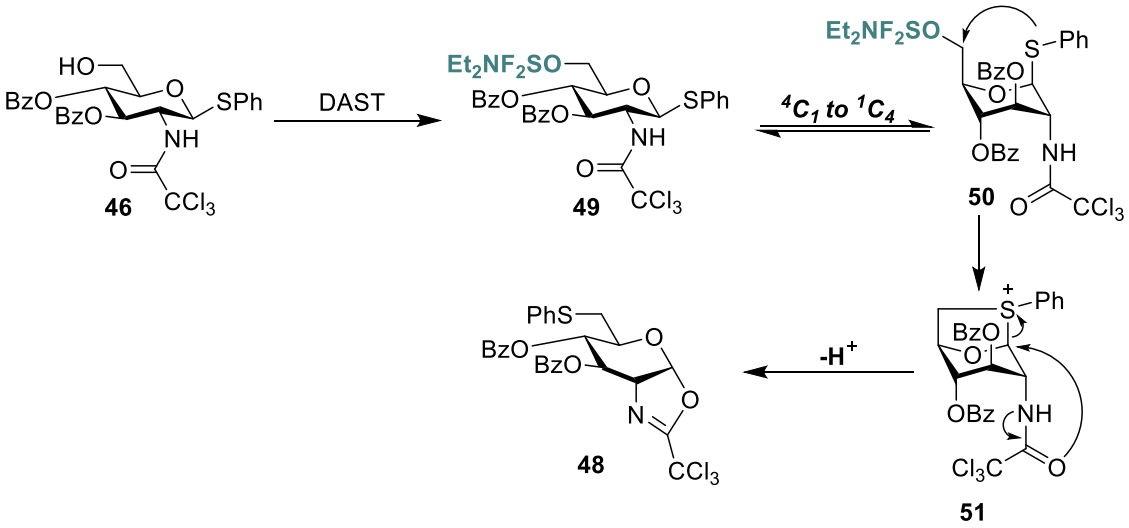
***Figure 14*:** HMBC analysis of **46** showing carbonyl cross peaks (400 × 100 MHz, $CDCl_3$).

The major component was isolated and characterised by ^{1}H NMR with the observed spectrum not matching that expected for structure **47**. More specifically the chemical shift for H-1 being unexpectedly downfield and the chemical shifts for H-6 being further up field. A clue to this was found in work presented by Lin *et al.*[76] From Lin's work, a C1 to C6 migration of the anomeric thiophenyl group was proposed. From C6–*N*,*N*-dialkylaminodifluorosulfane **50** intramolecular participation of the C2-trichloroacetyl

group forms oxazoline **48** (***Scheme 14 & 15***). This conclusion explained the observed chemical shifts for H1/H6 and was reinforced by HMBC analysis, observing crosspeaks from both H-1 and H-2 to the same ^{13}C environment (δ_C = 163.1 ppm). Following this failed fluorination of thioglycoside **46**, a new pathway was derived that instead left the 6-*O*-TIPS protecting group in place for installation of the oleyl moiety (***Scheme 16***).

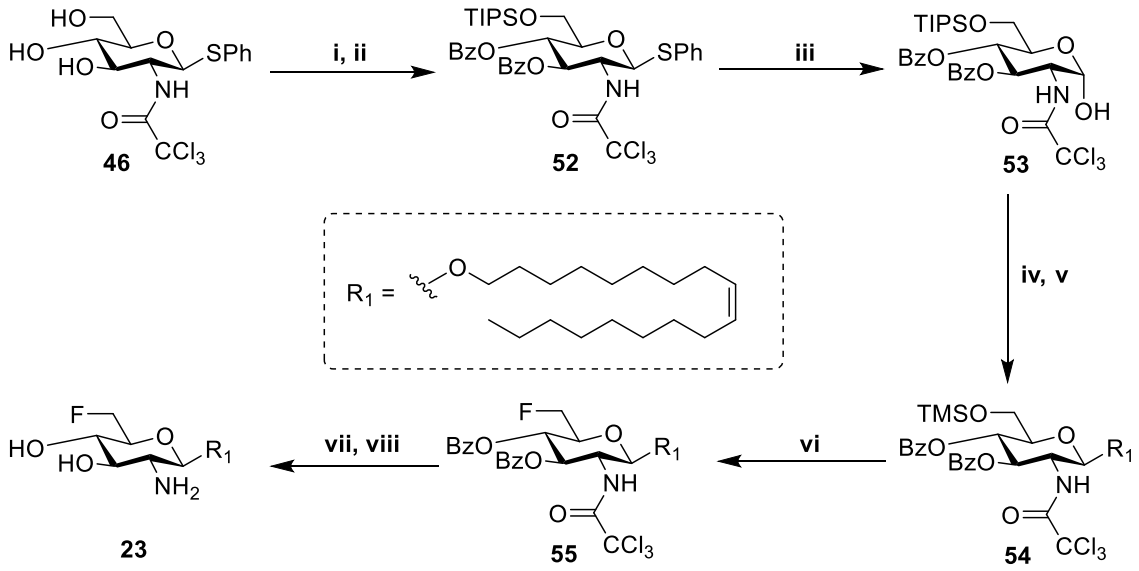


***Scheme 14*:** Attempted synthesis of 6-deoxy-6-fluoro oleyl glucosamine building block **47**. Reagents and conditions. i. DAST, DCM, -25 °C to RT.



***Scheme 15*:** Postulated mechanism of DAST mediated formation of oxazoline **48** from **46**.[21]

Treatment with TIPSCl and imidazole followed by BzCl delivered **52** in 91% yield. Anomeric hydrolysis of thioglycoside **53** was followed by conversion to the TCA donor.



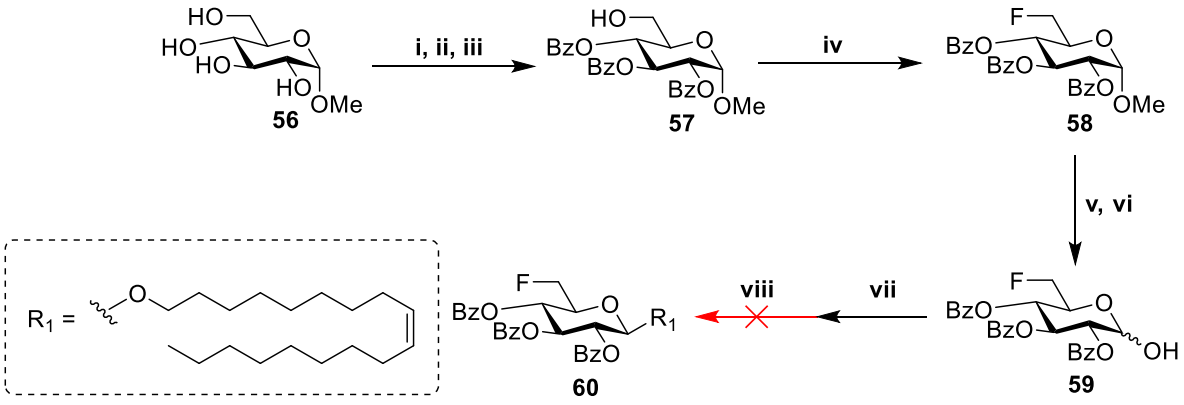
***Scheme 16*:** Synthesis of oleyl 6-deoxy-6-fluoro-β-D-glucosaminopyranoside **23**, Reagents and condition. i. TIPSCl, imidazole, RT; vi. BzCl, RT, 91%; iii. NBS, acetone/H_2O, 0°C to RT, 89%; iv. trichloroacetonitrile, DBU, DCM, RT; v. oleyl alcohol, TMSOTf, DCM, 0°C, Et_3N, 54% (2 steps); vi. DAST, DCM, -25°C to RT, 84%; vii. NaOMe, MeOH, RT; viii. KOH, THF, H_2O RT, 56% (2 steps).

Glycosidation of oleyl alcohol proceeded as expected and quenching of the reaction with Et_3N yielded 6-*O*-TMS protected GL **54** in 54% (2 steps). Oleyl installation was confirmed by the appearance of alkyl shifts in the ^{13}C NMR spectrum [δ_C 14.7- 33.2 ppm]. The alkene portion of the lipid moiety was also visible in the ^{1}H NMR spectrum [δ_H 5.35–5.24, m 2H, -C*H*=C*H*-]. C-6 DAST fluorination succeeded in delivering **55** in 56% yield. An observed chemical shift in the ^{19}F NMR spectrum [δ_F -75.73 ppm] supported successful fluorination similar to previous reports.[77] Deprotection was achieved in two steps. First the benzoates were removed under Zémplen conditions and the final step in the 12-step synthesis was base mediated removal of the TCA protecting group. Initially a combination of K_2CO_3 in MeOH was employed, but after proceeding at

a sluggish pace this was changed to KOH in THF/H_2O.This alteration successfully delivered oleyl-6-deoxy-6-fluoro-β-D-glucosaminopyranoside **23** in 62% yield (2 steps) with an overall yield of 5.7% from **43**.

2.7 Towards oleyl 6-deoxy-6-fluoro-β-D-glucopyranoside 21

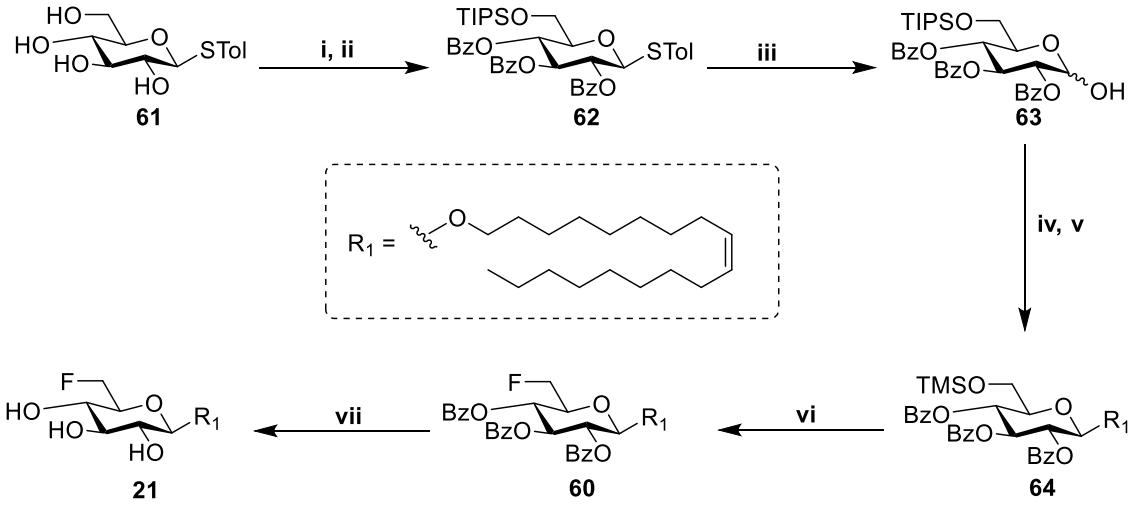
Synthesis of target compound **21** began from commercially available methyl α-D-glucopyranoside **56**. The first step saw installation of a TIPS protecting group at the 6-OH followed by benzoylation of 2-, 3- and 4-OH. Finally, the silyl protecting group was removed by TFA in THF/H_2O to deliver primary alcohol **57** in 67% yield (3 steps). ^{1}H NMR data matched that previously reported.[78] DAST treatment of **57** successfully furnished fluorinated glycoside **58** in low yield 22 % (***Scheme 17***). Work presented by Esmurziev details this same reaction using a stepped approach to reaction temperature and achieving a yield of 75%.[79] Starting at -25 °C the reaction was warmed to RT, followed by refluxing for 1 hr. When repeating fluorination using these conditions an improved yield of 45% was achieved. With compound **58** in hand, anomeric acetolysis was followed by subsequent deprotection with ammonium acetate to deliver hemi-acetal **59** (86:14, α/β).



***Scheme 17*:** Attempted synthesis of oleyl 2,3,4-tri-*O*-benzoyl-6-deoxy-fluoro-β-D-glucopyranoside **60**. Reagents and conditions. i. TIPSCl, imidazole, RT; ii. BzCl, RT; iii. TFA, THF, H_2O, RT, 67% (3 steps); iv. DAST, DCM, -25 °C to RT to 60 °C, 45%; v.

Ac_2O, AcOH, H_2SO_4; vi. NH_4OAc, DMF, RT, 50% (2 steps); vii. trichloroacetonitrile, DBU, DCM, RT; viii. oleyl alcohol, TMSOTf, DCM, 0°C.

Following general glycosylation procedure **E** (See section **6.2**); TCA formation of the glycosyl donor and attempted installation of the oleyl component yielded an array of products. The complex mixture proved difficult to characterise by NMR analysis and no structures were assigned. With success synthesising oleyl 6-deoxy-fluoro-β-D-glucosaminopyranoside **23**, a similar synthetic plan that relied on late-stage installation of the C6 fluorine and starting from thioglycoside **61** was implemented (***Scheme 18***). Starting from *p*-tolyl β-D-glucopyranoside **61** and making use of TIPSCl, a selective protection of the 6-OH was performed. Subsequent introduction of BzCl protected the remaining hydroxyl positions to deliver **62** in 70 % yield (2 steps). Structure confirmation by ^{13}C and ^{1}H NMR analysis, followed with the silyl moiety exhibiting a characteristic chemical shift [δ_H 1.02 – 1.08 ppm].



***Scheme 18*:** Synthesis of oleyl 6-deoxy-6-fluoro-β-D-glucopyranoside **21**. Reagents and conditions. i. TIPSCl, imidazole, RT; ii. BzCl, RT, 70% (2 steps); iii. NBS, acetone, H_2O, 0 °C to RT, 47%; iv. trichloroacetonitrile, DBU, DCM, RT; v. oleyl alcohol, TMSOTf, DCM, 0 °C, Et_3N, 56% (2 steps); vi. DAST, DCM, -25°C to RT, 48%; vii. NaOMe, MeOH, RT, 68%.

Three carbonyl chemical shifts were observed in the ^{13}C NMR [δ_C 166.0 (C=O, Bz), 165.9 (C=O, Bz), 165.2 (C=O, Bz) ppm], further supporting successful synthesis of **62**. Synthesis of the corresponding hemi-acetal was then completed *via* NBS-mediated hydrolysis of **62**, yielding **63** in 47% yield. Notably an improvement in the yield for this anomeric hydrolysis was achieved *using* Ph_2SO/Tf_2O and H_2O, furnishing **63** in 73% yield. The hemiacetal was converted into its corresponding TCA donor and subjected to glycosylation conditions yielding **64** in 56% yield (2 steps). Again, removal of the C6 *O*-TIPS group and TMS protection of the free C6 position was observed. HRMS analysis revealed a major signal in good agreement with **64**; HRMS [Found: $(M+Na)^+$ 837.4363, $C_{48}H_{66}O_9SiNa$ requires M^+ 837.4368]. Glycosylation success compared with the previous failed attempt can be attributed to the effect of the silyl protecting group at C6. Improved reactivity of glycosyl donors bearing silyl ethers is well-known.[80]

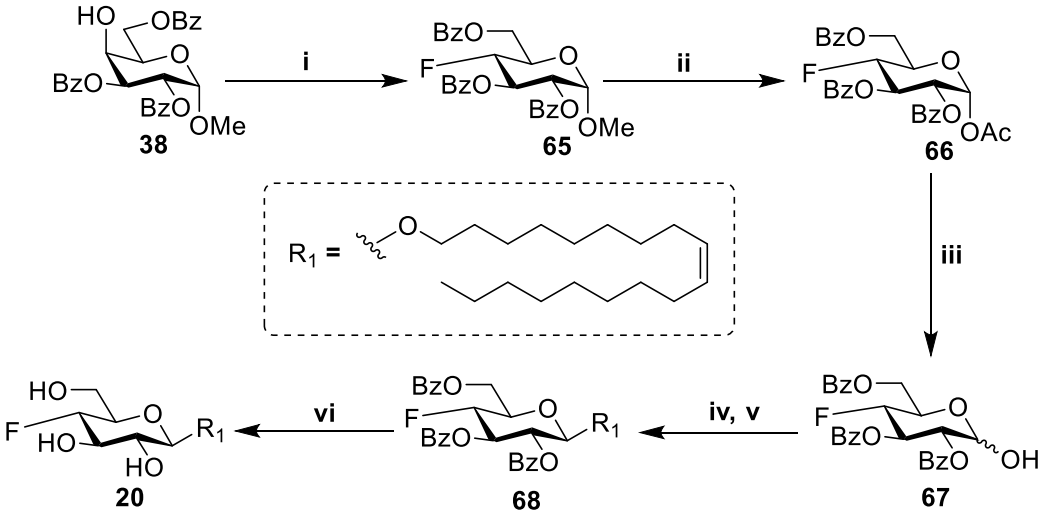
The next step was DAST mediated fluorination with these conditions simultaneously deprotecting the 6-*O*-TMS and installing fluorine. Immediate deprotection of the remaining benzoates under Zémplen conditions followed. This successfully delivered target compound **21** in 68% yield. The slightly lower than expected yield arose from multiple purification attempts of this final material. NMR analysis showed a distinctive triplet of doublets in the ^{19}F NMR spectrum [δ_F -233.75 ppm, $^2J_{H\text{-}6a/b\text{-}F}$ = 47.4 Hz, $^3J_{H5\text{-}F}$ = 23.0 Hz]. This was accompanied by characteristic heteroatom couplings in the ^{13}C NMR spectrum [d, $^2J_{C5\text{-}F}$ = 18.4 Hz], [d, $^1J_{C6\text{-}F}$ = 172.7 Hz] supporting structure **21**.

2.8 Towards oleyl 4-deoxy-4-fluoro-β-D-glucopyranoside 20

Synthesis of target compound **20** began from previously synthesised methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside **38** (***Scheme 12***, ***Section 2.5***). The C4-hydroxyl was treated with DAST successfully inverting the configuration at C4, providing 4-deoxy-4-

fluoro glucoside **65** in 82% yield. Successful synthesis of **65** was confirmed by ^{19}F NMR analysis [δ_F = −197.0 ppm (dd, J = 50.9, 14.0 Hz)]. **66** was subjected to acetolysis using a combination of Ac_2O, H_2SO_4 and AcOH to successfully deliver **66** in 54% yield. This was followed by removal of the anomeric acetate using NH_4OAc in DMF, delivering C4-fluorinated hemi-acetal **67** (91/9, α/β) in 78% yield (***Scheme 19***).

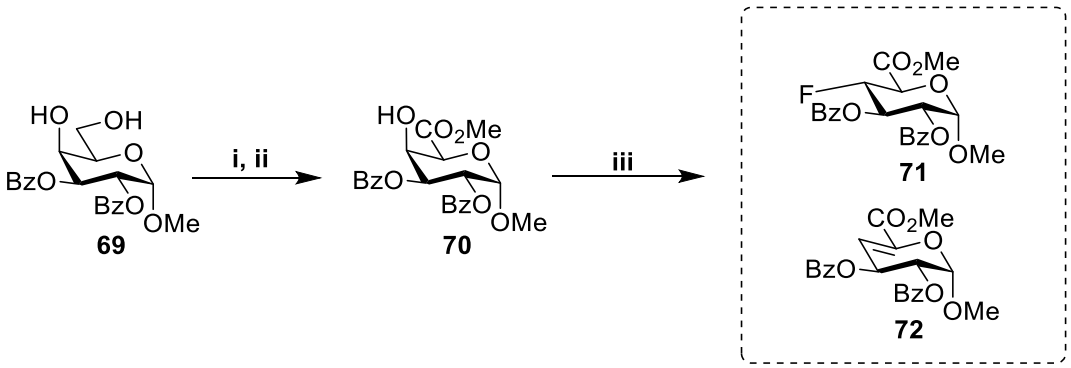
The hemiacetal was converted into the TCA donor and following purification *via* a short silica plug the donor was glycosidated with oleyl alcohol. This delivered C4-fluorinated oleyl glucoside **68** in 36% yield (2 steps). Deprotection of the benzoate protecting groups under Zémplen conditions followed to yield 4-deoxy-4-fluoro GL β-**20** in 67% yield ($^3J_{H1\text{-}H2}$ = 7.8 Hz). The alkene of the oleyl component was identified by characteristic chemical shifts in both the ^{13}C and ^{1}H NMR spectra; [-C*H*=C*H*-, δ_H = 5.41-5.30 ppm] and [*C*=*C*, δ_C = 130.0, 129.8 ppm]. HRMS analysis further confirmed structure **20**; [$(M-H)^-$ found 431.3177, $C_{24}H_{44}FO_5$ requires M^- 431.3172].



Scheme 19: Synthesis of oleyl 4-deoxy-4-fluoro-β-D-glucopyranoside **20**. Reagents and conditions. i. DAST, DCM -25 °C to RT, 82%; ii. Ac_2O, H_2SO_4, AcOH, 54%; iii. NH_4OAc, DMF, RT, 78%; iv. trichloroacetonitrile, DBU, DCM, RT; v. oleyl alcohol, TMSOTf, DCM, 0°C, 36% (2 steps); vi. NaOMe, MeOH, RT, 67%.

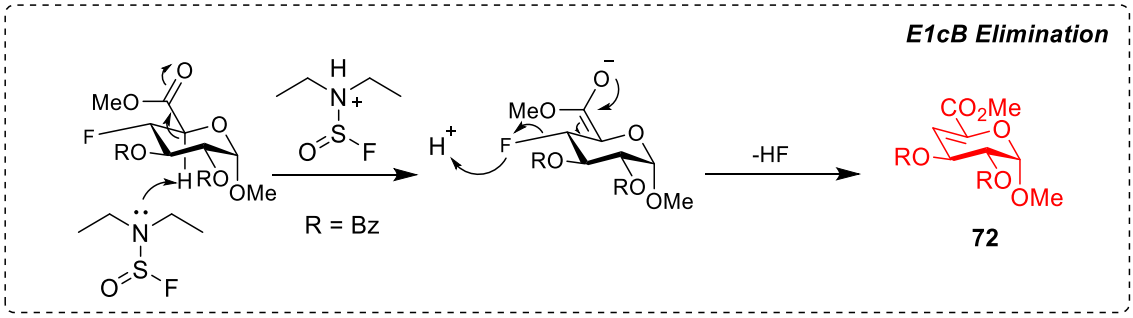
2.9 Towards oleyl 4-deoxy-4-fluoro-β-D-glucuronic acid 22

The next target was C4-fluorinated glycosyl uronate **22** The first step saw regioselective oxidation at C6 to give galacturonic acid. This transformation relied on TEMPO and (diacetoxyidodo) benzene and was followed by conversion to the methyl ester using MeI furnishing methyl uronate **70** in 57% yield. ^{1}H NMR revealed an additional chemical shift corresponding to the methyl group of the uronate [δ_H = 3.84 ppm]. Fluorination at C-4 was next attempted using DAST. Following purification ^{1}H NMR analysis revealed two compounds. A characteristic doublet of triplets was observed in the ^{19}F NMR spectrum [dt, $^{1}J_{H4\text{-}F}$ = 50.1 Hz, $^{3}J_{H3/H5}$ = 14.3 Hz] suggesting the minor product to be C4 fluorine derivative **71**. The major component was however indicated to be elimination product **72**, possibly resulting from a E1cB elimination (***Scheme 20***). This conclusion was based on the absence of H5 in the ^{1}H NMR spectrum and previously reported precedent of C4-C5 elimination for glucosyl uronates.[81, 82] Fluorine installation at C4 in combination with the nearby methoxycarbonyl increases the acidity of H5 resulting in elimination at C4/C5 in the presence of a suitable base.



Scheme 20: Attempted synthesis of methyl 2,3-di-*O*-benzoyl-4-fluoro-α-D-galactopyranoside uronate **71**. Reagents and conditions. i. $PhI(OAc)_2$, TEMPO, DCM/H_2O, RT; ii. MeI, K_2CO_3, DMF, RT, 57%; iii. DAST, DCM -40 °C to RT, MeOH, RT, 25% (**71**/**72**. 1:1.5)

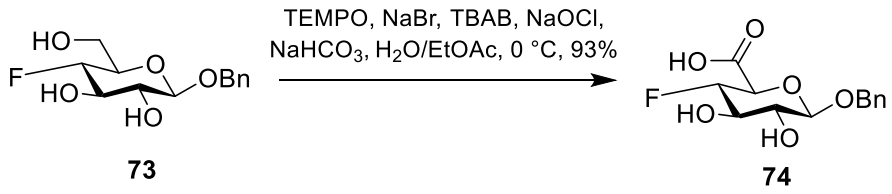
The ring oxygen and ester group at C6 serve to stabilise the enolate following proton abstraction. Degradation of chondroitin sulfate by chondroitin AC lysase proceeds by a similar elimination mechanism. [83] Withers previously reported proton abstraction at C5-H5 to be the rate limiting step whilst investigating this mechanism of polysaccharide cleavage and hence ruling out E1 elimination.[84] This work also found the C4-leaving group to be non-rate limiting step further ruling out E2 elimination and instead conforming to an E1cB. The first step of a E1cB is deprotonation to form a carbanion, followed by elimination (***Scheme 21***).



Scheme 21: Mechanism for the formation of elimination side product **72** *via* an E1cB.

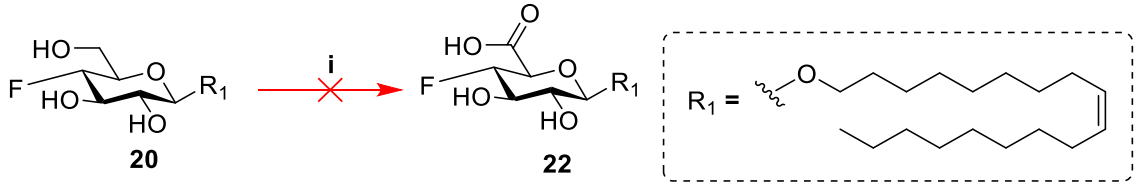
The two reaction products **71** and **72** were not separable and it was decided to progress the mixture, hoping further transformation would allow for adequate separation by chromatography. As such, acetolysis was completed using Ac_2O, AcOH and H_2SO_4. Upon reagent addition the reaction mixture turned dark brown and TLC analysis revealed multiple components. A crude aliquot was subjected to ^1H NMR analysis. From the spectrum obtained the reaction was determined to be unsuccessful, providing no structural information. A new protecting group pattern was considered that allowed for 6-OH oxidation post C-4 fluorine installation. Hoff and co-workers took a similar approach when facing elimination at C4/C5.[85] In this case, even after solving the initial issue through a post oxidation strategy they found when glycosylating later in the synthetic route the same issue occurred. As saponification was required to access **22** a

similar outcome seemed likely and so a different approach was taken. Withers reported C6 oxidation of semi-protected glycoside **73** post fluorine installation (***Scheme 22***).[84]



***Scheme 22*:** Oxidation of **73** as reported by Withers and co-workers.[84]

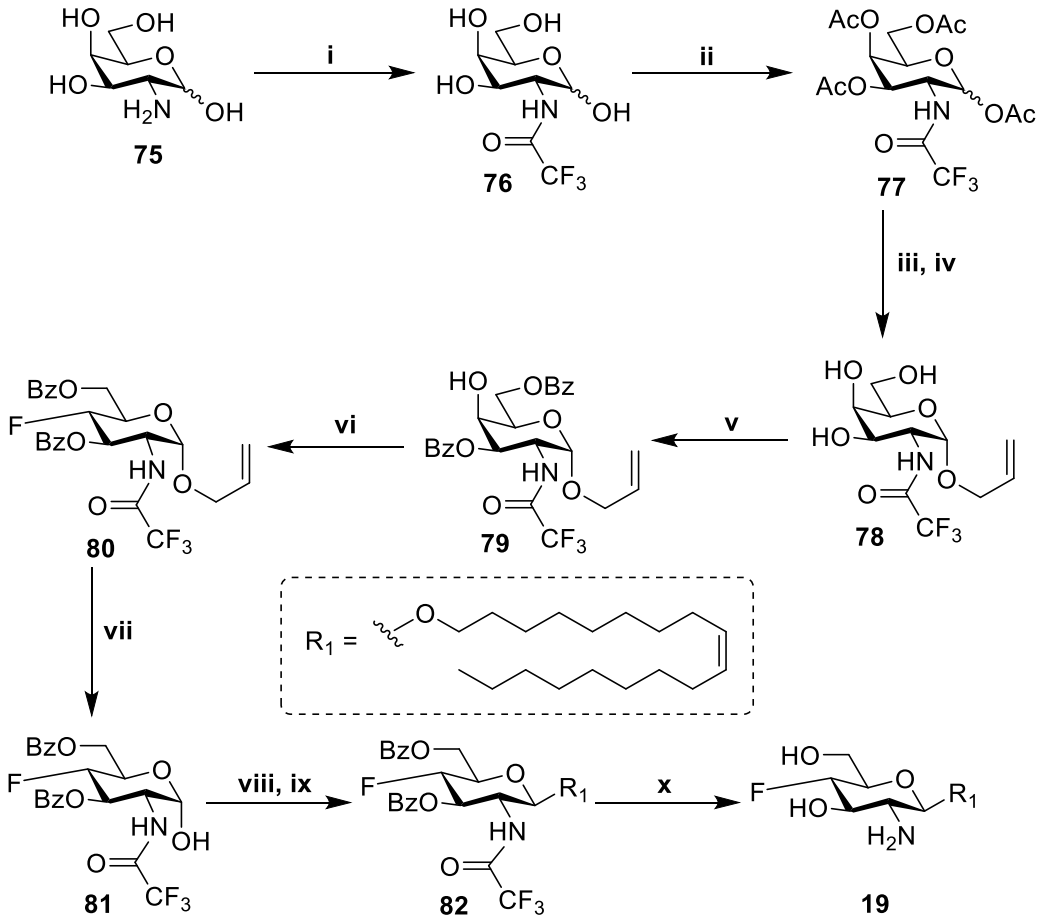
Utilising oleyl 4-deoxy-4-fluoro-β-D-glucopyranoside **20** a similar experiment was performed. After 2.5 hrs only starting material remained by TLC. This was allowed to stir overnight with no change (***Scheme 23***). An aliquot of the reaction mixture was analysed by ^{1}H NMR confirming no reaction had taken place. The emulsifying properties of **20** likely played a role in reaction failure by preventing formation of the biphasic mixture (H_2O/EtOAc).



***Scheme 23*:** Attempted synthesis of oleyl 4-deoxy-4-fluoro-β-D-glucuronic acid **22**. Reagents and conditions. TEMPO, NaBr, TBAB, NaOCl, $NaHCO_3$, H_2O/EtOAc, 0 °C.

2.10 Towards oleyl 4-deoxy-4-fluoro-β-D-glucosaminopyranoside 19

Starting from commercially available D-galactosamine **75**, the free amine was protected using a trifluoroacetamido (TFA) group (***Scheme 24***). Successful installation was confirmed by the appearance of two new shifts in the ^{19}F NMR spectrum [δ_F = -75.9, -76.1 ppm]. TFA protection was preferred over the previously employed TCA group due to a loss in yield attributed to furanose side products forming.[86, 87]



***Scheme 24*:** Synthesis of oleyl 4-deoxy-4-fluoro-β-D-glucosaminopyranoside **19**. Reagents and conditions. i. ethyl trifluoroacetate, Et_3N, MeOH, RT, 72%; ii. Ac_2O, pyridine, RT, 89%; iii. $FeCl_3$, allyl alcohol, DCE, RT, 71%; iv. 1M NaOH, MeOH, RT, 91%; v. BzCl, pyridine, DCM, - 40°C, 70%; vi. DAST, DCM, pyridine, -40 °C to RT, 79%; vii. $Pd(PPh_3)_4$, AcOH, 80 °C, 74%; viii. Cl_3CCN, DBU, DCM, RT; ix. oleyl alcohol, TMSOTf, DCM, 0 °C, Et_3N, 29% (2 steps); (x) NaOH, MeOH, RT (71%).

Acetylation of the free hydroxyl groups and purification *via* a short silica plug furnished acetylated glycoside **77** in 89% yield. Glycosidation of allyl alcohol using $FeCl_3$ produced a mixture of anomers with the α configuration favoured (α/β, 8:2). ^{13}C NMR chemical shifts assigned to the anomeric allyl group confirmed successful synthesis [δ_C = 33.9 (=*C*H-), 116.35 (*C*H_2=), 67.9 (O*C*H_2) ppm]. Deacetylation under basic conditions was complete in under 1 hr and the anomeric mix was separable by column chromatography with α-**78** taken forward. With allyl glycoside **78** in hand, regioselective benzoylation of

positions 3- and 6-OH was carried out to deliver **79** in 70% yield. ^{13}C NMR analysis revealed two carbonyl chemical shifts [δ_C = 166.9 (C=O), 166.1 (C=O) ppm] with cross peaks to H-3 and H-6 confirmed by HMBC. Fluorination with DAST successfully furnished 4-F glycoside **80** with the appearance of a second chemical shift [δ_F -197.02, $^2J_{H4\text{-}F}$ = 50.8, $^3J_{H3\text{-}F}$ = 13.4 Hz] corresponding with reaction success.

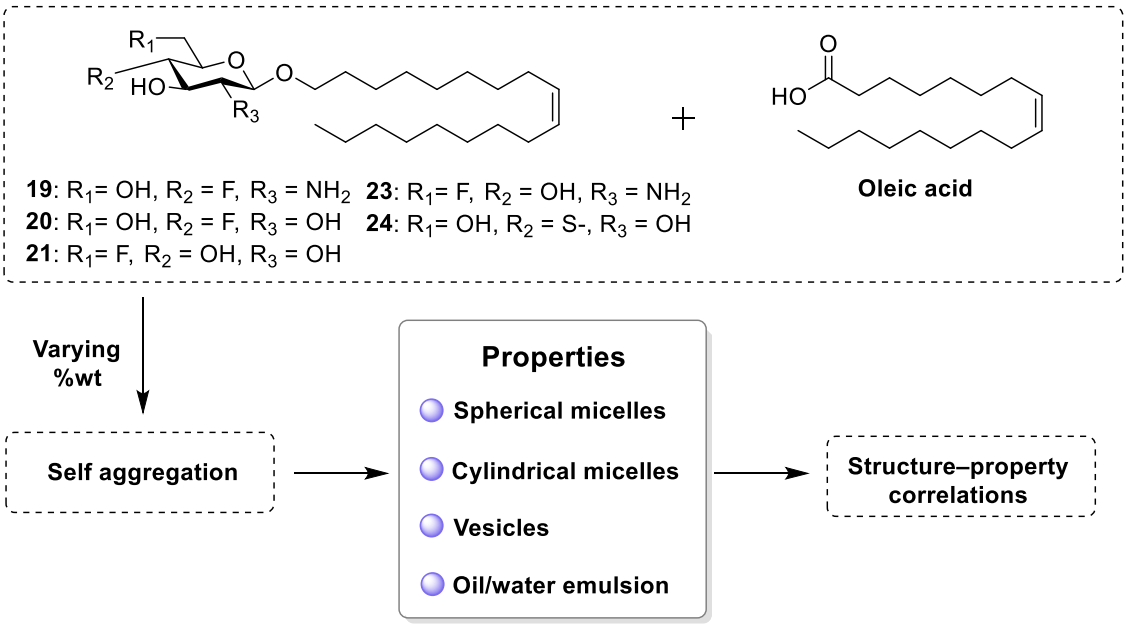
The anomeric allyl moiety was next cleaved in the presence of tetrakis(triphenylphosphine) palladium in AcOH at 80 °C, delivering α-**81** in 74% yield [δ_H $^3J_{H1\text{-}H2}$ = 3.2 Hz] Hemi-acetal **81** was subjected to the established glycosylation conditions successfully delivering 4-fluoro oleyl glycoside **82** in 42% yield. Global deprotection using 1M NaOH in MeOH successfully delivered the final target **19** in 71% yield. Only one chemical shift was visible in the ^{19}F NMR spectrum, assigned to the C4 moiety based on characteristic *J* couplings [δ_F = −197.95 (dd, $^2J_{H4\text{-}F}$ = 51.0, $^3J_{H3\text{-}F}$ = 14.3 Hz) ppm]. Absence of further chemical shifts confirmed *N*-TFA deprotection. HRMS was obtained for compound **19** [Found: $(M + Na)^+$ 758.3649, $C_{40}H_{53}F_4NO_7Na$ requires M^+ 758.3650].

2.11 Conclusion and Future Work

In summary an effective method for the glycosidation of oleyl alcohol utilising trichloroacetimidate donors with TMSOTf activation has been developed. This methodology was extended, granting access to a small library of 2-deoxyamino, 4- or 6-fluorinated and 4-sulfhydryl oleyl glycosides on multi-milligram scales. Yields for the key glycosylation step across these derivatives range from 36% to 54% with donors possessing 6-*O*-TMS protection providing the best yields: **54** (56%) and **64** (54%). Late-stage fluorination was accomplished in the presence of the fatty chain using DAST

avoiding C1 to C6 thiol migration for 6-F derivatives. These materials demonstrate an important entry for the wider development of amphiphilic glycoconjugates.

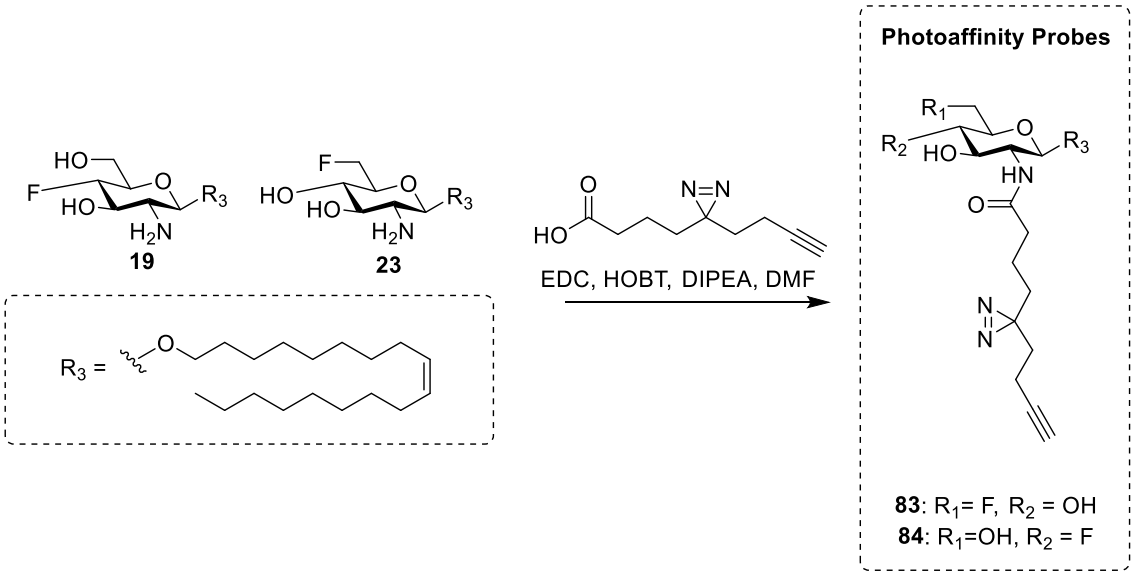
Future prospects for these materials include determination of structure function correlations. For example, comparison with oleic acid can be made with varying % wt. of an oleyl-glycolipid component **19**-**24**. Varying the composition and analysing the type of self-aggregation/emulsifying properties will allow structure property correlations to be established aiding future development of biosurfactants (***Scheme 25***).[88]



Scheme 25: Potential workflow for determination of structure function correlations utilising oleic acid and oleyl-glycolipids **19**-**24**.

Oleyl β-glycosides are of interest for their antimitotic potential and have demonstrated activity against a variety of cancer cell lines where they are suggested to alter glycosphingolipid metabolism.[89, 90, 91, 92] As such further utilisation of amino derivatives **19** and **23** could include synthesis of photoactivable probes **83** and **84** (***Scheme 26***). Through conjugation at the amine a suitable photoaffinity label can be introduced.[93] This handle serves to form covalently crosslinked complexes with proteins in an affinity

dependent manner. This allows for the capture of intracellular interactions for further analysis by HRMS and identification of protein binding partners.[94, 95]



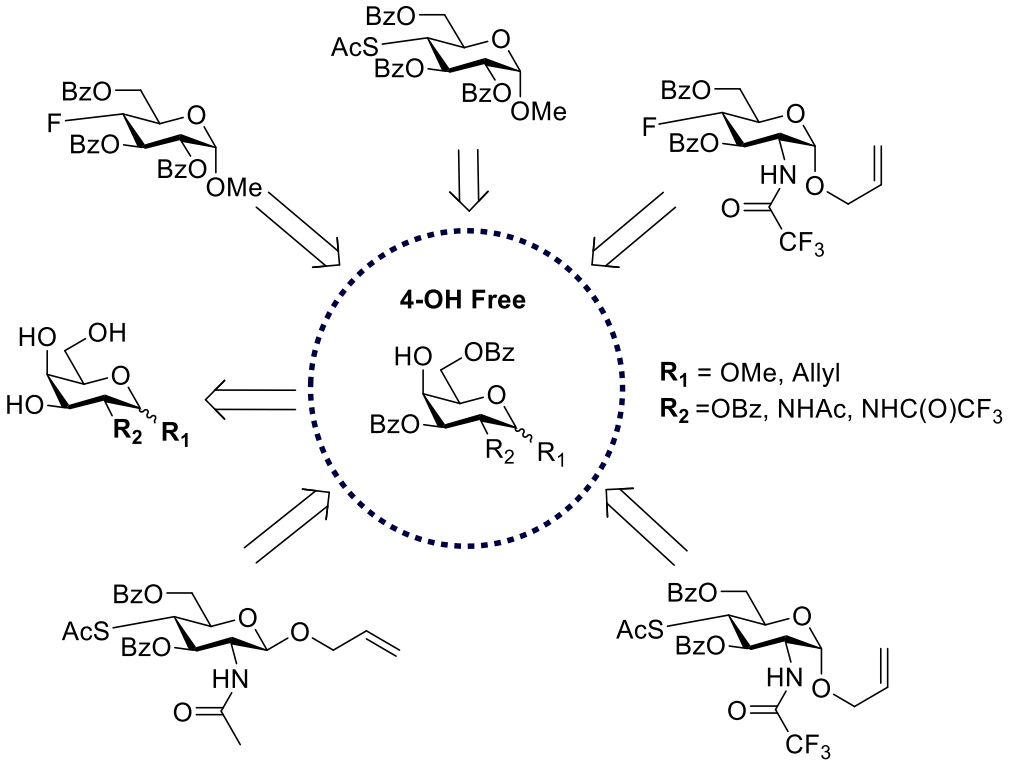
Scheme 26: Synthetic pathway towards photoaffinity probes **83** and **84** using a diazirine-alkyne-acid linker by conventional amide bond coupling.

Chapter 3

Regioselective Benzoylation of Galactose and Galactosamine Derivatives

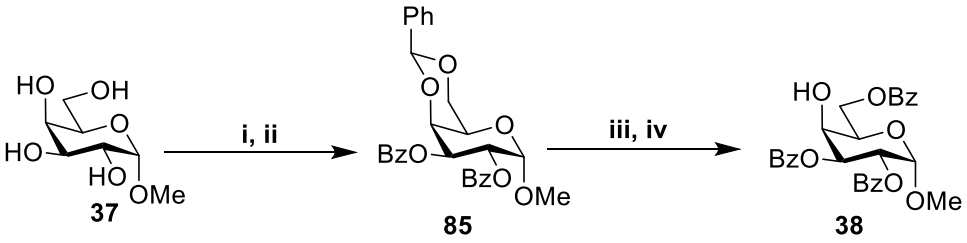
3.0 Initial observations and aims

During the course of this project a number of 4-position modified pyranoses were targeted for synthesis. Access to such materials required a suitable protecting group pattern to assure regioselective functionalisation (***Scheme 27***). This can be accomplished in a number of ways, for example, from methyl α-D-galactose a four-step synthesis utilising benzylidene protection at 4-, and 6-OH. Following benzylidene protection 2- and 3-OH were protected using BzCl. Acid mediated benzylidene hydrolysis allows for selective protection at 6-OH with BzCl to deliver **38** in 4 steps (***Scheme 28***).



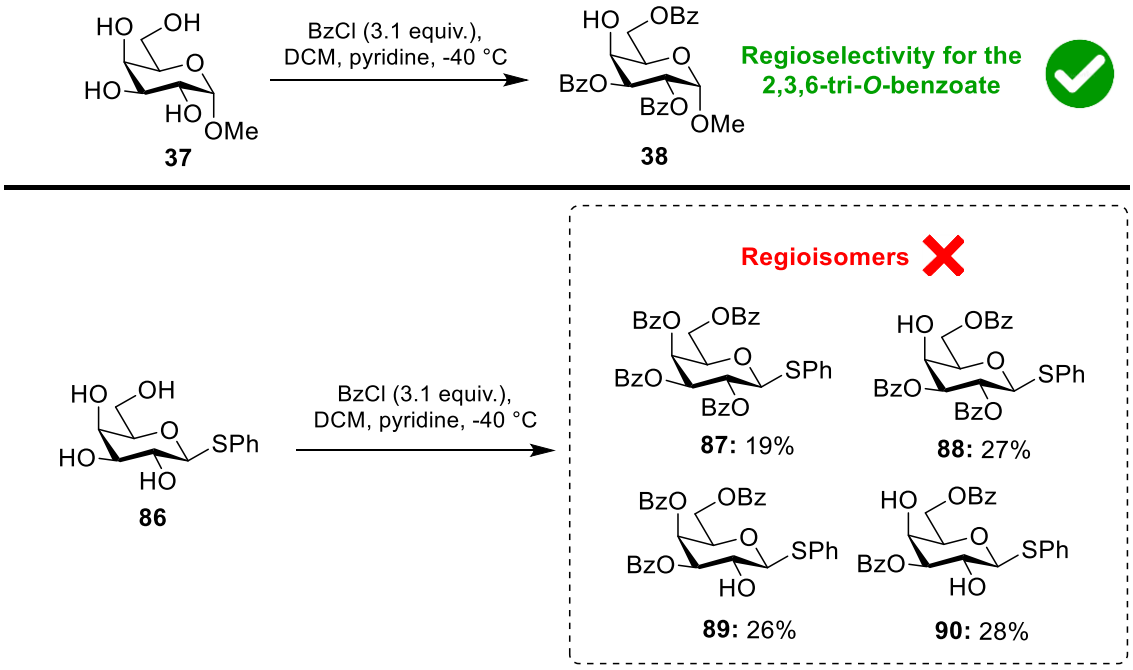
Scheme 27: Structures of 4-OH modified glucose molecules accessed in this thesis.

Initially benzylidene protection was relied on to access the necessary stocks of material. This approach was superseded by a method of low temperature benzoylation, reducing the number of steps, and increasing overall route efficiency. This reaction worked well for methyl α-D-galactose, providing desired glycoside **38** in 64% yield (***Scheme 28***).



Scheme 28: Example of benzylidene protection towards 2,3,6-tri-*O*-benzoate **38**. Reagents and conditions. i.$PhCH(OMe)_2$, $Cu(OTf)_2$, MeCN, RT; ii. BzCl, pyridine, RT, 85% (2 steps); iii. AcOH, H_2O, RT; iv. BzCl (1.0 equiv.), pyridine, RT, 81% (2 steps).

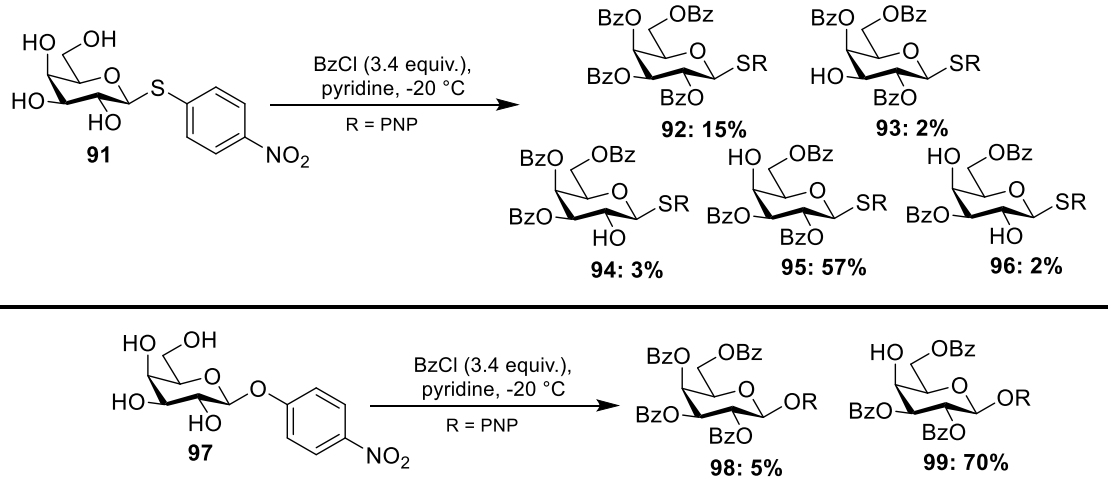
Considering this success, a similar experiment was performed on thioglycoside **86**, however a number of regioisomers were isolated from the product mixture **87**-**90** (***Scheme 26***). This idiosyncrasy raised questions as to possible determinant factors allowing for hydroxyl discrimination, to leave the 4-OH free, and based around the anomeric group's identity. This chapter aims to understand this effect upon on the outcome of regioselective low temperature benzoylation for galactose and galactosamine derivatives.



Scheme 29: Initial regioselective benzoylation experiments. Top: benzoylation of methyl α-D-galactose **37**; bottom: benzoylation of phenyl 1-thio-β-D-galactopyranoside **86**.

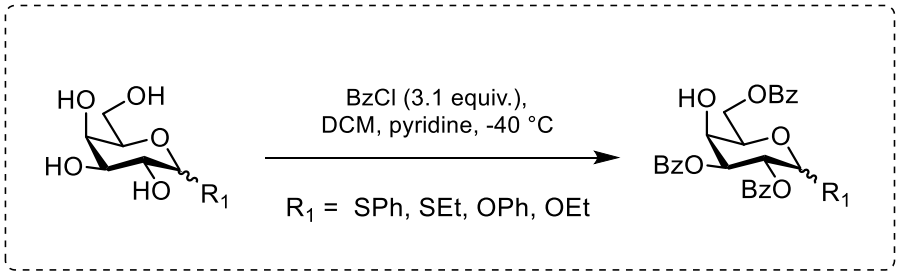
3.1 Introduction

Consulting the literature almost all of the available examples for 2,3,6-tri-*O*-benzoate protection of thioglycosides relied on benzylidene protection.[96-102] The involved steps are typically high yielding, but extended purification is required when compared with direct regioselective protection. One notable example of such a one-step process utilised *para*-nitrophenyl (PNP) thioglycoside **91** and low temperature benzoylation (-20 °C) to successfully deliver the corresponding 2,3,6-tri-*O*-benzoate **95** in 57% yield with four other regioisomers also isolated **92-94** & **96** (***Scheme 30***).[103] Interestingly, during this work an analogous *O*-PNP glycoside **97** was subjected to the same conditions, yielding 2,3,6-tri-*O*-benzoate **99** in 70% yield with only a small amount of the tetra-*O*-benzoate **98** (5%) also isolated.



Scheme 30: Low temperature benzoylation of **91** and **97** as reported by Apparu *et al*; (% = isolated yield).[103]

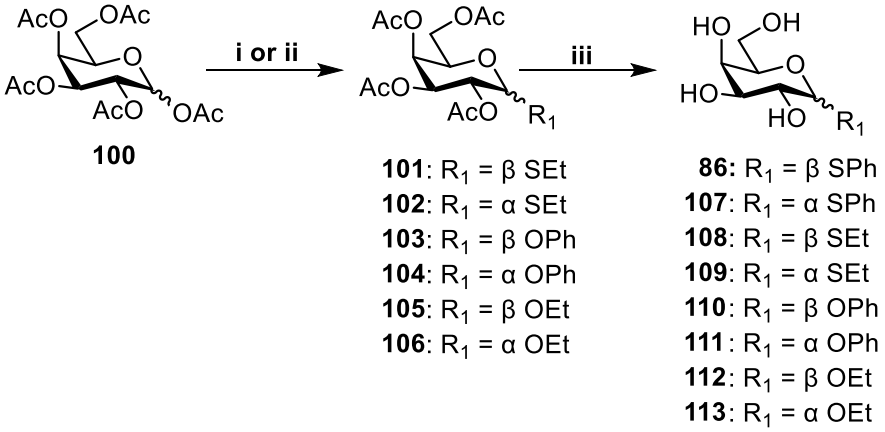
To gain further insight into these observed regioisomeric outcome differences, a range of galactopyranosides were synthesised and subjected to benzoylation conditions, as outlined in ***Scheme 31***. Benzoylation conditions were chosen using a slight excess of BzCl (3.1 equiv.) and reactions performed at -40 °C.



Scheme 31: Implemented benzoylation conditions and initial substrate scope.

3.2 Substrate scope: S-galactosides

The initial substrate scope was selected to allow comparison between *O*- and *S*-glycosides but also to provide insight to the role of the aglycon. The ubiquity of SEt and SPh thioglycosides made their selection straightforward. The substrates were synthesised by two methods of glycosylation. Thioglycosides were furnished using $BF_3{\cdot}OEt_2$ and conducting the reaction at RT produced a mixture of anomers. (***Scheme 32***). For *O*-glycosides $SnCl_4$ was relied upon with glycosylation favouring alpha-products (***Scheme 32***). Corresponding tetrols were then accessed using Zemplén conditions, furnishing **107-113** & **86** (11-87%). With all of the substrates in hand low temperature benzoylation experiments were next performed.



Scheme 32: Synthesis of *O*/*S*-galactoses **101-113** & **86**. Reagents and conditions. i. $BF_3{\cdot}OEt_2$, DCM, EtSH, RT, **86/107**, **101/102:** 64% (α: β, 59:41); ii. $SnCl_4$, DCM, RT, PhOH or EtOH, RT, **103/104**: 59% (α/β, 84:16), **105/106**: 55% (α/β, 7:3); iii. Na, MeOH, RT, **86**β (38%, 2 steps); **107α** (43%, 2 steps), **108β**: 87%; **109α**: 66%; **110β**: 79%; **111α**: 77%; **112β**: 85%; **113α**: 11%.

Starting with β-*S*-Ph glycoside **86** (***Table 4, entry 1***) a regio-isomeric mix was obtained upon application of benzoylation conditions, with three separate components visible by TLC. The lowest spot was found to be 3,6-di-*O*-benzoate **90** (20%) and the top spot fully benzoylated product **87** (13%), with NMR data matching those previously reported.[104] The middle spot revealed two inseparable sugars. These were determined to be 3,4,6-tri-*O*-benzoate **89** (19%) and 2,3,6-tri-*O*-benzoate **88** (20%) in similar amounts, giving a combined total yield of 72%. In each case assignments were made using HMBC cross peaks between ring protons and carbonyl shifts, to allow location of benzoyl groups.

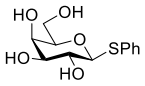
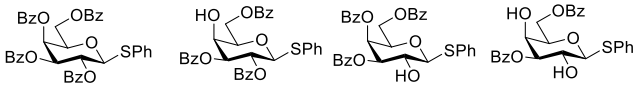
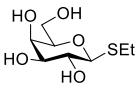
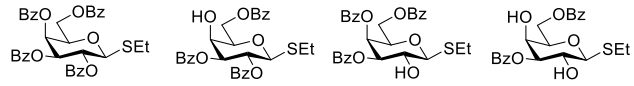
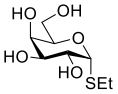
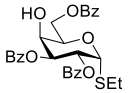
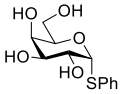
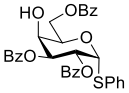
Entry	Substrate	Product(s) [A]	Total yield [B]
1	 **86**	 **87: 13%** **88: 20%** **89: 19%** **90: 20%**	72%
2	 **108**	 **114: 12%** **115: 21%** **116: 13%** **117: 12%**	68%
3	 **109**	 **118**	89%
4	 **107**	 **119**	78%

Table 4: Benzoylation of *S*-galactopyranosides **107**-**109** & **86**; [A] Product distribution percentages based on isolated yield; [B] total percentage yield; Reagents and conditions; BzCl, pyridine, DCM, -40 °C.

β-*S*-Et substrate **108** was next screened with results from this reaction mirroring the results of the previous entry (***Table 4, entry 2***). Both ***entry 1*** and ***2*** were repeated but instead cooled to -78 °C this had no effect on regioselectivity, observing a similar distribution of products. Interested to see if the anomeric configuration had an impact, α-

linked thioglycosides were next screened. α-*S*-Et substrate **109** was subjected to benzoylation conditions and after 30 mins reaction completion was observed by TLC. Isolation and characterisation by ^{1}H NMR revealed product **118** in 89% isolated yield. Intrigued by this result, α-*S*-Ph **107** was screened with the reaction proceeding in a similar fashion and delivering tri-*O*-benzoate **119** in 78% yield. These results indicated the anomeric stereochemistry to be a determining selectivity factor with α-thioglycosides delivering the desired regioselectivity. An explanation for this has been reported. Work presented by Schmidt showed selective protection through use of BzCN and DMAP at low temperature (-78 °C) providing access to triol and diol galactose derivatives leaving the 3-OH available.[105] Selectivity was the result of a "cyanide effect" with this methodology being extended to one pot protection of triol and tetrol carbohydrates.[106] A later publication by the same author and Peng reported regioselective benzoylation of 2,3-*O*-unprotected α-galactopyranosides and the capability to differentiate 2- and 3-OH protection by choice of amine catalyst.[107] A crucial observation in these examples was display of an "alkoxy group mediated diol effect" causing equatorial *trans*-diols with a vicinal alkoxy group to react with preference at the hydroxyl adjacent to the axial hydroxyl (***Figure 15***). This explanation accounts for the observed selectivity for α-entries detailed above.

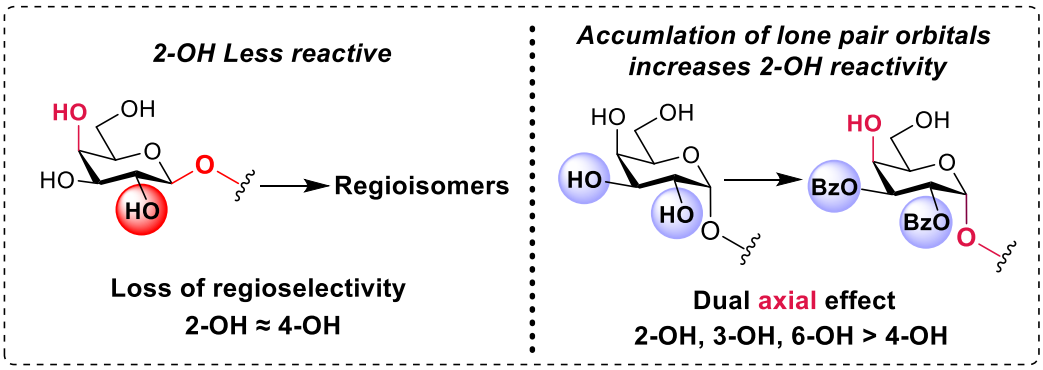


Figure 15: Alkoxy group mediated diol effect and resulting increased oxygen nucleophilicity at 2-OH for α-galactopyranosides when compared with β-galactopyranosides.

Based on results so far it seemed there wasn't a noticeable reactivity difference between 4 and 2-OH for β configured entries. This conclusion was based on two observations, all of the isolated regioisomers being benzoylated at 3- and 6-OH (***Table 4, entry 1 and 2***). Also, the isolation of regioisomers differing at positions 2 and 4 in similar amounts (**88** & **89**, **115** & **116**).

3.3 Substrate scope: O-galactosides

O-glycosides were next screened, starting with β-*O*-Ph glycoside **110**. After 2 hrs of reaction time TLC analysis revealed two components and complete consumption of the starting material. Following isolation by column chromatography and analysis by ^{1}H NMR, the top spot was identified as fully benzoylated product **120**. The second, and major component was found to be a mix of two inseparable regioisomers, 2,3,6-tri-*O*-benzoate **121** and 3,4,6-tri-*O*-benzoate **122** (***Table 5, entry 1***) favouring tri-*O*-benzoate **121**.

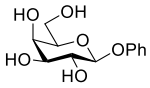
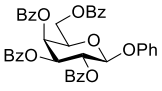
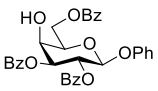
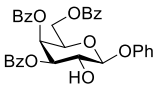
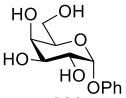
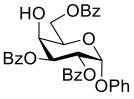
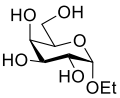
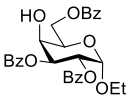
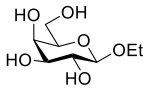
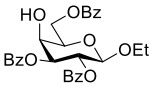
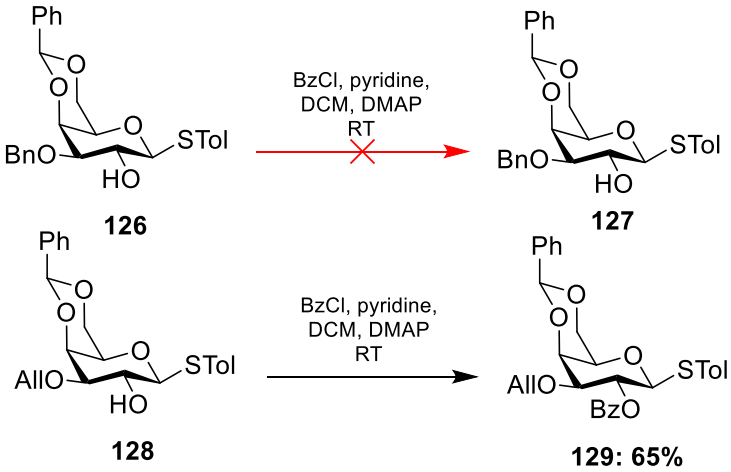
Entry	Substrate	Product(s) [A]	Total yield [B]
1	 **110**	 **10: 15%**  **121: 34%**  **122: 23%**	**67%**
2	 **111**	 **123**	**78%**
3	 **113**	 **124**	**73%**
4	 **112**	 **125**	**70%**

Table 5: Benzoylation of *O*-galactopyranosides **110**-**113**; [A] Product distribution percentages based on isolated yield; [B] total percentage yield; Reagents and conditions; BzCl, pyridine, DCM, -40 °C.

The next entry to be screened was α-*O*-Ph glycoside **111** and after 1 hr of reaction time TLC analysis revealed a single spot (R_f = 0.56, hexane/EtOAc, 7:3). Purification and ^{1}H NMR analysis revealed the product as 2,3,6-tri-*O*-benzoylated glycoside **123** in 78% yield. Moving onto *O*-Et substrates, α-configured galactopyranoside **113** delivered desired glycoside **124** in 73% yield (***Table 5, entry 3***). The next entry, β-*O*-Et substrate **112,** gave an unexpected result with 2,3,6-tri-*O*-benzoate **125** being isolated as the only product in 70% yield (***Table 5, entry 4***). This contrasting result suggested the nature of the aglycon was also a factor in achieving regioselectivity for β-galactopyranosides. The nature of the anomeric chalcogen also demonstrated the capacity to alter reaction outcome achieving regioselectivity for β-*O*-Et substrate **112** and isolating regioisomers from β-*S*-Et substrate **108**. Based on observed results it is clear the "alkoxy group mediated diol effect" is a strong influencer for both *O* and *S* galactopyranosides (***Figure 11***). This is based on the high degree of regioselectivity observed for ***all*** α configured entries.

Achieving regioselectivity for β-*O*-Et (***Table 5, entry 4***) is a standout result. Hydroxyls flanked by two other equatorial hydroxyls are often resistant to functionalisation due to unfavourable interactions involving ring substituents.[108, 109] Nucleophilic attack of a carbonyl follows the Bürgi–Dunitz angle of attack (107°). By following this path to approach the electrophile (BzCl) there is a clash with vicinal equatorial substituents masking the hydroxyl.[110] Work by Mattan Hurevich and co-workers found 2-OH of β 4,6-*O*-benzilidene protected galactose thioglycoside **126** to be completely resistant to functionalisation (***Scheme 33***).[111] The authors deduced this observation to be a result of steric effects from the bulky vicinal substituents. Replacing 3-*O*-Bn with an allyl group gave **129** in 65% yield. In this case benzylidene conformational locking and inclusion of DMAP must also be considered due to its catalytic effect. During screening of substrates

in ***Table 4*** and ***5 all*** of the regioisomers isolated had undergone benzoylation at 3-OH. In comparison many of the regioisomers in ***Table 4*** and ***5*** saw 2-OH remaining free. From this it seems likely 3-OH is more reactive than 2-OH and undergoes benzoylation prior to 2-OH.



Scheme 33: Benzoylation of 2-OH for β STol galactoses **126** and **128** using BzCl and DMAP in pyridine.[111]

This will have the effect of further blocking access to 2-OH increasing unfavourable interactions as the electrophile approaches the plane of the pyranose ring as previously discussed (***Figure 16***). Considering these points, a suggestion of steric masking at 2-OH by the aglycon and 3-*O*-Bz is put forward. Results from ***Table 4 and 5*** demonstrate a correlation between aglycon size and selectivity for the 2,3,6-*O*-tri-benzoate. The least sterically demanding entry β-*O*-Et **112** provided 100% selectivity whilst β-*O*-Ph **111** provided 34% selectivity. The largest aglycon β-*S*-Ph **86** provided the lowest selectivity (20%) (***Table 4, entry 1***). An example previously reported by Oscarson observed selective synthesis of the 2,3,6-tri-*O*-benzoate from β-*O*-Me galactopyranoside in 55% yield using BzCl in pyridine.[112] This example reinforces that smaller aglycons in the β configuration makes selective benzoylation to leave 4-OH free an easier task. Considering these points, the increased size of sulfur is likely a factor in preventing

complete selectivity for the 2,3,6-tri-*O*-benzoate in the β configuration for thioglycosides **86** and **108** (***Table 4, entries 1 & 2***).

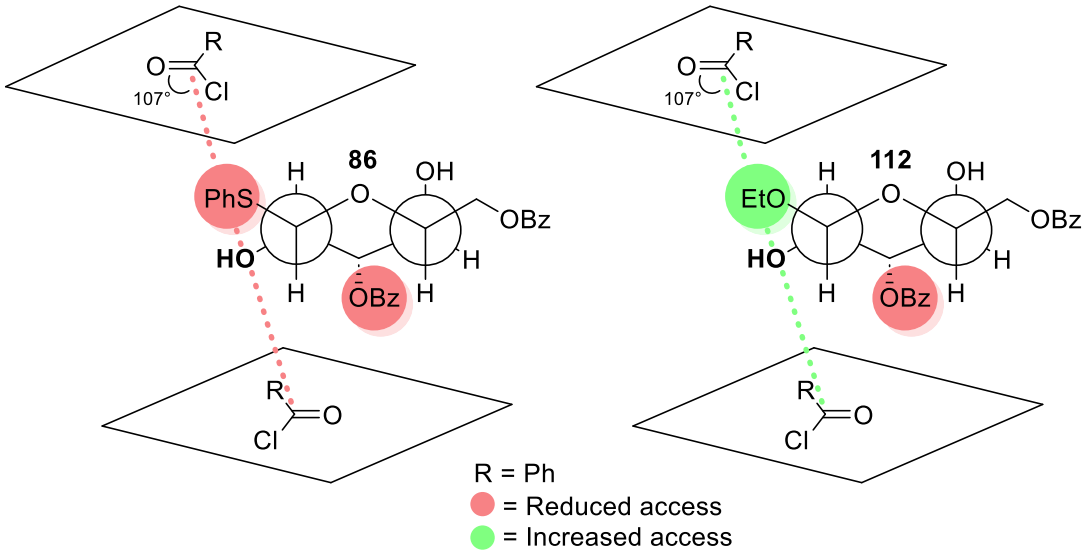
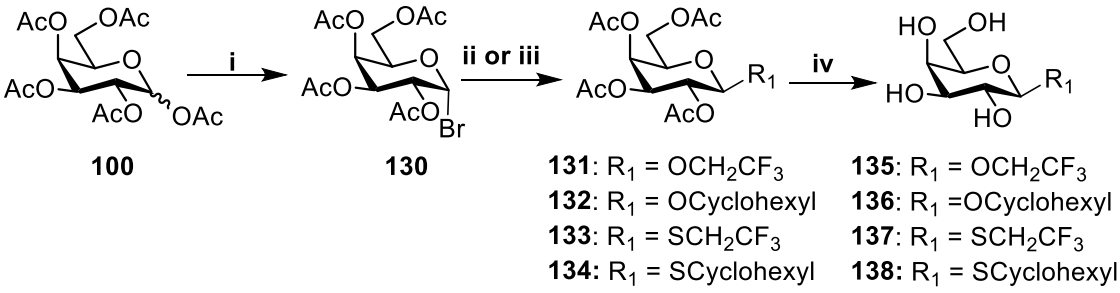


***Figure 16*:** Comparison of electrophile (BzCl) access to 2-OH following the Bürgi–Dunitz angle of attack in the horizontal plane for **86** and **112**.

3.4 Expanded substrate scope – Effect of EW and ED aglycons on reaction outcome

The steric effects discussed provide a possible explanation for the regioselectivity difference observed for β-*O*/*S*-PNP **91**/**97** substrates reported by Apparu *et al* (***Scheme 30***). The difference in regioselectivity for comparably sized β-*S*-Ph **86** and β-*S*-PNP **91** suggested other factors are also in effect. It was contemplated therefore that the electron withdrawing nature of the aglycon was influencing reaction outcome. To investigate this, several new substrates were synthesised. Electron donating cyclohexyl derivatives **136** and **138** were synthesised, based on work reported by Oscarson,[113] alongside 2,2,2-trifluoroethyl substrates **135** and **137** (***Scheme 34***). Starting from *per*-acetylated galactose the α-glycosyl bromide was synthesised. For *O*-galactosides a combination of AgOTf and Ag_2CO_3 furnished the desired substrates **131** and **132**. For thioglycosides **133**, **134** reaction of the bromide **130** with the corresponding acceptor in the presence of NaOH

successfully delivered targets **137** and **138**. Each was subsequently deprotected using Zemplén conditions to afford **135** - **138** in 69-86% yield.



Scheme 34: Synthesis of **135**-**138**. Reagents and conditions. i. HBr in AcOH, DCM, RT; ii **131**: AgOTf, Ag_2CO_3, DCM, 2,2,2-trifluoroethanol, 50% (2 steps); **132**: AgOTf, Ag_2CO_3, DCM, cyclohexanol, 73% (2 steps); iii. **134**: NaOH, DCM, cyclohexanethiol, RT, 46% (2 steps); **132**: NaOH, DCM, 2,2,2-trifluoroethanethiol, RT, 43%; iv. Na, MeOH, RT, **135**: 72%, **136**: 74%, **137**: 86%, **138**: 69%.

Thioglycoside **134** bearing a cyclohexyl aglycon was first subjected to benzoylation conditions and after 20 mins of reaction time only a single spot was observed by TLC (***Table 6, entry 1***). This was found to be 2,4-diol **139**. The reaction was repeated for 24 hrs but did not progress beyond the diol, affording **139** in 64% yield.

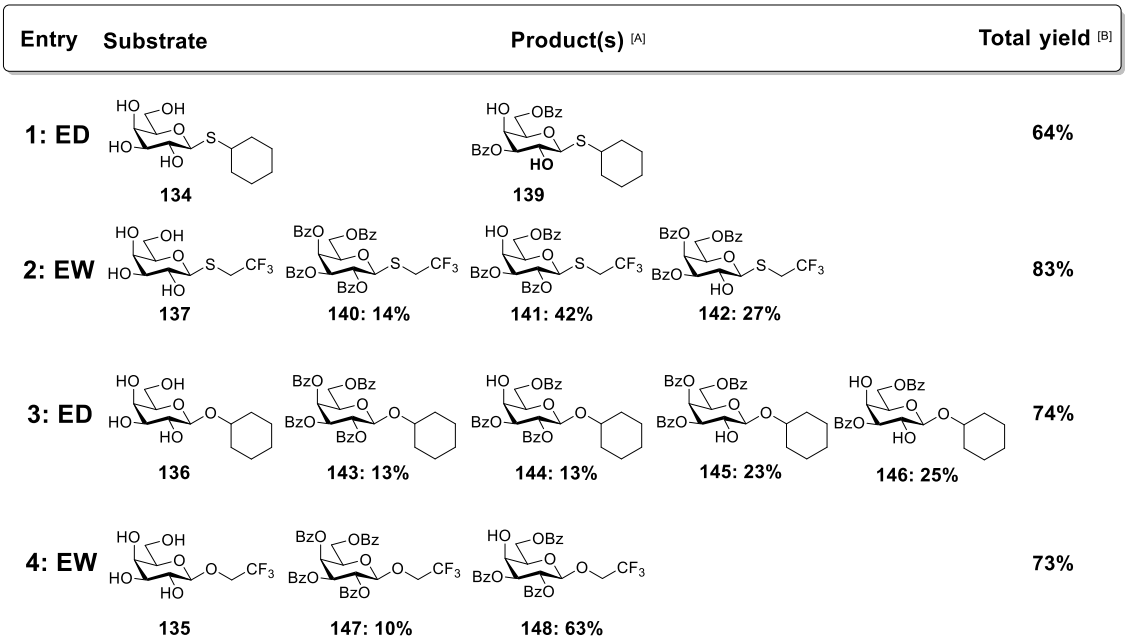


Table 6: Benzoylation of galactopyranosides **134**-**137**; [A] Product distribution percentages based on isolated yield; [B] total percentage yield; Reagents and conditions; BzCl, pyridine, DCM, -40 °C.

β-*S*-2,2,2-trifluoroethyl **137** was next screened identifying a small amount of fully benzoylated product **140** (14%) along with a mixture of 2,4-*O*-Bz regioisomers **141** and **142** (***Table 6, entry 2***). Notably, the inseparable mixture favoured 2,3,6-tri-*O*-benzoate **141** offering the best regioselectivity thus far for a β-configured thioglycoside. Cyclohexyl *O*-glycoside **136** was next screened. This entry delivered the poorest regioselectivity outcome for a β-configured system being the first example that saw isolation of 2,4-diol **146** for a β-*O*-glycoside. Notably the 3,4,6-tri-*O*-benzoate **145** was favoured over the 2,3,6-tri-*O*-benzoate **144** (23% vs 13%) (***Table 6, entry 3***). The final entry β-*O*-2,2,2-trifluoroethyl **135** produced a small amount of fully benzoylated material **147** (10%) with the major product being desired 2,3,6-tri-*O*-benzoate **148** (***Table 6, entry 4***).

Considering the results in ***Table 6***, it's reasonable to conclude the EW and ED nature of the aglycon is having an effect on the regioselectivity for β galactoses. The large difference in selectively for β *O*/*S*-PNP (**91** & **97)** and β *O*/*S*-phenyl (**86** & **110)** entries demonstrates an electronic effect alongside steric considerations. Close proximity of 2-OH to the EW endocyclic oxygen has been previously suggested to cause a decrease in nucleophilicity at this position.[114] For β configured carbohydrates the absence of the endo anomeric effect results in greater basicity of the ring oxygen further enhancing this effect (***Figure 17***).[115]

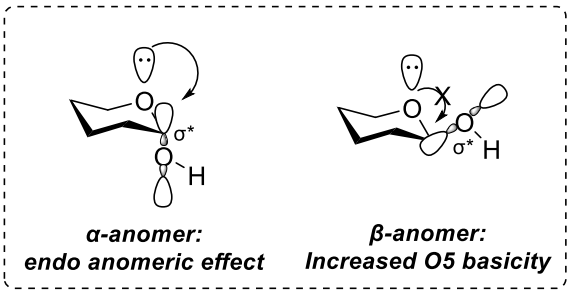


Figure 17: The *endo*-anomeric and effect on O5 basicity for β configured glycosides.

This connection between O5 and C2 might explain the observed regioselectivity differences for EW and ED aglycons. It seems plausible that a relationship between O5 and the nearby aglycon exists with the electronic effects of the aglycon being exerted on O5. In the case of an ED anomeric substituent electron density will be pushed towards O5 increasing negative charge and enhancing electron withdrawing capacity. This results in decreased reactivity of the 2-OH. EW aglycons will reverse this effect, and negative charge pulled away from O5 resulting in a more nucleophilic 2-OH (***Figure 18***). 4-, 2-OH are the same number of bonds away from O5 and so further consideration is required. Dipole-dipole interactions between equatorial hydroxyls and the sugar ring are maximised as they are in the same horizontal plane resulting in larger dipole vectors. Conversely axial hydroxyls are perpendicular to the dipole moment and so electron withdrawing capacity of O5 is minimised in respect to 4-OH.[114]

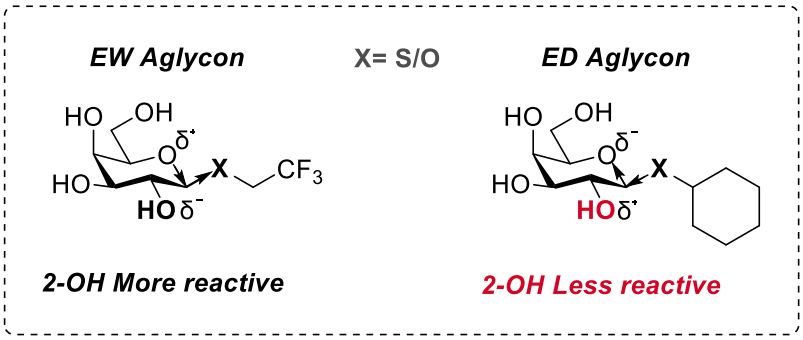


Figure 18: Effect of ED/EW aglycons on the charge of the endocyclic oxygen (O5) and resulting 2-OH reactivity.

Previous work by Jensen reports remote electronic effects of C2 *para*-substituted ether protecting groups on the reactivity of β thioglycosides.[116] The authors found ED C2 *para*-substituted ethers increased the reactivity of thioglycosides. Conversely EW *para*-substituted ethers decreased reactivity *via* destabilization of the oxocarbenium ion-like transition state during donor activation. This example highlights the effect of remote

electronic effects and the connection between O5/C1 and C2. Further work by Bols investigated the effect of ED and EW protecting groups on the p*K*a of the ring nitrogen in piperidine systems. It was found that ED benzyl PGs caused an increase in p*K*a when compared with EW benzoyl PGs demonstrating the effect of ED/EW ring substituents on ring heteroatom charge.[117]

Its well-known that steric and electronic effects are deeply intertwined and so these results must be taken into consideration with the already suggested steric factors in sections (**3.4** & **3.3**).[118] The most ED cyclohexyl groups produced the least selectivity at 2-OH (***Table 6, entry 1 and 3***). In the case of β *S*-cyclohexyl **134** (***Table 6, entry 1***), it is likely a combination of steric burden and electronic inactivation that resulted in no reaction taking place at 2-OH, resulting in isolation of just the 2,4-diol **139**. Conversely the EW and smaller *S*-2,2,2-trifluoroethyl substrate **137** (***Table 6, entry 2***) saw the best selectivity for the 2,3,6-tri-*O*-benzoate. In the context of the explanations put forward this result make sense being a small and also EW aglycon. Notably this entry is still being hindered by the size of sulfur and not allowing for complete selectivity. *O*-cyclohexyl derivative **136** provided the poorest selectivity for a β configured *O*-galactose (***Table 3, entry 3***). When compared with *S*-cyclohexyl derivative **134** the reduced size of oxygen probably allows some reaction to take place at 2-OH, but is still heavily disfavoured matching the trend of large and ED aglycons hindering selectivity at this position. Finally, *O*-2,2,2-trifluoroethyl substrate **135** achieved a large degree of selectivity (***Table 6, entry 4***) in line with developed expectations.

3.5 Expanded substrate scope – α-configured galactosides

The substrate scope was expanded next to different α *O*-glycosides. First, galactose **149** possessing an anomeric alkyne was screened; this handle can be readily functionalised

through either click chemistry or palladium catalysed reactions such as Songashira couplings. After 1.5 hrs complete consumption of the starting material was observed. Purification and ^{1}H NMR characterisation identified tri-*O*-benzoate **150** as the sole product in 76% yield. 6-*O*-TIPS protected methyl glycoside **151** yielded desired glycoside **152** in 74%. Interested to see if steric burden of the TIPS and low reactivity of 4-OH was sufficient to deliver regioselectivity, the reaction was repeated at RT. However, this change in reaction conditions saw a loss in regioselectivity. The final entry, **153**, furnished **154** in 87% yield, granting efficient access to a PMP glycoside.

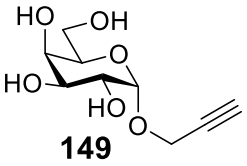
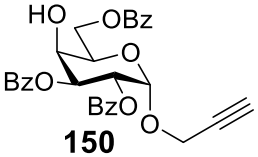
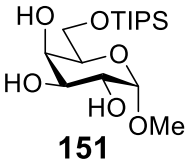
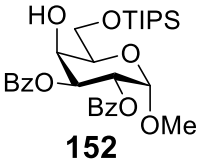
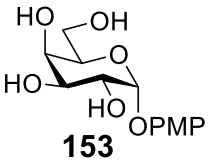
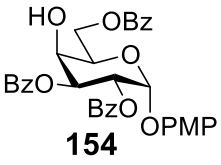
Entry	Substrate	Product [A]	Yield [B]
1	 **149**	 **150**	**76%**
2	 **151**	 **152**	**74%**
3	 **153**	 **154**	**87%**

Table 7: Benzoylation of α *O*-galactopyranosides **149**, **151**, **153**; [B], isolated yields of pure products after column chromatography; Reagents and conditions; BzCl, pyridine, DCM, -40 °C.

3.6 Expanded substrate scope – galactosamines

As regioselectivity seemed to be dependent on the reactivity of the 2-OH, extension to galactosamine derivatives was considered next. Initially α/β GalNAc entries **155** and **157** bearing an anomeric allyl moiety were synthesised reasoning the configuration would have no impact on reaction outcome. When screened, low temperature benzoylation successfully delivered 3,6-di-*O*-benzoates for both anomers in similar yields; 68% for β-allyl **155** (***Table 8, entry 1***) and 65% for α-allyl **157** (***Table 8, entry 2***).

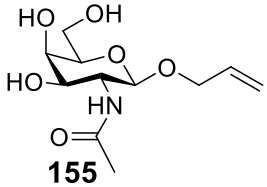
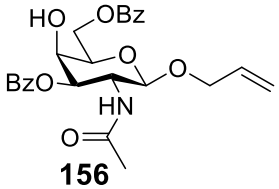
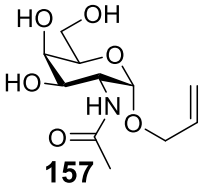
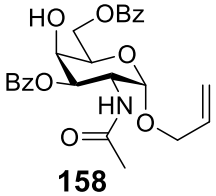
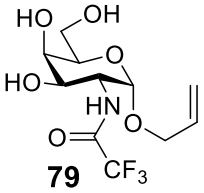
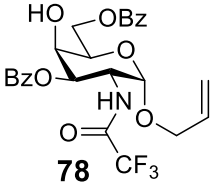
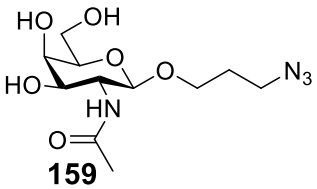
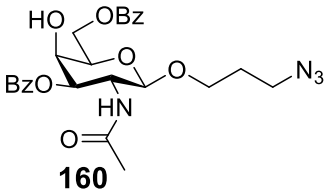
Entry	Substrate	Product [A]	Yield [B]
1	 **155**	 **156**	**68%**
2	 **157**	 **158**	**65%**
3	 **79**	 **78**	**70%**
4	 **159**	 **160**	**83%**

Table 8: Benzoylation of *O*-galactosamine entries **79**, **155**, **157**, **159**; [B], isolated yields of pure products after column chromatography; Reagents and conditions; BzCl, pyridine, DCM, -40 °C.

Next, *N*-TFA **79** was screened and successfully delivered target **160** in 70% yield. finally, benzoylation of **159**, bearing an azido propyl linker at the anomeric position, afforded 4,6-di-*O*-benzoate **160** in 83% yield.

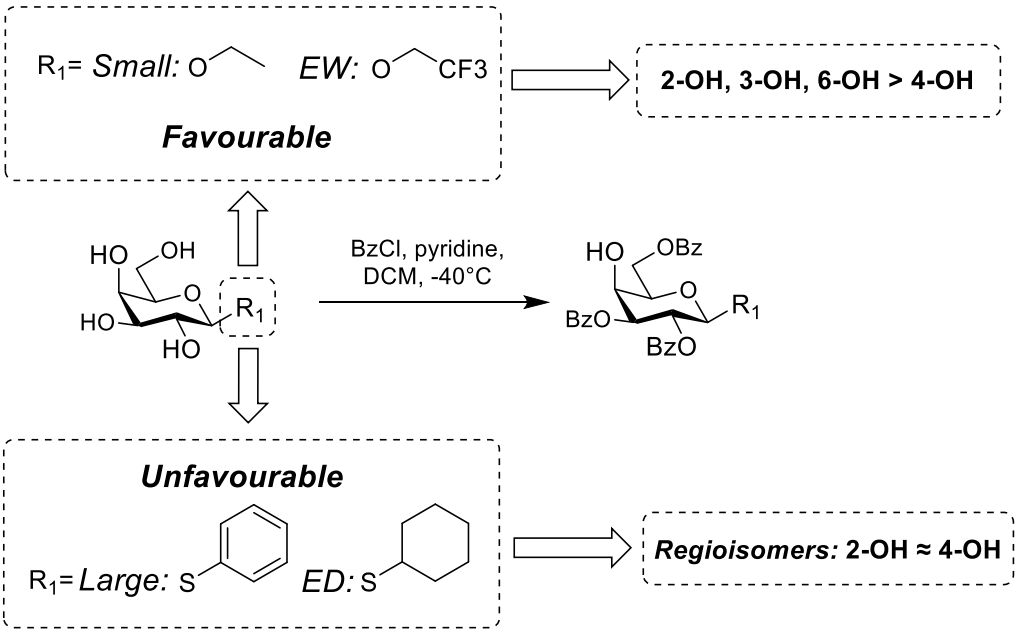
3.7 Conclusion and Future work

The reactivity of α galactosides is considered to be 6OH>2OH>3OH>4OH.[119] In this work all α configured substrates obeyed this reactivity series, allowing for regioselective synthesis of 2,3,6-tri-*O*-benzoates using low temperature benzoylation conditions. Further experiments were performed investigating galactosamine derivatives and as predicted the anomeric configuration did not have a detrimental impact on regioselectivity achieving good yields for all entries screened (***Table 8***). In the case of β-galactosides, seemingly a combination of different factors can affect the observed regioselectivity for *O*-benzoylation.

1) Size of the aglycon.
2) EW and ED donating capacity of the aglycon.

It was found that larger aglycons make selective protection more difficult. This was evident for all β thioglycosides with complete regioselectivity for the 2,3,6-tri-*O*-benzoate not being possible. It seems plausible that the larger size is restricting access to 2-OH making benzoylation a more difficult task (***Scheme 35***). Conversely smaller aglycons made regioselective protection easier successfully delivering 2,3,6-tri-*O*-benzoates in high yields (***Table 5, entry 4***) (***Table 6, entry 4***). The electronic effects of the aglycon must also be considered with ED cyclohexyl entries reducing reactivity at 2-OH. This was most evident for ***Table 6 entry 1*** producing only the 2,4-diol **139**. This effect was reversed for EW aglycons, best demonstrated by *S*-2,2,2-trifluoroethyl

substrate **137** (***Table 6 entry 2***) providing the best selectivity for the 2,3,6-tri-*O*-benzoate. Further study into the effect of aglycon on regioselectivity should consider looking at different reaction conditions and the effect on regioselectivity.



***Scheme 35*:** General trends for the effect of the aglycon on regioselective benzoylation outcome to favour 2,3,6-tri-*O*-benozates for β galactoses.

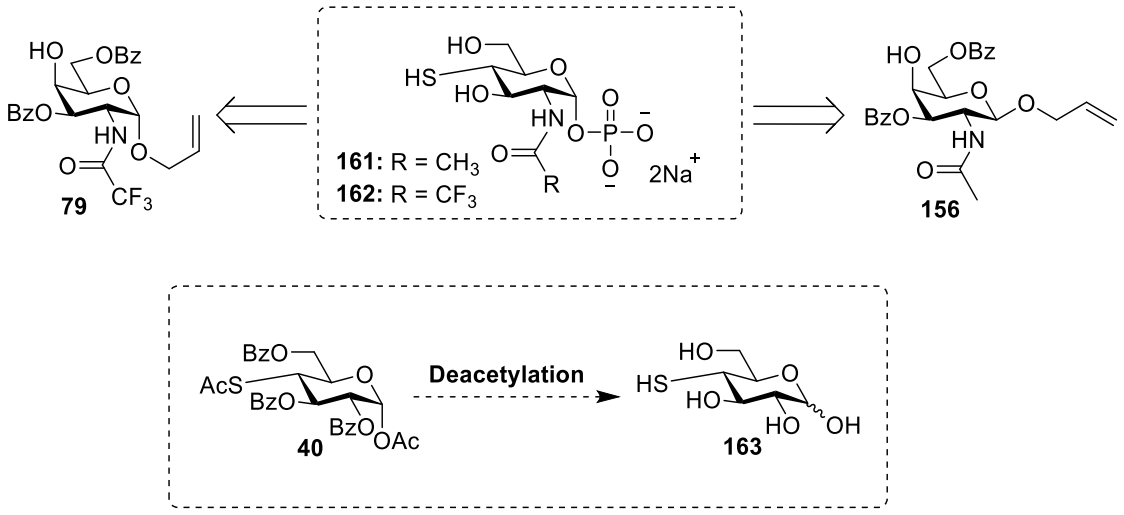
Pedersen and co-workers have recently demonstrated the large effect different conditions can have on regioselective outcome. By altering base type, base equiv., solvent, concentration and benzoylation reagent optimized protocols for selective benzoylation were developed.[120] Another avenue of investigation is looking at the synthesis of similar mannose derivatives. This would be of interest to see if aglycon effects on O5 extend to the now equatorial 4-OH. If a similar pattern of reactivity was observed when compared with 2-OH of galactose this would provide further support of the explanations put forward in this work.

Chapter 4

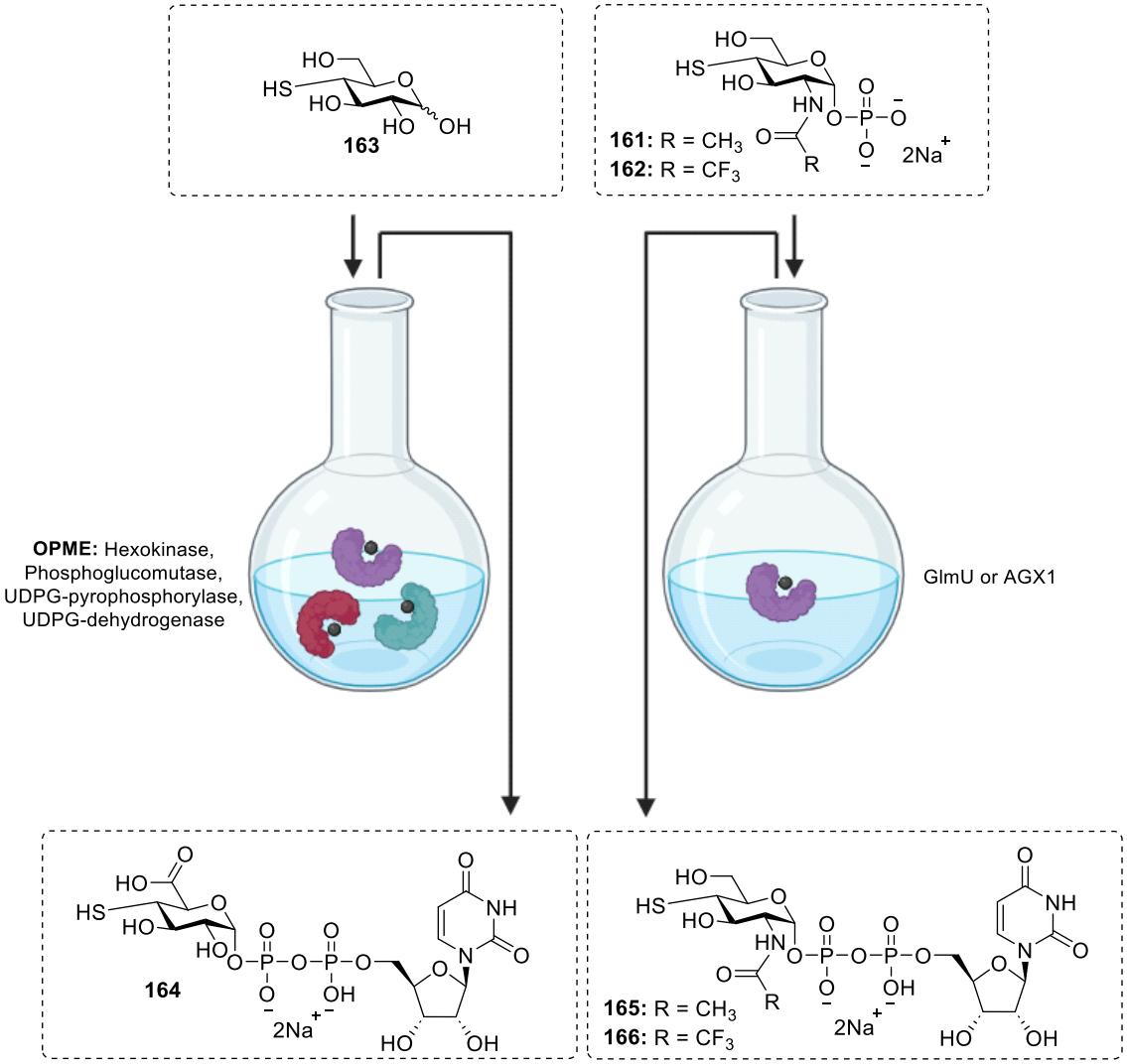
Synthesis of glycosyl 1-phosphates and free sugars that incorporate a 4-deoxy-4-thio modification

4.0 Aims and Introduction

Following the investigation into low temperature regioselective benzoylation and synthesis of modified oleyl GLs, further application of the accessed precursors was envisaged. With 3,6-di-*O*-benzoate protected galactosamine derivatives **79** and **156** (See section **3.6**) to hand a short synthetic route towards GlcNAc and GlcNTFA 4-thio 1-phosphates, **161** and **162** was designed. These targets were selected as novel substrates for chemoenzymatic synthesis of the corresponding UDP sugars (**165** & **166**), involving *N*-acetylglucosamine-1-phosphate uridyltransferase (GlmU) and Human UDP-GalNAc Pyrophosphorylase (AGX1) (***Scheme 37***).[121] Another previously synthesised and advanced precursor in the form of protected 4-thio-glucose derivative **40** would also be utilised in this chapter (See section **2.6**). Access to 4-deoxy-4-thio-glucose requires a 1-step deprotection towards **163** (***Scheme 36***). This will allow investigation of this material within a one-pot multienzyme system (OPME). With the aim of accessing 4-SH UDP glucuronic acid **164** in collaboration with Professor Jian Liu (University of North Carolina at Chapel Hill (***Scheme 33***).[122, 123, 124]



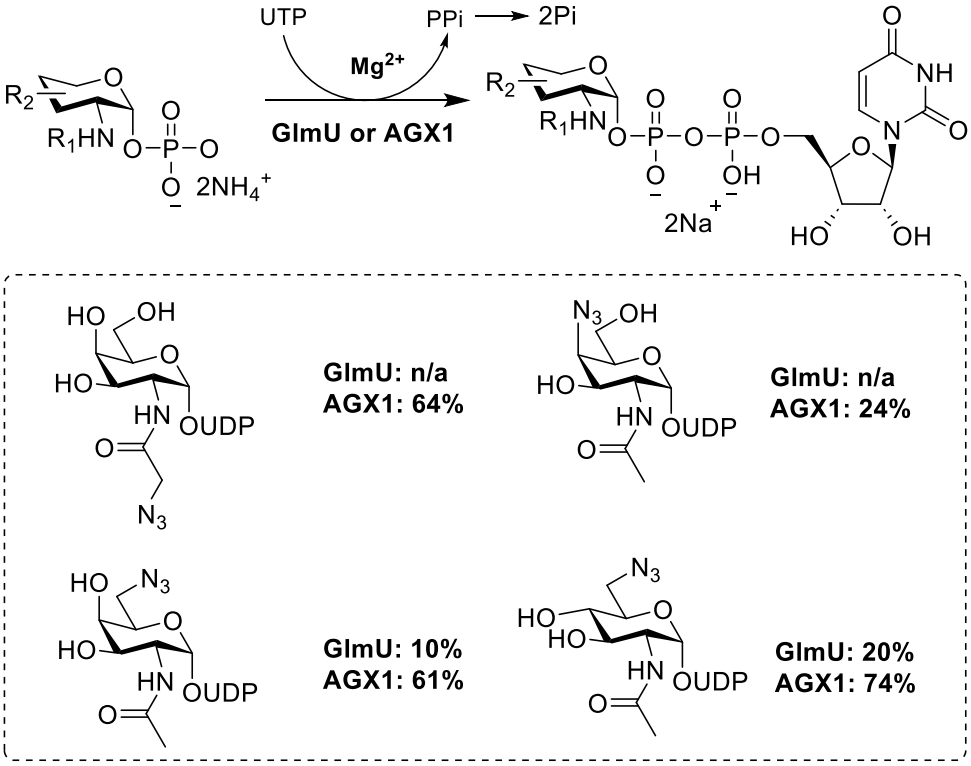
Scheme 36: Application of previously synthesised building blocks (**40**, **79**, **156**) towards the synthesis of towards 4-deoxy-4-thio glucose **163** and 4-thio 1-phosphates **161** and **162**.



Scheme 37: Enzymatic transformations of 4-thio 1-phosphates **161-162** to **165-166** and 4-thio-glucose **163** to **164**.

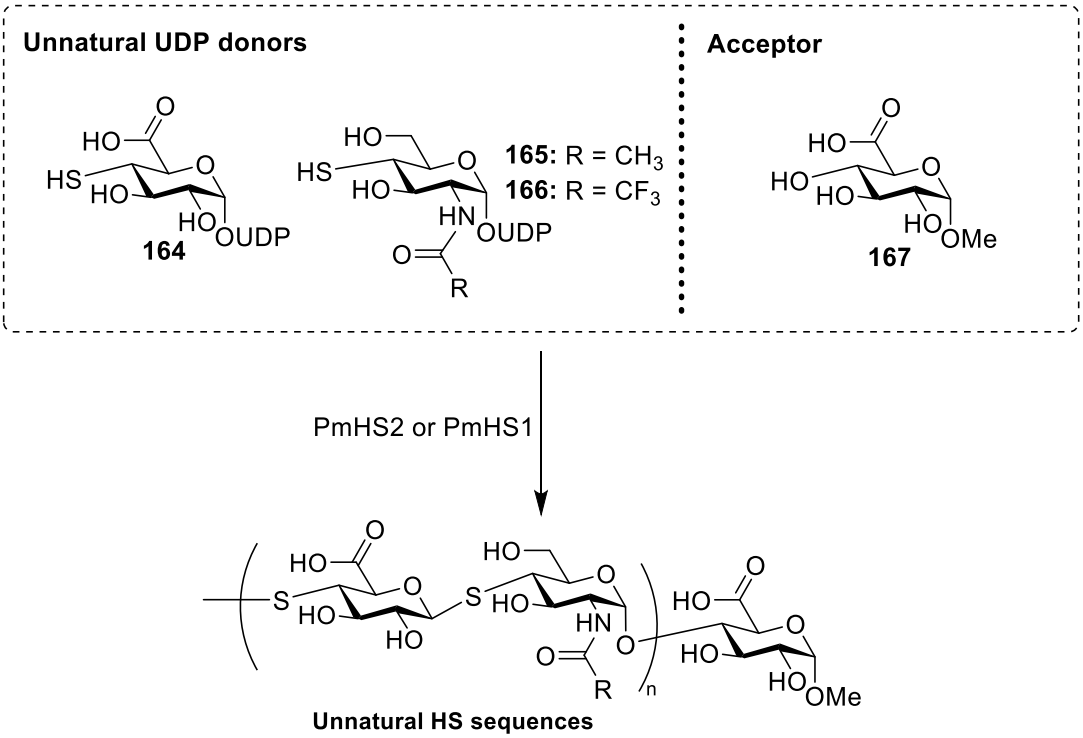
GlmU has proven to be an effective tool in accessing UDP sugars (***Scheme 38***) AGX1 has also seen success performing similar transformations. Work presented by Wang and co-workers carried out extensive studies to compare both GlmU and AGX1 with the aim of determining substrate specificity. From the results it was found that both enzymes demonstrated limited acceptance of C-4 modifications ultimately concluding AGX1 was the better choice for C-2,4,6 modifications.[121] Sugar nucleotides are activated versions of monosaccharides they are typically composed of a monosaccharide and a mono/di phosphate moiety linked through the anomeric carbon. Given their role as the universal

carbohydrate donor, much effort has been put into their efficient synthesis and modification to further enhance their role.[125] A number of nucleotide sugars can be found in mammals including UDP sugars for glucuronic acid, glucose and galactose including their *N*-acetyl derivatives. Sugar-nucleotide diphosphates are crucial for the biosynthesis of carbohydrates and glycoconjugates.[126, 127, 128]



Scheme 38: Comparison of substrate specificity between AGX1 and GlmU.[121]

Sugar nucleotides serve as activated sugar donors for glycosyl transferases (GTs). GTs are key enzymes that catalyse the formation of glycosidic bonds enabling the construction of oligosaccharides.[129] Accessing sugar nucleotides **164-166** *via* a chemoenzymatic approach would allow the construction of *S*-linked polysaccharides such as HS (***Scheme 39***).[130]



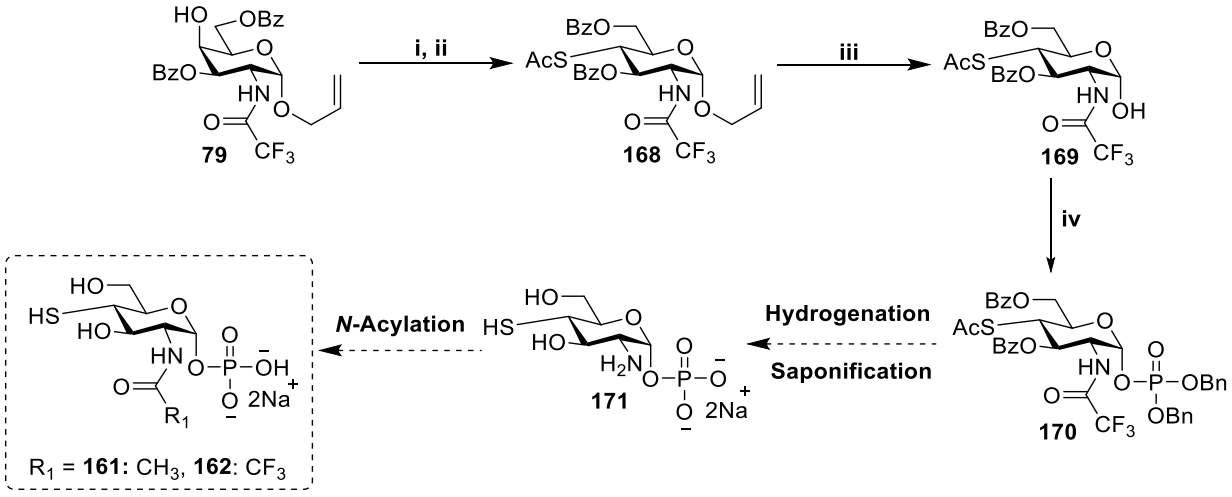
Scheme 39: Hypothetical application for sugar nucleotides **164-166**: construction of a partially *S*-linked HS sequence using pmHS1 or pmHS2.[7]

4-Thio GlcNTFA 1-phosphate **162** was selected as a non-natural alternative to GlcNAc 1-phosphate. This was based on work previously reported in which UDP-*N*-trifluoroacetylglucosamine was found to be a good substrate for GlcNAc-UDP specific transferases including 'core-2' GlcNAc transferase EC 2.4.1.102 and PmHS2.[131, 132] *N*-trifluoroacetamide protection offers mild removal and access to the free amine allowing for further modification such as *N*-sulfation. Accessing these materials *via* a chemoenzymatic approach will support accessing sulfur-containing mimetics aiding future development. *S*-glycosides are of particular interest as tools and probes. Close structural similarity to *O*-glycosides and increased stability of *S*-linkages offers the potential for hydrolysis resistant glycomimetics.[133] This resistance to metabolic events provides useful insight into binding and recognition events.[53] *S*-linked saccharides have

also demonstrated the capacity to act as competitive inhibitors for glycoside hydrolases.[134]

4.1 Chemical synthesis of glycosyl 1-phosphates incorporating a 4-thio modification

With galactosamine building block **79** to hand a pathway towards 4-thio-1-phosphate **171** was envisaged (***Scheme 40***). This route hoped to deliver both 4-thio-glucosamine-1-phoshates **161** and **162**, with the pathway relying on late-stage *N*-acylation.

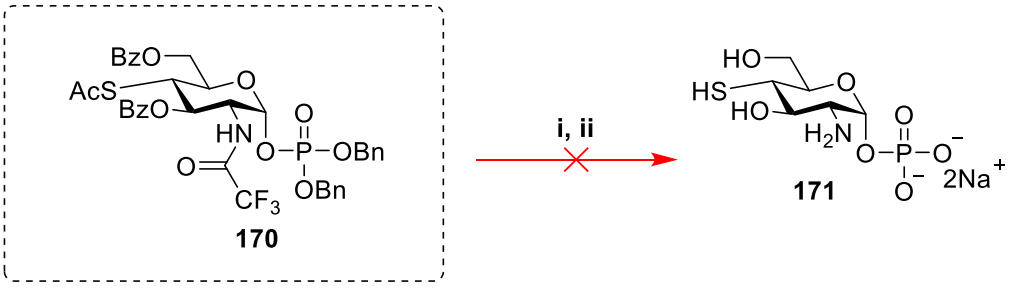


Scheme 40: Attempted synthesis of **171** for late-stage *N*-acylation to access **161**-**162**. Reagents and conditions; i. Tf_2O, DCM, pyridine; ii. KSAc, DCM, pyridine, RT, 73% (2 steps); iii. $Pd(PPh_3)_4$, DCM, AcOH, 80 °C, 92%; iv. LDA, TBPP, THF, -78 to 0 °C, 66%.

Relying on the procedure of first installing a triflate followed by thioacetate nucleophilic inversion, compound **168** was successfully synthesised in 73% yield. Reaction of allyl glycoside **168** with $Pd(PPh_3)_4$ in AcOH at 80 °C proceeded successfully and delivered α-hemi-acetal **169** in 74% yield ($^3J_{H1-\ H2}$ = 3.4 Hz). LDA and tetrabenzylpyrophosphate were utilised next to deliver the corresponding α-1-phosphate **170** in 66% yield.

4.2 Attempted deprotection

Hydrogenolysis of the benzyl groups present within **170** proceeded as expected. Tracking the reaction by TLC showed that after 3 hrs of reaction only a single spot was visible (R_f = 0.1, DCM/MeOH, 8:2). Pd/C was removed by filtration and the crude residue treated with 1M NaOH, stirring at RT overnight. Subsequent ^{1}H NMR analysis showed the presence of two compounds. One plausible explanation was formation of disulfide from the free sulfhydryl of **171**, accounting for the second compound. Furthermore, aromatic protons were still present, suggesting benzoyl migration; it seemed unlikely that *O*-Bz could survive the deprotection conditions, however, benzoyl group migration to nitrogen was possible.



Scheme 41: Attempted deprotection of **170**. Reagents and conditions; i. Pd/C, MeOH, H_2; ii. 1M NaOH, RT.

From the ^{1}H NMR spectrum the ratio of the free amine **171** to *N*-Bz side product **172** was 1:0.4, **172/171** (***Figure 19***). HMBC revealed a cross peak from H-2 [δ_H = 4.01 ppm] to a carbonyl [δ_C = 171.7 ppm] supporting benzoyl migration to the amine. Previous synthesis of *N*-TFA glucosamine 1-phosphate (lacking the 4-SH) didn't report acyl migration; seemingly therefore this results from the modification at C4.[135, 136] The absence of any chemical shifts in the ^{19}F NMR spectrum provided strong evidence that the second component was the free amine and not *N*-TFA protected target **162**. A number of

deprotection conditions were screened attempting to suppress benzoyl migration with results visible in ***Table 9***.

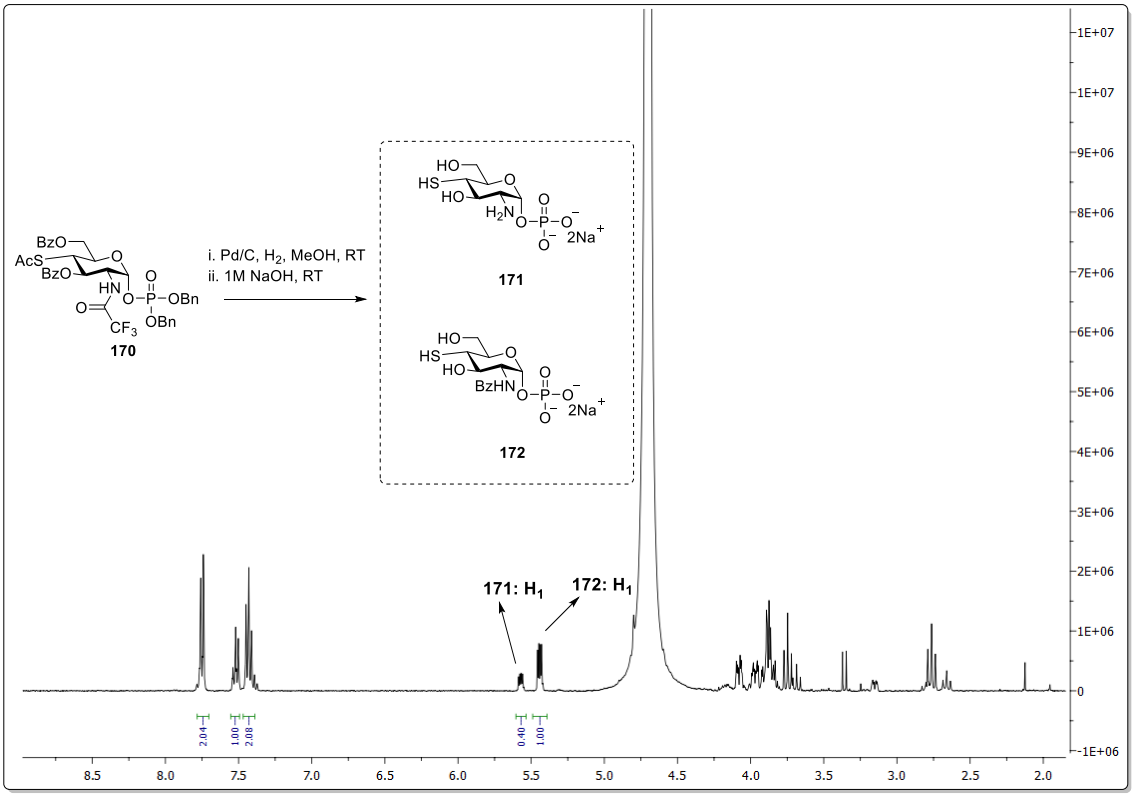


Figure 19: ^{1}H NMR (D_2O, 400 MHz) spectrum obtained after purification for inseparable mixture of **171/172** resulting from benzoyl migration to the amine.

The absence of any chemical shifts in the ^{19}F NMR spectrum provided strong evidence that the second component was the free amine and not *N*-TFA protected target **162**. A number of deprotection conditions were screened attempting to suppress benzoyl migration with results visible in ***Table 9***. As *N*-TFA glycosyl 1-phosphates are a glycomimetic of the native NHAc 1-phosphate it was considered pragmatic to shift focus towards the native target **161** instead. This change afforded two benefits, first providing a quicker route towards preliminary results as to the viability of 4-SH glucosamine 1-phosphates as enzyme substrates and secondly, working with NHAc circumvents the migration issues encountered serving as a permanent functionality from the outset of the route.

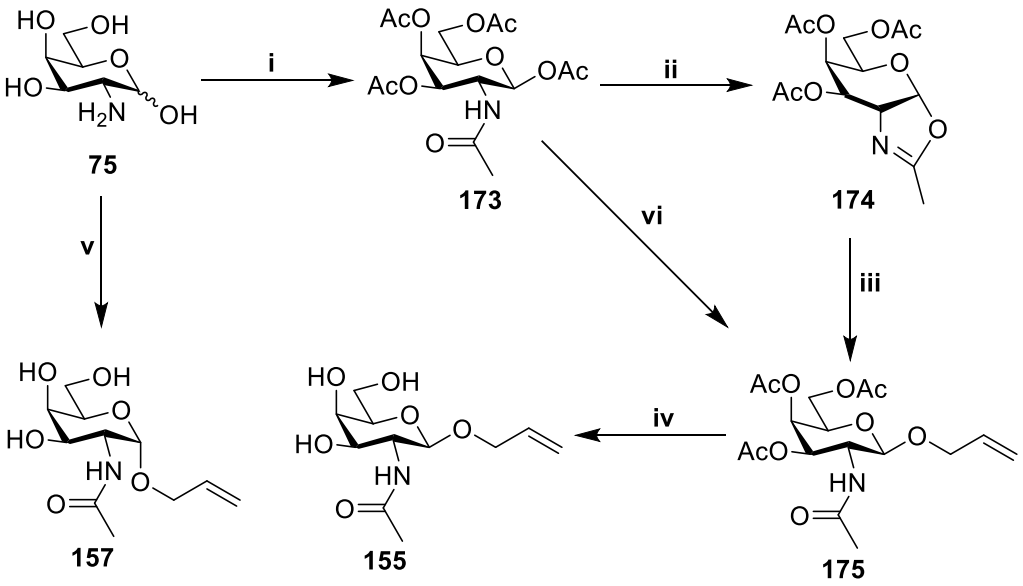
Table 9: Screened conditions for ester deprotection of **170.**

Deprotection conditions	Reaction outcome
1M NaOH, RT	Benzoyl migration
Na (0.1 equiv.), MeOH, RT	Benzoyl migration
1M LiOH, RT	Benzoyl migration
NH_3 in MeOH, RT	Benzoyl migration

4.3 Towards 2-acetamido-2-deoxy-4-thio-α-D-glucopyranoside phosphate (disodium salt) 171

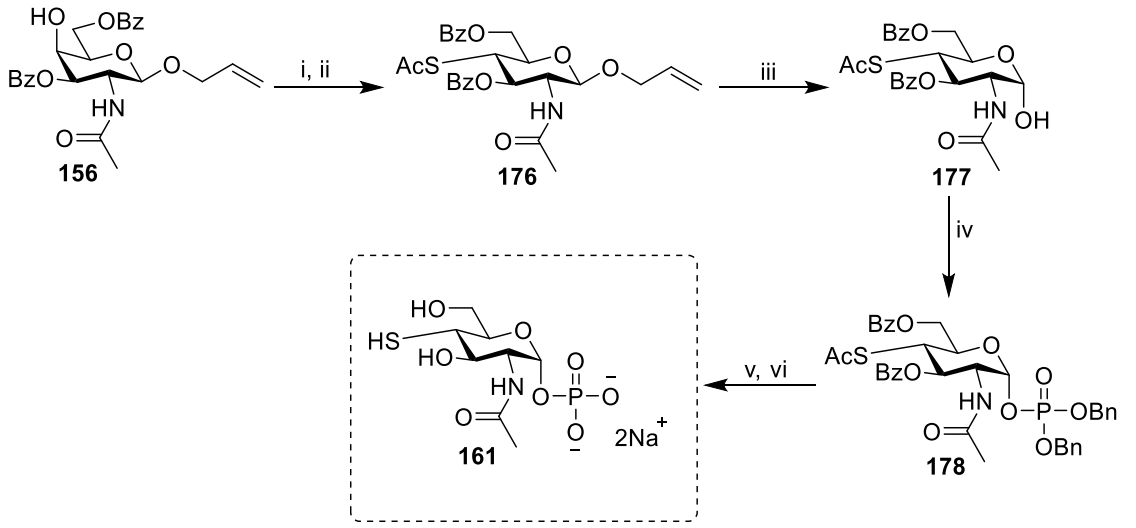
Starting from D-galactosamine **75** (***Scheme 39***), Ac_2O in pyridine with NaOMe gave the *N*-acylated pyranose. The crude residue was subsequently dissolved in allyl alcohol and refluxed at 110 °C with $BF_3{\cdot}OEt_2$, initially for 5 hrs. Upon addition of diethyl ether none of the desired allyl functionalised pyranose **157** precipitated. TLC analysis suggested product composition presenting a baseline spot that couldn't be moved up the plate. Work presented by Nishimura outlined a similar issue, observing decomposition of the desired product after extended reflux.[138]

To address this issue, the temperature was reduced to 70 °C and reaction time to 2 hrs. After making these changes a small amount of the desired **157** was precipitated in 13% yield. Alternatively, oxazoline **174** was synthesised from **173** using TMSOTf in DCE at 50 °C. With oxazoline **174** in hand, glycosylation with allyl alcohol successfully delivered allyl glycoside **175** in an improved yield of 50% (***Scheme 42***). Deacetylation under Zémplen conditions delivered allyl functionalised triol **155** in 83% yield.



Scheme 42: Towards allyl 2-deoxy-2-acetamido-α/β-D-galactopyranoside **157**/**155**. Reagents and conditions. i. Ac_2O, pyridine, 0 °C to RT, 79%; ii. TMSOTf, DCE, 50 °C, 57%; iii. TMSOTf, allyl alcohol, RT, 50%; iv, NaOMe, MeOH, RT, 83%; v. NaOMe, Ac_2O, MeOH, allyl alcohol, $BF_3{\cdot}OEt_2$, 70 °C, 13%; vi. $FeCl_3$, allyl alcohol, DCE, RT, 73%.

In the pursuit of higher yields and reduced purification, the method was carried out as a one pot process. Accordingly, direct treatment of glycosyl acetate **173** with allyl alcohol, $FeCl_3$ and DCE afforded allyl glycoside **174** in 73% yield. Whilst obtaining an improved yield, purification was also simpler. After quenching the reaction with $NaHCO_3$ and solvent removal, pure **174** could be precipitated through the addition of hexane/EtOAc, avoiding the need for column chromatography. Having optimised access to **155**, regioselective benzoate protection of 3-OH and 6-OH was carried as per section **2.6**. Functionalisation of the 4-OH proved straightforward; triflation and inversion using KSAc delivered **176** in 80% yield. Palladium-mediated allyl cleavage successfully delivered α-**177** ($^3J_{H1\text{-}H2}$ = 3.2 Hz) and access to the protected α-linked 1-phosphate was achieved using LDA and tetrabenzylpyrophosphate, furnishing **178** in 66% yield.



Scheme 43: Towards 2-deoxy-2-acetamido-4-thio-α-D-glucopyranoside 1-phosphate (disodium salt) **161**, i. Tf_2O, DCM, pyridine, 0 °C, ii. KSAc, pyridine, RT, 80% (2 steps), iii. $Pd(PPh_3)_4$, AcOH, 80 °C, 80%; iv. LDA, TBPP, THF, -78 °C to RT, 66%; v. Pd/C 10% wt., MeOH, vi. 1 M NaOH aq. 62% (2 steps).

When **178** was subjected to the same deprotection conditions as **170**, the reaction proceeded without issue. After purification by SAX, full characterisation of the target 1-phosphate **161** was completed. From ^{1}H NMR analysis it was evident a second species was again present; this was also evident in the ^{31}P NMR spectrum with two visible chemical shifts [δ_P 1.04 – 0.90 (m), 0.78 – 0.58 (m,) ppm]. To determine if a disulfide was present, HRMS was completed. Two major *m/z* signals were visible, the first corresponded to **161** (*m/z* = 315.0179) and the second corresponded with disulfide **179** (*m/z* = 631.0433) (***Figure 20***). In summary 4-SH GlcNAc 1-phosphate **161** was successfully synthesised using an optimised route. Benzoyl migration could not be mitigated when trying to access 4-SH GlcNTFA-phosphate **162**. Work presented by Busca and Martin previously reported deacetylation of *N*-TFA protected 1-phosphates utilising guanidine. With these conditions leaving the *N*-TFA amine protecting group in place, presenting a future avenue for accessing **162**.[138] Target 4-SH GlcNAc 1-phosphate **161** is currently undergoing substrate screening using AGX1 and GlmU to access 4-SH GlcNAc UDP sugar **165** Glc in collaboration with Dr Jonathan Dolan (Keele University).

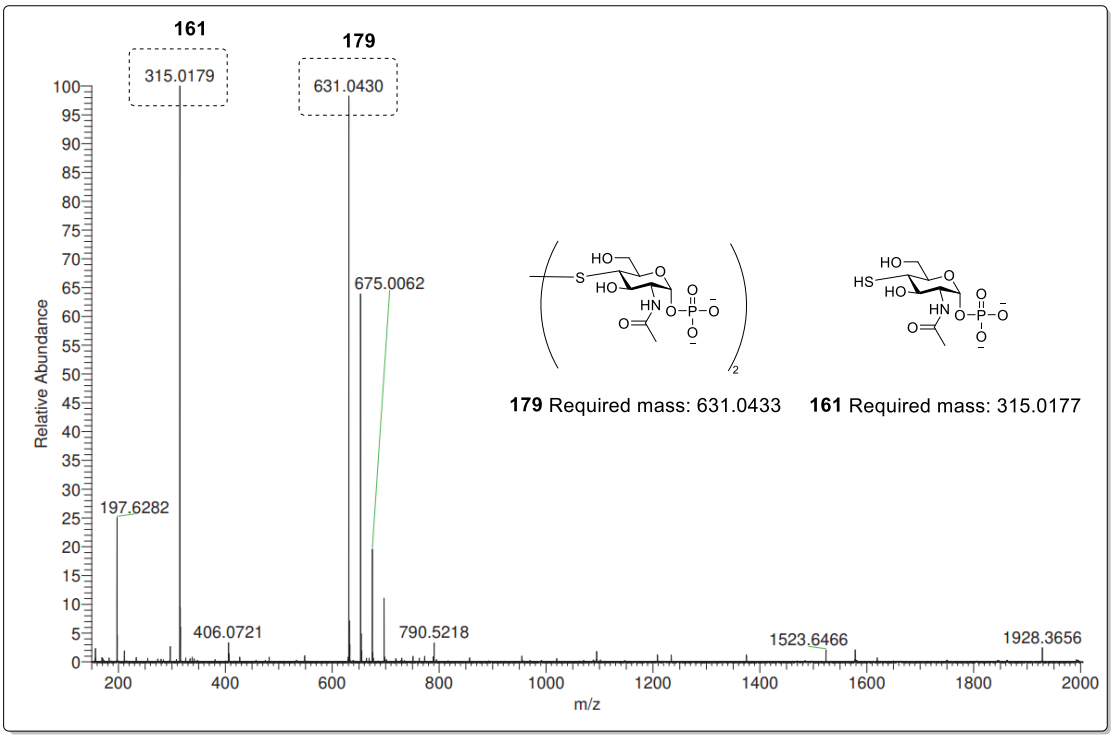
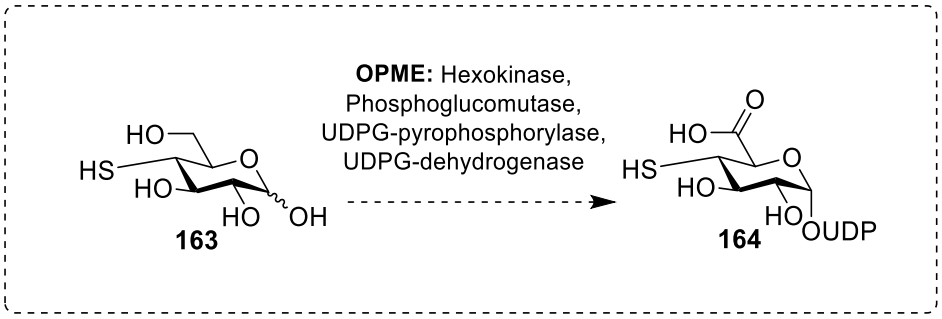


Figure 20: HRMS spectrum obtained for **161** including **179** with signal assignment.

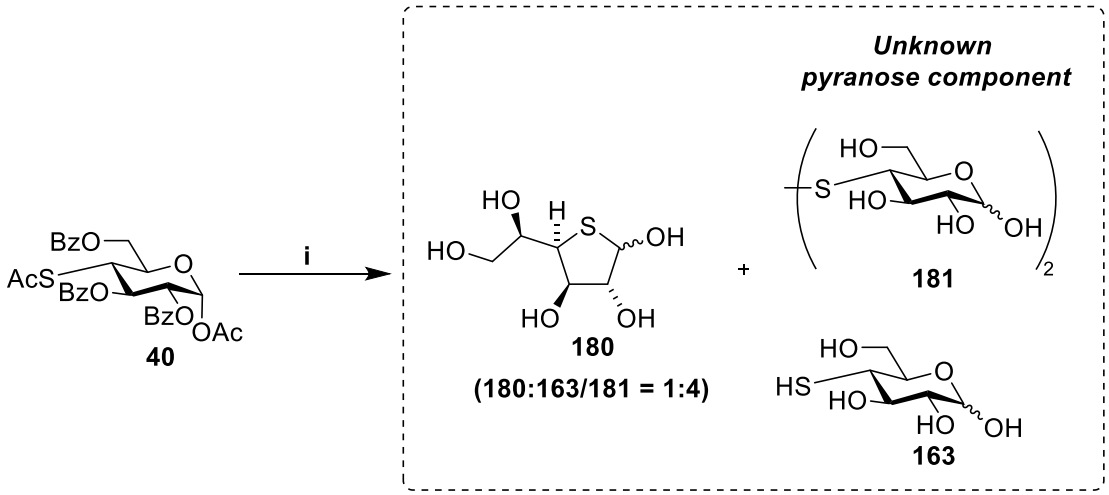
4.4 Attempted synthesis of 4-thio-D-glucopyranose 163

A related project, with the aim of expediting access to 4-SH UDP glucuronic acid **164** from 4-thio-D-glucopyranose, was carried out in collaboration with Professor Jian Liu (University of North Carolina at Chapel Hill). The transformation sought to explore a one pot multi enzyme (OPME) process detailed in ***Scheme 44*** to access 4-SH UDP-glucuronic acid **164**. Accordingly, the synthesis of **165** was explored. Acetyl 4-*S*-acetyl-2,3,6-tri-*O*-benzoyl-4-thio-α-D-glucopyranoside **163** was synthesised following a previous pathway developed (See section **2.6**, ***Scheme 12***). Accordingly, acetyl 4-*S*-acetyl-2,3,6-tri-*O*-benzoyl-4-thio-α-D-glucopyranoside **40** was subjected to global de-esterification using NaOMe in MeOH (***Scheme 45***).



Scheme 44: Transformation of 4-thio-D-glucopyranose **163** into 4-SH UDP glucuronic acid **164** utilising an OPME.

TLC analysis after 24 h revealed complete conversion of the starting material to a single spot [R_f = 0.54 (DCM/MeOH, 7:3]. The reaction mixture was neutralised with Amberlite IR120 (H^+) and the crude residue purified by column chromatography. ^{1}H NMR of the isolated material revealed four distinct anomeric environments. Two of these environments matched expected coupling constants and chemical shifts for 4-deoxy-4-thio pyranose **163** [δ_H 5.19 (d, $^{\alpha}J_{H1\text{-}H2}$ = 3.5 Hz), 4.52 (d, $^{\beta}J_{H1\text{-}H2}$ = 8.0 Hz), δ_C 92.1 C1α, 95.5 C1β ppm]. Coupling constants and chemical shifts for the remaining anomeric environments didn't match those typically observed for pyranose systems [δ ppm, 5.64 (d, $^{\alpha}J_{H1\text{-}H2}$ = 4.1 Hz), 5.33 (app t, $^{\beta}J_{H1\text{-}H2}$ = <1.0 Hz), δ_C 80.1, 86.1 ppm C1].



***Scheme 45*:** Attempted synthesis of 4-thio-D-glucopyranose **163.** Reagents and conditions; i. NaOMe, MeOH, RT. 71%.

It was considered from these observations that ring interconversion to a thermodynamically favoured furanose form had occurred.[17, 18] This aligned with previous examples reported in the literature, whereby 4-thiohexofuranose derivatives had been accessed from D/L-*ribo*, D-*xylo* , D-*ido* , 6-deoxy-D-*gluco*, and D-*galacto* configurations.[139-143] The product mixture was considered to contain both 4-deoxy-4-thio-furanose **180** and an unknown pyranose, either the free sugar or disulfide. The overall yield was 71% and obtained as an inseparable mixture (1/4 ratio of furanose/pyranose components). In response to these observations a further experiment was performed on the inseparable mixture, subjecting it to treatment with DTT.

4.5 Basic deprotection with the inclusion of DTT for disulfide suppression

DTT is widely used redox reagent also known as Cleland's reagent. In its reduced form DTT is capable of reducing disulfide bonds, typically being employed for the deprotection of thiolated DNA or to prevent protein cysteine interactions.[144] As the corresponding thiolate is the active species, DTT works best above pH 7 and not at all in strongly acidic environments. Upon formation of the thiolate, a thiol exchange occurs with DTT displacing one component of the bond. Furthermore, the propensity to cyclise from this intermediate drives the reaction forward delivering free sulfhydryl groups (***Scheme 46***). It was reasoned DTT could act to reduce disulfide species generated from the saponification of **40** (***Scheme 47***). Following treatment of mixture **163:180/181** with DTT (1.5 equiv.) ^{1}H NMR analysis revealed the preferred tautomer, furanose **180**, to be the major product (***Figure 21***).

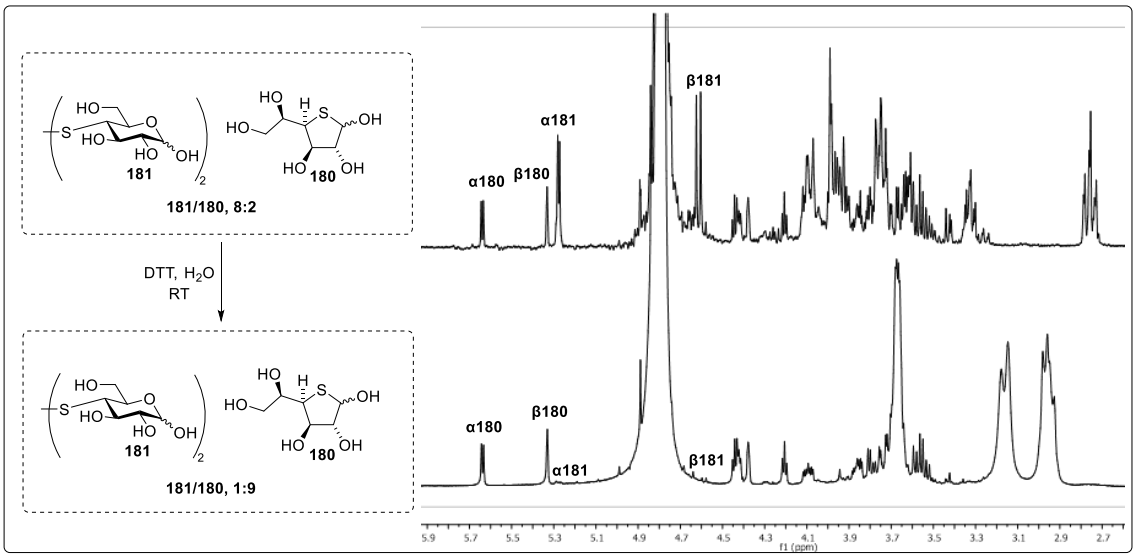
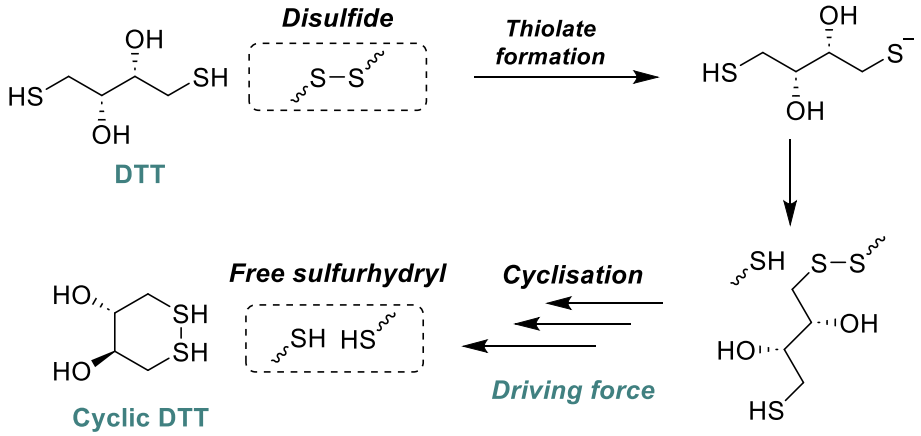


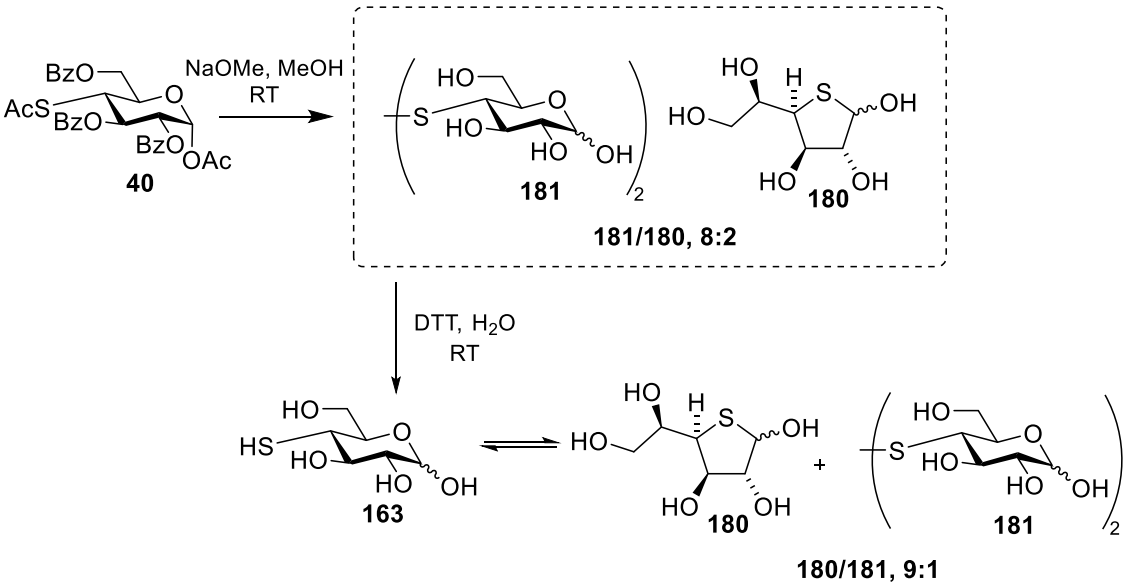
Figure 21: Stacked ^{1}H NMR spectra (400 MHz, D2O) showing top) an inseparable mixture of **180** and **181** after purification; bottom) after the mixture of **180** and **181** was subjected to DTT for 24 hrs.

Prior to DTT treatment the anomeric ratio of pyranose/furanose was 8:2. Following reduction the ratio favoured the furanose (pyranose/furanose, 1:9) (***Scheme 44***). This indicated the prior assigned pyranose was likely the disulfide form **181**.



Scheme 46: Reductive action of DTT on a disulfide bond to give the free sulfhydryl.

After observing preference towards the furanose tautomer, a repeat experiment that incorporated DTT into the reaction conditions was completed, reasoning the inclusion would enable *in situ* reduction of any disulfide species allowing full deprotection and tautomerization to the furanose form.



Scheme 47: Reduction of disulfide **181** and furanose **180** mixture using DTT (1.5 equiv.).

After 2 hrs of reaction time a single spot by TLC could be observed, a crude reaction aliquot was subjected to ^{1}H NMR analysis. This revealed four distinct anomeric shifts, assigned to furanose and pyranose forms, through observed vicinal ^{3}J coupling constants ($^{\beta-180}J_{H2\text{-}H3}$ = 2.0 Hz and $^{\beta-181}J_{H2\text{-}H3}$ = 9.2 Hz). The inclusion of DTT and comparison with the anomeric chemical shifts previously observed for **181** allowed reasoning that the major observed pyranose was in fact the free sulfhydryl form **163**. It should be noted that even with DTT present a small amount of the disulfide could be seen in the ^{1}H NMR spectrum obtained after 2 hrs, the relative ratio of each was determined to be **163**:**180**:**181** of 61/37/2 (***Figure 22***). After allowing the reaction to stir for a total of 24 hrs a further aliquot was analysed by ^{1}H NMR, at this point the furanose had become the dominant species and the new observed ratio for **163**:**180**:**181** was determined to be 13:84:3 (***Figure 18***).

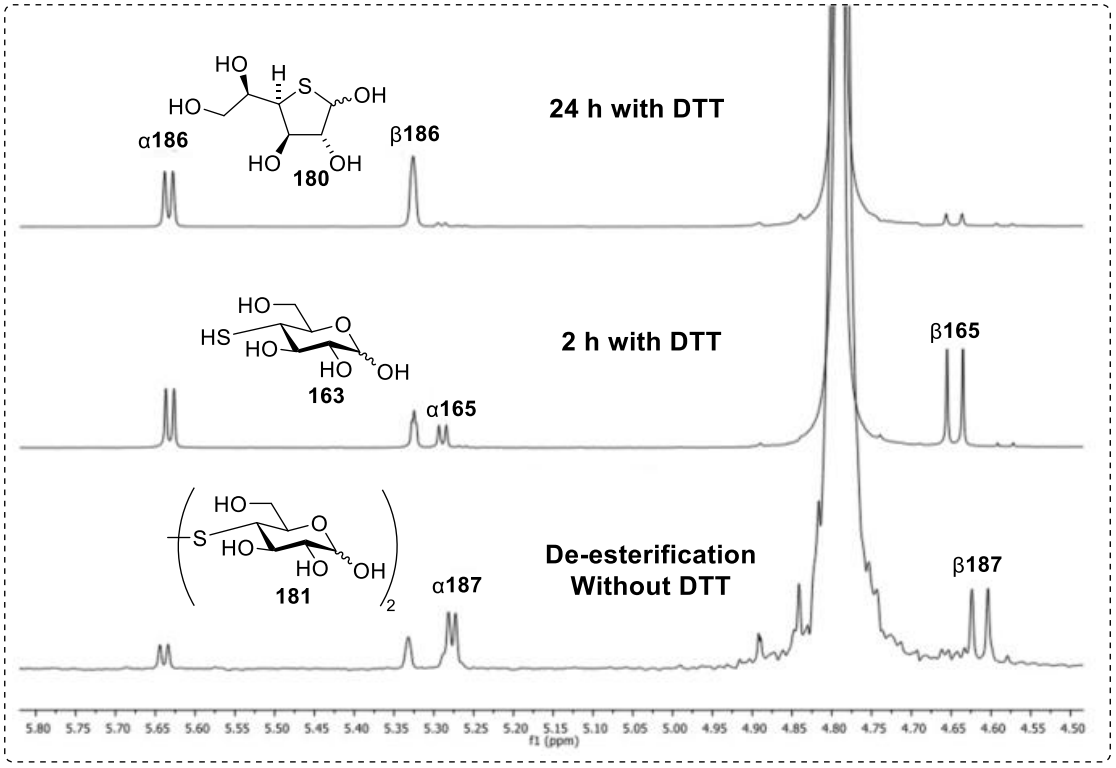
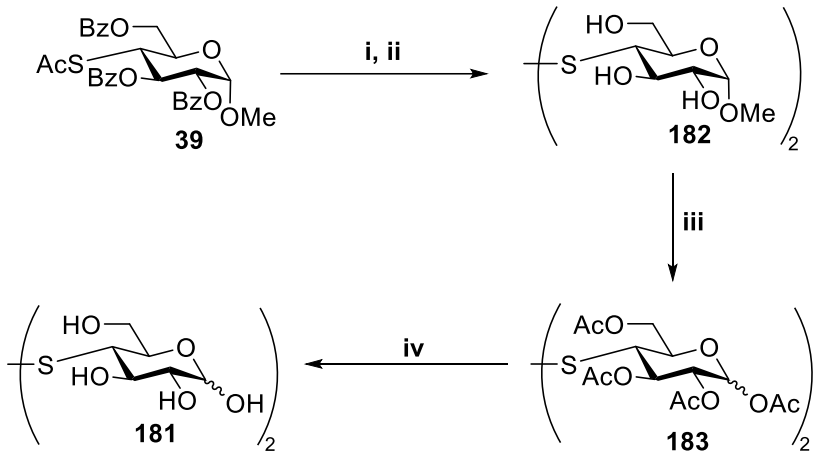


Figure 22: Stacked ^{1}H NMR spectra (400 MHz, D_2O) comparing de-esterification of **40** with and without DTT. Top spectrum: Crude NMR analysis after stirring for 24 h with DTT. Middle spectrum: Crude NMR analysis of a reaction aliquot after 2 h with DTT. Bottom spectrum: Crude NMR analysis of furanose **180** and disulfide **181** mixture from first pass de-esterification without DTT.

4.6 Synthesis of bis(4-thio-D-glucopyranose)-4,4'-disulfide 181

Having gained an understanding into the pyranose/furanose interconversion of 4-thio glucose **163**, a new approach was required. As the original goal was to access 4-thio glucose in the pyranose form, disulfide **181** was targeted, for controlled release to the pyranose form. Starting from methyl glycoside **39**, deprotection to the free 4-sulfhydryl was accomplished by use of 1M NaOH in MeOH and H_2O, followed by subsequent oxidation, to generate disulfide **182** in 86% yield over 2 steps.[145, 146] HRMS analysis confirmed the disulfide form (***Scheme 48***).



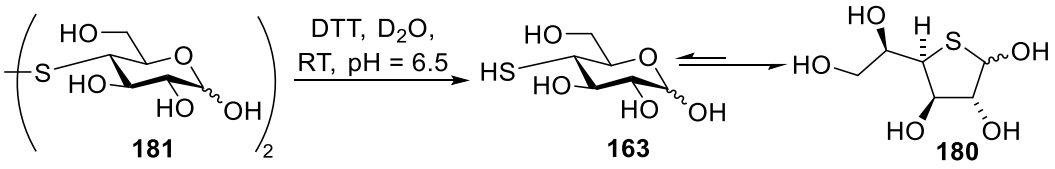
Scheme 48: Alternative synthesis of bis(4-thio-D-glucopyranose)-4,4′-disulfide **181**. Reagents and conditions. i. 1M NaOH, MeOH, H_2O, RT; ii, Et_3N, MeCN, sonication, RT 89% (2 steps); iii. Ac_2O, AcOH, H_2SO_4, RT, 47%; iv.1M NaOH, MeOH, RT, 77%.

With dimer **182** in hand, acetolysis was performed yielding tetra-*O*-acetyl **183** in 47% yield. The moderate yield was attributed to the reaction failing to reach completion. A final saponification successfully furnished the target disulfide **181** in 77% yield and demonstrating that interconversion to the furanose could be prevented by protecting the sulfhydryl as a disulfide.

4.7 NMR time studies for the reduction of bis(4-thio-D-glucopyranose)-4,4'-disulfide 181

An assessment of the viability of **181** to act as a reservoir to access 4-thio glucose **163** was carried out next. An NMR time scale reaction was performed with the goal of determining the rate of interconversion at pH = 6.5. The time scale of the experiment was over a period of 24 hrs and the results can be seen in ***Table 10*** and ***Figure 23***. Formation of the free thiol **163** could be observed 5 mins after DTT addition (***Table 10, entry 1***). After 1 h, trace amounts of the furanose **180** appeared (***Table 10, entry 2***). Compound **163** appeared to be the major species between 3 and 9 h (***Table 10 entries 3–5***), but from this point furanose **180** became dominant (***Table 10 entry 6–9***), until being the only

isomer visible after 24 h (***Table 10, entry 10***). Complete reduction of **181** required approximately 21 h (***Table 10, entry 9***). From these results it can be concluded that disulfide **181** can be harnessed for controlled, reductive release of **163**, allowing access to the free thiol in pyranose form. The window of access should be considered with full tautomerism to the furanose occurring after 24 hrs. In conclusion disulfide **181** has the potential to be utilised for enzymatic transformations, granting access to 4-thioglucose **163** as the substrate.



Entry	Time[b]	Ratio 181:163:180[c]
1	5 mins	78:22:0
2	1 h	56:40:4
3	3 h	43:44:13
4	6 h	32:42:26
5	9 h	27:40:33
6	12 h	17:33:50
7	15 h	14:31:55
8	18 h	6:29:65
9	21 h	0:17:83
10	24 h	0:0:100

Table 10: [a] NMR scale reaction for the reduction of disulfide **181**; reaction conditions: DTT (1.1 equiv.), D_2O (90 mM); [b] Time allowed to pass until ^1H NMR experiment repeated, [c] Ratio determined by combined anomeric integration values for each compound.

After assessing **181** was capable of granting access to **163** *via* controlled DTT reduction **181** was subjected to the OPME described in ***Scheme 44***. Disappointingly none of desired 4-SH UDP glucuronic acid **164** was observed.

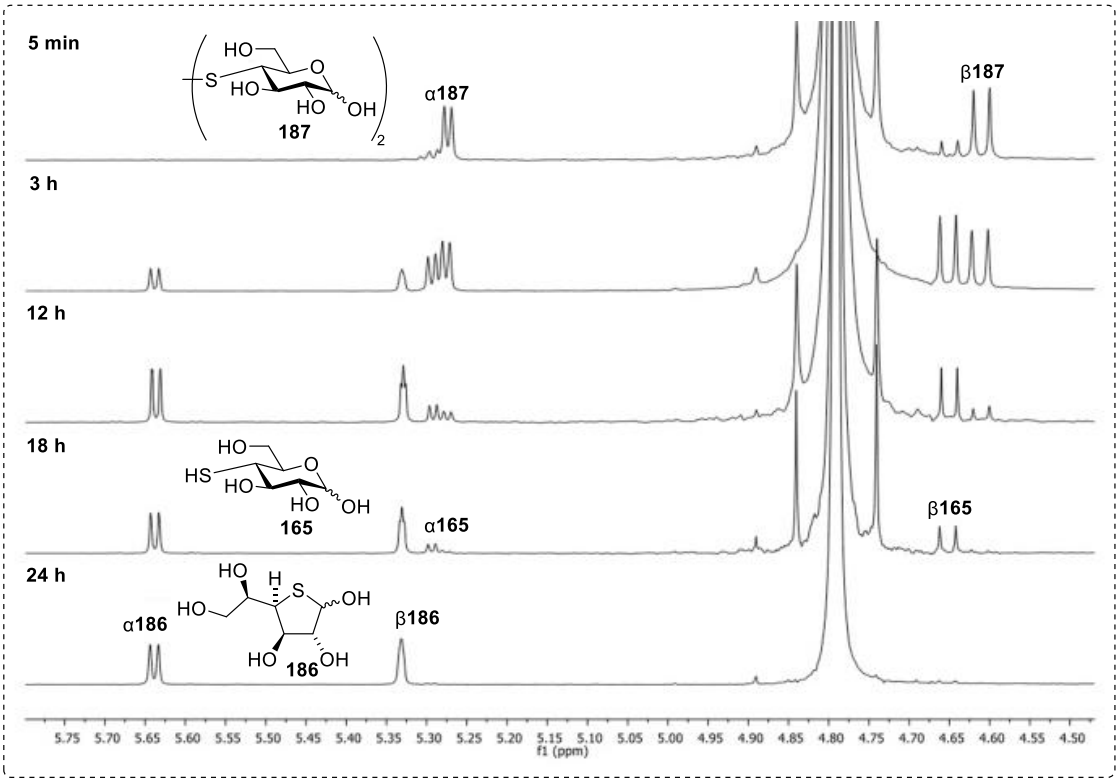
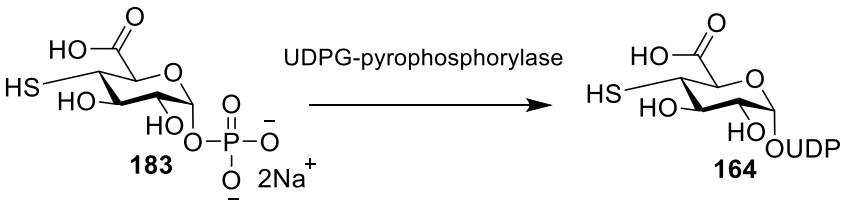


Figure 23: Stacked ^{1}H NMR spectra (400 MHz, D_2O) illustrating the interconversion of **163** and **180** from **181**, over 24 h.

4.8 Conclusion and future work

Synthesis of *N*-TFA protected 1-phosphate **162** was ultimately unsuccessful; the issue of benzoyl migration onto the free amine could not be mitigated. In the face of this issue attention was pivoted towards 4-SH containing GlcNAc 1-phosphate **161** leading to successful synthesis. Work is currently ongoing to determine the viability of **161** as a substrate to access the corresponding UDP sugar **165** *via* GlmU or AGX1. Preliminary data suggests **161** to be a poor substrate for GlmU with more promise being shown by AGX1. Efforts to synthesise 4-thio-glucose uncovered a competing interconversion to the preferred furanose form. Despite being unable to isolate homogeneous **163**, the disulfide form was successfully synthesised, and NMR time studies completed, monitoring the rate of disulfide reduction and subsequent interconversion to the furanose

form. The results showed complete interconversion occurs after 24 hrs following treatment with DTT. These NMR time studies demonstrated that disulfide **181** can be harnessed as a reservoir to access 4-thio glucose. Future work includes scaling up the enzymatic transformation of **161** into the corresponding UDP sugar via AGX1. If successful, this will allow for further investigation to take place and examination of **165** for GT catalysed construction of *S*-linked polysaccharides. A chemical approach to access **165** could also be taken. Hydrogenation of protected 4-SH GlcNAc 1 phosphate **178** would present a pathway towards the UDP sugar *via* pyrophosphorylation with uridine monophosphate. In the pursuit of 4-SH UDP glucuronic acid **164** a more refined approach could be taken. Rather than performing a OPME carrying out the transformations individually could provide improved results. This approach would likely make troubleshooting the cause of reaction failure an easier task. Alternatively chemical synthesis of a substrate later in the pathway for example 1-phoshate **183** and relying on a final enzymatic transformation to the UDP sugar could be investigated (***Scheme 49***).



Scheme 49: Enzymatic transformation of 4-SH glucuronic 1-phosphate **183** into of 4-SH UDP glucuronic acid **143** *via* UDPG-pyrophosphorylase,

Chapter 5

Towards a GLUT1 Targeting Gemcitabine Prodrug

5.0 Aims and Introduction

Cancer is a leading cause of death across the world, particularly in developed countries.[147] The high mortality rate associated with cancer can be partly attributed to a lack of treatment options and growing resistance towards therapeutics currently in use.[148] Antimetabolites are a class of chemotherapy drugs designed to mimic naturally occurring and biologically important structures. Nucleoside analogues (NA) including gemcitabine and cytarabine belong to this group of medications and are designed to mimic naturally occurring pyrimidine nucleosides (***Figure 24***).

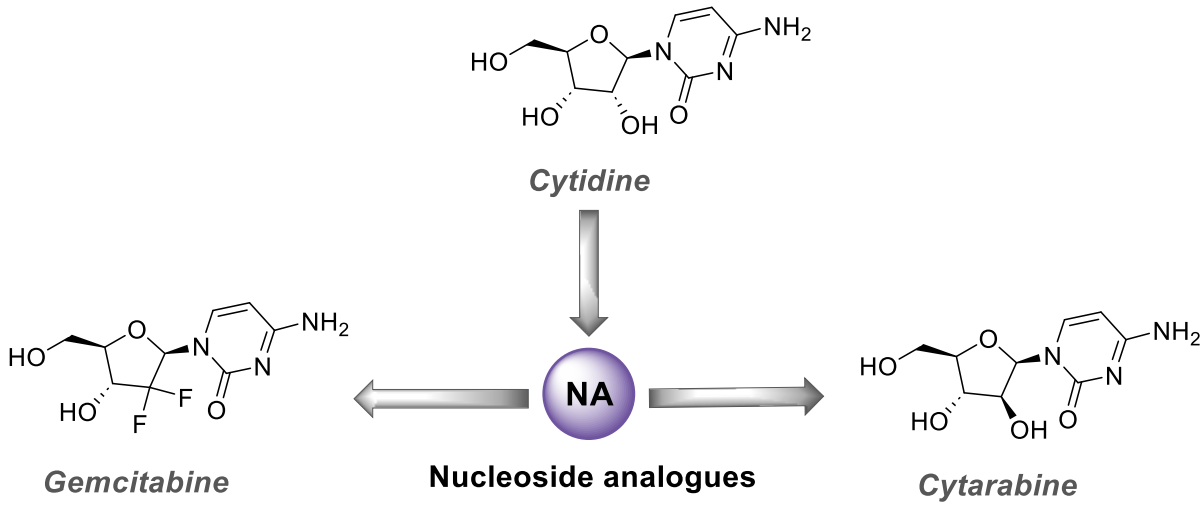


Figure 24: Structures of cytidine and common nucleoside analogues gemcitabine and cytarabine.

Several impressive gemcitabine prodrugs have been previously reported and each has their own advantages.[149] A gemcitabine prodrug that specifically targets glucose trasnsporter 1 (GLUT1) has not been previously reported, however. With the persistent issue of tumour resistance towards nucleoside analogues (NAs) ever growing, this chapter aims to help overcome one avenue associated with a decrease in NA effectiveness, namely downregulation of nucleoside transporters.[150]

Specialised transporter proteins such as human equilibrative nucleoside transporter 1 (hENT1) permit gemcitabine access to the intracellular space.[151, 152] Gemcitabine must enter the intracellular space to exert its toxic effects. As such the efficacy of treatment is significantly reduced for tumours that display low hENT1 expression (***Figure 25***).[153]

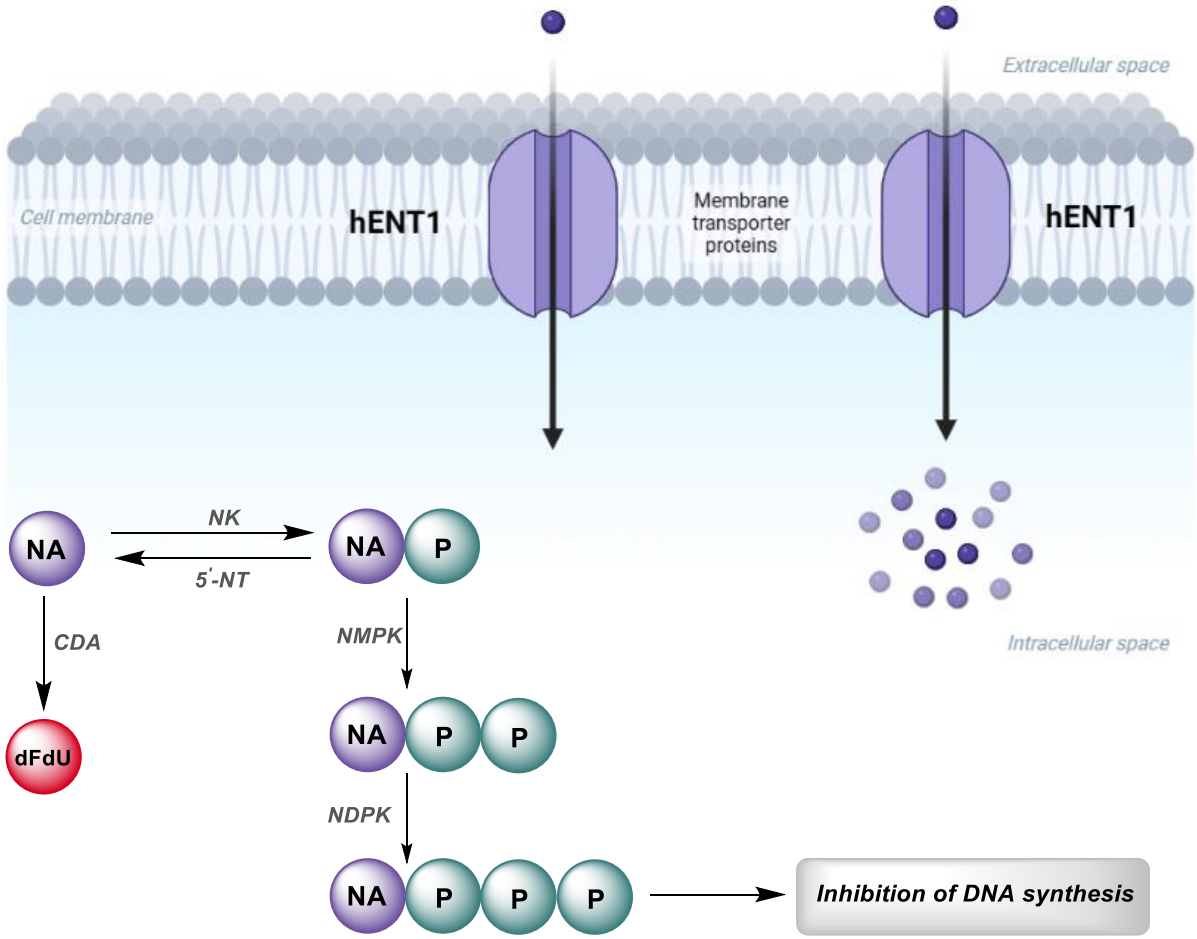


Figure 25: Metabolic pathway for Gem.

Cancer cells are significantly more reliant on aerobic glycolysis as their source of energy, in comparison healthy cells tend to rely on the Krebs cycle. Aerobic glycolysis provides energy through the metabolism of glucose, generating energy in the form of ATP. In an act to propagate and boost growth, cancer cells adjust their metabolism from that of healthy cells. In the 1920's Otto Warburg demonstrated that tumour tissues have high rates of glucose uptake and increased fermentation of glucose to lactate.[154] To

accommodate increased uptake of glucose, tumours typically overexpress glucose transporters such as GLUT1. By conjugating a glucose moiety to gemcitabine through a sulfur containing redox responsive immolative linker, it was hypothesised structure **184** could grant access to both NA transporters and GLUT1, bolstering entry of this cytotoxic material into the cell (***Figure 26***).

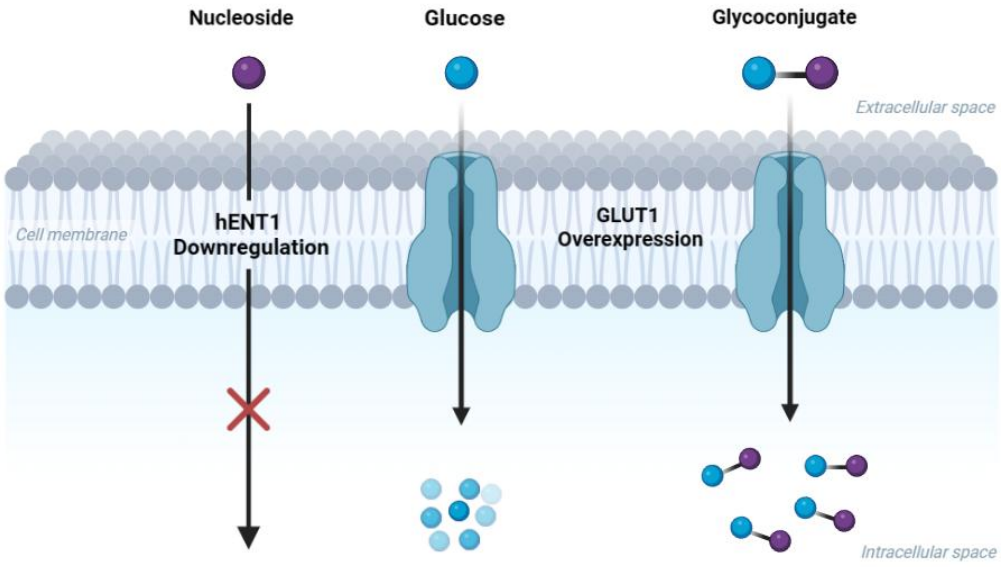
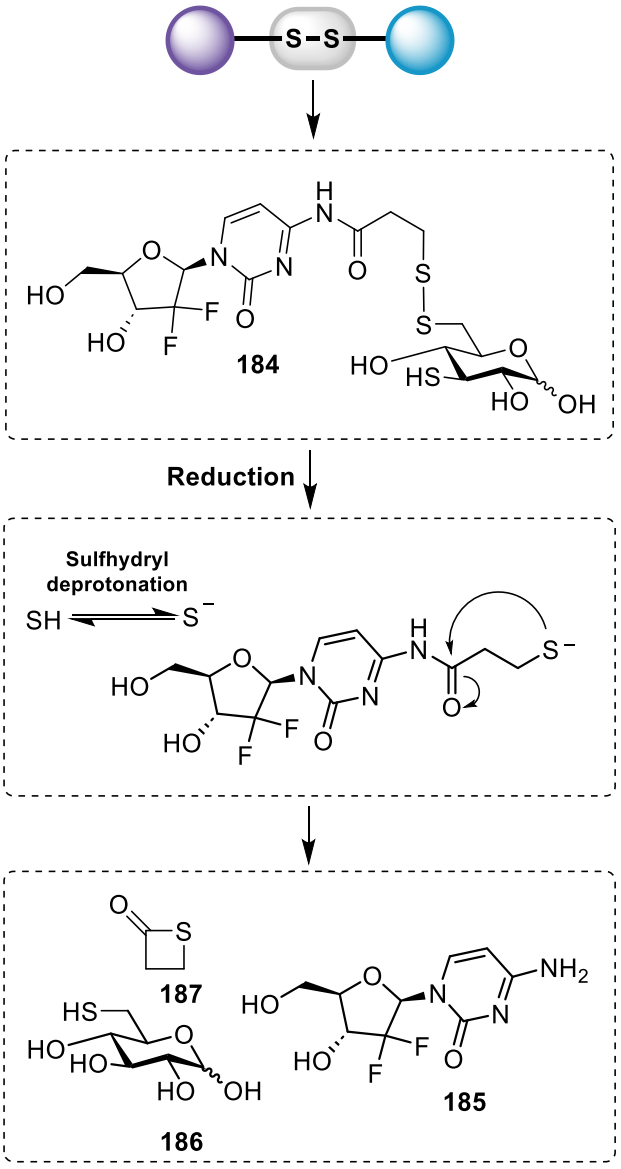


Figure 26: Scheme demonstrating the mode of action for intracellular localization of glucose-gemcitabine conjugate.

Having gained experience synthesising thiosugars in previous chapters, a 6-deoxy-6-thio glucose derived ligand was conceptualised that allowed for gemcitabine conjugation. This was preferred over 4-deoxy-4-thio glucose as conjugation through the 6-position has been show to the be more amenable to GLUT1 mediated intracellular localization.[155] Structure **184** was targeted for synthesis; this design sees a glucose moiety connected to gemcitabine through the amine present within cytosine. The design also sees the redox reactive component being incorporated as part of the pyranose, through C6. It was hypothesised that if structure **184** grants access to the intracellular space *via* GLUT1 or

HENT1, a subsequent reduction of the disulfide, and linker self-immolation could generate 6-deoxy-6-thio-glucose **186** thietane-2-one **187**, and gemcitabine **185**.[156]



Scheme 50: Initial gemcitabine-glucose conjugate design and reductive self-immolative action.

5.1 Pro-drug design and rational

The first decision made in the design of the prodrug was implementation of a redox responsive self immolative linker that serves to connect both gemcitabine and D-glucose moieties (***Figure 27***). A good linker should offer two properties, good stability whilst in

circulation and the capacity to rapidly self-immolate when the prodrug has reached its intended target.[157]

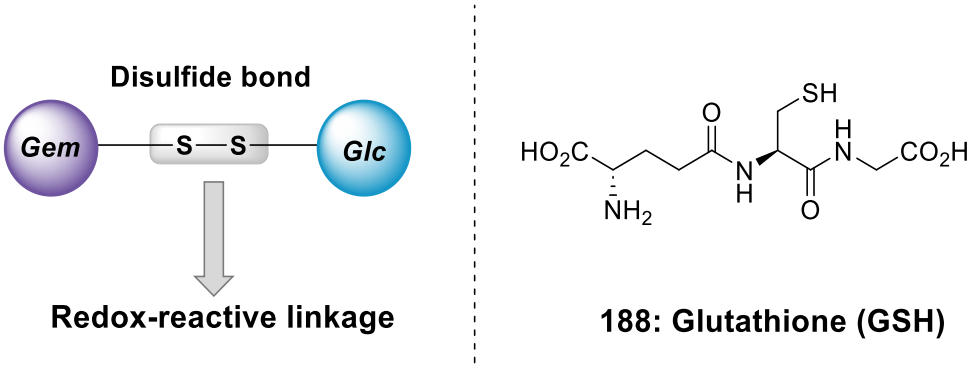


Figure 27: Disulfide containing linker design and structure of GSH.

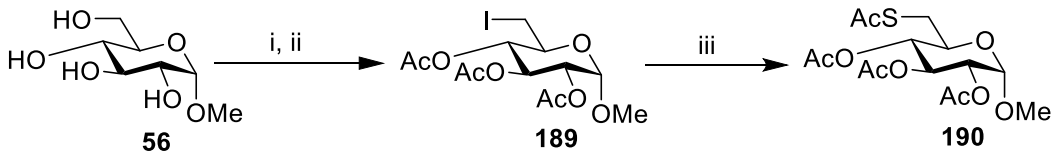
Disulfide bonds are an ideal candidate for meeting both criteria: they are stable and only 40% weaker than a carbon-carbon bond with a bond dissociation energy of 60 kcal/mol (251 kJ mol^{-1}).[157] Whilst offering good bond strength, disulfide bonds are redox-reactive and can be readily reduced. In the human body there are numerous biological components that serve as natural reducing agents. Good examples include glutathione (GSH) **188**, cysteine (Cys) residues and thioredoxin-1 (Trx1).[158] GSH is an important intracellular antioxidant, one of the functions of GSH is to protect cells against oxidative damage caused by reactive oxygen species (ROS). The metabolic rate in cancer cells is much higher compared with healthy cells and consequently the level of ROS produced also increases. To mitigate ROS associated oxidative damage tumours will upregulate production of antioxidants such as GSH affording the tumour a degree of protection and allowing proliferation.[158b]

Upon entering a cancer cell through a GLUT1 transporter upregulated GSH could act to reduce the disulfide bond within the linker. Intramolecular attack at the carbonate from the thiolate sees release of the active drug. There are numerous examples of disulfide

linked therapeutics that have been successful in enhancing efficacy. This includes work presented by Perez *et al*; through conjugation of folic acid to doxorubicin using a disulfide linker enhanced cellular toxicity was reported.[159] Hydroxyl groups at C2, C4 and C6 are not necessary for hydrogen bonding interactions between the sugar and GLUT1 amino acid residues.[160] This information and ease of selective functionalisation drove a decision to functionalise at the 6-OH of the pyranose. Choice of linker length was guided based on work by Lippard; it was found that an increased linker length resulted in lower translocation efficiency into the intracellular space through GLUT1, whilst investigating glucose-platinum conjugates.[161] As such, a propionic acid linker was selected. Finally, a choice of protecting group was required. As ester protecting groups can be readily cleaved using relatively mild conditions (Zemplén/NH_3 in MeOH) this class of protecting group was chosen.

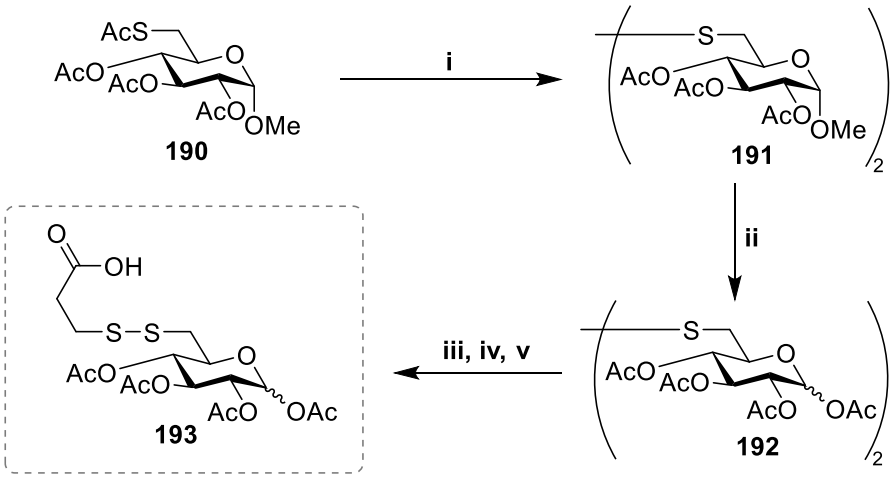
5.2 Synthesis of 1,2,3,4-tetra-O-acetyl-6-deoxy-6-thio-S-mercaptopropionic-acid-α/β-D-glucopyranoside 193

Starting from commercially available methyl glucose **56**, selective iodination of the primary 6-OH was achieved through use of iodine, imidazole and triphenylphosphine. To the same pot after 24 hrs was added pyridine and acetic anhydride, protecting the remaining hydroxyl groups. Precipitation with IPA furnished **189** in 76% yield (2 steps). Displacement of iodine using potassium thioacetate proceeded to completion after 24 hrs. As the starting material shared a similar R_f value with the product allowing enough time to reach completion was crucial. This also provided the benefit of avoiding column chromatography and after filtering excess KSAc a short silica plug furnished **190** in 70 % yield (***Scheme 51***).



Scheme 51: Synthesis of **190**, Reagents and conditions. i. I_2, PPh_3, Imidazole, THF, 70 °C; ii. Ac_2O, pyridine, 35 °C, (76% 2 steps); iii. KSAc, acetone, reflux, 70%.

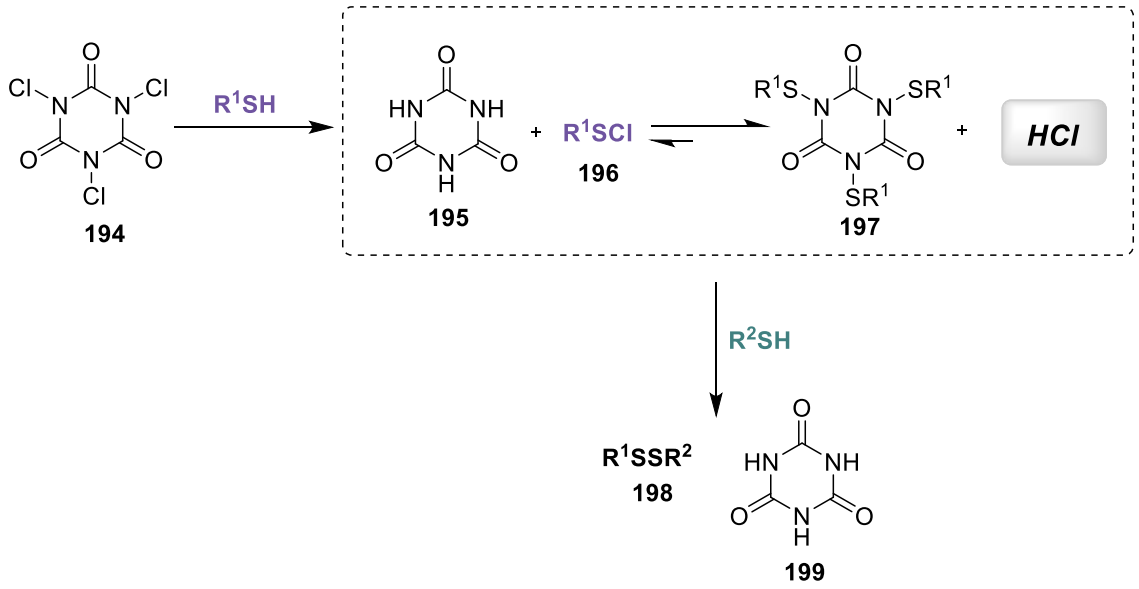
Based on work presented by Dong, oxidation of SAc *via* I_2 and NIS was attempted.[162] The reaction was found to work well on small scale (<500mg), however when scaling up the reaction was sluggish and failed to reach completion after 2 days (***Scheme 52***). When the reaction went to full completion a simple aqueous workup afforded pure **191**. Considering this, it was preferential to run parallel small-scale reactions to access larger amounts of the disulfide. Reaction success could be confirmed *via* disappearance of the *S*-acetyl chemical shift.



Scheme 52: Synthesis of protected glucose ligand **193**. Reagents and conditions; i. NIS, I_2, MeCN, 76%; ii. H_2SO_4, AcOH, Ac_2O, 68%; iii. DTT, MeCN; iv. TCCA, THF, NaH, -20 °C; v. 3-mercapto propionic acid, THF, 51% (3 steps).

Acetolysis of *O*-methyl glycoside **191** using a combination of Ac_2O, AcOH and H_2SO_4 generated an anomeric mixture of tetra-*O*-acetyl **192** (1:0.25, α/β). The final installation

required an asymmetric disulfide synthesis to take place. Consideration was given to the reaction conditions as the first step involved DTT mediated reduction of disulfide **192**. TCCA promoted disulfide synthesis is thought to proceed through either a sulfenyl chloride or *N*-sulfenyl isocyanuric acid intermediate (***Scheme 53***). Following formation of the intermediate further reaction with another sulfhydryl generating HCl as a reaction by-product.[162] Following DTT mediated reduction of **192** the reaction was cooled to -20 °C, NaH and TCCA added observing a colour change from colourless to yellow. This was likely a result of arylsulfenyl chloride generation in accordance with previous reports.[163]



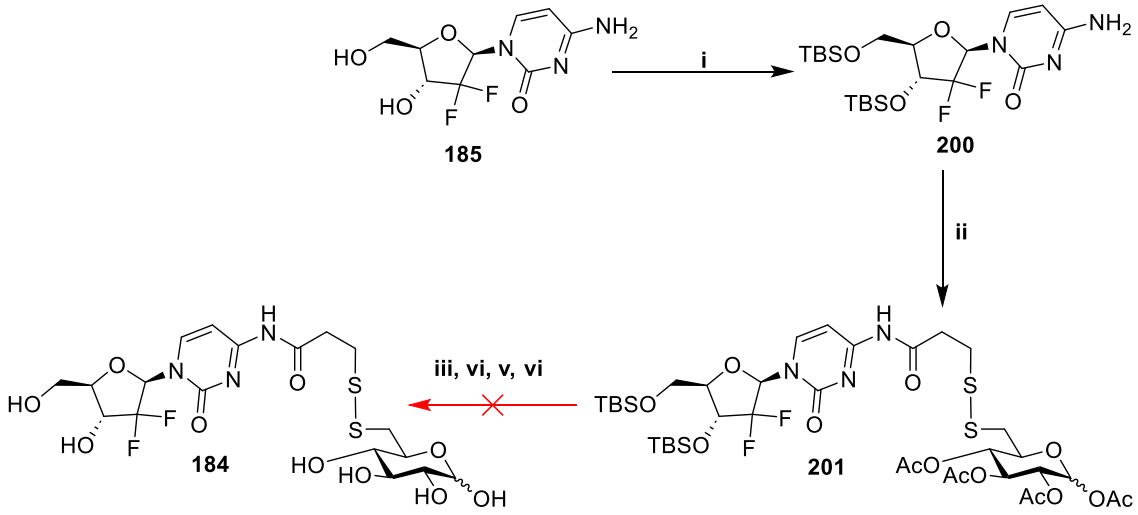
Scheme 53: Mechanism for TCCA mediated asymmetric disulfide synthesis.[162]

The final step saw addition of 3-mercapto propionic acid in THF and from this point the reaction proceeded at a rapid rate. After 20 mins of stirring TLC analysis revealed the reaction had gone to completion. Following work up and purification by column chromatography, ^{13}C NMR analysis was carried out to determine reaction success. Characteristic chemical shifts could be observed belonging to the disulfide linker, namely a carbonyl in the ^{13}C NMR spectrum [δ_C 176.9 (C=O) ppm] belonging to the amide. This

was accompanied by further shifts [δ_C 33.7 (CH_2), 32.8 (CH_2) ppm] assigned to the alkyl chain. HRMS further supported structure **193** [Found: $(M-H)^-$ 467.0694, $C_{17}H_{23}NO_{11}S_2$ requires M^- 467.0687].

5.3 Gemcitabine preparation and glucose conjugation

With the glucose ligand in hand, attention shifted towards the coupling partner, gemcitabine. Preparation of the compound required TBS protection of the 3' and 5' hydroxyl groups, which was accomplished using TBSCl in pyridine with imidazole. After stirring overnight, the reaction reached completion to deliver **200** in 86% yield similar to previous reports.[165] With protected gemcitabine in hand the coupling reaction with **193** was performed using EDC (***Scheme 54***).



Scheme 54: Attempted synthesis of glycoconjugate **184**. Reagents and conditions; i. TBSCl, imidazole, DMF, 86%; ii. EDC, DMAP, DCM, **193**, 65%; iii. TBAF; iv. HCl/MeOH; v. TsOH/H_2O; vi. NH_3/MeOH (***Table 11***).

EDC promoted amide formation successfully yielded glycoconjugate **201** in 65% yield. NMR and HRMS analysis were employed for characterisation of the product. All three expected anomeric carbons could be seen in the HSQC spectrum obtained for **201**, one

from gemcitabine and two for the α/β glucose moiety [δ_H 6.37 – 6.28 (m, 2H, H-1'', H-1α), (d, *J* = 8.3 Hz, 1H, H-1β) ppm] (***Figure 28***). The appearance of a chemical shift in the ^{19}F NMR spectrum provided further confidence the correct structure had been successfully synthesised being attributable to the gemcitabine moiety. Having confirmed reaction success attention was shifted towards deprotection.

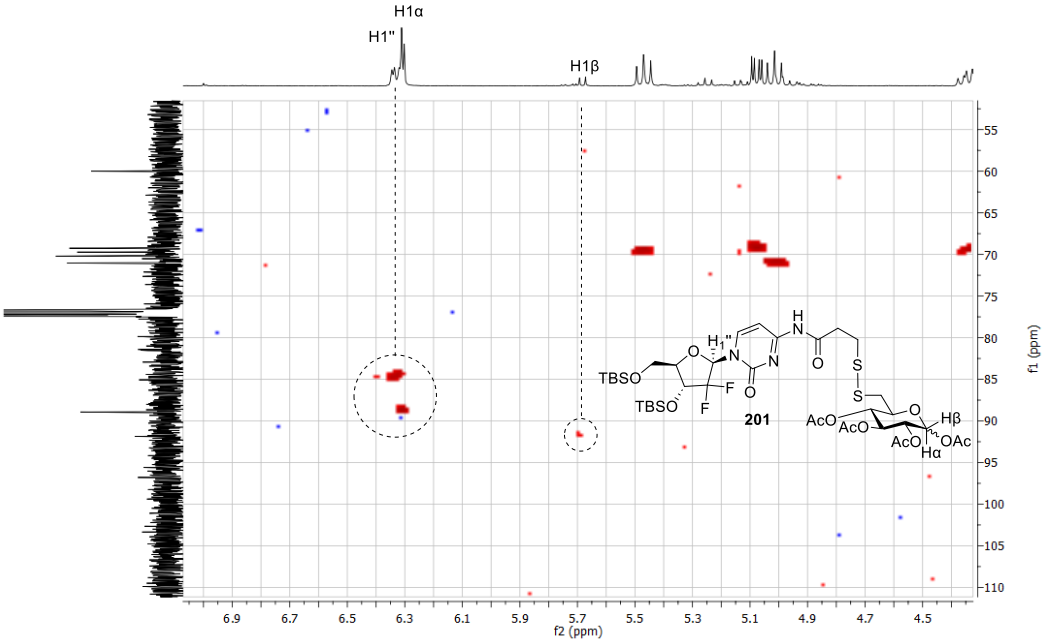


Figure 28: HSQC (400 × 100 MHz, $CDCl_3$) analysis of **201** highlighting anomeric shifts for each glucose anomer and gemcitabine.

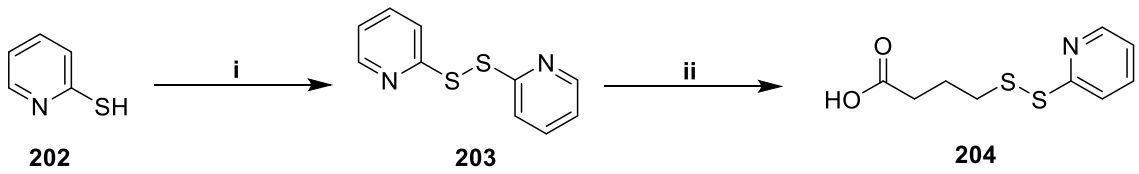
Table 11: Screened conditions for glycoconjugate **201** deprotection.

Deprotection conditions	**Reaction outcome**
TBAF (4.0 equiv.), THF, 0 °C	Linker hydrolysis
Na (0.1 equiv.), MeOH, RT	Linker hydrolysis
HCl 10% in MeOH, RT	Linker hydrolysis
TsOH H_2O, RT	Linker hydrolysis
NH_3 in MeOH, RT	Linker hydrolysis

The first set of conditions screened saw **201** being subjected to Zemplén conditions and after progressing for 1 hr TLC analysis revealed several different components. Following column chromatography, it was evident linker hydrolysis had occurred; gemcitabine and glucose were isolated separately. Following this result, several different deprotection conditions were screened including reversal of the deprotection order shown in ***Table 11***. In each case the linker cleaved, and an alternative strategy was sought.

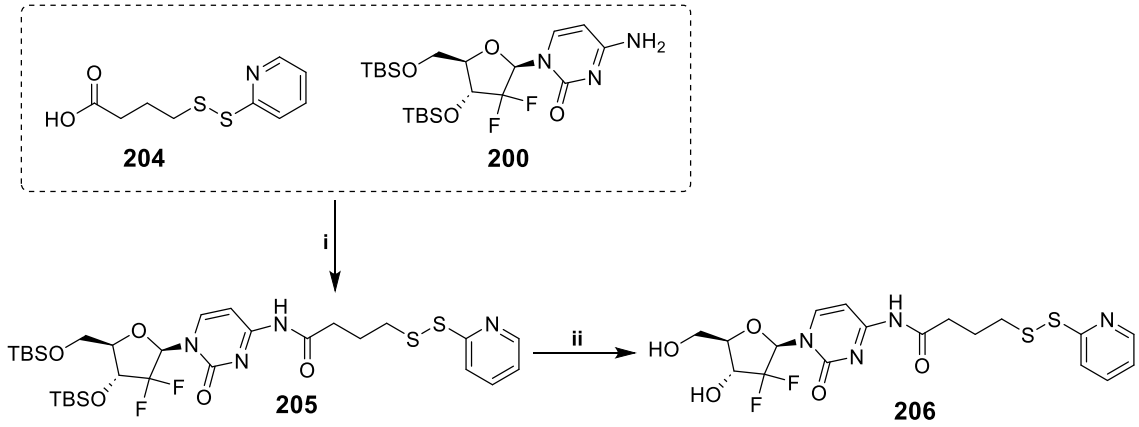
5.4 Glucose conjugation using thiol–pyridyl disulfide exchange.

A new route was envisioned that saw coupling take place using a deprotected gemcitabine conjugate and 6-thio-glucose. For this to be effective a new means of coupling was necessary, and a pyridyl disulfide-thiol exchange reaction was considered to be a good candidate. This reaction sees a thiol exchange with a pyridyl disulfide with the reaction being driven by formation of a pyridothione**.** Starting from 2-mercpatopyridine **202**, oxidation to the disulfide **203** was accomplished using I_2 in DMSO (***Scheme 55***). This was followed by reaction with 4-mercapto butyric acid in ethanol and acetic acid, to deliver conjugable disulfide **204** with data matching that previously reported.[166] Relying on coupling reagent EDC, connecting 4-(2-pyridyldithio) butanoic acid **204** through the amine of TBS protected gemcitabine **200** proved straightforward. TLC analysis of the reaction revealed complete consumption of the starting material to a higher R_f spot. Characterisation by NMR provided strong evidence for coupling success. Chemical shifts in the ^{19}F NMR [δ_F -115.98 (dd, J = 239.1, 12.2 Hz), -117.35 (dt, J = 239.2, 10.6 Hz) ppm] represents the gem-difluoro functionality of gemcitabine.



Scheme 55: Synthesis of 4-(2-pyridyldithio)butanoic acid **204**. Reagents and conditions; i. I_2, DMSO, RT, 77%; ii. 4-mercapto butyric acid, MeOH, RT, 68%.

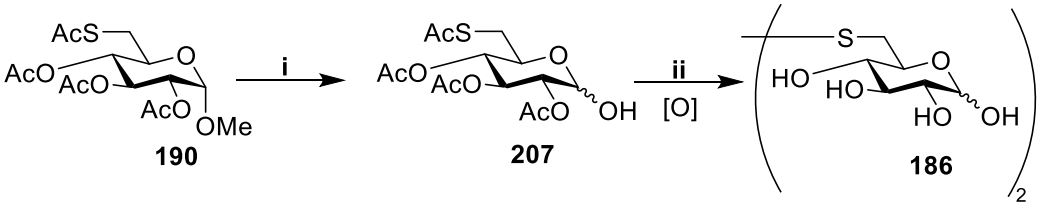
Chemical shifts in the ^{19}F NMR spectrum [δ_F -115.98 (dd, J = 239.1, 12.2 Hz), -117.35 (dt, J = 239.2, 10.6 Hz) ppm] represents the gem-difluoro functionality of gemcitabine. This was accompanied by new shifts in the ^{13}C NMR spectrum belonging to the alkyl linker carbons [δ 23.69 (CH_2), 37.73 (CH_2), 35.6 (CH_2) ppm]. Additionally, a new chemical shift corresponding with the newly formed amide could be seen [δ_C 160.1 (C=O) ppm]. With the linker in place, deprotection of the silyl groups at 3' and 5' was achieved using TBAF in THF to deliver **206** in 66% yield. (***Scheme 56***)



Scheme 56: Towards thiol–pyridyl disulfide linked gemcitabine **206**. Reagents and conditions; i. EDC, DMAP, DCM, 80%; ii. TBAF, THF, 0 °C, 66%.

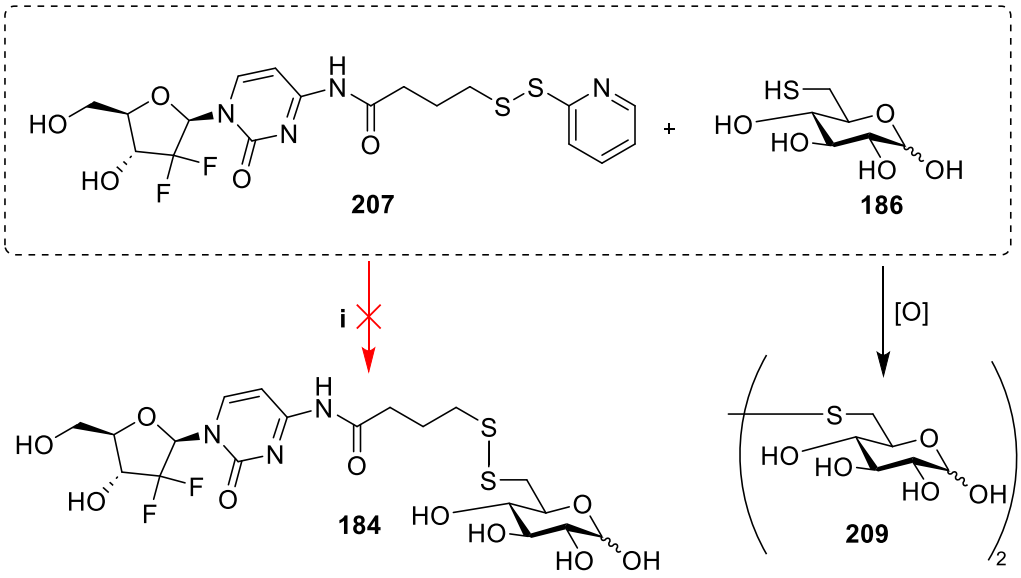
With gemcitabine component **206** in hand, a route towards 6-deoxy-6-thio-glucose **186** was also required. Building on the previous route (***Scheme 51***) and starting from **190**, anomeric OMe deprotection was accomplish using AcOH and H_2SO_4 to generate a

mixture of anomers (1:0.15, α/β). Finally global deacetylation under Zemplén conditions successfully removed the remaining acetates in 85% yield (***Scheme 57***).



Scheme 57: Synthesis of 6-thio-glucose **186**. See ***Scheme 51*** for synthesis of **190**. Reagents and conditions; i. AcOH, H_2SO_4, RT, 62%; ii. Na, MeOH, RT, 85%.

Following purification of **186** a protecting group free thiol exchange reaction between **186** and **207** was carried out. After stirring in MeCN for 24 hrs, TLC analysis suggested no reaction had taken place with only starting materials visible.



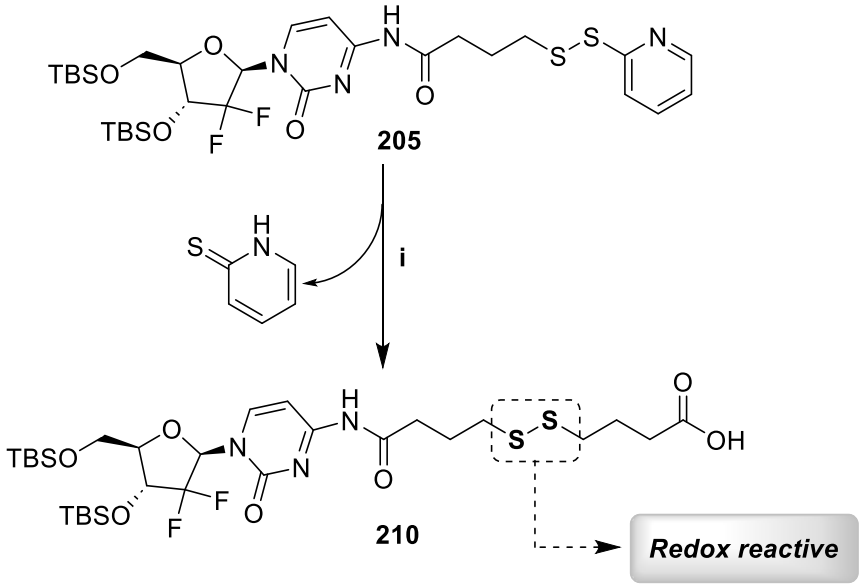
Scheme 58: Attempted coupling of **207** and **186** *via* thiol–pyridyl disulfide exchange and oxidation of **186** to disulfide **209**. Reagents and conditions. i. MeCN, RT.

Following further scrutiny of the reaction components ^{13}C NMR data obtained for 6-thio-glucose **186** suggested oxidation to the disulfide had taken place. Interestingly the ^{1}H NMR spectrum for **186** appeared as expected with two assignable sugars corresponding with each anomer. Conversely the ^{13}C NMR spectrum contained more shifts than could

be accounted for. These extra shifts were assigned to the anomeric mix that can arise from disulfides. HRMS analysis confirmed structure **209**; [Found: $(M-H)^-$ 389.0588 $C_{12}H_{21}O_{10}S_2$ requires M^- 389.0582] (***Scheme 58***).

5.5 Redox responsive disulfide relocation and synthesis of Glc-Gemcitabine conjugate

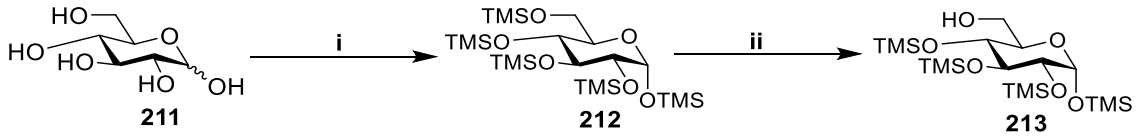
Instead of being a component of the pyranose, the disulfide bond was relocated to the linker. To achieve this, previously synthesised thiol–pyridyl disulfide linked gemcitabine **205** was reacted with 4-mercapto butyric acid **204** with this reaction progressing well and delivering **210** in 63% yield (***Scheme 56***) This reaction also reinforced previous disulfide formation in the attempted coupling of **207** and **186** as the cause for reaction failure (***Scheme 59***).



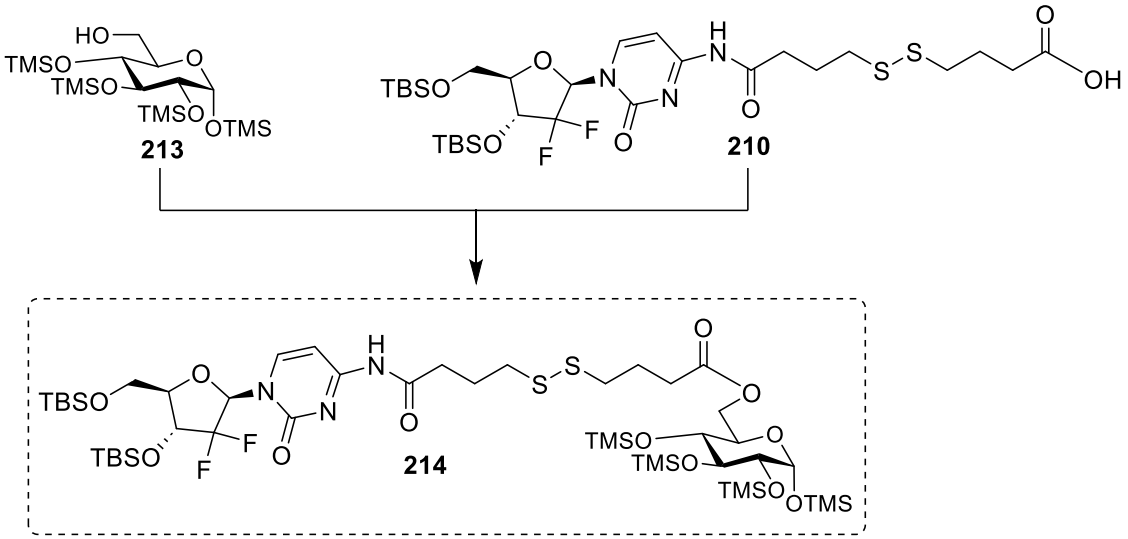
Scheme 59: Synthesis of **210** *via* a thiol–pyridyl disulfide exchange. Reagents and conditions; i. 4-mercapto butyric acid, MeCN, RT, 61%.

As esters had already proven to be incompatible with the amide linkage an alternative protecting group was required for the pyranose component that allowed for selective C6

conjugation. The protecting group chosen was TMS. This allowed for a one-step global de-silylation, following coupling of the pyranose to gemcitabine. D-glucose was treated with HMDS/TMSCl and after 1 hr of reaction time TLC analysis revealed full conversion to the fully *O*-TMS protected sugar **212** (R_f = 0.9, hexane) (***Scheme 60***). ^{1}H NMR analysis revealed shifts assigned to the *O*-TMS groups and revealed the presence of just the α anomer (d, $^3J_{H\text{-}1\text{-}H\text{-}2}$ = 3.0 Hz). Following an aqueous work up the crude residue was progressed to the next step and selective removal of the primary 6-*O*-TMS group completed through treatment with AcOH. To avoid cleavage of the other TMS groups the temperature was closely monitored ensuring it did not rise above 5 °C. Confirming primary *O*-TMS removal and structure **213** was straightforward with the 6-OH proton now visible in the ^{1}H NMR [δ 1.60 (dd, *J* = 7.0, 5.4 Hz (6-OH) ppm].



Scheme 60: Synthesis of **213**. Reagents and conditions; i. HMDS, TMSCl, pyridine, RT; ii. AcOH, DCM, MeOH, 0-5 °C, 75% (2 steps).



Scheme 61: Synthesis of protected glycoconjugate **214**. Reagents and conditions; i. EDC, DMAP, RT, 45%.

An EDC mediated coupling between **210** and silylated pyranose **213** was performed (***Scheme 61***). This reaction successfully yielded **214** in 45% yield. ^{1}H NMR analysis revealed the expected anomeric signals for gemcitabine and the glucose moiety [δ_H dd, ($J_{H\text{-}1''\text{-}Fa/Fb}$ = 10.2, 3.8 Hz, 1H, H-1''), 4.87 (d, J = 3.0 Hz, 1H, H-1) ppm] (***Figure 29***).

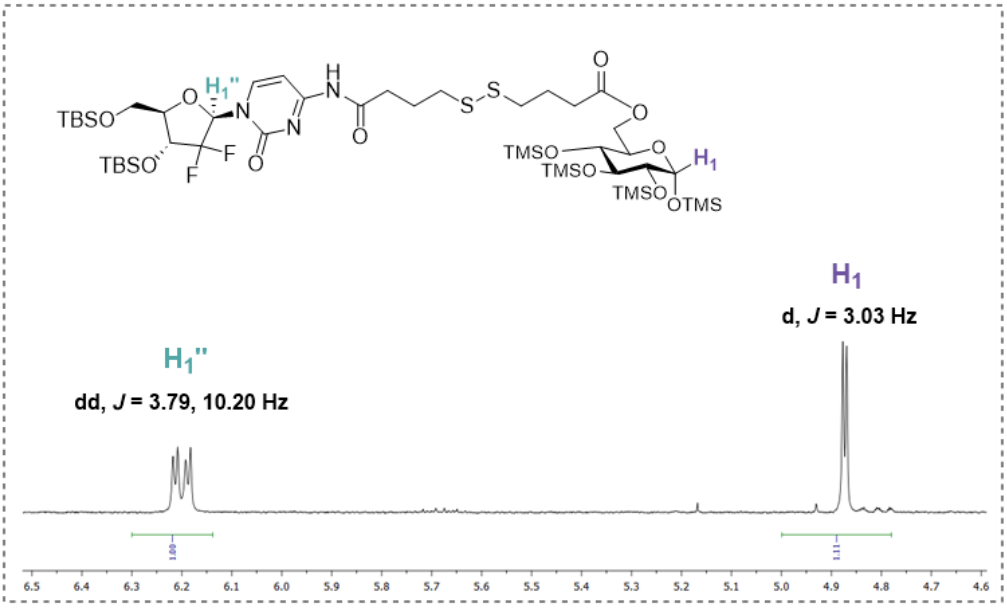
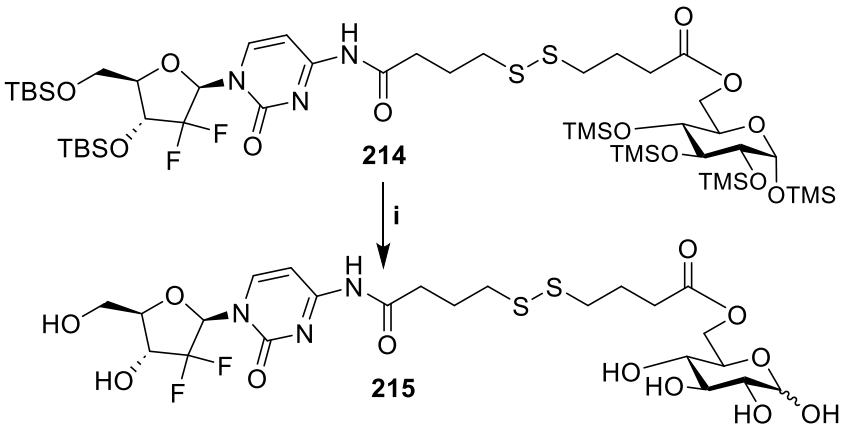


Figure 29: ^{1}H NMR (400 MHz, $CDCl_3$) analysis of **214** highlighting anomeric shifts for α glucose (H1) and gemcitabine (H1'').

A global deprotection utilising TBAF in THF was thus performed on **214** (***Scheme 62***). After 1 hr of stirring at 0 °C, TLC analysis revealed transition of the starting material to a lower spot (R_f = 0.30, DCM/MeOH, 85:15). Following purification by column chromatography characterisation of the final glycoconjugate **215** was completed. Absence of any TBS/TMS chemical shifts in the ^{1}H NMR suggested complete removal of all silyl PGs. Furthermore, observation in the ^{1}H NMR spectrum included the appearance of a new anomeric shift when compared with the protected material **214** (***Figure 29***). This was to be expected and correlated with an expected anomeric mix for the pyranose component of the prodrug. Additionally, the three anomeric shifts integrated as anticipated (H1'':H1α:H1β, 2:1:1) (***Figure 26***).



Scheme 62: Final deprotection of glycoconjugate **214** to give final gemcitabine-glucose conjugate **215**. Reagents and conditions; i. TBAF, THF, 0 °C, 54%.

Further support was obtained from the ^{19}F NMR spectrum revealing two shifts [δ_F -119.18 (dd, J = 240.0, 12.5 Hz), -120.10 (d, J = 244.7 Hz) ppm] to correspond with the gemcitabine di-fluoro functionality at C2''. Further analysis by HRMS and HPLC confirmed the linkage to still be intact, an observed *m/z* signal at matched the expected mass for structure **215**. An analytical trace was also obtained confirming 100% purity of glycoconjugate **215**.

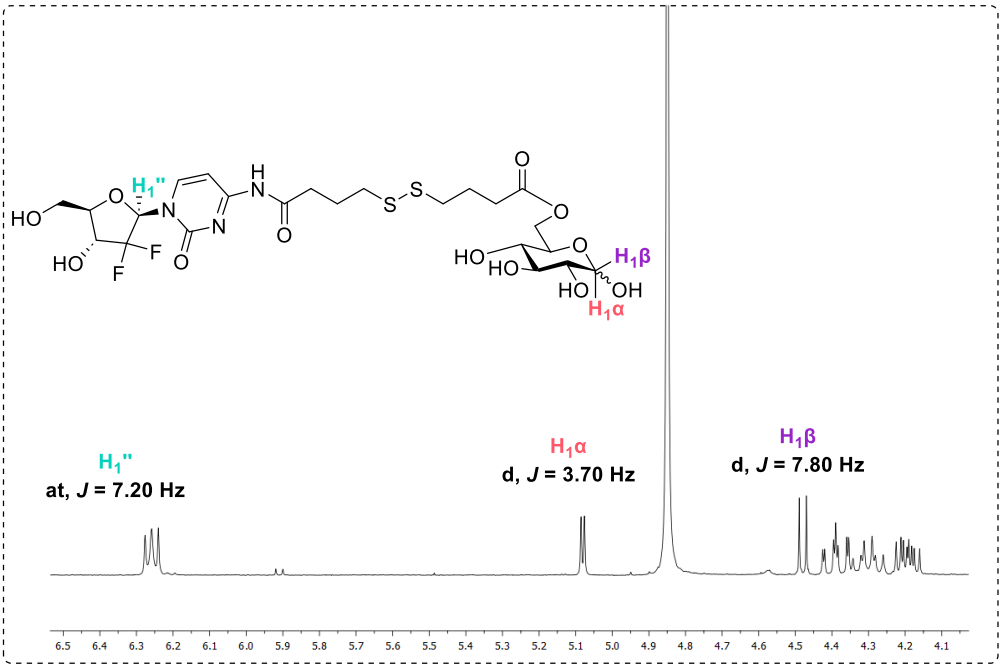
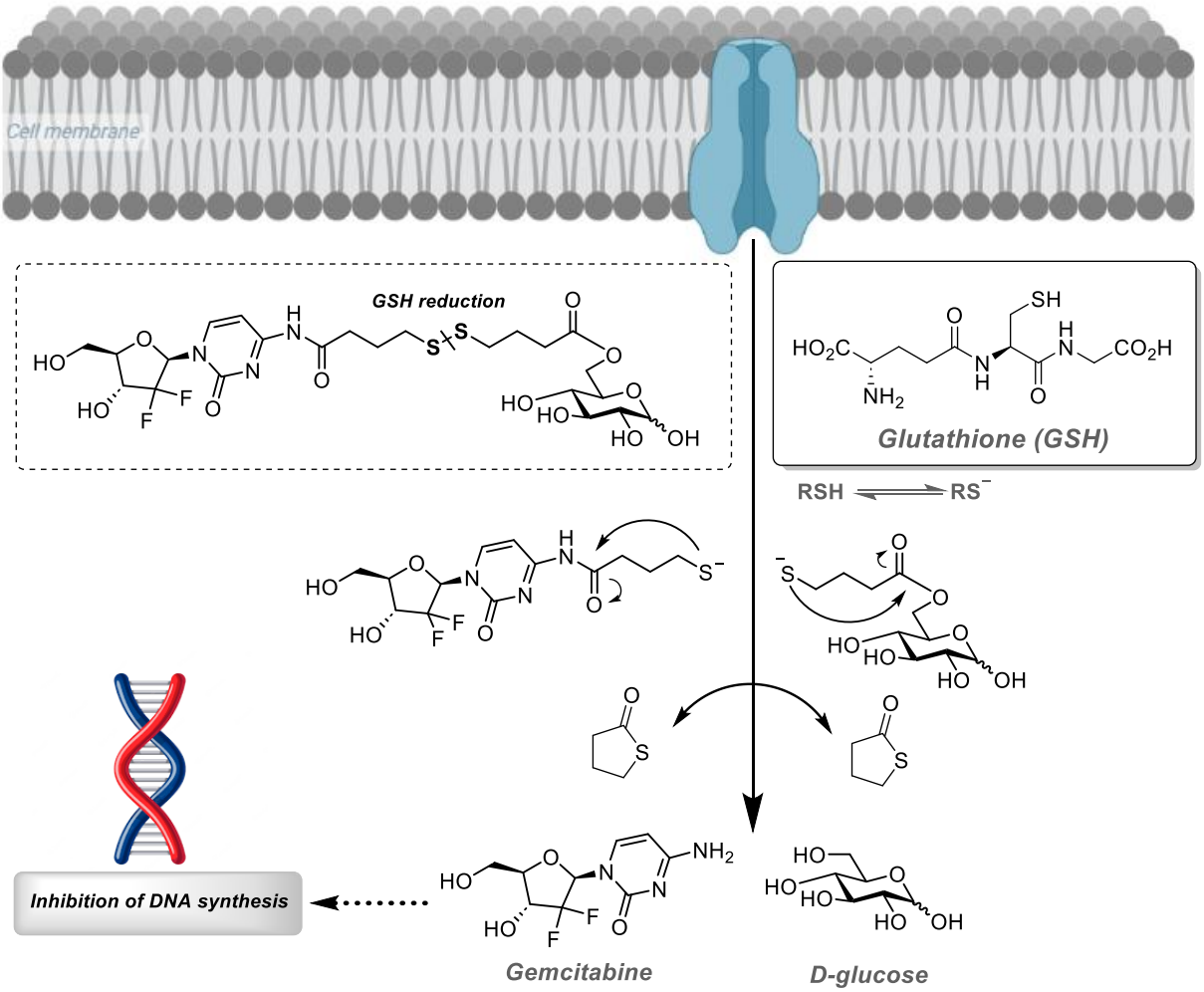


Figure 30: ^1H NMR (400 MHz, $CDCl_3$) analysis of **215** highlighting anomeric shifts for α glucose (H1) and gemcitabine (H1'').

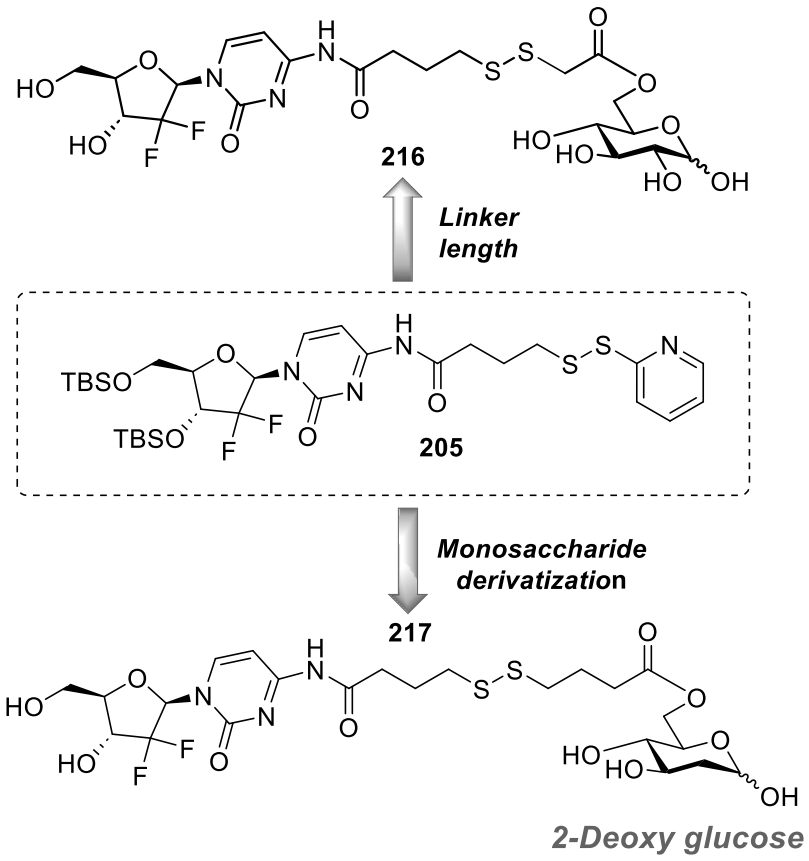
5.6 Conclusion and Future work

The first approach towards a GLUT1 targeting redox responsive prodrug saw 6-thio glucose being coupled to gemcitabine. All attempts to remove the pyranose acetate protecting groups saw linker hydrolysis. In response a protecting group free approach was implemented relying on a thiol–pyridyl disulfide exchange for coupling. Rapid oxidation of 6-thio glucose to the corresponding disulfide meant a re-evaluation was necessary. After consideration the redox responsive disulfide was relocated into the linker and alternate pyranose protecting groups were also implemented allowing for a final global de-silylation to be carried out.



Scheme 63: Schematic diagram detailing the intended pathway for prodrug **215**.

These changes allowed for the successful synthesis of novel gemcitabine-glucose glycoconjugate **215**. Future work will include biological screening of gemcitabine conjugate **215** with the intended biological pathway seen in ***Scheme 63***. Namely, determining increased efficacy against a nucleoside transported deficient cell line or GLUT1 overexpressed cell lines with comparison against gemcitabine. Glucose-gemcitabine conjugate **215** is currently undergoing evaluation against PC3 and LNCaP prostate cancer cell lines in collaboration with Dr Martin Fascione (University of York). Future work in this area could look at investigating linkers of differing length or varying the identity of monosaccharide linked to gemcitabine, for example 2-deoxy glucose (***Scheme 64***).



Scheme 64: Potential avenues for future work: 2-deoxy glucose-gemcitabine conjugate **217** and glucose-gemcitabine conjugate **216** bearing a shorter linker.

Chapter 6

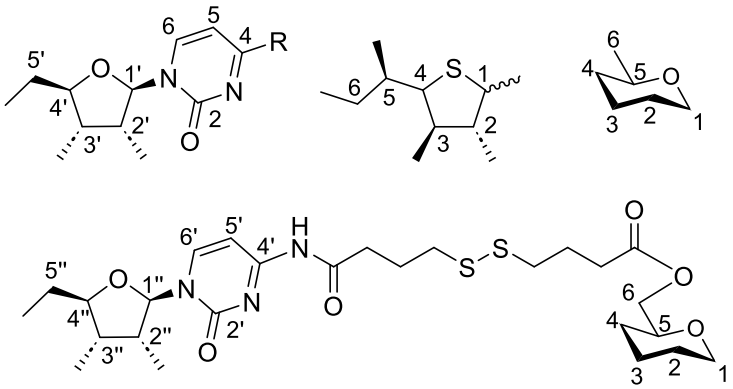
Experimental

6.0 Experimental Section

General Experimental Methods

All chemicals were purchased from Acros Organics, Alfa Aesar, Biosynth Carbosynth, Fisher Scientific, Fluorochem, Sigma Aldrich or TCI Chemicals and were used without further purification unless otherwise stated.NMR spectra were recorded on a Bruker Avance 400 spectrometer. The chemical shift data for each signal are given as δ in units of parts per million (ppm) relative to tetramethylsilane, where δ = 0.00 ppm. The number of protons (n) for a given resonance is indicated by nH. The multiplicity of each signal is indicated by: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), p (pentet), sep (septet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dddd (doublet of doublet of doublet of doublets), dt (doublet of triplets), tt (triplet of triplets), dqd (doublet of quartets of doublets) or m (multiplet). Coupling constants (*J*) are quoted in Hz and calculated to the nearest 0.1 Hz. Anhydrous DMF, MeOH, pyridine and Et_3N were obtained from Sure/Seal^{TM} bottles *via* chemical suppliers. Anhydrous THF, DCM and toluene were obtained by passing solvent through activated alumina columns and dispensed from a PureSolv MD ASNA solvent purification system and stored over 4 Å molecular sieves. Unless otherwise stated, all reactions were conducted using anhydrous solvents, under an atmosphere of N_2 which was passed through a Drierite® drying column. All high-resolution mass spectra were measured at the EPSRC National Mass Spectrometry Facility at Swansea University, UK. HPLC was performed using an Agilent 1260 Infinity II preparative HPLC system equipped with a variable wavelength detector and a fraction collector, on a reverse phase column (Polaris 180 Å C18-A. 21.2 × 250 mm, 5 μm) to achieve a purity level >95%. Visualisation was achieved using UV detection at 210 and 254 nm Analytical thin layer chromatography (TLC) was carried out

on pre-coated 0.25 mm Merck KGaA 60 F254 silica gel plates. Visualisation was by adsorption of UV light, or thermal development after dipping in a methanolic solution of sulfuric acid (5% v/v). Manual column chromatography was carried out on silica gel (VWR International 40-63 μm) under a positive pressure of compressed air. Flash chromatography was carried out using the Reveleris X2 flash purification system. Assignment of ^{1}H and ^{13}C atoms in NMR analysis follows the generic ring numbering system shown below. IR spectra were recorded on a Diamond 1000 FTIR spectrometer. Absorption maxima are reported in wavenumbers (cm-1). Intensities of the maxima are quoted as strong (s), medium (m) or weak (w).



General procedures for the glycosidation of oleyl alcohol

A: A mixture of the thioglycoside donor (1.0 equiv.), molecular sieves (4 Å, 100 mg) and oleyl alcohol (1.1 equiv.) was dissolved in DCM and stirred at RT for 1 hr before being cooled to 0 °C. NIS (1.0 equiv.) and the respective Lewis acid (1.0 equiv.) were added. The reaction was stirred until completion, as adjudged by TLC. The mixture was diluted with DCM, washed with saturated aqueous $NaHCO_3$, saturated aqueous $Na_2S_2O_3$, brine and then dried ($MgSO_4$). After filtering, the solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography to deliver the corresponding alkyl glycoside.

B: A mixture of the thioglycoside donor (1.0 equiv.), and molecular sieves (4 Å, 100 mg) was dissolved in DCM and stirred at RT for 1 hr before being cooled to 0 °C. NIS (1.0 equiv.) and the respective Lewis acid (1.0 equiv.) were added. After stirring for 10 mins., oleyl alcohol (1.1 equiv.) was added and the reaction mixture was stirred until completion, as adjudged by TLC. The mixture was diluted with DCM (10 mL), washed with saturated aqueous $NaHCO_3$, saturated aqueous $Na_2S_2O_3$, water, brine and dried ($MgSO_4$). After filtration, the solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography to deliver the corresponding alkyl glycoside.

C: A solution containing thioglycoside (1.0 equiv.), sulfoxide (2.8 equiv.), and activated 4 Å powdered sieves in DCM was cooled to -60 °C and slowly treated with Tf_2O (1.4 equiv.). After 5 mins., a solution of oleyl alcohol (1.5 equiv.) in DCM was added. The reaction mixture was stirred for 10 mins at -60 °C and then warmed gradually to RT. Upon reaction completion, as adjudged by TLC, the mixture was diluted with DCM, washed with saturated aqueous $NaHCO_3$, brine and dried ($MgSO_4$). After filtering, the solvent was removed under reduced pressure and the crude residue was purified by column chromatography to deliver the corresponding alkyl glycoside.

D: To a solution of glycosyl hemi-acetal (1.0 equiv.) in DCM (5 mL), was added Cl_3CCN (10.0 equiv.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.1 equiv.). The reaction mixture was stirred for between 30 mins. and 2 h at 0 °C. After removal of the solvent under reduced pressure, a silica pad was neutralised (9:1, EtOAc/Et_3N, 100 mL), the crude residue loaded onto the silica and washed with EtOAc (100 mL). Removal of solvent under reduced pressure delivered the trichloroacetimidate donor. The donor was dissolved in DCM/toluene and oleyl alcohol (1.1 equiv.) and TMSOTf (0.1 – 1.0 equiv.) were then added at 0°C. The reaction mixture was stirred for between 30 mins. and 24 h.

After which time Et_3N (2 mL) was added, the organic layer extracted with DCM, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography to deliver the corresponding alkyl glycoside.

General deacetylation procedure

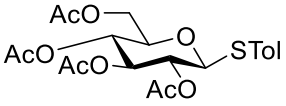
To the acetylated glycoside (1.0 equiv.) was added Na (0.1 equiv.) in MeOH, the resulting mixture was stirred at RT for 1 hr. After TLC analysis revealed reaction completion Amberlite IR20 (H^+) ion exchange resin was added. The mixture was stirred until neutral, after which the mixture was filtered and washed with methanol (100 mL). The combined organic filtrates were concentrated under reduced pressure and the crude residue purified by column chromatography.

General Benzoylation Procedure

A solution of the galactose substrate (1.0 equiv.) in pyridine and DCM (1:1, 40 mM) was cooled to -40 °C and treated dropwise with a solution of BzCl (3.1 or 2.1 equiv.) in DCM (1 mL). The reaction mixture was maintained at -40 °C until reaction completion as seen by TLC, sat. aq. $NaHCO_3$ (50 mL) was added with stirring and the aqueous layer extracted with DCM (3 × 50 mL). The combined organic phases were washed with water (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to yield the crude product, which was purified by column chromatography.

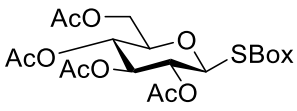
6.1 Chapter 2 compounds

p-Tolyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside 29



A solution of *p*-tolyl-1-thio-β-D-glucopyranoside (500 mg, 1.75 mmol, 1.0 equiv.) in pyridine (10 mL) was cooled to 0 °C and slowly treated with Ac_2O (1.16 mL 1.07 g, 10.4 mmol, 5.9 equiv.). The solution was allowed to warm to RT and the reaction mixture was stirred until TLC analysis indicated reaction completion (to R_f = 0.50, hexane/EtOAc, 7:3). The crude material was taken in EtOAc (50 mL) and washed with 1 M HCl (5 × 50 mL), saturated aqueous $NaHCO_3$ (3 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-50%) to deliver **29** as a white solid (720 mg, 1.58 mmol, 91%). R_f = 0.50 (hexane/EtOAc, 7:3);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.1 Hz, 2H, Ar*H*), 7.12 (d, *J* = 7.9 Hz, 2H, Ar*H*), 5.21 (t, *J* = 9.4 Hz, 1H, H-3), 5.02 (t, *J* = 9.8 Hz, 1H, H-4), 4.93 (t, *J* = 9.7 Hz, 1H, H-2), 4.63 (d, *J* = 10.1 Hz, 1H, H-1), 4.25 – 4.14 (m, 2H, H-6a, H-6b), 3.70 (ddd, *J* = 10.0, 4.8, 2.7 Hz, 1H, H-5), 2.35 (s, 3H, PhC*H*$_3$), 2.09 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.99 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 (C=O, Ac), 170.2 (C=O, Ac), 169.4 (C=O, Ac), 169.3 (C=O, Ac), 138.8 (Ar-C), 133.9 (Ar-C), 129.7(Ar-C), 127.6 (Ar-C), 85.8 (C1), 75.8 (C5), 74.0 (C3), 69.9 (C2), 68.2 (C4), 62.1 (C6), 21.2 (Ph-CH_3), 20.8 (Ac-CH_3), 20.7 (Ac-CH_3), 20.6 (Ac-CH_3), 20.58 (Ac-CH_3); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 472.1632, $C_{14}H_{23}O_9N$ requires $M^{+\cdot}$ 472.1636]. Data matched those reported previously.[167]

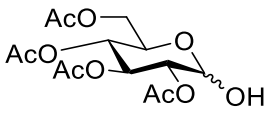
Benzoxazolyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside 27



1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranoside (1.00 g, 2.56 mmol, 1.0 equiv.) was dissolved in DCM (10 mL) and 33% (*w/v*) HBr in acetic acid (5 mL) was added dropwise at 0 °C. The mixture was allowed to reach RT and stirred until complete consumption of

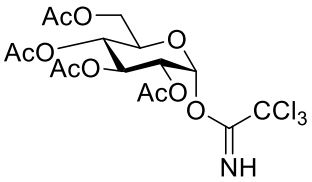
the starting material, as seen by TLC (to R_f = 0.23, hexane/EtOAc, 7:3). The reaction mixture was diluted with DCM (100 mL) and washed successively with saturated aqueous $NaHCO_3$ (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to deliver 1-bromo-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside as a colourless oil which was used in the next step without further purification. A solution of the glycosyl bromide in acetone (20 mL) was treated with 2-mercaptobenzoxazole (542 mg, 3.58 mmol, 1.4 equiv.) and potassium carbonate (495 mg, 3.58 mmol, 1.4 equiv.). The reaction mixture was stirred at 40 °C until complete consumption of the starting material was observed by TLC (to R_f = 0.18, hexane/EtOAc, 7:3). The reaction mixture was diluted with DCM (30 mL) and washed with 1% NaOH (25 mL) and water (2 × 25 mL). The organic extract was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure, yielding **27** as an orange solid (984 mg, 2.04 mmol, 80%). R_f = 0.18 (hexane/EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.61 (m, 1H, Ar*H*), 7.49 – 7.46 (m, 1H, Ar*H*), 7.28 – 7.35 (m, 2H, Ar*H*), 5.70 (d, *J* = 10.3 Hz, 1H, H-1), 5.36 (t, *J* = 9.3 Hz, 1H, H-3), 5.25 (dd, *J* = 10.3, 9.3 Hz, 1H, H-2), 5.18 (t, *J* = 9.7 Hz, 1H, H-4), 4.29 (dd, *J* = 12.5, 4.7 Hz, 1H, H-6a), 4.15 (dd, *J* = 12.5, 2.2 Hz, 1H, H-6b), 3.96 (ddd, *J* = 10.1, 4.7, 2.2 Hz, 1H, H-5), 2.03 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.02 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 (C=O, Ac), 170.1 (C=O, Ac), 169.5 (C=O, Ac), 169.4 (C=O, Ac), 160.9 (Ar-C), 152.0 (Ar-C), 141.5 (Ar-C), 124.6 (Ar-C), 124.5 (Ar-C), 118.9 (Ar-C), 110.2 (Ar-C), 83.5 (C1), 76.4 (C5), 73.7 (C3), 69.7 (C2), 67.9 (C4), 61.7 (C6), 20.7 (Ac-CH_3), 20.6 (Ac-CH_3 × 3); HRMS *m/z* (ES^+) [Found: $(M+H)^+$ 482.1115, $C_{21}H_{24}NO_{10}S$ requires M^+ 482.1115]; Data matched those reported previously.[168]

2,3,4,6-Tetra-*O*-acetyl-α/β-D-glucopyranoside 32



A solution of 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranoside (1.00 g, 2.56 mmol, 1.0 equiv.) in DMF (8 mL) was treated with benzylamine (0.57 mL, 555 mg, 5.12 mmol, 2.0 equiv.) and stirred at 60 °C until complete consumption of the starting material was observed by TLC (to R_f = 0.23 hexane/EtOAc, 7:3). The solvent was removed under reduced pressure and the crude residue was dissolved in DCM (50 mL) and washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), water (2 × 50 mL) and brine (50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-50%) to afford the title compound as a colourless oil (704 mg, 2.02 mmol, 79%, α:β 0.6:1). R_f = 0.23 (hexane/EtOAc, 7:3); **Selected chemical shifts**: ^{1}H NMR (400 MHz, CDCl3) δ 5.47 (as, 0.6 H, H-1α), 4.75 (m, 1 H, H-1β); 13C NMR (101 MHz, CDCl3) δ 95.6 (C1β), 90.2 (C1α); HRMS *m/z* (ES^+) [Found: $(M+Na)^+$ 371.0947, $C_{14}H_{20}O_{10}Na$ requires M^+ 371.0949]; Data matched those reported previously.[169]

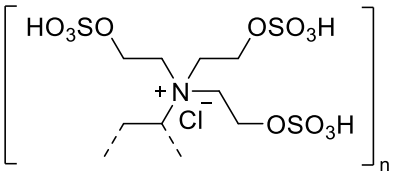
2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranoside trichloroacetimidate 33



A solution of 2,3,4,6-tetra-*O*-acetyl-α/β-D-glucopyranoside (844 mg, 2.42 mmol, 1.0 equiv.) and activated 4 Å molecular sieves (100 mg) in DCM (20 mL) was treated with Cl_3CCN (2.42 mL, 3.49 g, 24.2 mmol, 10.0 equiv.) and DBU (36.1 µL, 37.0 mg, 24.2 µmol, 0.10 equiv.). The reaction mixture was stirred for 4 h at RT, TLC analysis revealed

complete consumption of the starting material. The solvent was removed under reduced pressure and the crude residue was purified on a short, neutralised silica pad (100 % EtOAc) to deliver the title compound (957 mg, 1.94 mmol, 80%) as an orange oil. R_f = 0.55 (hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H, N*H*), 6.56 (d, *J* = 3.6 Hz, 1H, H-1), 5.57 (t, *J* = 9.8 Hz, 1H, H-3), 5.19 (t, *J* = 9.9 Hz, 1H, H-4), 5.16 – 5.11 (m, 1H, H-2), 4.28 (dd, *J* = 12.3, 4.1 Hz, 1H, H-6a), 4.25 – 4.19 (m, 1H, H-5), 4.17 – 4.09 (m, 1H, H-6b), 2.08 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.03 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 (C=O, Ac), 170.0 (C=O, Ac), 169.9 (C=O, Ac), 169.5 (C=O, Ac), 160.7 (*C*=N), 92.9 (C1), 90.6 (CCl_3), 70.0 (C5), 69.8 (C3), 69.7 (C2), 67.8 (C4), 61.4 (C6), 21.0 (Ac-CH_3), 20.6 (Ac-CH_3), 20.55 (Ac-CH_3), 20.4 (Ac-CH_3); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 509.0482, $C_{16}H_{24}Cl_3N_2O_{10}$ requires M^+ 509.0491]. Data matched those reported previously. [170]

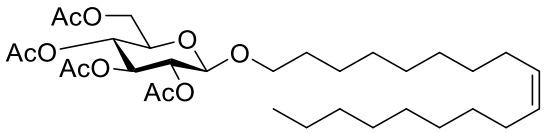
Polyvinyl bound trisulfonate triethyl amine chloride (PV-TSEAC) 35



Polyvinyl chloride (PVC) (5.00 g, 80.0 mmol, 1.0 equiv.), diethanolamine (7.71 mL, 8.40 g, 80.1 mmol, 1.0 equiv.) and MeCN (50 mL) were heated at 80 °C for 48 h with stirring. After cooling, the solid residue was collected by filtration and washed successively with water (200 mL) and acetone (200 mL). The solid was dried under vacuum at 60 °C for 12 h and afforded polyvinyl-bound diethanolamine (PV-DEA) (4.73 g, 75.7 mmol, 95%). Chloroethanol (7.08 mL, 8.50 g, 10 mmol, 1.4 equiv.), PV-DEA (4.73 g, 75.7 mmol, 1.0 equiv.) and acetonitrile (40 mL) were added to a round bottom flask and the mixture was refluxed at 80 °C for 24 h. The liquid phase was decanted, and the solid residue washed

with acetone (200 mL). The solid was further dried under vacuum at 60 °C and polyvinyltriethanolamine chloride (PV-THEAC) was obtained. PV-THEAC (3.50 g, 56.6 mmol, 1.0 equiv.) and chlorosulphonic acid (9.31 mL, 16.3 g, 140 mmol, 2.5 equiv.) were added into a round bottom flask and the reaction mixture was vigorously stirred for 48 h. After this, the solid residue was collected by filtration and washed separately with water (1 L) and acetone (1 L) to give PV-TSEAC (3.12 g, 49.9 mmol, 62 %). IR νmax/cm-1 1745 (w, C-H), 1329 (m, C-C), 1253 (s, C-N), 1090 (w, O=S=O), 957 (m, SO_3H). Data matched those reported previously.[72]

Oleyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside 30



Following general procedure **A**, glycosyl donor **29** (100 mg, 0.220 mmol, 1.0 equiv.), NIS (74.0 mg, 0.330 mmol, 1.5 equiv.), $BF_3{\cdot}OEt_2$ (31.0 mg, 27.0 μL, 0.24 mmol, 1.0 equiv.) and oleyl alcohol (62.0 mg, 73.0 μL, 0.230 mmol, 1.1 equiv.) were used. The reaction was stirred at RT for 3 h. Purification by column chromatography (hexane/EtOAc, 0–30%) afforded **30** as a colourless oil (15.0 mg, 25.0 μmol, 11%).

Following general procedure **B**, glycosyl donor **29** (100 mg, 0.220 mmol, 1.0 equiv.), NIS (74.0 mg, 0.330 mmol, 1.5 equiv.), $BF_3{\cdot}OEt_2$ (31.0 mg, 27.0 μL, 0.240 mmol, 1.0 equiv.) and oleyl alcohol (62.0 mg, 73.0 μL, 0.230 mmol, 1.1 equiv) were used. The reaction was stirred at RT for 2 h. Purification by column chromatography (hexane/EtOAc, 0–30%) afforded **30** as a colourless oil (25.0 mg, 42.0 μmol, 18%).

Following general procedure **B**, glycosyl donor **27** (100 mg, 0.210 mmol, 1.0 equiv.), NIS (72.0 mg, 0.320 mmol, 1.5 equiv.), $BF_3{\cdot}OEt_2$ (30.0 mg, 26.1 μL, 0.230 mmol, 1.0 equiv.) and oleyl alcohol (62.0 mg, 73.0 μL, 0.230 mmol, 1.1 equiv.) were used. The

reaction was stirred at RT for 24 h. Purification by column chromatography (hexane/EtOAc, 0–30%) afforded **30** as a colourless oil (29.0 mg, 48.4 μmol, 22%).

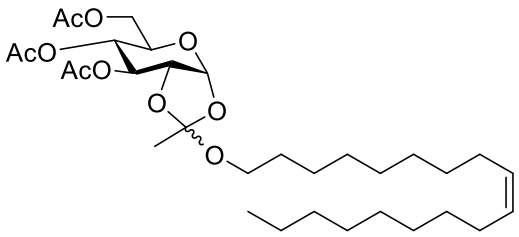
Following general procedure **C**, glycosyl donor **27** (75.0 mg, 0.155 mmol, 1.0 equiv.), Ph_2SO (87.0 mg, 0.430 mmol, 2.8 equiv.), TTBP (117 mg, 0.470 mmol, 3.0 equiv.), oleyl alcohol (66.0 mg, 77.7 μL 0.245 mmol, 1.6 equiv.) and Tf_2O (61.0 mg, 34.9 μL, 0.217 mmol, 1.4 equiv.) were used. The reaction was stirred at RT for 3 h. Purification by column chromatography (hexane/EtOAc, 0–30%) afforded **30** as a colourless oil (15.0 mg, 25.0 μmol, 16%).

Following general procedure **D**, glycosyl donor **33** (383 mg, 0.777 mmol, 1.0 equiv.), oleyl alcohol (0.37 mL, 313 mg, 1.17 mmol, 1.5 equiv.) and TMSOTf (0.14 mL, 173 mg, 0.778 mmol, 1.0 equiv) in DCM were used. The reaction was stirred at RT for 24 h. Purification by column chromatography (hexane/EtOAc, 0–30%) afforded **30** as a colourless oil (255 mg, 0.426 mmol, 55%).

Following general procedure **D,** glycosyl donor **33** (308 mg, 0.625 mmol, 1.0 equiv.), oleyl alcohol (0.30 mL, 252 mg, 0.937 mmol, 1.5 equiv.) and PV-TSEAC (15%wt, 46 mg) in toluene were used. The reaction was stirred at 60 °C for 24 h. Purification by column chromatography (hexane/EtOAc, 0–30%) afforded **30** as a colourless oil (273 mg, 0.456 mmol, 73%). R_f = 0.39 (hexane/EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 – 5.30 (m, 2H, -C*H*=C*H*-), 5.21 (t, *J* = 9.5 Hz, 1H, H-3), 5.09 (t, *J* = 9.6 Hz, 1H, H-4), 4.98 (t, *J* = 8.8 Hz, 1H, H-2), 4.49 (d, *J* = 8.0 Hz, 1H, H-1), 4.27 (dd, *J* = 12.3, 4.6 Hz, 1H, H-6a), 4.16 – 4.09 (m, 1H, H-6b), 3.91 – 3.83 (m, 1H, OC*H*H), 3.72 – 3.66 (m, 1H, H-5), 3.51 – 3.42 (m, 1H, OC*H*H), 2.09 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.63 – 1.52 (m, 4H, 2 x CH_2), 1.39 – 1.20 (m, 24H, 12 x CH_2), 0.88 (t, *J* = 6.5 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7 (C=O, Ac), 170.4 (C=O, Ac), 169.4 (C=O, Ac), 169.3 (C=O, Ac), 130.0, 129.8, 100.9 (C1), 72.9 (C3), 71.8

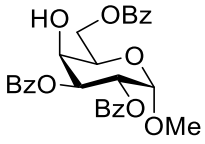
(C5), 71.4 (C2), 70.3, 68.5 (C4), 62.0 (C6), 31.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.32, 29.27, 27.22, 27.21, 25.8, 22.7, 20.8 (Ac-CH_3), 20.7 (Ac-CH_3), 20.66 (Ac-CH_3), 20.64 (Ac-CH_3), 14.1; HRMS *m/z* (ES^+) [Found: $(M+Na)^+$ 621.3620 $C_{32}H_{54}O_{10}Na$ requires M^+, 621.3609]. Data matched those reported previously. [171]

1,2-*O*-(Oleyl)-orthoacetyl-3,4,6-tri-*O*-acetyl-α-D-glucopyranoside **36**



R_f = 0.27 (hexane/EtOAc, 7:3); $[\alpha]_D^{19}$ = +5.6 (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.71 (d, *J* = 5.2 Hz, 1H, H-1), 5.39–5.33 (m, 2H, -C*H*=C*H*-), 5.19 (t, *J* = 2.9 Hz, 1H, H-3), 4.90 (dd, *J* = 9.6, 1.9 Hz, 1H, H-4), 4.31 (ddd, *J* = 5.2, 3.0, 0.9 Hz, 1H, H-2), 4.21–4.18 (m, 2H, H-6a, H-6b), 3.98–3.93 (m, 1H, H-5) 3.46 (td, *J* = 6.6, 1.0 Hz, 2H, OCH_2), 2.11 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.05–1.99 (m, 4H, 4H, 2 x CH_2), 1.71 (s, 3H, CH_3), 1.54–1.49 (m, 2H, CH_2), 1.30–1.25 (m, 22H, 11 × CH_2), 0.88 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7 (C=O, Ac), 169.7 (C=O, Ac), 169.2 (C=O, Ac), 130.0 (C=C), 129.8 (C=C), 121.33 (CCH_3), 96.9 (C1), 73.1 (C2), 70.2 (C3), 68.2 (C4), 70.0 (C5), 63.8 (OCH_2), 63.1 (C6), 31.9, 29.78, 29.76, 29.70, 29.67, 29.53, 29.48, 29.4, 29.33, 29.26, 27.23, 27.20, 26.10, 22.7, 20.82 (Ac-CH_3), 20.79 (Ac-CH_3), 20.76 (Ac-CH_3), 14.12; HRMS *m/z* (ES^+)[Found: $(M+NH4)^+$ 616.4053, $C_{32}H_{58}O_{10}N_1$ requires M^+ 616.4055].

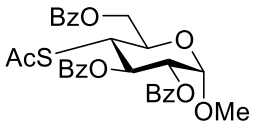
Methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside **38**



Methyl-α-D-galactopyranoside **5** (10.0 g, 51.5 mmol 1.0 equiv.) was dried under vacuum for 1 h before being dissolved in MeCN (150 mL). $Cu(OTf)_2$ (1.12 g, 3.09 mmol, 0.06 equiv.) and benzaldehyde dimethyl acetal (9.27 mL, 9.40 g, 61.8 mmol, 1.2 equiv.) were added, and the solution was sonicated for 70 mins. The reaction was quenched by addition of Et_3N (5 mL) and the solvent was removed under reduced pressure. The crude product was purified by recrystallisation (1:1 Hexane/EtOAc, 500 mL) to afford methyl 4,6-*O*-benzylidene-α-D-galactopyranoside. The resulting white solid was dissolved in pyridine (50 mL), cooled to 0 °C and treated with BzCl (17.9 mL, 21.7 g, 154.5 mmol, 3.0 equiv.). The reaction mixture was stirred at RT for 18 h. The reaction mixture was then added dropwise with stirring to saturated aqueous $NaHCO_3$ (200 mL). The mixture was extracted into $CHCl_3$ (3 × 100 mL) and the combined organic phases washed with water (100 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude residue was purified by recrystallisation (1:1, hexane/EtOAc, 150 mL) yielding methyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-galactopyranoside (21.5 g, 43.8 mmol, 85%, 2 steps) as a white solid. This material (10.0 g, 20.5 mmol, 1.0 equiv.) was dissolved in AcOH/H_2O (9/1, 100 mL) and stirred at RT for 4 hrs. The reaction mixture was cooled to 0 °C, quenched with saturated aqueous $NaHCO_3$ (250 ml) and stirred for a further 30 mins. The organic layer was washed with saturated aqueous $NaHCO_3$ (4 × 250 mL) and the combined organic phases dried ($MgSO_4$), filtered and concentrated under reduced pressure to give crude methyl 2,3-di-*O*-benzoyl-α-D-galactopyranoside. A solution of this crude material (8.03 g, 20.0 mmol, 1.0 equiv.) in pyridine (25 mL) was cooled to 0 °C

and treated with BzCl (2.32 mL, 2.81 g, 20.0 mmol, 1.0 equiv.). The reaction mixture was stirred at RT for 18 h, before being added dropwise to a stirring solution of saturated aqueous $NaHCO_3$ (200 mL). The mixture was extracted into $CHCl_3$ (3 × 100 mL), and the combined organic phases washed with water (100 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure yielding the crude product, which was purified by column chromatography (hexane/EtOAc, 0-50%) to deliver **38** (8.41 g, 16.6 mmol, 81%) as a white foam. R_f = 0.48 (toluene/EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.96 (m, 6H, ArH), 7.59 – 7.53 (m, 1H, Ar*H*), 7.51 – 7.40 (m, 4H, Ar*H*), 7.39 – 7.31 (m, 4H, Ar*H*), 5.76 (dd, *J* = 10.7, 2.9 Hz, 1H, H-3), 5.71 (dd, *J* = 10.7, 3.4 Hz, 1H, H-2), 5.22 (d, *J* = 3.3 Hz, 1H, H-1), 4.67 (dd, J = 11.5, 5.7 Hz, 1H, H-6a), 4.58 (dd, *J* = 11.5, 7.0 Hz, 1H, H-6b), 4.44 – 4.42 (m, 1H, H-4), 4.36 (at, *J* = 6.3 Hz, 1H, H-5), 3.45 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (C=O, Bz), 166.2 (C=O, Bz) 165.9 (C=O, Bz), 133.4 (Ar-C), 133.3 (Ar-C), 130.2 (Ar-C), 129.9 (Ar-C), 129.8 (Ar-C), 129.7 (Ar-C), 129.66 (Ar-C), 129.4 (Ar-C), 129.3 (Ar-C), 128.5 (Ar-C), 128.44 (Ar-C), 128.41 (Ar-C), 97.6 (C1), 70.9 (C3), 69.0 (C2), 68.2 (C4), 67.8 (C5), 63.6 (C6), 55.5 (O*C*H_3); HRMS *m/z* (ES^+) [Found: $(M+H)^+$ 507.1669, $C_{28}H_{27}O_9$ requires M^+ 507.1654]; Data matched those previously reported.[73]

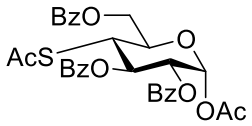
Methyl 4-*S*-acetyl-2,3,6-tri-*O*-benzoyl-4-deoxy-4-thio-α-D-glucopyranoside 39



A solution of methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside **38** (2.50 g, 4.94 mmol, 1.0 equiv.) in DCM (80 mL) and pyridine (20 mL) was cooled to 0 °C and slowly treated with Tf_2O (1.90 mL, 3.20 g, 11.4 mmol, 2.3 equiv.). After stirring for 1h at 0 °C, TLC analysis revealed a single spot (R_f = 0.52, hexane/EtOAc, 7:3) DCM (75 mL) was added

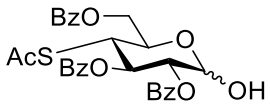
and the solution washed sequentially with ice cold 1M HCl (50 mL), cold saturated aqueous $NaHCO_3$ (50 mL) and cold brine (50 mL), dried ($MgSO_4$), filtered and condensed under reduced pressure to give a yellow residue. This material was purified by column chromatography (0-30%, Hexane/EtOAc) to deliver methyl 2,3,6-tri-*O*-benzoyl-4-*O*-trifluoromethanesulfonyl-α-D-galactopyranoside (2.57 g, 4.02 mmol, 82%) as a white solid. A suspension of this material (1.50 g, 2.35 mmol, 1.0 equiv.) and KSAc (800 mg, 7.05 mmol, 3.0 equiv.) in pyridine (15 mL) was subsequently stirred at RT for 24 h TLC analysis revealed complete consumption of the starting material (R_f = 0.40, hexane/EtOAc, 9:1) and the reaction mixture was diluted with EtOAc (100 mL), washed with water (3 × 50 mL), brine (50 mL), dried ($MgSO_4$), filtered and condensed under reduced pressure to give a yellow residue. Purification by column chromatography (hexane/EtOAc, 0-30%) delivered **39** (1.17g, 2.07 mmol, 89%) as a white foam. R_f = 0.40 (hexane/EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.14 (m, 2H, Ar*H*), 7.92 – 7.97 (m, 4H, Ar*H*), 7.58 – 7.62 (m, 1H, Ar*H*), 7.48 – 7.52 (m, 4H, Ar*H*), 7.34 – 7.39 (m, 4H, Ar*H*), 5.94 (dd, *J* = 11.0 Hz, 9.6 Hz, 1H, H-3), 5.28 – 5.23 (m, 2H, H-1, H-2).4.65 (dd, *J* = 12.1 Hz, 2.2 Hz, 1H, H-6a), 4.56 (dd, *J* = 12.1 Hz, 5.1 Hz, 1H, H-6b), 4.28 (ddd, *J* = 11.4 Hz, 5.1 Hz, 2.1 Hz, 1H, H-5), 4.10 – 4.21 (m, 1H, H-4), 3.44 (s, 3H, OC*H*$_3$), 2.21 (s, 3H, SAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6 (C=O, Ac), 169.3 (C=O, Bz), 165.9 (C=O, Bz), 165.7 (C=O, Bz), 133.3 (Ar-C), 133.22 (Ar-C), 133.18 (Ar-C), 129.9 (Ar-C), 129.81 (Ar-C), 129.80 (Ar-C), 129.78 (Ar-C), 129.3 (Ar-C), 129.1 (Ar-C), 128.5 (Ar-C), 128.40 (Ar-C), 128.38 (Ar-C), 97.2 (C1), 73.2 (C2), 69.2 (C3), 68.6 (C5), 63.9 (C6), 55.6 (OCH_3), 44.1 (C4), 30.7 (Ac-CH_3); HRMS *m/z* (ES^+) [Found: $(M+H)^+$ 565.1541 $C_{30}H_{29}O_9S$ requires $M^{+\cdot}$ 565.1532]. Data matched those reported previously [172]

Acetyl 4-*S*-acetyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-thio-α-D-glucopyranoside **40**



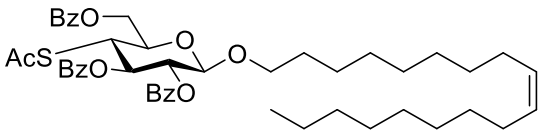
A solution of methyl 4-*S*-acetyl-2,3,6-tri-*O*-benzoyl-4-thio-α-D-glucopyranoside **39** (1.12 g, 1.89 mmol, 1.0 equiv.) in Ac_2O/AcOH/H_2SO_4 (35:15:1, *v/v/v*, 14 mL) was stirred overnight at RT. Upon reaction completion as seen by TLC (R_f = 0.50 (hexane/EtOAc, 3:1), the mixture was diluted with $CHCl_3$ (100 mL), washed with water (50 mL), saturated aqueous $NaHCO_3$ (3 × 50 mL) and brine (50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-30%) to give the title compound (797 mg, 1.35 mmol, 71%) as a white foam. R_f = 0.50 (hexane/EtOAc, 3:1); $[\alpha]_D^{22}$ = 150.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.12 (m, 2H, Ar*H*), 7.88 – 7.94 (m, 4H, Ar*H*), 7.59 – 7.63 (m, 1H, Ar*H*), 7.49 – 7.52 (m, 4H, Ar*H*), 7.35 – 7.50 (m, 4H, Ar*H*), 6.62 (d, *J* = 3.6 Hz, 1H, H-1), 5.94 – 6.00 (m, 1H, H-3), 5.48 (dd, *J* = 10.0 Hz, 3.6 Hz, 1H, H-2), 4.56 – 4.64 (m, 2H, H-6a, H-6b), 4.40 – 4.45 (m, 1H, H-5), 4.23 (t, *J* = 11.3 Hz, 1H, H-4), 2.21 (s, 3H, SAc), 2.18 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2 (C=O, Ac), 168.6 (C=O, Ac), 166.3 (C=O, Bz), 165.8 (C=O, Bz), 165.3 (C=O, Bz), 133.5 (Ar-C), 133.4 (Ar-C), 133.3 (Ar-C), 129.9 (Ar-C), 129.84 (Ar-C), 129.79 (Ar-C), 129.7 (Ar-C), 128.9 (Ar-C), 128.7 (Ar-C), 128.49 (Ar-C), 128.45 (Ar-C), 128.4 (Ar-C), 89.6 (C1), 71.4 (C2), 71.1 (C5), 69.0 (C3), 63.4 (C6), 43.8 (C4), 30.7 (Ac-CH_3), 20.9 (Ac-CH_3); HRMS *m/z* (ES$^+$) [Found: $(M+Na)^+$ 615.1322 $C_{31}H_{28}O_{10}SNa$ requires M^+, 615.1300].

4-*S*-acetyl-2,3,6-tri-*O*-benzoyl-4-deoxy-4-thio-α/β-D-glucopyranoside **41**



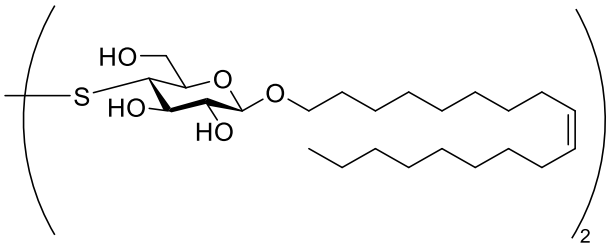
A solution of **40** (240 mg, 0.425 mmol, 1.0 equiv.) in DCM (10 mL) and EtOAc (1 mL) was treated with $TiBr_4$ (586 mg, 1.59 mmol, 3.75 equiv.) and the reaction mixture was stirred at RT. The progress of the reaction was monitored using TLC, after 24 hrs NaOAc (390 mg, 4.76 mmol, 11.2 equiv.) was added, and the reaction mixture was stirred for 15 mins. The mixture was then filtered over Celite, and the Celite pad washed with DCM (50 mL). The organic phase was washed with water (100 mL) and evaporated to dryness under reduced pressure. The crude product was dissolved in acetone (30 mL) and water (1 mL). Silver carbonate (221 mg, 0.803 mmol, 1.89 equiv.) was added and the mixture was stirred for 6 h at RT with the exclusion of light. Upon completion, the mixture was filtered, washed with acetone (30 mL) and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-30%) to deliver **41** (199 mg, 0.361 mmol, 85%) as a white foam. R_f = 0.48 (hexane/EtOAc, 7:3); $[\alpha]_D^{19}$= +10.5 (*c* = 1.0, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.12 (m, 2H, Ar*H*), 7.98 – 7.92 (m, 4H), 7.62 – 7.57 (m, 1H), 7.52 – 7.46 (m, 5H, Ar*H*), 7.37 (t, *J* = 7.8 Hz, 3H, Ar*H*), 6.02 (dd, *J* = 11.2, 10.0 Hz, 1H, H-3), 5.74 (app s, 1H, H-1), 5.28 (dd, *J* = 9.9, 3.5 Hz, 1H, H-2), 4.66 (dd, *J* = 13.8, 3.8 Hz, 1H, H-6a), 4.60 – 4.53 (m, 2H, H-6b, H-5), 4.22 (t, *J* = 11.0 Hz, 1H, H-4), 2.21 (s, 3H, SAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.5 (C=O, SAc), 166.4 (C=O, Bz), 165.8 (C=O, Bz × 2), 133.4 (Ar-C), 133.3 (Ar-C), 133.2 (Ar-C), 130.0 (Ar-C), 129.92 (Ar-C), 129.88 (Ar-C), 129.8 (Ar-C), 129.2 (Ar-C), 129.0 (Ar-C), 128.47 (Ar-C), 128.45 (Ar-C), 128.4 (Ar-C), 90.7 (C1), 73.3 (C2), 69.0 (C3), 68.7 (C5), 63.7 (C6), 44.1 (C4), 30.7 (Ac-CH_3); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 568.1636 requires $C_{29}H_{30}O_9SN$ M^+ 568.1641].

Oleyl 4-*S*-acetyl-2,3,6-tri-*O*-benzoyl-4-deoxy-4-thio-α-D-glucopyranoside **42**



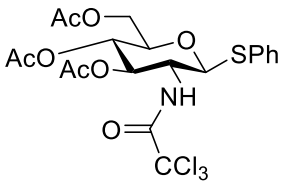
Following general procedure **D**, hemi-acetal **41** (148 mg, 0.269 mmol, 1.0 equiv.), DBU (4.00 mg, 3.92 μL, 26.9 μmol, 0.1 equiv.) and Cl_3CCN (0.27 mL, 389 mg, 2.69 mmol, 10.0 equiv.) gave the corresponding trichloroacetimidate donor. After reacting the donor with oleyl alcohol (64.0 mg, 0.238 mmol, 1.1 equiv.) and TMSOTf (48.0 mg, 39.1 μL, 0.216 mmol, 1.0 equiv.) for 2 h, purification by column chromatography (hexane/EtOAc, 0-10%) delivered the title compound (80.0 mg, 0.100 mmol, 37%) as a colourless oil. R_f = 0.27 (hexane/EtOAc, 9:1); $[\alpha]_D^{24}$ =-15.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.09 (m, 2H, Ar*H*), 7.96 – 7.88 (m, 4H, Ar*H*), 7.63 – 7.55 (m, 1H, Ar*H*), 7.52 – 7.45 (m, 4H, Ar*H*), 7.40 – 7.33 (m, 4H, Ar*H*), 5.72 (app t, *J* = 10.1 Hz, 1H, H-3), 5.43 (dd, *J* = 9.4, 8.0 Hz, 1H, H-2), 5.38 – 5.28 (m, 2H, -C*H*=C*H*-), 4.73 (d, *J* = 7.9 Hz, 1H, H-1), 4.63 (m, 2H, H-6a, H-6b), 4.12 (dd, *J* = 11.0, 3.0 Hz, 1H, H-5), 4.03 (t, *J* = 10.9 Hz, 1H, H-4), 3.87 (dt, *J* = 9.7, 6.2 Hz, 1H, OC*H*H), 3.49 (dt, *J* = 9.6, 6.7 Hz, 1H, OC*H*H), 2.20 (s, 3H, SAc), 2.06 – 1.90 (m, 4H, 2 x CH_2), 1.54 – 1.43 (m, 2H, CH_2), 1.35 – 1.03 (m, 22H, 11 x CH_2), 0.87 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.7 (C=O, Ac), 166.3 (C=O, Bz), 165.8 (C=O, Bz), 165.1 (C=O, Bz), 133.3 (Ar-C), 133.2 (Ar-C), 133.1 (Ar-C), 130.3 (*C*=C), 129.90 (Ar-C), 129.89 (Ar-C), 129.85 (Ar-C), 129.82 (Ar-C), 129.81 (*C*=C), 129.75 (Ar-C), 129.5 (Ar-C), 129.0 (Ar-C), 128.43 (Ar-C), 128.38 (Ar-C), 128.3 (Ar-C), 101.1 (C1), 73.1 (C2), 72.9 (C5), 71.9 (C3), 70.2 (O*C*H_2), 64.0 (C6), 44.7 (C4), 32.6, 30.7 (Ac-CH_3), 29.8, 29.73, 29.67, 29.5, 29.39, 29.36, 29.33, 29.32, 29.23, 29.20, 27.21, 27.19, 25.7, 22.7, 14.1; HRMS *m/z* (ES^+) [Found: $(M+Na)^+$ 823.3844 requires $C_{47}H_{60}O_9SNa$ M^+ 823.3850].

Di(Oleyl 4-deoxy-4-thio-α-D-glucopyranoside)-4-4'-disulfide **24**



To a solution of oleyl 4-*S*-acetyl-2,3,6-tri-*O*-benzoyl-4-thio-β-D-glucopyranoside (80.0 mg, 100 µmol, 1.0 equiv.) in MeOH (5 mL) was added NaOMe (5.00 mg, 100 µmol, 1.0 equiv.) in MeOH (1 mL). The reaction mixture was left stirring at RT for 48 h, upon reaction completion as seen by TLC (R_f = 0.41, hexane/EtOAc, 2:8), Amberlite IR20 (H^+) ion exchange resin was added until neutral. The mixture was filtered, washed with methanol (50 mL) and the combined filtrates were concentrated under reduced pressure. The crude residue was purified by flash chromatography (hexane/EtOAc, 0-100%) yielding **24** (30.0 mg, 67.2 µmol, 67%) as a colourless oil. R_f = 0.36 (hexane/EtOAc, 2/8); $[\alpha]_D^{27}$ = -48.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, MeOD) δ 5.40 – 5.30 (m, 2H, -C*H*=C*H*-), 4.24 (d, *J* = 7.9 Hz, 1H, H-1), 4.00 (dd, *J* = 12.1, 1.9 Hz, 1H, H-6a), 3.93 – 3.83 (m, 2H, H-6b, OC*H*H), 3.65 – 3.46 (m, 3H, H-3, H-5, OC*H*H), 3.23 (dd, *J* = 8.7, 8.0 Hz, 1H, H-2), 2.71 (t, *J* = 10.7 Hz, 1H, H-4), 2.07 – 1.95 (m, 4H, 2 x CH_2), 1.65 – 1.57 (m, 2H, CH_2), 1.38 – 1.26 (m, 22H, 11 x CH_2), 0.90 (t, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, MeOD) δ 130.1 (*C*=C), 129.4 (*C*=C), 102.4 (C1), 76.1 (C5), 75.1 (C2), 72.6 (C3), 69.4 (OCH_2), 61.6 (C6), 54.5 (C4), 32.2, 31.7, 29.5, 29.43, 29.40, 29.24, 29.20, 29.0, 28.94, 28.93, 26.8, 26.71, 25.73, 22.3, 13.1; HRMS *m/z* (ES^-) [Found: $(M-H)^-$ 889.5887 requires $C_{48}H_{89}O_{10}S_2$ M^- 889.5903].

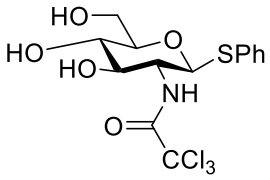
Phenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-1-thio-β-D-glucopyranoside **44**



D-Glucosamine **43** (40.0 g, 186 mmol, 1.0 equiv.) was suspended in MeOH (500 mL) at RT. Et_3N (51.6 mL, 37.5 g, 371 mmol, 2.0 equiv.) was added, and the suspension cooled to 0 °C. Trichloroacetyl chloride (20.8 mL, 33.7 g, 186 mmol, 1.0 equiv.) was then added dropwise. The suspension was warmed to RT and stirred for 4 days. The reaction was filtered through a plug of Celite, washed with MeOH (1 L), and the solvent was removed under reduced pressure. The crude residue was dissolved in pyridine (370 mL) and cooled to 0 °C. Ac_2O (140 mL) was added dropwise, and the solution was allowed to warm to RT and stirred for 24 h. The reaction was filtered through a tightly packed Celite plug, washed with EtOAc (1 L) and the solvent was removed under reduced pressure. After azeotroping with toluene (3 × 250 mL), the crude material was taken in EtOAc (500 mL), washed with 1M HCl (5 × 250 mL), saturated aqueous $NaHCO_3$ (3 × 250 mL), brine (1 × 250 mL), and the combined organic phases were dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure and the resulting brown solid was recrystallized from EtOH (300 mL) to yield 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-trichloroacetamido-α/β-D-glucopyranoside (58.5 g, 118.6 mmol, 64%). This material (58.5 g, 118.6 mmol, 1.0 equiv.) was dissolved in DCM (400 mL) at RT. PhSH (15.6 mL 16.9 g, 154.2 mmol, 1.3 equiv.) was added followed by dropwise addition of TMSOTf (21.5 mL, 26.4 g, 118.6 mmol, 1.0 equiv.). The resulting dark red solution was stirred at RT for 18 h and then poured onto a vigorously stirred solution of saturated aqueous $NaHCO_3$ and stirred for 30 mins. I_2 (15 g) was then added, and the solution was stirred

vigorously for another 30 mins. $Na_2S_2O_3$ (13.1 g, 83.0 mmol, 0.70 equiv.) was added, and stirring was continued for a final 30 mins. The layers were separated, and the aqueous extracted with DCM (1 × 200 mL). The combined organic phases were combined, dried ($MgSO_4$), and solvent removed under reduced pressure to afford the crude residue, which was then recrystallized from hexane/EtOAc (400 mL, 1:1), filtered and washed with cold hexane/EtOAc (400 mL, 2:1) to yield the title compound (45.2 g, 83.3 mmol, 70%) as a tan solid. R_f = 0.44 (hexane/EtOAc,1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.50 (m, 2H, Ar*H*), 7.37 – 7.28 (m, 3H, Ar*H*), 6.87 (d, *J* = 9.1 Hz, 1H, N*H*), 5.32 (dd, *J* = 10.3, 9.5 Hz, 1H, H-3), 5.08 (t, *J* = 9.7 Hz, 1H, H-4), 4.86 (d, *J* = 10.4 Hz, 1H, H-1), 4.25 (dd, *J* = 12.3, 5.2 Hz, 1H, H-6a), 4.19 (dd, *J* = 12.3, 2.6 Hz, 1H, H-6b), 4.01 (td, *J* = 10.4, 9.2 Hz, 1H, H-2), 3.76 (ddd, *J* = 10.0, 5.2, 2.6 Hz, 1H, H-5), 2.10 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.99 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9 (C=O, Ac), 170.6 (C=O, Ac), 169.3 (C=O, Ac), 161.6 (C=O), 133.4 (Ar-C), 131.5 (Ar-C), 129.1 (Ar-C), 128.7 (Ar-C), 86.4 (C1), 77.2 (CCl_3), 76.1 (C5), 73.0 (C3), 68.2 (C4), 62.2 (C6), 54.6 (C2), 20.8 (Ac-CH_3), 20.6 (Ac-CH_3), 20.5 (Ac-CH_3); HRMS *m/z* (ES^+) [Found: $(M+Na)^+$ 564.0024 requires $C_{20}H_{22}Cl_3NO_8SNa$ M^+ 564.0018]. Data matched those previously reported. [75]

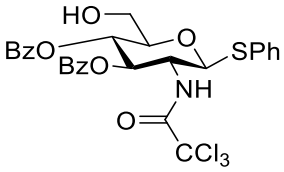
Phenyl 2-deoxy-2-trichloroacetamido-1-thio-β-D-glucopyranoside 45



Phenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-1-thio-β-D-glucopyranoside (2.30 g, 4.24 mmol, 1.0 equiv.) was then dissolved in MeOH (20 mL) and treated with a solution of NaOMe (229 mg, 4.24 mmol, 1.0 equiv.) in MeOH (5 mL). The reaction mixture was left stirring at RT for 30 mins, TLC revealed complete consumption of the

starting material (R_f = 0.53, EtOAc) Amberlite IR20 (H^+) ion exchange resin was added until neutral, after which the mixture was filtered and washed with methanol (100 mL). The combined organic filtrates were concentrated under reduced pressure yielding **45** (1.65 g, 3.96 mmol, 93 %) as a colourless oil. R_f = 0.53 (EtOAc); ^{1}H NMR (400 MHz, MeOD) δ 7.52 – 7.47 (m, 2H, Ar*H*), 7.31 – 7.20 (m, 3H, Ar*H*), 4.95 (d, *J* = 10.3 Hz, 1H, H-1), 3.89 (dd, *J* = 12.1, 2.1 Hz, 1H, H-6a), 3.78 (t, *J* = 10.0 Hz, 1H, H-2), 3.72 (dd, *J* = 12.1, 5.2 Hz, 1H, H-6b), 3.62 (dd, *J* = 9.8, 8.1 Hz, 1H., H-3), 3.41 – 3.36 (m, 2H, H-4, H-5); ^{13}C NMR (101 MHz, MeOD) δ 164.4 (C=O, CCl_3), 134.6 (Ar-C), 130.9 (Ar-C), 128.5 (Ar-C), 126.8 (Ar-C), 94.9 (CCl_3) 87.2 (C1), 80.5 (C5), 76.7 (C3), 71.0 (C4), 61.6 (C6), 58.1 (C2); HRMS *m/z* (ES^-) [Found: $(M-H)^-$ 413.9738 requires $C_{14}H_{15}Cl_3N_1O_5S$ M^- 413.9742]. Data matched those previously reported. [75]

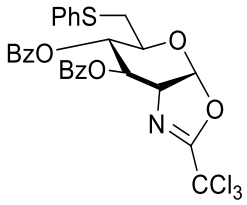
Phenyl 3,4-di-*O*-benzoyl-2-deoxy-2-trichloroacetamido-1-thio-β-D-glucopyranoside 46



Phenyl 2-deoxy-2-trichloroacetamido-1-thio-β-D-glucopyranoside **45** (1.00 g, 2.39 mmol, 1.0 equiv.) was dissolved in pyridine (15 mL), imidazole (326 mg, 4.78 mmol, 2.0 equiv.) and TIPSCl (1.02 mL, 922 mg, 4.78 mmol, 2.0 equiv.) were added and the solution was then stirred at RT. After 16 h, BzCl (2.21 mL, 2.68 g, 19.1 mmol, 8.0 equiv.) was added and the reaction was stirred for 24 h, at which point it was quenched with MeOH (5 mL). The solution was diluted with DCM (100 mL), washed with 1M HCl (2 x 75 mL), saturated aqueous $NaHCO_3$ (100 mL), water (75 mL), the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was dissolved in a solution of THF (32 mL), H_2O (12 mL) and TFA (16 mL), this

mixture was stirred at RT for 18 h, TLC analysis revealed reaction completion (R_f = 0.62, hexane/EtOAc, 7:3) and the solution was concentrated under reduced pressure azeotroping with toluene (2 × 100 mL). Purification by column chromatography (hexane/EtOAc, 0-30%) afforded **46** (816 mg, 1.31 mmol, 55%) as a colourless oil. R_f = 0.62 (hexane/EtOAc, 7:3); $[\alpha]_D^{23}$ = -50.5 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.84 (m, 4H, Ar*H*), 7.58 – 7.53 (m, 2H, Ar*H*), 7.53 – 7.46 (m, 2H, Ar*H*), 7.37 – 7.30 (m, 7H, Ar*H*), 7.13 (d, *J* = 9.1 Hz, 1H, N*H*), 5.88 (dd, *J* = 10.3, 9.7 Hz, 1H, H-3),), 5.50 (t, *J* = 9.7 Hz, 1H, H-4), 5.15 (d, *J* = 10.3 Hz, 1H, H-1), 4.31 – 4.20 (m, 1H, H-2), 3.89 – 3.79 (m, 2H, H-5, H-6a), 3.72 (dd, *J* = 12.5, 4.7 Hz, 1H, H-6b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7 (C=O, Bz), 165.8 (C=O, Bz), 161.8 (C=O), 133.8 (Ar-C), 133.7 (Ar-C), 133.1 (Ar-C), 131.7 (Ar-C), 129.9 (Ar-C), 129.8 (Ar-C), 129.2 (Ar-C), 128.6 (Ar-C), 128.54 (Ar-C), 128.49 (Ar-C), 128.46 (Ar-C), 128.4 (Ar-C), 92.1 (CCl_3), 86.5 (C1), 78.9 (C5), 73.3 (C3), 69.0 (C4), 61.6 (C6), 55.1 (C2); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 641.0675 requires $C_{28}H_{28}Cl_3N_2O_7S$ M^+ 641.0682].

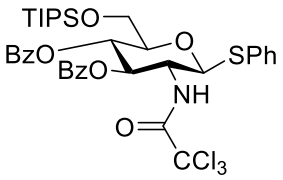
2-Trichloroacetamido-(3,4-di-*O*-benzoyl-6-*S*-phenyl-1,2-dideoxy-α-D-glucopyrano)[1,2-d]-oxazoline 48



In a Teflon™ flask, a solution of **46** (630 mg, 1.01 mmol, 1.0 equiv.) in DCM (10 mL) was cooled to -40 °C and DAST (0.27 mL, 326 mg, 2.02 mmol, 2.0 equiv.) was added dropwise. Upon reaction completion as seen by TLC (R_f = 0.27, hexane/EtOAc, 8:2), the solution was cooled to -20 °C and MeOH (5 mL) was added slowly. After stirring for 30 mins at RT the solution was concentrated, diluted with DCM (20 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 50 mL). The combined organic phases were dried

($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-20%) to deliver the title compound **48** as a colourless oil (398 mg, 0.656 mmol, 65%). R_f = 0.69 (hexane/EtOAc, 7:3); $[\alpha]_D^{19}$ = -30.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.03 (m, 4H, Ar*H*), 7.65 – 7.58 (m, 2H, Ar*H*), 7.50 – 7.42 (m, 4H, Ar*H*), 7.25 – 7.22 (m, 2H, Ar*H*), 7.15 – 7.09 (m, 3H, Ar*H*), 6.44 (d, *J* = 7.4 Hz, 1H, H-1), 5.78 (dd, *J* = 2.8, 1.4 Hz, 1H, H-3), 5.43 (dt, *J* = 7.3, 1.5 Hz, 1H, H-4), 4.66 (ddd, *J* = 7.4, 2.8, 1.5 Hz, 1H, H-2), 3.95 (td, *J* = 7.2, 4.5 Hz, 1H, H-5), 3.41 (dd, *J* = 14.2, 4.4 Hz, 1H, H-6b), 3.29 (dd, *J* = 14.3, 7.1 Hz, 1H, H-6b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9 (C=O, Bz), 164.5 (C=O, Bz), 163.1 (C=N), 134.9 (Ar-C), 133.73 (Ar-C), 133.68 (Ar-C), 130.2 (Ar-C), 130.0 (Ar-C), 129.4 (Ar-C), 129.0 (Ar-C), 128.94 (Ar-C), 128.86 (Ar-C), 128.6 (Ar-C), 128.4 (Ar-C), 126.3 (Ar-C), 103.3 (C1), 86.0 (CCl_3), 70.7 (C4), 69.4 (C5), 68.5 (C3), 64 (C2) 37.6 (C6); HRMS *m/z* (ES^+) [Found: $(M+H)^+$ 606.302 $C_{28}H_{23}O_6NSCl_3$ requires $M^{+\cdot}$ 606.0306].

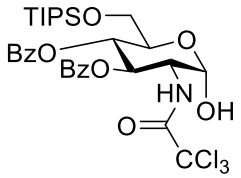
Phenyl 3,4-di-*O*-benzoyl-6-*O*-TIPS-2-deoxy-2-trichloroacetamido-1-thio-β-D-glucopyranoside 52



Phenyl 2-trichloroacetamido-2-deoxy-1-thio-β-D-glucopyranoside (6.00 g, 14.4 mmol, 1.0 equiv.) (6.00 g, 14.4 mmol, 1.0 equiv.) was dissolved in pyridine (50 mL) and DCM (50 mL). Imidazole (1.96 g, 28.7 mmol, 2.0 equiv.) and TIPSCl (6.15 mL, 5.54 g, 28.7 mmol, 2.0 equiv.) were added and the solution was then stirred at RT. After 16 h, BzCl (13.4 mL, 16.2 g, 115 mmol, 8.0 equiv.) was added and the reaction was stirred for a further 24 h, TLC analysis revealed a single spot (R_f = 0.63, hexane/EtOAc, 8:2), and the reaction was quenched with MeOH (15 mL). The solution was diluted with DCM

(100 mL), washed with 1M HCl (2 x 75 mL), saturated aqueous $NaHCO_3$ (100 mL), water (75 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-20%) to deliver **52** (10.2 g, 13.1 mmol, 91%) as a white solid. R_f = 0.63 (hexane/EtOAc, 8:2); mp = 130 - 135 °C; $[\alpha]_D^{23}$ = -23.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.83 (m, 4H, Ar*H*), 7.60 – 7.55 (m, 2H, Ar*H*), 7.61 – 7.54 (m, 2H, Ar*H*), 7.38 – 7.29 (m, 7H, Ar*H*), 6.91 (d, *J* = 9.0 Hz, 1H, N*H*), 5.72 (t, 1H, *J* = 9.8 Hz, H-3), 5.56 (t, *J* = 9.7 Hz, 1H, H-4), 5.06 (d, *J* = 10.3 Hz, 1H, H-1), 4.18 (td, *J* = 10.3, 9.1 Hz, 1H, H-2), 3.97 – 3.89 (m, 2H, H-6a, H-6b), 3.86 (ddd, *J* = 9.8, 4.4, 3.0 Hz, 1H, H-5), 1.07 – 0.98 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7 (C=O, Bz), 165.0 (C=O, Bz), 161.7 (C=O), 133.5 (Ar-C), 133.3 (Ar-C), 132.9 (Ar-C), 132.7 (Ar-C), 129.9 (Ar-C), 129.7 (Ar-C), 129.6 (Ar-C), 129.1 (Ar-C), 129.0 (Ar-C), 128.42 (Ar-C), 128.36 (Ar-C), 128.2 (Ar-C), 92.1 (CCl_3), 86.8 (C1), 79.9 (C5), 73.9 (C3), 68.8 (C4), 62.9 (C6), 55.2 (C2), 17.9 (CH_3, ^{i}Pr), 11.9 (CH, ^{i}Pr); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 797.2014 requires $C_{37}H_{48}Cl_3N_2O_7SSi$ M^+ 797.2017].

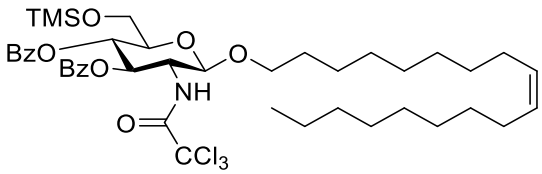
3,4-Di-*O*-benzoyl-6-*O*-TIPS-2-deoxy-2-trichloroacetamido-α-D-glucopyranose 53



Thioglycoside **52** (2.26 g, 2.89 mmol, 1.0 equiv.) was dissolved in a mixture of acetone/water (9:1 *v/v*, 3 mL). NBS (1.54 g, 8.67 mmol, 3.0 equiv.) was added at 0 °C, and the reaction mixture was warmed up to RT. After 1 hr TLC analysis revealed a new spot (R_f = 0.30, hexane/EtOAc, 8:2). The reaction mixture was diluted with water (50 mL) and extracted with DCM (3 × 75 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (100 mL), dried ($MgSO_4$), filtered and the solvent

removed under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-20%) to deliver **53** as a white foam (1.31 g, 1.90 mmol, 89%); **52** was recovered (0.668 mmol). R_f = 0.30 (hexane/EtOAc, 8:2); $[\alpha]_D^{23}$ = -4.5 (*c* = 1.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.89 (m, 4H, Ar*H*), 7.54 – 7.44 (m, 2H, Ar*H*), 7.40 – 7.32 (m, 4H, Ar*H*). 7.26 (d, *J* = 8.8 Hz, 1H), N*H*), 5.88 – 5.78 (t, 1H, *J* = 10.3 Hz, H-3), 5.60 (t, *J* = 9.8 Hz, 1H, H-4), 5.51 (t, 1H, *J* = 3.5 Hz, H-1), 4.41 (ddd, *J* = 11.0, 9.1, 3.5 Hz, 1H, H-2), 4.38 – 4.33 (m, 1H, H-5), 3.93 – 3.85 (m, 2H, H-6a, H-6b), 3.52 (s, 1H, OH), 1.07 – 0.97 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2 (C=O, Bz), 165.1 (C=O, Bz), 162.0 (C=O), 133.4 (Ar-C), 133.3 (Ar-C), 129.9 (Ar-C), 129.7 (Ar-C), 129.2 (Ar-C), 128.8 (Ar-C), 128.4 (Ar-C), 92.0 (CCl_3), 91.2 (C1), 71.4 (C5), 71.2 (C3), 68.8 (C4), 62.8 (C6), 54.7 (C2), 17.9 (CH_3, ^{i}Pr), 11.9 (CH, ^{i}Pr); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 705.1928 requires $C_{31}H_{44}Cl_3N_2O_8Si$ M^+ 705.1932].

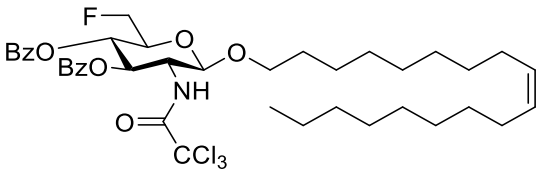
Oleyl 3,4-di-*O*-benzoyl-6-*O*-TMS-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside 54



Following general procedure **D**, hemi-acetal **53** (402 mg, 0.583 mmol, 1.0 equiv.), DBU (9.00 mg, 8.65 μL, 58.3 μmol, 0.1 equiv.) and Cl_3CCN (0.58 mL, 842 mg, 5.83 mmol, 10.0 equiv) gave the corresponding trichloroacetimidate donor. After reacting the donor with oleyl alcohol (0.19 mL, 168 mg, 0.627 mmol, 1.1 equiv.) and TMSOTf (0.10 mL, 127 mg, 0.570 mmol, 1.0 equiv.) for 30 mins, purification by column chromatography (hexane/EtOAc, 0-20%,) successfully delivered alkyl glycoside **54** (192 mg, 0.245 mmol, 54%) as a colourless oil. R_f = 0.72 (hexane/EtOAc, 7:3); $[\alpha]_D^{25}$ = -8.5 (*c* = 2.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.82 (m, 4H, Ar*H*), 7.48 – 7.40 (m,

2H, Ar*H*), 7.30 (td, *J* = 7.7, 4.1 Hz, 4H, Ar*H*),) 6.83 (d, *J* = 8.7 Hz, 1H, N*H*), 5.75 – 5.58 (m, 1H, H-3), 5.47 (t, *J* = 9.3 Hz, 1H, H-4), 5.35 – 5.24 (m, 2H, -C*H*=C*H*-), 4.74 (d, *J* = 8.2 Hz, 1H, H-1), 4.14 – 4.02 (m, 1H, H-2), 4.08 (m, 1H, H-6a), 3.91 – 3.83 (m, 3H, H-5, OCH_2), 3.45 (m, 1H, H-6b), 1.93 (m, 4H, 2 x CH_2), 1.51 (dd, *J* = 11.4, 6.3 Hz, 2H, CH_2), 1.21 (s, 22H, 11 x CH_2), 0.82 (t, *J* = 6.8 Hz, 3H, CH_3), 0.00 (s, 9H, TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3 (C=O, Bz), 165.7 (C=O, Bz), 162.4 (C=O), 134.1 (Ar-C), 133.9 (Ar-C), 130.5 (C=C), 130.43 (Ar-C), 130.38 (Ar-C), 130.3 (Ar-C), 129.7 (*C*=C*)*, 129.2 (Ar-C), 129.0 (Ar-C), 101.2 (C1), 92.9 (CCl_3), 75.5 (C5), 73.0 (C3), 70.7 (C6), 70.1 (C4), 62.8 (O*C*H_2), 57.1 (C2), 33.2, 32.4, 30.3, 30.24, 30.20, 30.1, 30.0, 29.92, 29.87, 29.85, 29.8, 27.8, 26.5, 23.2, 14.7, -0.01 (Si(CH_3)$_3$); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 799.3247 requires $C_{40}H_{58}Cl_3N_2O_8$ M^+ 799.3258].

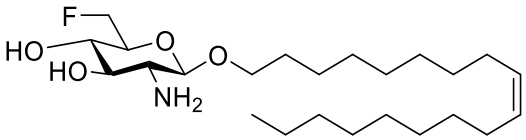
Oleyl 3,4-di-*O*-benzoyl-6-fluoro-2-trichloroacetamido-2,6-dideoxy-β-D-glucopyranoside 55



In a Teflon™ flask, a solution of **54** (192 mg, 0.245 mmol, 1.0 equiv.) in DCM (10 mL) was cooled to -40 °C and DAST (0.070 mL, 79.0 mg, 0.490 mmol, 2.0 equiv.) was added dropwise. Upon reaction completion as seen by TLC (R_f = 0.27, hexane/EtOAc, 8:2), the solution was cooled to -20 °C and MeOH (5 mL) was added slowly. After stirring for 30 mins at RT the solution was concentrated, diluted with DCM (20 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-20%) to deliver the title compound (107 mg, 0.136 mmol, 56%) as a colourless oil. R_f = 0.24 (hexane/EtOAc,

8:2); $[\alpha]_D^{25}$ = -5.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.83 (m, 4H Ar*H*), 7.56 – 7.47 (m, 2H, Ar*H*), 7.42 – 7.31 (m, 4H, Ar*H*), 6.89 (d, *J* = 8.6 Hz, 1H, N*H*), 5.85 (dd, *J* = 10.8, 9.4 Hz, 1H, H-3), 5.51 (t, *J* = 9.7 Hz, 1H, H-4), 5.39 – 5.30 (m, 2H, -C*H*=C*H*-), 4.91 (d, *J* = 8.2 Hz, 1H, H-1), 4.59 (dd, $^2J_{H6a/b\text{-}F}$ = 47.0 Hz, *J* = 3.9 Hz, 2H, H-6a, H-6b), 4.11 (dt, *J* = 10.8, 8.4 Hz, 1H, H-2), 3.99 (m, 2H, H-5, OC*H*H), 3.58 – 3.49 (m, 1H, OC*H*H), 1.99 (m, 4H, 2 x CH_2), 1.27 (s, 24H, 12 x CH_2), 0.88 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (C=O, Bz), 165.2 (C=O, Bz), 162.0, (C=O), 133.66 (Ar-C), 133.63 (Ar-C), 130.0 (*C*=C), 129.9 (*C*=C), 129.84 (Ar-C), 129.79 (Ar-C), 128.63 (Ar-C), 128.55 (Ar-C), 128.54 (Ar-C), 128.48 (Ar-C), 100.5 (C1), 92.2 (CCl_3), 81.5 (d, $^1J_{C\text{-}F}$ = 175.5 Hz, C6), 73.2 (d, $^2J_{C\text{-}F}$ = 19.7 Hz, C5), 71.8 (C3), 70.4 (O*C*H_2), 68.6 (d, $^3J_{C\text{-}F}$ = 6.9 Hz, C4), 56.6 (C2), 32.6, 31.9, 29.8, 29.70, 29.67, 29.53, 29.49, 29.47, 29.4, 29.32, 29.28, 27.2, 25.9, 22.7, 14.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ -231.45 (td, $^2J_{H\text{-}6a/b\text{-}F}$ = 47.4, $^3J_{H5\text{-}F}$ = 22.8 Hz); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 801.3206 requires $C_{40}H_{57}Cl_3FN_2O_7$ M^+ 801.3215].

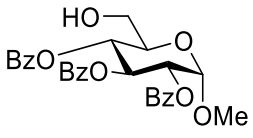
Oleyl 6-deoxy-6-fluoro-β-D-glucosaminopyranoside 23



Oleyl 3,4-di-*O*-benzoyl-6-deoxy-6-fluoro-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside **55** (107 mg, 0.136 mmol, 1.0 equiv.) was dissolved in MeOH (5 mL), after which NaOMe (7.40 mg, 0.136 mmol, 1.0 equiv.) was added in MeOH (1 mL). The reaction mixture was left stirring at RT for 24 h After 48 h TLC analysis revealed full consumption of the starting material (R_f = 0.21, DCM/MeOH, 95:5). Amberlite IR20 (H^+) ion exchange resin was added until the reaction mixture was neutral, after which the mixture was filtered and washed with methanol (25 mL). The combined organic filtrates

were concentrated under reduced pressure and the crude residue dissolved in THF (25 mL) and H_2O (5 mL), KOH (23.0 mg, 0.408 mmol, 3.0 equiv.) was then added and the reaction mixture stirred at RT for 1 hr. The reaction mixture was washed with brine (50 mL) and THF (2 × 50 mL). The combined organic phases were dried ($MgSO_4$) filtered, and the solvent removed under reduced pressure, the crude residue was purified by column chromatography (DCM/MeOH, 0-10%) to deliver **23** (36.0 mg, 83.0 μmol, 62%) as a colourless oil. R_f = 0.21 (DCM/MeOH, 95:5); $[\alpha]_D^{23}$= -17.2 (*c* = 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, MeOD) δ 5.41 – 5.29 (m, 2H, -C*H*=C*H*-), 4.71 – 4.61 (m, 1H, H-6a), 4.59 – 4.48 (m, 1H, H-6b), 4.23 (d, *J* = 8.0 Hz, 1H, H-1), 3.87 (dt, *J* = 9.5, 6.6 Hz, 1H, OC*H*H), 3.52 (dt, *J* = 9.5, 6.6 Hz, 1H, OC*H*H), 3.47 – 3.33 (m, 2H, H-4, H-5), 3.29 – 3.23 (m, 1H, H-3), 2.58 (dd, *J* = 9.5, 8.1 Hz, 1H, H-2), 2.06 – 1.97 (m, 4H, 2 x CH_2), 1.66 – 1.58 (m, 2H, CH_2), 1.40 – 1.25 (m, 22H, 11 x CH_2), 0.90 (t, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, MeOD) δ 129.5 (*C*=C), 129.4 (*C*=C), 103.2 (C1), 81.9 (d, $^1J_{C\text{-}F}$ = 171.6 Hz, C6), 76.0 (C3), 75.3 (d, $^2J_{C\text{-}F}$ = 18.0 Hz, C5), 69.5 (O*C*H$_2$), 69.2 (d, $^3J_{C\text{-}F}$ = 6.9 Hz, C4), 56.9 (C2), 31.7, 29.5, 29.43, 29.36, 29.20, 29.18, 29.1, 29.0, 28.93, 28.91, 26.73, 26.71, 25.7, 22.3, 13.0; ^{19}F NMR (377 MHz, $CDCl_3$) δ -233.58 (td, $^2J_{H\text{-}6a/b\text{-}F}$ = 47.4, $^3J_{H5\text{-}F}$ = 22.8 Hz); HRMS *m/z* (ES^-) [Found: ($M\text{-}H^-$) 430.3337 requires $C_{24}H_{45}FNO_4$ M^- 430.3332].

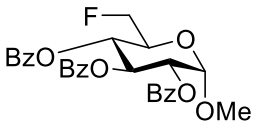
Methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside 57



Methyl α-D-glucopyranoside **56** (1.00 g, 5.15 mmol, 1.0 equiv.) was dissolved in pyridine (15 mL) under nitrogen atmosphere. Imidazole (700 mg, 10.3 mmol, 2.0 equiv.) and TIPSCl (2.20 mL, 1.98 g, 10.3 mmol, 2.0 equiv.) were added and the solution was then

stirred at RT. After 16 h, BzCl (4.79 mL, 5.79 g, 41.2 mmol, 8.0 equiv.) was added and the reaction was stirred for 24 h at which point it was quenched with MeOH (2 mL). The solution was diluted with DCM (100 mL), washed with 1M HCl (2 x 75 mL), sat. aq. $NaHCO_3$ (100 mL), water (75 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was dissolved in a solution of THF (11 mL), H_2O (4.5 mL) and TFA (8 mL) and stirred at RT for 18 h after which the solution was concentrated under reduced pressure azeotroping with toluene (2 × 100 mL). Purification by column chromatography (hexane/EtOAc, 0-30%) afforded **57** (1.75 g, 3.47 mmol, 67%) as a white amorphous foam. R_f = 0.44 (hexane/EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.95 (m, 4H, Ar*H*), 7.89 – 7.85 (m, 2H, Ar*H*), 7.57 – 7.48 (m, 2H, Ar*H*), 7.45 – 7.35 (m, 5H, Ar*H*), 7.33 – 7.27 (m, 2H, Ar*H*), 6.23 (dd, *J* = 12.4, 6.9 Hz, 1H, H-3), 5.50 (t, *J* = 9.9 Hz, 1H, H-4), 5.32 – 5.25 (m, 2H, H-1, H-2), 4.07 – 4.01 (m, 1H, H-5), 3.83 (dd, *J* = 12.9, 2.2 Hz, 1H, H-6a), 3.74 (dd, *J* = 13.0, 3.7 Hz, 1H, H-6b), 3.47 (s, 3H, OMe); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (2 × C=O, Bz), 165.8 (C=O, Bz), 133.7 (Ar-C) , 133.4 (Ar-C), 133.2 (Ar-C), 130.0 (Ar-C), 129.9 (Ar-C), 129.7 (Ar-C), 129.2 (Ar-C), 129.1 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 128.3 (Ar-C), 97.2 (C1), 72.1 (C2), 70.1 (C3), 69.8 (C5), 69.6 (C4), 61.1 (C6), 55.7 (O*C*H$_3$); HRMS *m/z* (ES$^+$) [Found: M+NH$_4$)$^+$ 524.1912 requires $C_{28}H_{30}O_9N$ M^+ 524.1915]. Data matched those reported previously.[173]

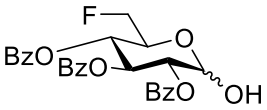
Methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-fluoro-α-D-glucopyranoside 58



In a Teflon™ flask a solution of Methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (1.75 g, 3.46 mmol, 1.0 equiv.) in DCM (20 mL) was cooled to -25 °C and DAST (1.83 mL,

2.23 g, 13.85 mmol, 4.0 equiv.) added dropwise, the reaction mixture allowed to warm to RT and refluxing for 1hr. Upon completion the solution was cooled to -20 °C and MeOH (10 mL) added slowly. After stirring for 30 mins at RT the solution was concentrated, diluted with DCM (20 mL), and washed with water 2 × (50 mL). The organic layer was dried ($MgSO_4$), concentrated and the product isolated by column chromatography (hexane/EtOAc, 0-50%) to deliver **58** (373 mg, 0.734 mmol, 45%) as a white amorphous foam.R_f = 0.55 (hexane/EtOAc, 0-30%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.94 (m, 4H, ArH), 7.86 (dt, *J* = 6.0, 1.9 Hz, 2H, ArH), 7.56 – 7.48 (m, 2H, ArH), 7.45 – 7.35 (m, 5H, ArH),) 7.29 (t, *J* = 7.7 Hz, 2H, ArH), 6.18 (tt, *J* = 9.7, 1.9 Hz, 1H, H-3), 5.56 (t, *J* = 9.9 Hz, 1H, H-4), 5.28 (dd, *J* = 8.9, 2.7 Hz, 2H, H-1, H-2), 4.59 (dd, *J* = 47.1, 3.6 Hz, 2H, H-6a & H-6b), 4.27 (ddt, *J* = 22.8, 10.3, 3.6 Hz, 1H, -5), 3.49 (s, 3H, OC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.81 (C=O, Bz), 165.79(C=O, Bz), , 165.3 (C=O, Bz), 133.6 (Ar-C), 133.4 (Ar-C), 133.2 (Ar-C), 130.0 (Ar-C), 129.9 (Ar-C), 129.7 (Ar-C), 129.2 (Ar-C), 129.0 (Ar-C), 128.8 (Ar-C), 128.50 (Ar-C), 128.45 (Ar-C), 128.3 (Ar-C), 97.1 (C1), 81.52 (d, $^1J_{C\text{-}F}$ = 175.1 Hz, C6), 72.0 (C2), 70.3 (C3), 68.62 (d, ^3J = 7.1 Hz, C4), 68.59 (d, ^2J = 19.1 Hz, C5), 55.8 (Ac-CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ(ppm) -232.2 (td, *J* = 47.0, 23.1 Hz); HRMS *m/z* (ES^+) [Found: $M+NH_4)^+$ 526.1869 requires $C_{28}H_{29}FO_8N$ M^+ 526.1872]. Data matched those reported previously.[174]

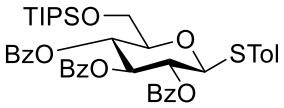
2,3,4-Tri-*O*-benzoyl-6-deoxy-fluoro-α/β-D-glucopyranose 59



Methyl glycoside **58** (373 mg, 0.695 mmol, 1.0 equiv.) was dissolved in Ac_2O/AcOH/H_2SO_4 (35:15:1 *v/v/v*, 6.25 mL). After being stirred overnight TLC analysis revealed complete consumption of the starting material (R_f = 0.50, hexane/EtOAc, 2:8).

The mixture was diluted with DCM (50 mL), washed with water (20 mL), sat. aq. $NaHCO_3$ (3 × 20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), concentrated and the crude residue purified by column chromatography (EtOAc/hexane (1:9) to deliver acetyl 2,3,4-tri-*O*-benzoyl-6-deoxy-fluoro-α/β-D-glucopyranoside (224 mg, 0.418 mmol, 60%, α/β). NH_4OAc (126 mg, 1.64 mmol, 4.0 equiv.) was added to a solution of acetyl 2,3,4-tri-*O*-benzoyl-6-deoxy-6-fluoro-α-D-glucopyranose (224 mg, 0.418 mmol, 1.0 equiv.) in DMF (2 mL) and stirred for 24 hrs at RT. When TLC indicated reaction completion (R_f = 0.20, hexane/EtOAc, 7:3); the remaining NH_4OAc was filtered off, and the filtrate was concentrated to dryness. The crude residue purified by column chromatography (hexane/EtOAc, 1:1) to deliver **59** (170 mg, 0.344 mmol, 82%, α/β, 1:0.15) as a colourless oil. R_f = 0.2 (hexane/EtOAc, 7:3); ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.97 (td, *J* = 8.3, 1.4 Hz, 4H, Ar*H*), 7.87 (dd, *J* = 8.4, 1.3 Hz, 2H, Ar*H*), 7.56 – 7.48 (m, 2H, Ar*H*), 7.45 – 7.34 (m, 5H, Ar*H*), 7.29 (t, *J* = 7.8 Hz, 2H, Ar*H*), 6.25 (t, *J* = 9.9 Hz, 1H, H-3), 5.79 (d, *J* = 3.6 Hz, 1H, H-1), 5.58 (t, *J* = 9.9 Hz, 1H, H-4), 5.31 (dd, *J* = 10.3, 3.6 Hz, 1H, H-2), 4.66 – 4.48 (m, 2H, H-6a, H-6b), 4.63 – 4.49 (m, 1H, H-5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9 (C=O, Bz), 165.8 (C=O, Bz), 165.3 (C=O, Bz), 133.6 (Ar-C), 133.5 (Ar-C), 133.2 (Ar-C), 130.0 (Ar-C), 129.93 (Ar-C), 129.91 (Ar-C), 129.87 (Ar-C), 129.8 (Ar-C), 129.7 (Ar-C), 129.1 (Ar-C), 128.9 (Ar-C), 128.8 (Ar-C), 128.51(Ar-C), 128.50 (Ar-C), 128.3 (Ar-C), 90.48 (C1), 81.55 (d, $^1J_{C\text{-}F}$ = 175.0 Hz, C6), 72.1 (C2), 70.0 (C3), 68.70 (d, $^2J_{C\text{-}F}$ = 19.0 Hz, C5), 68.52 (d, $^3J_{C\text{-}F}$ = 6.9 Hz, C4); ^{19}F NMR (377 MHz, $CDCl_3$) δ -231.35 (td, *J* = 47.0, 21.2 Hz, β), -231.95 (td, *J* = 47.2, 23.6 Hz, α); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 512.1718 requires $C_{27}H_{27}FO_8N$ M^+ 512.1720].

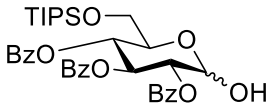
p-Tolyl 2,3,4-tri-*O*-benzoyl-6-*O*-TIPS-1-thio-β-D-glucopyranoside **62**



A solution of *p*-tolyl 1-thio-β-D-glucopyranoside (950 mg, 3.12 mmol, 1.0 equiv.) and imidazole (452 mg, 6.64 mmol, 2.0 equiv.) in pyridine (50 mL) was treated with TIPSCl (1.05 mL, 1.28 g, 6.64 mmol, 2.0 equiv.) and the solution was then stirred at RT. After 16 h, BzCl (3.08 mL, 3.73 g, 26.6 mmol, 8.0 equiv.) was added and the reaction was stirred for 24 h, TLC analysis revealed conversion to a major spot (R_f = 0.95 (hexane/EtOAc, 7:3) at which point it was quenched with MeOH (5 mL). The solution was diluted with DCM (100 mL), washed with 1M HCl (2 x 75 mL), saturated aqueous $NaHCO_3$ (100 mL), water (75 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-5%) to deliver the title compound (1.75 g, 2.32 mmol, 70%) as a colourless oil. R_f = 0.95 (hexane/EtOAc, 7:3); $[\alpha]_D^{24}$ = 10.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.3, 1.2 Hz, 2H, Ar*H*), 7.90 (dd, *J* = 5.1, 3.3 Hz, 2H, Ar*H*), 7.80 (dd, *J* = 8.3, 1.2 Hz, 2H, Ar*H*), 7.47 – 7.39 (m, 4H, Ar*H*), 7.36 – 7.26 (m, 5H, Ar*H*), 7.19 (t, *J* = 7.7 Hz, 2H, Ar*H*), 7.08 (d, *J* = 7.9 Hz, 2H, Ar*H*), 5.91 (t, *J* = 9.5 Hz, 1H, H-3), 5.58 (t, *J* = 9.6 Hz, 1H, H-4) 5.47 (t, *J* = 9.7 Hz, 1H, H-2), 5.02 (d, *J* = 10.0 Hz, 1H, H-1), 4.02 – 3.85 (m, 3H, H-5, H-6a, H-6b), 2.30 (s, 3H, PhC*H*$_3$), 1.08 – 1.02 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0 (C=O, Bz), 165.14 (C=O, Bz) 165.13 (C=O, Bz), 138.4 (Ar-C), 133.5 (Ar-C), 133.29 (Ar-C), 133.26 (Ar-C), 133.2 (Ar-C), 129.9 (Ar-C), 129.80 (Ar-C), 129.75 (Ar-C), 129.7 (Ar-C), 129.5 (Ar-C), 129.3 (Ar-C), 129.0 (Ar-C), 128.5 (Ar-C), 128.40 (Ar-C), 128.38 (Ar-C), 128.3 (Ar-C), 86.5 (C1), 79.9 (C5), 74.9 (C3), 70.9 (C2), 69.3 (C4), 63.0 (C6), 21.3 (Ph-

*C*H$_3$), 18.0 (CH$_3$, ^{i}Pr), 12.0 (CH, ^{i}Pr); HRMS *m/z* (ES$^+$) [Found: (M+K)$^+$ 793.2613 requires $C_{43}H_{50}O_8SSiK$ M$^+$ 793.2627].

2,3,4, Tri-*O*-benzoyl-6-*O*-TIPS-1-thio-α/β-D-glucopyranose 63

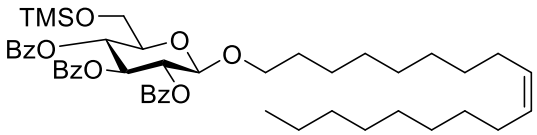


Using NBS: *p*-Tolyl 2,3,4-tri-*O*-benzoyl-6-*O*-triisopropylsilyl-1-thio-β-D-glucopyranoside (1.75 g, 2.32 mmol, 1.0 equiv.) was dissolved in a mixture of acetone/water (9:1, 30 mL). NBS (1.24 g, 6.95 mmol, 3.0 equiv.) was added at 0 °C, and the reaction mixture warmed to RT. After 3 h TLC revealed complete consumption of the starting material (R_f = 0.70, hexane/EtOAc, 7:3), the reaction mixture was diluted with water (100 mL) and extracted with DCM (3 × 100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude residue was then purified by column chromatography (hexane/EtOAc, 0-20%) to yield **63** (703 mg, 1.08 mmol, 47%, α/β 85:15) as a colourless oil.

Using Ph_2SO/Tf_2O: To a solution of *p*-tolyl 2,3,4-tri-*O*-benzoyl-6-*O*-triisopropylsilyl-1-thio-β-D-glucopyranoside (215 mg, 0.340 mmol, 1.0 equiv.) in DCM (10 mL) were added Ph_2SO (89.0 mg, 0.442 mmol, 1.3 equiv.), and the mixture cooled to −78 °C before the addition of Tf_2O (0.074 mL, 125 mg, 0.442 mmol, 1.3 equiv.). Next, water (1 mL) was added, and the reaction was stirred at RT after 30 mins, TLC revealed reaction completion. (R_f = 0.70, hexane/EtOAc). The mixture was washed with saturated aqueous $NaHCO_3$ (50 mL), the organic layer dried ($MgSO_4$), filtered and the filtrates concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 0-20%) to deliver **63** (168 mg, 0.248 mmol, 73%, α/β, 8:2) as a colourless oil. R_f = 0.70

(hexane/EtOAc, 7:3); **α anomer** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.84 (m, 5H, Ar*H*), 7.56 – 7.47 (m, 2H, Ar*H*), 7.43 – 7.35 (m, 5H, Ar*H*), 7.32 – 7.25 (m, 3H, Ar*H*), 6.20 (t, *J* = 9.9 Hz, 1H, H-3), 5.75 (d, *J* = 3.6 Hz, 1H, H-1), 5.60 (t, *J* = 9.8 Hz, 1H, H-4), 5.27 (dd, *J* = 10.2, 3.6 Hz, 1H, H-2), 4.45 – 4.37 (m, 1H, H-5), 3.91 – 3.87 (m, 2H, H-6a, H-6b), 1.04 – 0.96 (m, 21H, TIPS);); **α anomer** ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0 (C=O, Bz), 165.9 (C=O, Bz), 165.2 (C=O, Bz), 133.4 (Ar-C), 133.2 (Ar-C), 133.0 (Ar-C), 130.0 (Ar-C), 129.9 (Ar-C), 129.8 (Ar-C), 129.7 (Ar-C), 129.37 (Ar-C), 129.35 (Ar-C), 128.4(Ar-C), 128.34 (Ar-C), 128.27 (Ar-C), 90.4 (C1), 72.5 (C2), 70.8 (C5), 70.5 (C3), 69.4 (C4), 62.8 (C6), 17.9 (CH_3, ^{i}Pr), 11.9 (CH, ^{i}Pr); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 666.3090 requires $C_{36}H_{48}O_9NSi$ M^+ 666.3093].

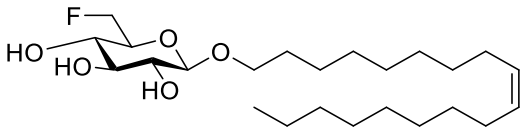
Oleyl 2,3,4-tri-*O*-benzoyl-6-*O*-TMS-β-D-glucopyranoside 64



Following general procedure **D**, hemi-acetal **63** (453 mg, 0.698 mmol, 1.0 equiv.), DBU (11.0 mg, 10.8 µL, 70.0 µmol, 0.1 equiv.) and Cl_3CCN (0.70 mL, 1.01 g, 7.00 mmol, 10.0 equiv.) gave the corresponding trichloroacetimidate donor. After reacting the donor with oleyl alcohol (206 mg, 0.770 mmol, 1.1 equiv.) and TMSOTf (0.12 mL, 156 mg, 0.698 mmol, 1.0 equiv.) for 30 mins, purification by column chromatography (hexane/EtOAc, 0-5%) successfully delivered **64** (321 mg, 0.394 mmol, 56%) as a colourless oil. R_f = 0.79 (hexane/EtOAc, 7:3); $[\alpha]_D^{24}$ = -1.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.83 (m, 4H, Ar*H*), 7.79 – 7.74 (m, 2H, Ar*H*), 7.46 – 7.41 (m, 2H, Ar*H*), 7.38 – 7.28 (m, 5H, Ar*H*), 7.22 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.78 (t, *J* = 9.7 Hz, 1H, H-3), 5.43 (t, *J* = 9.5 Hz, 1H, H-4), 5.39 (dd, *J* = 9.8, 7.9 Hz, 1H, H-2), 5.32 – 5.20 (m, 2H, -C*H*=C*H*-), 4.71 (d, *J* = 7.9 Hz, 1H, H-1), 3.86 (dt, *J* = 9.6, 6.2 Hz, 1H, OC*H*H), 3.81 – 3.70 (m, 3H,

H-5, H-6a, H-6b), 3.47 (dt, *J* = 9.6, 6.7 Hz, 1H, OC*H*H), 2.02 – 1.82 (m, 4H, 2 x C*H*$_2$), 1.49 – 1.40 (m, 2H, C*H*$_2$), 1.28 – 1.02 (m, 22H, 11 x CH$_2$), 0.81 (t, *J* = 6.9 Hz, 3H, C*H*$_3$), 0.00 (s, 9H, TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (C=O, Bz), 165.7 (C=O, Bz), 165.6 (C=O, Bz), 133.8 (Ar-C), 133.59 (Ar-C), 133.55 (Ar-C), 130.41 (*C*=C), 130.37 (Ar-C), 130.28 (Ar-C), 130.26 (Ar-C), 130.2 (Ar-C), 130.1 (Ar-C), 129.8 (*C*=C), 129.6 (Ar-C), 128.9 (Ar-C), 128.79 (Ar-C), 128.75 (Ar-C),101.6 (C1), 75.5 (C5), 73.8 (C3), 72.6 (C2), 70.6 (O*C*H$_2$), 70.5 (C4), 62.9 (C6), 33.1, 32.4, 30.29, 30.25, 30.04, 29.96, 29.9, 29.83, 29.78, 29.7, 27.73, 27.71, 26.4, 23.2, 14.6, 0.01 (Si(CH$_3$)$_3$); HRMS *m/z* (ES$^+$) [Found: (M+Na)$^+$ 837.4363 requires $C_{48}H_{66}O_9SiNa$ M$^+$ 837.4368].

Oleyl 6-deoxy-6-fluoro-β-D-glucopyranoside 21

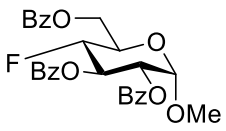


In a Teflon^{TM} flask, a solution of **60** (303 mg, 0.372 mmol, 1.0 equiv.) in DCM (5 mL) was cooled to -40 °C and DAST (0.10 mL, 132 mg, 0.816 mmol, 2.2 equiv.) added dropwise. Upon completion as seen by TLC analysis (R_f = 0.36, hexane/EtOAc, 9:1,) the solution was cooled to -20 °C and MeOH (5 mL) added slowly. After stirring for 30 mins the solution was diluted with DCM (20 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated under reduced pressure and the crude residue was purified by column chromatography (hexane/EtOAc 0-20%) to deliver **60** (147 mg, 0.197 mmol, 48%) as a colourless oil. This material was then subjected to immediate deprotection.

Oleyl 2,3,4-tri-*O*-benzoyl-6-deoxy-fluoro-β-D-glucopyranoside **60** (103 mg, 0.138 mmol, 1.0 equiv.) was then dissolved in MeOH (5 mL) and treated with a solution of NaOMe (8.00 mg, 0.138 mmol, 1.0 equiv.) in MeOH (1 mL). The reaction mixture was

left stirring at RT for 24 h, TLC revealed complete consumption of the starting material (R_f = 0.65, EtOAc). Amberlite IR20 (H^+) ion exchange resin was added. The mixture was stirred until neutral, after which the mixture was filtered and washed with methanol (100 mL). The combined organic filtrates were concentrated under reduced pressure and the crude residue purified by column chromatography to deliver **21** (41.0 mg, 95.0 µmol, 68%) as a colourless oil. R_f = 0.65 (EtOAc); $[\alpha]_D^{24}$ = -18.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 – 5.27 (m, 2H, -C*H*=C*H*-), 4.72 (m, 1H, H-6a), 4.60 (m, 1H, H-6b), 4.28 (d, *J* = 7.7 Hz, 1H, H-1), 3.91 (dt, *J* = 9.5, 6.9 Hz, 1H, OC*H*H) 3.61 – 3.44 (m, 4H, H-3, H-4, H-5, OC*H*H), 3.38 (t, *J* = 8.5 Hz, 1H, H-2), 2.06 – 1.94 (m, 4H, 2 x CH_2), 1.68 – 1.56 (m, 2H, CH_2), 1.39 – 1.21 (m, 22H, 11 x CH_2), 0.88 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.0 (*C*=C), 129.8 (*C*=C*)*, 102.5 (C1), 82.1 (d, $^1J_{C\text{-}F}$ = 172.7 Hz, C6), 76.4 (C3), 74.5 (d, $^2J_{C\text{-}F}$ = 18.4 Hz, C5), 73.7 (C2), 70.3 (OCH_2), 69.1 (d, $^3J_{C\text{-}F}$ = 7.2 Hz, C4), 31.9, 29.78, 29.76, 29.7, 29.6, 29.53, 29.48, 29.4, 29.32, 29.26, 27.22, 27.21, 25.9, 22.7, 14.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ -233.75 (td, $^2J_{H\text{-}6a/b\text{-}F}$ = 47.4 Hz, $^3J_{H5\text{-}F}$ = 23.0 Hz); HRMS *m/z* (ES^-) [Found: $(M\text{-}H)^-$ 432.3185 requires $C_{24}H_{44}FO_5$ M^- 431.3178].

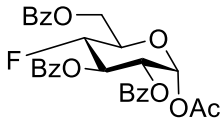
Methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-fluoro-α-D-glucopyranoside 65



In a Teflon™ flask, a solution of **38** (500 mg, 0.983 mmol, 1.0 equiv.) in DCM (10 mL) was cooled to -65 °C and treated with DAST (0.78 mL, 947 mg, 5.88 mmol, 6.0 equiv.) dropwise. Upon reaction completion as adjudged by TLC (to R_f = 0.62, hexane/EtOAc, 7:3). The solution was cooled to -20 °C and MeOH (5 mL) was added slowly. After stirring for 30 mins at RT the solution was concentrated, diluted with DCM (20 mL) and

washed with saturated aqueous $NaHCO_3$ (2 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography (hexane/EtOAc, 0-30%) delivered **7** (410 mg, 0.810 mmol, 82%) as a white foam. R_f = 0.62 (hexane/EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.08 (m, 2H, Ar*H*), 8.03 – 7.94 (m, 4H, Ar*H*), 7.65 – 7.57 (m, 1H, Ar*H*), 7.56 – 7.46 (m, 4H, Ar*H*), 7.42 – 7.35 (m, 4H, Ar*H*), 6.18 – 6.06 (m, 1H, H-3), 5.26 – 5.13 (m, 2H, H-1, H-2), 4.85 – 4.65 (m, 2H, H-6a, H-4), 4.61 (ddd, *J* = 12.2, 5.0, 1.2 Hz, 1H, H-6b), 4.38 – 4.27 (m, 1H, H-5), 3.47 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2 (C=O, Bz), 165.9 (C=O, Bz), 165.6 (C=O), 133.4 (Ar-C), 133.3 (Ar-C), 130.2 (Ar-C), 129.9 (Ar-C), 129.8 (Ar-C), 129.7 (Ar-C), 129.66 (Ar-C), 129.4 (Ar-C), 129.3 (Ar-C), 128.5 (Ar-C), 128.44 (Ar-C), 128.41 (Ar-C), 96.9 (C1), 87.4 (d, $^1J_{C\text{-}F}$ = 188.3 Hz, C4), 71.4 (d, $^3J_{C\text{-}F}$ = 7.7 Hz, C2), 70.5 (d, $^3J_{C\text{-}F}$ = 19.9 Hz, C3), 67.1 (d, $^2J_{C\text{-}F}$ = 23.0 Hz, C5), 62.6 (C6), 55.7 (OCH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ -197.03 (dd, $^1J_{H4\text{-}F}$ = 50.9 Hz, $^3J_{H3/5\text{-}F}$ = 14.0 Hz); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 526.1866, $C_{28}H_{29}FO_8N$ requires M^+ 526.1877]. Data matched those reported previously.[175]

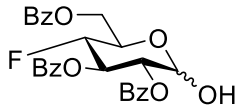
Acetyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-fluoro-α-D-glucopyranoside **66**



Methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-fluoro-α-D-glucopyranoside **65** (1.23 g, 2.41 mmol, 1.0 equiv.) was dissolved in Ac_2O/AcOH/H_2SO_4 (35:15:1 *v/v/v*, 18.8 mL) and stirred overnight. TLC analysis revealed complete consumption of the starting material (R_f = 0.56, hexane/EtOAc, 7:3). The reaction mixture was diluted with $CHCl_3$ (100 mL), washed with water (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under

reduced pressure. The resulting crude residue was purified by column chromatography (hexane/EtOAc, 0-30%) to give the title compound (694 mg, 1.29 mmol, 54%) as a white solid. R_f = 0.56 (hexane/EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.06 (m, 2H, Ar*H*), 8.03 – 7.99 (m, 2H, Ar*H*), 7.93 – 7.89 (m, 2H, Ar*H*), 7.64 – 7.59 (m, 1H, Ar*H*), 7.57 – 7.47 (m, 4H, Ar*H*), 7.43 – 7.34 (m, 4H, Ar*H*), 6.55 (app t, *J* = 3.1 Hz, 1H, H-1), 6.12 (m, 1H, H-3), 5.43 (dd, *J* = 10.3 Hz, 3.6 Hz, 1H, H-2), 4.86 (dt, $^2J_{H4\text{-}F}$ = 50.5 Hz, *J* = 9.6 Hz, 1H, H-4), 4.61 (ddd, *J* = 12.4, 4.0, 1.5 Hz, 1H, H-6a), 4.73 – 4.68 (m, 1H, H-6b), 4.45 – 4.38 (m, 1H, H-5), 2.21 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6 (C=O, Ac), 166.1 (C=O, Bz), 165.7 (C=O, Bz), 165.4 (C=O, Bz), 133.7 (Ar-C), 133.6 (Ar-C), 133.4 (Ar-C), 129.91 (Ar-C), 129.88 (Ar-C), 129.84 (Ar-C), 129.81 (Ar-C), 129.6 (Ar-C), 129.0 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 89.0 (C1), 86.7 (d, $^1J_{C\text{-}F}$ = 188.7 Hz, C4), 70.2 (d, $^2J_{C\text{-}F}$ = 19.8 Hz, C3), 69.70 (d, $^2J_{C\text{-}F}$ = 23.5 Hz, C5), 69.73 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, C2), 62.1 (C6), 20.9 (Ac-CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ -197.82 (bs); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 554.1821, $C_{29}H_{29}FO_9N$ requires M^+ 526.1826]; Data matched those previously reported.[73]

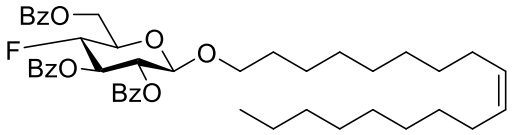
2,3,6-Tri-*O*-benzoyl-4-deoxy-4-fluoro-α/β-D-glucopyranoside **67**



NH_4OAc (400 mg, 5.16 mmol, 4.0 equiv.) was added to a solution of 1-*O*-acetyl-2,3,6-tri-*O*-benzoyl-4-deoxy-4-fluoro-α-D-glucopyranoside (694 mg, 1.29 mmol, 1.0 equiv.) in DMF (3 mL) and stirred for 2 days at RT. When TLC indicated reaction completion (to R_f = 0.23, hexane/EtOAc, 7:3) undissolved NH_4Oac was filtered off, and the filtrate concentrated under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-50%) to give **67** (496 mg, 1.00 mmol, 78%, α/β 1:5)

as a colourless oil. R_f = 0.23 (hexane/EtOAc, 7:3); **α-anomer** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.12 (m, 2H, Ar*H*), 7.96 – 8.04 (m, 4H, Ar*H*), 7.60 (dd, *J* = 8.8 Hz, 1.3 Hz, 1H, Ar*H*), 7.46 – 7.55 (m, 4H, Ar*H*), 7.35 – 7.42 (m, 4H, Ar*H*), 6.26 – 6.13 (m, 1H, H-3), 5.67 (d, *J* = 3.3 Hz, 1H, H-1), 5.21 (dd, *J* = 10.2 Hz, 2.6 Hz, 1H, H-2), 4.88 – 4.71 (m, 2H, H-4, H-6a), 4.64 – 4.55 (m, 2H, H-6b, H-5); **α -anomer** ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3 (C=O, Bz), 165.9 (C=O, Bz) , 165.7 (C=O, Bz), 133.6 (Ar-C), 133.4 (Ar-C), 133.3 (Ar-C), 129.94 (Ar-C), 129.86 (Ar-C), 129.83 (Ar-C), 129.80 (Ar-C), 128.50 (3 × Ar-C), 128.46 (Ar-C), 128.4 (Ar-C), 90.3 (C1), 87.3 (d, $^1J_{C\text{-}F}$ = 188.1 Hz, C4), 71.6 (d, $^3J_{C\text{-}F}$ = 7.8 Hz, C2), 70.2 (d, $^2J_{C\text{-}F}$ = 19.9 Hz, C3), 67.3 (d, $^2J_{C\text{-}F}$ = 23.0 Hz, C5), 62.4 (C6); ^{19}F NMR (377 MHz, $CDCl_3$) δ -197.28 (dd, $^2J_{H4\text{-}F}$ = 50.9 Hz, 13.8 Hz, **β anomer**), -199.51 (dd, $^2J_{H4\text{-}F}$ = 50.1 Hz, $^3J_{H3\text{-}F}$ = 12.6 Hz, **α anomer**); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 512.1708, $C_{27}H_{27}FO_8N$ requires M^+ 512.1720]; HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 512.1708 $C_{27}H_{27}FO_8N$ requires M^+ 512.1720]. Data matched those reported previously.[175]

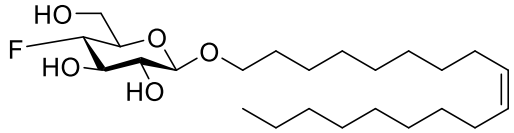
Oleyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-fluoro-β-D-glucopyranoside **68**



Following general procedure **D**, 2,3,6-tri-*O*-benzoyl-4-deoxy-4-fluoro-α/β-D-glucopyranoside **67** (467 mg, 0.944 mmol, 1.0 equiv.), DBU (14.0 mg, 13.7 µL, 94.0 µmol, 0.1 equiv.) and Cl_3CCN (0.94 mL, 1.36 g, 9.44 mmol, 10.0 equiv.) gave the corresponding trichloroacetimidate donor. After reacting the donor with oleyl alcohol (0.29 mL, 254 mg, 0.946 mmol, 1.1 equiv.) and TMSOTf (0.16 mL, 191 mg, 0.860 mmol, 1.0 equiv.) for 1 hr, purification by column chromatography (hexane/EtOAc, 0-50%) successfully furnished the title compound (233 mg, 0.313 mmol,

36%) as a colourless oil. R_f = 0.14 (hexane/EtOAc, 9:1); $[\alpha]_D^{22}$ = 11.5 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.06 (m, 2H, Ar*H*), 8.01 – 7.93 (m, 4H, Ar*H*), 7.63 – 7.57 (m, 1H, Ar*H*), 7.54 - 7.46 (m, 4H, Ar*H*), 7.38 (ddd, *J* = 7.5, 4.2, 2.5 Hz, 4H, Ar*H*), 5.88 – 5.78 (m, 1H, H-3), 5.42 (dd, *J* = 9.9, 7.9 Hz, 1H, H-2), 5.37 – 5.28 (m, 2H, -C*H*=C*H*-), 4.88 – 4.69 (m, 3H, H-1, H-4, H-6a), 4.59 (ddd, *J* = 12.1, 5.0, 1.3 Hz, 1H, H-6b), 4.07 – 4.00 (m, 1H, H-5), 3.88 (dt, *J* = 9.7, 6.3 Hz, 1H, OC*H*H), 3.50 (dt, *J* = 9.7, 6.7 Hz, 1H, OC*H*H), 2.04 – 1.88 (m, 4H, 2 x CH_2), 1.54 – 1.41 (m, 2H, CH_2), 1.36 – 0.99 (m, 22H, 11 x CH_2), 0.87 (t, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2 (C=O, Bz), 165.7 (C=O, Bz), 165.1 (C=O, Bz), 133.4 (Ar-C), 133.29 (Ar-C), 133.26 (Ar-C), 129.9 (*C*=C), 129.83 (Ar-C), 129.80 (Ar-C), 129.79 (Ar-C), 129.7 (*C*=C*)*, 129.2 (Ar-C), 129.0 (Ar-C), 128.5 (Ar-C), 128.41 (Ar-C), 128.37 (Ar-C), 101.2 (C1), 87.5 (d, $^1J_{C\text{-}F}$ = 188.9 Hz, C4), 72.9 (d, $^2J_{C\text{-}F}$ = 19.6 Hz, C3), 71.6 (d, $^2J_{C\text{-}F}$ = 23.2 Hz, C5), 71.4 (d, $^3J_{C\text{-}F}$ = 7.7 Hz, C2), 70.5 (O*C*H_2), 62.7 (C6), 31.9, 29.8, 29.7, 29.5, 29.4, 29.34, 29.33, 29.22, 29.20, 27.22, 27.19, 25.8, 22.7, 14.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ -199.21 (dd, $^2J_{H4\text{-}F}$ = 50.8 Hz, $^3J_{H3\text{-}F}$ = 14.1 Hz); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 762.4377, $C_{45}H_{61}FNO_8$ requires M^+ 762. 4381].

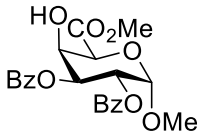
Oleyl 4-deoxy-4-fluoro-β-D-glucopyranoside 20



To a stirred solution of oleyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-fluoro-β-D-glucopyranoside (233 mg, 0.312 mmol, 1.0 equiv.) in MeOH (5 mL), NaOMe (17.0 mg, 0.312 mmol, 1.0 equiv.) dissolved in MeOH (1 mL) was added dropwise at RT. After 48 h TLC analysis revealed full conversion of the starting material to a lower spot (R_f = 0.60, hexane/EtOAc, 2:8). The reaction was quenched by adding Amberlite IR20 (H^+) resin and stirring

continued for another 10 mins until the reaction mixture pH was neutral. The mixture was filtered and washed with MeOH (100 mL). After evaporation of the filtrate under reduced pressure, the crude residue was purified by column chromatography (hexane/EtOAc, 0-80%) to deliver **20** (91.0 mg, 0.210 mmol, 67%) as a colourless oil. R_f = 0.60 (hexane/EtOAc, 2:8); $[\alpha]_D^{24}$ = -66.7 (*c* = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 – 5.30 (m, 2H, -C*H*=C*H*-), 4.41 (dt, $^2J_{H4\text{-}F}$ = 50.8 Hz, 9.5 Hz, 1H, H-4), 4.35 (d, *J* = 7.8 Hz, 1H, H-1), 3.97 – 3.75 (m, 4H, H-3, H-6a, H-6b, OC*H*H), 3.53 (m, 2H, H-5, OCH*H*) 3.40 (t, *J* = 8.6 Hz, 1H, H-2), 2.06 – 1.91 (m, 4H, 2 x CH_2) 1.66 – 1.58 (m, 2H, CH_2), 1.41 – 1.14 (m, 22H, 11 x CH_2), 0.88 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.0 (*C*=C*)*, 129.8 (*C*=C*)*, 102.5 (C1), 88.8 (d, $^1J_{C\text{-}F}$ = 181.2 Hz, C4), 74.4 (d, $^2J_{C\text{-}F}$ = 18.6 Hz, C3), 73.6 (d, $^2J_{C\text{-}F}$ = 25.1 Hz, C5), 73.5 (d, $^3J_{C\text{-}F}$ = 8.8 Hz, C2), 70.6 (O*C*H$_2$), 61.4 (C6), 31.9, 29.77, 29.76, 29.6, 29.53, 29.47, 29.38, 29.33, 29.25, 27.23, 27.20, 25.9, 22.7, 14.13; ^{19}F NMR (377 MHz, $CDCl_3$) δ -200.85 (dd, $^2J_{H4\text{-}F}$ = 51.0, $^3J_{H3\text{-}F}$ = 13.5 Hz); HRMS *m/z* (ES^-) [Found: ($M\text{-}H^-$) 431.3177, requires $C_{24}H_{44}FO_5$ M^- 431.3172].

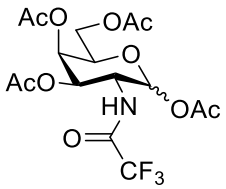
Methyl (methyl 2,3-bis-*O*-benzoyl-α-D-galactopyranoside uronate 70



To a solution of methyl 2,3-bis-*O*-benzoyl-α-D-galactopyranoside (1.00 g, 2.48 mmol, 1.0 equiv.) in DCM/H_2O (5/1, *v/v*, 20.00 mL) at 0 °C was added diacetoxy iodobenzene (1.90 g, 6.2 mmol, 2.5 equiv.) and TEMPO (78.0 mg, 0.49 mmol, 0.2 equiv.). The mixture was vigorously stirred for 25 h and quenched by the addition of 10% aq. $Na_2S_2O_3$. The reaction mixture was extracted with DCM 2 × (30 mL). The aqueous layer was acidified (pH 1) with 1M aq. HCL and extracted with DCM (30 mL). The combined organic layers were washed

with water (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude carboxylic acid was co-evaporated with toluene (2 × 75 mL) and dissolved in DMF (20 mL). MeI (700 mg, 4.95 mmol, 2.0 equiv.) and potassium carbonate (680 mg, 4.98 mmol, 2.0 equiv.) were added and stirred for 3 hrs. The reaction was quenched with AcOH (0.42 mL, 7.44 mmol, 3.0 equiv.) and diluted with H_2O and brine. The organic fractions were dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography (hexane/EtOAc, 0-50%) to deliver **70** (608 mg, 1.41 mmol, 57%) as a white foam. R_f = 0.44 (hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.89 (m, 4H, Ar*H*), 7.56 – 7.47 (m, 2H, Ar*H*), 7.45 – 7.30 (m, 4H, Ar*H*), 5.75 (dd, *J* = 10.7, 3.1 Hz, 1H, H-3), 5.68 (dd, *J* = 10.7, 3.5 Hz, 1H, H-2), 5.31 (d, *J* = 3.5 Hz, 1H, H-1), 4.73 (as, 1H, 4OH), 4.67 (d, *J* = 1.4 Hz, 1H, H-5), 3.85 (s, 3H, OMe), 3.48 (s, 3H, OMe); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6 (C=O, Bz), 165.9 (C=O, Bz), 165.7 (C=O, Bz), 133.5 (Ar-C), 133.3(Ar-C), 129.9 (Ar-C) 129.8 (Ar-C), 129.24 (Ar-C), 129.16 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 98.0 (C1), 70.2 (C3), 69.8 (C5), 69.1 (C4), 68.3 (C2), 56.3 (*C*H_3), 52.7 (*C*H_3); HRMS *m/z* (ES^+) [Found: $(M+H)^+$ 431.1352 $C_{22}H_{22}O_8$ requires M^+ 431.1341]. Data matched those reported previously.[176]

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-trifluoroacetamido-α/β-D-galactopyranoside 77

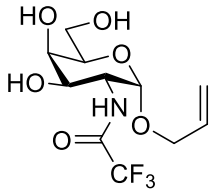


A solution of D-galactosamine hydrochloride **75** (5.00 g, 93 mmol, 1.0 equiv.) in MeOH (200 mL) was cooled to 0 °C and treated slowly with Et_3N (14.2 mL, 10.3 g, 102 mmol, 1.1 equiv.) and ethyl trifluoroacetate (12.1 mL, 14.5 g, 102 mmol, 1.1 equiv.). The mixture was allowed to reach RT and stirred overnight. The reaction mixture was

concentrated under reduced pressure and then recrystallised (EtOAc) to deliver 2-deoxy-2-trifluoroacetamido-α/β-D-galactopyranoside (25.1 g, 91.2 mmol, 98%) as a white solid. A solution of 2-deoxy-2-trifluoroacetamido-α/β-D-galactopyranoside (12.6 g, 45.6 mmol, 1.0 equiv.) in pyridine (150 mL) was cooled to 0 °C and slowly treated with Ac_2O (50 mL). The mixture was allowed to warm to RT and stirred until TLC analysis indicated reaction completion (R_f =. 0.67, hexane/EtOAc, 1:1). After removal of the solvent, the crude material was taken in EtOAc (100 mL) washed with 1 M HCl (5 × 100 mL), saturated aqueous $NaHCO_3$ (3 × 100 mL), brine (1 × 100 mL), dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude residue was then purified by column chromatography to deliver the title compound as a white foam (18.0 g, 40.4 mmol, 89%, α/β, 1:2). R_f =. 0.67 (hexane/EtOAc, 1:1); **α anomer** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (d, *J* = 8.9 Hz, 1H, N*H*), 6.30 (d, *J* = 3.7 Hz, 1H, H-1), 5.49 – 5.46 (m, 1H, H-4), 5.30 (dd, *J* = 11.4, 3.2 Hz, 1H, H-3), 4.74 – 4.66 (m, 1H, H-2), 4.32 – 4.26 (m, 1H, H-5), 4.24 – 4.03 (m, 2H, H-6a, H-6b), 2.20 (3H, OAc), 2.19 (3H, OAc), 2.13 (3H, OAc), 2.04 (3H, OAc); **β anomer** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 9.4 Hz, 1H, N*H*), 5.78 (d, *J* = 8.8 Hz, 1H, H-1), 5.43 – 5.41 (m, 1H, H-4), , 5.18 (dd, *J* = 11.3, 3.3 Hz, 1H, H-3), 4.50 (dd, *J* = 11.1, 9.3 Hz, 1H, H-2), 4.24 – 4.03 (m, 3H, H-6a, H-6b. H-5), 2.19 (3H, OAc), 2.06 (3H, OAc), 2.04 (3H, OAc), 2.02 (3H, OAc); **Anomeric mix** ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3 (C=O, Ac), 170.7 (C=O, Ac), 170.6 (C=O, Ac), 170.5 (C=O, Ac), 170.1 (C=O, Ac), 170.1 (C=O, Ac) , 169.5 (C=O, Ac), 168.7 (C=O, Ac), 157.7 (q, $^2J_{C\text{-}F}$ = 37.7 Hz, C=O), 157.5 (q, $^2J_{C\text{-}F}$ = 38.2 Hz, CF_3, C=O)**,** 115.6 (q, $^1J_{C\text{-}F}$ = 288.3 Hz, CF_3)**,** 92.3 (C1β), 90.4 (C1α), 72.0 (C5β), 69.9 (C3β), 68.7 (C5α), 67.6 (C3α), 66.5 (C4α), 66.2 (C4β), 61.3, 61.2, 60.5, 50.3 (C2β), 47.9 (C2α), 20.8 (Ac-CH_3), 20.7 (Ac-CH_3), 20.6 (Ac-CH_3), 20.5 (Ac-CH_3), 20.4 (Ac-CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ -75.9 (s, α), -

76.1 (s, β); HRMS *m/z* (ES^+) [Found: $(M+Na)^+$ 466.0920 requires $C_{16}H_{20}F_3NO_{10}Na$ M^+ 466.0932] Data matched those reported previously.[177]

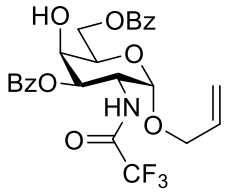
Allyl 2-deoxy-2-trifluoroacetamido-α-D-galactopyranoside 78



A solution of 1,3,4,6-tetra-*O*-acetyl-2-trifluoroacetamido-2-deoxy-α/β-D-galactopyranoside **77** (29.0 g, 65.4 mmol, 1.0 equiv.) in DCE (75 mL) was treated with allyl alcohol (8.89 mL, 7.59 g, 130.8 mmol, 2.0 equiv.). This was followed by addition of $FeCl_3$ (15.9 g, 98.1 mmol, 1.5 equiv.) After stirring overnight at RT, TLC analysis revealed complete consumption of the starting material. The reaction was quenched with saturated aqueous $NaHCO_3$ (500 mL) and the aqueous phase was extracted with DCM (4 × 250 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by a silica plug (500 mL, hexane/EtOAc 7:3 then 500 mL 1:1) to yield allyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-α/β-D-galactopyranoside (14.9 g, 33.7 mmol, 71%); 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-trifluoroacetamido-α/β-D-galactopyranoside was recovered (6.64g, 12.73 mmol, 19%). A solution of allyl 3,4,6-tri-*O*-acetyl-2-trifluoroacetamido-2-deoxy-α-D-galactopyranoside (14.9 g, 33.7 mmol, 1.0 equiv.) in methanol (50 mL) was treated with 1M NaOH (10 mL). The reaction mixture was left stirring at RT until complete consumption of the starting material by TLC (R_f = 0.49, DCM/MeOH, 9:1). The reaction mixture was neutralized by addition of IR-120(H+) ion exchange resin, the mixture was filtered, washed with methanol (250 mL) and the combined filtrates concentrated under reduced pressure to deliver **16** (9.62 g, 30.52 mmol, 91%) as a yellow oil without the need for further purification. R_f = 0.49 (DCM/MeOH, 9:1); ^{1}H NMR (400 MHz, MeOD)

δ 5.97 – 5.85 (m, 1H, =C*H*-), 5.30 (dq, *J* = 17.3, 3.3, 1.7 Hz, 1H, CH_2=), 5.17 (dq, *J* = 10.4, 3.0, 1.3 Hz, 1H, CH_2=), 4.92 (d, *J* = 3.7 Hz, 1H, H-1), 4.29 (dd, *J* = 10.9, 3.7 Hz, 1H, H-2), 4.20 (ddt, *J* = 13.2, 5.0, 1.5 Hz, 1H, OC*H*H), 4.01 (ddt, *J* = 13.2, 6.2, 1.3 Hz, 1H, OC*H*H), 3.97 – 3.88 (m, 2H, H-3, H-4), 3.85 (t, *J* = 6.1 Hz, 1H, H-5), 3.77 – 3.67 (m, 2H, H-6a, H-6b); ^{13}C NMR (101 MHz, MeOD) δ 158.0 (q, $^{2}J_{C\text{-}F}$ = 36.9 Hz, C=O), 133.9 (=*C*H-), 116.35 (*C*H_2=), 116.12 (q, $^{1}J_{C\text{-}F}$ = 286.6 Hz, CF_3), 95.8 (C1), 71.3 (C5), 68.9 (C4), 67.9 (O*C*H_2), 67.2 (C3), 61.4 (C6), 51.2 (C2); ^{19}F NMR (377 MHz, MeOD) δ -76.99 (s); HRMS *m/z* (ES^-) [Found: $(M\text{-}H)^-$ 314.0857 requires $C_{11}H_{15}F_3NO_6$ M^- 314.0857]. Data matched those reported previously. [1]

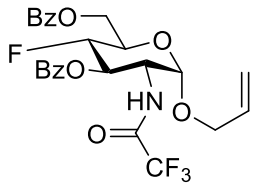
Allyl 3,6-di-*O*-benzoyl-2-deoxy-2-trifluoroacetamido-α-D-galactopyranoside 79



A solution of allyl 2-deoxy-2-trifluoroacetamido-α-D-galactopyranoside **78** (3.62 g, 11.5 mmol, 1.0 equiv.) in pyridine (40 mL) and DCM (10 mL) was cooled to -40 °C and treated dropwise with a solution of BzCl (2.80 mL, 3.39 g, 24.1 mmol, 2.1 equiv.) in DCM (5 mL). The reaction mixture was maintained at -40 °C until reaction completion as seen by TLC (R_f = 0.25, DCM/EtOAc, 9:1). Saturated aqueous $NaHCO_3$ (50 mL) was added with stirring and the aqueous layer extracted with DCM (3 × 50 mL). The combined organic phases were washed with water (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure, yielding the crude product, which was purified by column chromatography DCM/EtOAc, 0-30%) to deliver **79** (4.22 g, 8.06 mmol, 70%) as a white solid. R_f = 0.25 (DCM/EtOAc, 9:1); mp = 179 -182 °C; $[\alpha]_D^{23}$ = +49.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.98 (m, 4H, Ar*H*), 7.61 – 7.53 (m, 2H,

Ar*H*), 7.47 – 7.39 (m, 4H, Ar*H*), 6.65 (d, *J* = 9.6 Hz, 1H, N*H*), 5.95 – 5.83 (m, 1H, =C*H*-), 5.40 (dd, *J* = 11.1, 2.9 Hz, 1H, H-3), 5.30 – 5.21 (m, 2H, C*H*$_2$=), 5.07 (d, *J* = 3.7 Hz, 1H, H-1), 4.96 – 4.87 (m, 1H, H-2), 4.65 (dd, *J* = 11.5, 5.8 Hz, 1H, H-6a), 4.54 (dd, *J* = 11.5, 6.8 Hz, 1H, H-6b), 4.31 (m, 2H, H-4, H-5), 4.25 (ddt, *J* = 12.7, 5.5, 1.3 Hz, 1H ,OC*H*H), 4.12 – 4.05 (m, 1H, OC*H*H), 2.72 (s, 1H, 4-O*H*); ^{13}C NMR (101 MHz, CDCl3) δ 166.45 (C=O, Bz x 2), 157.3 (q, $^{2}J_{C\text{-}F}$ = 37.5 Hz, C=O), 133.8 (Ar-C), 133.4 (Ar-C), 132.8 (=*C*H-), 129.9 (Ar-C), 129.7 (Ar-C), 129.6 (Ar-C), 128.7 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 119.0 (*C*H$_2$=), 115. 6 (q, $^{1}J_{C\text{-}F}$ = 287.9 Hz, CF_3), 96.1 (C1), 71.7 (C3), 68.9 (C5), 68.7 (O*C*H$_2$), 67.1 (C4), 63.3 (C6), 48.1 (C2); ^{19}F NMR (377 MHz, $CDCl_3$) δ −76.13 (s); HRMS *m/z* (ES$^+$) [Found: (M + Na)$^+$ 546.1343 requires $C_{25}H_{24}F_3NO_8Na$ M$^+$ 546.1346].

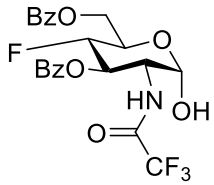
Allyl 3,6-di-*O*-benzoyl-4-fluoro-2-trifluoroacetamido-2,4-dideoxy-α-D-glucopyranoside 80



In a Teflon^{TM} flask, a solution of **79** (515 mg, 0.984 mmol, 1.0 equiv.) in DCM (10 mL) was cooled to -40 °C and DAST (0.39 mL, 475 mg, 2.95 mmol, 3.0 equiv.) added dropwise. Upon reaction completion as seen by TLC (R_f = 0.63, hexane/EtOAc, 7:3), the solution was cooled to -20 °C and MeOH (5 mL) added slowly. After stirring for 15 mins at RT the solution was concentrated, diluted with DCM (20 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-30%) yielding the title compound **80** as a colourless oil. (293 mg, 0.558 mmol, 79%); **79** was recovered (0.224 mmol). R_f =

0.63 (hexane/EtOAc, 7:3); $[\alpha]_D^{24}$ = 66.9 (*c* = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.00 (m, 4H, Ar*H*), 7.64 – 7.55 (m, 2H, Ar*H*), 7.52 – 7.42 (m, 4H, Ar*H*), 6.83 (d, *J* = 9.1 Hz, 1H, N*H*), 5.90 (dddd, *J* = 17.0, 10.3, 6.6, 5.4 Hz, 1H, =C*H*-),)5.73 (m, 1H, H-3), 5.34 – 5.25 (m, 2H, CH_2=), 5.03 (t, *J* = 3.3 Hz, 1H, H-1), 4.88 – 4.68 (m, 2H, H-6a, H-4), 4.59 (ddd, *J* = 12.3, 4.7, 1.3 Hz, 1H, H-6b), 4.48 – 4.40 (m, 1H, H-2), 4.31 – 4.24 (m, 2H, H-5, OC*H*H), 4.09 (ddt, *J* = 12.7, 6.6, 1.1 Hz, 1H, OC*H*H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9 (C=O, Bz), 166.1 (C=O, Bz), 157.3 (d, $^2J_{C\text{-}F}$ = 38.0 Hz, C=O), 133.8 (Ar-C), 133.4 (Ar-C), 132.4 (=*C*H-), 130.0 (Ar-C), 129.7 (Ar-C), 129.6 (Ar-C), 128.58 (Ar-C), 128.56 (Ar-C), 119.4 *C*H_2=, 115.4 (q, $^1J_{C\text{-}F}$ = 287.8 Hz, CF_3), 95.4 (C1), 86.7 (d, $^1J_{C\text{-}F}$ = 188.2 Hz, C4), 71.3 (d, $^2J_{C\text{-}F}$ = 19.4 Hz, C3), 69.2 (O*C*H_2), 67.9 (d, $^2J_{C\text{-}F}$ = 23.3 Hz, C5), 62.3 (C6), 52.6 (d, $^3J_{C\text{-}F}$ = 7.1 Hz, C2); ^{19}F NMR (377 MHz, $CDCl_3$) δ -76.13 (s), -197.02 (dd, $^2J_{H4\text{-}F}$ = 50.8, $^3J_{H3\text{-}F}$ = 13.4 Hz); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 543.1744 requires $C_{25}H_{27}F_4N_2O_7$ M^+ 543.1749].

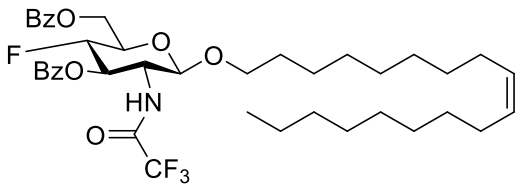
3,6-Di-*O*-benzoyl-4-fluoro-2-trifluoroacetamido-2,4-dideoxy-α-D-glucopyranose **81**



Tetrakis(triphenylphosphine)palladium (275 mg, 0.238 mmol, 0.5 equiv.) was added to a solution of allyl 3,6-di-*O*-benzoyl-4-fluoro-2-trifluoroacetamido-2,4-dideoxy-α-D-glucopyranoside **80** (250 mg, 0.476 mmol, 1.0 equiv.) in AcOH (5 mL) and the resulting mixture was heated at 80 °C. After 1 hr TLC revealed complete consumption of the starting material (R_f = 0.32, hexane/EtOAc, 7:3). The reaction mixture was concentrated under reduced pressure and the crude residue was purified by flash column chromatography (hexane/EtOAc, 0-50%) to yield **81** (170 mg, 0.350 mmol, 74%) as a colourless oil. R_f = 0.32 (hexane/EtOAc, 7:3); $[\alpha]_D^{25}$ = 10.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR

(400 MHz, $CDCl_3$) δ 8.14 – 8.01 (m, 4H, Ar*H*), 7.65 – 7.56 (m, 2H, Ar*H*), 7.52 – 7.43 (m, 4H, Ar*H*), 6.91 (d, *J* = 9.1 Hz, 1H, N*H*), 5.85 – 5.73 (m, 1H, H-3), 5.40 (t, *J* = 3.2 Hz, 1H, H-1), 4.90 – 4.70 (m, 2H, H-4, H-6a), 4.57 (ddd, *J* = 12.3, 4.1, 1.4 Hz, 1H, H-6b), 4.52 – 4.46 (m, 1H, H-5), 4.45 – 4.38 (m, 1H, H-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0 (C=O, Bz), 166.3 (C=O, Bz), 157.4 (q, $^{2}J_{C\text{-}F}$ = 38.1 Hz, C=O), 133.9 (Ar-C), 133.4 (Ar-C), 130.0 (Ar-C), 129.8 (Ar-C), 129.5 (Ar-C), 128.57 (Ar-C), 128.56 (2 × Ar-C), 115. 4 (q, $^{1}J_{C\text{-}F}$ = 287.7 Hz, CF_3), 91.0 (C1), 86.6 (d, $^{1}J_{C\text{-}F}$ = 188.2 Hz, C4), 77.2, 70.9 (d, $^{2}J_{C\text{-}F}$ = 19.2 Hz, C3), 67.7 (d, $^{2}J_{C\text{-}F}$ = 23.5 Hz, C5), 62.2 (C6), 52.8 (d, $^{3}J_{C\text{-}F}$ = 7.1 Hz, C2); ^{19}F NMR (377 MHz, $CDCl_3$) δ -76.09 (s), -197.16 (dd, $^{2}J_{H4\text{-}F}$ = 50.7, $^{3}J_{H3\text{-}F}$ = 13.2 Hz); HRMS *m/z* (ES^+) [Found: $(M+Na)^+$ 508.0990 requires $C_{22}H_{19}F_4NO_7Na$ M^+ 508.0990].

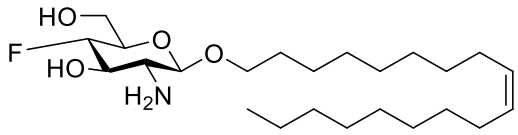
Oleyl 3,6-di-*O*-benzoyl-4-fluoro-2-trifluoroacetamido-2,4-dideoxy-β-D-glucopyranoside **82**



Following general procedure **D**, hemi-acetal **81** (402 mg, 0.583 mmol, 1.0 equiv.), DBU (8.70 μL, 9.00 mg, 58.3 μmol, 0.1 equiv.) and Cl_3CCN (0.59 mL, 842 mg, 5.83 mmol, 10.0 equiv) gave the corresponding trichloroacetimidate donor. After reacting the donor with oleyl alcohol (0.20 mL, 168 mg, 0.627 mmol, 1.1 equiv.) and TMSOTf (0.10 mL, 127 mg, 0.570 mmol, 1.0 equiv.) for 30 mins, purification by column chromatography (hexane/EtOAc, 0-20%) delivered the title compound (192 mg, 0.245 mmol, 42%) as a colourless oil. R_f = 0.28 (toluene/acetone, 95:5); $[\alpha]_D^{21}$ = -4.9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.93 (m, 4H, Ar*H*), 7.57 – 7.49 (m, 2H, Ar*H*), 7.39 (td, *J* = 7.7, 3.9 Hz, 4H, Ar*H*), 7.13 (d, *J* = 9.3 Hz, 1H, N*H*), 5.78– 5.64 (m, 1H, H-3), 5.32 – 5.24 (m, 2H, -C*H*=C*H*-), 4.82 – 4.60 (m, 3H, H-1, H-4, H-6a), 4.54 – 4.47 (m, 1H, H-6b),

4.23 (q, *J* = 10.3, 9.5 Hz, 1H, H-2), 3.93 – 3.86 (m, 1H, H-5), 3.81 (dt, *J* = 9.6, 6.3 Hz, 1H, OC*H*H), 3.41 (dt, *J* = 9.5, 6.8 Hz, 1H, OC*H*H), 1.99 – 1.81 (m, 4H, 2 x CH_2), 1.53 – 1.43 (m, 2H, CH_2), 1.18 (m, 22H, 11 x CH_2), 0.80 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2 (C=O, OBz), 166.1 (C=O, OBz) , 157.6 (q, $^2J_{C\text{-}F}$ = 37.8 Hz, C=O), 134.2 (Ar-C), 133.3 (Ar-C), 130.4 (*C*=C), 130.3 (Ar-C), 130.0 (Ar-C), 129.82 (*C*=C*)*, 129.78 (Ar-C), 129.6 (Ar-C), 128.7 (Ar-C), 128.5 (Ar-C), 128.2 (Ar-C), 115.6 (q, $^1J_{C\text{-}F}$ = 288.2 Hz, CF_3), 100.7 (C1), 87.3 (d, $^1J_{C\text{-}F}$ = 187.6 Hz, C4), 72.8 (d, $^2J_{C\text{-}F}$ = 19.6 Hz, C3), 71.5 (d, $^2J_{C\text{-}F}$ = 23.3 Hz, C5), 70.5 (O*C*H_2), 62.6 (C6), 54.4 (d, $^3J_{C\text{-}F}$ = 7.3 Hz, C2), 38.3, 32.6, 31.9, 29.7, 29.5, 29.44, 29.37, 29.32, 29.30, 29.26, 29.2, 27.2, 25.8, 22.7, 14.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ -76.30 (s), -197.95 (dd, $^2J_{H4\text{-}F}$ = 51.0, $^3J_{H3\text{-}F}$ = 14.3 Hz); HRMS *m/z* (ES^+) [Found: $(M+Na)^+$ 758.3649 requires $C_{40}H_{53}F_4NO_7Na$ M^+ 758.3650].

Oleyl 4-deoxy-4-fluoro-β-D-glucosaminopyranoside 19

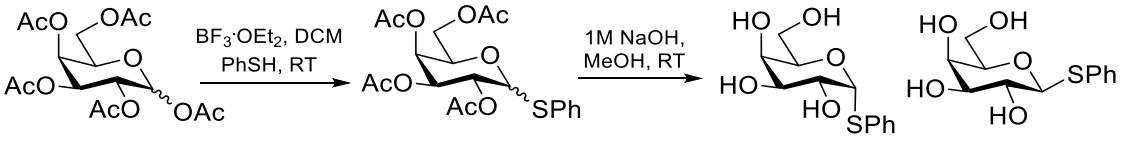


A solution of oleyl 3,6-di-*O*-benzoyl-4-fluoro-2-trifluoroacetamido-2,4-dideoxy-β-D-glucopyranoside **82** (64.0 mg, 87.0 μmol, 1.0 equiv.) in MeOH (5 mL) was treated with NaOH (200 mg). The reaction mixture was left stirring at RT for 24 h. TLC analysis revealed complete consumption of the starting material *(*R_f = 0.20, EtOAc). Amberlite IR20 (H^+) ion exchange resin was added until the pH was neutral. The mixture was filtered, washed with methanol (100 mL) and the combined organic filtrates were concentrated under reduced pressure. The crude residue was purified by column chromatography (DCM/MeOH, 0-10%) to deliver **19** (27.0 mg, 63.0 μmol 71%) as a white solid. R_f = 0.20 (EtOAc); $[\alpha]_D^{27}$ = -9.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz,

MeOD) δ 5.40 – 5.31 (m, 2H, - C*H*=C*H*-), 4.26 (d, *J* = 8.0 Hz, 1H, H-1), 4.25 (ddd, $^{2}J_{H4\text{-}F}$ = 51.0, 9.6, 8.7 Hz, 1H, H-4), 3.91 (dt, *J* = 9.5, 6.7 Hz, 1H, OC*H*H), 3.82 (dt, *J* = 12.2, 2.1 Hz, 1H, H-6a), 3.69 (ddd, *J* = 12.2, 4.8, 1.7 Hz, 1H, H-6b), 3.58 – 3.48 (m, 2H, H-3, OC*H*H), 3.48 – 3.43 (m, 1H, H-5), 2.62 (ddd, *J* = 9.9, 8.0, 0.7 Hz, 1H, H-2), 2.06 – 1.96 (m, 4H, 2 x CH_2), 1.66 – 1.56 (m, 2H, CH_2), 1.40 – 1.25 (m, 22H, 11 x CH_2), 0.90 (t, *J* = 6.7 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, MeOD) δ 129.5 (*C*=C*)*, 129.4 (*C*=C*)*, 102.3 (C1), 89.5 (d, $^{1}J_{C\text{-}F}$ = 179.7 Hz, C4), 74.1 (d, $^{2}J_{C\text{-}F}$ = 24.6 Hz, C5), 73.2 (d, $^{2}J_{C\text{-}F}$ = 18.8 Hz, C3), 69.6 (OCH_2), 60.3 (C6), 56.5 (d, $^{3}J_{C\text{-}F}$ = 7.9 Hz, C2), 32.2, 31.7, 29.5, 29.43, 29.37, 29.3, 29.20, 29.17, 29.0, 28.9, 26.74, 26.71, 25.8, 22.3, 13.0; ^{19}F NMR (377 MHz, MeOD) δ -202.10 (dd, $^{2}J_{H4\text{-}F}$ = 51.1, $^{3}J_{H3\text{-}F}$ = 15.0 Hz); HRMS *m/z* (ES^-) [Found: $(M\text{-}H)^-$ 430.3340 requires $C_{24}H_{45}FNO_4$ M^- 430.3338].

6.2 Chapter 3 compounds

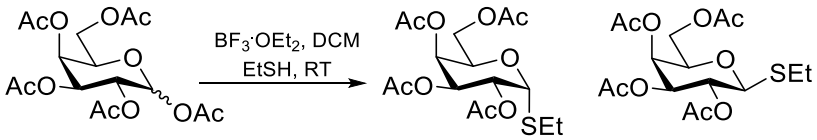
Phenyl 1-thio-α/β-D-galactopyranoside 86 & 107



1,2,3,4,6-Penta-*O*-acetyl-α/β-D-galactopyranoside (6.50 g, 16.7 mmol, 1.0 equiv.) was dissolved in DCM (25 mL) and $BF_3{\cdot}OEt_2$ (8.24 mL, 66.8 mmol, 4.0 equiv.) was added dropwise at RT and stirred overnight. The reaction mixture was diluted with DCM (100 mL) and washed successively with sat. aq. $NaHCO_3$ (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure and the crude residue progressed without further purification. To the crude material was added 1M NaOH (5 mL) and MeOH (5 mL), the resulting mixture was stirred at RT for 1 hr (R_f = α 0.37, β 0.24 acetone/toluene, 6:4). Amberlite IR20 (H^+) ion

exchange resin was added, and the mixture stirred until neutral, filtered and washed with methanol (100 mL). The combined organic filtrates were concentrated under reduced pressure and the crude residue purified by column chromatography (toluene/acetone, 0-100%) to yield the title compounds **α-107** (1.95 g, 7.16 mmol, 43%) and **β-86** (1.72 g, 6.32 mmol, 38%) individually as white solids. **α-107:** ^{1}H NMR (400 MHz, MeOD) δ 7.56 – 7.53 (m, 2H, Ar*H*), 7.32 – 7.22 (m, 3H, Ar*H*), 5.58 (d, *J* = 5.5 Hz, 1H, H-1), 4.34 (ddd, *J* = 6.6, 6.0, 0.9 Hz, 1H, H-5, 4.16 (dd, *J* = 10.2, 5.5 Hz, 1H, H-2), 3.97 (dd, *J* = 3.3, 1.2 Hz, 1H, H-4), 3.73 (dd, *J* = 11.4, 5.8 Hz, 1H, H-6b), 3.69 – 3.63 (m, 2H, H-3, H-6a); ^{13}C NMR (101 MHz, MeOD) δ 134.8 (Ar-C), 132.0 (Ar-C), 128.5, (Ar-C) 126.8 (Ar-C), 90.3 (C1), 71.8 (C4), 70.9 (C3), 69.4 (C5), 68.6 (C2), 60.9 (C6); **β-86:** ^{1}H NMR (400 MHz, MeOD) δ 7.59 – 7.51 (m, 2H, Ar*H*), 7.33 – 7.18 (m, 3H, Ar*H*), 4.58 (d, *J* = 9.7 Hz, 1H, H-1), 3.90 (dd, *J* = 3.3, 0.8 Hz, 1H, H-4), 3.76 (dd, *J* = 11.4, 6.8 Hz, 1H, H-6b), 3.70 (dd, *J* = 11.4, 5.3 Hz, 1H, H-6a), 3.60 (t, *J* = 9.4 Hz, 1H, H-2), 3.56 (ddd, *J* = 6.6, 5.3, 1.0 Hz, 1H, H-5), 3.49 (dd, *J* = 9.2, 3.3 Hz, 1H, H-3); ^{13}C NMR (101 MHz, MeOD) δ 134.7 (Ar-C), 130.7 (Ar-C), 128.5 (Ar-C), 126.6 (Ar-C), 88.9 (C1), 79.2 (C4), 75.0 (C3), 69.6 (C2), 69.0 (C5), 61.2 (C6); HRMS *m/z* (ES^-) [Found: $(M-H)^-$ 271.0647, $C_{12}H_{15}O_5S$, requires M^- 271.0646]. Data matched those reported previously.[179]

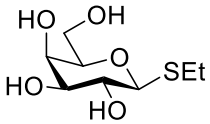
Ethyl 2,3,4,6-tetra-*O*-acteyl-1-thio-α/β-D-galactopyranoside 101 & 102



1,2,3,4,6-Penta-*O*-acetyl-α/β-D-galactopyranoside (2.00 g, 5.12 mmol, 1.0 equiv.) was dissolved in DCM (20 mL) and $BF_3{\cdot}OEt_2$ (2.53 mL, 20.5 mmol, 4.0 equiv.) was added dropwise at RT and stirred until complete consumption of the starting material, as seen by TLC (R_f = β 0.70, α 0.65, hexane/EtOAc, 6/4). The reaction mixture was diluted with

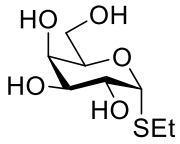
DCM (100 mL) and washed with sat. aq. $NaHCO_3$ (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude residue purified by column chromatography (0-50%, hexane/EtOAc) to yield the title compounds **α-102** (525 mg, 1.34 mmol, 26%) and **β-101** (756 mg, 1.93 mmol, 38%) individually as white solids. **β-101:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (d, *J* = 5.4 Hz, 1H, H-1), 5.45 (dd, *J* = 3.1, 0.9 Hz, 1H, H-4), 5.28 (dd, *J* = 10.9, 5.4 Hz, 1H, H-2), 5.22 (dd, *J* = 10.6, 2.9 Hz, 1H, H-3), 4.60 (t, *J* = 6.5 Hz, 1H, H-5), 4.12 (as, 1H, H-6a), 4.10 (as, 1H, H-6b), 2.66 – 2.47 (m, 2H, C*H*$_2$), 2.15 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.04 (s, 3H, OAc), 1.99 (s, 3H, OAc), 1.28 (t, *J* = 7.4 Hz, 3H, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (C=O, Ac), 170.2 (2 × C=O, Ac), 169.9 (C=O, Ac), 82.0 (C1), 68.2 (C3), 68.00 (C2), 67.97 (C4), 66.5 (C5), 61.8 (C6), 24.0 (CH_2), 20.9 (Ac-CH_3), 20.68 (Ac-CH_3), 20.65 (Ac-CH_3), 20.6 (Ac-CH_3), 14.7 (CH_3); **α-102:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (dd, *J* = 3.4, 0.9 Hz, 1H, H-4), 5.24 (t, *J* = 10.0 Hz, 1H, H-2), 5.05 (dd, *J* = 10.0, 3.4 Hz, 1H, H-3), 4.50 (d, *J* = 9.9 Hz, 1H, H-1), 4.17 (dd, *J* = 11.3, 6.7 Hz, 1H, H-6b), 4.11 (dd, *J* = 11.3, 6.6 Hz, 1H, H-6a), 3.94 (td, *J* = 6.6, 1.0 Hz, 1H, H-5), 2.82 – 2.63 (m, 2H, C*H*$_2$), 2.15 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.05 (s, 3H, OAc), 1.99 (s, 3H, OAc), 1.29 (t, *J* = 7.5 Hz, 3H, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (C=O, Ac), 170.2 (C=O, Ac), 170.1 (C=O, Ac), 169.6 (C=O, Ac), 84.1 (C1), 74.4 (C5), 71.9 (C3), 67.3 (C2), 67.2 (C4), 61.5 (C6), 24.4 (CH_2), 20.8 (Ac-CH_3), 20.7 (2 × Ac-CH_3), 20.6 (Ac-CH_3), 14.9 (CH_3): HRMS *m/z* (ES^+) [Found: $(M+Na)^+$ 415.1042, $C_{16}H_{24}O_9SNa$, requires M^+ 415.1038]. Data matched those reported previously.[180, 181]

Ethyl 1-thio-β-D-galactopyranoside 108



Following the general deacetylation procedure, ethyl 2,3,4,6-tetra-*O*-acteyl-1-thio-β-D-galactopyranoside **101** (520 mg, 1.33 mmol, 1.0 equiv.) was deprotected using Na (3.00 mg, 0.133 mmol, 0.1 equiv.) in MeOH (5 mL). Following column chromatography (DCM/MeOH, 0-20%) the title compound was obtained as a colourless oil (260 mg, 1.16 mmol, 87%). R_f = 0.54 (DCM/MeOH, 8:2); ^{1}H NMR (400 MHz, MeOD) δ 4.33 (d, *J* = 9.5 Hz, 1H, H-1), 3.90 (dd, *J* = 3.2, 0.8 Hz, 1H, H-4), 3.74 (dd, *J* = 11.4, 6.8 Hz, 1H, H-6b), 3.69 (dd, *J* = 11.4, 5.3 Hz, 1H, H-6a), 3.58 – 3.51 (m, 2H, H-2, H-5), 3.48 (dd, *J* = 9.2, 3.3 Hz, 1H, H-3), 2.84 – 2.65 (m, 2H, CH_2), 1.28 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 90.0 (C1), 83.2 (C2), 78.8 (C3), 73.9 (C5), 73.1 (C4), 65.2 (C6), 27.5 (CH_2), 18.0 (CH_3); HRMS *m/z* (ES^-) [Found: $(M-H)^-$ 223.0646, $C_8H_{15}O_5S$, requires M^- 223.0646]. Data matched those reported previously.[182]

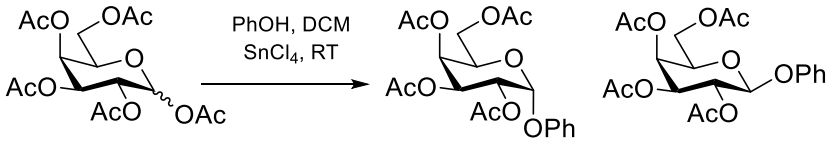
Ethyl 1-thio-α-D-galactopyranoside 109



Following the general deacetylation procedure, ethyl 2,3,4,6-tetra-*O*-acteyl-1-thio-α-D-galactopyranoside **102** (520 mg, 1.33 mmol, 1.0 equiv.) was deprotected using Na (3.00 mg, 0.133 mmol, 0.1 equiv.) in MeOH (5 mL), following column chromatography (DCM/MeOH, 0-20%) the title compound was obtained as a colourless oil (236 mg, 0.870 mmol, 66%). R_f = 0.54 (DCM/MeOH, 8:2); ^{1}H NMR (400 MHz, MeOD) δ 5.41 (d, *J* = 5.6 Hz, 1H, H-1), 4.18 (ddd, *J* = 6.5, 5.9, 0.8 Hz, 1H, H-5), 4.08 (dd, *J* = 10.1, 5.6 Hz, 1H, H-2), 3.89 (dd, *J* = 3.3, 1.1 Hz, 1H, H-4), 3.72 (s, 1H, H-6b), 3.71 (s, 1H, H-6a), 3.60 (dd, *J* = 10.1, 3.3 Hz, 1H, H-3), 2.70 – 2.51 (m, 2H, CH_2), 1.28 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, MeOD) δ 85.6 (C1), 71.3 (C5), 70.9 (C3), 69.5 (C4), 68.3

(C2), 61.2 (C6), 23.3 (CH_2), 13.8 (CH_3); HRMS *m/z* (ES^-) [Found: $(M-H)^-$ 223.0646, $C_8H_{15}O_5S$ requires M^- 223.0646]. Data matched those reported previously.[183]

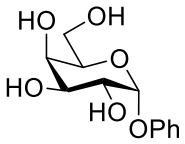
Phenyl 2,3,4,6-tetra-*O*-acteyl-α/β-D-galactopyranoside 103 & 104



1,2,3,4,6-Penta-*O*-acetyl-α/β-D-galactopyranoside (2.00 g, 5.12 mmol, 1.0 equiv.) was dissolved in DCM (25 mL) then treated with phenol (964 mg, 10.24 mmol, 2.0 equiv.) and $SnCl_4$ (588 µL, 5.12 mmol, 1.0 equiv.). The reaction was stirred at RT until complete consumption of the starting material, as seen by TLC (R_f = α 0.44, β 0.40, hexane/EtOAc, 7:3). The reaction mixture was diluted with DCM (100 mL) and washed successively with sat. aq. $NaHCO_3$ (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-30%) yielding **α-104** and **β-103** (1.29 g, 3.04 mmol, 59%, α/β, 84:16) individually as white solids. **α-104:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H, Ar*H*), 7.10 – 7.03 (m, 3H, Ar*H*), 5.78 (d, *J* = 3.6 Hz, 1H, H-1), 5.59 (dd, *J* = 10.8, 3.4 Hz, 1H, H-3), 5.53 (dd, *J* = 3.4, 1.2 Hz, 1H, H-4), 5.29 (dd, *J* = 10.8, 3.6 Hz, 1H, H-2), 4.39 – 4.32 (t, *J* = 6.2 Hz, 1H, H-5), 4.13 (dd, *J* = 11.2, 6.1 Hz, 1H, H-6b), 4.06 (dd, *J* = 11.3, 7.1 Hz, 1H, H-6a), 2.17 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.04 (s, 3H, OAc), 1.94 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (C=O, Ac), 170.3 (C=O, Ac), 170.2 (C=O, Ac), 170.0 (C=O, Ac), 156.3 (Ar-C), 129.6 (Ar-C), 123.0 (Ar-C), 116.8 (Ar-C), 94.9 (C1), 67.9 (C4), 67.8 (C2), 67.6 (C3), 67.2 (C5), 61.5 (C6), 20.71 (Ac-CH_3), 20.66 (Ac-CH_3), 20.6 (Ac-CH_3), 20.5 (Ac-CH_3). **β-103:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 2H, Ar*H*), 7.11 – 6.98 (m, 3H, Ar*H*), 5.50 (dd, *J* = 10.5, 8.0 Hz, 1H, H-2), 5.46 (dd, *J* = 3.4, 0.9 Hz, 1H, H-4), 5.12 (dd, *J* = 10.5, 3.4 Hz, 1H, H-3), 5.06 (d, *J*

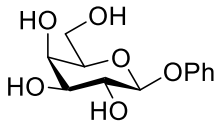
= 8.0 Hz, 1H, H-1), 4.24 (dd, *J* = 11.3, 7.0 Hz, 1H, H-6b), 4.16 (dd, *J* = 10.8, 5.8 Hz, 1H, H-6a), 4.09 – 4.05 (at, *J* = 6.1 Hz, 1H, H-5), 2.18 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.02 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.34 (C=O, Ac), 170.25 (C=O, Ac), 170.1 (C=O, Ac), 169.4 (C=O, Ac), 157.0 (Ar-C), 129.6 (Ar-C), 123.3 (Ar-C), 117.0 (Ar-C), 99.7 (C1), 71.0 (C5), 70.9 (C3), 68.7 (C2), 66.9 (C4), 61.4 (C6), 20.72 (Ac-CH_3), 20.65 (Ac-CH_3), 20.64 (Ac-CH_3), 20.58 (Ac-CH_3); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 442.1705, $C_{20}H_{28}O_{10}N$ requires M^+ 442.1708]. Data matched those reported previously.[184]

Phenyl α-D-galactopyranoside 111



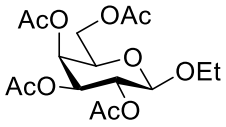
Following the general deacetylation procedure, phenyl 2,3,4,6-tetra-*O*-acteyl-α-D-galactopyranoside **104** (436 mg, 1.03 mmol, 1.0 equiv.) was deprotected using Na (3.00 mg, 0.103 mmol, 0.1 equiv.) in MeOH (5 mL), following column chromatography (DCM/MeOH, 0-20%) the title compound was obtained as a colourless oil (203 mg, 0.793 mmol, 77%); R_f = 0.33 (DCM/MeOH, 9:1); ^{1}H NMR (400 MHz, MeOD) δ 7.31 – 7.25 (m, 2H, Ar*H*), 7.20 – 7.13 (m, 2H, Ar*H*), 7.02 – 6.93 (m, 1H, Ar*H*), 5.49 (d, *J* = 2.8 Hz, 1H, H-1), 4.00 – 3.90 (m, 4H, H-2, H-3, H-4, H-5), 3.74 – 3.62 (m, 2H, H-6b, H-6a); ^{13}C NMR (101 MHz, MeOD) δ 157.5 (Ar-C), 129.0 (Ar-C), 122.0 (Ar-C), 117.0 (Ar-C), 98.4 (C1), 71.7, 70.0, 69.4, 68.6, 61.0 (C6); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 274.1295, $C_{12}H_{12}O_6Na$ requires M^+ 274.1290]. Data matched those reported previously.[185]

Phenyl β-D-galactopyranoside 110



Following the general deacetylation procedure, phenyl 2,3,4,6-tetra-*O*-acteyl-β-D-galactopyranoside **104** (212 mg, 0.500 mmol, 1.0 equiv.) was deprotected using Na (1.00 mg, 50.0 µmol, 0.1 equiv.) in MeOH (5 mL), following column chromatography (DCM/MeOH, 0-20%) the title compound was obtained as a colourless oil (101 mg, 0.395 mmol, 79%); R_f = 0.30 (DCM/MeOH, 9:1); ^{1}H NMR (400 MHz, MeOD) δ 7.29 – 7.24 (m, 2H, Ar*H*), 7.15 – 7.07 (m, 2H, Ar*H*), 7.03 – 6.97 (m, 1H, Ar*H*), 4.85 (d, *J* = 8.3 Hz, 1H, H-1), 3.90 (dd, *J* = 3.3, 0.6 Hz, 1H, H-4), 3.82 – 3.74 (m, 3H, H-2, H-6b, H-6a), 3.70 – 3.65 (m, 1H, H-5), 3.58 (dd, *J* = 9.7, 3.4 Hz, 1H, H-3); ^{13}C NMR (101 MHz, MeOD) δ 157.9 (Ar-C), 129.0 (Ar-C), 121.9 (Ar-C), 116.4 (Ar-C), 101.6 (C1), 75.5 (C5), 73.5 (C3), 70.9 (C2), 68.8 (C4), 61.0 (C6); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 274.1295, $C_{12}H_{16}O_6$ requires M^+ 274.1290]. Data matched those reported previously.[186]

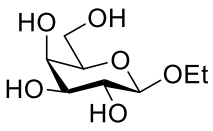
Ethyl 2,3,4,6-tetra-*O*-acteyl-β-D-galactopyranoside 105



1,2,3,4,6-Penta-*O*-acetyl-α/β-D-galactopyranoside (2.00 g, 5.12 mmol, 1.0 equiv.) was dissolved in DCM (10 mL) and HBr in acetic acid (5 mL) 33% (*w/v*) added dropwise at 0 °C. The mixture was allowed to reach RT and stirred until complete consumption of the starting material, as seen by TLC (R_f = 0.23, hexane/EtOAc, 7:3). The reaction mixture was diluted with DCM (100 mL) and washed successively with sat. aq. $NaHCO_3$ (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to deliver 1-bromo-2,3,4,6-tetra-*O*-acetyl-α-D-

galactopyranoside as a colourless oil which was used in the next step without further purification. Ethanol (40 mL) was added to 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (5.12 mmol, 1.0 equiv.) followed by silver triflate (1.32 g, 5.12 mmol, 1.0 equiv.) and silver carbonate (1.41 g, 5.12 mmol, 1.0 equiv.). The suspension was stirred for 20 hrs at RT, TLC analysis revealed reaction completion (R_f = 0.33, hexane/EtOAc, 7:3) and the mixture was diluted with DCM (100 mL) and filtered through a pad of Celite® to remove the silver salts. The solution was concentrated, and the yellow residue was purified by column chromatography (hexane/EtOAc, 0-40%) to yield the title compound as a clear oil (1.48 g, 3.94 mmol, 77%). R_f = 0.33 (hexane/EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (dd, *J* = 3.4, 1.0 Hz, 1H, H-4), 5.20 (dd, *J* = 10.5, 8.0 Hz, 1H, H-2), 5.02 (dd, *J* = 10.5, 3.4 Hz, 1H, H-3), 4.48 (d, *J* = 8.0 Hz, 1H, H-1), 4.19 (dd, *J* = 11.2, 6.5 Hz, 1H, H-6b), 4.13 (dd, *J* = 11.2, 6.9 Hz, 1H, H-6a), 3.98 – 3.86 (m, 2H, H-5, OC*H*H), 3.59 (dq, *J* = 9.7, 7.1 Hz, 1H, OC*H*H), 2.15 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.05 (s, 3H, OAc), 1.99 (s, 3H, OAc), 1.22 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (C=O, Ac), 170.3 (C=O, Ac), 170.2 (C=O, Ac), 169.5 (C=O, Ac), 101.1 (C1), 71.0 (C3), 70.6 (C5), 69.0 (C2), 67.1 (C4), 65.7 (CH_2), 61.3 (C6), 20.8 (Ac-CH_3), 20.7 (2 × Ac-CH_3), 20.6 (Ac-CH_3), 15.1 (CH_3); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 394.1709, $C_{16}H_{28}O_{10}N$ requires M^+ 394.1708]. Data matched those reported previously.[187]

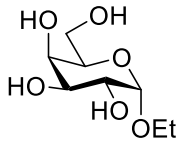
Ethyl β-D-galactopyranoside 112



Following the general deacetylation procedure, ethyl 2,3,4,6-tetra-*O*-acteyl-β-D-galactopyranoside **105** (366 mg, 0.973 mmol, 1.0 equiv.) was deprotected using Na (2.00 mg, 97.0 μmol, 0.1 equiv.) in MeOH (5 mL), following column chromatography

(DCM/MeOH, 0-20%) the title compound was obtained as a colourless oil (172 mg, 0.830 mmol, 85%). R_f = 0.44 (DCM/MeOH, 8:2); ^{1}H NMR (400 MHz, MeOD) δ 4.21 (d, *J* = 7.2 Hz, 1H, H-1), 3.95 (dq, *J* = 9.5, 7.1 Hz, 1H, OC*H*H), 3.82 (ad, *J* = 3.0 Hz, 1H, H-4), 3.75 (dd, *J* = 9.8, 5.2 Hz, 1H, H-6b), 3.71 (dd, *J* = 9.8, 4.1 Hz, 1H, H-6a), 3.61 (dq, *J* = 9.6, 7.1 Hz, 1H, OC*H*H), 3.52 – 3.43 (m, 3H, H-2, H-3, H-5), 1.23 (t, *J* = 7.1 Hz, 1H, C*H*$_3$); ^{13}C NMR (101 MHz, MeOD) δ 103.3 (C1), 75.2 (C3), 73.6 (C5), 71.1 (C2), 68.9 (C4), 64.7 (CH_2), 61.1 (C6), 14.1 (CH_3); HRMS *m/z* (ES^-) [Found: $(M-H)^-$ 207.0875, $C_8H_{15}O_6$ requires M^- 207.0874]. Data matched those reported previously.[188]

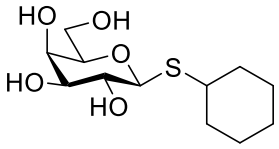
Ethyl α-D-galactopyranoside 113



1,2,3,4,6-Penta-*O*-acetyl-α/β-D-galactopyranoside (1.00 g, 2.56 mmol, 1.0 equiv.) was dissolved in DCM (25 mL). Ethanol (5 mL) and $SnCl_4$ (293 µL, 2.56 mmol, 1.0 equiv.) were added at RT and stirred until reaction completion, as seen by TLC (R_f = 0.23, hexane/EtOAc, 7:3). The reaction mixture was diluted with DCM (100 mL) and washed successively with sat. aq. $NaHCO_3$ (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-30%) yielding ethyl 2,3,4,6-tetra-*O*-acteyl-α/β-D-galactopyranoside (530 mg, 1.41 mmol, 55%, α/β, 7:3) as an inseparable mixture. The mixture was deprotected following the general deacetylation procedure, using Na (3.24 mg, 141 µmol, 0.1 equiv.) in MeOH (5 mL) and following column chromatography (DCM/MeOH, 0-20%) a small amount of the title compound was crystallized from acetone as a white solid (32.0 mg, 0.154 mmol, 11%). R_f = 0.44 (DCM/MeOH, 8:2); ^{1}H NMR (400 MHz, MeOD) δ 4.84 (d, *J* = 3.2 Hz, 1H, H-1), 3.92 –

3.89 (m, 1H, H-3), 3.85 – 3.80 (m, 2H, H-5, OC*H*H), 3.79 – 3.74 (m, 2H, H-2, H-4), 3.74 – 3.69 (m, 2H, H-6a, H-6b), 3.58 – 3.48 (m, 1H, OC*H*H), 1.26 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, MeOD) δ 98.7 (C1), 70.9 (C5), 70.2 (C2), 69.7 (C3), 68.8 (C4), 63.1 (CH_2), 61.4 (C6), 13.9 (CH_3); HRMS *m/z* (ES^-) [Found: $(M-H)^-$ 207.0875, $C_8H_{15}O_6$ requires M^- 207.0874]. Data matched those reported previously.[188]

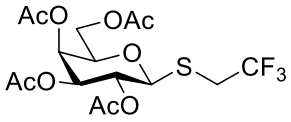
Cyclohexyl 1-thio-β-D-galactopyranoside 138



1,2,3,4,6-Penta-*O*-acetyl-α/β-D-galactopyranoside (1.00 g, 2.56 mmol, 1.0 equiv.) was dissolved in DCM (10 mL) and HBr in acetic acid (3 mL) 33% (*w/v*) added dropwise at 0 °C. The mixture was allowed to reach RT and stirred until complete consumption of the starting material, as seen by TLC (R_f = 0.23, hexane/EtOAc, 7:3). The reaction mixture was diluted with DCM (100 mL) and washed successively with sat. aq. $NaHCO_3$ (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to deliver 1-bromo-2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranoside as a colourless oil which was used in the next step without further purification. To the glycosyl bromide in acetone (20 mL) was added NaOH (102 mg, 2.56 mmol, 1.0 equiv.) and cyclohexyl mercaptan (345 µL, 2.82 mmol, 1.1 equiv.) and the mixture stirred at RT. After 2 hrs TLC analysis revealed complete consumption of the starting material (R_f = 0.20, hexane/EtOAc, 7:3). The mixture was diluted with DCM (50 mL) washed with sat. aq. $NaHCO_3$ (3 × 100 mL) and the combined organic layers dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-40%) yielding cyclohexyl 2,3,4,6-tetra-*O*-acteyl-1-thio-β-D-galactopyranoside as a colourless oil (526 mg, 1.18 mmol, 46%).

Following the general deacetylation procedure, cyclohexyl 2,3,4,6-tetra-*O*-acteyl-1-thio-β-D-galactopyranoside (526 mg, 1.18 mmol, 1.0 equiv.) was deprotected using Na (2.71 mg, 0.118 mmol, 0.1 equiv.) in MeOH (5 mL), following column chromatography (DCM/MeOH, 0-20%) the title compound was obtained as a colourless solid (261 mg, 0.934 mmol, 79%); R_f = 0.69 (DCM/MeOH, 8:2); ^{1}H NMR (400 MHz, MeOD) δ 4.40 (d, *J* = 9.1 Hz, 1H, H-1), 3.87 (ad, *J* = 3.0 Hz, 1H, H-4), 3.78 – 3.63 (m, 2H, H-6a, H-6b), 3.58 – 3.43 (m, 3H, H-2, H-3, H-5), 3.08 – 2.91 (m, 1H, C*H*), 2.13 – 1.93 (m, 2H, CH_2), 1.80 – 1.66 (m, 2H, CH_2), 1.65 – 1.50 (m, 1H, C*H*H), 1.47 – 1.17 (m, 5H, 2 × CH_2, C*H*H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 89.5 (C1), 83.0, 78.9, 74.2, 73.0 (C4), 65.2 (C6), 46.7 (CH), 38.0 (CH_2), 37.8 (CH_2), 29.7 (CH_2), 29.5 (2 × CH_2); HRMS *m/z* (ES^-) [Found: $(M-H)^-$ 277.1119, $C_{12}H_{21}O_5S$ requires M^- 277.1119]. Data matched those reported previously.[189]

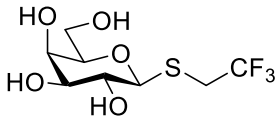
Trifluoroethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside 133



1,2,3,4,6-Penta-*O*-acetyl-α/β-D-galactopyranoside (3.00 g, 7.70 mmol, 1.0 equiv.) was dissolved in DCM (10 mL) and HBr in acetic acid (5 mL) 33% (*w/v*) added dropwise at 0 °C. The mixture was allowed to reach RT and stirred until complete consumption of the starting material, as seen by TLC (R_f = 0.23, hexane/EtOAc, 7:3). The reaction mixture was diluted with DCM (100 mL) and washed successively with sat. aq. $NaHCO_3$ (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to deliver 1-bromo-2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranoside as a colourless oil which was used in the next step without further purification. To the glycosyl bromide in acetone (20 mL) was added NaOH (308 mg, 7.70

mmol, 1.0 equiv.) and trifluoroethanethiol (759 µL, 8.50 mmol, 1.1 equiv.) and the mixture stirred at RT. After 2 hrs TLC analysis revealed complete consumption of the starting material (R_f = 0.20, hexane/EtOAc, 7:3). The mixture was diluted with DCM (50 mL) washed with sat. aq. $NaHCO_3$ (3 × 100 mL) and the combined organic layers dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-40%) yielding the title compound as a colourless oil (1.49 g, 3.34 mmol, 43%). R_f = 0.20 (hexane/EtOAc, 7:3), $[\alpha]_D^{23}$ = 14.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (dd, *J* = 3.3, 1.0 Hz, 1H, H-4), 5.12 (t, *J* = 9.9 Hz, 1H, H-2), 4.99 (dd, *J* = 10.0, 3.4 Hz, 1H, H-3), 4.57 (d, *J* = 9.9 Hz, 1H, H-1), 4.11 (dd, *J* = 11.4, 6.9 Hz, 1H, H-6a), 4.05 (dd, *J* = 11.4, 6.3 Hz, 1H, H-6b), 3.91 – 3.87 (m, 1H, H-5), 3.35 (dq, *J* = 15.4, 9.7 Hz, 1H, SC*H*H), 3.08 (dq, *J* = 15.4, 10.0 Hz, 1H, SC*H*H), 2.10 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.98 (s, 3H OAc), 1.92 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (C=O, Ac), 170.1 (C=O, Ac), 170.0 (C=O, Ac) 169.7 (C=O, Ac), 125.2 (q, $^1J_{C\text{-}F}$ = 276.2 Hz, CF_3), 82.8 (C1), 74.8 (C5), 71.6 (C3), 67.5 (C2), 67.1 (C4), 61.4 (C6), 31.7 (q, $^2J_{C\text{-}F}$ = 33.7 Hz, CH_2), 20.64 (Ac-CH_3), 20.62 (Ac-CH_3), 20.58 (Ac-CH_3), 20.5 (Ac-CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.19 (t, *J* = 9.8 Hz); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 464.1187, $C_{16}H_{25}F_3O_9SN$ requires M^+ 464.1202].

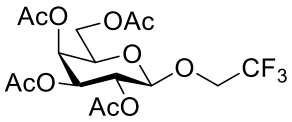
Trifluoroethyl 1-thio-β-D-galactopyranoside 137



Following the general deacetylation procedure, trifluoroethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside **133** (740 mg, 1.66 mmol, 1.0 equiv.) was deprotected using Na (3.82 mg, 0.166 mmol, 0.1 equiv.) in MeOH (5 mL), following column

chromatography (DCM/MeOH, 0-20%) the title compound was obtained as a colourless oil (398 mg, 1.43 mmol, 86%). R_f = 0.35 (DCM/MeOD, 8:2); $[\alpha]_D^{23}$ = -6.5 (*c* = 1.0, H_2O); ^{1}H NMR (400 MHz, MeOD) δ 4.45 (d, *J* = 9.3 Hz, 1H, H-1), 3.88 (dd, *J* = 3.2, 1.0 Hz, 1H, H-4), 3.77 (dd, *J* = 11.5, 7.1 Hz, 1H, H-6a), 3.69 (dd, *J* = 11.5, 4.9 Hz, 1H, H-6b), 3.65 – 3.56 (m, 1H, SC*H*H), 3.56 – 3.49 (m, 2H, H-2, H-5), 3.46 (dd, *J* = 9.2, 3.3 Hz, 1H, H-3), 3.39 – 3.32 (m, 1H, SC*H*H); ^{13}C NMR (101 MHz, MeOD) δ 126.1 (q, $^1J_{C\text{-}F}$ = 284.4 Hz, CF_3), 84.6 (C1), 79.5 (C5), 74.7 (C3), 70.6 (C2), 69.1 (C4), 61.3 (C6), 30.1 (q, $^2J_{C\text{-}F}$ = 32.9 Hz, CH_2); ^{19}F NMR (376 MHz, MeOD) δ -67.8 (t, *J* = 10.4 Hz); HRMS *m/z* (ES^+) [Found: $(M+Na)^+$ 301.0322, $C_8H_{13}F_3O_5SNa$ requires $C_8H_{13}F_3O_5SNa$ M^+ 301.0333].

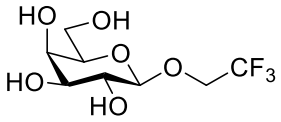
Trifluoroethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside 131



1,2,3,4,6-Penta-*O*-acetyl-α/β-D-galactopyranoside (2.00 g, 5.12 mmol, 1.0 equiv.) was dissolved in DCM (10 mL) and 33% (*w/v*) HBr in acetic acid (5 mL) 33% (*w/v*) added dropwise at 0 °C. The mixture was allowed to reach RT and stirred until complete consumption of the starting material, as seen by TLC (R_f = 0.23, hexane/EtOAc, 7:3). The reaction mixture was diluted with DCM (100 mL) and washed successively with sat. aq. $NaHCO_3$ (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to deliver 1-bromo-2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranoside as a colourless oil which was used in the next step without further purification. To the glycosyl bromide was added trifluoroethanol (405 µL, 5.63 mmol, 1.1 equiv.) followed by silver triflate (1.32 g, 5.12 mmol, 1.0 equiv.) and silver carbonate (1.41 g, 5.12 mmol, 1.0 equiv.). The suspension was stirred for 20 hrs at RT, TLC analysis revealed reaction completion (R_f = 0.44, hexane/EtOAc, 1:1) and the reaction mixture

was diluted with DCM (50 mL) and filtered through a pad of Celite® to remove the silver salts. The solution was concentrated under reduced pressure, and the crude residue purified by column chromatography (hexane/EtOAc, 0-50%) to yield the title compound as a colourless oil (1.10 g, 2.56 mmol, 50%). R_f = 0.44 (hexane/EtOAc, 1:1); $[\alpha]_D^{23}$ = 14.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (dd, *J* = 3.4, 1.0 Hz, 1H, H-4), 5.24 (dd, *J* = 10.5, 7.9 Hz, 1H, H-2), 5.04 (dd, *J* = 10.5, 3.4 Hz, 1H, H-3), 4.62 (d, *J* = 7.9 Hz, 1H, H-1), 4.22 – 4.06 (m, 3H, H-6a, H-6b, OC*H*H), 4.06 – 3.91 (m, 2H, H-5, OC*H*H), 2.17 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.06 (s, 3H, OAc), 1.99 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (C=O, Ac), 170.14 (C=O, Ac), 170.06 (C=O, Ac), 169.4 (C=O, Ac), 123.4 (q, $^1J_{C\text{-}F}$ = 278.7 Hz, CF_3),101.3 (C1), 71.1 (C5), 70.5 (C3), 68.2 (C2), 66.8 (C4), 65.8 (t, $^2J_{C\text{-}F}$ = 35.0 Hz, CH_2), 61.2 (C6), 20.62 (Ac-CH_3), 20.61 (Ac-CH_3), 20.52 (Ac-CH_3), 20.47 (Ac-CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.44 (t, *J* = 8.5 Hz); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 448.1417, $C_8H_{17}F_3O_6N$ requires M^+ 448.1430].

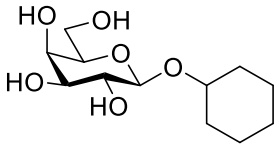
Trifluoroethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside 135



Following the general deacetylation procedure, trifluoroethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside **131** (450 mg, 1.05 mmol, 1.0 equiv.) was deprotected using Na (2.42 mg, 0.105 mmol, 0.1 equiv.) in MeOH (5 mL), following column chromatography (DCM/MeOH, 0-20%) the title compound was obtained as a colourless oil (198 mg, 0.755 mmol, 72%). R_f = 0.30 (DCM/MeOD, 8:2); $[\alpha]_D^{23}$ = -3.7 (*c* = 1.0, H_2O); ^{1}H NMR (400 MHz, MeOD) δ 4.34 (d, *J* = 7.6 Hz, 1H, H-1), 4.26 (dq, *J* = 12.3, 9.1 Hz, 1H, OC*H*H), 4.09 (dq, *J* = 12.3, 8.9 Hz, 1H, OC*H*H), 3.83 (dd, *J* = 3.3, 0.9 Hz, 1H, H-4), 3.78 (dd, *J* = 11.4, 7.1 Hz, 1H, H-6a), 3.72 (dd, *J* = 11.4, 5.0 Hz, 1H, H-6b), 3.58 – 3.51 (m, 2H, H-2, H-5), 3.47 (dd, *J* = 9.7, 3.4 Hz, 1H, H-3); ^{13}C NMR (101 MHz, MeOD) δ 124.1

(q, $^{1}J_{C\text{-}F}$ = 277.1 Hz, CF_3), 103.4 (C1), 75.6 (C5), 73.4 (C3), 70.8 (C2), 68.8 (C4), 65.1 (q, ^{2}J = 34.7 Hz, CH_2), 61.1 (C6); ^{19}F NMR (376 MHz, MeOD) δ -75.7 (t, *J* = 9.0 Hz); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 280.0994, $C_8H_{17}F_3O_6N$ requires M^+ 280.1007].

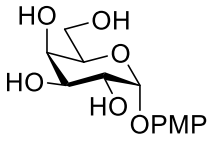
Cyclohexyl β-D-galactopyranoside 136



1,2,3,4,6-Penta-*O*-acetyl-α/β-D-galactopyranoside (2.00 g, 5.12 mmol, 1.0 equiv.) was dissolved in DCM (10 mL) and HBr in acetic acid (5 mL) 33% (*w/v*) added dropwise at 0 °C. The mixture was allowed to reach RT and stirred until complete consumption of the starting material, as seen by TLC (R_f = 0.23, hexane/EtOAc, 7:3). The reaction mixture was diluted with DCM (100 mL) and washed successively with sat. aq. $NaHCO_3$ (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to deliver 1-bromo-2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranoside as a colourless oil which was used in the next step without further purification. To the glycosyl bromide was added cyclohexanol (20 mL, 189 mmol, 36.8 equiv.) followed by silver triflate (1.32 g, 5.12 mmol, 1.0 equiv.) and silver carbonate (1.41 g, 5.12 mmol, 1.0 equiv.). The suspension was stirred for 20 hrs at RT, TLC analysis revealed reaction completion (R_f = 0.75, hexane/EtOAc, 1:1) and the reaction mixture was diluted with DCM (50 mL) and filtered through a pad of Celite® to remove the silver salts. The solution was concentrated, and the crude residue purified by column chromatography (hexane/EtOAc, 0-50%) to yield cyclohexyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (1.62 g, 3.76 mmol, 73%) as a colourless oil. Following the general deacetylation procedure, cyclohexyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (435 mg, 1.01 mmol, 1.0 equiv.) was deprotected using Na (2.32 mg, 0.101 mmol, 0.1 equiv.)

in MeOH (5 mL), following column chromatography (DCM/MeOH, 0-20%) the title compound was obtained as a white solid (215 mg, 0.818 mmol, 81%). R_f = 0.45 (DCM/MeOD, 8:2); ^{1}H NMR (400 MHz, MeOD) δ 4.32 (d, *J* = 7.3 Hz, 1H, H-1), 3.86 – 3.80 (m, 1H), 3.78 – 3.65 (m, 3H, H-6a, H-6b, C*H*), 3.54 – 3.41 (m, 3H), 1.94 (s, 2H, CH_2), 1.85 – 1.68 (m, 2H, CH_2), 1.60 – 1.50 (m, 1H, C*H*H), 1.40 – 1.21 (m, 5H, 2 × CH_2, C*H*H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 105.6 (C1), 80.8, 79.1, 77.6, 75.2, 72.8, 65.0 (C6), 37.3 (CH_2), 35.4 (CH_2), 29.4 (CH_2), 27.8 (CH_2), 27.6 (CH_2); HRMS *m/z* (ES^+) [Found: $(M+Na)^+$ 285.1308, $C_{12}H_{22}O_6Na$ requires M^+ 285.1314]. Data matched those reported previously.[190]

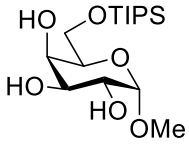
p-Methoxy phenyl-α-D-galactopyranoside 153



1,2,3,4,6-Penta-*O*-acetyl-α/β-D-galactopyranoside (2.31 g, 5.92 mmol, 1.0 equiv.) was dissolved in DCM (25 mL), *p*-methoxy phenol (634 mg, 5.92 mmol, 1.0 equiv.) and $SnCl_4$ (677 µL, 5.92 mmol, 1.0 equiv.) were then added. The mixture was stirred at RT until reaction completion, as seen by TLC (R_f = 0.36, hexane/EtOAc, 7:3). The reaction mixture was diluted with DCM (100 mL) and washed successively with sat. aq. $NaHCO_3$ (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure and the crude residue was purified by column chromatography (hexane/EtOAc, 0-30%) yielding *p*-methoxy phenyl 2,3,4,6-tetra-*O*-acteyl-α-D-galactopyranoside (1.22 g, 2.68 mmol, 45%) as a white foam. R_f = 0.36 (hexane/EtOAc, 7:3). Following the general deacetylation procedure, *p*-methoxy phenyl 2,3,4,6-tetra-*O*-acteyl-α-D-galactopyranoside (858 mg, 1.89 mmol, 1.0 equiv.) was deprotected using Na (4.34 mg, 0.189 mmol, 0.1 equiv.) in MeOH (5 mL), following column chromatography (DCM/MeOH, 0-20%) the title compound was obtained as a

white solid (452 mg, 1.58 mmol, 84%). R_f = 0.63 (DCM/MeOH, 8:2); ^{1}H NMR (400 MHz, MeOD) δ 7.12 – 7.07 (m, 2H, Ar*H*), 6.86 – 6.80 (m, 2H, Ar*H*), 5.34 (d, *J* = 2.9 Hz, 1H, H-1), 4.01 – 3.94 (m, 2H, H-4, H-5), 3.94 – 3.91 (m, 2H, H-2, H-3), 3.73 (s, 3H, OMe), 3.74 – 3.70 (m, 1H, H-6b), 3.68 (dd, *J* = 9.7, 4.9 Hz, 1H, H-6a); ^{13}C NMR (101 MHz, MeOD) δ 155.3 (Ar-C), 151.5 (Ar-C), 118.5 (Ar-C), 114.1 (Ar-C), 99.4 (C1), 71.6, 70.0, 69.5, 68.7, 61.1 (C6), 54.7 (CH_3); HRMS *m/z* (ES^-) [Found: $(M-H)^-$ 285.0981, $C_{13}H_{17}O_7$ requires M^- 285.0980].

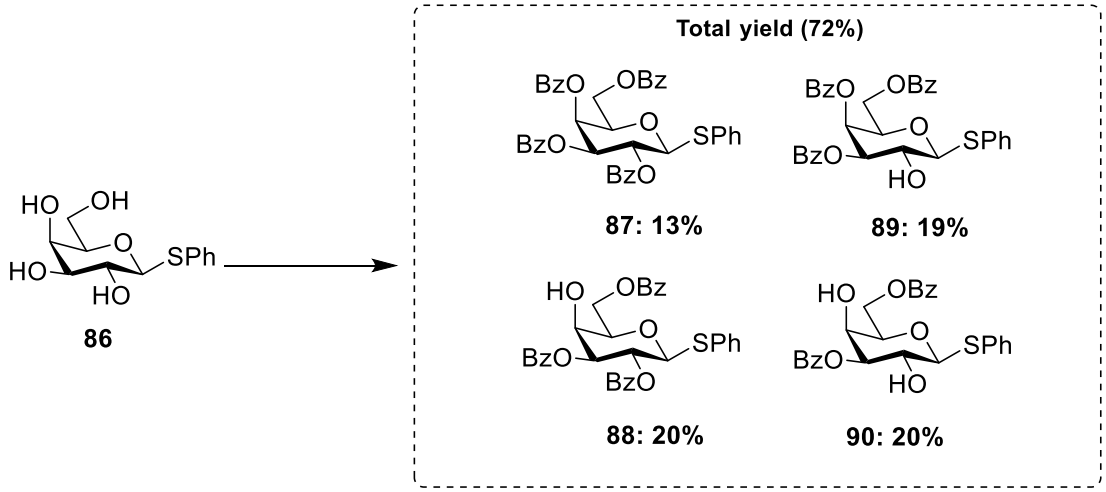
Methyl 6-*O*-TIPS-α-D-galactopyranoside 151



A solution of methyl α-D-galactopyranoside (250 mg, 1.29 mmol, 1.0 equiv.) and imidazole (176 mg, 2.58 mmol, 2.0 equiv.) in pyridine (20 mL) was treated with TIPSCl (552 µL, 2.58 mmol, 2.0 equiv.) and the solution stirred at RT for 24 hrs. At this point TLC analysis revealed complete conversion to another spot (R_f = 0.22 (hexane/EtOAc, 1:1) and the reaction was quenched with MeOH (5 mL). The solution was diluted with DCM (100 mL), washed with 1M HCl (2 x 75 mL), sat. aq. $NaHCO_3$ (100 mL) and water (75 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-60%) to deliver the title compound (375 mg, 1.07 mmol, 83%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (d, *J* = 3.9 Hz, 1H, H-1), 4.12 – 4.10 (m, 1H, H-4), 3.99 (dd, *J* = 10.4, 5.6 Hz, 1H, H-6b), 3.93 (dd, *J* = 10.3, 5.0 Hz, 1H, H-6a), 3.87 (bs, 1H, H-2), 3.79 – 3.72 (m, 2H, H-3, H-5), 3.42 (s, 3H, OMe), 3.31 (bs, 1H, 4-OH), 3.20 (bs, 1H, 3-OH), 2.56 (bs, 1H, 2-OH), 1.10 – 1.03 (m, 21H, ^{i}PrSi); ^{13}C NMR (101 MHz, $CDCl_3$) δ 99.6 (C1), 71.4 (C3), 70.0 (C5), 69.79 (C2), 69.76 (C4), 63.6, (C6),

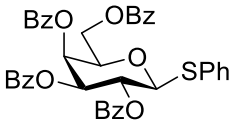
55.4 (CH_3), 17.91 (CH_3, ^{i}Pr), 17.89 (CH_3, ^{i}Pr), 11.8 (CH_3, ^{i}Pr); HRMS *m/z* (ES^-) [Found: $(M-H)^-$ 349.2056, $C_{16}H_{33}O_6Si$ requires M^- 349.2052]. Data matched those reported previously.[191]

Benzoylation of phenyl 1-thio-β-D-galactopyranoside 86



Following the general benzoylation procedure, phenyl 1-thio-β-D-galactopyranoside **86** (74.0 mg, 0.272 mmol, 1.0 equiv.) and BzCl (98.0 µL, 0.843 mmol, 3.1 equiv.) were reacted. Purification by column chromatography (hexane/EtOAc, 0-30%) yielded the below compounds in a total yield of 72%.

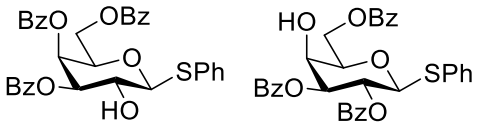
Phenyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-galactopyranoside 87



87 (25.3 mg, 36.7 µmol, 13%) as a colourless oil. R_f = 0.48 (hexane/EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.96 (m, 4H, Ar*H*), 7.92 – 7.88 (m, 2H, Ar*H*), 7.79 – 7.72 (m, 2H, Ar*H*), 7.65 – 7.52 (m, 5H, Ar*H*), 7.49 – 7.33 (m, 8H, Ar*H*), 7.30 – 7.20 (m, 4H, Ar*H*), 6.00 (ad, *J* = 2.6 Hz, 1H, H-4), 5.76 (t, *J* = 9.9 Hz, 1H, H-2), 5.60 (dd, *J* = 9.9, 3.3 Hz, 1H, H-3), 5.04 (d, *J* = 9.9 Hz, 1H, H-1), 4.65 (dd, *J* = 11.1, 6.7 Hz, 1H, H-6b),

4.49 – 4.38 (m, 2H, H-5, H-6a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1 (C=O, Bz), 165.5 (C=O, Bz), 165.4 (C=O, Bz), 165.2 (C=O, Bz), 134.0 (Ar-C), 133.6 (Ar-C), 133.4 (Ar-C), 133.30 (Ar-C), 133.28 (Ar-C), 131.2 (Ar-C), 130.0 (Ar-C), 129.83 (Ar-C), 129.78 (Ar-C), 129.4 (Ar-C), 129.3 (Ar-C), 128.90 (Ar-C), 128.86 (Ar-C), 128.7 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 128.3 (Ar-C), 85.6 (C1), 75.1 (C5), 73.0 (C3), 68.3 (C4), 67.9 (C2), 62.5 (C6); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 706.2110, $C_{40}H_{36}O_1NS$ requires M^+ 706.2105]. Data matched those reported previously.[192]

Phenyl 3,4,6-tri-*O*-benzoyl-1-thio-β-D-galactopyranoside 89 & phenyl 2,3,6-tri-*O*-benzoyl-1-thio-β-D-galactopyranoside 88

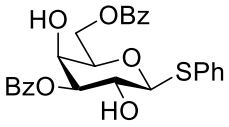


89: 19% **88: 20%**

89/88 were isolated as an inseparable mixture appearing as a white foam (61.2 mg, 0.105 mmol, **89/88**, 1:1.07); ratio determined from ^{1}H NMR integration values. R_f = 0.35 (hexane/EtOAc, 7:3); The following were observed for both regioisomers **89** and **88**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 7.95 (m, 9H, Ar*H*), 7.89 – 7.86 (m, 2H, Ar*H*), 7.83 – 7.79 (m, 2H, Ar*H*), 7.69 – 7.65 (m, 2H, Ar*H*), 7.62 – 7.52 (m, 4H, Ar*H*), 7.50 – 7.27 (m, 20H, Ar*H*), 7.20 – 7.14 (m, 2H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.9 (Ar-C), 133.6 (Ar-C), 133. 55 (Ar-C), 133.54 (Ar-C), 133.4 (Ar-C), 133.31 (Ar-C), 133.29 (Ar-C), 132.9 (Ar-C), 132.4 (Ar-C), 130.7 (Ar-C), 130.1 (Ar-C), 129.94 (Ar-C), 129.90 (Ar-C), 129.8 (×Ar-C), 129.7 (Ar-C), 129.6 (Ar-C), 129.5 (Ar-C), 129.4 (Ar-C), 129.2 (Ar-C), 129.14 (Ar-C), 129.07 (Ar-C), 128.94 (Ar-C), 128.91 (Ar-C), 128.6 (Ar-C), 128.50 (Ar-C), 128.46 (Ar-C), 128.44 (Ar-C), 128.42 (Ar-C), 128.3 (Ar-C), 128.0 (Ar-C); **89:** ^{1}H NMR (400 MHz, $CDCl_3$) 5.91 (dd, *J* = 3.3, 0.8 Hz, 1H, H-4), 5.42 (dd, *J* = 9.7, 3.3 Hz, 1H, H-3), 4.77 (d, *J* = 9.6 Hz, 1H, H-1), 4.62 (dd, *J* = 11.3, 6.8 Hz, 1H, H-6b), 4.39 (dd, *J* = 11.3, 5.9 Hz, 1H, H-6a), 4.31 (t, *J* = 6.4 Hz, 1H, H-5), 4.06 (t, *J* = 9.6 Hz, 1H, H-

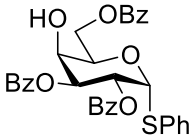
2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0 (C=O, Bz), 165.9 (C=O, Bz), 165.3 (C=O, Bz), 88.2 (C1), 75.1 (C5), 74.6 (C3), 68.6 (C4), 67.5 (C2), 62.5 (C6); **88:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (t, *J* = 10.0 Hz, 1H, H-2), 5.39 (dd, *J* = 9.9, 3.1 Hz, 1H, H-3), 4.99 (d, *J* = 10.1 Hz, 1H, H-1), 4.72 – 4.56 (m, 2H, H-6a, H-6b), 4.44 – 4.40 (m, 1H, H-4), 4.16 – 4.12 (m, 1H, H-5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (C=O, Bz), 165.8 (C=O, Bz), 165.4 (C=O, Bz), 86.9 (C1), 76.3 (C5), 75. (C3), 67.9 (C2), 67.6 (C4), 63.4 (C6); HRMS *m/z* (ES^+) [Found: $(M+Na)^+$ 607.1390, $C_{33}H_{28}O_8NaS$ requires M^+ 607.1397].

Phenyl 3,6-di-*O*-benzoyl-1-thio-β-D-galactopyranoside 90



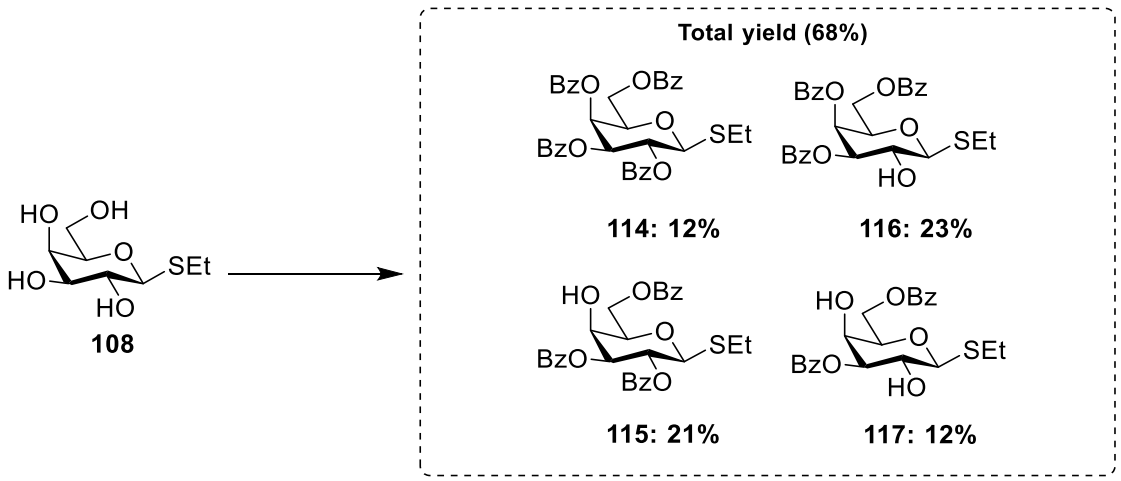
90 (26.5 mg, 55.1 μmmol, 20%) as a white foam. R_f = 0.25 (hexane/EtOAc, 7:3); $[\alpha]_D^{23}$ = 12.4 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 7.98 (m, 4H, Ar*H*), 7.64 – 7.57 (m, 4H, Ar*H*), 7.51 – 7.39 (m, 4H, Ar*H*), 7.30 – 7.18 (m, 3H, Ar*H*), 5.18 (dd, *J* = 9.6, 3.2 Hz, 1H, H-3), 4.71 (d, *J* = 9.7 Hz, 1H, H-1), 4.66 (dd, *J* = 11.6, 5.8 Hz, 1H, H-6b), 4.57 (dd, *J* = 11.6, 6.9 Hz, 1H, H-6a), 4.27 (s, *J* = 14.8 Hz, 1H, H-4), 4.14 – 4.00 (m, 2H, H-2, H-5);^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (C=O, Bz), 166.1 (C=O, Bz), 133.6 (Ar-C), 133.4 (Ar-C), 132.6 (Ar-C), 132.1 (Ar-C), 129.9 (Ar-C), 129.8 (Ar-C), 129.6 (Ar-C), 129.4 (Ar-C), 129.1 (Ar-C), 128.53 (Ar-C), 128.49 (Ar-C), 128.2 (Ar-C), 89.4 (C1), 76.6 (C3), 76.2 (C5), 67.6 (C4), 67.5 (C2), 63.1 (C6); HRMS *m/z* (ES^-) [Found: $(M-H^-)$ 479.1175, $C_{26}H_{23}O_7S$ requires M^- 479.1170}.

Phenyl 2,3,6-tri-*O*-benzoyl-1-thio-α-D-galactopyranoside 119



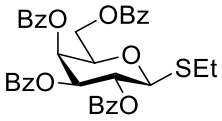
Following the general benzoylation procedure, phenyl 1-thio-α-D-galactopyranoside **107** (194 mg, 0.712 mmol, 1.0 equiv.) and BzCl (257 µL, 2.21 mmol, 3.1 equiv.) were reacted. Purification by column chromatography (hexane/EtOAc, 0-30%) yielded the title compound (325 mg, 0.556 mmol, 78%) as a white foam. R_f = 0.63 (hexane/EtOAc, 7:3); $[\alpha]_D^{23}$ = 119.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.99 (m, 4H, Ar*H*), 7.97 – 7.93 (m, 2H, Ar*H*), 7.58 – 7.50 (m, 3H, Ar*H*), 7.46 – 7.35 (m, 8H, Ar*H*), 7.18 – 7.07 (m, 3H, Ar*H*), 6.16 (d, *J* = 5.7 Hz, 1H, H-1), 5.97 (dd, *J* = 10.8, 5.7 Hz, 1H, H-2), 5.70 (dd, *J* = 10.8, 3.1 Hz, 1H, H-3), 4.94 (dd, *J* = 6.9, 5.4 Hz, 1H, H-5), 4.67 (dd, *J* = 11.7, 4.9 Hz, 1H, H-6b), 4.56 (dd, *J* = 11.7, 7.5 Hz, 1H, H-6a), 4.47 (d, *J* = 2.1 Hz, 1H, H-4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (C=O, Bz), 165.74 (C=O, Bz), 165.7 (C=O, Bz), 133.6 (Ar-C), 133.5 (Ar-C), 133.2 (Ar-C), 132.8 (Ar-C), 132.0 (Ar-C), 130.0 (Ar-C), 129.9 (Ar-C), 129.8 (Ar-C), 129.6 (Ar-C), 129.2 (Ar-C), 129.1 (Ar-C), 129.0 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 127.5 (Ar-C), 86.1 (C1), 71.4 (C3), 69.0 (C5), 68.5 (C2), 68.2 (C4), 63.6 (C6); HRMS *m/z* (ES^+) [Found: $(M+Na)^+$ 607.1392, $C_{33}H_{28}O_8NaS$ requires M^+ 607.1397].

Benzoylation of ethyl 1-thio-β-D-galactopyranoside 108



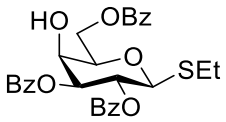
Following the general benzoylation procedure, ethyl 1-thio-β-D-galactopyranoside **108** (117 mg, 0.522 mmol, 1.0 equiv.) and BzCl (188 µL, 1.62 mmol, 3.1 equiv.) were reacted. Purification by column chromatography (hexane/EtOAc, 0-30%) yielded the below compounds in a total yield of 68%.

Ethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-galactopyranoside 114



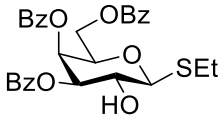
114 (39.1 mg, 61.0 µmmol, 12%) as a white foam. R_f = 0.40 (hexane/EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.07 (m, 2H, Ar*H*), 8.05 – 7.99 (m, 2H, Ar*H*), 7.98 – 7.94 (m, 2H, Ar*H*), 7.79 – 7.76 (m, 2H, Ar*H*), 7.65 – 7.60 (m, 1H Ar*H*), 7.58 – 7.46 (m, 4H, Ar*H*), 7.46 – 7.35 (m, 5H, Ar*H*), 7.25 – 7.21 (m, 2H, Ar*H*), 6.04 (dd, *J* = 3.3, 0.6 Hz, 1H, H-4), 5.84 (t, *J* = 10.0 Hz, 1H, H-2), 5.66 (dd, *J* = 10.0, 3.4 Hz, 1H, H-3), 4.88 (d, *J* = 10.0 Hz, 1H, H-1), 4.67 (dd, *J* = 10.9, 6.2 Hz, 1H, H-6b), 4.44 – 4.35 (m, 2H, H-6a, H-5), 2.92 – 2.76 (m, 2H, C*H*$_2$), 1.32 (t, *J* = 7.4 Hz, 3H, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1 (C=O, Bz), 165.54 (C=O, Bz), 165.53 (C=O, Bz), 165.4 (C=O, Bz), 133.6 (Ar-C), 133.34 (Ar-C), 133.31 (Ar-C), 130.0 (Ar-C), 129.84 (Ar-C), 129.79 (Ar-C), 129.78 (Ar-C), 129.4 (Ar-C), 129.2 (Ar-C), 129.1 (Ar-C), 128.8 (Ar-C), 128.7 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 128.3 (Ar-C), 84.3 (C1), 75.1 (C5), 72.8 (C3), 68.4 (C4), 68.3 (C2), 62.3 (C6), 24.6 (CH_2), 15.0 (CH_3); HRMS *m/z* (ES^+) [Found: $(M+Na)^+$ 663.1659, $C_{36}H_{32}O_9NaS$ requires M^+ 663.1659]. Data matched those reported previously.[193]

Ethyl 2,3,6-tri-*O*-benzoyl-1-thio-β-D-galactopyranoside 115



115 (59.7 mg, 0.111 mmol, 21%) as a white foam. R_f = 0.34 (hexane/EtOAc, 7:3); $[\alpha]_D^{23}$ = 26.9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.03 (m, 2H, Ar*H*), 7.99 – 7.95 (m, 4H, Ar*H*), 7.61 – 7.55 (m, 1H, Ar*H*), 7.53 – 7.42 (m, 4H, Ar*H*), 7.40 – 7.34 (m, 4H, Ar*H*), 5.83 (t, *J* = 10.0 Hz, 1H, H-2), 5.40 (dd, *J* = 9.9, 3.1 Hz, 1H, H-3), 4.76 (d, *J* = 10.0 Hz, 1H, H-1), 4.69 (dd, *J* = 11.5, 6.4 Hz, 1H, H-6b) 4.58 (dd, *J* = 11.5, 6.4 Hz, 1H, H-6a), 4.39 (as, 1H, H-4), 4.10 (dd, *J* = 6.8, 6.1 Hz, 1H, H-5), 2.89 – 2.70 (m, 2H, C*H*$_2$), 1.27 (t, *J* = 7.4 Hz, 3H, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (C=O, Bz), 165.8 (C=O, Bz), 165.5 (C=O, Bz), 133.5 (Ar-C), 133.4 (Ar-C), 133.2 (Ar-C), 129.9 (Ar-C), 129.82 (Ar-C), 129.79 (Ar-C), 129.5 (Ar-C), 129.4 (Ar-C), 129.0 (Ar-C), 128.51 (Ar-C), 128.49 (Ar-C), 128.4 (Ar-C), 84.0 (C1), 76.1 (C5), 75.1 (C3), 67.9 (C2), 67.5 (C4), 62.9 (C6), 24.2 (CH_2), 15.0 (CH_3); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 554.1838, $C_{29}H_{32}O_8NS$ requires M^+ 554.1843]. Data matched those reported previously.[194]

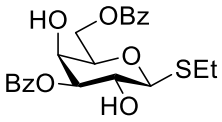
Ethyl 3,4,6-tri-*O*-benzoyl-1-thio-β-D-galactopyranoside 116



116 (65.5 mg, 0.122 mmol, 24%) as a white foam. R_f = 0.28 (hexane/EtOAc, 7:3); $[\alpha]_D^{23}$ = 6.7 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.04 (m, 2H, Ar*H*), 8.04 – 8.00 (m, 2H, Ar*H*), 7.90 – 7.84 (m, 2H, Ar*H*), 7.65 – 7.60 (m, 1H, Ar*H*), 7.58 – 7.53 (m, 1H, Ar*H*), 7.50 – 7.39 (m, 5H, Ar*H*), 7.33 – 7.28 (m, 2H, Ar*H*), 5.95 (dd, *J* = 3.4, 0.8 Hz, 1H, H-4), 5.41 (dd, *J* = 9.6, 3.4 Hz, 1H, H-3), 4.65 (d, *J* = 9.7 Hz, 1H, H-1), 4.62 (dd, *J* = 11.1, 6.6 Hz, 1H, H-6b), 4.36 (dd, *J* = 11.2, 6.4 Hz, 1H, H-6a), 4.28 (dt, *J* = 6.5, 3.2 Hz, 1H, H-5), 4.14 (t, *J* = 9.7 Hz, 1H, H-2), 2.91 – 2.79 (m, 2H, C*H*$_2$), 1.39 (t, *J* = 7.4 Hz, 3H, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1 (C=O, Bz), 165.9 1 (C=O, Bz), 165.5 1 (C=O, Bz), 133.6 (Ar-C), 133.3 (Ar-C), 129.9 (Ar-C), 129.84 (Ar-C), 129.77 (2 × Ar-C),

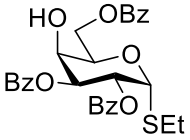
129.44 (Ar-C), 129.28 (Ar-C), 129.25 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 128.3 (Ar-C), 87.2 (C1), 75.0 (C5), 74.3 (C3), 68.51 (C4), 68.45 (C2), 62.3 (C6), 25.1 (CH_2), 15.4 (CH_3); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 554.1838, $C_{29}H_{32}O_8NS$ requires M^+ 554.1843].

Ethyl 3,6-di-*O*-benzoyl-1-thio-β-D-galactopyranoside 117



117 (27.9 mg, 64.5 µmmol, 12%) as a white foam. R_f = 0.22 (hexane/EtOAc, 7:3); $[\alpha]_D^{23}$ = 0.20 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.08 (m, 2H, Ar*H*), 8.05 – 8.01 (m, 2H, Ar*H*), 7.62 – 7.55 (m, 2H, Ar*H*), 7.50 – 7.40 (m, 4H, Ar*H*), 5.17 (dd, *J* = 9.6, 3.2 Hz, 1H, H-3), 4.65 (dd, *J* = 11.5, 6.6 Hz, 1H, H-6b), 4.55 – 4.50 (m, 1H, H-6a), 4.52 (d, *J* = 9.6 Hz, 1H, H-1), 4.27 (as, 1H, H-4), 4.11 – 4.05 (m, 1H, H-2), 4.01 (dd, *J* = 6.9, 6.1 Hz, 1H, H-5), 2.89 – 2.72 (m, 2H, C*H*$_2$), 1.34 (t, *J* = 7.4 Hz, 1H, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (C=O, Bz), 166.1 (C=O, Bz), 133.5 (Ar-C), 133.4 (Ar-C), 129.9 (Ar-C), 129.8 (Ar-C), 129.50 (Ar-C), 129.48 (Ar-C), 128.52 (Ar-C), 128.47 (Ar-C), 87.1 (C1), 76.5 (C3), 76.1 (C5), 67.9 (C2), 67.5 (C4), 62.8 (C6), 24.9 (CH_2), 15.4 (CH_3); HRMS *m/z* (ES^-) [Found: $(M-H)^-$ 431.1174, $C_{22}H_{23}O_7S$ requires M^- 431.1170].

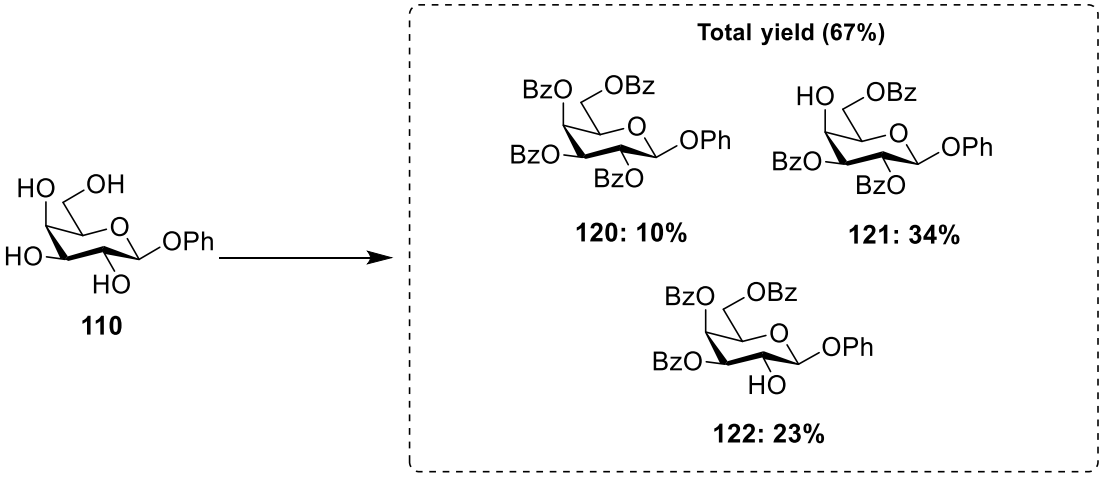
Ethyl 2,3,6-tetra-*O*-benzoyl-1-thio-α-D-galactopyranoside 118



Following the general benzoylation procedure, ethyl 1-thio-α-D-galactopyranoside **109** (111 mg, 0.495 mmol, 1.0 equiv.) and BzCl (178 µL, 1.53 mmol, 3.1 equiv.) were reacted. Purification by column chromatography (hexane/EtOAc, 0-30%) yielded the title

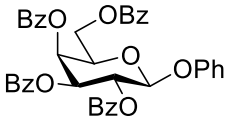
compound (236 mg, 0.440 mmol, 89%) as white foam. R_f = 0.58 (hexane/EtOAc, 7:3); $[\alpha]_D^{24}$ = 181.4 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.95 (m, 6H, Ar*H*), 7.60 – 7.55 (m, 1H, Ar*H*), 7.54 – 7.49 (m, 2H, Ar*H*), 7.47 – 7.41 (m, 2H, Ar*H*), 7.41 – 7.35 (m, 4H, Ar*H*), 5.93 (d, *J* = 5.8 Hz, 1H, H-1), 5.88 (dd, *J* = 10.3, 5.8 Hz, 1H, H-2), 5.64 (dd, *J* = 10.3, 3.2 Hz, 1H, H-3), 4.78 (t, *J* = 6.3 Hz, 1H, H-5), 4.70 (dd, *J* = 11.5, 5.4 Hz, 1H, H-6b), 4.57 (dd, *J* = 11.5, 7.0 Hz, 1H, H-6a), 4.42 (d, *J* = 2.4 Hz, 1H, H-4), 2.67 – 2.50 (m, 2H, C*H*$_2$), 1.22 (t, *J* = 7.4 Hz, 3H, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (C=O, Bz), 165.7 (C=O, Bz), 165.6 (C=O, Bz), 133.5 (Ar-C), 133.4 (Ar-C), 133.3 (Ar-C), 129.9 (Ar-C), 129.8 (Ar-C), 129.7 (Ar-C), 129.6 (Ar-C), 129.19 (Ar-C), 129.18 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 82.2 (C1), 71.4 (C3), 68.4 (C2), 68.14 (C4), 68.12 (C5), 63.3 (C6), 23.9 (CH_2), 14.6 (CH_3); HRMS *m/z* (ES^+) [Found: $(M+H)^+$ 537.1572, $C_{29}H_{29}O_8S$, requires M^+ 537.1578].

Benzoylation of Phenyl β-D-galactopyranoside 110



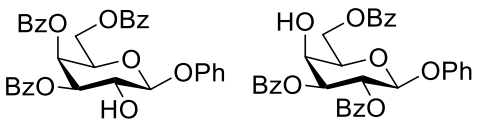
Following the general benzoylation procedure, phenyl β-D-galactopyranoside **110** (78.0 mg, 0.304 mmol, 1.0 equiv.) and BzCl (110 µL, 0.943 mmol, 3.1 equiv.) were reacted. Purification by column chromatography (hexane/EtOAc, 0-30%) yielded the below compounds in a total yield of 67%.

Phenyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside 120



120 (20.6 mg, 30.6 umol, 10%) as a colourless oil. R_f = 0.48 (hexane/EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.10 (m, 4H, Ar*H*), 8.08 – 8.02 (m, 2H, Ar*H*), 7.99 – 7.93 (m, 2H, Ar*H*), 7.85 – 7.76 (m, 2H, Ar*H*), 7.72 – 7.64 (m, 1H, Ar*H*), 7.64 – 7.56 (m, 2H, Ar*H*), 7.56 – 7.43 (m, 6H, Ar*H*), 7.39 – 7.32 (m, 2H, Ar*H*), 7.24 – 7.12 (m, 2H, Ar*H*), 7.09 – 6.96 (m, 2H, Ar*H*), 6.08 (dd, *J* = 10.4, 8.0 Hz, 1H, H-2), 6.05 (dd, *J* = 3.4, 0.7 Hz, 1H, H-4), 5.69 (dd, *J* = 10.4, 3.5 Hz, 1H, H-3), 5.38 (d, *J* = 8.0 Hz, 1H, H-1), 4.67 (dd, *J* = 11.3, 7.5 Hz, 1H, H-6b), 4.55 (dd, *J* = 11.3, 5.4 Hz, 1H, H-6a), 4.52 – 4.47 (m, 1H, H-5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0 (C=O, Bz), 165.57 (C=O, Bz), 165.56 (C=O, Bz), 165.3 (C=O, Bz), 157.1 (Ar-C), 134.5 (Ar-C), 133.7 (Ar-C), 133.4 (Ar-C), 133.3 (Ar-C), 130.6 (Ar-C), 130.1 (Ar-C), 129.83 (Ar-C), 129.80 (Ar-C), 129.76 (Ar-C), 129.5 (Ar-C), 129.4 (Ar-C), 129.2 (Ar-C), 128.9 (Ar-C), 128.7 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 128.3 (Ar-C), 123.3 (Ar-C), 117.3 (Ar-C), 100.2 (C1), 71.8 (C3), 71.7 (C5), 69.5 (C2), 68.0 (C4), 62.3 (C6); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 690.2340, $C_{40}H_{36}O_{10}N$ requires M^+ 690.2334]. Data matched those reported previously.[195]

Phenyl 3,4,6-tri-*O*-benzoyl-β-D-galactopyranoside 122 & phenyl 2,3,6-tri-*O*-benzoyl-β-D-galactopyranoside 121

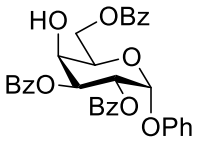


122: 23% **121: 34%**

122/121 were isolated as an inseparable mixture appearing as a colourless oil (98.6 mg, 0.173 mmol, **122/121**, 0.33:1.00); ratio determined from ^{1}H NMR integration values. The

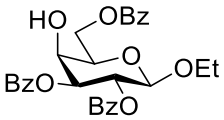
following were observed for both regio-isomers **122** and **121**: R_f = 0.38 (hexane/EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 7.92 (m, 7H, Ar*H*), 7.91 – 7.84 (m, 0.5H, Ar*H*), 7.63 – 7.55 (m, 1.5H, Ar*H*), 7.51 – 7.41 (m, 5.5H, Ar*H*), 7.40 – 7.27 (m, 4.5H, Ar*H*), 7.24 – 7.21 (m, 1H, Ar*H*), 7.18 – 7.11 (m, 2.5H, Ar*H*), 7.11 – 6.91 (m, 3.5H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.7 (Ar-C), 133.6 (Ar-C), 133.4 (Ar-C), 133.33 (Ar-C), 133.27 (Ar-C), 130.03 (Ar-C), 129.95 (2 × Ar-C), 129.86 (Ar-C), 129.81 (2 × Ar-C), 129.77 (Ar-C), 129.61 (Ar-C), 129.60 (Ar-C), 129.48 (Ar-C), 129.45 (2 × Ar-C), 129.4 (Ar-C), 129.2 (Ar-C), 129.1 (Ar-C), 128.9 (Ar-C), 128.64 (Ar-C), 128.55 (Ar-C), 128.51 (2 × Ar-C), 128.49 (Ar-C), 128.41 (Ar-C), 128.35 (Ar-C), 123.23 (Ar-C), 123.20 (Ar-C), 117.32 (Ar-C), 116.99 (Ar-C); **121:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (dd, *J* = 10.3, 8.0 Hz, 1H, H-2), 5.43 (dd, *J* = 10.3, 3.2 Hz, 1H, H-3), 5.28 (d, *J* = 8.0 Hz, 1H, H-1), 4.75 (dd, *J* = 11.6, 5.4 Hz, 1H, H-6b), 4.66 (dd, *J* = 11.6, 7.4 Hz, 1H, H-6a), 4.43 – 4.38 (m, 1H, H-4), 4.26 – 4.21 (m, 1H, H-5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (C=O, Bz), 165.9 (C=O, Bz), 165.4 (C=O, Bz), 100.0 (C1), 74.1 (C3), 72.8 (C5), 69.3 (C4), 67.3 (C2), 63.0 (C6); **122:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (dd, *J* = 3.5, 0.8 Hz, 1H, H-4), 5.50 (dd, *J* = 10.1, 3.5 Hz, 1H, H-3), 5.16 (d, *J* = 7.8 Hz, 1H, H-1), 4.61 (dd, *J* = 11.3, 7.6 Hz, 1H, H-6b), 4.48 (dd, *J* = 11.4, 5.4 Hz, 1H, H-6a), 4.45 – 4.43 (m, 2H, H-2, H-5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0 (2 × C=O, Bz), 165.5 (C=O, Bz), 101.5 (C1), 73.3 (C3), 71.7 (C2), 69.7 (C5), 68.1 (C4), 62.4 (C6); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 586.2079, $C_{33}H_{32}O_9N$ requires M^+ 586.2072].

Phenyl 2,3,6-tri-*O*-benzoyl-*α*-D-galactopyranoside 123



Following the general benzoylation procedure, phenyl α-D-galactopyranoside **111** (137 mg, 0.534 mmol, 1.0 equiv.) and BzCl (192 µL, 1.66 mmol, 3.1 equiv.) were reacted. Purification by column chromatography (hexane/EtOAc, 0-30%) yielded the title compound (237 mg, 0.417 mmol, 78%) as a colourless oil. R_f = 0.39 (hexane/EtOAc, 7:3); $[\alpha]_D^{24}$ = 117.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.09 (m, 1H, Ar*H*), 8.06 – 7.96 (m, 4H, Ar*H*), 7.92 – 7.86 (m, 2H, Ar*H*), 7.60 – 7.45 (m, 4H, Ar*H*), 7.38 (dd, *J* = 10.7, 4.7 Hz, 4H, Ar*H*), 7.23 – 7.18 (m, 2H, Ar*H*), 7.15 – 7.09 (m, 2H, Ar*H*), 7.04 – 6.95 (m, 1H, Ar*H*), 6.01 – 5.95 (m, 2H, H-2, H-3), 5.98 (d, *J* = 3.7 Hz, 1H, H-1), 5.90 (dd, *J* = 10.7, 3.5 Hz, 1H, H-2), 4.66 – 4.55 (m, 3H, H-5, H-6b, H-6a), 4.50 (d, *J* = 3.0 Hz, 1H, H-4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (C=O, Bz), 166.1 (C=O, Bz), 165.9 (C=O, Bz), 133.5 (Ar-C), 133.38 (Ar-C), 133.35 (Ar-C), 133.2 (Ar-C), 130.1 (Ar-C), 129.9 (Ar-C), 129.8 (Ar-C), 129.6 (Ar-C), 129.5 (Ar-C), 129.24 (Ar-C), 129.22 (Ar-C), 128.5 (Ar-C), 128.44 (Ar-C), 128.42 (Ar-C), 128.35 (Ar-C), 122.8 (Ar-C), 95.5 (C1), 80.0 (C3), 68.9 (C5), 68.4 (C2), 68.1 (C4), 63.5 (C6); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 586.2073, $C_{33}H_{32}O_9N$ requires M^+ 586.2072].

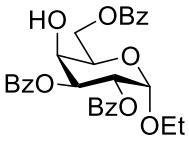
Ethyl 2,3,6-tri-*O*-benzoyl-β-D-galactopyranoside 125



Following the general benzoylation procedure, ethyl β-D-galactopyranoside **112** (66.0 mg, 0.317 mmol, 1.0 equiv.) and BzCl (114 µL, 0.983 mmol, 3.1 equiv.) were reacted. Purification by column chromatography (hexane/EtOAc, 0-30%) yielded the title compound (115 mg, 0.221 mmol, 70%) as a colourless oil.as a colourless oil. R_f = 0.38 (hexane/EtOAc, 7:3); $[\alpha]_D^{24}$ = 26.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.04 (m, 2H, Ar*H*), 8.01 – 7.95 (m, 4H, Ar*H*), 7.62 – 7.55 (m, 1H, Ar*H*), 7.55 – 7.49 (m, 2H, Ar*H*), 7.48 – 7.43 (m, 2H, Ar*H*), 7.41 – 7.36 (m, 4H, Ar*H*), 5.75 (dd, *J* = 10.3,

7.9 Hz, 1H, H-2), 5.35 (dd, *J* = 10.3, 3.2 Hz, 1H, H-3), 4.74 (d, *J* = 7.9 Hz, 1H, H-1), 4.70 (dd, *J* = 11.4, 6.6 Hz, 1H, H-6b), 4.61 (dd, *J* = 11.4, 6.4 Hz, 1H, H-6a), 4.35 (dd, *J* = 3.2, 0.7 Hz, 1H, H-4), 4.07 (td, *J* = 6.5, 0.8 Hz, 1H, H-5), 3.96 (dq, *J* = 9.8, 7.1 Hz, 1H, OC*H*H), 3.65 (dq, *J* = 9.8, 7.0 Hz, 1H, OC*H*H), 1.17 (t, *J* = 7.1 Hz, 3H, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (C=O, Bz), 165.9 (C=O, Bz), 165.4 (C=O, Bz), 133.5 (Ar-C), 133.4 (Ar-C), 133.1 (Ar-C), 129.9 (Ar-C), 129.8 (Ar-C), 129.7 (Ar-C), 129.63 (Ar-C), 129.59 (Ar-C), 129.0 (Ar-C), 128.50 (Ar-C), 128.46 (Ar-C), 128.4 (Ar-C), 101.2 (C1), 74.2 (C3), 72.3 (C5), 69.6 (C2), 67.3 (C4), 65.6 (CH_2), 62.7 (C6), 15.1 (CH_3); HRMS m/z (ES^+) [Found: $(M+NH_4)^+$ 538.2073, $C_{29}H_{32}O_9N$ requires M^+ 538.2072].

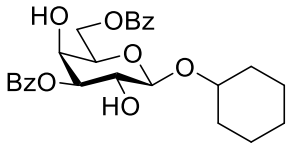
Ethyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside 124



Following the general benzoylation procedure, ethyl α-D-galactopyranoside **113** (32.0 mg, 0.154 mmol, 1.0 equiv.) and BzCl (55.3 µL, 0.476 mmol, 3.1 equiv.) were reacted. Purification by column chromatography (hexane/EtOAc, 0-30%) yielded the title compound (58.5 mg, 0.112 mmol, 73%) as a colourless oil. R_f = 0.40 (hexane/EtOAc, 7:3); $[\alpha]_D^{24}$ = 111.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.96 (m, 6H, Ar*H*), 7.60 – 7.55 (m, 1H, Ar*H*), 7.54 – 7.48 (m, 2H, Ar*H*), 7.48 – 7.42 (m, 2H, Ar*H*), 7.41 – 7.35 (m, 4H, Ar*H*), 5.77 (dd, *J* = 10.7, 3.1 Hz, 1H, H-3), 5.68 (dd, *J* = 10.7, 3.7 Hz, 1H, H-2), 5.32 (d, *J* = 3.7 Hz, 1H, H-1), 4.67 (dd, *J* = 11.4, 6.1 Hz, 1H, H-6b), 4.55 (dd, *J* = 11.4, 6.7 Hz, 1H, H-6a), 4.45 – 4.38 (m, 2H, H-4, H-5), 3.81 (dq, *J* = 9.9, 7.1 Hz, 1H, OC*H*H), 3.56 (dq, *J* = 10.0, 7.0 Hz, 1H, OC*H*H), 1.21 (t, *J* = 7.1 Hz, 3H, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (C=O, Bz), 166.1 (C=O, Bz), 165.8 (C=O, Bz), 133.4 (Ar-C), 133.3 (Ar-C), 133.2 (Ar-C), 129.83 (Ar-C), 129.82 (Ar-C), 129.73 (Ar-C),

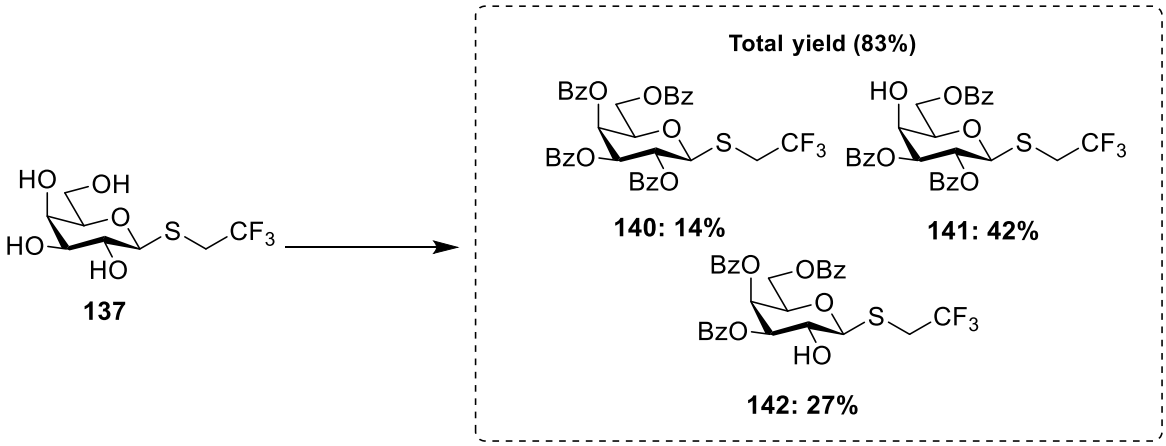
129.67 (Ar-C), 129.5 (Ar-C), 129.4 (Ar-C), 128.49 (Ar-C), 128.47 (Ar-C), 128.4 (Ar-C), 96.4 (C1), 71.0 (C3), 68.9 (C2), 68.2 (C4), 67.7 (C5), 64.1 (CH_2), 63.3 (C6), 15.1 (CH_3); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 538.2071, $C_{29}H_{32}O_9N$ requires M^+ 538.2072].

Cyclohexyl 3,6-di-*O*-benzoyl-β-D-galactopyranoside 146



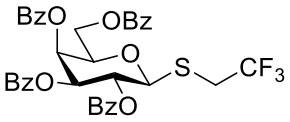
146 (43.2 mg, 91.8 µmol, 25%) as a colourless oil; R_f = 0.26 (hexane/EtOAc, 7:3); $[\alpha]_D^{24}$ = 13.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.98 (m, 2H, Ar*H*), 7.99 – 7.93 (m, 2H, Ar*H*), 7.54 – 7.46 (m, 2H, Ar*H*), 7.42 – 7.32 (m, 4H, Ar*H*), 5.08 (dd, *J* = 10.1, 3.3 Hz, 1H, H-3), 4.60 – 4.47 (m, 2H, H-6a, H-6b), 4.45 (d, *J* = 7.7 Hz, 1H, H-1), 4.19 – 4.13 (m, 1H, H-4), 3.96 (dd, *J* = 10.1, 7.7 Hz, 1H, H-2), 3.89 (td, *J* = 6.5, 0.6 Hz, 1H, H-5), 3.68 – 3.54 (m, 1H, C*H*), 1.98 – 1.80 (m, 2H, CH_2), 1.71 – 1.58 (m, 2H, CH_2), 1.47 – 1.05 (m, 6H, 3 × CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (C=O, Bz), 166.1 (C=O, Bz), 133.6 (Ar-C), 133.4 (Ar-C), 133.3 (Ar-C), 130.2 (Ar-C), 129.9 (Ar-C), 129.7 (Ar-C), 129.6 (Ar-C), 128.5 (Ar-C), 101.9 (C1), 78.5 (*C*H), 75.4 (C3), 72.3 (C5), 69.4 (C2), 67.4 (C4), 62.8 (C6), 33.6 (CH_2), 32.0 (CH_2), 25.5 (CH_2), 24.13 (CH_2), 24.07 (CH_2); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 493.1843, $C_{26}H_{34}O_8N$ requires M^+ 493.1838].

Benzoylation of trifluoroethyl 1-thio-β-D-galactopyranoside 137



Following the general benzoylation procedure, trifluoroethyl 1-thio-β-D-galactopyranoside **137** (107 mg, 0.385 mmol, 1.0 equiv.) and BzCl (138 µL, 1.19 mmol, 3.1 equiv.) were reacted. Purification by column chromatography (hexane/EtOAc, 0-40%) yielded the below compounds in a total yield of 83%.

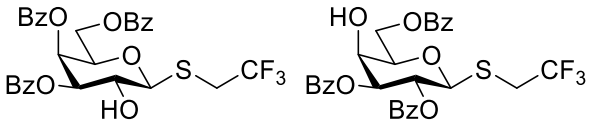
Trifluoroethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-galactopyranoside 140



140 (38.0 mg, 54.7 µmol), 14%) as an off-white foam. $[\alpha]_D^{23} = 94.1$ (*c* = 1.0, $CHCl_3$); R_f = 0.31 (hexane/EtOAc, 6:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.96 (m, 2H, Ar*H*), 7.96 – 7.90 (m, 2H, Ar*H*), 7.89 – 7.83 (m, 2H, Ar*H*), 7.73 – 7.64 (m, 2H, Ar*H*), 7.60 – 7.51 (m, 1H, Ar*H*), 7.51 – 7.40 (m, 4H, Ar*H*), 7.39 – 7.27 (m, 5H, Ar*H*), 7.22 – 7.09 (m, 2H, Ar*H*), 5.97 (d, *J* = 2.7 Hz, 1H, H-4), 5.72 (t, *J* = 9.9 Hz, 1H, H-2), 5.59 (dd, *J* = 9.9, 3.4 Hz, 1H, H-3), 4.96 (d, *J* = 9.9 Hz, 1H, H-1), 4.57 (td, *J* = 10.9, 4.5 Hz, 1H, H-6a), 4.43 – 4.23 (m, 2H, H-6b, H-5), 3.47 (dq, *J* = 15.5, 9.7 Hz, 1H, SC*H*H), 3.13 (dq, *J* = 15.5, 10.0 Hz, 1H, SC*H*H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0 (C=O, Bz), 165.49 (C=O, Bz), 165.46 (2 × C=O, Bz), 133.8 (Ar-C), 133.6 (Ar-C), 133.41 (Ar-C), 133.40

(Ar-C), 130.0 (Ar-C), 129.9 (Ar-C), 129.78 (Ar-C), 129.75 (Ar-C), 129.3 (Ar-C), 128.9 (Ar-C), 128.8 (Ar-C), 128.74 (Ar-C), 128.66 (Ar-C), 128.51 (Ar-C), 128.49 (Ar-C), 128.4 (Ar-C), 125.3 (d, $^{1}J_{C\text{-}F}$ = 276.4 Hz, CF_3), 82.8 (C1), 75.6 (C5), 72.5 (C6), 68.6 (C2), 68.3 (C4), 62.2 (C6), 31.6 (q, $^{2}J_{C\text{-}F}$ = 33.7 Hz, CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ -65.98 (t, *J* = 9.8 Hz); HRMS m/z (ES^+) [Found: $(M+NH_4)^+$ 712.1813, $C_{36}H_{33}F_3O_9SN$ requires M^+ 712.1828].

Trifluoroethyl 2,3,6-tri-*O*-benzoyl-1-thio-β-D-galactopyranoside 141 & trifluoroethyl 3,4,6-tri-*O*-benzoyl-1-thio-β-D-galactopyranoside 142

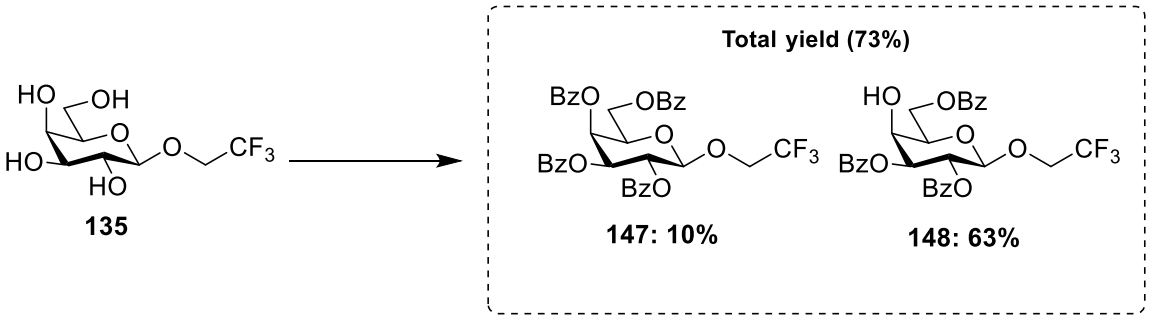


142: 27% **141: 42%**

141/142 were isolated as an inseparable mixture appearing as a yellow foam (158 mg, 0.268 mmol, **141/142**, 1.55:1.00); ratio determined from ^{19}F NMR integration values. R_f = 0.26 (hexane/EtOAc, 6:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 7.94 (m, 8H, Ar*H*), 7.91 – 7.80 (m, 1H, Ar*H*), 7.72 – 7.26 (m, 14H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.7 (Ar-C), 133.6 (Ar-C), 133.5 (Ar-C), 133.4 (Ar-C), 129.91 (Ar-C), 129.86 (2 × Ar-C), 129.84 (Ar-C), 129.75 (2 × Ar-C), 129.7 (Ar-C), 129.4 (Ar-C), 129.3 (Ar-C), 129.1 (Ar-C), 129.04 (Ar-C), 129.01 (Ar-C), 128.8 (2 × Ar-C), 128.7 (Ar-C), 128.52 (2 × Ar-C), 128.49 (Ar-C), 128.45 (Ar-C), 128.4 (Ar-C); **141:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (t, *J* = 9.9 Hz, 1H, H-2), 5.42 (dd, *J* = 9.9, 3.1 Hz, 1H, H-3), 4.91 (d, *J* = 10.0 Hz, 1H, H-1), 4.69 (dd, *J* = 11.6, 5.8 Hz, 1H, H-6a), 4.63 – 4.58 (m, 1H, H-6b), 4.43 – 4.40 (m, 1H, H-4), 4.12 (t, *J* = 6.3 Hz, 1H, H-5), 3.61 – 3.42 (m, 1H, SC*H*H), 3.16 (dq, *J* = 15.4, 10.1 Hz, 1H, SC*H*H), 2.94 (d, *J* = 4.6 Hz, 1H, 4-OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (C=O, Bz), 165.8 (C=O, Bz), 165.6 (C=O, Bz), 125.4 (q, $^{1}J_{C\text{-}F}$ = 276.3 Hz, CF_3), 84.7 (C1), 75.4 (C5), 74.6 (C3), 69.4 (C2), 68.5 (C4), 62.3 (C6), 31.3 (q, $^{2}J_{C\text{-}F}$ = 33.5 Hz, CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.16 (t, *J* = 9.9 Hz); 1**42:** ^{1}H NMR (400 MHz, $CDCl_3$)

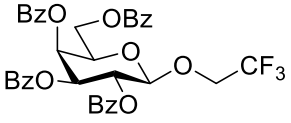
δ 5.95 (dd, *J* = 3.4, 0.7 Hz, 1H, H-4), 5.43 – 5.40 (m, 1H, H-3), 4.80 (d, *J* = 9.6 Hz, 1H, H-1), 4.60 – 4.58 (m, 1H, H-6a), 4.38 (dd, *J* = 11.4, 5.8 Hz, 1H, H-6b), 4.32 – 4.28 (m, 1H, H-5), 4.16 (dd, *J* = 9.3, 5.1 Hz, H-2), 3.58 – 3.43 (m, 1H, SC*H*H), 3.37 – 3.23 (m, 1H, SC*H*H), 2.88 (d, *J* = 4.3 Hz, 1H, 2-OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.12 (C=O, Bz), 166.06 (C=O, Bz), 165.4 (C=O, Bz), 125.4 (q, $^{1}J_{C\text{-}F}$ = 276.3 Hz, CF_3), 84.7 (C1), 75.4 (C5), 74.6 (C3), 69.4 (C2), 68.5 (C4), 62.3 (C6), 31.3 (q, $^{2}J_{C\text{-}F}$ = 33.5 Hz, CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.16 (t, *J* = 9.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.16 (t, *J* = 9.9 Hz); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 608.1556, $C_{29}H_{29}F_3O_8SN$ requires M^+ 608.1566].

Benzoylation of trifluoroethyl β-D-galactopyranoside 135



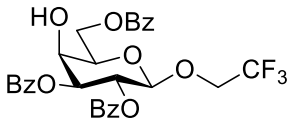
Following the general benzoylation procedure, trifluoroethyl β-D-galactopyranoside **135** (121 mg, 0.462 mmol, 1.0 equiv.) and BzCl (167 µL, 1.43 mmol, 3.1 equiv.) were reacted. Purification by column chromatography (hexane/EtOAc, 0-40%) yielded the below mix of compounds in a total yield of 73%.

Trifluoroethyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside 147



147 (32.0 mg, 47.2 µmol, 10%) as a colourless oil. R_f = 0.57 (hexane/EtOAc, 7:3); $[\alpha]_D^{23}$ = -68.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.05 (m, 2H, Ar*H*), 8.05 – 8.00 (m, 2H, Ar*H*), 7.99 – 7.91 (m, 2H, Ar*H*), 7.82 – 7.77 (m, 2H, Ar*H*), 7.68 – 7.54 (m, 3H, Ar*H*), 7.54 – 7.31 (m, 9H, Ar*H*), 6.01 (dd, *J* = 3.4, 0.9 Hz, 1H, H-4), 5.83 (dd, *J* = 10.4, 7.9 Hz, 1H, H-2), 5.61 (dd, *J* = 10.4, 3.4 Hz, 1H, H-3), 4.99 (d, *J* = 7.9 Hz, 1H, H-1), 4.69 (dd, *J* = 11.2, 6.4 Hz, 1H, H-6a), 4.44 (dd, *J* = 11.2, 6.5 Hz, 1H, H-6b), 4.37 (td, *J* = 6.4, 0.9 Hz, 1H, H-5), 4.21 (dq, *J* = 12.8, 8.7 Hz, 1H, OC*H*H), 4.15 – 4.03 (m, 1H, OC*H*H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1 (C=O, Bz), 165.54 (C=O, Bz), 165.48 (C=O, Bz), 165.3 (C=O, Bz), 133.8 (Ar-C), 133.7 (Ar-C), 133.4 (Ar-C), 133.3 (Ar-C), 130.2 (Ar-C), 130.0 (Ar-C), 129.83 (Ar-C), 129.79 (Ar-C), 129.7 (Ar-C), 129.1 (Ar-C), 128.9 (Ar-C), 128.70 (Ar-C), 128.65 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 128.3 (Ar-C), 123.4 (q, ^1J = 279.1 Hz, CF_3), 101.4 (C1), 71.8 (C5), 71.5 (C3), 69.3 (C2), 67.9 (C4), 65.8 (q, ^2J = 35.0 Hz, CH_2), 61.9 (C6); ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.17 (t, *J* = 8.5 Hz); HRMS *m/z* (ES^+) [Found: $(M+Na)^+$ 701.1584, $C_{36}H_{29}F_3O_{10}Na$ requires M^+ 701.1610].

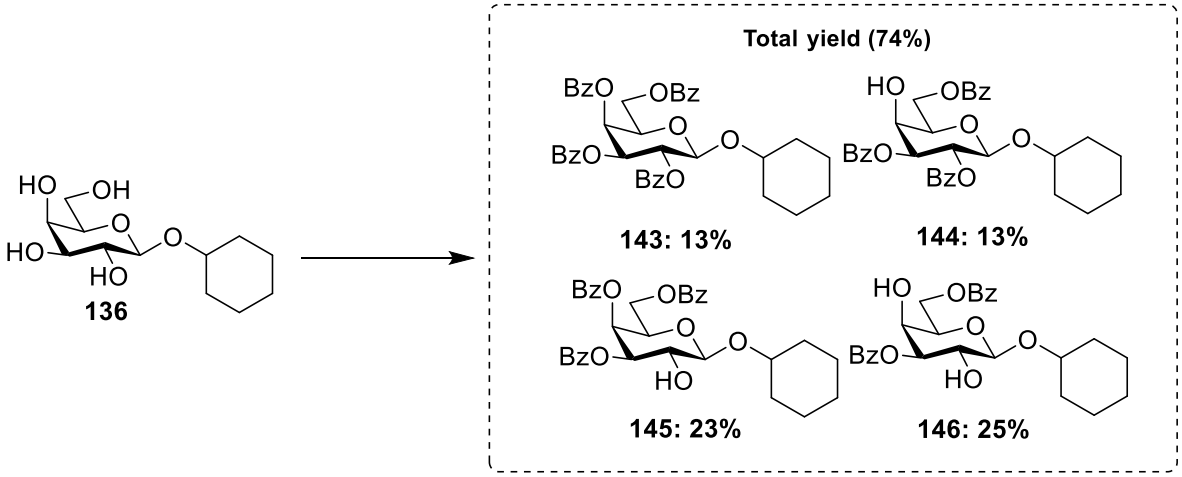
Trifluoroethyl 2,3,6-tri-*O*-benzoyl-β-D-galactopyranoside 148



148 (167 mg, 0.291 mmol, 64%) as a white foam. R_f = 0.51 (hexane/EtOAc, 7:3); $[\alpha]_D^{23}$ = -50.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.03 (m, 2H, Ar*H*), 7.99 – 7.94 (m, 4H, Ar*H*), 7.62 – 7.56 (m, 1H, Ar*H*), 7.56 – 7.44 (m, 4H, Ar*H*), 7.44 – 7.33 (m, 4H, Ar*H*), 5.83 (dd, *J* = 10.3, 7.9 Hz, 1H, H-2), 5.37 (dd, *J* = 10.3, 3.2 Hz, 1H, H-3), 4.91 (d, *J* = 8.0 Hz, 1H, H-1), 4.72 (dd, *J* = 11.5, 6.3 Hz, 1H, H-6a), 4.62 (dd, *J* = 11.5, 5.2 Hz, 1H, H-6b), 4.39 (dd, *J* = 3.1, 0.7 Hz, 1H, H-4), 4.19 – 4.00 (m, 3H, CH_2, H-5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (C=O, Bz), 165.8 (C=O, Bz), 165.5 (C=O, Bz),

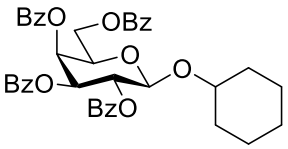
133.6 (Ar-C), 133.5 (Ar-C), 133.3 (Ar-C), 130.2 (Ar-C), 129.9 (Ar-C), 129.8 (Ar-C), 129.7 (Ar-C), 129.4 (Ar-C), 129.3 (Ar-C), 128.8 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 123.5 (q, $^{1}J_{C\text{-}F}$ = 278.9 Hz, CF_3), 101.1 (C1), 73.8 (C3), 72.8 (C5), 68.9 (C2), 67.1 (C4), 65.3 (q, $^{2}J_{C\text{-}F}$ = 35.0 Hz, CH_2), 62.6 (C6); ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.16 (t, *J* = 8.5 Hz); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 592.1786, $C_{29}H_{29}F_3O_9N$ requires M^+ 592.1794].

Benzoylation of Cyclohexyl β-D-galactopyranoside 136



Following the general benzoylation procedure, Cyclohexyl β-D-galactopyranoside **136** (97.0 mg, 0.370 mmol, 1.0 equiv.) and BzCl (134 µL, 1.15 mmol, 3.1 equiv.) were reacted. Purification by column chromatography (hexane/EtOAc, 0-40%) yielded the below compounds in a total yield of 74%.

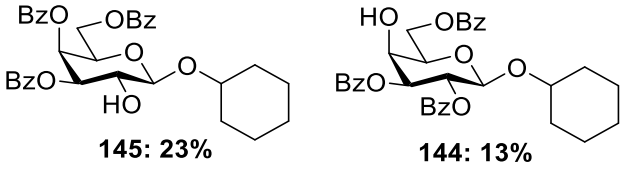
Cyclohexyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside 143



143 (33.9 mg, 49.9 µmol, 13%) as a white solid. R_f = 0.71 (hexane/EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 8.00 (m, 2H, Ar*H*), 7.97 – 7.94 (m, 2H, Ar*H*), 7.91 – 7.87

(m, 2H, Ar*H*), 7.72 (dd, *J* = 8.3, 1.2 Hz, 2H, Ar*H*), 7.57 – 7.45 (m, 2H, Ar*H*), 7.44 – 7.26 (m, 8H, Ar*H*), 7.19 – 7.13 (m, 2H, Ar*H*), 5.91 (dd, *J* = 3.4, 0.8 Hz, 1H, H-4), 5.70 (dd, *J* = 10.4, 8.0 Hz, 1H, H-2), 5.52 (dd, *J* = 10.4, 3.5 Hz, 1H, H-3), 4.83 (d, *J* = 8.0 Hz, 1H, H-1), 4.60 (dd, *J* = 11.2, 6.8 Hz, 1H, H-6a), 4.35 (dd, *J* = 11.2, 6.6 Hz, 1H, H-6b), 4.24 (td, *J* = 6.6, 0.7 Hz, 1H, H-5), 3.79 – 3.41 (m, 1H, C*H*), 1.95 – 1.82 (m, 1H, C*H*H), 1.75 – 1.35 (m, 6H, 3 × CH_2), 1.34 – 0.95 (m, 3H, CH_2, C*H*H).^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1 (C=O, Bz), 165.72 (C=O, Bz), 165.65 (C=O, Bz), 165.2 (C=O, Bz), 133.6 (Ar-C), 133.3 (Ar-C), 133.2 (Ar-C), 133.1 (Ar-C), 130.1 (Ar-C), 129.81 (Ar-C), 129.78 (Ar-C), 129.7 (Ar-C), 129.6 (Ar-C), 129.5 (Ar-C), 129.1 (Ar-C), 128.9 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 128.3 (Ar-C), 100.4 (C1), 78.8 (CH), 71.3 (C3), 70.0 (C5), 68.2 (C2), 62.1 (C6), 33.4 (CH_2), 31.7 (CH_2), 25.4 (CH_2), 23.9 (CH_2), 23.7 (CH_2); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 696.2803, $C_{40}H_{42}O_{10}N$ requires M^+ 696.2808]. Data matched those reported previously.[196]

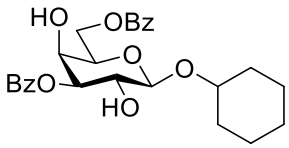
Cyclohexyl 3,4,6-tri-*O*-benzoyl-β-D-galactopyranoside 145 & cyclohexyl 2,3,6-tri-*O*-benzoyl-β-D-galactopyranoside 144



145/144 were isolated as an inseparable mixture appearing as a white foam (78.3 mg, 0.136 mmol, **145/144**, 1.00:0.55); ratio determined from ^{1}H NMR integration values. R_f = 0.40 (hexane/EtOAc, 7:3); The following were observed for both regio-isomers **145** and 1**44**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 7.80 (m, 10H, Ar*H*), 7.65 – 7.27 (m, 13H, Ar*H*), 2.08 – 1.85 (m, 2H, CH_2), 1.81 – 1.05 (m, 8H, 4 x CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.2 (Ar-C), 130.1 (Ar-C), 129.94 (Ar-C), 129.88 (Ar-C), 129.82 (Ar-C), 129.78 (Ar-C), 129.77 (Ar-C), 129.7 (Ar-C), 129.50 (Ar-C), 129.45 (Ar-C), 129.2 (Ar-C), 128.7 (Ar-C), 128.59 (Ar-C), 128.57 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C); **145:** ^{1}H

NMR (400 MHz, $CDCl_3$) δ 5.89 (dd, *J* = 3.7, 1.2 Hz, 1H, H-4), 5.42 (dd, *J* = 10.2, 3.6 Hz, 1H, H-3), 4.70 – 4.59 (m, 2H, H-6a, H-1), 4.40 – 4.35 (m, 1H, H-6b), 4.23 (td, *J* = 6.7, 1.2 Hz, 1H, H-5), 4.10 (dd, *J* = 10.2, 7.7 Hz, 1H, H-2), 3.74 (tt, *J* = 9.8, 4.0 Hz, 1H, C*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2 (C=O), 166.0 (C=O), 165.8 (C=O), 102.0 (C1), 79.0 (*C*H), 73.3 (C3), 71.4 (C5), 70.0 (C2), 68.4 (C4), 62.3 (C6), 33.8 (CH_2), 32.1 (CH_2), 25.6 (CH_2), 24.34 (CH_2), 24.27 (CH_2); **144:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (dd, *J* = 10.3, 7.9 Hz, 1H, H-2), 5.34 (dd, *J* = 10.3, 3.2 Hz, 1H, H-3), 4.81 (d, *J* = 7.9 Hz, 1H, H-1), 4.69 – 4.57 (m, 2H, H-6a, H-6b), 4.36 – 4.33 (m, 1H, H-4), 4.09 – 4.03 (m, 1H, H-5), 3.65 (td, *J* = 9.0, 4.3 Hz, 1H, C*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (C=O), 166.1 (C=O), 165.5 (C=O), 100.3 (C1), 78.5 (*C*H), 74.5 (C3), 72.4 (C5), 70.0 (C2), 67.5 (C4), 62.8 (C6), 33.4 (*C*H_2), 31.8 (CH_2), 25.5 (CH_2), 23.9 (CH_2), 23.7 (CH_2); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 592.2536, $C_{33}H_{38}O_9N$ requires M^+592.2546].

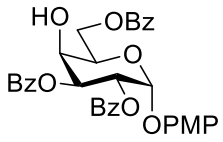
Cyclohexyl 3,6-di-*O*-benzoyl-β-D-galactopyranoside 146



146 (43.2 mg, 91.8 µmol, 25%) as a colourless oil; R_f = 0.26 (hexane/EtOAc, 7:3); $[\alpha]_D^{24}$ = 13.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.98 (m, 2H, Ar*H*), 7.99 – 7.93 (m, 2H, Ar*H*), 7.54 – 7.46 (m, 2H, Ar*H*), 7.42 – 7.32 (m, 4H, Ar*H*), 5.08 (dd, *J* = 10.1, 3.3 Hz, 1H, H-3), 4.60 – 4.47 (m, 2H, H-6a, H-6b), 4.45 (d, *J* = 7.7 Hz, 1H, H-1), 4.19 – 4.13 (m, 1H, H-4), 3.96 (dd, *J* = 10.1, 7.7 Hz, 1H, H-2), 3.89 (td, *J* = 6.5, 0.6 Hz, 1H, H-5), 3.68 – 3.54 (m, 1H, C*H*), 1.98 – 1.80 (m, 2H, CH_2), 1.71 – 1.58 (m, 2H, CH_2), 1.47 – 1.05 (m, 6H, 3 × CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (C=O, Bz), 166.1 (C=O, Bz), 133.6 (Ar-C), 133.4 (Ar-C), 133.3 (Ar-C), 130.2 (Ar-C), 129.9 (Ar-C), 129.7 (Ar-C), 129.6 (Ar-C), 128.5 (Ar-C), 101.9 (C1), 78.5 (*C*H), 75.4 (C3), 72.3 (C5), 69.4

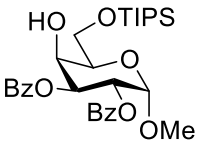
(C2), 67.4 (C4), 62.8 (C6), 33.6 (CH_2), 32.0 (CH_2), 25.5 (CH_2), 24.13 (CH_2), 24.07 (CH_2); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 493.1843, $C_{26}H_{34}O_8N$ requires M^+ 493.1838].

p-Methoxy phenyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside 154



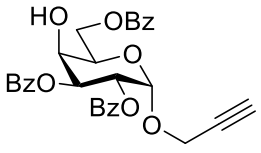
Following the general benzoylation procedure, *p*-methoxy phenyl α-D-galactopyranoside **153** (286 mg, 1.00 mmol, 1.0 equiv.) and BzCl (360 µL, 3.1 mmol, 3.1 equiv.) were reacted. Purification by column chromatography (hexane/EtOAc, 0-30%) yielded the title compound **14** (521 mg, 0.870 mmol, 87%) as a colourless oil. R_f = 0.41 (hexane/EtOAc, 7:3); $[\alpha]_D^{24}$ = 139.0 (*c* = 2.0, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.99 (m, 4H, Ar*H*), 7.98 – 7.90 (m, 2H, Ar*H*), 7.61 – 7.47 (m, 3H, Ar*H*), 7.47 – 7.34 (m, 6H, Ar*H*), 7.07 – 7.01 (m, 2H, Ar*H*), 6.75 – 6.68 (m, 2H, Ar*H*), 5.98 – 5.94 (m, 1H, H-3), 5.87 – 5.81 (m, 2H, H-1, H-2), 4.65 (dd, *J* = 14.3, 8.3 Hz, 1H, H-6b), 4.61 – 4.55 (m, 2H, H-5, H-6a), 4.48 (t, *J* = 2.9 Hz, 1H, H-4), 3.71 (s, 3H, OCH_3), 2.63 (d, *J* = 3.9 Hz, 1H, 4-OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (C=O, Bz), 166.0 (C=O, Bz), 165.8 (C=O, Bz), 155.4 (Ar-C), 150.5 (Ar-C), 133.6 (Ar-C), 133.4 (Ar-C), 133.2 (Ar-C), 129.9 (2 × Ar-C), 129.8 (Ar-C), 129.6 (Ar-C), 129.24 (Ar-C), 129.21 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 118.5 (Ar-C), 114.6 (Ar-C), 96.3 (C1), 70.9 (C3), 68.6 (C5), 68.5 (C2), 68.2 (C4), 63.5 (C6), 55.6 (CH_3); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 616.2177, $C_{34}H_{34}O_{10}N$ requires M^+ 616.2177].

Methyl 2,3-di-*O*-benzoyl-6-*O*-triisopropylsilyl-α-D-galactopyranoside 152



Following the general benzoylation procedure, methyl 6-*O*-triisopropylsilyl-α-D-galactopyranoside **151** (100 mg, 0.285 mmol, 1.0 equiv.) and BzCl (69.60 µL, 0.599 mmol, 2.1 equiv.) were reacted. Purification by column chromatography (hexane/EtOAc, 0-30%) yielded the title compound as a colourless oil (117 mg, 0.209 mmol, 74%). R_f = 0.44 (hexane/EtOAc, 8:2); $[\alpha]_D^{24}$ = 124.8 (*c* = 1.0, $CHCl_3$);^{1}H NMR (400 MHz, MeOD) δ 8.01 – 7.97 (m, 2H, Ar*H*), 7.96 – 7.91 (m, 2H, Ar*H*), 7.58 – 7.48 (m, 2H, Ar*H*), 7.44 – 7.33 (m, 4H, Ar*H*), 5.65 (dd, *J* = 10.7, 3.5 Hz, 1H, H-2), 5.59 (dd, *J* = 10.7, 2.9 Hz, 1H, H-3), 5.13 (d, *J* = 3.5 Hz, 1H, H-1), 4.35 (d, *J* = 2.5 Hz, 1H, H-4), 4.06 – 3.98 (m, 2H, H-5, H-6b), 3.94 (dd, *J* = 9.5, 5.9 Hz, 1H, H-6a), 3.45 (s, 3H, OMe), 1.14 – 1.10 (m, 21H, ^{i}PrSi); ^{13}C NMR (101 MHz, MeOD) δ 166.1 (C=O, Bz), 166.0 (C=O, Bz), 133.1 (Ar-C), 133.0 (Ar-C), 129.7 (Ar-C), 129.3 (Ar-C), 129.2 (Ar-C), 128.1 (Ar-C), 128.1 (Ar-C), 97.5 (C1), 71.5 (C3), 71.0 (C5), 69.3 (C2), 67.4 (C4), 62.5 (C6), 54.3 (CH_3), 17.06 (CH_3, ^{i}Pr), 17.05 (CH_3, ^{i}Pr), 11.8 (CH_3, ^{i}Pr); HRMS *m/z* (ES^+) [Found: $(M+Na)^+$ 581.2523, $C_{30}H_{42}O_8NaSi$ requires M^+ 581.2541].

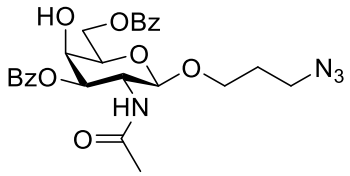
Propargyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside 150



Following the general benzoylation procedure, propargyl-α-D-galactopyranoside **149** (47.0 mg, 0.215 mmol, 1.0 equiv.) and BzCl (77.6 µL, 0.668 mmol, 3.1 equiv.) were reacted. Purification by column chromatography (hexane/EtOAc, 0-30%) yielded the title compound as a white foam (87.0 mg, 0.164 mmol, 76%). R_f = 0.49 (hexane/EtOAc, 7:3); $[\alpha]_D^{24}$ = 124.2; ^{1}H NMR (400 MHz, MeOD) δ 8.14 – 7.84 (m, 6H, Ar*H*), 7.71 – 7.54 (m, 2H, Ar*H*), 7.56 – 7.47 (m, 4H, Ar*H*), 7.45 – 7.36 (m, 4H, Ar*H*), 5.72 (dd, *J* = 10.8, 3.5

Hz, 1H, H-2), 5.67 (dd, *J* = 10.8, 2.9 Hz, 1H, H-3), 5.50 (d, *J* = 3.4 Hz, 1H, H-1), 4.59 (dd, *J* = 11.2, 7.4 Hz, 1H, H-6a), 4.53 (dd, *J* = 11.2, 5.0 Hz, 1H, H-6b), 4.48 – 4.40 (m, 3H, H-4, H-5, C*H*H), 4.34 (dd, *J* = 15.9, 2.4 Hz, 1H, C*H*H), 2.78 (t, *J* = 2.4 Hz, 1H, C*H*); ^{13}C NMR (101 MHz, MeOD) δ 166.3 (C=O, Bz), 166.00 (C=O, Bz), 165.96 (C=O, Bz),133.12 (Ar-C), 133.07 (Ar-C), 133.0 (Ar-C), 129.8 (Ar-C), 129.6 (Ar-C), 129.33 (Ar-C), 129.30 (Ar-C), 129.27 (Ar-C), 129.2 (Ar-C), 128.3 (Ar-C), 128.2 (Ar-C), 128.1 (Ar-C), 95.0 (C1), 78.1 (propargyl-C), 75.1 (propargyl-CH), 70.9 (C3), 68.9 (C5), 68.7 (C2), 67.4 (C4), 63.6 (CH_2), 54.3 (C6); HRMS *m/z* (ES^+) [Found: $(M+H)^+$ 531.1639, $C_{30}H_{27}O_9$ requires M^+ 531.1655].

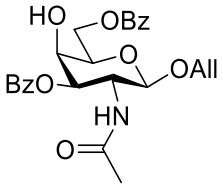
3-Azidopropyl-3,6-di-*O*-benzoyl-2-deoxy-2-acetamido-β-D-galactopyranoside **160**



Following the general benzoylation procedure, 3-azidopropyl-2-deoxy-2-acetamido-β-D-galactopyranoside **159** (37 mg, 121.6 µmol, 1.0 equiv.) and BzCl (29.7 µL, 255.4 µmol, 2.1 equiv.) were reacted. Purification by column chromatography (DCM/EtOAc, 0-50%) yielded the title compound as a white solid (52.0 mg, 101.5 µmol, 83%). R_f = 0.30 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.97 (m, 4H, Ar*H*), 7.61 – 7.46 (m, 2H, Ar*H*), 7.43 – 7.34 (m, 4H, Ar*H*), 6.04 (d, *J* = 8.9 Hz, 1H, N*H*), 5.37 (dd, *J* = 11.2 Hz, 3.1 Hz, 1H, H-3), 4.71 (d, *J* = 8.3 Hz, 1H, H-1), 4.67 – 4.54 (m, 2H, H-6a, H-6b), 4.44 (dt, *J* = 11.1, 8.8 Hz, 1H, H-2), 4.25 (ad, *J* = 2.8 Hz, 1H, H-4), 4.09 – 4.00 (m, 1H, H-5), 3.97 (dt, *J* = 10.7, 5.5 Hz, 1H, OC*H*H), 3.63 (ddd, *J* = 9.8 Hz, 8.3 Hz, 4.8 Hz, 1H, OC*H*H), 3.45 – 3.32 (m, 2H, CH_2), 1.89 (s, 3H, OAc), 1.80 – 0.94 (m, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 (C=O, Ac), 166.5 (C=O, Bz), 166.4 (C=O, Bz), 133.6 (Ar-C), 133.3 (Ar-C), 129.9 (Ar-C), 129.7 (Ar-C), 129.7 (Ar-C), 129.1 (Ar-C), 128.54

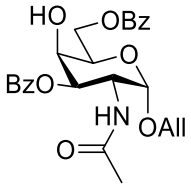
(Ar-C), 128.45 (Ar-C), 101.4 (C1), 73.6 (C3), 72.3 (C5), 66.9 (C4), 66.1 (CH_2), 63.0 (C6), 50.8 (C2), 48.1 (CH_2), 29.0 (CH_2), 23.3 (Ac-CH_3); HRMS *m/z* (ES^+) [Found: $(M+H)^+$ 513.1977, $C_{25}H_{29}O_8N_4$ requires M^+ 513.1985]. Data matched those reported previously.[197]

Allyl 3,6-di-*O*-benzoyl-2-acetamido-2-deoxy-β-D-galactopyranoside 156



Following the general benzoylation procedure, allyl 2-acetamido-2-deoxy-β-D-galactopyranoside **155** (1.07 g, 4.10 mmol, 1.0 equiv.) and BzCl (1.00 mL, 8.6 mmol, 2.1 equiv.) were reacted. Purification by column chromatography (DCM/EtOAc, 0-50%) yielded the title compound (1.32 g, 2.81 mmol, 69%) as a white solid. R_f = 0.43 (DCM/EtOAc, 8:2); ^{1}H NMR (400 MHz, MeOD) δ 8.16 – 7.89 (m, 4H, Ar*H*), 7.71 – 7.58 (m, 2H, Ar*H*), 7.58 – 7.41 (m, 4H, Ar*H*), 5.98 – 5.86 (m, 1H, =C*H*), 5.26 (ddd, *J* = 17.3, 3.5, 1.7 Hz, 1H, CH_2=), 5.19 – 5.11 (m, 2H, H-3, CH_2=), 4.69 (d, *J* = 8.5 Hz, 1H, H-1), 4.63 (dd, *J* = 11.3, 7.4 Hz, 1H, H-6b), 4.57 – 4.46 (m, 2H, H-2, H-6a), 4.34 (ddt, *J* = 13.2, 5.0, 1.6 Hz, 1H, OC*H*H), 4.28 (d, *J* = 2.8 Hz, 1H, H-4), 4.15 (ddt, *J* = 13.2, 6.0, 1.4 Hz, 1H, OC*H*H), 4.09 – 4.04 (m, 1H, H-5), 1.87 (s, 3H, Ac); ^{13}C NMR (101 MHz, MeOD) δ 172.1 (C=O, Ac), 166.4 (C=O, Bz), 166.2 (C=O, Bz), 134.1 (=CH-), 133.1 (Ar-C), 133.0 (Ar-C), 129.8 (Ar-C), 129.7 (Ar-C), 129.5 (Ar-C), 129.2 (Ar-C), 128.3 (Ar-C), 128.2 (Ar-C), 116.0 (CH_2=), 100.5 (C1), 74.4 (C3), 72.5 (C5), 69.5 (CH_2) 65.9 (C4), 63.5 (C6), 50.1 (C2), 21.4 (Ac-CH_3); HRMS *m/z* (ES^+) [Found: $(M+H)^+$ 470.1809, $C_{25}H_{28}O_8N$ requires M^+ 470.1802]. Data matched those reported previously.[197]

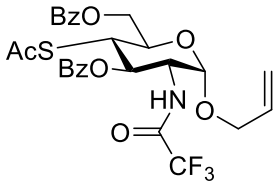
Allyl 3,6-di-*O*-benzoyl-2-acetamido-2-deoxy-α-D-galactopyranoside 158



Following the general benzoylation procedure, allyl 2-acetamido-2-deoxy-α-D-galactopyranoside **157** (782 mg, 3.00 mmol, 1.0 equiv.) and BzCl (732 µL, 6.3 mmol, 2.1 equiv.) were reacted. Purification by column chromatography (hexane/EtOAc, 0-100%) yielded the title compound as a white solid (1.07 g, 2.28 mmol, 76%). R_f = 0.58 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 7.96 (m, 4H, Ar*H*), 7.60 – 7.53 (m, 2H, Ar*H*), 7.48 – 7.38 (m, 4H, Ar*H*), 5.96 – 5.85 (m, 1H, =C*H*-), 5.79 (d, *J* = 9.8 Hz, 1H, N*H*), 5.37 (dd, *J* = 11.1, 3.0 Hz, 1H, H-3), 5.27 (dq, *J* = 17.2, 1.5 Hz, 1H, CH_2=), 5.20 (dd, *J* = 10.3, 1.3 Hz, 1H, CH_2=), 4.99 (d, *J* = 3.7 Hz, 1H, H-1), 4.92 (ddd, *J* = 11.1, 9.9, 3.7 Hz, 1H, H-2), 4.62 (dd, *J* = 11.5, 5.6 Hz, 1H, H6-b), 4.55 (dd, *J* = 11.5, 6.9 Hz, 1H, H-6a), 4.30 – 4.26 (m, 2H, H-4, H-5), 4.26 – 4.20 (m, 1H, OC*H*H), 4.07 – 4.01 (m, 1H, OC*H*H), 1.88 (s, 3H, Ac); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1 (C=O, Ac), 166.6 (C=O, Bz), 166.4 (C=O, Bz), 133.5 (Ar-C), 133.4 (=CH-), 133.2 (Ar-C), 130.0 (Ar-C), 129.74 (Ar-C), 129.67 (Ar-C), 129.3 (Ar-C), 128.6 (Ar-C), 128.4 (Ar-C), 118.2 (CH_2=), 97.1 (C1), 72.0 (C3), 68.6 (CH_2), 68.4 (C5), 67.5 (C4), 63.6 (C6), 47.3 (C2), 23.3 (Ac-CH_3); HRMS *m/z* (ES^+) [Found: $(M+H)^+$ 470.1809, $C_{25}H_{28}O_8N$ requires M^+ 470.1802]. Data matched those reported previously.[198]

6.3 Chapter 4 compounds

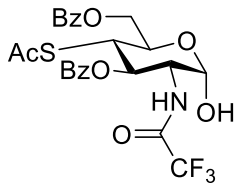
Allyl 4-*S*-acetyl-3,6-di-*O*-benzoyl-2-deoxy-4-thio-2-trifluoroacetamido-α-D-glucopyranoside 168



A solution of allyl 3,6-di-*O*-benzoyl-2-trifluoroacetamido-2-deoxy-α-D-galactopyranoside **79** (500 mg, 0.955 mmol, 1.0 equiv.) in DCM (40 mL) and pyridine (10 mL) was cooled to 0 °C and slowly treated with Tf_2O (0.37 mL, 619 mg, 2.20 mmol, 2.3 equiv.). After 20 mins of stirring, DCM (75 mL) was added, and the mixture washed sequentially with ice cold 1M HCl (50 mL) and cold sat. aq. $NaHCO_3$ (50 mL). The combined organic phases were dried ($MgSO_4$), filtered and condensed under reduced pressure to give a yellow residue. The resulting crude material was dissolved in pyridine (10 mL) followed by addition of KSAc (378 mg, 2.87 mmol, 3.0 equiv.). The mixture was stirred at RT for 1 hr. The reaction mixture was then diluted with EtOAc (100 mL), washed with H_2O (3 × 50 mL), brine (50 mL), dried ($MgSO_4$), filtered and condensed under reduced pressure giving a yellow residue. Purification by column chromatography (hexane/EtOAc, 0-30%) delivered **168** (408 mg, 0.702 mmol, 73%) as a yellow solid. R_f = 0.57 (hexane/EtOAc, 7:3); $[\alpha]_D^{24}$ = 89.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.09 (m, 2H, Ar*H*), 7.97 – 7.93 (m, 2H, Ar*H*), 7.63 – 7.54 (m, 2H, Ar*H*), 7.53 – 7.47 (m, 2H, Ar*H*), 7.45 – 7.40 (m, 2H, Ar*H*), 6.74 (d, *J* = 9.1 Hz, 1H, N*H*), 5.95 – 5.84 (m, 1H,, =C*H*-), 5.54 (t, *J* = 10.7 Hz, 1H, H-3), 5.33 – 5.23 (m, 2H, CH_2=), 5.10 (d, *J* = 3.6 Hz, 1H, H-1), 4.64 (dd, *J* = 12.2, 2.2 Hz, 1H, H-6a), 4.55 (dd, *J* = 12.2, 4.8 Hz, 1H, H-6b), 4.52 – 4.46 (m, 1H, H-2), 4.30 – 4.22 (m, 2H, H-5, OC*H*H), 4.16 (t, *J* = 11.2 Hz, 1H, H-4), 4.07 (ddt, *J* = 12.7, 6.6, 1.2 Hz, 1H, OC*H*H), 2.23 (s, 3H, SAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2 (C=O, Ac), 166.9 (C=O, Bz), 166.3 (C=O), 157.1 (q, *J* = 37.6 Hz, C=O), 133.8 (Ar-C), 133.3 (Ar-C), 132.6 (=*C*H-), 130.0 (Ar-C), 129.8 (Ar-C), 129.7 (Ar-

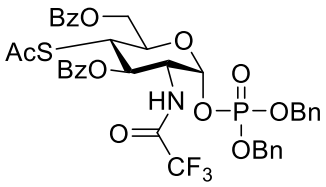
C), 128.6 (Ar-C), 128.15 (Ar-C), 128.59 (Ar-C), 119.2 (*C*H_2=), 95.7 (C1), 70.4 (C3), 69.2 (C5), 63.7 (C6), 69.0 (O*C*H_2), 53.9 (C2), 43.8 (C4), 30.7 (Ac-CH_3); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$, $C_{27}H_{30}O_8N_2F_3S_1$ 599.1673 requires M^+ 599.1669].

4-*S*-acetyl 3,6-di-*O*-benzoyl-2-deoxy-4-thio-2-trifluoroacetamido-α-D-glucopyranose **169**



Tetrakis(triphenylphosphine)palladium (199 mg, 0.172 mmol, 0.5 equiv.) was added to a solution of **168** (200 mg, 0.344 mmol, 1.0 equiv.) in AcOH (5 mL) and the resulting mixture was heated at 80 °C. After 1 hr, the mixture was concentrated under reduced pressure and the crude residue purified by column chromatography (hexane/EtOAc, 0-100%) to yield **169** (186 mg, 0.318 mmol, 92%) as a yellow oil. R_f = 0.43 (hexane/EtOAc, 7:3); $[\alpha]_D^{24}$ = 53.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.10 (m, 2H, Ar*H*), 8.02 – 7.91 (m, 2H, Ar*H*), 7.65 – 7.55 (m, 2H, Ar*H*), 7.54 – 7.48 (m, 2H, Ar*H*), 7.47 – 7.40 (m, 2H, Ar*H*), 6.87 (d, *J* = 9.1 Hz, 1H, N*H*), 5.61 (t, *J* = 10.8 Hz, 1H, H-3), 5.48 (t, *J* = 3.4 Hz, 1H, H-1), 4.67 (dd, *J* = 12.1, 2.0 Hz, 1H, H-6a), 4.58 – 4.42 (m, 3H, H-6b, H-2, H-5), 4.19 (t, *J* = 11.2 Hz, 1H, H-4), 3.51 (ad, *J* = 2.2 Hz, 1H, OH), 2.23 (s, 3H, SAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.4 (C=O, Ac) , 167.1 (C=O, Bz), 166.6 (C=O, Bz), 157.3 (q, $J_{C\text{-}F}$ = 37.6 Hz, C=O), 133.8 (Ar-C), 133.4 (Ar-C), 130.0 (Ar-C), 129.9 (Ar-C), 129.6 (Ar-C), 128.61 (Ar-C), 128.56 (Ar-C), 114.08 (q, $J_{C\text{-}F}$ = 288.4 Hz, CF_3), 91.4 (C1), 70.2 (C3), 68.8 (C5), 63.7 (C6), 54.2 (C2), 43.9 (C4), 30.7 (Ac-CH_3);^{19}F NMR (376 MHz, $CDCl_3$) δ -76.15 (s); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$, 599.1343 $C_{24}H_{26}F_3N_2O_8S$ requires M^+ 559.1362].

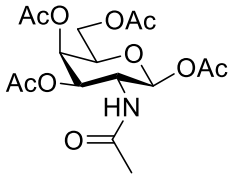
Dibenzyl 4-*S*-acetyl-3,6-di-*O*-benzoyl-2-deoxy-4-thio-2-trichloroacetamido-α-D-glucopyranoside phosphate 170



A solution of **169** (356 mg, 0.657 mmol, 1.0 equiv.) in THF (20 mL) was cooled to −78 °C and LDA (0.36 mL, 77.0 mg, 0.723 mmol, 1.1 equiv.) was added dropwise. After 15 mins, a solution of tetrabenzyl pyrophosphate (460 mg, 0.854 mmol, 1.3 equiv.) in THF (2 mL) was added. The reaction was warmed to 0 °C and stirred for 2 hrs. The solution was subsequently diluted with DCM (50 mL), washed with sat. aq. $NaHCO_3$ (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-50%) to yield **170** (105 mg, 0.123 mmol, 66%) as a colourless oil. R_f = 0.31 (hexane:EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.07 (m, 2H, Ar*H*), 7.95 – 7.90 (m, 2H, Ar*H*), 7.62 – 7.53 (m, 2H, Ar*H*), 7.48 – 7.38 (m, 4H, Ar*H*), 7.38 – 7.28 (m, 10H, Ar*H*), 5.86 (dd, *J* = 6.1, 3.2 Hz, 1H, H-1), 5.48 (t, *J* = 10.3 Hz, 1H, H-3), 5.11 – 5.00 (m, 4H, 2 x CH_2Ph), 4.57 – 4.50 (m, 1H, H-2), 4.50 – 4.42 (m, 2H, H-6a, H-6b), 4.27 – 4.16 (m, 2H, H-4, H-5), 2.20 (s, 3H, SAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.8 (C=O, Ac), 166.8 (C=O, Bz), 166.1 (C=O, Bz), 157.5 (q, $^2J_{C-F}$ = 38.2 Hz, C=O), 135.2 (Ar-C), 135.11 (Ar-C), 135.09 (Ar-C), 135.0 (Ar-C), 130.0 (Ar-C), 129.8 (Ar-C), 129.6 (Ar-C), 129.0 (Ar-C), 128.78 (Ar-C), 128.76 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 128.3 (Ar-C), 128.2 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 115.4 (q, $^1J_{C-F}$ = 287.8 Hz, CF_3), 95.5 (d, $^2J_{C-P}$ = 6.1 Hz, C1), 70.8 (C5), 70.3 (d, $^2J_{C-P}$ = 5.5 Hz, *C*H_2Ph), 70.2 (d, $^2J_{C-P}$ = 5.6 Hz, *C*H_2Ph), 69.5 (C3), 63.0, (C6), 43.3 (C4), 54.0 (d, $^3J_{C-P}$ = 7.6 Hz, C2), 30.7 (Ac-CH_3);^{19}F NMR (377 MHz, $CDCl_3$)

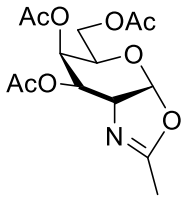
δ -75.91 (s), ^{31}P NMR (162 MHz, $CDCl_3$) δ -2.49 – -2.92 (m); HRMS *m/z* (ES^+) [Found: $(M+NH_4)^+$ 819.1971, $C_{38}H_{39}O_{11}N_2F_3S_1P_1$ requires M^+ 819.1959].

1,3,4,6-Tetra-*O*-acetyl-2-acetamido-2-deoxy-β-D-galactopyranoside 173



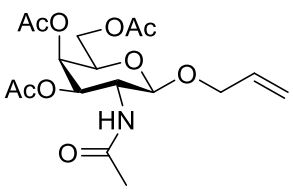
Galactosamine hydrochloride **75** (5.00 g, 23.2 mmol, 1.0 equiv.) was dissolved in pyridine (50 mL) and acetic anhydride (10 mL) was added to the solution at 0 ºC. The reaction mixture was allowed to warm to RT and stirred overnight. TLC analysis revealed complete consumption of the starting material (100 %, EtOAc). The reaction mixture was co-evaporated with toluene (3 x 50 mL) and the crude solid recrystallised from MeOH (100 mL) yielding **173** (7.10 g, 18.2 mmol, 79%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (d, *J* = 8.8 Hz, 1H, H-1), 5.41 (d, *J* = 9.5 Hz, 1H, N*H*), 5.38 (dd, *J* = 3.3, 0.8 Hz, 1H, H-4), 5.09 (dd, *J* = 11.3, 3.3 Hz, 1H, H-3), 4.50 – 4.40 (m, 1H, H-2), 4.21 – 4.08 (m, 2H, H-6a, H-6b), 4.02 (td, *J* = 6.5, 1.1 Hz, 1H, H-5), 2.17 (s, 3H, Ac), 2.13 (s, 3H, Ac), 2.05 (s, 3H, Ac), 2.02 (s, 3H, Ac), 1.94 (s, 3H, Ac); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C=O, Ac), 170.4 (C=O, Ac), 170.3 (C=O, Ac), 170.2 (C=O, Ac), 169.6 (C=O, Ac), 93.1 (C1), 71.9 (C5), 70.3 (C3), 66.3 (C4), 61.3 (C6), 49.8 (C2), 23.3 (Ac-CH_3), 20.9 (Ac-CH_3), 20.67 (Ac-CH_3), 20.65 (Ac-CH_3); HRMS *m/z* (ES^+) [Found $(M+H)^+$ 390.1395, $C_{16}H_{24}O_{10}N_1$ requires M^+ 390.1395]. Data matched those reported previously.[199]

2-Methyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-galactopyrano)[1,2]-oxazoline 174



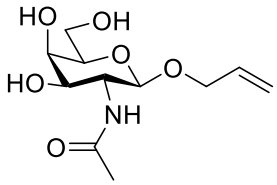
A solution of peracetate **173** (1.28 g, 3.30 mmol, 1.0 equiv.) in dichloroethane (40 mL) was treated slowly with TMSOTf (0.90 mL, 1.10 g, 4.95 mmol, 1.5 equiv.). After stirring overnight at 50 °C, TLC analysis revealed reaction completion (to R_f = 0.44, EtOAc). The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (100 mL). The layers were separated, and the aqueous phase was extracted with DCM (2 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by column chromatography (hexane/EtOAc, 0-100%) delivered **174** (623 mg, 1.89 mmol, 57%) as a colourless oil. R_f = 0.44 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (d, *J* = 6.8 Hz, 1H, H-1), 5.46 (t, *J* = 2.9 Hz, 1H, H-4), 4.91 (dd, J = 3.3, 7.4 Hz, 1H, H-3), 4.29 – 4.09 (m, 3H, H-6a, H-6b, H-5), 4.00 (m, 1H, H-2), 2.13 (s, 3H, Ac), 2.07 (s, 6H, Ac), 2.05 (s, 3H, Ac); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5 (C=O, Ac), 170.1 (C=O, Ac), 169.8 (C=O, Ac), 166.4 (C=N), 101.5 (C1), 71.8 (C3), 69.5 (C5), 65.3 (C4), 63.6 (C2), 61.6 (C6), 20.8 (Ac-CH_3), 20.7 (Ac-CH_3), 20.6 (Ac-CH_3), 14.4 (CH_3); HRMS *m/z* (ES^+) [Found $(M+H)^+$ 330.1182, $C_{14}H_{20}O_8N_1$ requires M^+ 320.1183]. Data matched those reported previously.[200]

Allyl 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-β-D-galactopyranoside 175



To 1,3,4,6-tetra-*O*-acetyl-2-acetamido-2-deoxy-β-D-galactopyranoside **174** (4.00 g, 10.27 mmol, 1.0 equiv.) in DCE (50 mL) was added $FeCl_3$ (2.50 g, 15.4 mmol, 1.5 equiv.), followed by subsequent addition of allyl alcohol (1.39 mL, 1.19 g, 20.54 mmol, 2.0 equiv.). The resulting clear brown/yellow solution was stirred at RT for 24 hrs. At this point reaction completion was confirmed by TLC (2: R_f = 0.33, 1: R_f = 0.11, EtOAc). Saturated aqueous $NaHCO_3$ (175 mL) was then added. Upon addition a brown precipitate formed, the now biphasic mixture was stirred vigorously at RT for 30 mins. The mixture was diluted with DCM (150 mL) and washed with DCM (3 × 150 mL), the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. To the crude residue was added hexane/EtOAc (1:1, 100 mL) producing an off-white precipitate, the reaction flask was settled for 15 mins and then the solid was filtered, followed by washing of the filtered material with cold hexane (100 mL) yielding **175** (2.90 g, 7.5 mmol, 73%) as a white solid. R_f = 0.33 (100% EtOAc); mp: 170-175°C; $[\alpha]_D^{20}$ = -19.8 (*c* = 1.0, $CHCl_3$); Ref.[1] -17.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, MeOD) δ 5.89 (dddd, *J* = 17.2, 10.6, 5.8, 5.0 Hz, 1H, =C*H*-), 5.33 (dd, *J* = 3.3, 0.7 Hz, 1H, H-4), 5.28 (dq, *J* = 17.2, 1.7 Hz, 1H, CH_2=), 5.16 (ddd, *J* = 10.5, 3.1, 1.4 Hz, 1H, CH_2=), 5.06 (dd, *J* = 11.3, 3.4 Hz, 1H, H-3), 4.60 (d, *J* = 8.5 Hz, 1H, H-1), 4.31 (ddt, *J* = 13.2, 5.0, 1.6 Hz, 1H, OC*H*H), 4.19 – 4.06 (m, 4H, H-2, H-6a, H-6b, OC*H*H), 4.00 (td, *J* = 6.6, 1.0 Hz, 1H, H-5), 2.14 (s, 3H, OAc), 2.02 (s, 3H, Ac), 1.95 (s, 3H, Ac), 1.92 (s, 3H, Ac); ^{13}C NMR (101 MHz, MeOD) δ 172.2 (C=O, Ac), 170.71 (C=O, Ac), 170.70 (Ac, C=O), 170.3 (C=O, Ac), 133.9 (=*C*H-), 115.9 (*C*H_2=), 100.5 (C1), 70.8 (C3), 70.4 (C5), 69.6 (O*C*HH), 66.8 (C4), 61.4 (C6), 50.2 (C2), 21.4 (Ac-CH_3), 19.2 (3 × Ac-CH_3); HRMS *m/z* (ES^+) [Found: $(M+H)^+$ 388.1606, $C_{17}H_{26}N_1O_9$ requires M^+ 388.1602]. Data matched those reported previously.[201]

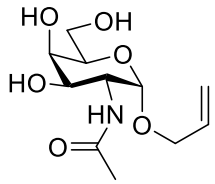
Allyl 2-acetamido-2-deoxy-β-D-galactopyranoside 155



A solution of allyl 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-β-D-galactopyranoside **175** (2.51 g, 6.48 mmol, 1.0 equiv.) in MeOH (10 mL) was treated with 1M NaOH (5 mL) and the reaction mixture was left stirring at RT after 30 mins TLC analysis revealed full conversion of the starting material to a single lower spot (R_f = 0.35, DCM/MeOH, 8:2). The reaction mixture was neutralised with Amberlite IR20 (H+) ion exchange resin. The mixture was filtered and washed with MeOH (100 mL) and the filtrate concentrated under reduced pressure to give an off-white solid. EtOAc (50 mL) was added to the crude residue followed by DCM (150 mL), the mixture was heated at reflux, after 15 mins the round bottom flask was placed into an ice bath and left without stirring for 30 mins giving a white precipitate, this was filtered to deliver **155** as a white solid (1.41 g, 5.38 mmol, 83%). R_f = 0.35 (DCM/MeOH, 8:2); mp: 198-203 °C; $[\alpha]_D^{20}$ = 12.3 (*c* = 1.0, H_2O); Ref.[1] $[\alpha]_D$= -45 (*c* = 0.6, H_2O); ^{1}H NMR (400 MHz, MeOD) δ 5.89 (dddd, *J* = 15.5, 10.6, 5.7, 5.0 Hz, 1H, =C*H*-), 5.27 (ddd, *J* = 17.3, 3.5, 1.7 Hz, 1H, CH_2=), 5.12 (dd, *J* = 10.5, 1.8 Hz, 1H, CH_2=), 4.41 (d, *J* = 8.4 Hz, 1H, H-1), 4.33 (ddt, *J* = 13.3, 4.9, 1.6 Hz, 1H, OC*H*H), 4.07 (ddt, *J* = 13.3, 5.8, 1.4 Hz, 1H, OC*H*H), 3.94 (dd, *J* = 10.5, 8.6 Hz, 1H, H-2), 3.83 (d, *J* = 2.4 Hz, 1H, H-4), 3.80 – 3.71 (m, 2H, H-6a, H-6b), 3.59 (dd, *J* = 10.7, 3.2 Hz, 1H, H-3), 3.48 (dd, *J* = 6.6, 5.5 Hz, 1H, H-5), 1.97 (s, 3H, Ac); ^{13}C NMR (101 MHz, MeOD) δ 172.7 (C=O, Ac), 134.3 (=*C*H-), 115.5 (*C*H_2=), 100.8 (C1), 75.3 (C5), 71.9 (C3), 69.2 (O*C*HH), 68.3 (C4), 61.1 (C6), 52.9 (C2), 21.6 (Ac-CH_3); HRMS *m/z* (ES^-) [Found: (M-

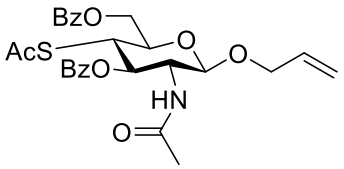
H)$^-$ 260.1134, $C_{11}H_{18}N_1O_6$ requires M^- 260.1140]. Data matched those reported previously.[38]

Allyl 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-α-D-galactopyranoside **157**



Galactosamine hydrochloride **75** (5.0 g, 23.3 mmol, 1.0 equiv.) and NaOMe (1.51 g, 28.0 mmol, 1.2 equiv.) in MeOH (50 mL) was stirred for 30 mins and filtered, the filtrate was cooled to 0 °C and Ac_2O added (2.42 mL, 2.62 g, 25.6 mmol, 1.1 equiv.). After 1 hr of stirring the solvent was removed under reduced pressure and the crude residue put into allyl alcohol (50 mL). To the mixture was added $BF_3{\cdot}OEt_2$ (2.88 mL, 3.31 g, 23.3 mmol, 1.0 equiv.) and the reaction heated at 70 °C for 2 hrs. TLC analysis revealed full consumption of the starting material (R_F = 0.63, DCM/MeOH, 8:2). After the solution was cooled to room temperature, the solvent was evaporated, and **157** wa**s** precipitated through the addition of ethanol appearing as a white solid (791 mg, 3.03 mmol, 13%.). R_F = 0.63 (DCM/MeOH, 8:2); ^{1}H NMR (400 MHz, D_2O) δ 5.89 (ddd, *J* = 22.5, 10.9, 5.7 Hz, 1H, =C*H*-), 5.27 (d, *J* = 17.3 Hz, 1H, CH_2=), 5.18 (d, *J* = 10.4 Hz, 1H, CH_2=), 4.87 (d, *J* = 3.7 Hz, 1H, H-1), 4.18 – 4.05 (m, 2H, H-2 , OC*H*H), 3.99 – 3.81 (m, 4H, H-3, H-6a, H-6b, OC*H*H), 3.77 – 3.62 (m, 2H, H-4, H-5), 1.96 (s, *J* = 8.9 Hz, 3H, Ac); ^{13}C NMR (101 MHz, D_2O) δ 174.6 (C=O, Ac), 133.7 (=*C*H-), 117.9 (*C*H_2=), 96.2 (C1), 71.0, 68.50, 68.46, 67.7, 61.2, 49.9 (C2), 21.9 (Ac-CH_3). HRMS *m/z* (ES^+) [Found: $(M-H)^-$ 260.1135, $C_{11}H_{18}N_1O_6$ requires M^- 260.1140].

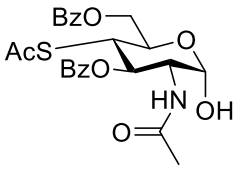
Allyl 2-acetamido-4-*S*-acetyl-3,6-di-*O*-benzoyl-2-deoxy-4-thio-β-D-glucopyranoside **176**



Under a stream of nitrogen, Tf_2O (0.98 mL, 1.65 g, 5.87 mmol, 2.3 equiv.) was added dropwise to a solution of **156** (1.20 g, 2.55 mmol, 1.0 equiv.) in DCM (40 mL) and pyridine (10 mL) at 0 °C. After 1 hr of stirring at this temperature, DCM (50 mL) was added and washed sequentially with ice cold 1M HCl (50 mL), cold sat.aq. $NaHCO_3$ (50 mL) and cold brine (50 mL). The residue was dried ($MgSO_4$), filtered, condensed under reduced pressure, and progressed without purification. The crude triflate was dissolved in pyridine (10 mL) and KSAc (874 mg, 7.65 mmol, 3.0 equiv.) was added. The suspension was stirred at RT until complete consumption of the starting material was seen by TLC (R_f = 0.58, hexane:EtOAc, 1:1). The reaction mixture was diluted with EtOAc (50 mL), washed with H_2O (3 × 50 mL), brine (50 mL), dried ($MgSO_4$), filtered and condensed under reduced pressure. Purification by column chromatography (0-50%, hexane/EtOAc) delivered **176** (657 mg, 1.25 mmol, 49%) as a white foam. R_f = 0.58 (hexane:EtOAc, 1:1); $[\alpha]_D^{24}$ = 16.6 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.08 (m, 2H, Ar*H*), 8.01 – 7.96 (m, 2H, Ar*H*), 7.62 – 7.54 (m, 2H, Ar*H*), 7.46 (m, 4H, Ar*H*), 5.93 – 5.81 (m, 1H, =C*H*-), 5.72 (d, *J* = 8.9 Hz, 1H, N*H*), 5.54 (t, *J* = 10.3 Hz, 1H, H-3), 5.24 (dd, *J* = 17.2, 1.6 Hz, 1H, CH_2=), 5.15 (dd, *J* = 10.4, 1.4 Hz, 1H, CH_2=), 4.79 (d, *J* = 8.4 Hz, 1H, H-1), 4.67 (dd, *J* = 12.0, 1.8 Hz, 1H, H-6a), 4.53 (dd, *J* = 12.0, 5.0 Hz, 1H, H-6b), 4.34 (ddt, *J* = 13.0, 5.0, 1.4 Hz, 1H, OC*H*H), 4.16 – 4.08 (m, 2H, H-2, OC*H*H), 4.05 – 3.96 (m, 2H, H-4, H-5), 2.19 (s, 3H, SAc), 1.86 (s, 3H, Ac); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.7 (C=O, SAc), 170.3 (C=O, Ac), 166.6 (C=O, Bz) 166.3 (C=O, Bz), 133.7 (=*C*H-), 133.6 (Ar-C), 133.2 (Ar-C), 130.0 (Ar-C), 129.81 (Ar-C), 129.79 (Ar-

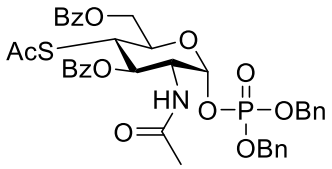
C), 128.9 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 117.8 (*C*H_2=), 99.8 (C1), 72.8 (C5), 72.3 (C3), 69.8 (O*C*HH), 64.1 (C6), 56.0 (C2), 44.7 (C4), 30.8 (Ac-CH_3), 23.3 (Ac-CH_3); HRMS *m/z* (ES^+) [Found: $(M+H)^+$ 528.1690, $C_{27}H_{30}O_8NS$ requires M^+ 528.1687].

2-Acetamido-4-*S*-acetyl-3,6-di-*O*-benzoyl-2-deoxy-4-thio-β-D-glucopyranoside 177



Tetrakis(triphenylphosphine)palladium (245 mg, 0.212 mmol, 0.5 equiv.) was added to a solution of **176** (224 mg, 0.425 mmol,1.0 equiv.) in AcOH (5 mL) and the resulting mixture was heated at 80 °C. After 1 hr, the mixture was concentrated under reduced pressure and the crude residue purified by column chromatography (hexane/EtOAc, 0-100%) to yield **177** (166 mg, 0.340 mmol, 80%) as a yellow oil. R_f = 1.0 (hexane:EtOAc, 4:6); $[\alpha]_D^{23}$= 51.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.08 (m, 2H, Ar*H*), 8.02 – 7.95 (m, 2H, Ar*H*), 7.61 – 7.53 (m, 2H, Ar*H*), 7.53 – 7.40 (m, 4H, Ar*H*), 6.00 (d, *J* = 9.3 Hz, 1H, N*H*), 5.55 (t, *J* = 10.8 Hz, 1H, H-3), 5.38 (t, *J* = 3.2 Hz, 1H, H-1), 4.62 (dd, *J* = 12.1, 2.1 Hz, 1H, H-6a), 4.53 – 4.43 (m, 3H, H-2, H-5, H-6b), 4.17 (t, *J* = 11.2 Hz, 1H, H-4), 4.00 (s, 1H, 1-OH), 2.19 (s, 3H, SAc), 1.85 (s, 3H, Ac); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.4 (C=O, SAc), 170.4 (C=O, Ac), 170.0 (C=O, Bz), 166.5 (C=O, Bz), 133.5 (Ar-C), 133.3 (Ar-C), 130.0 (Ar-C), 129.9 (Ar-C), 129.7 (Ar-C), 129.0 (Ar-C), 128.53 (Ar-C), 128.48 (Ar-C), 92.0 (C1), 70.6 (C3), 68.7 (C5), 63.8 (C6), 53.6 (C2), 44.1 (C4), 30.70 (Ac-CH_3), 23.2 (Ac-CH_3); HRMS *m/z* (ES^+) [Found: $(M+Na)^+$ 510.1192, $C_{24}H_{25}O_8NSNa$ requires M^+ 510.1193].

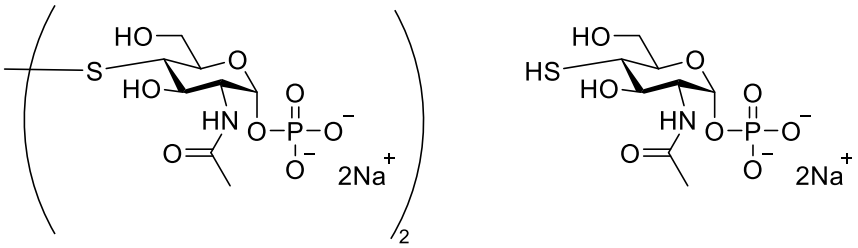
Dibenzyl 2-acetamido-4-*S*-acetyl-3,6-di-*O*-benzoyl-2-deoxy-4-thio-β-D-glucopyranoside phosphate **178**



A solution of **177** (166 mg, 0.340 mmol, 1.0 equiv.) in THF (10 mL) was cooled to −78 °C under a nitrogen atmosphere and LDA (0.18 mL, 40.0 mg, 0.374 mmol, 1.1 equiv.) was added dropwise. After 15 mins, a solution of tetrabenzyl pyrophosphate (238 mg, 0.442 mmol, 1.3 equiv.) in THF (1 mL) was added. The reaction was warmed to 0 °C after stirring for 1 hr at this temperature TLC analysis revealed reaction completion (R_f = 0.63, hexane:EtOAc, 4:6). The solution was diluted with DCM (50 mL), washed with sat. aq. $NaHCO_3$ (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-50%) to yield **178** (105 mg, 0.123 mmol, 66%) as a white foam. R_f = 0.63 (hexane:EtOAc, 4:6); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.04 (m, 2H, Ar*H*), 7.96 (m, 2H, Ar*H*), 7.57 (m, 2H, Ar*H*), 7.44 (m, *J* = 7.5, 5.8 Hz, 4H, Ar*H*), 7.39 – 7.32 (m, 10H, Ar*H*), 5.80 (dd, *J* = 5.9, 3.2 Hz, 1H, H-1), 5.73 (d, *J* = 8.8 Hz, 1H, N*H*), 5.39 (t, *J* = 10.6 Hz, 1H, H-3), 5.16 – 5.00 (m, 4H, 2 x CH_2Ph), 4.59 – 4.51 (m, 1H, H-2), 4.49 – 4.38 (m, 2H, H-6a, H-6b), 4.15- 4.18 (m, 2H, H-4, H-5), 2.19 (s, 3H, SAc), 1.61 (s, 3H, Ac); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9 (C=O, SAc), 170.2 (C=O, Ac), 166.7 (C=O, Bz), 166.2 (C=O, Bz), 135.4 (Ar-C), 135.3 (Ar-C), 133.6 (Ar-C), 133.2 (Ar-C), 130.0 (Ar-C), 129.8 (Ar-C), 129.6 (Ar-C), 128.97 (Ar-C), 128.95 (Ar-C), 128.83 (Ar-C), 128.78 (Ar-C), 128.7 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 128.2 (Ar-C), 128.1 (Ar-C), 96.8 (d, $^2J_{C\text{-}P}$ = 6.4 Hz, C1), 70.7 (C5), 70.1 (d, $^2J_{C\text{-}P}$ = 5.6 Hz, *C*H_2Ph), 69.9 (d, $^2J_{C\text{-}P}$ = 5.6 Hz, *C*H_2Ph), 69.7 (C3), 63.2 (C6), 53.1 (d, $^3J_{C\text{-}P}$ = 7.6 Hz, C2), 43. 4 (C4), 30.7 (Ac-CH_3), 22.8 (Ac-

CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ -2.14 – -2.47 (m); HRMS *m/z* (ES^+) [Found: $(M+Na)^+$ 770.1784, $C_{38}H_{38}O_{12}NPSNa$ requires M^+ 770.1800].

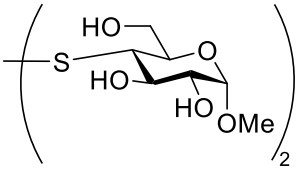
2-Acetamido-2-deoxy-4-thio-α-D-glucopyranoside phosphate (disodium salt) 161 & bis(2-acetamido-2-deoxy-4-thio-α-D-glucopyranoside phosphate (disodium salt)-4,4'-disulfide 179



Pd/C 10% wt. (50 mg, 0.047 mmol, 0.56 equivs.) was added to a solution of **178** (62.0 mg, 0.083 mmol, 1 equiv.) in MeOH (5 mL) and the resulting solution stirred under a H_2-atmosphere. After 1 hr TLC analysis revealed a baseline spot (DCM/MeOH, 7:3) indicating complete removal of the benzyl groups. The solution was filtered using a Fisherbrand™ Non-sterile PTFE Syringe Filter (0.20 μm). The filtrate was condensed under reduced pressure and 1M NaOH aq. (5 mL) was added. The resulting solution was stirred overnight and then neutralised by the addition of Amberlite IR20 H^+ resin. The reaction mixture was filtered, washed with MeOH (25 mL) and H_2O (25 mL) and the filtrate was concentrated under reduced pressure. The crude residue was dissolved in the minimal amount of H_2O and purified by strong anion exchange chromatography (Bio-Scale™ Mini UNOsphere™ Q) eluting with H_2O (15 mL) then 1M $(NH_4)_2CO_3$) (15 mL). Fractions containing the desired 1-phosphate lyophilized (1× 10 mL, H_2O) to afford the title compounds (16.0 mg, 50.7μmol, 62%) as a white fluffy solid. ^1H NMR (400 MHz, D_2O) δ 5.41 – 5.33 (m, 1H, H-1), 4.05 – 3.82 (m, 4H, H-6a, H-6b, H-2, H-5), 3.65 (t, *J* = 10.2 Hz, 1H, H-3), 2.76 (t, *J* = 10.3 Hz, 1H, H-4), 2.00 (s, 3H, Ac); ^{13}C NMR (101 MHz, D_2O) δ 174.7 (C=O, Ac), 93.1 (C1), 74.1 (C5), 72.1 (C3), 61.5 (C6), 55.0 (C2), 42.2 (C4),

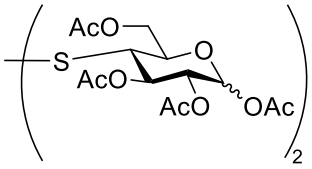
22.1 (Ac-CH_3); ^{31}P NMR (162 MHz, D_2O) δ 1.01 – 0.92 (m), 0.72 – 0.64 (m); HRMS *m/z* (ES^+) [Found: $(M+Na)^+$ 653.0246, $C_{16}H_{28}O_{16}N_2P_2S_2Na$ requires M^+ 653.0.259].

Bis(Methoxy 4-deoxy-4-thio-α-D-glucopyranoside)-4,4'-disulfide 182



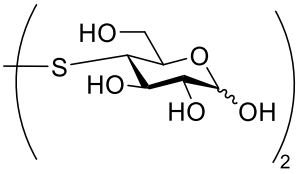
A solution of methyl 4-*S*-acetyl-2,3,6-tri-*O*-benzoyl-4-thio-α-D-glucopyranoside **39** (300 mg, 0.510 mmol, 1.0 equiv.) in MeOH (5 mL) was treated with 1M NaOH (5 mL). The reaction mixture was left stirring at RT for 24 hrs, followed by addition of Amberlite IR20 (H^+) ion exchange resin until the pH of the reaction mixture was neutral. The mixture was filtered, washed with methanol (25 mL) and then the filtrate was concentrated under reduced pressure. A solution of the crude residue in MeCN (25 mL) was treated with Et_3N (52.0 mg, 0.510 mmol., 1.0 equiv.) and the reaction was sonicated for 1 h 30 mins. After removal of the solvent under reduced pressure the crude residue was purified by column chromatography (DCM/MeOH, 0-20%) to deliver disulfide **182** (95.0 mg, 0.453 mmol, 89%) as a white amorphous foam. R_f = 0.22 (DCM/MeOH, 9:1); $[\alpha]_D^{26}$ = -61.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, MeOD) δ 4.71 (d, *J* = 3.6 Hz, 1H, H-1), 3.94 – 3.88 (m, 2H, H-6a, H-6b), 3.82 – 3.73 (m, 2H, H-3, H-5), 3.46 (dd, *J* = 9.3, 3.6 Hz, 1H, H-2), 3.39 (s, 3H, OMe), 2.74 (t, *J* = 10.7 Hz, 1H, H-4); ^{13}C NMR (101 MHz, MeOD) δ 99.9 (C1), 73.4 (C2), 71.9 (C5), 69.4 (C3), 61.6 (C6), 54.4 (OCH_3), 54.3 (C4); HRMS *m/z* (ES^-) [Found: $(M-H)^-$ 417.0896 $C_{14}H_{25}O_{10}S_2$ requires M^-, 417.0895].

Bis(1,2,3,6-tetra-*O*-acetyl-4-deoxy-4-thio-α/β-D-glucopyranoside)-4,4'-disulfide **183**



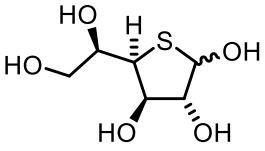
Bis(methy 4-deoxy-4-thio-α/β-D-glucopyranoside)-4,4'-disulfide **182** (95.0 mg, 0.453 mmol, 1.0 equiv.) was dissolved in Ac_2O/AcOH/H_2SO_4 (35:15:1 *v/v/v*, 3.00 mL). After being stirred overnight, the mixture was diluted with $CHCl_3$ (100 mL) and washed successively with water (100 mL), sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated and the crude residue was purified by column chromatography (hexane/EtOAc, 0-50%) to deliver disulfide **183** (78.0 mg, 0.215 mmol, 47%, α/β, 1:0.2) as a white amorphous foam. R_f = 0.42 (hexane/EtOAc, 1:1); **α**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (d, *J* = 3.6 Hz, 1H, H-1), 5.47 – 5.41 (t, *J* = 10.1 Hz, 1H, H-3), 5.03 (dd, *J* = 9.9, 3.6 Hz, 1H, H-2), 4.53 (dd, *J* = 12.3, 2.1 Hz, 1H, H-6a), 4.39 (dd, *J* = 12.3, 4.2 Hz, 1H, H-6b), 4.17 – 4.06 (m, 1H, H-5), 3.11 (t, *J* = 11.1 Hz, 1H, H-4), 2.17 (s, 3H, OAc), 2.15 (s, 3H, OAc), 2.14 (s, 3H, OAc), 2.01 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 89.3 (C1), 71.1 (C5), 70.5 (C2), 68.8 (C3), 62.7 (C6), 52.2 (C4), 20.91 (Ac-CH_3), 20.85 (Ac-CH_3), 20.7 (Ac-CH_3), 20.5 (Ac-CH_3); **β**: ^{1}H NMR (400 MHz, $CDCl_3$) selected signals δ 5.65 (d, *J* = 8.3 Hz, 1H, H-1), 5.25 (dd, *J* = 10.7, 9.2 Hz, 1H, H-3), 4.70 (dd, *J* = 12.3, 2.0 Hz, 1H, H-6a), 4.30 (dd, *J* = 12.3, 5.3 Hz, 1H, H-6b), 3.96 (ddd, *J* = 10.8, 5.3, 2.0 Hz, 1H, H-5), 2.94 (t, *J* = 10.7 Hz, 1H, H-4). ^{13}C NMR (101 MHz, $CDCl_3$) selected signals from HSQC; δ 91.2 (C1), 73.6 (C5), 71.3 (C3), 62.9 (C6), 50.7 (C4); HRMS *m/z* (ES^+) [Found: $(M+Na)^+$ 749.1387 $C_{28}H_{38}O_{18}S_2Na$ requires M^+, 749.1392].

Bis(4-deoxy-4-thio-α/β-D-glucopyranose)-4,4'-disulfide 181



A solution of bis(1,2,3,6-tetra-*O*-acetyl-4-deoxy-4-thio-α/β-D-glucopyranoside)-4,4'-disulfide **183** (65.0 mg, 0.179 mmol., 1.0 equiv.) in MeOH (5 mL) was treated with 1M NaOH (5 mL) and the reaction mixture was left stirring at RT for 1 hr. The reaction mixture was neutralised with Amberlite IR20 (H^+) ion exchange resin, after which the resin was filtered and washed with methanol (25 mL). The filtrate was concentrated under reduced pressure and the crude residue was purified by column chromatography (DCM/MeOH, 0-30%), lyophilisation delivered **181** (27.0 mg, 0.138 mmol, 77%, α/β, 0.7:1) as a fluffy white solid. R_f = 0.54 (DCM/MeOH, 7:3); **α**: ^{1}H NMR (400 MHz, D_2O) δ 5.28 (d, *J* = 3.6 Hz, 1H, H-1), 4.15 – 4.07 (m, 1H, H-5), 4.03 – 3.89 (m, 3H, H-6a, H-6b, H-3), 3.62 (dt, *J* = 9.5, 3.7 Hz, 1H, H-2), 2.81 – 2.71 (m, 1H, H-4). ^{13}C NMR (101 MHz, D_2O) δ 92.1 (C1), 72.7 (C2), 71.2 (C5), 68.6 (C3), 61.3 (C6), 53.8 (C4); **β**: ^{1}H NMR (400 MHz, D_2O) δ 4.61 (d, *J* = 8.0 Hz, 1H, H-1), 4.13 – 4.04 (m, 1H, H-6a), 4.03 – 3.91 (m, 1H, H-6b), 3.81 – 3.71 (m, 2H, H-3, H-5), 3.36 – 3.29 (m, 1H, H-2), 2.83 – 2.67 (m, 1H, H-4). ^{13}C NMR (101 MHz, D_2O) δ 95.5 (C1), 75.7 (C3 or C5), 75.4 (C2), 72.0 (C3 or C5), 61.3 (C6), 54.0 (C4); HRMS *m/z* (ES^-) [Found: $(M-H)^-$ 389.0579 $C_{12}H_{21}O_{10}S_2$ requires M^-, 389.0582].

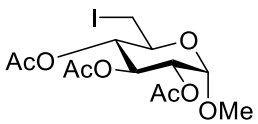
4-Thio-α/β-D-glucofuranose 180



A solution of **40** (317 mg, 0.535 mmol., 1.0 equiv.) and DTT (91.0 mg, 0.590 mmol, 1.1 equiv.) in MeOH (5 mL) was treated with 1M NaOH (5 mL) and the reaction mixture was left stirring at RT for 1 h. The reaction mixture was neutralised with Amberlite IR20 (H^+) ion exchange resin, the mixture was filtered, washed with methanol (25 mL) and the filtrate concentrated under reduced pressure. To the crude residue was added diethyl ether (50 mL), after stirring for 5 mins the diethyl ether was decanted, this step was repeated a further 3 times. Lyophilisation (1×10 mL, H_2O) of the resulting residue delivered **180** (100 mg, 0.510 mmol, 95%, α/β, 1:0.6) as a fluffy white solid. R_f = 0.54 (DCM/MeOH, 7:3); α: ^{1}H NMR (400 MHz, D_2O) δ 5.64 (d, *J* = 4.1 Hz, 1H, H-1), 4.46 – 4.43 (m, 1H, H-3), 4.21 (t, *J* = 4.0 Hz, 1H, H-2), 3.86 (ddd, *J* = 9.2, 5.9, 2.7 Hz, 1H, H-5), 3.79 (dd, *J* = 9.2, 4.3 Hz, 1H, H-4), 3.69 (dd, *J* = 12.2, 2.7 Hz, 1H, H- 6a), 3.54 (dd, *J* = 12.2, 5.9 Hz, 1H, H-6b). ^{13}C NMR (101 MHz, D_2O) δ 80.1 (C1), 77.3 (C2), 75.9 (C3), 71.2 (C5), 64.9 (C6), 49.1 (C4); β: ^{1}H NMR (400 MHz, D_2O) δ 5.33 (app t, *J* = 1.1 Hz, 1H, H-1), 4.43 – 4.40 (m, 1H, H-3), 4.38 (app t, *J* = 2.0 Hz, 1H, H-2), 4.09 (ddd, *J* = 9.6, 6.0, 2.8 Hz, 1H, H-5), 3.74 (dd, *J* = 12.1, 2.8 Hz, 1H, H-6a), 3.66 (dd, *J* = 9.6, 4.2 Hz, 1H, H-4), 3.57 (dd, *J* = 12.1, 6.0 Hz, 1H, H-6b). ^{13}C NMR (101 MHz, D_2O) δ 86.1 (C1), 82.2 (C2), 76.8 (C3), 71.4 (C5), 65.2 (C6), 52.0 (C4); HRMS *m/z* (ES^-) [Found: $(M-H)^-$ 195.0333, $C_6H_{11}O_5S$ requires M^- 195.0333].

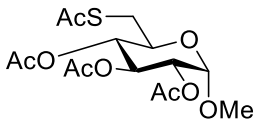
6.4 Chapter 5 compounds

Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside 189



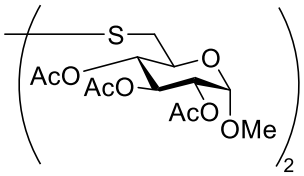
PPh_3 (4.16 g, 15.9 mmol, 1.1 equiv.) and imidazole (1.38 g, 20.2 mmol, 1.4 equiv.) were added to a mixture of methyl-α-D-glucopyranoside **56** (3.00 g, 15.5 mmol, 1.0 equiv.) in THF (150 mL) at RT. The reaction mixture was warmed to 70 °C, and then a solution of I_2 (4.33 g, 17.1 mmol, 1.1 equiv.) in THF (50 mL) was added dropwise over 3 hrs. After 2 hrs, completion of the reaction was confirmed by TLC (R_f = 0.25, EtOAc), the mixture was cooled to RT, and then pyridine (7.52 mL, 7.36 g, 93.0 mmol, 6.0 equiv.) and Ac_2O (7.33 mL, 7.91 g, 77.5 mmol, 5.0 equiv.) were added to the mixture. The mixture was warmed to 35 °C and stirred for 17 hrs. After completion of the reaction as seen by TLC (R_f = 0.46, hexane/EtOAc, 7:3), EtOAc (100 mL) was added, and the organic layer was separated. The organic layer was washed with sat. aq. $Na_2S_2O_3$(100 mL) and brine (100 mL). *i*-PrOH (100 mL) was added, and the mixture was concentrated. Precipitation was observed during the concentration and further *i*-PrOH (100 mL) was added to the slurry, cooled to 0 °C and stirred for 1 hr. The solid was filtered and washed with cold *i*-PrOH (100 mL) to afford the title compound as a white solid (4.71 g, 11.0 mmol, 71%). R_f = 0.46 (hexane/EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (t, *J* = 10.0 Hz, 1H, H-3), 4.96 (d, *J* = 3.7 Hz, 1H, H-1), 4.88 (dd, *J* = 10.3, 3.7 Hz, 1H, H-2), 4.87 (t, *J* = 9.6 Hz, 1H, H-4), 3.83 – 3.76 (m, 1H, H-5), 3.48 (s, 3H, OMe), 3.30 (dd, *J* = 10.9, 2.5 Hz, 1H, H-6a), 3.14 (dd, *J* = 10.9, 8.3 Hz, 1H, H-6b), 2.08 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.01 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1 (C=O, Ac), 170.0 (C=O, Ac), 169.7 (C=O, Ac), 96.7 (C1), 72.5 (C4), 70.9 (C2), 69.7 (C3), 68.6 (C5), 55.8 (OCH_3), 20.7 (Ac-CH_3), 20.7 (Ac-CH_3), 20.7 (Ac-CH_3), 3.6 (C6); HRMS *m/z* (ES^+) Found: $(M+NH_4)^+$ 448.0469, $C_{13}H_{23}NO_8I$ requires M^+ 448.0463. Data matched those reported previously.[202]

Methyl 6-deoxy-6-*S*-acetyl-6-thio-2,3,4-tri-*O*-acetyl-α-D-glucopyranoside 190



Methy1 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside **189** (2.00 g, 4.65 mmol, 1.0 equiv.) and KSAc (1.27 g, 11.2 mmol, 2.4 equiv.) in acetone (100 mL) was refluxed for 1 hr. Upon reaction completion as seen by TLC (R_f = 0.36, hexane/EtOAc, 7:3), the mixture was filtered, and the filtrate concentrated under reduced pressure. The crude residue was dissolved in EtOAc (100 mL), washed with water (100 mL), brine (100 mL), dried ($MgSO_4$) and filtered. The combined organic phases were evaporated under reduced pressure and purified by column chromatography (hexane/EtOAc, 0-50%) yielding the title compound (1.23 g, 3.25 mmol, 70%) as a white solid. R_f = 0.33 (hexane/EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (t, *J* = 9.7 Hz, 1H, H-3), 4.94 (t, *J* = 9.6 Hz, 1H, H-4), 4.89 (d, *J* = 3.7 Hz, 1H, H-1), 4.86 (dd, *J* = 10.1, 3.7 Hz, 1H, H-2), 3.92 (ddd, *J* = 10.0, 7.0, 3.0 Hz, 1H, H-5), 3.40 (s, 3H, OMe), 3.21 (dd, *J* = 14.2, 3.0 Hz, 1H, H-6a), 3.07 (dd, *J* = 14.2, 7.0 Hz, 1H, H-6b), 2.35 (s, 3H, SAc), 2.08 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.00 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.6 (C=O, SAc), 170.1 (C=O, Ac), 170.0 (C=O, Ac), 169.9 (C=O, Ac), 96.6 (C1), 70.94 (C4), 70.88 (C2), 70.0 (C3), 68.2 (C5), 55.4 (OCH_3), 30.4 (Ac-CH_3), 30.0 (C6), 20.72 (2 × Ac-CH_3), 20.68 (Ac-CH_3); HRMS *m/z* (ES^+) Found: $(M+NH_4)^+$ 396.1320, $C_{15}H_{26}NO_9S$ requires M^+ 396.1323. Data matched those reported previously.[203]

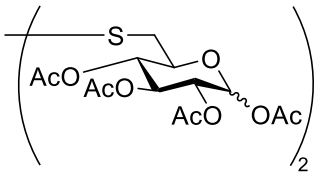
Bis(methoxy 2,3,4-tri-*O*-acetyl-6-thio-α-D-glucopyranoside)-6,6'-disulfide 191



To a solution of **190** (487 mg, 1.29 mmol, 1.0 equiv.), in MeCN (10 mL) was added I_2 (819 mg, 3.22 mmol, 2.5 equiv) and NIS (145 mg, 0.645 mmol, 0.5 equiv.). The reaction mixture was stirred at RT for 2 hrs. When TLC indicated full conversion of the starting

material (R_f = 0.29, hexane/EtOAc, 7:3), the resulting mixture was diluted with water (50 mL), then extracted with DCM (50 mL). The combined organic phases were washed with sat. aq. $Na_2S_2O_3$ (50 mL), brine (50 mL), dried ($MgSO_4$), and filtered. After removal of the solvent under reduced pressure the crude residue was purified by column chromatography affording the title compound as a colourless oil (330 mg, 0.984 mmol, 76%). R_f = 0.29 (hexane/EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (dd, *J* = 10.1, 9.4 Hz, 1H, H-3), 4.95 – 4.78 (m, 3H, H-1, H-2, H-4), 4.02 (td, *J* = 9.9, 2.8 Hz, 1H, H-5), 3.44 (s, 3H, OMe), 2.92 (dd, *J* = 13.8, 2.9 Hz, 1H, H-6a), 2.84 (dd, *J* = 13.8, 8.7 Hz, 1H, H-6b), 2.07 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.01 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3 (C=O, Ac), 168.1 (C=O, Ac), 168.0 (C=O, Ac), 94.7 (C1), 69.9 (C2), 69.0 (C4), 68.1 (C3), 65.6 (C5), 53.7 (OCH_3), 39.6 (C6), 18.83 (2 × Ac-CH_3), 18.8 (Ac-CH_3); HRMS *m/z* (ES^+) Found: $(M+NH_4)^+$ 688.1940, $C_{26}H_{42}NO_{16}S_2$ requires M^+ 688.1940. Data matched those previously reported.[204]

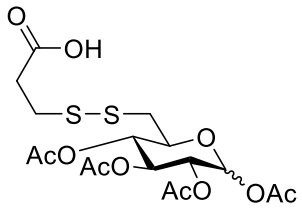
Bis(1,2,3,4-tetra-*O*-acetyl-6-thio-α/β-D-glucopyranoside)-6,6'-disulfide 192



A solution of **191** (369 mg, 1.10 mmol, 1.0 equiv.) was dissolved in Ac_2O (5 mL) and H_2SO_4 (100 µL). The resulting mixture was stirred overnight at RT and upon reaction completion as seen by TLC (R_f = 0.19 (hexane/EtOAc, 6:4), the mixture was diluted with $CHCl_3$ (100 mL), washed with water (50 mL), sat. aq. $NaHCO_3$ (3 × 50 mL) and brine (50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-40%) yielding the title compound (272 mg, 0.749 mmol, 68%, α/β, 1:0.25) as a yellow oil. R_f = 0.19 (hexane/EtOAc, 6:4); **Selected signals:** ^{1}H NMR (400

MHz, $CDCl_3$) δ 6.31 (d, *J* = 3.7 Hz, 1H, H-1α), 5.71 (d, *J* = 8.28 Hz, 1H, H-1β), 5.46 (t, *J* = 9.8 Hz, 1H, H-3α), 5.13 – 4.97 (m, 2H, H-2α, H-4α), 4.19 – 4.12 (m, 1H, H-5α), 2.94 (dd, *J* = 14.1, 3.4 Hz, 1H, H-6bα), 2.82 (dd, *J* = 14.1, 7.5 Hz, 1H, H-6aα), 2.18 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.01 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2 (C=O, Ac), 169.67 (C=O, Ac), 169.66, 168.7 (C=O, Ac), 91.6 (C1β), 88.9 (C1α), 71.1 (C4α), 70.2 (C5α), 69.7 (C3α), 69.3 (C2α), 41.3 (C6α), 20.9 (Ac-CH_3), 20.70 (Ac-CH_3), 20.66 (Ac-CH_3), 20.5 (Ac-CH_3); HRMS *m/z* (ES^+) Found: $(M+H)^+$ 726.1489, $C_{28}H_{39}O_{18}S_2$ requires M^+ 726.1499.

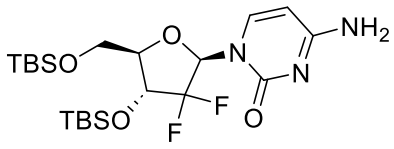
1,2,3,4-Tetra-*O*-acetyl-6-deoxy-*S*-mercaptopropionic-acid-6-thio-α/β-D-glucopyranoside 193



To a solution of 1**92** (493 mg, 1.36 mmol, 1.0 equiv.) in MeCN (5 mL) was added DTT (230 mg, 1.49 mmol, 1.1 equiv.) and the mixture was stirred overnight at RT. After evaporation of the solvent under reduced pressure, THF (5 mL) and NaH (33.0 mg, 1.36 mmol, 1.0 equiv.) were added and the mixture was cooled to -20 °C. A solution of TCCA (316 mg, 1.36 mmol, 1.0 equiv.) in MeCN (5 mL) was added, followed by quick addition of 3-mercaptopropionic acid (0.18 mL, 217 mg, 2.04 mmol, 1.5 equiv.). The reaction mixture was kept stirring for 20 min at -20 °C, at this point TLC revealed reaction completion (R_f = 1.0, EtOAc) and the solvent was removed under reduced pressure. The crude residue was purified directly by column chromatography (hexane/EtOAc, 0-100%) to deliver the title compound as a colourless oil (326 mg, 0.696 mmol, 51%, 4:1, α/β,). R_f = 1.0 (EtOAc), **Selected signals:** ^1H NMR (400 MHz, $CDCl_3$) δ 6.32 (d, *J* = 3.7 Hz,

1H, αH-1), 5.73 (d, *J* = 8.2 Hz, 1H, βH-1), 5.50 – 5.43 (t, *J* = 9.8 Hz, 1H, H-3), 5.07 (dd, *J* = 10.3, 3.7 Hz, 1H, H-2), 5.01 (at, *J* = 10.0 Hz 1H, H-4), 4.17 (ddd, *J* = 10.4, 7.8, 2.8 Hz, 1H, H-5), 2.99 – 2.88 (m, 3H, H-6a, CH_2), 2.86 – 2.72 (m, 3H, H-6b, CH_2), 2.18 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.02 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9 (C=O), 170.3 (C=O, Ac), 169.74 (C=O, Ac), 169.73 (C=O, Ac), 168.9 (C=O, Ac), 91.7 (C1β), 88.9 (C1α), 71.1 (C4), 70.2 (C5), 69.8 (C3), 69.3 (C2), 41.3 (C6), 33.7 (CH_2), 32.8 (CH_2), 20.9 (Ac-CH_3), 20.7 (Ac-CH_3), 20.7 (Ac-CH_3), 20.5 (Ac-CH_3); HRMS *m/z* (ES^-) Found: $(M-H)^-$ 467.0694, $C_{17}H_{23}NO_{11}S_2$ requires M^- 467.0687.

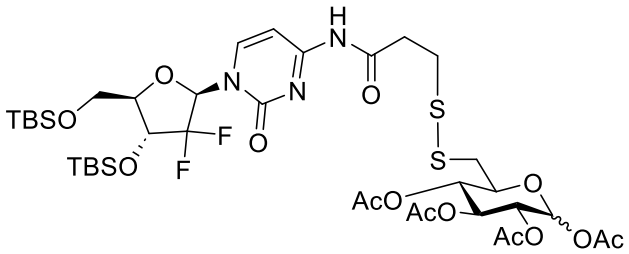
3',5'-di-*O*-TBS-2'-deoxy-2'-gem-difluoro-1'-(β-D-ribofuranosyl)cytosine 200



A solution of Gemcitabine (200 mg, 0.760 mmol, 1.0 equiv.) in DMF (20.0 mL) was treated with imidazole (155 mg, 2.28 mmol, 3.0 equiv.) and TBDMSCl (0.59 mL, 627 mg, 2.28 mmol, 3.0 equiv.). After stirring at RT for 24 hrs TLC analysis revealed reaction completion (R_f = 0.57, DCM/MeOH, 9:1). The resulting mixture was diluted with water (50 mL), then extracted with DCM (50 mL). The combined organic phases were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (DCM/MeOH, 0-10%) to yield the title compound (322 mg, 0.656 mmol, 86%) as a crystalline white solid. R_f = 0.57 (DCM/MeOH, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.5 Hz, 1H, CH), 6.20 (dd, $^3J_{H\text{-}1'\text{-}Fa/Fb}$ = 10.8, 4.5 Hz, H-1'), 5.70 (d, *J* = 7.5 Hz, 1H, CH), 4.19 (td, *J* = 11.5, 8.1 Hz, 1H, H-3'), 3.87 (d, *J* = 11.7 Hz, 1H, H-5a'), 3.76 (ad, *J* = 8.0 Hz, 1H, H-4'), 3.68 (dd, *J* = 11.8, 2.1 Hz, 1H, H-5b'), 0.82 (s, 9H, Si-^{t}Bu), 0.79 (s, 9H, Si-^{t}Bu), 0.02 – 0.01 (m, 12H, Si-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0 (C-NH_2, C4), 155.7 (C=O, C2),

140. 4 (C6), 122.1 (d, $^{1}J_{C\text{-}F}$ = 259.2 Hz, 120.79, d, $^{1}J_{C\text{-}F}$ = 260.7 Hz, C2'), 95.4 (C5), 84.2 (dd, $^{2}J_{C\text{-}F}$ = 40.6, 23.2 Hz, C1'), 80.9 (d, = $^{3}J_{C\text{-}F}$ = 8.8 Hz, C4'), 69.8 (dd, $^{2}J_{C\text{-}F}$ = 18.2 Hz, C3'). 60.1 (C5', 25.8 (Si-^{t}Bu), 25.5(Si-^{t}Bu), 18.3 (Si-^{t}Bu), 18.0 (Si-^{t}Bu), -4.8 (Si-CH_3), -5.3 (Si-CH_3), -5.46 (Si-CH_3), -5.51 (Si-CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ -115.92 (dd, *J* = 238.0, 11.7 Hz), -117.52 (dt, *J* = 238.7, 10.6 Hz); HRMS *m/z* (ES^+) Found: $(M+Na)^+$ 514.2336, $C_{21}H_{39}N_3O_4F_2Si_2Na$ requires M^+ 514.2339. Data matched those previously reported.[205]

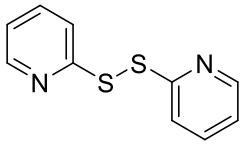
OAc/TBS-*O*-Glucose-gemcitabine **201**



To a solution of **193** (105 mg, 0.224 mmol, 1.0 equiv.) in DCM (10 mL) was added EDC (104 mg, 0.671 mmol, 3.0 equiv.) followed by DMAP (2.74 µg, 22.4 µmmol, 0.1 equiv.). The reaction mixture was stirred at RT for 15 min. **200** (220 mg, 0.448 mmol, 2.0 equiv.) was next added and the reaction mixture was stirred for a further 45 min. TLC analysis revealed reaction completion (R_f = 0.86, EtOAc/hexane, 7:3). The reaction mixture was diluted with DCM (50 mL) and washed with sat. aq. $NaHCO_3$ (2 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography (hexane/EtOAc, 0-30%) delivered the title compound (139 mg, 0.146 mmol, 65%, 1:0.15, α/β) as a colourless oil. R_f = 0.86 (EtOAc/hexane, 7:3); **Selected Signals:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H, NH'), 8.07 (d, *J* = 7.5 Hz, 1H, CH'), 7.40 (d, *J* = 7.1 Hz, 1H, CH'), 6.37 – 6.28 (m, 2H, H-1'', H-1α), 5.68 (d, *J* = 8.3 Hz, 1H, H-1β), 5.47 (t, *J* = 9.8 Hz, 1H, H-3α), 5.08 (dd, *J* = 10.3, 3.7 Hz, 1H, H-2α), 5.02 (t, *J* = 9.7 Hz, 1H, H-4α), 4.34 (td, *J* = 11.6, 8.2 Hz, 1H, H-3''),

4.16 – 4.10 (m, 1H, H-5α), 4.02 (d, *J* = 11.8 Hz, 1H, H-5a''), 3.96 (d, *J* = 8.0 Hz, 1H, H-4''), 3.81 (dd, *J* = 11.9, 1.8 Hz, 1H, H-5b''), 3.06 – 2.87 (m, 5H, H-6aα, 2 × CH_2), 2.78 (dd, *J* = 14.2, 7.7 Hz, 1H, H-6bα), 2.20 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.02 (s, 3H, OAc), 0.95 (s, 9H, Si-^{t}Bu), 0.91 (s, 9H, Si-^{t}Bu), 0.13 (s, 3H, Si-CH_3), 0.13 (s, 3H, Si-CH_3), 0.13 (s, 3H, Si-CH_3), 0.10 (s, 3, Si-CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ -115.92 (dd, *J* = 239.4, 12.3 Hz), -117.37 (dt, *J* = 239.9, 10.6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): 170.2, 169.8 (C=O), 169.6 (C=O), 169.1 (C=O), 144.4 (CH'), 96.8 (CH'), 91.8 (C1β), 88.9 (C1α), 84.7 (C1''), 71.0 (C4α), 70.2 (C5α), 69.7 (C3α), 69.3 (C2α), 60.0 (C5''), 41.5 (C6α), 36.9 (CH_2), 32.5 (CH_2), 25.9 (Si-^{t}Bu''), 25.5 (Si-^{t}Bu''), 20.9 (Ac-CH_3), 20.72 (Ac-CH_3), 20.68 (Ac-CH_3), 20.5 (Ac-CH_3), 18.3 (Si-^{t}Bu''), 18.0 (Si-^{t}Bu''), -4.8 (Si-CH_3), -5.3 (Si-CH_3), -5.4 (Si-CH_3), -5.5 (Si-CH_3).

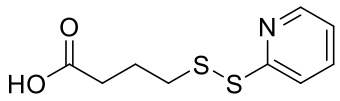
Bis(2-pyridinyl) disulfide **203**



To a solution of 2-mercaptopyridine (2.50 g, 22.5 mmol, 1.0 equiv.) in DMSO (2 mL) was added I_2 (571 mg, 2.25 mmol, 0.1 equiv.) the resulting mixture was stirred at RT for 1 hr. TLC analysis revealed complete consumption of the starting material (R_f = 0.54, hexane/EtOAc, 1:1) the mixture was diluted with DCM (50 mL) and washed with sat. aq. $Na_2S_2O_3$· (100 mL) and brine (100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-50%) to yield the title compound (3.79 g, 17.2 mmol, 77%) as a yellow oil. R_f = 0.54 (hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 – 8.42 (m, 2H, ArH), 7.66 – 7.58 (m, 4H, ArH), 7.17 – 7.06 (m, 2H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 149.6, 137.4, 121.1, 119.7; HRMS *m/z* (ES^+)

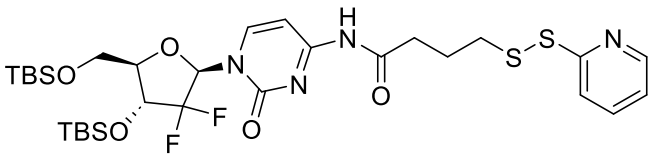
Found: (M+H) $^{+}$ 221.0197, $C_{10}H_9N_2S_2$ requires M^{+} 221.0202. Data matched those previously reported.[206]

4-(2-pyridyldithio)butanoic acid 204



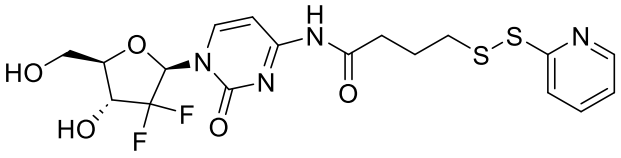
To a solution of bis(2-pyridinyl) disulfide **203** (1.83 g, 8.31 mmol, 2.0 equiv.) in MeOH was added 4-mercaptobutyric acid (0.43 mL, 500 mg, 4.16 mmol, 1.0 equiv.) and the resulting mixture was stirred at RT for 2 hrs. TLC analysis revealed complete consumption of the starting material (R_f = 0.63, DCM/MeOH, 9:1) and the solvent was removed under reduced pressure. The crude residue was directly purified by column chromatography (DCM/MeOH, 0-10%) to deliver the title compound (649 mg, 2.83 mmol, 68%) as a colourless oil. R_f = 0.63 (DCM/MeOH, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (bs, 1H, COOH), 8.48 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H, ArH), 7.74 (dt, *J* = 8.1, 1.0 Hz, 1H, ArH), 7.70 – 7.64 (m, 1H, ArH), 7.11 (ddd, *J* = 7.3, 4.9, 1.1 Hz, 1H, ArH), 2.86 (t, *J* = 7.1 Hz, 2H, CH_2), 2.50 (t, *J* = 7.2 Hz, 2H, CH_2), 2.04 (p, *J* = 7.2 Hz, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.7 (C=O), 160.0 (Ar-C), 149.3 (Ar-C), 137.5 (Ar-C), 120.9 (Ar-C), 120.0 (Ar-C), 37.8 (CH_2), 32.4 (CH_2), 23.8 (CH_2); HRMS *m/z* (ES^{+}) Found: $(M+H)^{+}$ 230.0303, $C_9H_{12}O_2NS_2$ requires M^{+} 230.0304. Data matched those previously reported.[207]

4-*N*-(2-pyridyl-disulfanyl-butylcarbonylamino)-3',5'-di-*O*-TBS-2'-deoxy-2'-gem-difluoro-1'-(β-D-ribofuranosyl)cytosine 205



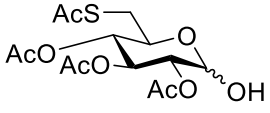
To a solution of 4-(2-pyridyldithio) butanoic acid **204** (113 mg, 0.492 mmol, 2.0 equiv.) in DCM (10 mL) was added EDC (115 mg, 0.738 mmol, 3.0 equiv.) followed by DMAP (3.00 mg, 24.6 μmmol, 0.1 equiv.). The reaction mixture was stirred at RT for 15 min and **206** (121 mg, 0.246 mmol, 1.0 equiv.) was added, the reaction mixture was stirred for a further 1 hr. TLC analysis revealed reaction completion (R_f = 0.66, DCM/MeOH, 9:1) and the reaction mixture was diluted with DCM (50 mL) and washed with sat. aq. $NaHCO_3$ (2 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography (hexane/EtOAc, 0-30%) delivered the title compound (139 mg, 0.198 mmol, 80%) as a colourless oil. R_f = 0.66 (DCM/MeOH, 9:1); $[\alpha]_D^{23}$ = +26.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (bs, 1H, NH), 8.34 – 8.32 (m, 1H, ArH), 7.94 (d, *J* = 7.6 Hz, 1H, CH), 7.58 – 7.44 (m, 2H, ArH), 7.27 (d, *J* = 7.4 Hz, 1H, CH), 6.94 (ddd, *J* = 7.1, 4.8, 1.2 Hz, 1H, ArH), 6.18 (dd, $^3J_{H\text{-}1'\text{-}Fa/Fb}$ = 10.2, 3.6 Hz, 1H, H1'), 4.20 (td, *J* = 11.6, 8.2 Hz, 1H, H-3'), 3.89 (d, *J* = 11.9 Hz, 1H, H-5a'), 3.82 (ad, *J* = 8.0 Hz, 1H, H-4'), 3.68 (dd, *J* = 11.9, 1.7 Hz, 1H, H-5b'), 2.74 (t, *J* = 7.0 Hz, 2H, CH_2), 2.54 (t, *J* = 7.2 Hz, 2H, CH_2), 1.97 (p, *J* = 7.1 Hz, 2H, CH_2), 0.82 (s, 9H, Si-^{t}Bu), 0.77 (s, 9H, Si-^{t}Bu), 0.05 – -0.05 (m, 12H, Si-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0 (C-NH, C4), 160.1 (C=O), 154.9 (C=O, C2), 149.7 (Ar-C), 144.0 (C6'), 137.0 (2 × Ar-C), 120.7 (Ar-C), 119.9 (Ar-C), 97.0 (C5'), 84.7 (dd, $^2J_{C\text{-}F}$ = 40.7, 23.7 Hz, C1'), 81.5 (d, $^3J_{C\text{-}F}$ = 8.8 Hz, C4'), 69.4 (dd, $^2J_{C\text{-}F}$ = 26.8, 18.7 Hz, C3'), 59.96 (C5'), 37.73 (CH_2), 35.6 (CH_2), 25.9 (Si-^{t}Bu), 25.5 (Si-^{t}Bu), 23.69 (CH_2), 18.3 (Si-^{t}Bu), 18.0 (Si-^{t}Bu), -4.8 (Si-CH_3), -5.3 (Si-CH_3), -5.4 (Si-CH_3), -5.5 (Si-CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ -115.98 (dd, *J* = 239.1, 12.2 Hz), -117.35 (dt, *J* = 239.2, 10.6 Hz); HRMS *m/z* (ES$^+$) Found: $(M+H)^+$ 703.2644 $C_{30}H_{49}O_5N_4F_2S_2Si_2$ requires M^+ 703.2645.

4-*N*-(2-pyridyl-disulfanyl-butylcarbonylamino)-2'-deoxy-2'-gem-difluoro-1'-(β-D-ribofuranosyl)cytosine 207



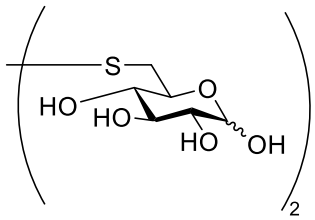
To a solution of **207** (70 mg, 100 µmol, 1.0 equiv.) in THF (2 mL) was added 1M TBAF in THF (0.60 mL, 157.0 mg, 0.600 mmol, 3.0 equiv.) After 2 hrs of stirring TLC analysis revealed reaction completion (R_f = 0.33, DCM/MeOH, 9:1) and the mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$ (2 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography (DCM/MeOH, 0-20%) delivered the title compound (31.0 mg, 65.3 µmmol, 66%) as colourless oil. R_f = 0.33 (DCM/MeOH, 9:1); $[\alpha]_D^{19}$ = +19.5 (*c* = 05.5, $CHCl_3$); ^{1}H NMR (400 MHz, MeOD) δ 8.41 – 8.34 (m, 1H, ArH), 7.90 – 7.76 (m, 3H, ArH, CH), 7.35 – 7.18 (m, 1H, ArH), 6.27 (at, *J* = 8.7 Hz, 1H, H1'), 5.93 (d, *J* = 7.6 Hz, 1H, CH), 5.44 – 5.35 (m, 1H, H3'), 4.15 – 4.11 (m, 1H, H4'), 3.89 (dd, *J* = 12.8, 2.6 Hz, 1H, H-5a'), 3.73 (dd, *J* = 12.8, 3.4 Hz, 1H, H-5b'), 2.88 (t, *J* = 7.1 Hz, 2H, CH_2), 2.62 (t, *J* = 7.2 Hz, 2H, CH_2), 2.07 – 2.00 (m, 2H, CH_2); ^{13}C NMR (101 MHz, MeOD) δ 171.3 (C-NH, C4), 166.3 (C=O), 159.9 (C=O), 149.0 (CH), 137.8 (Ar-C), 121.0 (Ar-C), 119.9 (Ar-C), 95.1 (CH), 84.4 (C1'), 79.4 (d, ^3J = 7.1 Hz, C4'), 69.4 (C2'), 59.27 (C5'), 37.2 (CH_2), 31.3 (CH_2), 23.6 (CH_2); ^{19}F NMR (377 MHz, MeOD) δ -111.22 – -123.14 (m).

2,3,4-Tri-*O*-acetyl-6-deoxy-6-*S*-acetyl-6-thio-α/β-D-glucopyranoside 207



A solution of **190** (1.90 g, 5.03 mmol, 1.0 equiv.) in AcOH (5 mL) and H_2SO_4 (10.0 µL) was stirred for 3 hrs at RT. Upon reaction completion as seen by TLC (R_f = 0.15, hexane/EtOAc, 1:1), the mixture was diluted with DCM (100 mL), washed with water (50 mL), sat. aq. $NaHCO_3$ (3 × 50 mL) and brine (50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-60%) to yield the title compound (1.13 g, 3.11 mmol, 62%, 1:0.15, α/β) as a colourless oil. R_f = 0.15 (hexane/EtOAc, 1:1); **Selected signals:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (d, *J* = 3.7 Hz, 1H, H-1α), 5.71 (d, *J* = 8.3 Hz, 1H, H-1β), 5.46 (t, *J* = 9.7 Hz, 1H, H-3α), 5.07 (dd, *J* = 10.3, 3.8 Hz, 1H, H-2α), 5.01 (t, *J* = 9.7 Hz, 1H, H-4α), 4.19 – 4.13 (m, 1H, H-5α), 2.94 (dd, *J* = 14.1, 3.4 Hz, 1H, H-6aα), 2.82 (dd, *J* = 14.1, 7.4 Hz, 1H, H-6bα), 2.18 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.01 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2 (C=O, Ac), 169.7 (2 × C=O, Ac), 168.7 (C=O, Ac), 91.6 (C1β), 88.9 (C1α), 71.1 (C4α), 70.2 (C5α), 69.8 (C3α), 69.3 (C2α), 41.3 (C6α), 20.8 (Ac-CH_3), 20.69 (Ac-CH_3), 20.65 (Ac-CH_3), 20.5 (Ac-CH_3); HRMS *m/z* (ES^+) Found: $(M+NH_4)^+$ 382.1174, $C_{14}H_{24}O_9SN$ requires M^+ 382.1171.

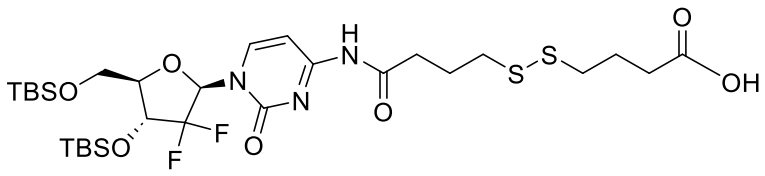
Bis(6-thio-α/β-D-glucopyranoside)-6,6'-disulfide 209



A solution of **207** (186 mg, 0.511 mmol, 1.0 equiv.) in MeOH (5 mL) was treated with Na (1.18 µg, 51.1 µmmol, 0.1 equiv.) The reaction mixture was left stirring at RT for 30 min, TLC analysis revealed reaction completion (R_f = 0.16, DCM/MeOH, 7:3). Amberlite IR20 (H^+) ion exchange resin was added until the pH of the reaction mixture was neutral.

The mixture was filtered, washed with methanol (25 mL) and the filtrate concentrated under reduced pressure, the crude residue was purified by column chromatography (DCM/MeOH, 0-30%) yielding the title compound (84.7 µg, 0.434 mmol, 85%, 1:1, α/β) as a colourless oil. R_f = 0.16 (DCM/MeOH, 7:3); **Selected signals:** ^{1}H NMR (400 MHz, MeOD) δ 5.08 (d, *J* = 3.4 Hz, 1H, H-1α), 4.48 (add, *J* = 7.8, 2.1 Hz, 1H, H-1β), 4.01 (td, *J* = 10.5, 2.1 Hz, 1H), 3.65 (t, *J* = 9.3 Hz, 1H), 3.56 – 3.46 (m, 5H), 3.23 – 3.12 (m, 3H), 2.86 – 2.71 (m, 2H); ^{13}C NMR (101 MHz, MeOD) δ 96.85 (C1β), 96.84 (C1β), 92.5 (C1α), 76.51, 76.49, 74.94, 74.60, 74.23, 73.61, 73.58, 73.37, 73.25, 73.24, 72.47, 69.96, 69.67, 48.46, 42.24, 42.02, 41.89, 41.54; HRMS *m/z* (ES^-) Found: $(M-H)^-$ 389.0588 $C_{12}H_{21}O_{10}S_2$ requires M^- 389.0582.

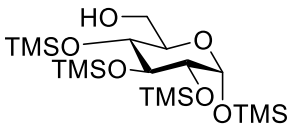
Compound 210



To a solution of **205** (254 mg, 0.361 mmol, 1.0 equiv.) in MeCN was added 4-mercaptobutyric acid **204** (75.0 µL, 87.0 mg, 0.722 mmol, 2.0 equiv.) and the reaction mixture stirred at RT for 2 hrs. TLC analysis revealed reaction completion (R_f = 0.47, EtOAc/DCM, 7:3), the solvent was removed under reduced pressure and the crude residue purified by column chromatography (DCM/EtOAc, 0-40%) to yield the title compound (156 mg, 0.219 mmol, 61%) as a colourless oil. R_f = 0.47 (EtOAc/DCM, 7:3); $[\alpha]_D^{23}$ = +16.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.6 Hz, 1H, CH), 7.32 (d, *J* = 7.6 Hz, 1H, CH), 6.18 (dd, $J_{H\text{-}1'\text{-}Fa/Fb}$ = 10.0, 3.8 Hz, 1H, H-1'), 4.20 (td, *J* = 11.6, 8.1 Hz, 1H, H-3'), 3.89 (d, *J* = 11.9 Hz, 1H, H-5a'), 3.83 (d, *J* = 8.0 Hz, 1H, H-4'), 3.68 (dd, *J* = 11.9, 1.8 Hz, 1H, H-5b'), 2.72 (t, *J* = 6.4 Hz, 2H, CH_2), 2.61 – 2.46 (m, 4H, 2 × CH_2), 2.41 – 2.34 (m, 2H, CH_2), 2.03 – 1.90 (m, 4H, 2 × CH_2), 0.82 (s, 9H, Si-

^{t}Bu), 0.77 (s, 9H, Si-^{t}Bu), 0.00 (s, 3H, Si-CH_3), -0.00 (s, 3H, Si-CH_3), -0.01 (s, 3H, Si-CH_3), -0.03 (s, 3H, Si-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C-NH, C4), 163.3 (C=O), 154.15 (C=O), 154.17 (C=O), 144.8 (C6), 123.2 (d, $^{1}J_{C\text{-}F}$ = 261.2 Hz, d, $^{1}J_{C\text{-}F}$ = 260.7 Hz, C2'), 96.8 (C5), 84.7 (dd, $^{2}J_{C\text{-}F}$ = 41.1, 23.7 Hz, C1'), 81.6 (d, $^{3}J_{C\text{-}F}$ = 8.7 Hz, C4'), 69.5 (d, $^{2}J_{C\text{-}F}$ = 17.8 Hz, C3'), 60.0 (C5'), 40.6 (CH_2), 38.0 (CH_2), 36.7 (CH_2), 32.5 (CH_2), 25.9 (Si-^{t}Bu), 25.8 (CH_2), 25.5 (Si-^{t}Bu), 24.7 (CH_2), 18.3 (Si-^{t}Bu), 18.0 (Si-^{t}Bu), -4.8 (Si-CH_3), -5.3 (Si-CH_3), -5.4 (Si-CH_3), -5.5 (Si-CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ -115.94 (dd, *J* = 239.5, 11.3 Hz), -117.56 (ad, *J* = 239.7 Hz); HRMS *m/z* (ES^-) Found: $(M\text{-}H)^-$ 710.2610 $C_{29}H_{50}O_7N_3F_3S_2Si_2$ requires M^- 710.2602.

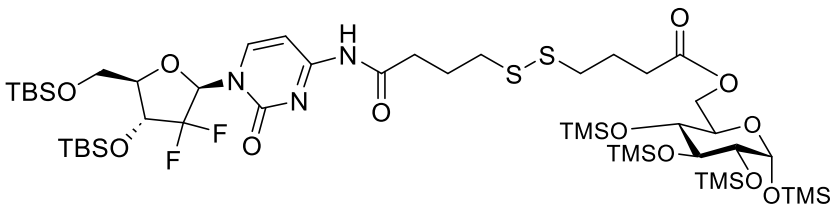
1,2,3,4-Tetra-*O*-TMS-α-D-glucopyranoside 213



To a solution of D-glucose (360 mg, 2.00 mmol, 1.0 equiv.) in pyridine (20 mL) was added HMDS (0.94 mL, 726 mg, 4.50 mmol, 2.25 equiv.) and TMSCl (1.78 mL, 1.52 g, 14.8 mmol, 7.4 equiv.) at 0 °C. The reaction was allowed to reach RT and stirred for 1 hour, TLC analysis revealed reaction completion (R_f = 0.90, hexane). The reaction mixture was diluted with DCM (50 mL) and washed with H_2O (2 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Crude 1,2,3,4,6-Penta-*O*-TMS-α-D-glucopyranoside was obtained as a colourless oil and progressed to the next step without further purification. To 1,2,3,4,6-Penta-*O*-TMS-α-D-glucopyranoside in DCM (15 mL) at 0 °C was added AcOH (65.0 µL) in MeOH (12 mL) dropwise. The reaction was maintained at 0 °C for 1 hr, at this point TLC analysis revealed reaction completion (R_f = 0.17, hexane). The reaction mixture was diluted with DCM (50 mL), washed with H_2O (2 × 50 mL) and the combined organic

phases dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 0-10%) to yield the title compound (681 mg, 1.45 mmol, 73%) as a colourless oil. R_f = 0.17 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (d, *J* = 3.0 Hz, 1H, H-1), 3.64 (t, *J* = 8.9 Hz, 1H, H-3), 3.61 – 3.49 (m, 3H, H-5, H-6a, H-6b), 3.30 (t, *J* = 9.1, 1H, H-4), 3.19 (dd, *J* = 9.1, 3.1 Hz, 1H, H-2), 1.60 (dd, *J* = 7.0, 5.4 Hz, 1H, 6-OH), 0.04 (s, 9H, Si-CH_3), -0.00 (s, 9H, Si-CH_3), -0.00 (s, 9H, Si-CH_3), -0.01 (s, 9H, Si-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 93.1 (C1), 73.2 (C2), 72.7 (C3), 71.1 (C5), 71.0 (C4), 61.0 (C6), 0.3 (Si-CH_3), -0.0 (Si-CH_3), -0.5 (Si-CH_3), -0.7 (Si-CH_3); HRMS *m/z* (ES^+) Found: $(M+Na)^+$ 491.2103 $C_{18}H_{44}O_6NaSi_4$ requires M^+ 491.2107. Data matched those previously reported.[208]

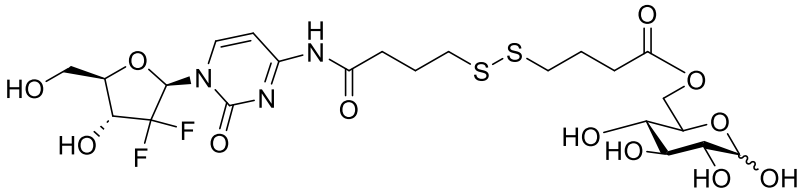
TMS/TBS-*O*-Glucose-gemcitabine 214



To a solution of **210** (95.0 mg, 0.133 mmol. 1.0 equiv.) in DCM (15 mL) was added EDC (62.0, 0.400 mmol, 3.0 equiv.) followed by DMAP (1.62 µg, 13.3 µmmol, 0.1 equiv.). The reaction mixture was stirred at RT for 15 min. 1,2,3,4-Tetra-*O*-TMS-α-D-glucopyranoside **213** (94.0 mg, 0.200 mmol, 1.5 equiv.) was next added and the reaction mixture stirred for a further 1 hr. TLC analysis revealed reaction completion (R_f =0.25, hexane/EtOAc, 7:3) the reaction mixture was diluted with DCM (50 mL) and washed with sat. aq. $NaHCO_3$ (2 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography (hexane/EtOAc, 0-30%) delivered the title compound (70.0 mg, 60.2 µmol, 45%) as a colourless oil. R_f = 0.25 (hexane/EtOAc), $[\alpha]_D^{22}$ = +59.78 (*c* = 1.0,

$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (bs, 1H, NH), 7.94 (d, *J* = 7.6 Hz, 1H, CH’), 7.27 (d, *J* = 7.5 Hz, 1H, CH’), 6.20 (dd, $J_{H\text{-}1''\text{-}Fa/Fb}$ = 10.2, 3.8 Hz, 1H, H-1’’), 4.87 (d, *J* = 3.0 Hz, 1H, H-1), 4.27 – 4.15 (m, 2H, H-6a, H-3’’), 3.97 – 3.86 (m, 2H, H-6b, H-5a’’), 3.82 (d, *J* = 8.1 Hz, 1H, H-4’’), 3.78 (ddd, *J* = 9.7, 5.2, 2.2 Hz, 1H, H-5), 3.67 (m, 2H, H-3, H-5b’’), 3.30 (dd, *J* = 9.7, 8.6 Hz, 1H, H-4), 3.23 (dd, *J* = 9.1, 3.1 Hz, 1H, H-2), 2.59 (aq, *J* = 6.8 Hz, 6H, 2 × CH_2), 2.46 (t, *J* = 7.2 Hz, 3H, CH_2), 2.36 (m, 2H, CH_2), 2.01 – 1.84 (m, 6H, 2 × CH_2), 0.82 (s, 9H, Si-^{t}Bu), 0.77 (s, 9H, Si-^{t}Bu), 0.02 (s, 9H, Si-CH_3), 0.02 (s, 9H, Si-CH_3), 0.01 (s, 9H, Si-CH_3), 0.00 – -0.01 (m, 15H, Si-CH_3), -0.03 (s, 3H, Si-CH_3), -0.13 (s, 3H, Si-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9 (C=O), 171.4 (C-NH, C4’), 161.4 (C=O), 153.9 (C=O), 143.3 (CH, C6’), 95.6 (CH, C5’), 93.0 (C1), 84.03 – 83.16 (m, C1’’), 80.5 (d, ^2J = 8.6 Hz, C3’’), 73.0 (C2), 72.8 (C3), 71.4 (C4), 68.9 (C5), 68.48 (C4’’), 63.0 (C6), 59.0 (C5’’), 36.6 (CH_2), 34.7 (CH_2), 31.4 (CH_2), 31.4 (CH_2), 24.9 (Si-^{t}Bu), 24.6 (Si-^{t}Bu), 23.1 (CH_2), 22.7 (CH_2), 17.4 (Si-^{t}Bu), 17.1 (Si-^{t}Bu), 0.28 (Si-CH_3), -0.5 (Si-CH_3), -0.8 (Si-CH_3) - 1.0, (Si-CH_3) -5.7 (Si-CH_3), -6.3 (Si-CH_3), -6.39 (Si-CH_3), -6.41 (Si-CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ -115.96 (dd, *J* = 239.5, 11.9 Hz), -117.37 (dt, *J* = 239.3, 10.5 Hz).

Glucose-gemcitabine 215



To a solution of **214** (60.0 mg, 51.6 µmol, 1.0 equiv.) in THF (5 mL) was added 1M TBAF in THF (0.16 mL, 41.0 mg, 0.155 mmol, 3.0 equiv.) at 0 °C. After 1 hr of stirring at this temperature TLC analysis revealed reaction completion (R_f = 0.30, DCM/MeOH, 85:15) and the mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$ (2 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under

reduced pressure. Purification by column chromatography (DCM/MeOH, 0-20%) delivered the title compound (18.0 mg, 27.9 μmol, 54%, α/β, 1:1) as a colourless oil. R_f = 0.30 (DCM/MeOH, 85:15); **Selected signals:** ^{1}H NMR (400 MHz, MeOD) δ 8.34 (d, *J* = 7.6 Hz, 1H, CH'), 7.49 (d, *J* = 7.6 Hz, 1H, CH'), 6.30 – 6.23 (m, 1H, H-1''), 5.08 (d, *J* = 3.7 Hz, 1H, 0.5H, H-1α), 4.48 (d, *J* = 7.8 Hz, 1H, H-1β), 4.39 (m, 1H), 4.30 (td, *J* = 12.2, 8.6 Hz, 1H, H-4''), 4.19 (m, 2H, 1H), 4.01 – 3.93 (m, 2.5H, H-5a'', H-3''), 3.81 (dd, *J* = 12.4, 2.8 Hz, 1H, H-5b''), 3.67 (t, *J* = 9.3 Hz, 0.5H), 3.47 (ddd, *J* = 9.1, 5.8, 2.1 Hz, 0.5H), 3.39 – 3.32 (m, 1.5H, H-3β, H-4α), 3.14 (dd, *J* = 8.8, 8.1 Hz, 0.5H), 2.76 (dt, *J* = 9.7, 7.2 Hz, 4H, 2 × CH_2), 2.61 (t, *J* = 7.3 Hz, 2H, CH_2), 2.48 (t, *J* = 7.3 Hz, 2H, CH_2), 2.12 – 1.95 (m, 4H, 2 x CH_2); ^{13}C NMR (101 MHz, MeOD) δ 173.3 (C-NH, C4'), 166.3 (C=O), 156.5 (C=O), 144.6 (CH, C6'), 96.93 (CH, C5'), 96.86 (C1β), 92.6 (C1α), 84.77 – 84.12 (m, C1''), 80.9 (d, *J* = 8.8 Hz, C3''), 76.5, 74.8, 73.9, 73.3, 72.4, 70.5, 70.31, 70.29, 69.3, 69.20 (C4''), 63.5, 59.1 (C5''), 37.07, 37.03, 34.96, 31.94, 31.92, 31.86, 31.74, 23.96, 23.92, 23.90, 23.66; ^{19}F NMR (377 MHz, MeOD) δ -119.18 (dd, *J* = 238.8, 11.3 Hz), -120.10 (d, *J* = 244.7 Hz); HRMS *m/z* (ES^-) Found: $(M-H)^-$ 644.1398 $C_{23}H_{32}O_{12}N_3F_2S_2$ requires M^- 644.1401.

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