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The anomerisation of glycosyl thiols and synthesis of multivalent GlcNAc and GalNAc glycoclusters

By

Shane O'Sullivan



A Thesis presented to
The National University of Ireland
For the degree of
Doctor of Philosophy.

Based on the research carried out in the
School of Chemistry,
National University of Ireland,
Galway.

Under the supervision and direction of
Prof. Paul V. Murphy
National University of Ireland,
Galway.

Declaration

Date 02-04-2015

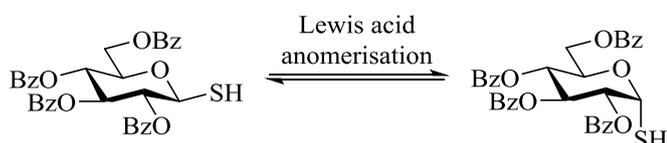
Declaration

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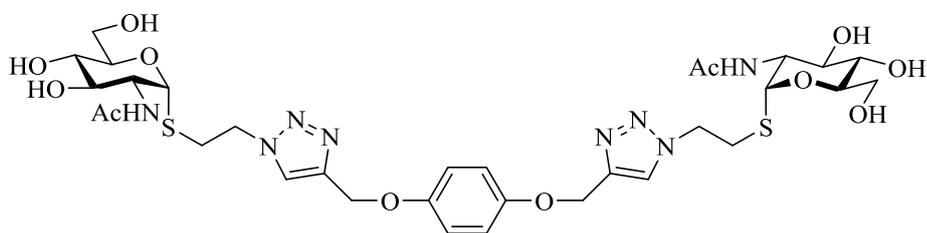
Shane O'Sullivan

Abstract

There are several published procedures available for the synthesis of β -thiopyranoses such as gluco- or galacto-pyranoses. Given the ease with which one can access such β -thiopyranoses, the development of a reproducible anomerisation of these β -thiopyranoses to give the α -thiopyranoses would greatly facilitate the synthesis of various types of α -S-glycoconjugates. This was a major aim of this thesis work. To that end, a variety of thio-glycopyranoses were prepared and their anomerisation reactions investigated using Lewis acid promoters. The anomerisation of benzoylated thiopyranoses have been shown to be achievable in moderate to very good yields. Reactions were carried out for gluco-, galacto-, xylo-, arabino-, fuco- and rhamno-pyranose derivatives. In addition some disaccharide derivatives containing a thiol functional group were anomerised. Alkylation of these glycosyl thiols was also demonstrated during the course of the thesis work. These results are reported in chapter one.

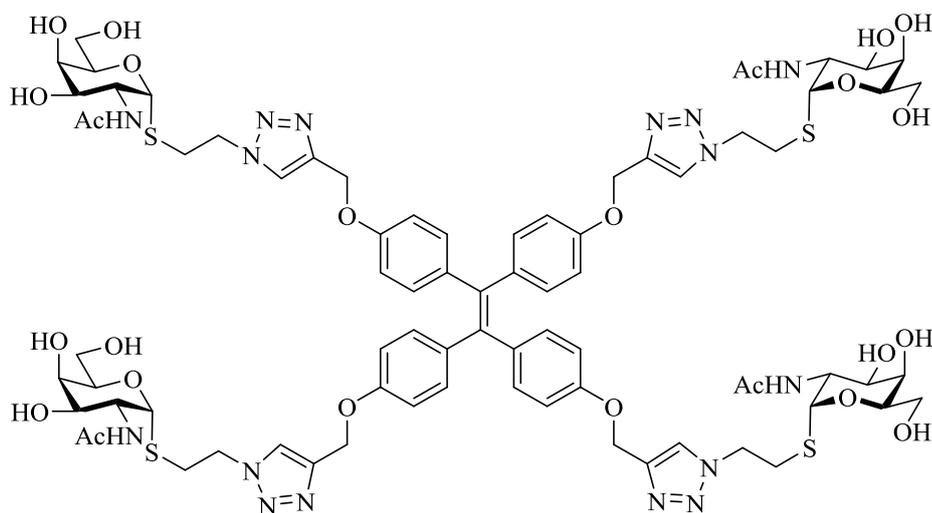


The second chapter of the thesis describes the synthesis of glycoclusters containing *N*-acetyl glucosamine (GlcNAc) for evaluation as bactericidal agents against *Helicobacter Pylori*. This is a spiral shaped bacterium that lives in the stomach and duodenum and infects about half of the world's population with some of these infected individuals developing peptic ulcers, gastric cancer and mucosa-associate lymphoma. This research was based on work showing that *O*-glycans expressing terminal 1,4-linked α -GlcNAc residues have antimicrobial activity against *Helicobacter Pylori*. Previous work from the Murphy laboratory has identified two bivalent GlcNAc derivatives with activity against two different strains of *Helicobacter Pylori*. Analogues of these bivalent structures were prepared. This included *S*-glycoside based analogues.



Abstract

The final chapter of this thesis work describes the synthesis of *N*-acetyl galactosamine containing glycoclusters. In this case bivalent, trivalent and tetravalent structures were prepared, which included α -thiopyranose derivatives. A tetravalent compound synthesised was shown to have very high potency for a macrophage galactose C-type lectin receptor when compared to GalNAc itself. The work on this topic has been published in *Organic and Biomolecular Chemistry* (*Org. Biomol. Chem.*, **2015**, *13*, 4190-4203).



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Outside of Galway the most important people have always been there for me – my family. To my father, Thomas O'Sullivan, no words of thanks could correctly express the gratitude that is due to you from either me or the rest of our family. You are an absolute credit. If we can even partly mirror your example, we'll all do well in this game of life. You have never left any of us wanting or ever let us down and for all that has passed and for all that is yet to come, I thank you sincerely. To my brothers, Kevin and Colin, and sister, Aisling, I thank you for your help. Be it board games or just general banter, your presence and ability to be there to switch the pace or change the subject has always been appreciated.

Finally I'd like to thank Jadwiga O'Brien. She came into my life at a rocky time and guided me through. She has been through it all with me and has always stood fast. Her help and support, once again, are hard to express enough thanks for. You have always been there for me and for all this; I thank you and love you.

Lastly I'd like to dedicate this work to my mother, Marian Gallery; she is partly the reason for me following the path I have. It is my hope that we - myself, my brothers and sister, not only make Dad proud but we continue to follow the path you laid out for us and that we make both of you proud.

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Symbols and abbreviations

α	Alpha
Å	Angstrom
Ac	Acetyl
ACES	<i>N</i> -(2-Acetamido)-2-aminoethanesulfonic acid
All	Allyl
AGRC	Alimentary Glycoscience Research Cluster
APC	Antigen presenting cell
aq.	Aqueous
Ar	Aromatic
β	Beta
Bn	Benzyl
br d	Broad doublet (spectral)
br s	Broad singlet (spectral)
Bu	Butyl
Bz	Benzoyl
BzOH	Benzoic acid
<i>c</i>	Concentration
°C	Degrees Celsius
Calcd	Calculated
cat.	Catalytic
CG	Chicken galectin
CIA	Collagen induced arthritis
cm ⁻¹	Wavenumber (IR units)
ConA	Concanavalin A
COSY	Correlation Spectroscopy
Cp	Cyclopentadienyl

Symbols and abbreviations

CRD	Carbohydrate recognition domain
CS	Chondroitin sulfate
CuAAC	Copper(I)-catalyzed Azide-Alkyne Cycloaddition
Cy	Cyclohexyl
δ	Chemical shift in ppm downfield from TMS
d	Doublet (spectral)
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	Diazabicycloundecene
DC	Dendritic cell
DCE	Dichloroethane
dd	Doublet of doublets (spectral)
ddd	Doublet of doublets of doublets (spectral)
DEPT	Distortionless Enhancement by Polarisation Transfer
DIPEA	Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DPAP	2,2-Dimethoxy-2-phenylacetophenone
DS	Dermatan sulfate
dt	Doublet of triplets (spectral)
EDTA	Ethylenediaminetetraacetic acid
eq.	Equivalents
ES-HRMS	High-Resolution Mass Spectrometry - Electrospray Ionization
Et	Ethyl
Fig.	Figure

Symbols and abbreviations

FTIR	Fourier transform infrared (spectroscopy)
Fuc	Fucose
g	Gram
GAG	Glycosaminoglycans
Gal	Galactose
GalNH ₂ , GalNAc	Galactosamine, <i>N</i> -acetyl galactosamine
GC	Glycoconjugate
Glc	Glucose
GalNH ₂ , GalNAc	Glucosamine, <i>N</i> -acetyl glucosamine
h	Hour(s)
HA	Hyaluronic acid
HBr	Hydrobromic acid
HCl	Hydrochloric acid
HMBC	Heteronuclear multiple bond correlation
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HSQC	Heteronuclear single quantum correlation
Hz	Hertz
IC ₅₀	50% inhibition concentration
IR	Infrared (spectroscopy)
<i>J</i>	Coupling constant (nmr), in Hz
Lac	Lactose
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
<i>m</i>	Meta
M	Molar
M ⁺ , M ⁻	Mass of the molecular ion (mass spectrometry)

Symbols and abbreviations

Me	Methyl
MGL, hMGL	Macrophage galactose type C-type lectin, human MGL
MHz	Megahertz
min	Minutes
mL, μ L	Milliliter, microliter
mol, mmol	Mole, millimole
mM, μ M	Millimolar, micromolar
MSA	Methanesulfonic acid
NK	Natural Killer
NMR	Nuclear Magnetic Resonance
NaOMe	Sodium methoxide
NaN ₃	Sodium azide
OTf	Trifluoromethanesulfonate/triflate
<i>p</i>	Para
Ph	Phenyl
pm	Picometre
ppm	Parts per million (NMR)
Py.	Pyridine
q	Quartet (spectral)
RA	Rheumatoid arthritis
RE	Recognition element
R _f	Retention factor
RNA, tRNA	Ribonucleic acid, transfer RNA
r.t.	Room temperature
RuAAC	Ruthenium catalysed Azide-Alkyne Cycloaddition
$[\alpha]_D$	Specific rotation
s	Singlet (spectral)

Symbols and abbreviations

sat.	Saturated
Ser	Serine
S _N 2	Bimolecular nucleophilic substitution
t	Triplet (spectral)
td	Triplet of doublets (spectral)
TBAI	Tetrabutylammonium iodide
Thr	Threonine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
VAA	Viscum album agglutinin
WGA	Wheat germ agglutinin

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Chapter 1: Studies in the anomerisation of glycosyl thiols

1.1 Background to carbohydrates

The word carbohydrate is used to govern a class of polyhydroxylated aldehydes (aldoses) and ketones (ketoses) referred to as sugars or in the world of biochemistry, saccharides. The word carbohydrate itself comes from the fact that glucose, $C_6H_{12}O_6$, the earliest pure form of a carbohydrate to be obtained was originally thought to be a hydrate of carbon, $C_6(H_2O)_6$. This view has, as with most forms of chemistry and science in general, evolved with better understanding and studies on the topic in question, but what has lived on is the term carbohydrate. The understanding of these biomolecules has evolved with time also, promoting them from “simple” energy storage molecules, to what are now considered one of the four major classes of macromolecules in biology¹ - DNA, proteins, carbohydrates and lipids.

With a few exceptions, the basic form of carbohydrates, the monosaccharides, have the chemical formula $C_x(H_2O)_y$, where $x \geq 3$. The simplest example of these is glyceraldehyde. These monosaccharides are carbohydrates, such as those in Fig. 1.1 that cannot be hydrolysed into smaller sugars. The other class of carbohydrate, are called complex carbohydrates, these are compounds where two or more monosaccharide units are linked together to form a longer carbohydrate chain. These polysaccharides are capable of being hydrolysed back to their constituent monosaccharides or smaller sugar residues.

Each of the monosaccharides in Fig. 1.1, have been shown in their D-absolute configuration but can also exist as their enantiomeric, mirror image, L-configuration. This D-/L-system works by relating all simple carbohydrates to glyceraldehyde, with respect to the absolute configuration of the secondary alcohol at the highest numbered stereocentre i.e. the chiral centre that is furthest from the aldehyde terminus of the carbohydrate structure being studied. This absolute configuration can be looked at through more common place nomenclature that is the *R/S* system for donating enantiomers. Working at the chiral centre furthest from the carbonyl group in the Fischer projections in Fig. 1.1 if the stereogenic centre has an absolute *R* (*Rectus*, Latin for right) configuration it will be referred to as a D-sugar, while if this stereocentre has an *S* (*Sinister*, Latin for left) configuration, it will be an L-sugar².

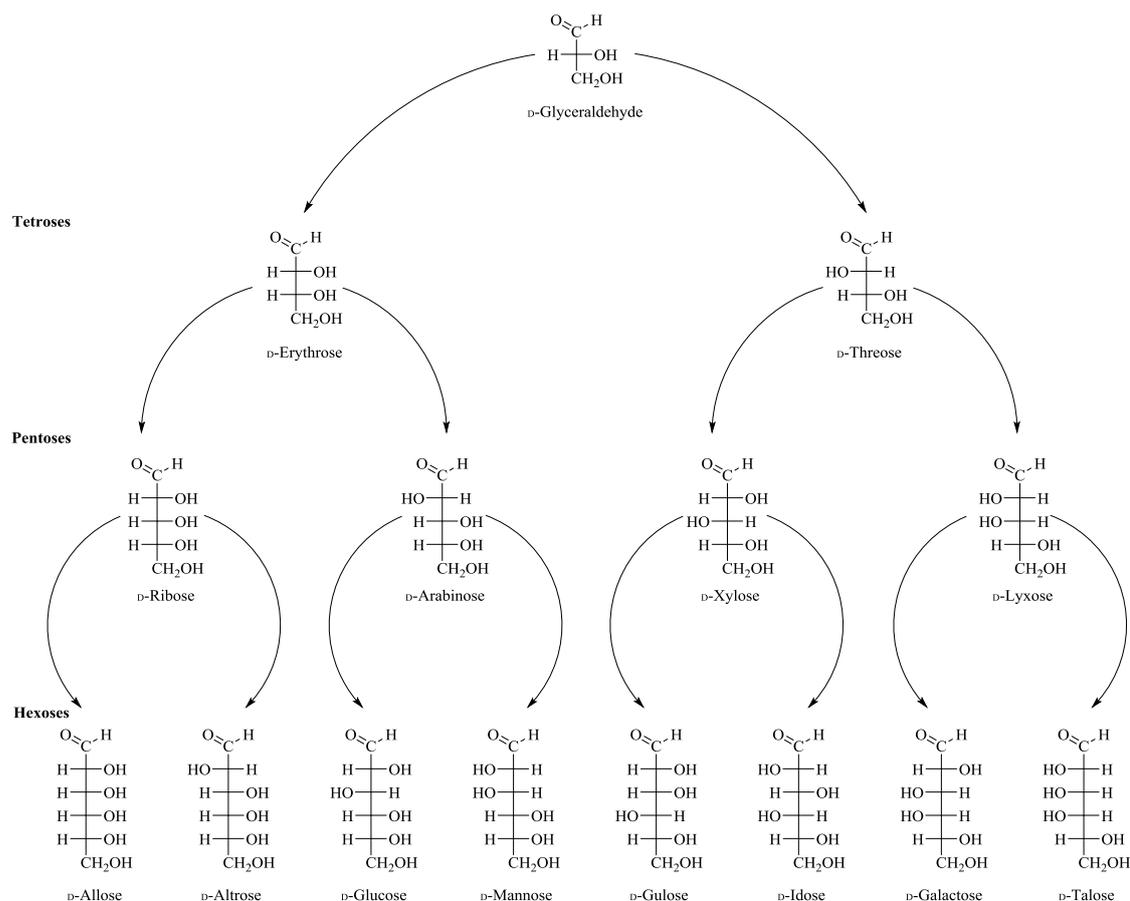


Fig. 1.1 Fischer projections of monosaccharides.

These Fischer projections are convenient for representing the diversity in monosaccharides but are not a true representation of how carbohydrates exist. They show the choice that is available to chemists who might wish to synthesise a variety of differing chiral compounds. Even with this diversity and the multi stereocentres that exist, in varying degrees, in these carbohydrates, it is at the anomeric centre, C-1, where a large proportion of the chemistry of a carbohydrate is focused, with control of the stereochemistry at this position being one of the main factors of thought for a carbohydrate chemist.

Carbohydrates exist almost exclusively in a ring structure through an acid catalysed cyclisation reaction of the open chain form. As shown, Fig. 1.2, carbohydrates possess multiple hydroxyl groups giving rise to several possible formations of a number of different sized cyclic hemiacetals (lactols). Five and six membered rings are thermodynamically more stable than four and seven membered rings since they are less strained. Of the thermodynamically stable rings six membered lactols are more favoured due to their ability to adopt a chair conformation, which are essentially free from all types of ring strain. The cyclisation reaction for carbohydrates, e.g. the cyclisation of D-glucose, Fig. 1.2, leads to a new stereogenic centre being formed at C-1, the anomeric centre. This gives rise to two new diastereomers, the α -anomer which has its substituent in down/axial position at the anomeric centre of D-sugars in a 4C_1

conformation and the β -anomer which has its substituent in up/equatorial position at the anomeric centre of D-sugars in a 4C_1 conformation. In terms of a precise definition for α and β anomers it is necessary to work out their respective stereochemistry as α and β are stereodescriptors. If the anomeric centre has an R configuration, as worked out by the Cahn-Ingold-Prelog priority rules, and so too does the highest number chiral centre, i.e. the configuration reference carbon (the chiral centre that denotes either D or L to a sugar) the sugar is said to be β and if the configuration of these two chiral centres differ (say R, S) the sugar is said to be α . That is, in the α -anomer the anomeric carbon and the reference atom have opposite configurations (R, S or S, R), while in the β -anomer the configurations are the same (R, R or S, S).

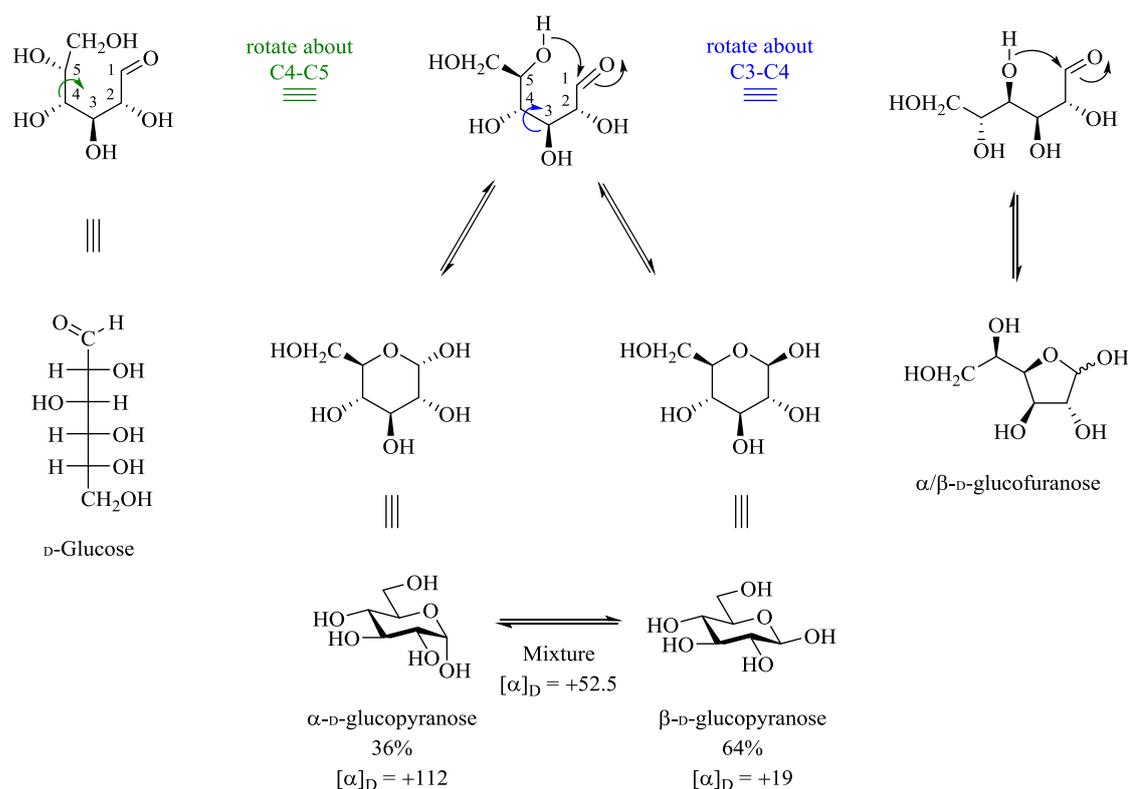


Fig. 1.2 The cyclisation of D-glucose.

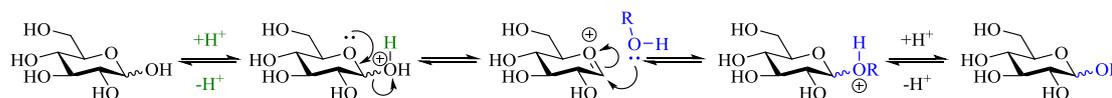
As alluded to - there does exist the possibility of a five membered ring (furanose) being formed. This in turn, as for the six membered pyranose, would also yield two separate and distinguishable diastereomers, Fig. 1.2. In the case of D-glucose, the six membered ring is the only form present in significant amounts under equilibrating conditions.

Equilibration, and the percentage of each anomer of these lactols present in water, can be calculated through optical rotation or NMR measurements. It has been shown, at a variety of temperatures (predominately 20 °C) that for D-glucose, at equilibrium, a mixture of 36% α -glucose and 64% β -glucose are present. These percentages are calculated with respect to the specific rotation of each of the pure isomers and that of the equilibrium mixture, Fig. 1.2.

The stereochemistry at the anomeric centre is capable of inversion due to the formation of the hemiacetals being an equilibrium process. These α - and β -anomers are easily interconverted under acid catalysis via the open chain form through a process known as mutarotation. The mechanism is based around hemiacetal hydrolysis of either pyranose forms of glucose to the open chain polyhydroxylated aldehyde which may then re-cyclise by one of several ring closure processes similar to that in Fig. 1.2 to reform a hemiacetal, again through another acid catalysed process. In the above cyclisation the equatorial conformation at the anomeric centre (β -anomer) is the major product observed, this can be attributed to a steric effect. Depending on the reaction this distribution of α - and β -anomers does not always occur, with many factors contributing to different quantities of anomers being observed. The factors influencing the selectivity of either α - or β -anomers is what will be discussed in the next few sections and the considerations that need to be made so that control can be achieved on the distribution of anomers at this centre.

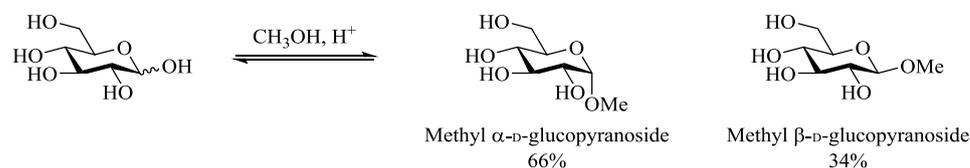
1.1.1 Anomeric distribution

As shown previously D-glucose can exist as two separate hemiacetals that are in equilibrium with each other through an open chain form in aqueous media under acid catalysed conditions. These cyclical hemiacetals are capable of reacting with alcohols to form acetals, which, in carbohydrate chemistry, are called glycosides Scheme 1.1.



Scheme 1.1 Acetal/glycoside synthesis from hemiacetals.

To obtain the desired glycoside an excess of the alcohol is usually used to drive the reaction to completion, so as to avoid the reverse reaction to the parent carbohydrate occurring. As the reaction is under thermodynamic control the thermodynamically most stable product is formed. For the reaction of D-glucose with methanol and an acid catalyst, Scheme 1.2, the product formation leads to a mixture of α - and β -anomers. This time though, opposite to that of the ring formation of the parent carbohydrate, it is the α -anomer that is the major product.



Scheme 1.2 The reaction of glucose with methanol and an acid catalyst.

This is opposite to what would be expected on steric grounds, i.e. that the substituent would take up an equatorial (β -) configuration to avoid steric hindrance. This preference for a substituent at the anomeric center to adopt an axial (α -) configuration,

the opposite stereochemistry as to what one might expect is attributed to a phenomenon known as the anomeric effect.

1.1.2 The anomeric effect

The term, anomeric effect, was first introduced by R.U. Lemieux in 1958 at a conference of the American Chemical Society. It was originally observed and proposed, in 1955 by J.T. Edward who stated that in pyranose rings, axial alkoxy groups at the anomeric centre are more stable than those in an equatorial orientation³. The year 1955 also saw the start of Lemieux's study on the anomerisation equilibrium of fully acetylated aldohexopyranoses⁴. Due to the observations, by these two chemists, of a preference for alkoxy and acetyl groups to reside in an axial orientation means that the anomeric effect is now synonymous with the Edward-Lemieux effect.

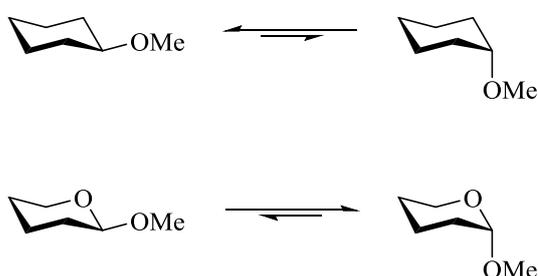


Fig. 1.3 The equilibrium of a substituted cyclohexane and the equilibrium of the corresponding substituted tetrahydropyran.

This anomeric (stereoelectronic) effect refers to the tendency of an electronegative atom/substituent at the anomeric centre to reside in an axial position rather than an equatorial one. It was soon recognised that this phenomenon was not restricted to carbohydrates. As such a generalised anomeric effect was established. It is characterized as the preference for the synclinal (*gauche*) position over the antiperiplanar (*anti*) position. This preference in orientation occurs in sections of the form R-X-A-Y, where A is an element of intermediate electronegativity (e.g. C, P, S), Y denotes an atom that is more electronegative than A (e.g. O, N, or halogen), X denotes an element which possesses lone pairs (obstructed from view in the Newman Projections of Fig. 1.4), and R stands for H or C.⁴

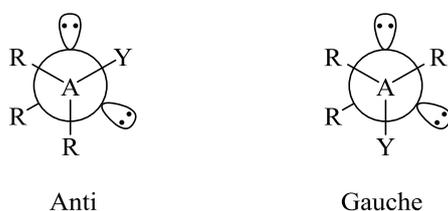


Fig. 1.4 Newman Projections for the anomeric effect.

While this preference for electronegative atoms to adopt an axial conformation is not limited to carbohydrates the consequence of the anomeric effect can be quite evident in respect to monosaccharides and their derivatives. The two most widely accepted

rationalizations to explain and understand the phenomenon that is the anomeric effect are an electrostatic model and a hyperconjugation resonance theory.

1.1.2.1 The electrostatic model

Edward postulations for the anomeric effect are that of the electrostatic model. It describes the increased stability of an electronegative substituent in an axial orientation at the anomeric centre as being due to the preference of this substituent to orientate in such a way that the product conformation, which has a minimal net dipole moment between the electronegative substituent and the ring dipole, as generated by the lone pair electrons of the ring oxygen, is achieved³ Fig. 1.5

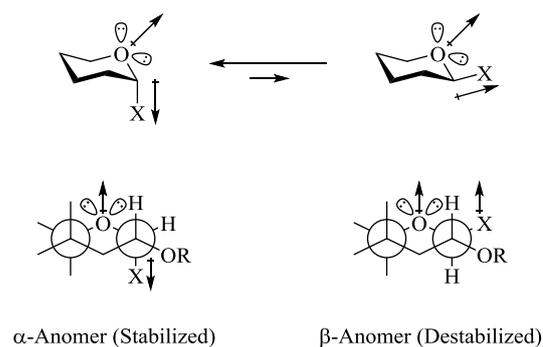


Fig. 1.5 The electrostatic model.

In the equatorial conformer, the dipoles are nearly parallel, giving rise to an unfavoured repulsive dipole-dipole interactions between the carbon-heteroatom of the ring, i.e. the endocyclic oxygen, and the electronegative substituent at C-1, the anomeric position. In the opposite conformer, where the electronegative substituent at the anomeric centre has an axial configuration, these dipoles oppose each other leading to a smaller net dipole, thus giving rise to a plausible rationalisation of the anomeric effect⁴.

Based on the difference in dipole-dipole interactions between the two anomers, it would be expected, when studied experimentally, that in increasingly polar solvents, the preference for the axial anomer would decrease, as, the more polar equatorial anomer would be stabilized and therefore favoured. This solvent effect was measured in studies of 2-methoxytetrahydropyrans⁵ and showed that the anomeric effect is higher, i.e. the axial isomer predominates at equilibrium, in less polar media, e.g. CCl_4 , than in more polar solvents, e.g. MeCN, thereby providing evidence for the electrostatic explanation of the anomeric effect.

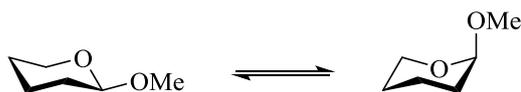


Fig. 1.6 Studies with 2-methoxytetrahydropyrans on the effect of solvent on the anomeric conformation.

There also exist contradictory literature to that just stated, which provide other variables and examples which show a favourable stabilization of the axial isomer in increasingly

polar solvents. One study which demonstrated this looked at solvent effects at both room temperature, which proceeded as expected - with an enhancement of the anomeric effect in reduced polar media; and also at low temperature, where an opposite trend was observed with the axial/equatorial ratio increasing with increasing solvent polarity⁶. This behaviour was attributed to a solvent compression effect.

Due to continued studies in the field of the anomeric effect, further evidence and results emerged of which the electrostatic model provided insufficient rationalisation on its own. These shortcomings of the electrostatic model included the inability to explain the variations of both the bond lengths and angles that are typically associated with the anomeric effect. This led to an alternative explanation for this phenomenon to be proposed, that now is known as the hyperconjugation resonance theory.

1.1.2.2 The hyperconjugation resonance model

The theory proposed by Edward, on the dipole-dipole interactions, does not account for the changes in structure that are characteristic of axial conformers arising as a cause of the anomeric effect. From investigations on cyclic-halogen ethers an alternative theory of hyperconjugation was proposed to explain the anomeric effect. The study of these cyclic-halogen ethers revealed that the anomeric effect – a preference for the axial conformer, is associated with a significant lengthening of the carbon-halogen bond as well as an associated shortening of the adjacent carbon-oxygen bond⁷. The resonance form, Fig. 1.7, explains why the anomeric effect only operates when the anomeric substituent is an electronegative atom, such as O, F, Cl, or Br. This is due to an electronegative atom being ‘happy’ with a formal negative charge.



Fig. 1.7 Resonance forms with an electronegative atom, to explain the anomeric effect.

According to the hyperconjugation model the associated stabilization achieved in the axial conformation is due to electron donation, Fig. 1.8. In detail, it is attributed to delocalization (donation) of the antiperiplanar orbital of lone-pair electrons of the ring oxygen to the anti-bonding orbital of the carbon-halogen (or other electronegative substituent) bond. This interaction creates the characteristic observed lengthening of the carbon-halogen bond through electron transfer to its σ anti-bonding orbital, as well as the shortening of the carbon-oxygen bond by increasing its double-bond character. Due to this new partial sp^2 character there is also an observed increase of the O-C-X (where X is electronegative atom such as O or a halogen atom like Cl) bond-angle when compared to the typical tetrahedral value. This hyperconjugation can only occur when the orbitals involved in this stabilizing effect are antiperiplanar to each other, this in turn can only happen when the electronegative substituent at the anomeric centre adopts an axial conformation, Fig. 1.8.

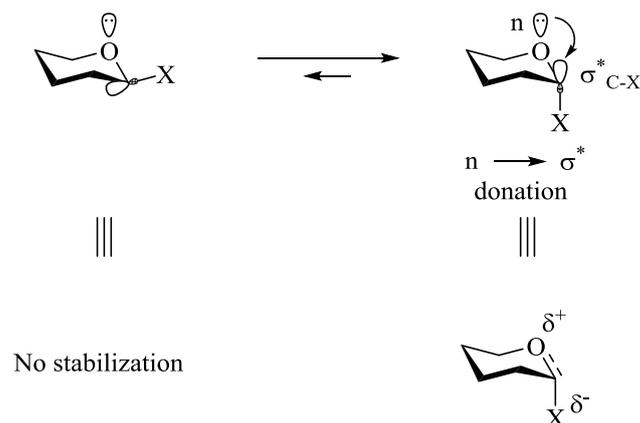
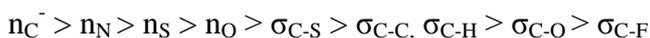


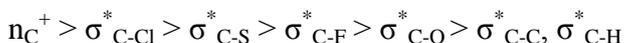
Fig. 1.8 The hyperconjugation resonance model.

The stabilization effect obtained through the axial conformation by the interaction of a pair of electrons ($n \rightarrow \sigma^*$), as illustrated in Fig. 1.8 is inversely proportional to the energy difference between the high energy donor orbital and low energy empty acceptor orbital⁸. It therefore stands to reason that the greatest stabilisation will be generated from the interaction of the most effective donors, i.e. those with high energy orbitals, with the most effective acceptors, i.e. low energy orbitals. This effect is brought about by having the LUMO of the acceptor as close as possible in energy to the HOMO of the donor.

The most effective donors - non-bonding orbitals or lone pairs, such as a carbanions lone pair (n_{C^-}) or unshared pairs of electrons in heteroatoms, are generally more effective donors than bonding orbitals due to the high energy levels they possess. The most effective donors can be listed according to the following sequence:



The most effective acceptors are the empty p orbital in a carbonium ion (n_{C^+}) followed by other empty/low energy orbitals. For halide species, a decrease in electronegativity of the halide equates to an increase in acceptor ability. The most effective acceptors can be organized according to the following sequence:



The net effect of this electronic interaction is electronic delocalization, as has been shown, and therefore it is stabilizing.

Using the idea of electronic interactions, the anomeric effect in nitrogen heterocycles vs. oxygen heterocycles was studied by Perrin et al.⁹ As shown in the list above, nitrogen is a more effective donor $n \rightarrow \sigma^*$ than oxygen and as such the anomeric effect should be stronger in nitrogen heterocycles when compared to their analogous oxygen counterparts. If this were found true, it would give weight to the hyperconjugation model.

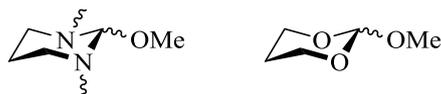


Fig. 1.9 Nitrogen heterocycles vs. oxygen heterocycles.

When the structures in Fig. 1.9 were studied and compared it was found, experimentally, that there is as much axial conformer for one structure when compared to the other. Were $n \rightarrow \sigma^*$ interactions dominant for the anomeric effect it would have led to a contrary result. It led Perrin et al. to conclude that the anomeric effect arises primarily from electrostatic interactions, though this conclusion was limited to non-polar solvents.

Despite the number of studies attributed to the anomeric effect a consensus on which theory is the actual basis of this phenomenon has yet to be agreed. Literature papers providing evidence for or against one theory over the other are a common sight. For example the electrostatic model had all but been completely discarded in recent years, until a recent publication provided computational evidence in favour of it¹⁰.

Even with a lot of people falling down on one side or the other, in terms of what facilitates the phenomena of the anomeric effect, some researchers are trying to delve further by proposing alternative reasons for it or if it is indeed a sum of a number of factors, providing additional contributing factors to the anomeric effect¹¹. Here they propose that the CH/ n hydrogen bond, where n are lone pair electrons on an electronegative atom, is an important factor in the stabilization of axial conformers of cyclohexane derivatives and thereby glycosides, Fig. 1.10 and Fig. 1.11.

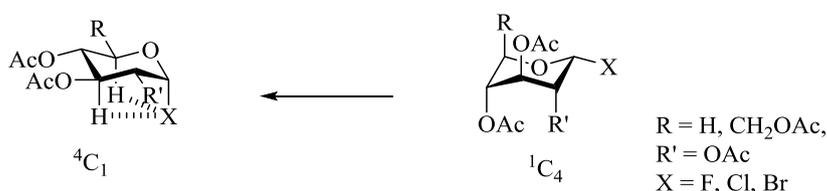


Fig. 1.10 Explanation, in terms of the five-membered CH/O hydrogen bonds, for the axial preference of pyranosyl halides of α -anomers with the D-xylo and D-gluco configuration.

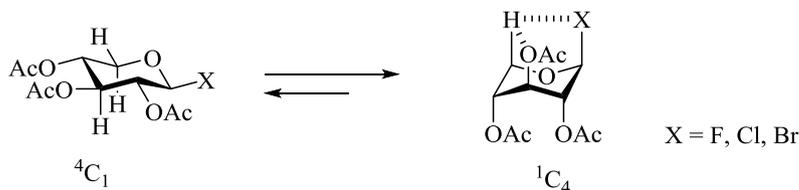


Fig. 1.11 Explanation, in terms of the five-membered CH/O hydrogen bonds, for the axial preference of β -anomers of xylosyl halides

Due to this continued debate and numerous publications on the topic of the anomeric effect, many researchers in the field of carbohydrate chemistry have become pragmatic

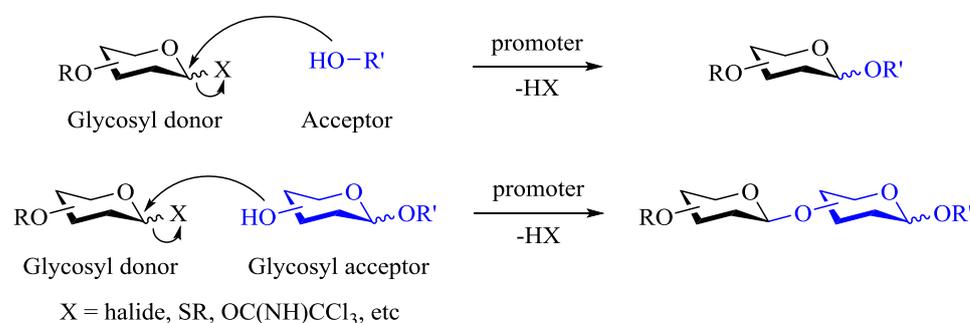
and rather than dispelling reasonable evidence from both sides of the divide on which model is more correct, either the electrostatic model or the hyperconjugation resonance model, many believe the anomeric effect to be a cause of a combination of contributing factors.

The combination of these factors, attributed to the anomeric effect, are employed throughout the field of carbohydrate chemistry in predicting or making assumptions on the distribution of the anomeric ratio of products at the anomeric centre.

1.1.3 Stereoselective control in glycosidation

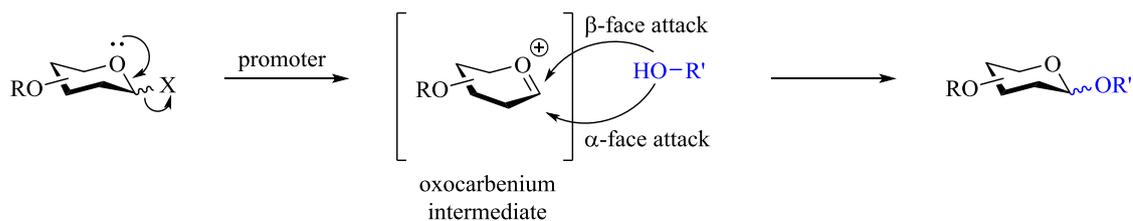
1.1.3.1 The glycosidic bond

Stereochemical control or rather a desire for stereochemical control exists throughout organic chemistry. As has been shown there is a pool of compounds available in carbohydrate chemistry with a variety of stereocentres (chiral centres). This selection of starting materials can prove invaluable to the chemist looking to synthesise chiral compounds. During synthesis using these compounds, glycosidic bonds can be formed. These glycosidic linkages are covalent bonds joining a carbohydrate (glycon) moiety to another residue which may be a non-carbohydrate residue (aglycon) or another carbohydrate derivative, via an *O*-, *N*-, or *S*- (acetal form) or *C*- (ether form) glycosidic linkage, making compounds termed, glycosides. These are formed by the nucleophilic displacement of a leaving group (X) from a carbohydrate, termed the glycosyl donor, at the anomeric centre by an acceptor generally in the presence of a promoter, which is present to activate this leaving group, Scheme 1.3



Scheme 1.3 The synthesis of glycosides.

The displacement generally follows a unimolecular S_N1 mechanism. In this process, Scheme 1.4, an oxocarbenium intermediate will typically form following the activation and subsequent elimination of the leaving group from the anomeric centre of the glycosyl donor. Nucleophilic attack on either face of this intermediate by the acceptor is possible and therefore a mixture of α and β -products can form.



Scheme 1.4 Mechanism of glycoside synthesis.

The ratio of products that are formed is subjective to a number of factors, including but not limited to the anomeric effect, as previously discussed. It also involves neighbouring group participation and the solvent choice for the glycosidation

1.1.3.2 Neighbouring group participation

The orientation of the hydroxyl group (OH) at C-2 position in a pyranose ring of the 'parent' carbohydrate has a substantial effect on the anomeric equilibrium. This can be demonstrated when comparing D-mannose, where the hydroxyl group at C-2 is in an axial/up position, relative to D-glucose, where the hydroxyl group at C-2 is in the equatorial/down position. The proportion of the α -anomer present decreases from 69% for the mannose derivative to 36% for the glucose moiety.

This C-2 position and the substituent on it is also important when viewed as a way of predicting the product that might be achieved in the glycosidation reaction. There exist four types of glycoside, Fig. 1.12. These are named according to the orientation of both the glycosidic linkage and the substituent at the C-2 position.

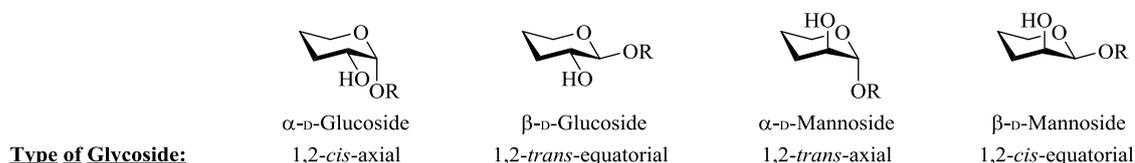
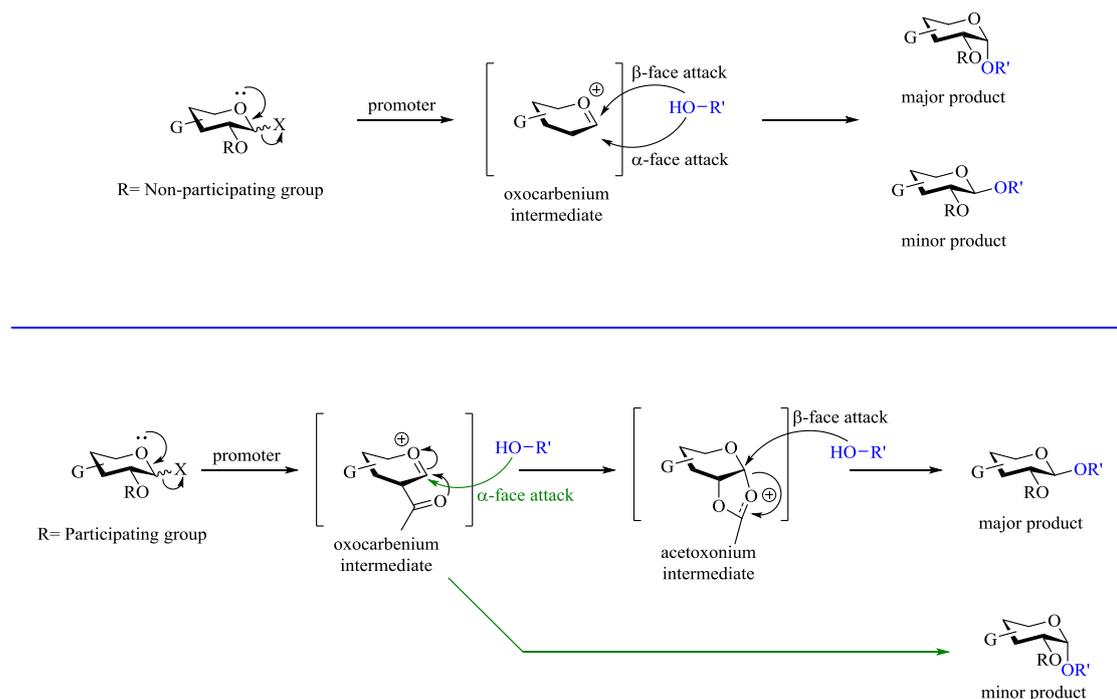


Fig. 1.12 Types of glycosides.

Protecting groups used on the glycosyl donor are important especially that of the C-2 position. Sugars with protecting groups at C-2 such as esters and amides are capable of a process known as neighbouring group participation. Scheme 1.5.



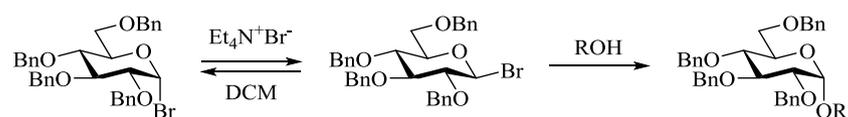
Scheme 1.5 Influence of protecting groups on glycoside synthesis.

Following formation of the oxocarbenium intermediate, a donor with a protecting group at C-2 capable of the neighbouring group participation (e.g. acetate, benzoyl) will form a cyclic acetoxonium ion. This cyclic intermediate ‘blocks’ one face from nucleophilic attack, resulting in 1,2-*trans* products. As such this neighbouring group participation gives β -products for sugars bearing an equatorial C-2 group (e.g. glucose, galactose) and α -products for those with an axial C-2 group (e.g. mannose) for the D- series of sugars with protecting groups capable of neighbouring group participation.

For donors bearing a non-participating group at the C-2 position (e.g. benzyl, azide), stereoselective synthesis of 1,2-*cis*-glycosides can be achieved. Here we also see a preference for the 1,2-*cis*-axial glycoside for reasons already discussed in section 1.1.2.

1.1.3.3 *In situ* anomerisation

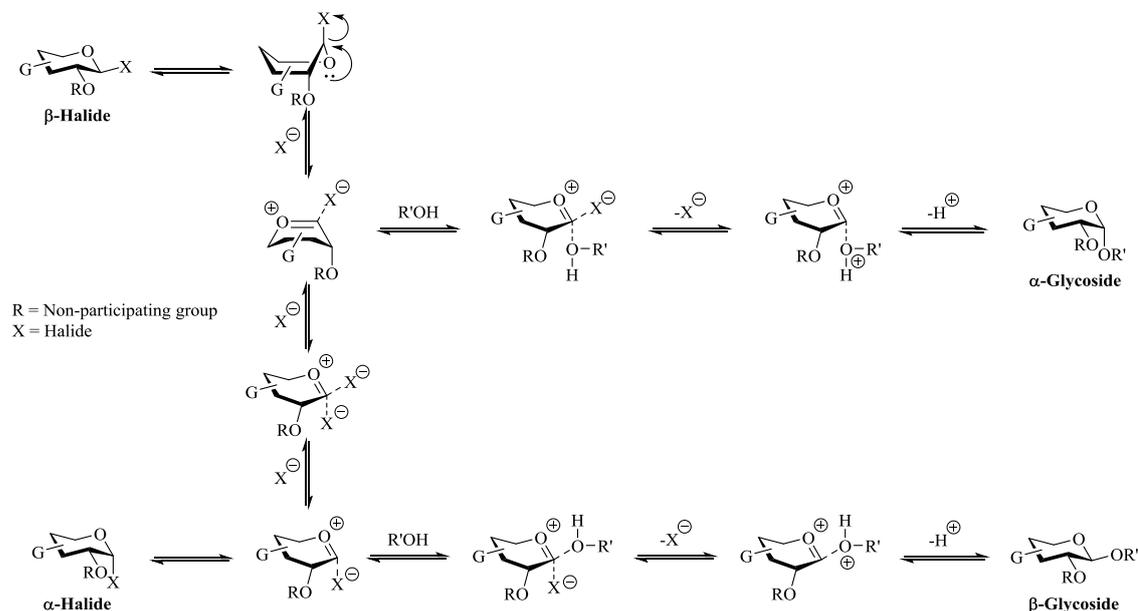
Lemieux proposed an alternative glycosidation pathway which employed donors with non-participating groups at the C-2 position, which yielded the desired 1,2-*cis*-product¹² Scheme 1.6.



Scheme 1.6 Lemieux's alternative glycosidation pathway.

This was achieved through the halide ion catalyzed glycosidation reaction of tetra-*O*-benzyl- α -D-glucopyranosyl chloride and bromide with simple alcohols. The reaction is considered to proceed by way of the highly reactive β -glycosyl halide which is brought into rapid equilibrium with the more stable α -anomer by halide ions donated from the

tetra-alkyl ammonium halide used. The reaction proceeds in an S_N2 fashion with inversion of the highly reactive β-glycosyl halide species with an acceptor as shown in Scheme 1.7



Scheme 1.7 Lemieux's glycosylation mechanism (halide assisted in situ anomerization).¹³

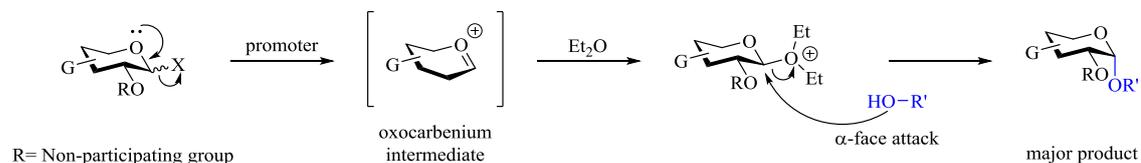
The rate of conversion between α-glycosyl halide and β-glycosyl halide was observed to be considerably faster than glycosidation of the α-glycosyl halide when in the presence of the added halide ions. As such, high selectivity of the 1,2-*cis*-product can be achieved, as the rate of equilibrium between the two glycosyl halides is faster than the rate of reaction between that of the more favoured/stable α-glycosyl halide and the acceptor.

1.1.3.4 Solvent choice

The choice of solvent in glycosidations has been studied and has been shown to play an important role in anomeric control of these reactions⁴. This is particularly relevant for reactions where donors containing non-participating groups are being used. Glycosidations carried out in nitriles (e.g. acetonitrile) and ethers (e.g. diethyl ether, THF) have been shown to produce different anomeric products.

Reactions carried out in ethers favour the formation of α-products while those carried out in nitriles favour the formation of β-product. This is believed to be due to participation of the solvent with the oxocarbenium intermediate and, similar to that illustrated in the neighbouring group participation, this solvent molecule 'blocks' one face of the intermediate from nucleophilic attack thus leading to product formation of the opposite anomer.

Diethyl ether was shown to participate by forming equatorial oxonium cations due to either the reverse anomeric effect⁴ or due to steric reasons, both of which would account for the subsequent favoured formation of an α -glycoside, Scheme 1.8.



Scheme 1.8 The formation of an α -glycoside by diethyl ether participation.

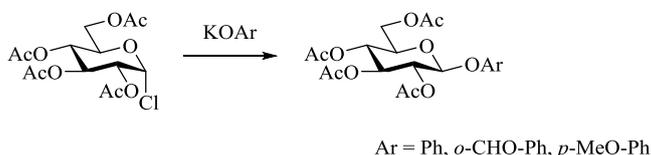
The proposed α -configuration of the intermediate, when using nitrile solvents, was supported by work carried out by Fraser-Reid¹⁴. Previous to this study there was a divide in opinion as to which configuration the glycosylacetoneitrilium ion adopted, with some groups advocating a β -configuration^{15,16} because of a proposed reverse anomeric effect¹⁷, which was considered the tendency of positively charged substituents, at the anomeric centre, to adopt an equatorial orientation. This was dispelled by the work of Fraser-Reid due to the trapping of the intermediate ion with 2-chlorobenzoic acid. Another postulation would be, contrary to diethyl ether example above, that the MeCN could adopt an axial configuration, as it would be less sterically hindered when compared to the analogous glycosyl diethyl ether ion intermediate. The overall effect when using nitrile solvents is the synthesis of β -glycosides.

With the factors that can be attributed to the distribution of the anomeric ratio in a glycosidation reactions now discussed, it is worth briefly looking at a few glycosidation reactions where these influencing factors may arise and how they can be utilised to predict and manipulate a reaction to give a product of the desired stereochemistry.

1.1.4 Glycoside synthesis

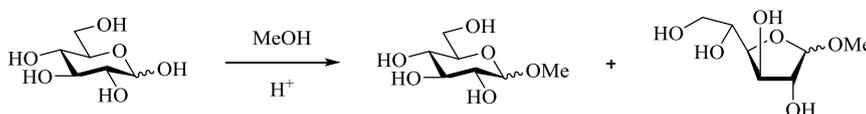
1.1.4.1 Glycosidation background

Nature, as is her prerogative, is far better at most things over man, that extends to the scope of chemistry and in this particular instance, to her ability to produce complex poly- and oligo-saccharides through the glycosidation reaction. The first chemical glycosidation was reported in 1879 by Arthur Michael¹⁸ (better known for the Michael reaction), in which the reaction proceeds with nucleophilic displacement of chlorine at the anomeric position.



Scheme 1.10 The first chemical glycosidation as reported by Arthur Michael.

This work along with Emil Fischer's approach in 1893, as briefly discussed in section 1.1.1, in which an unprotected sugar is reacted under acidic conditions with an excess of an acceptor, leads to an equilibrium of inter-converting species.

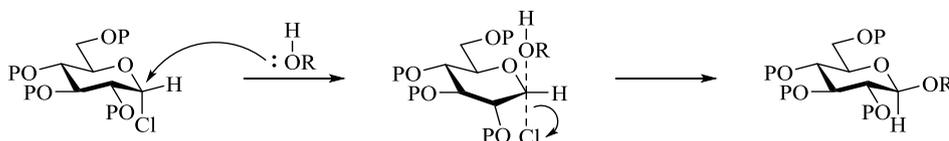


Scheme 1.11 Emil Fischer's approach to glycosidation.

These early studies by Michael and Fisher provided some of the key fundamentals for achieving successful glycosidation reactions. These observations were, that protecting groups can be used to give products of desired ring size, that the use of a leaving group can be utilised to provide a variety of glycosides and that the glycosidation reaction could not be viewed as a typical acetal formation reaction. These considerations have lead to a number of glycosidation methods being developed which in some form or other base their techniques or procedures on the pioneering work carried out by these two chemists.

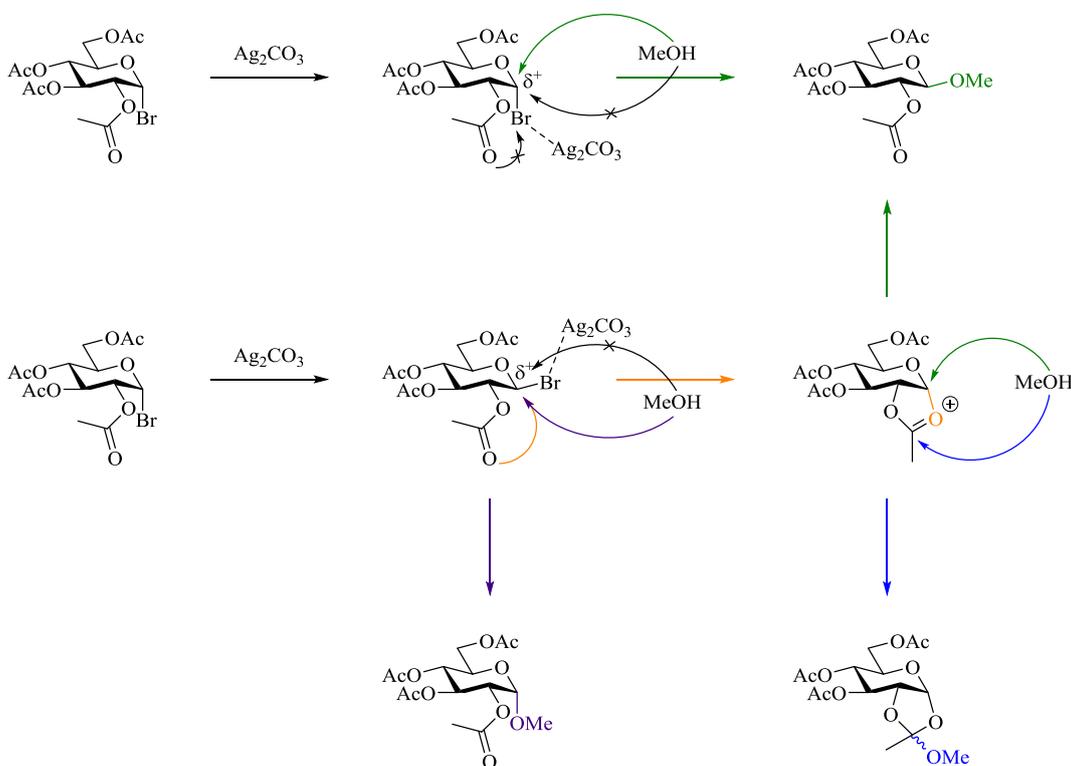
One of these glycosidation methods, the Koenigs-Knorr glycosidation, reported in 1901¹⁹, reacts glycosyl halides, (the general preparation of which is achieved through treatment of an anomeric acetate or 1,2-orthoester with HBr or HCl, with the reaction typically giving α -halide products due to reasons previously discussed in section 1.1.2), with alcohol acceptors in the presence of Ag salts. Initially these salts e.g. Ag₂CO₃ or Ag₂O, were thought to be used primarily to mop up or scavenge the HX by-product, but

it was later realised that these silver salts were actually playing a more important role within the reaction. It was found that these silver salts were assisting in leaving group departure. It was also noted, at the time, that this method was very selective, often providing products with complete inversion at the anomeric centre, rationalized, at the time, as due to Walden inversion, which is where the incoming nucleophile attacks from the reverse side of the leaving group²⁰.



Scheme 1.12 Inversion at the anomeric centre due to the glycosidation reaction.

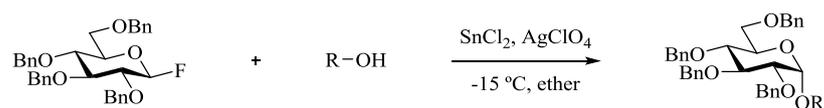
This mechanistic pathway had to be re-evaluated as a greater understanding of the mechanics of carbohydrates and their various substituents began to unfold. One of which has been already touched on in section 1.1.3.2, that of neighbouring group participation provided by the ester protecting group at C-2. It was shown that two distinct pathways existed for glycosidation depending on the configuration of the glycosyl halide being used, 1,2-*cis* or 1,2-*trans*. The anomeric halide, of the glycosyl donor, complexes with a silver salt, regardless of the configuration of the donor, which, decreases the electron density at the anomeric centre, thereby making it more susceptible to nucleophilic attack. Subsequent to this the pathways diverge depending on what is possible for either the incoming nucleophile or what the glycosyl donor is capable of achieving through neighbouring group participation Scheme 1.13.



Scheme 1.13 Possible pathways by which glycosidation may occur.

An alternative pathway, very similar to the Koenigs-Knorr glycosidation, is that of the Helfrich method, which also employs glycosyl halides as the glycosyl donor but in place of Ag salts uses Hg salts. Further distinction between these two methods arises in the polarity of the solvents in which they are carried out in. Koenigs-Knorr reactions are run in non-polar solvents while Helfrich glycosidations are carried out in polar solvents. Due to the instability of the halide and use of Ag or Hg salts and the disposal of these as waste at the end of the reaction, meant other methods of glycosidation were also investigated.

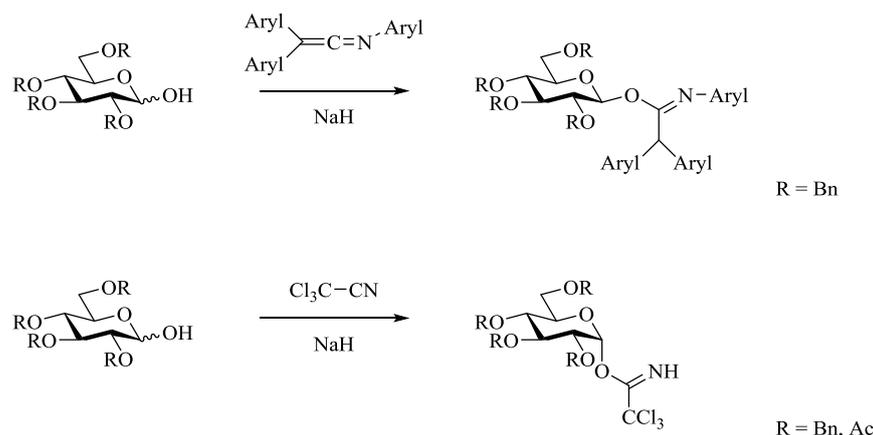
The use of glycosyl fluorides was reported by Mukaiyama in 1981²¹. These fluorides are more stable than their corresponding bromides and chlorides, i.e. those used in the Koenigs-Knorr glycosidation. These glycosyl fluorides can be synthesised through a number of different ways, one of which is the treatment of an anomeric acetate with HF and pyridine. Mukaiyama found, after screening a variety of Lewis acids, that the combined use of SnCl₂ and AgClO₄ effectively promotes the stereoselective reaction of a glucosyl fluoride and with an alcohol acceptor. The 1,2-*cis*-glycoside (α -glycoside) is predominantly prepared in this fashion by the reaction of 2,3,4,6-tetra-*O*-benzyl- β -D-glucopyranosyl fluoride with a variety of alcohol acceptors, Scheme 1.14.



Scheme 1.14 The use of glycosyl fluorides in glycosidation.

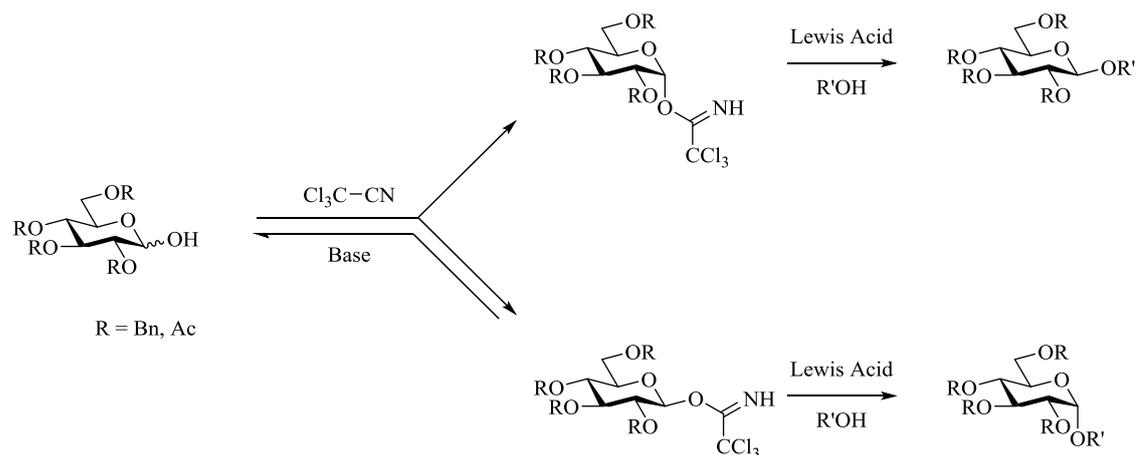
These glycosyl fluorides, even with their enhanced stability, have not proven to be superior to other glycosyl halides in terms of glycosyl efficacy in glycosidation reactions.

Another method of glycosidation was reported by Schmidt in 1980, as an alternative to the Koenigs-Knorr. The view of Schmidt was to prepare readily isolable intermediates with leaving groups, other than those halides already discussed, that do not require activation by undesirable heavy metal salts. It was proposed that suitable candidates would be glycosyl imidates. These can be readily synthesised from their corresponding hemiacetals. Initial studies were carried out using NaH as the base and it was found that reactions with aryl-substituted ketenimines gave exclusively the β -imidates, while reactions with trichloroacetonitrile led to α -imidates, Scheme 1.15.



Scheme 1.15 The synthesis of glycosyl imidates as reported by Schmidt.

Further work in this area has advanced the chemistry to where, now, depending on the base used, either the α - or β -trichloroacetimidate can be selectively achieved²². A strong base e.g. DBU, NaH, will give the α -trichloroacetimidate selectively while a weak base, e.g. K_2CO_3 , will give the opposite anomer, i.e. the β -trichloroacetimidate, Scheme 1.16.



Scheme 1.16 The synthesis of either α - or β -trichloroacetimidates and subsequent use towards glycosides.

These imidates can be then be used in the glycosidation reaction, where, generally, one would use the opposite anomer of the trichloroacetimidate to achieve the desired glycoside anomer, as illustrated in Scheme 1.16. With that said, the products achieved are once again subjective to the other parameters involved in the reaction, such as participating groups and solvent choice, both of which can affect the stereocontrol, i.e. product conformation.

The above glycosidation methods cover some of the more popular techniques used but there are plenty of other synthetic procedures available to the chemist interested in forming glycosides. The name of the glycosidation method is generally derived from the functionality of the glycosyl donor being used, other than the named reactions

already covered. A few more examples of some of the main glycosyl donors, other than those already covered, are included below in Fig. 1.13.

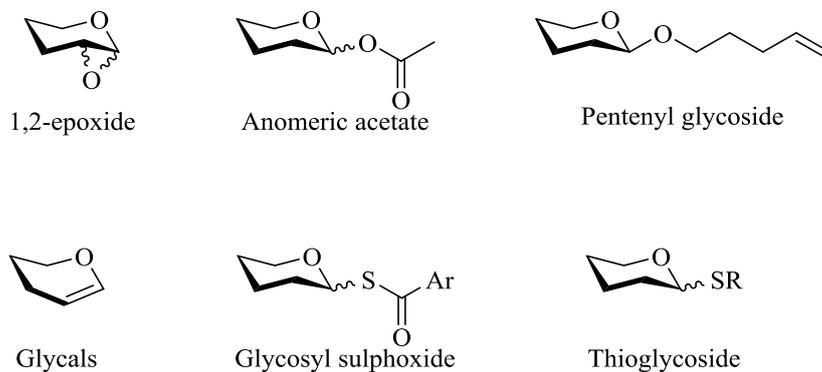


Fig. 1.13 An examples of some of the other main glycosyl donors.

These by no means are the only donors capable of glycosidation but give a brief overview of the diversity available to do so.

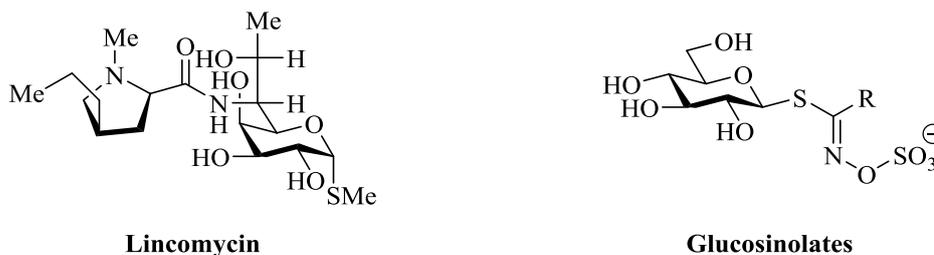
1.1.5 Thiols and thioglycosides

1.1.5.1 Thiols

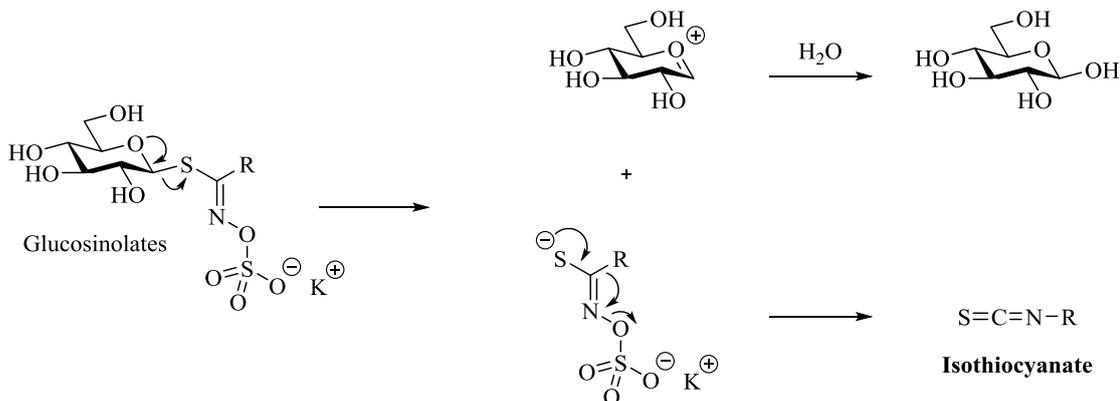
Thiols, R-SH, are analogous to alcohols differing in the chalcogen (chemical element in group 16 of the periodic table) used, where the oxygen atom, of an alcohol is replaced by a sulfur atom, in a thiol. This sulfur atom due to its size and the relatively non-polarized S-H bond, due to the small electronegativity difference between the sulfur atom (2.58) and the hydrogen atom (2.20), especially when compared to the electronegativity difference of the oxygen (3.44) and hydrogen (2.20) of an alcohol, mean it does not undergo efficient hydrogen bonding. Other chemical differences that can be observed, for example, are that thiols are stronger acids than the corresponding alcohol and that thiols have a lower dipole moment than equivalent alcohols.

Thiols, along with the sulfur analogues of ethers, thioethers/sulphides, have one very notable and obvious physical characteristic, their extremely noxious odours. For this reason, volatile thiols are used as a safety measure by being added to natural gas (methane), which is odourless, so that any leaks can be easily detected. Its use as an easily detectable warning was seen on a mass scale as recently as Jan. 22nd 2013 when a gas cloud of methanethiol was released from a company called Lubrizol, in Rouen, France. The gas was detected in regions of southern England as well as areas southwest of Rouen, France, towards and including Paris. The incident, which was dubbed “Le Pong”, led to emergency phone lines at Britain’s gas infrastructure being inundated with calls about the ‘smell’ of gas²³.

The -SH functional group is also called a mercapto group/mercaptan, because of the violent reaction it has with mercury (II) oxide. Mercaptan being derived from the Latin *mercurium captans* (capturing mercury).

**Fig. 1.14** Naturally occurring *S*-glycosides.

Glucosinolates, also known as mustard oil glycosides, are predominantly found in plants of the order Brassicales²⁸ (e.g. turnips, the mustard plant, cabbages, horseradishes). These glucosinolates act as an anti-herbivore defence in these plants by enzymatic activation, i.e. myrosinase-catalyzed hydrolysis upon plant tissue damage. This happens by cleavage of the thioglycoside, with the most commonly formed hydrolysis product, the isothiocyanate, being toxic to a wide range of organisms, Scheme 1.20.

**Scheme 1.20** Glucosinolates as an anti-herbivore defence.

These isothiocyanates, and also indoles, are the two major products produced as a cause of autolytic breakdown, i.e. the self-digestion/destruction of a cell through the action of its own enzymes. Both of these derivatives demonstrate protective activities against many forms of cancer. Research has been reported on the *in vitro* and *in vivo* studies of these compounds, showing that they affect many stages of cancer development, including the induction of detoxification enzymes (Phase II enzymes) and the inhibition of activation enzymes (Phase I enzymes).²⁹ Apoptosis, i.e. programmed cell death, and cell cycle perturbations, due to these isothiocyanates, seem to be another potential chemopreventive pathway or mechanism by which they may act, especially with respect to the effects on initiated tumor cells.

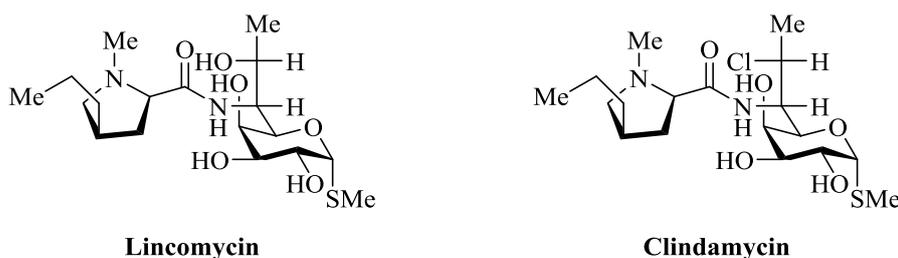


Fig. 1.14 Lincosamides.

The lincosamides (e.g. lincomycin, clindamycin) are a class of antibiotics which prevent bacteria replicating, by interfering with the synthesis of protein in these bacteria. They bind to the 50S ribosomal subunit and have been found to cause dissociation of peptidyl-tRNA from the ribosome³⁰. The aforementioned, lincomycin, has been found to be effective against the likes of mycoplasma, which refers to a genus of bacteria that lack a cell wall. Without a cell wall, these bacteria are unaffected by many common antibiotics such as penicillin or other beta-lactam antibiotics, that target cell wall synthesis. They can also be used to treat plasmodium, which is a genus of parasitic protozoa. Infection with this genus is known as malaria. Lincomycin, due to its adverse effects and toxicity has, in large parts, been replaced by clindamycin, which is synthesised from lincomycin by substitution of the 7-hydroxy group with a chloride³¹. Clindamycin exhibits improved antibacterial activity, with respect to the native lincomycin, and as with lincomycin, exhibits some activity against parasitic protozoa, amongst other ailments.

Thus these thioglycosides are interesting from a therapeutic point of view and therefore the synthesis of further derivatives could prove useful. *S*-Glycosides offer attractive alternatives to natural glycosides, *O*- or *N*-glycosides, due to their enhanced stability, that is that they are less susceptible to chemical degradation and enzymatic cleavage³². Sulfur is less basic than oxygen, so in terms of the hydrolysis of *S*-glycosides the concentration of the *S*-protonated conjugate acid would be lower than the corresponding *O*-glycoside³³.

Sulfur, while being less basic than oxygen, is, also, more nucleophilic. It is the stability to enzymatic cleavage, as well as the similarity in conformation of *S*-glycosides to the analogous *O*-glycoside that make them appealing analogues. In terms of bond lengths and angles, ethers, C-O-C, have a bond angle of about 104° and a C-O bond length of about 140 pm (where 1 Å = 100 pm) with the analogous thioethers having a functional group, C-S-C, bond angle of about 90° and a C-S bond length of about 180 pm. With respect to carbohydrates it has been reported, by Montero et al.³⁴ that the C-S bond length (1.78 Å) and C-S-C bond angle (99°) 'strongly differ' from the analogous structure with the C-O bond length (1.41 Å) and C-O-C bond angle (116°). The differences, between both the bond lengths and angles, result in comparatively small variations between the positions of the atoms along the glycosidic bond. The *S*-glycosides, however, are substantially more flexible due to their longer bonds and weaker stereoelectronic effects³⁵. Due to the aforementioned properties, thioglycosides

have an overall similar conformation with their corresponding *O*-glycosides and as such are attractive alternatives to the native *O*- or *N*-glycosides. This has led thioglycosides, including thiooligosaccharides and *S*-glycoconjugates, to be frequently sought as synthetic targets in carbohydrate chemistry³⁶.

Unlike hemiacetals, such as those discussed in Fig. 1.2, glycosyl thiols, precursors to *S*-glycosides, are quite stable. It has been reported that thio-glycosyl anions do not mutarotate - that is the change of configuration at the anomeric centre, from either α - or β - to the opposite anomeric configuration, even under basic conditions. As such the anomeric configuration of a glycosyl thiol can be retained throughout its use in the synthesis of its corresponding thioglycoside products. Due to this ability to maintain its configuration, the stereoselective synthesis of independent α - and β -glycosyl thiols, and control of this stereoselectivity, is extremely important for subsequent work³⁷.

These thioglycosides often exhibit analogous conformation, as discussed above, as well as comparable or even more potent bioactivities when compared to their corresponding *O*-glycosides.

Bioassays demonstrated that the α -*S*-galactosylceramide mimic of KRN7000, Fig. 1.16, possessed similar potency to KRN7000 in human NKT cell activation³⁸.

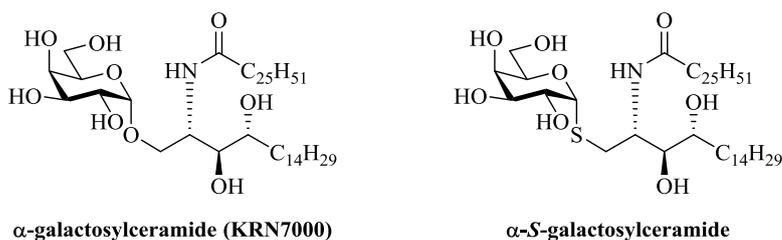


Fig. 1.16 KRN7000 and the α -*S*-galactosylceramide mimic.

While the below *S*-linked glycopeptide mimic of tyrocidine, Fig 1.16, exhibited superior inhibitory activity against *Bacillus subtilis* than the natural antibiotic³⁹.

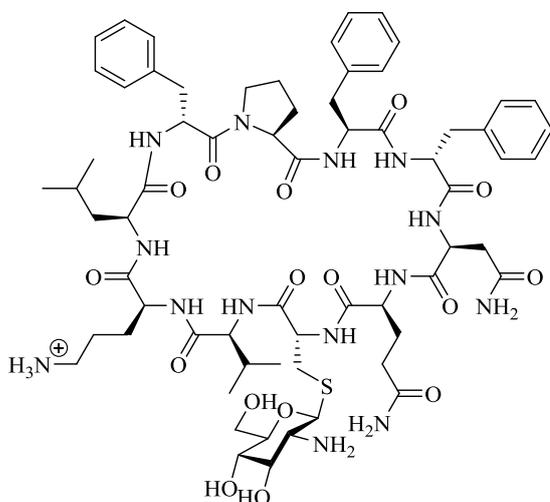
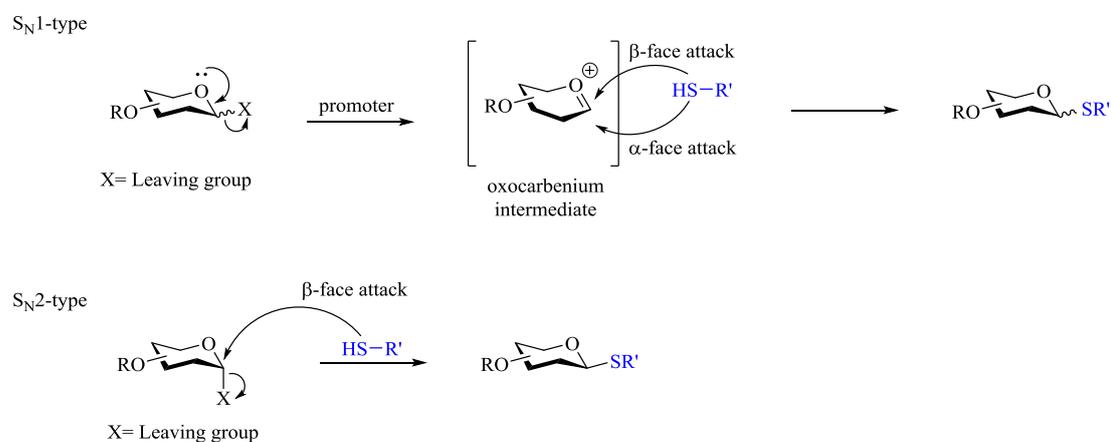


Fig. 1.17 *S*-linked glycopeptide mimic of tyrocidine.

The ability to control the stereoselectivity of glycosidic linkages is an intriguing one. As such the synthesis of glycosyl thiols, with a focus on the less common α -thiols, which are not susceptible mutarotation and their subsequent reaction to thioglycoside of known and controlled glycosidic linkages, is an appealing one, especially those with an α -configuration. A Lewis acid promoted anomerisation system, such as that described herein, to give α -glycosyl thiols would, as such, greatly facilitate the synthetic efforts of those involved in the synthesis of α -S-glycoconjugates.

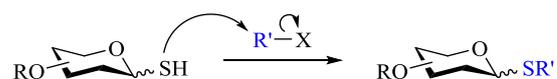
1.1.5.3 Synthesis of thioglycosides

There exists two general synthetic pathways to thioglycosides, the first is very similar to those discussed for *O*-glycosides, through the direct introduction of, in this instance, a mercaptan through the nucleophilic displacement of an anomeric leaving group, which can be activated by a promoter.



Scheme 1.21 Thioglycoside synthesis by means of a leaving group.

The alternative is to synthesis an anomeric thiol or thiolate, which can then be reacted with an alkyl electrophile to give the desired thioglycosides

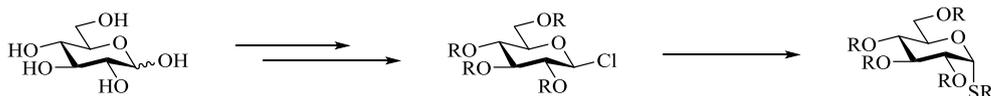


Scheme 1.22 Thioglycoside synthesis by way of a thiol/thiolate.

Both of these pathways are practical and there are numerous examples in the literature of their application.

1.1.5.4 Towards α -glycosyl thiols

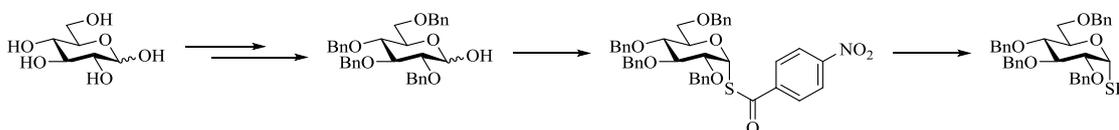
To date only a small number of procedures exist towards α -glycosyl thiols. Of the most commonly reported in the literature there exists one of 3 problems. The first type of procedure utilizes the β -chloride product, Scheme 1.23, to access the α -thiol⁴⁰ through a mechanism such as that discussed in section 1.1.3.3.



Scheme 1.23 The synthesis of an α -glycosyl thiol via a β -chloride.

The problem that exists with this type of reaction is the stability of the β -chloride. It is a highly reactive species that prefers to be in an axial/ α -conformation for reasons discussed in section 1.1.2. This type of procedure has been tried within many groups with some reporting that it failed to give them the desired α -product due to this high reactivity of the halide species⁴¹. It is the reproducibility/efficiency of this procedure that make it an undesirable reaction, again, due to the use of highly reactive β -chlorides.

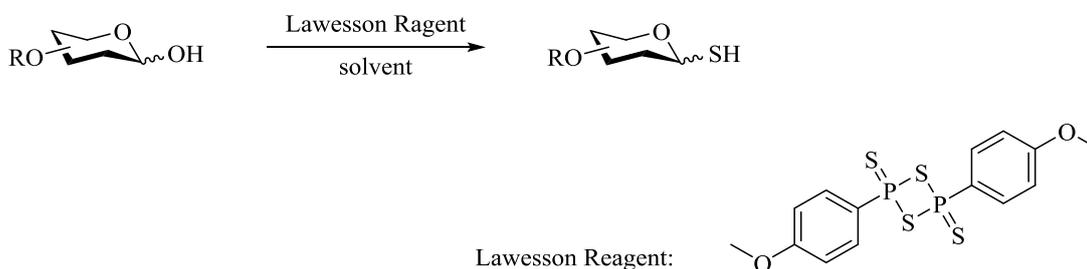
Alternative routes towards α -glycosyl thiols are based on relatively long synthetic sequences⁴², Scheme 1.24.



Scheme 1.24 The synthesis of an α -glycosyl thiol based on relatively long synthetic sequence.

This preparation becomes disadvantageous, due to the number of linear steps needed to synthesis the α -glycosyl thiol, which may be needed for further synthetic steps to access *S*-oligosaccharides and/or *S*-glycoconjugates. This increase in synthetic manipulation could potentially lead to a proportional decrease in the mass of product obtained and as such is a disadvantageous synthetic route.

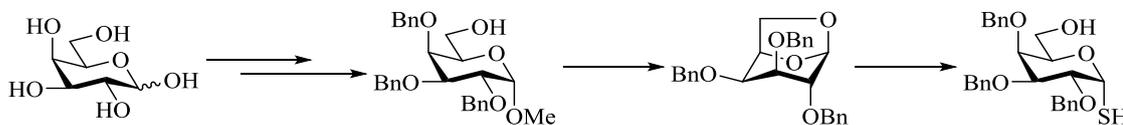
An alternative route towards α -glycosyl thiols, is reported by Davis et al. using Lawesson's reagent⁴³. They found that the Lawesson reagent had the capability to covert reducing sugars or/and unprotected sugars into their analogous glycosyl thiols, Scheme 1.25.



Scheme 1.25 The synthesis of an α -glycosyl thiol using Lawesson's reagent.

However, as shown, this synthetic procedure fails to provide stereochemical control at the anomeric centre of the glycosyl thiols that are synthesised, leading to a mixture of anomers.

One of the most practical and efficient routes to α -glycosyl thiols has been reported by Zhu et al²⁴. The synthesis reported by these researchers involves the synthesis of 1,6-anhydrosugars and then subsequent ring opening using commercially available bis(trimethylsilyl)sulfide and TMSOTf, Scheme 1.26.



Scheme 1.26 The synthesis of an α -glycosyl thiol using 1,6- anhydrosugars.

Where this falls short is, again, in the required synthetic steps needed to obtain the desired α -glycosyl thiol due to the various protecting group manipulations. With each additional step the overall quantity of product obtained decreases so therefore the shorter the synthetic procedure, in theory, the greater overall yield obtained at the end.

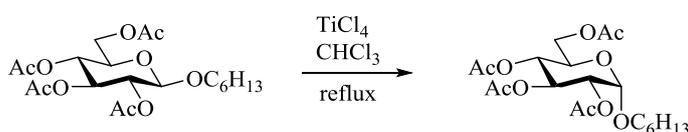
The development of an efficient reaction, using novel methodology, towards α -glycosyl thiols therefore provides a desirable endeavour and if achieved would greatly facilitate the synthetic efforts of those involved in the synthesis of α -S-glycoconjugates.

1.2 Anomerisation

1.2.1 Background

As far back as the 1930s, it was being proposed to use Lewis acids for the anomerisation of *O*-glycosides, and the methodology has not changed significantly since.

Lewis acid promoted anomerisation can be useful in stereoselective glycoside synthesis as demonstrated by Pacsu⁴⁴. This author describes the, then, novel synthesis of pure tetra-acetyl- β -*n*-hexylglucoside, which can be anomerised - by heating in chloroform, with an equimolecular quantity of titanium tetrachloride to the then, inaccessible α -anomer.



Scheme 1.27 Pacsu's Lewis acid promoted anomerisation of tetra-acetyl- β -*n*-hexylglucoside.

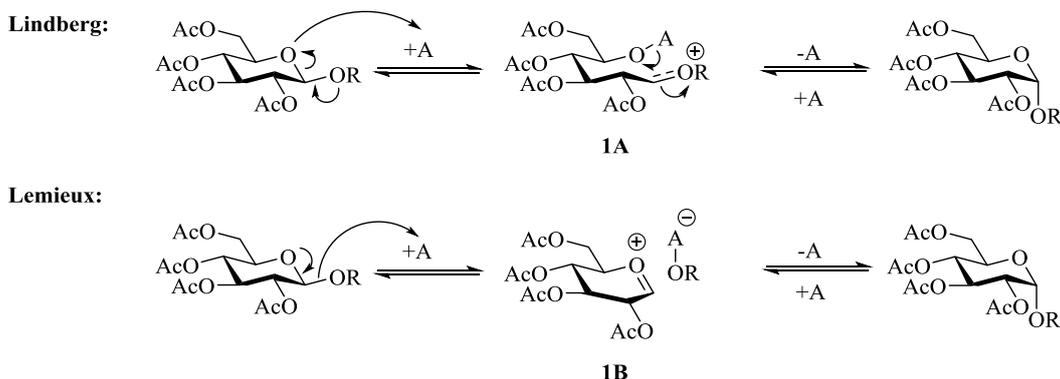
The anomerisation reaction was investigated by two widely known carbohydrate chemists, Lemieux and Lindberg, and from their studies two possible pathways are usually considered when trying to understand the mechanism of the anomerisation reaction, Scheme 1.28.

Both Lindberg and Lemieux demonstrated that the anomerisation reaction proceeds by way of an intramolecular mechanism. Lemieux demonstrated this by anomerising a racemic mixture of methyl β -glucopyranoside tetraacetate. The methoxyl group of the D-isomer of this mixture was labelled with the radioactive isotope, C-14. Anomerisations of the racemic mixture were carried out using both boron trifluoride and titanium tetrachloride as catalysts of the anomerisation reaction. Subsequent analysis of the products, by isotopic dilution, showed, in both cases, that all the radioactivity was in the methyl α -D-glucopyranoside tetraacetate, i.e. no transfer of the radioactive C-14 was detected in the L-isomer, as such indicating an intramolecular reaction⁴⁵.

Lindberg discusses, with the knowledge that the anomerisation reaction is intramolecular, that the acid (A), catalysing the reaction, can coordinate with the ring oxygen leading to endocyclic cleavage of the O-5 – C-1 bond, resulting in the open chain intermediate **1A**; rotation of the C-1 – C-2 bond can occur, with ring closure resulting in a mixture of α,β products.⁴⁶

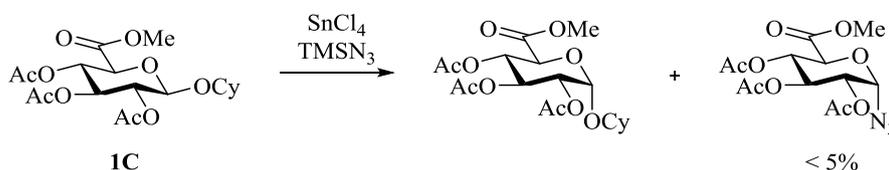
The alternative and earlier reported mechanism of Lemieux, involved cleavage of the exocyclic C-1 – O-1 bond through the acid (A) coordinating with the aglycone. In his model, Lemieux postulates that both anomerisation and glycosidic cleavage result from

the presence of the acid catalyst (A), resulting in two ions which do not fully dissociate, but instead exist as an ion-pair **1B** which can collapse to an α -glycoside.⁴⁵



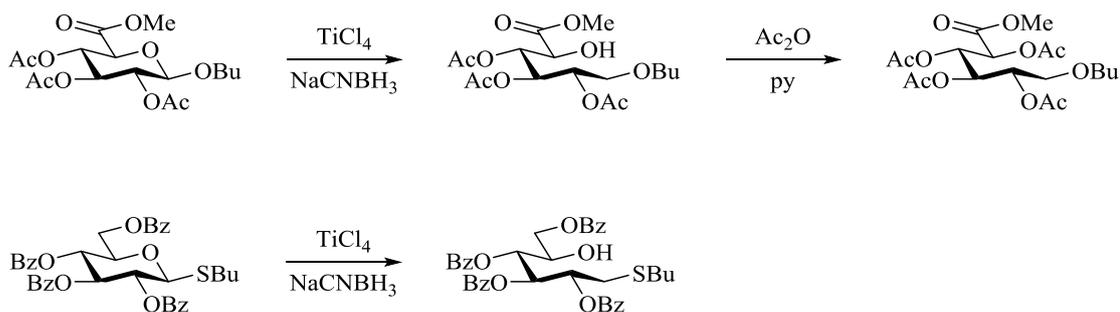
Scheme 1.28 Proposed mechanisms for glycoside anomerisation.

Recent studies⁴⁷ also indicate that it is not one or the other, but rather contributions from both these pathways which result in anomerisation, albeit the probable contribution from the exocyclic pathway, in the anomerisation of glucuronic acid derivatives, is small. This was attempted to be illustrated through the reaction of the glucuronic acid derivative **1C**, Scheme 1.29 in the presence of SnCl_4 , acting as the Lewis acid necessary for an anomerisation reaction to occur, and a competing azido-trimethylsilane nucleophile. Results of < 5% of the α -azide product after one week could be postulated as demonstrating that the predominate mechanism of reaction, for anomerisation, is probably that of the pathway proposed by Lindberg.



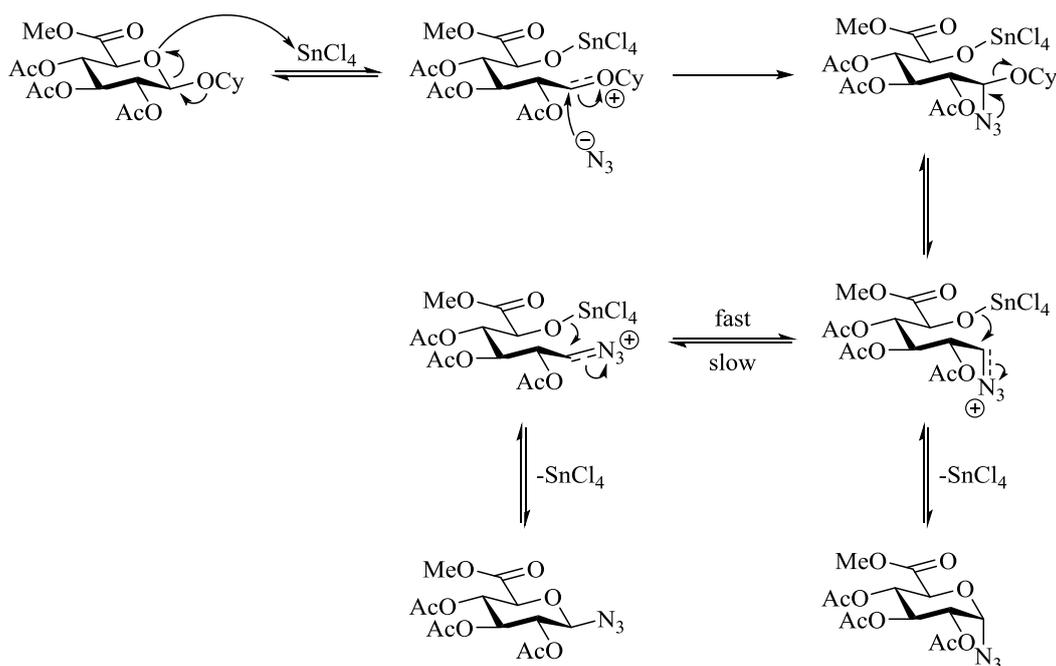
Scheme 1.29 A competitive reaction to try and elucidate the reaction mechanism.

This competitive reaction was used to demonstrate that, for the two mechanisms under consideration, the endocyclic mechanism is probably the favoured one. If the exocyclic pathway, as proposed by Lemieux, were in operation to any significant degree, one would expect a probable higher proportion of azide product. Another reaction carried out to provide further evidence for the endocyclic cleavage mechanism, was presented by Pilgrim et al.⁴⁸ Within this article a trapping experiment was carried out, Scheme 1.30, using sodium cyanoborohydride to facilitate the identification of the intermediate generated during the endocyclic cleavage mechanism of a Lewis acid promoted anomerisation. This trapping was carried out using both an *O*- and *S*-glycosides. The experiment provided support that TiCl_4 promoted anomerisations proceeds, at least to some extent, through endocyclic cleavage.



Scheme 1.30 A trapping experiment carried out to illustrate that the endocyclic cleavage mechanism is the mechanism by which TiCl_4 promoted anomerisations occur.

The azide product, synthesised as part of the competitive experiment in Scheme 1.29, may not even be as a result of an exocyclic mechanism, as an alternative endocyclic mechanism, Scheme 1.31, may also be used to account for the formation of the small amount of azide. If the rate of interconversion between the two acyclic azido-intermediates, α and β - leading to an α -intermediate, was fast compared to the rate of ring closure, such as that demonstrated for the anomeric effect in section 1.1.3.3, this would account for the absence of any β -azido product.



Scheme 1.31 Accounting for the azide product by means of the endocyclic mechanism.

Much like the anomeric effect, it is hard to say definitively which of the mechanisms, is the true mechanism of reaction for the Lewis acid promoted anomerisation reaction. It is probable that there is a contribution from both proposed mechanisms but as discussed above there is now mounting evidence that it is the mechanism as proposed by Lindberg, i.e. the endocyclic mechanism that is the main mechanism of reaction.

Anomerisation is also evident in some glycosidation reactions which utilise Lewis acids within their reaction conditions. 1,2-Trans glycosides can be isolated from reactions using Lewis acids - TiCl_4 or SnCl_4 , when donors containing 2-acyl groups are used, due to neighbouring group participation as discussed in section 1.1.3.2.^{45, 49, 50} However, in a number of such glycosidation reactions either the α -product or a mixture of both the α - and the β -products can be obtained.⁵¹ The formation of these 1,2-cis glycosides (α -products) can be explained by first the synthesis, through glycosidation, of the β -anomer, which subsequently undergoes anomerisation to give a product with α -configuration (glycosidation-anomerisation).⁴⁷

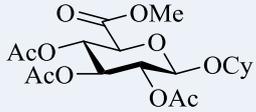
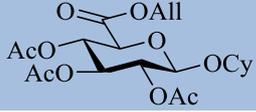
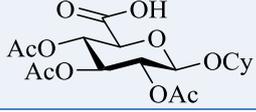
As in the case of glycosidations, anomerisation reactions do not yield completely the α -anomer. This is on account of many contributing factors, from solvent choice, to protecting groups used. A *JOC* featured article from the Murphy laboratory⁴⁸ reports on the study of these factors and discusses the conditions necessary to achieve faster rates of anomerisation as well as increasing the selectivity of the desired anomer obtained, in respect to a range of glucopyranoses, galactopyranoses, glucopyruonic acid methyl esters, and galactopyruonic methyl esters.

Within this study it was found that galactose derivatives anomerised faster than their corresponding glucose compounds but for one exception (**1M** and **1Q**, Table 1.1). This superior rate of anomerisation for galactose derivatives is believed to be on account of the orientation of the substituent at C-4. For glucose, substituents at C-4 adopt an equatorial orientation which leads to glucose derivatives being more electron withdrawing than their galactose counterparts, whose C-4 substituents adopt an axial configuration. With this increased electron density available to the ring in galactose compounds, the ring oxygen has an enhanced ability to coordinate to the Lewis acid and thereby facilitate anomerisation. In addition, the increased electron density, within galactose derivatives, should stabilize the positively charged intermediate of the anomerisation reaction.

It was shown that the anomerisation of *S*-glycosides were consistently faster than those for corresponding *O*-glycosides, by a varying factors e.g. 2.5 times faster for *S*-glycoside **1G** (Table 1.1) than *O*-glycoside **1E** (Table 1.1). This, again, is believed to be on account of increased electron density being presented to the ring oxygen, this time in respect to the anomeric position, with the sulfur atom of the *S*-glycoside being less electronegative than oxygen of its *O*-glycoside counterpart. This electronegativity factor also affects the proportion of the α -anomer achieved, at equilibrium, for *S*-glycosides when compared to corresponding *O*-glycosides. In this instance it has a negative effect, with *S*-glycosides generally having lower proportions of the desired α -anomer. This can be attributed to sulfur being less electronegative than oxygen, which results in a less pronounced anomeric effect and therefore less of the desired α -*S*-glycoside. In addition, sulfur is larger than oxygen and as such would have an increased preference for an equatorial position, on steric grounds.

Table 1.1: Overview of the kinetics obtained for the SnCl₄ promoted anomerisations studies carried out by Pilgrim et al.

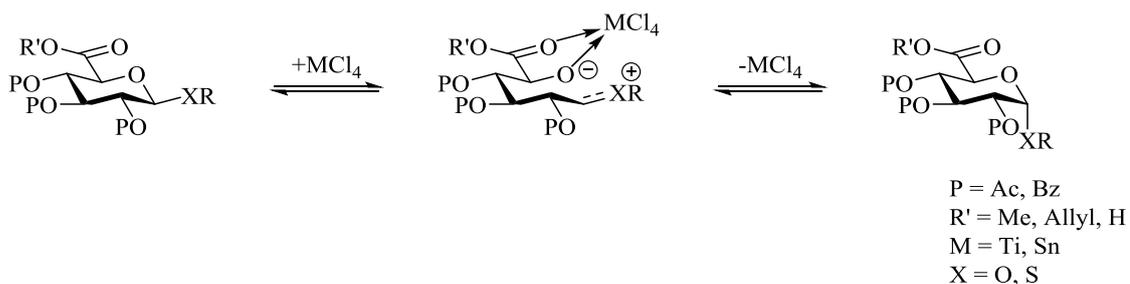
Label	Substrate	10 ⁶ (k _r +k _r) (s ⁻¹)	Relative Rate	α:β
1D		4	1	10:1
1E		170	42.5	16:1
1F		470	117.5	24:1
1G		420	105	4:1
1H		920	230	7:1
1I		290	72.5	19:1
1J		19	4.75	16:1
1K		400	100	13:1
1L		6.9	1.725	2:1
1M		43	10.75	4:1
1N		4.9	1.225	15:1
1O		42	10.5	11:1
1P		14	3.5	2:1
1Q		20	5	4:1

1R		21	5.25	11.5:1
1S		210	52.5	13:1
1T		1100	275	11.5:1
1U		12000 ^a	3000	19:1

Reactions were carried out at 30 °C with 0.08 M substrate and 0.04 M SnCl₄ in CDCl₃.

^aKinetics were determined by polarimetry

The anomerisation of uronic acid derivatives were shown to anomerise significantly faster than their non-uronic counterparts. This can be illustrated through the following – the allyl ester derivative **1T** (Table 1.1) was found to be greater than five times faster than methyl ester **1S** (Table 1.1), and the unprotected acid **1U** (Table 1.1) was an order of magnitude faster than both of these sugars. All of these derivatives, **1S**, **1T** and **1U** were significantly faster than the non-uronic pyranose derivative **1R** (Table 1.1). This faster rate of anomerisation for glycosides possessing a carbonyl at C-6, was found to follow a similar pattern for all the derivatives reported within this article. The enhanced rate of anomerisation was proposed to be due to coordination of the carbonyl, of the uronic acid/ester functional group, to the Lewis acid, promoting an endocyclic mechanism, as proposed by Lindberg – Scheme 1.28, such as that displayed in Scheme 1.32.



Scheme 1.32 Proposed mechanism for the Lewis acid promoted anomerisation of uronic acids/esters.

The unprotected acid **1U** (Table 1.1) was shown to be the fastest of all the uronic acid derivatives reported, which, as already mentioned, were faster than all the non-uronic pyranoses tested. This enhanced rate of anomerisation for **1U** is in line with the original observations by Lemieux and Hindsgaul.⁵² They demonstrated that isopropyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside in the presence of an equimolar amount of SnCl₄ was found to anomerise very slowly (half-time of reaction ($t_{1/2}$) of about 1400 min.) but when the reaction was repeated with the same conditions except for the addition of one

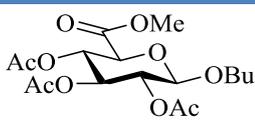
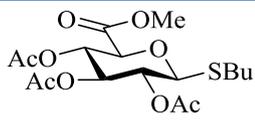
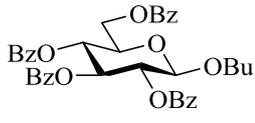
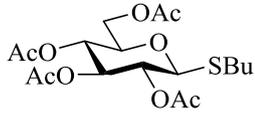
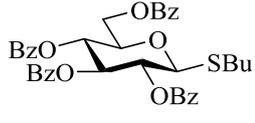
molar equivalent of acetic acid (AcOH), anomerisation was found to proceed nearly 100 times faster ($t_{1/2} = 14$ min). This work by Lemieux and Hindsgaul, coupled with the observations of the Murphy laboratory^{47,48}, shows that the combination of a Lewis acid - SnCl₄ in the reported articles, and a carboxylic acid, can afford powerful inter- or intramolecular promotion for the β - to α - anomerisation of, in these instances, glucopyranoside derivatives.

The faster anomerisation reaction observed for the allyl ester **1T** (Table 1.1), compared to the methyl ester **1S** (Table 1.1) within the studies by Pilgrim et al., could be attributed to the allyl group being a π -donor and as such would coordinate more effectively to the Lewis acid. This would allow the facilitation of the Lewis acid promoted anomerisation to be more effectively achieved and as such provide the observed enhanced rate of reaction.

The protecting groups present (OAc or OBz) on the carbohydrate were also reported as having an influence on the outcome of the α : β ratios obtained at equilibrium. Higher selectivity of the α -anomer was reported for derivatives possessing benzoate (OBz) protecting groups as opposed to their analogous derivative possessing acetyl (OAc) protecting groups. The rate of anomerisation was also reported to increase when employing benzoates in place of acetyl protecting groups. The enhanced rate observed for the derivatives possessing benzoates can be reasoned as being due to the increased ability of the benzoyl groups to donate electron density into the ring of the carbohydrate when compared to acetyl groups. This increased electron density, as mentioned for the differences between galactose and glucose derivatives, contributes to an enhancement in the capability of the ring oxygen to coordinate to the Lewis acid and thereby assist anomerisation.

The effect of varying the Lewis acid, used to promote the anomerisation reaction, from SnCl₄ to TiCl₄, as well as temperature variations were also investigated in the study by Pilgrim. These alterations were studied using both *O*- and *S*- glycosides as well as uronic and non-uronic pyranosides. The derivatives tested were – **1E**, **1G**, **1J**, **1L** and **1M** from Table 1.1 above.

Table 1.2: Lewis acid changes in the studies carried out by Pilgrim et al.

Compound	Lewis acid (0.04 M, 0.5 eq.)	$10^5 (k_f+k_r) (s^{-1})$	$\alpha:\beta$
 1E	SnCl ₄	17	16:1
	TiCl ₄	- ^a	47:1
 1G	SnCl ₄	42	4:1
	TiCl ₄	- ^a	8:1
 1J	SnCl ₄	1.9	14:1
	TiCl ₄	23	15.5:1
 1L	SnCl ₄	0.69	2:1
	TiCl ₄	4.7	1.2:1
 1M	SnCl ₄	4.3	4:1
	TiCl ₄	28	1.9:1

Reactions were carried out at 30 °C with 0.08 M substrate. ^aRates were too fast to measure by NMR

The reactions catalysed by TiCl₄ were shown to have faster rates of anomerisation than those catalysed by SnCl₄. In some cases, such as that observed for entries **1E** and **1G** (Table 1.2) the rate of anomerisation, when using TiCl₄, was so quick that they were essentially instantaneous under the conditions described within the study. The selectivity for the α -anomer was also shown to be higher for the anomerisation of the glucuronides already mentioned - derivatives **1E** and **1G**, when catalysed by TiCl₄ than for the anomerisation of these carbohydrates when catalysed by SnCl₄. This increase of the α -anomer was not as evident or at least the trend was not as clear for glucosides **1J**, **1L** and **1M**. The $\alpha:\beta$ ratio obtained for anomerisation of the *O*-glucoside **1J** was higher for the TiCl₄ catalyzed reaction than for the SnCl₄ catalyzed reaction, as observed for the anomerisation of the glucuronides. However, the reverse was found for both the *S*-glucosides **1L** and **1M**, even with there being a variation in protecting groups between these two glucosides. The obtained ratios, i.e. differences between *O*- and *S*-glucosides reported in the study, could possibly be accounted for through the formation of a complex such as Fig. 1.18 which is favourable for *O*-glucosides but may be less so for *S*-glucosides, in Lewis acid promoted anomerisations.

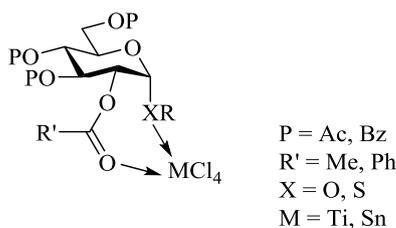


Fig. 1.18 A possible complex accounting for differences in obtained ratios.

Table 1.3: Temperature variations in the studies carried out by Pilgrim et al.

Compound	Temp (°C)	$10^5 (k_f+k_r) (s^{-1})$	$\alpha:\beta$
 1E	0	4.7	26.8:1
	20	7.1	17.2:1
	30	17	15.7:1
	40	29	14.4:1
 1G	-15	6.4	7.5:1
	0	14	5.8:1
	30	42	3.7:1

Reactions were carried out with 0.08 M substrate and 0.04 M SnCl_4 .

As mentioned, the influence of temperature on the anomerisation reaction was also investigated. This variation was studied using, once again, glucuronides **1E** and **1G** (Table 1.3). When the reactions were carried out at lower temperatures it was found that the rate of anomerisation was reduced for both sugars. While the rate decreased it was also observed that there was an improvement in the quantity of α -anomer obtained, when carrying the anomerisation reactions out at lower temperatures, Table 1.3.

Finally, the effect of increasing the concentration of Lewis acid was also reported. One of the experiments to study this modification was achieved by carrying out a series of anomerisations using *O*-glycoside **1E** (Table 1.3). This particular series of reactions showed that increasing the Lewis acid concentration also improved the amount of the α -anomer obtained. The experiment in question showed that by doubling the number of equivalents of TiCl_4 used to promote the anomerisation, it was possible to increase the $\alpha:\beta$ equilibrium ratio from 29:1 to 255:1, which roughly equates to a ~ 9 -fold increase in selectivity. The same experiment but employing SnCl_4 , as the promoter of the anomerisation, also led to an increase in the $\alpha:\beta$ equilibrium when doubling the amount of said Lewis acid used. This time the selectivity increased from 16:1 to 20:1. It can be reasoned that if the Lewis acid promoter was capable of coordinating to the anomeric substituent – the oxygen/sulfur atom, as in Fig. 1.18, then this complex could augment the electronegativity of the substituent at the anomeric position of the glycoside, and thus lead to a more pronounced anomeric effect and thereby increase the quantity of the α -anomer generated. It was also postulated that the consistently higher proportion of α -anomer produced through the Lewis acid promoted anomerisation of the

glucuronides/galacturonides studied compared to glucosides/galactosides in the article, could be explained by a chelate such as **1V** in Fig. 1.19.

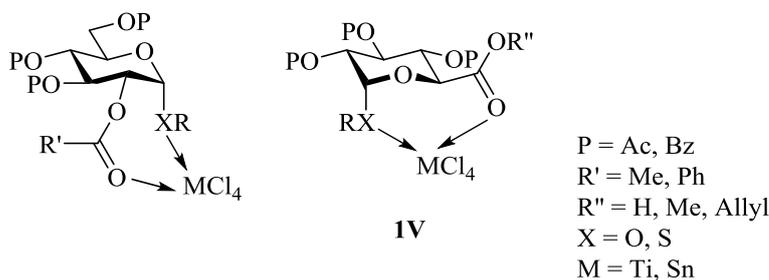


Fig. 1.19 Chelates for glucuronides/galacturonides and glucosides/galactosides studied by Pilgrim et al.

The observations and results, of the work discussed, are used as a guide within the studies of this project, to develop a strategy towards a system for the anomerisation of β -thio-glycopyranoses to the less accessible α -anomers.

1.2.2 Investigations of Lewis acid/Brønsted acid or Lewis acid/Lewis base systems

As previously mentioned the rates of anomerisation for glucuronic acids are significantly faster than those for the corresponding glucuronic esters, which in turn are faster than the parent glycopyranoses, Fig. 1.19.

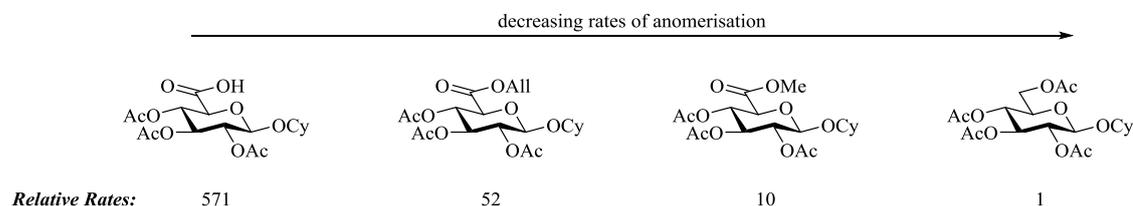
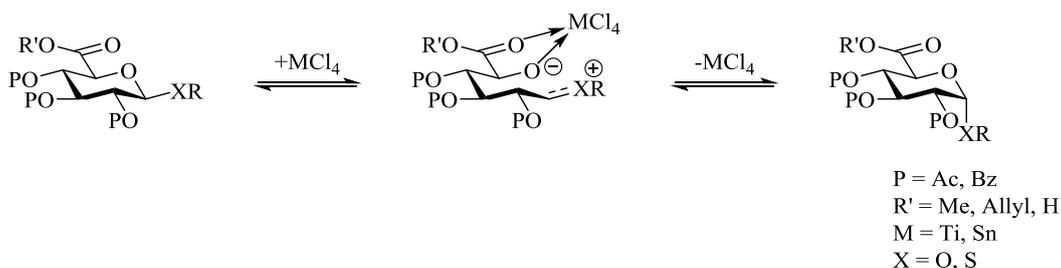


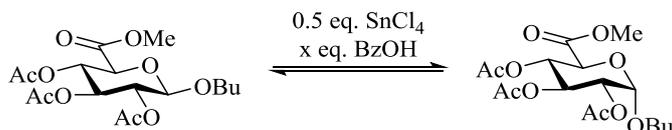
Fig. 1.20 Depiction of decreasing rates of anomerisation for derivatives tested by Pilgrim et al.

It has been shown that the differences in rate of anomerisation can be contributed to by a number of factors one of which may be due to inter- or intra-molecular catalysis, such as that observed and reported by Lemieux and Hindsgaul⁵². This increase in rate is postulated as being brought about by the acidic or uronic nature, whether 'native', as illustrated for the glucuronides/galacturonides in Scheme 1.33, or introduced as an additive to the anomerisation reaction – such as that in the Lemieux and Hindsgaul observations.



Scheme 1.33 Proposed mechanism for the Lewis acid promoted anomerisation of uronic acids/esters.

The observations by Lemieux⁵² - that the SnCl₄ catalysed anomerisation of isopropyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside proceeds 100 times faster in the presence of one equivalent of acetic acid than in its absence open up the idea of additives to a reaction to increase rate and/or selectivity. It was observed, during the preparation of the Pilgrim et al paper⁴⁸, that an unusually high rate of anomerisation was being achieved during a SnCl₄ catalysed anomerisation of butyl-2,3,4,6-tetra-*O*-benzoyl- β -D-glucopyranoside. This anomaly was eventually attributed to the presence of a trace amount of benzoic acid in the reaction mixture. Quantification of the effect of benzoic acid on anomerisation was then carried out, using butyl-2,3,4-*O*-acetyl- β -D-glucopyranoside as the test substrate, Scheme 1.34.



Scheme 1.34 Quantification of the effect of benzoic acid on anomerisation.

It was shown, that by increasing the equivalents of benzoic acid, a rate increase could be observed during the SnCl₄ anomerisation of this substrate. This “co-operative” experiment was repeated, using TFA as the co-promoter, but strangely produced no rate enhancement, this despite TFA having a lower p*K*_a, 0.23, than benzoic acid, 4.23.

The idea that a Lewis acid is capable of combining with an additive, such as a Brønsted acid, to produce a complex that has the ability to increase the rate of anomerisation and/or increase the α : β ratio, is an intriguing one.

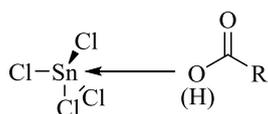


Fig. 1.21 Possible complexation of acids with the Lewis acid SnCl₄.

It can be reasoned that the observed differences in rates of reaction between the anomerisation studies using benzoic acid and those using TFA, could possibly be attributed to the stability of the conjugate base of TFA. The stability of the trifluorocarboxylate anion may inhibit the beneficial complexation with SnCl₄, such as

that in Fig. 1.21, and thus no increase in rate would be observed. Complexation theories aside, an anomerisation rate increase should still be observed when using TFA, due to the direct acid catalysis as shown by Lemieux.⁵² Due to these conflicting arguments it is necessary to approach the mechanistic side of this “co-operative” system from another viewpoint. To that end it is worth discussing the contents of a review written by Denmark et al.⁵³

In this review they discuss complexes similar to that of Fig. 1.21. It was shown that a Lewis acids metal centre can be made more electrophilic by the binding through the donation of a pair of electrons, of a Lewis base. The binding of a Lewis base leads the bonds around the metal centre of the Lewis acid becoming lengthened which corresponds to a “spill over” effect, where the initial increased electron density about the metal centre is redistributed to the more electronegative peripheral atoms. As a result of this, the Lewis acid centre, of this new complex, is often rendered more electrophilic than the ‘parent’ Lewis acid.

If this augmented electrophilicity of the Lewis acid can be implemented in the chemistry of the anomerisation being studied herein, it could lead to greater rate enhancements in the reaction.

This type of “co-operative” system was initially studied by McKinney with a focus on Brønsted acids⁵⁴. As part of this M.Sc. thesis, screening of a variety of aromatic and aliphatic acids was carried out to try and find any physical parameters apart from pK_a , such as steric and/or electronic effects that consistently influenced the rate of anomerisation. It was found that no such similarities could be found. What was observed was that the rate of anomerisation in the presence of 0.5 eq. MSA and 0.5 eq. SnCl_4 was 60 times that observed in the presence of 0.5 eq. SnCl_4 alone.

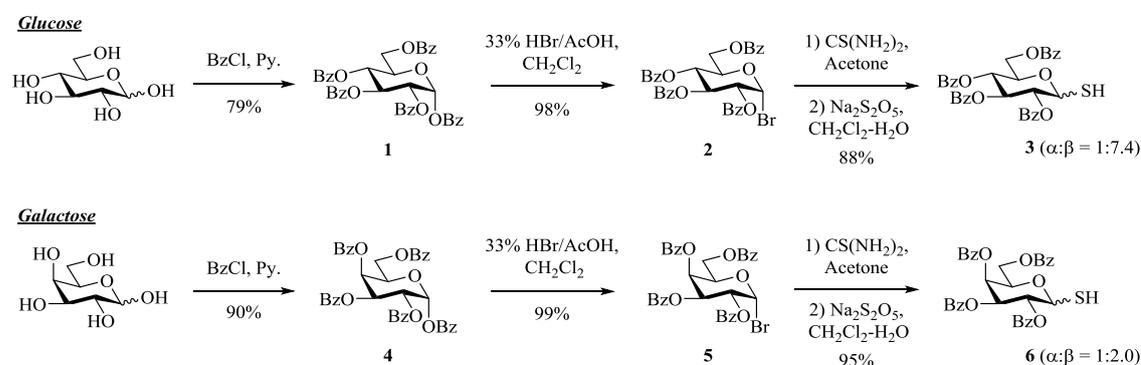
This work by McKinney and others, cited above, on Lewis acid-Brønsted acid combinations, to enhance the rate of anomerisation, is a premise on which the anomerisation work of this section of the thesis is based. It is being investigated with the intention of finding a Lewis acid-co-promoter species that would significantly enhance the rate of the anomerisation reaction and lead to an increase in the scope of the reaction.

1.3 Results and discussions

From the work on Lewis acid promoted anomerisations, developed and studied, within the Murphy laboratory, it was proposed that the development of a reliable and general route to α -thiopyranoses would be useful and was defined as an aim of this thesis work. The results discussed here, on the anomerisation of these thiopyranoses, using a co-promoter, show that in some cases, good to excellent yields of the α -thiol can be generated.

1.3.1 Synthesis of glycosyl thiols for anomerisation study

Glycosyl thiols were prepared according to literature procedures. These involved the displacement of an anomeric bromide with thiourea to give the glycosyl thiouronium salt. This was subsequently hydrolysed under mildly basic conditions to give the thiopyranose **3** and **6**, as displayed in Scheme 1.35.



Scheme 1.35 The synthesis of glucose and galactose thiols.

The reactions, as illustrated, did not proceed with high stereoselectivity, instead giving a mixture of anomers with the β -anomer being the predominant anomer produced. The mixture obtained was used for the anomerisation reactions.

1.3.2 Anomerisation reactions

The anomerisation reactions of the above, glucopyranosyl and galactopyranosyl, thiols **3** and **6**, were investigated under a variety of conditions. Firstly the effect of varying the number of equivalents of the anomerisation promoter, TiCl_4 , was tested. The reactions were carried out in the presence of additives or potential co-promoters, to study their potential beneficial factors. The temperature was also varied, as was the choice of solvent in which the reactions were carried out in. The main objective was to identify if anomerisation of the thiols could be achieved and to optimise the yields and maximise the proportion of the α -anomer synthesised as a result of these studies.

Note: The relative $\alpha:\beta$ ratios, reported in the following tables, were determined by integration of well isolated, well defined signals of each derivative by ^1H NMR. The spectra for each of these derivatives were obtained following work up, as discussed in experimental section. This integration provided the anomeric distribution, of each carbohydrate tested, subsequent to its anomerisation reaction. In addition, in the

majority of cases, a small amount of α -chloride, example for the galactose derivative shown in Fig. 1.22, was formed as a by-product (labelled x in subsequent tables) of the Lewis acid promoted anomerisation. This by-product has also been noted, in the following tables, through the integration procedure described. These ratios ($\alpha:\beta:x$) are also reported as a percentage, based on the relative integration of ^1H NMR signals, for ease of comparison.

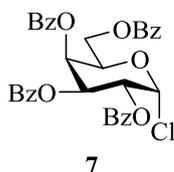


Fig. 1.22 The galactose example of the chloride by-product from the Lewis acid promoted anomerisation of glycosyl thiols.

These glycosyl chloride by-products, generated from the Lewis acid promoted anomerisations of the glycosyl thiols synthesised herein, were confirmed by means of a literature search. This search provided ^1H NMR data for **7**⁵⁵, i.e. the by-product from the anomerisation reactions of galactose derivative **6**, showing a value of 6.66 (d, $J = 3.9$ Hz, 1H). This reported data corresponds with the observed by-product signal, in the Lewis acid promoted anomerisation of **6** - 6.64 (d, $J = 5.3$ Hz, 1H).

An alternative possible by-product is that of the hemi-acetal, e.g. Fig. 1.23, but no data, from the literature, corresponded to any of the data obtained from the various Lewis acid promoted anomerisation reactions herein.

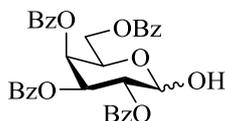


Fig. 1.23 An example of the possible alternative by-product.

Although there is not experimental data, e.g. ^1H NMR data, for each of the glycosyl chloride by-products, it is believed that the by-products are the glycosyl chlorides as the anomeric proton signals for each of the side products are in the expected regions for a glycosyl chloride derivatives, within the ^1H -NMR spectrum - between 6.0 and 7.0 ppm. In addition to these assumptions, it has also been reported in the Pilgrim et al. article⁴⁸ that the anomerisation of the *S*-glucuronide **1G**, when using a 3-fold excess of TiCl_4 led to a small quantity of the glycosyl chloride (< 2%) being formed. In this instance it was put that the formation of the glycosyl chloride is slow when compared the actual desired anomerisation.

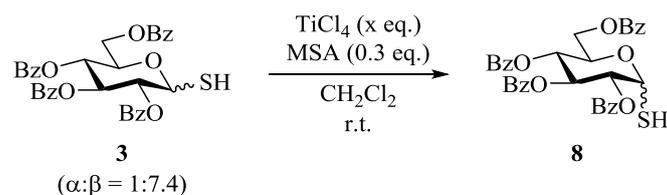
Further support towards the generation of the glycosyl chloride by-product as a result of the Lewis acid promoted anomerisation of glycosyl thiols is given in section 1.3.4.2.

Herein the results of the anomerisation studies are presented and discussed.

1.3.2.1 Methanesulfonic acid (MSA) as a co-promoter for the anomerisation of glycosyl thiols

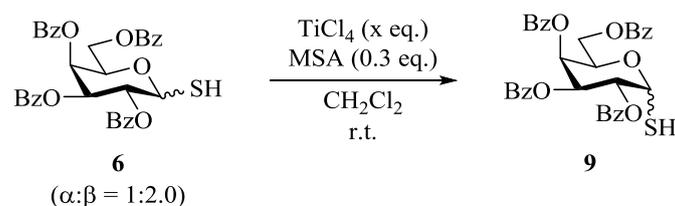
The first set of conditions tested, were based on the M.Sc. thesis work of Michelle McKinney. McKinney had found that methane sulfonic acid could enhance the rates of anomerisation reactions promoted by SnCl₄ or TiCl₄ for *O*-glycoside substrates. This TiCl₄-MSA promoted anomerisation was investigated for the anomerisation of the glycosyl thiols **3** and **6**. The parameters varied as part of this study were - reaction time and the amount of Lewis acid, TiCl₄, used.

Table 1.4: TiCl₄ promoted anomerisation of **3** in the presence of MSA, in CH₂Cl₂



Time	Temp.	Solvent	TiCl ₄	MSA	$\alpha:\beta:x$	% α	% β	% x
16 h.	r.t.	CH ₂ Cl ₂	1.0 eq.	0.3 eq.	1:0.84:0.04	53	45	2
16 h.	r.t.	CH ₂ Cl ₂	2.0 eq.	0.3 eq.	1:0.23:0.04	79	18	3
16 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	0.3 eq.	1:0.14:0.07	83	12	5
17 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	-	1:0.21:0.02	81	17	2
4 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	0.3 eq.	1:1.08:0.10	46	50	4
19 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	0.3 eq.	1:0.23:0.07	77	18	5
70 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	0.3 eq.	1:0.07:0.08	87	6	7

Table 1.5: TiCl₄ promoted anomerisation of **6** in the presence of MSA, in CH₂Cl₂



Time	Temp.	Solvent	TiCl ₄	MSA	$\alpha:\beta:x$	% α	% β	% x
16 h.	r.t.	CH ₂ Cl ₂	1.0 eq.	0.3 eq.	1:0.57:0.06	61	35	4
16 h.	r.t.	CH ₂ Cl ₂	2.0 eq.	0.3 eq.	1:0.18:0.05	81	15	4
16 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	0.3 eq.	1:0.16:0.06	82	13	5
17 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	-	1:0.27:0.03	77	21	2
4 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	0.3 eq.	1:0.74:0.05	56	41	3
19 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	0.3 eq.	1:0.18:0.06	81	15	4
70 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	0.3 eq.	1:-:0.10	91	-	9

In comparison with the results from McKinney, with acetylated thiosugars, the results in Table 1.4 and 1.5 indicated that anomerisation of the thiols could be achieved using

TiCl₄-MSA. After 70 h (Table 1.4 and 1.5) both alpha thiols were present to a significant degree in each of the reaction mixtures.

These reactions represented a significant step towards the synthesis of α -thiopyranoses by Lewis acid promoted anomerisation. The effect of reducing the temperature of the anomerisation reaction was studied next, with a view to trying to increase selectivity further, especially in the case of the glucose derivative. A previous study indicated that reduction in temperature could have this effect⁴⁸. Also it was thought that, in carrying the reactions out at a lower temperature, it would lead to lower amounts of the chloride by-product

Temperature and solvent are discussed together in the coming sections.

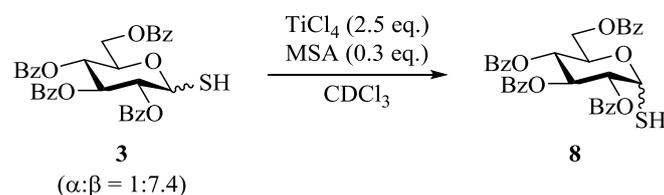
1.3.2.2 Solvents for the anomerisation of glycosyl thiols

The following tables summarise the ratio of α : β anomers of the thiols achieved through the Lewis acid and MSA promoted anomerisations of glycosyl thiols **3** and **6**, where both the solvent and the temperature, in which the anomerisation reactions were carried out in, were varied.

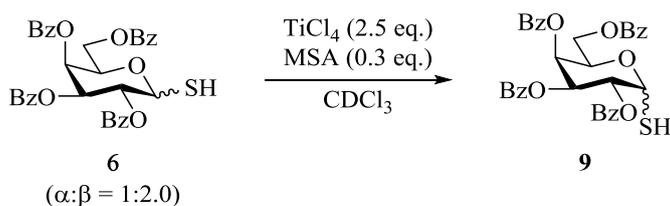
Reactions were carried out in nitromethane at varying temperatures (r.t., 4 °C and -20 °C) for both **3** and **6** with and without the co-promoter MSA. No thiol peaks for either α - or β - derivatives were visible in any of the ¹H-NMR spectra acquired for the product mixtures obtained. For the galactose derivative **6**, in which only TiCl₄ was used to promote the anomerisation reaction (i.e. no MSA was used) the only product which formed was the per-benzoylated galactose chloride, **7** Fig. 1.22. Data for this compound was in good agreement with that reported in the literature.

The reaction was also carried out in CDCl₃ and the results are summarised in Tables 1.6 and 1.7. Only partial anomerisation was observed under these conditions.

Table 1.6: TiCl₄ promoted anomerisation of **3** in the presence of MSA, in CDCl₃



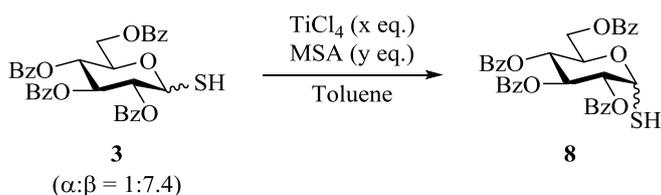
Time	Temp.	Solvent	TiCl ₄	MSA	$\alpha:\beta:x$	% α	% β	% x
16 h.	r.t.	CDCl ₃	2.5 eq.	0.3 eq.	1:2.02:0.10	32	65	3
16 h.	4 °C	CDCl ₃	2.5 eq.	0.3 eq.	1:4.00:0.10	20	78	2
16 h.	-20 °C	CDCl ₃	2.5 eq.	0.3 eq.	No Reaction	12	88	-

Table 1.7: TiCl_4 promoted anomerisation of **6** in the presence of MSA, in CDCl_3 

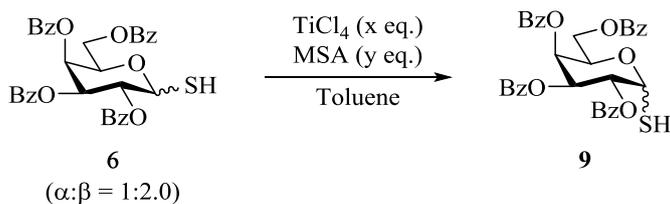
Time	Temp.	Solvent	TiCl_4	MSA	$\alpha:\beta:x$	% α	% β	% x
16 h.	r.t.	CDCl_3	2.5 eq.	0.3 eq.	1:1.39:0.12	40	55	5
16 h.	4 °C	CDCl_3	2.5 eq.	0.3 eq.	1:2.02:0.10	32	65	3
16 h.	-20 °C	CDCl_3	2.5 eq.	0.3 eq.	No Reaction	33	64	-

Results here show, not unexpectedly, that carrying the reactions out under colder conditions actually slowed down the rate of the reaction. Thus a lower proportion of the α -anomer is formed at lower temperatures. It was also shown, with these reactions, that formation of the glycosyl chloride control cannot be reduced by lowering temperature as roughly the same quantities were seen throughout the temperature range.

The anomerisation reaction in aromatic solvents was investigated next. This was sought to be studied as increased rates and selectivities had been observed in the presence of benzoyl protecting groups or when benzoate additives were added to the reaction mixtures⁴⁸. In this case anomerisation reactions did proceed, (Tables 1.8 and 1.9 with toluene) but to a lesser degree than with dichloromethane.

Table 1.8: TiCl_4 promoted anomerisation of **3** with/without co-promoter MSA, in toluene

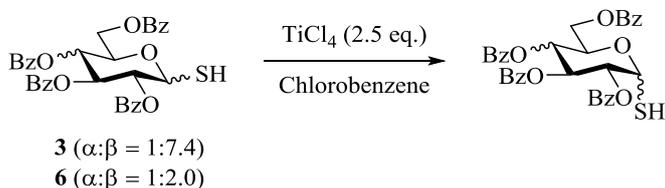
Time	Temp.	Solvent	TiCl_4	MSA	$\alpha:\beta:x$	% α	% β	% x
18 h.	r.t.	Toluene	2.5 eq.	0.3 eq.	1:5.07:0.31	16	79	5
18 h.	r.t.	Toluene	2.5 eq.	-	1:0.95:0.57	40	38	22
74 h.	r.t.	Toluene	2.5 eq.	-	1:0.75:0.25	50	38	12
74 h.	r.t.	Toluene	5.0 eq.	-	1:0.60:0.06	60	36	4

Table 1.9: TiCl₄ promoted anomerisation of **6** with/without co-promoter MSA, in toluene

Time	Temp.	Solvent	TiCl ₄	MSA	$\alpha:\beta:x$	% α	% β	% x
18 h.	r.t.	Toluene	2.5 eq.	0.3 eq.	1:1.98:0.06	33	65	2
18 h.	r.t.	Toluene	2.5 eq.	-	1:0.97:0.43	42	40	18
74 h.	r.t.	Toluene	2.5 eq.	-	1:0.77:0.11	53	41	6
74 h.	r.t.	Toluene	5.0 eq.	-	1:0.91:0.11	50	45	5

It was observed, during the anomerisation studies in toluene that the use of the co-promoter, MSA, led to messy NMRs but also reduced the quantity of the desired α -product obtained.

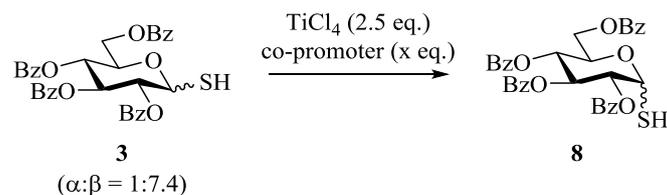
Chlorobenzene (Cl-Benz.) was next investigated as a solvent in the absence of MSA, and the results are shown in Table 1.10. The reactions again had not gone to completion after 74 h.

Table 1.10: TiCl₄ promoted anomerisation of **3** and **6**, in chlorobenzene

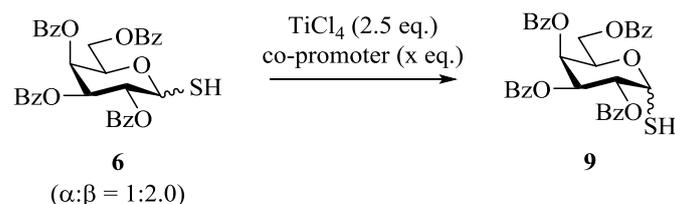
Sugar	Time	Temp.	Solvent	TiCl ₄	MSA	$\alpha:\beta:x$	% α	% β	% x
3	74 h.	r.t.	Cl-Benz.	2.5 eq.	-	1:0.16:0.05	83	13	4
6	74 h.	r.t.	Cl-Benz.	2.5 eq.	-	1:0.36:0.10	68	25	7

The reaction time required for the above reactions (74 h), make the reactions less desirable for practical purposes.

As shorter reaction times would be more desirable and the use of MSA can sometimes lead to decomposition, then the reactions were investigated using benzoic acid (PhCO₂H), in place of MSA, as the co-promoter. There was no major effect of benzoic acid noted in these reactions in this case. However, reactions in dichloromethane in the presence of MSA proceed to give the α -anomers to a greater extent. It was also shown that for the anomerisation reactions carried out in CH₂Cl₂, over a short reaction time, 4 h, that the results of the anomerisations are, almost, comparable to that of the reactions carried out in chlorobenzene, over a longer reaction time, 19 h.

Table 1.11: TiCl₄ promoted anomerisation of **3** with/without co-promoter MSA/benzoic acid, in toluene/chlorobenzene/CH₂Cl₂

Time	Temp.	Solvent	TiCl ₄	MSA	PhCO ₂ H	$\alpha:\beta:x$	% α	% β	% x
4 h.	r.t.	Toluene	2.5 eq.	-	-	1:3.02:0.11	24	73	3
19 h.	r.t.	Toluene	2.5 eq.	-	-	1:1.69:0.14	35	60	5
4 h.	r.t.	Toluene	2.5 eq.	-	0.3 eq.	1:3.25:0.11	23	75	2
19 h.	r.t.	Toluene	2.5 eq.	-	0.3 eq.	1:1.82:0.13	34	62	4
4 h.	r.t.	Cl-Benz.	2.5 eq.	-	-	1:1.26:0.06	43	54	3
19 h.	r.t.	Cl-Benz.	2.5 eq.	-	-	1:0.73:0.05	56	41	3
4 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	0.3 eq.	-	1:1.09:0.09	46	50	4
19 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	0.3 eq.	-	1:0.23:0.05	78	18	4

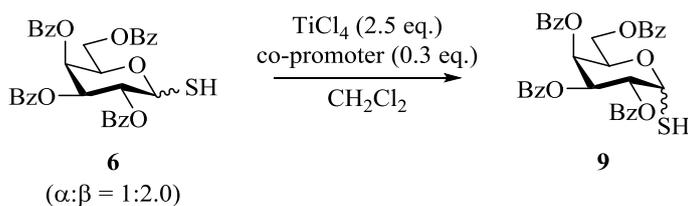
Table 1.12: TiCl₄ promoted anomerisation of **6** with/without co-promoter MSA/benzoic acid, in toluene/chlorobenzene/CH₂Cl₂

Time	Temp.	Solvent	TiCl ₄	MSA	Bz. acid	$\alpha:\beta:x$	% α	% β	% x
4 h.	r.t.	Toluene	2.5 eq.	-	-	1:1.79:0.10	35	62	3
19 h.	r.t.	Toluene	2.5 eq.	-	-	1:1.41:0.11	40	56	4
4 h.	r.t.	Toluene	2.5 eq.	-	0.3 eq.	1:1.77:0.10	35	62	3
19 h.	r.t.	Toluene	2.5 eq.	-	0.3 eq.	1:1.45:0.10	39	57	4
4 h.	r.t.	Cl-Benz.	2.5 eq.	-	-	1:1.40:0.08	40	57	3
19 h.	r.t.	Cl-Benz.	2.5 eq.	-	-	1:0.98:0.11	48	47	5
4 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	0.3 eq.	-	1:0.74:0.08	55	41	4
19 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	0.3 eq.	-	1:0.18:0.04	82	15	3

It was next decided to screen a variety of potential co-promoters, for the anomerisation of the glycosyl thiols **3** and **6**, in CH₂Cl₂, beyond those previously studied in the Murphy laboratory.

1.3.2.3 Screening co-promoters for the anomerisation of glycosyl thiols

The most efficient co-promoter to date, as previously mentioned, was MSA and so, analogues of this were screened. In choosing these and subsequent co-promoters, the theory that if you were to use Lewis bases to coordinated to the metal centre of a Lewis

Table 1.14: TiCl₄ promoted anomerisation of **6** with MSA analogue co-promoters, in CH₂Cl₂

Time	Temp.	Solvent	TiCl ₄	0.3 eq. co-promoter	$\alpha:\beta:x$	% α	% β	% x
19 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	MSA	1:0.18:0.06	81	15	4
17 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	-	1:0.27:0.03	77	21	2
16 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	Sulfamic acid	1:0.21:0.09	77	16	7
16 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	Sulfuric acid	1:0.14:0.11	80	11	9
16 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	Sulfuric diamide	1:0.13:0.06	84	11	5
16 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	Dimethyl sulfone	1:0.17:0.06	81	14	5
16 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	Methansulfonamide	1:0.17:0.06	81	14	5
16 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	Dimethyl sulfoxide	n/a	n/a	n/a	n/a

Similar or enhanced selectivities of the α -anomer were observed on varying the co-promoter from MSA, with improved ratios being observed for the glucose derivative, **3**, in particular. To continue with the study and see if these improved selectivities could be achieved with other co-promoters it was decided to move beyond S-O co-promoter derivatives.

Phosphine type co-promoters

Thus phosphines were investigated as Lewis bases in the reaction.

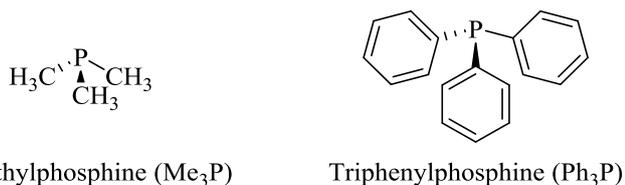
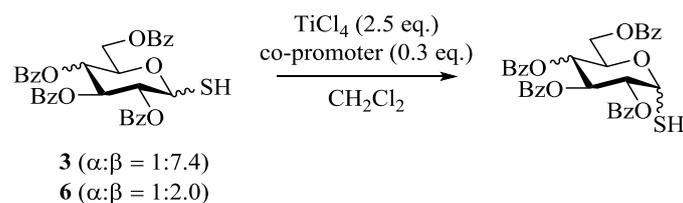


Fig. 1.25 Phosphine co-promoters.

Table 1.15: TiCl₄ promoted anomerisation of **3** and **6** with phosphine type co-promoters, in CH₂Cl₂

Sugar	Time	Temp.	Solvent	TiCl ₄	0.3 eq. co-promoter	$\alpha:\beta:x$	% α	% β	% x
3	17 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	-	1:0.21:0.02	81	17	2
3	16 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	Me ₃ P	1:0.07:0.02	92	6	2
3	16 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	Ph ₃ P	1:0.05:0.02	93	5	2
6	17 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	-	1:0.27:0.03	77	21	2
6	16 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	Me ₃ P	1:0.11:0.06	86	9	5
6	16 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	Ph ₃ P	1:0.08:0.05	89	7	4

The Lewis bases tested here showed similar if not slightly improved selectivities when compared to the TiCl₄ and MSA analogues, Tables 1.13 and 1.14.

Nitrogen based co-promoters

The reactions were also tested using nitrogen containing Lewis bases.

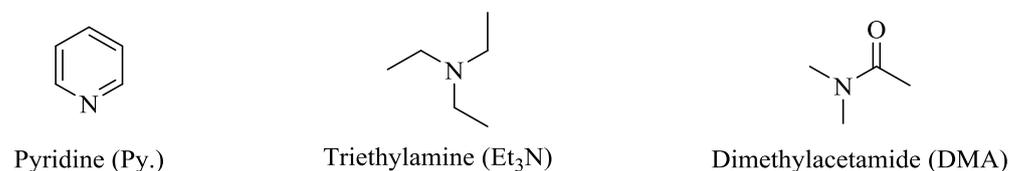
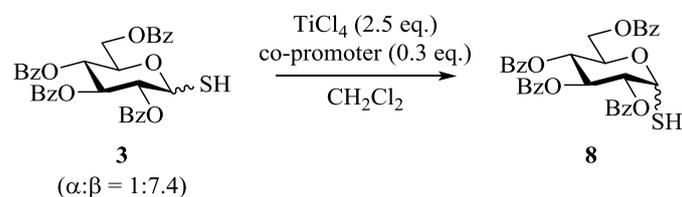
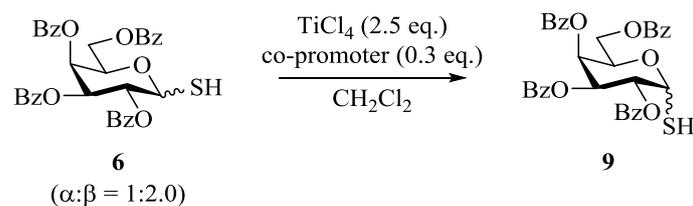


Fig. 1.26 Nitrogen based co-promoters.

Table 1.16: TiCl₄ promoted anomerisation of **3** with nitrogen based co-promoters, in CH₂Cl₂

Time	Temp.	Solvent	TiCl ₄	0.3 eq. co-promoter	$\alpha:\beta:x$	% α	% β	% x
17 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	-	1:0.21:0.02	81	17	2
16 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	Py.	1:0.03:0.02	95	3	2
16 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	Et ₃ N	1:0.04:0.03	93	4	3
16 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	DMA	1:0.07:0.02	92	6	2

Table 1.17: TiCl₄ promoted anomerisation of **6** with nitrogen based co-promoters, in CH₂Cl₂

Time	Temp.	Solvent	TiCl ₄	0.3 eq. co-promoter	$\alpha:\beta:x$	% α	% β	% x
17 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	-	1:0.27:0.03	77	21	2
16 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	Py.	1:0.08:0.06	88	7	5
16 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	Et ₃ N	1:0.08:0.05	88	8	4
16 h.	r.t.	CH ₂ Cl ₂	2.5 eq.	DMA	1:0.10:0.04	88	9	3

The results achieved here indicated that pyridine gave slightly higher ratios than other co-promoters for the TiCl₄-co-promoter anomerisation of the thiopyranoses **3** and **6**, and significantly higher than using no promoter.

Work was continued on the investigation of the co-promoter of the TiCl₄ promoted anomerisation reaction

Further nitrogen containing co-promoters were tested, including nitrogen derivatives which also had sulfonic acid derivatives and the results are shown in Tables 1.18 and 1.19.

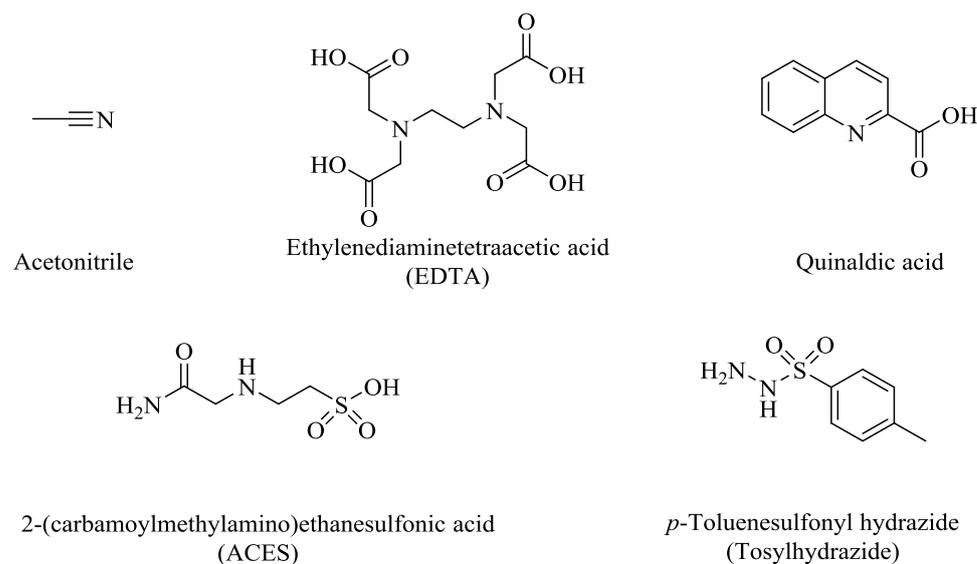
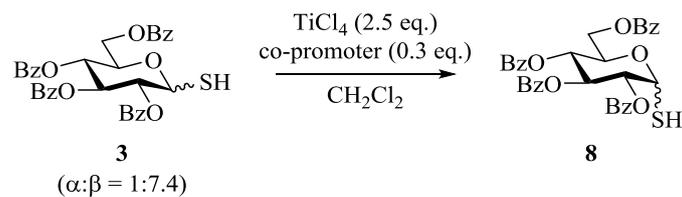
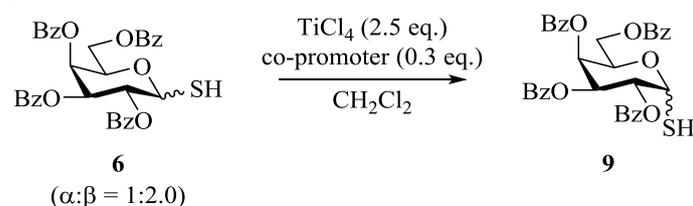


Fig. 1.27 Further nitrogen containing co-promoters.

Table 1.18: TiCl_4 promoted anomerisation of **3** with further nitrogen based co-promoters, in CH_2Cl_2 

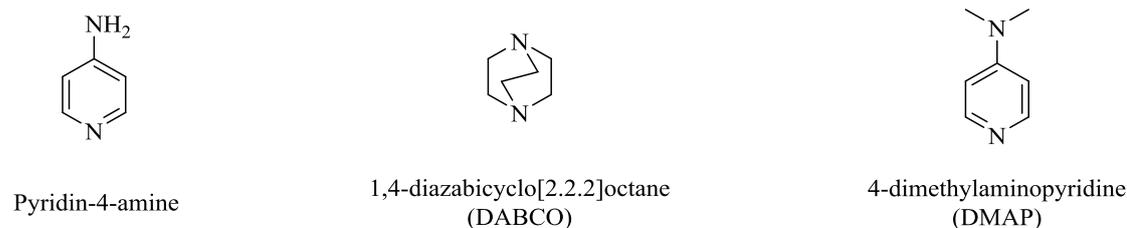
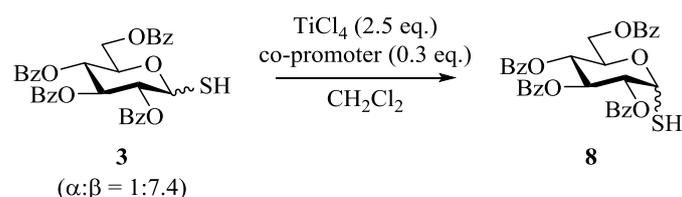
Time	Temp.	Solvent	TiCl_4	0.3 eq. co-promoter	$\alpha:\beta:x$	% α	% β	% x
16 h.	r.t.	CH_2Cl_2	2.5 eq.	Acetonitrile	1:0.07:0.03	91	6	3
16 h.	r.t.	CH_2Cl_2	2.5 eq.	EDTA	1:0.10:0.02	89	9	2
16 h.	r.t.	CH_2Cl_2	2.5 eq.	Quinaldic acid	1:0.15:0.02	85	13	2
16 h.	r.t.	CH_2Cl_2	2.5 eq.	ACES	1:0.10:0.02	89	9	2
16 h.	r.t.	CH_2Cl_2	2.5 eq.	Tosylhydrazide	1:0.10:0.14	81	8	11

Table 1.19: TiCl_4 promoted anomerisation of **6** with further nitrogen based co-promoters, in CH_2Cl_2 

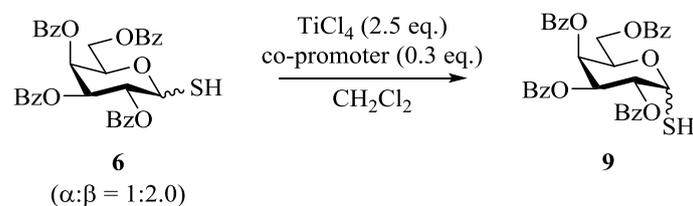
Time	Temp.	Solvent	TiCl_4	0.3 eq. co-promoter	$\alpha:\beta:x$	% α	% β	% x
16 h.	r.t.	CH_2Cl_2	2.5 eq.	Acetonitrile	1:0.58:0.08	60	35	5
16 h.	r.t.	CH_2Cl_2	2.5 eq.	EDTA	1:0.39:0.10	67	26	7
16 h.	r.t.	CH_2Cl_2	2.5 eq.	Quinaldic acid	1:0.27:0.06	75	20	5
16 h.	r.t.	CH_2Cl_2	2.5 eq.	ACES	1:0.25:0.07	76	19	5
16 h.	r.t.	CH_2Cl_2	2.5 eq.	Tosylhydrazide	1:-:0.11(0.34)	69	-	8(23)

The results obtained from these set of reactions were comparable with the $\alpha:\beta$ ratios obtained for the anomerisation reactions using TiCl_4 -MSA, with no significant improvements being observed.

Next some derivatives of pyridine, the best co-promoter of the study so far, and DABCO were investigated and the results are shown in Tables 1.20 and 1.21.

**Fig. 1.28** Derivatives of pyridine and DABCO as co-promoters.Table 1.20: TiCl_4 promoted anomerisation of **3** with pyridine and related co-promoters, in CH_2Cl_2 

Time	Temp.	Solvent	TiCl_4	0.3 eq. co-promoter	$\alpha:\beta:x$	% α	% β	% x
17 h.	r.t.	CH_2Cl_2	2.5 eq.	-	1:0.21:0.02	81	17	2
16 h.	r.t.	CH_2Cl_2	2.5 eq.	Py.	1:0.03:0.02	95	3	2
16 h.	r.t.	CH_2Cl_2	2.5 eq.	Pyridin-4-amine	1:0.07:0.02	92	6	2
16 h.	r.t.	CH_2Cl_2	2.5 eq.	DABCO	1:0.10:0.03	88	9	3
16 h.	r.t.	CH_2Cl_2	2.5 eq.	DMAP	1:0.07:0.02	92	6	2

Table 1.21: TiCl_4 promoted anomerisation of **6** with pyridine and related co-promoters, in CH_2Cl_2 

Time	Temp.	Solvent	TiCl_4	0.3 eq. co-promoter	$\alpha:\beta:x$	% α	% β	% x
17 h.	r.t.	CH_2Cl_2	2.5 eq.	-	1:0.27:0.03	77	21	2
16 h.	r.t.	CH_2Cl_2	2.5 eq.	Py.	1:0.08:0.06	88	7	5
16 h.	r.t.	CH_2Cl_2	2.5 eq.	Pyridin-4-amine	1:0.14:0.07	83	11	6
16 h.	r.t.	CH_2Cl_2	2.5 eq.	DABCO	1:0.36:0.08	69	25	6
16 h.	r.t.	CH_2Cl_2	2.5 eq.	DMAP	1:0.15:0.03	85	13	2

As there was no improvement in the reaction it was decided to focus on the structures where the best α -selectivity had been achieved.

Studies on the best co-promoters

Three of the co-promoters were next investigated over a longer reaction period (72 h). Those chosen were pyridine, triethylamine and methanesulfonamide. The effect of temperature was also investigated.

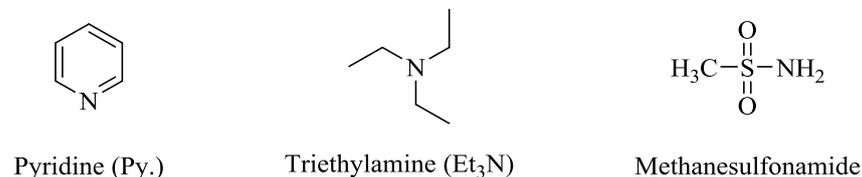
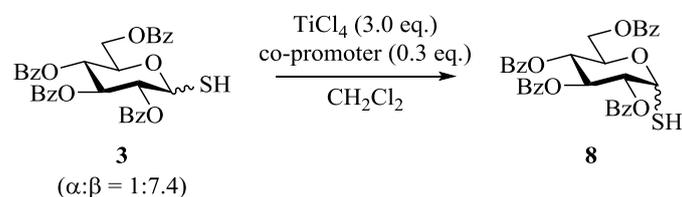


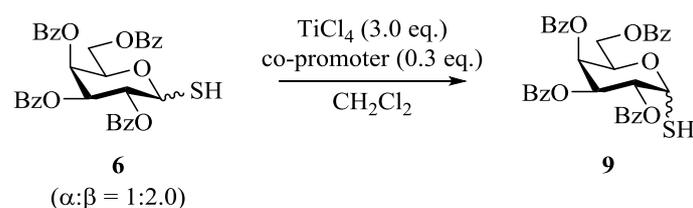
Fig. 1.29 The best co-promoters of the Lewis acid promoted anomerisation reaction of glycosyl thiols.

Table 1.22: TiCl₄ promoted anomerisation of **3** with the best co-promoters over 72 h., in CH₂Cl₂



Time	Temp.	Solvent	TiCl ₄	0.3 eq. co-promoter	$\alpha:\beta:x$	% α	% β	% x
72 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	Py.	1:0.02:0.02	96	2	2
72 h.	0 °C	CH ₂ Cl ₂	3.0 eq.	Py.	1:1.67:0.01	37	62	1
72 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	Et ₃ N	1:-:0.03	97	-	3
72 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	Methanesulfonamide	1:0.02:0.02	96	2	2

Table 1.23: TiCl₄ promoted anomerisation of **6** with the best co-promoters over 72 h., in CH₂Cl₂



Time	Temp.	Solvent	TiCl ₄	0.3 eq. co-promoter	$\alpha:\beta:x$	% α	% β	% x
72 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	Py.	1:0.01:0.07	93	1	6
72 h.	0 °C	CH ₂ Cl ₂	3.0 eq.	Py.	1:1.64:0.04	37	61	2
72 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	Et ₃ N	1:-:0.06	94	-	6
72 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	Methanesulfonamide	1:-:0.05	95	-	5

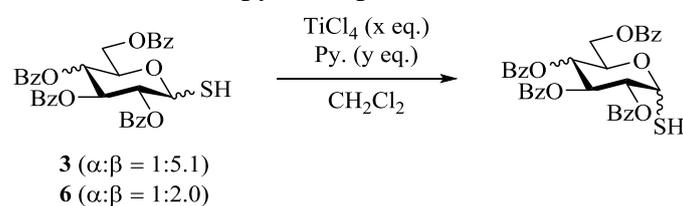
Carrying out the reaction at lower temperature, again, proved ineffective in gaining control of the, chloride, by-product or increasing the desired α -thiopyranose product of the reaction. It was observed, however, that a slight increase of the $\alpha:\beta$ ratio could be obtained by having long reaction times, 72 h, when compared to the the $\alpha:\beta$ ratio for the

anomerisations carried out over a shorter reaction time, 16 h. (Tables 1.16 and 1.17 for Py. and Et₃N, and Tables 1.13 and 1.14 for methanesulfonamide.)

As the results for the co-promoters above, tables 1.22 and 1.23, are essentially comparable and as pyridine was readily available as an anhydrous solution in the laboratory, titanium tetrachloride and pyridine were selected for further investigation. The reaction was therefore investigated in the presence of the increased equivalents of TiCl₄ alone and pyridine alone.

1.3.2.4 More thorough investigations with pyridine as co-promoter of the anomerisation reaction

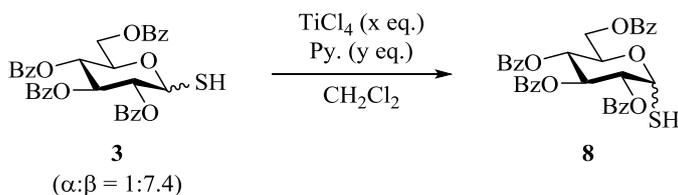
Table 1.24: TiCl₄/pyridine promoted anomerisation of **3** and **6**, in CH₂Cl₂



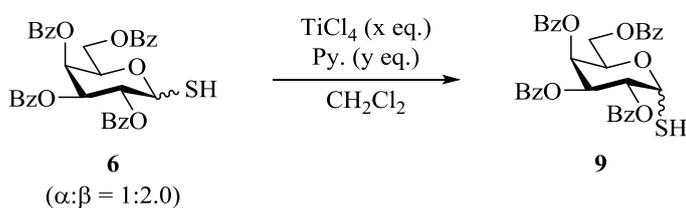
Sugar	Time	Temp.	Solvent	TiCl ₄	Py.	$\alpha:\beta:x$	% α	% β	% x
3	72 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	-	1:0.05:0.01	94	5	1
3	72 h.	r.t.	CH ₂ Cl ₂	-	0.3eq.	1:5.0:0.23	16	80	4
6	72 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	-	1:0.11:0.03	88	10	2
6	72 h.	r.t.	CH ₂ Cl ₂	-	0.3eq.	1:1.98:0.03	33	66	1

As can be established from the data in Table 1.24, the effect of the pyridine on its own is either negligible or has no anomerisation capability at all. However the use of TiCl₄ (3.0 eq.) was effective and gave a high proportion of the α -anomer even in the absence of pyridine.

To further understand the reaction, more studies were done, this time varying the equivalents used for both the Lewis acid and/or the pyridine co-promoter, to see if any differences in selectivity could be observed.

Table 1.25: TiCl₄ promoted anomerisation of **3** with pyridine as co-promoter, varying equivalents of each, in CH₂Cl₂

Entry	Time	Temp.	Solvent	TiCl ₄	Py.	$\alpha:\beta:x$	% α	% β	% x
1	16 h.	r.t.	CH ₂ Cl ₂	0.5 eq.	0.3 eq.	1:0.61:0.02	61	37	2
2	16 h.	r.t.	CH ₂ Cl ₂	1.0 eq.	0.3 eq.	1:0.49:0.03	66	32	2
3	16 h.	r.t.	CH ₂ Cl ₂	2.0 eq.	0.3 eq.	1:0.17:0.04	83	14	3
4	16 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	0.3 eq.	1:0.03:0.02	95	3	2
5	24 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	-	1:0.13:0.02	87	11	2
6	24 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	0.3 eq.	1:0.05:0.03	93	5	2
7	16 h.	r.t.	CH ₂ Cl ₂	5.0 eq.	0.3 eq.	1:0.06:0.02	93	6	1
8	16 h.	r.t.	CH ₂ Cl ₂	5.0 eq.	0.5 eq.	1:-:0.03	97	-	3
9	16 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	0.5 eq.	1:-:0.02	98	-	2

Table 1.26: TiCl₄ promoted anomerisation of **6** with pyridine as co-promoter, varying equivalents of each, in CH₂Cl₂

Entry	Time	Temp.	Solvent	TiCl ₄	Py.	$\alpha:\beta:x$	% α	% β	% x
1	16 h.	r.t.	CH ₂ Cl ₂	0.5 eq.	0.3 eq.	1:0.82:0.05	53	44	3
2	16 h.	r.t.	CH ₂ Cl ₂	1.0 eq.	0.3 eq.	1:0.60:0.05	61	36	3
3	16 h.	r.t.	CH ₂ Cl ₂	2.0 eq.	0.3 eq.	1:0.21:0.08	78	16	6
4	16 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	0.3 eq.	1:0.16:0.03	84	13	3
5	24 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	-	1:0.24:0.06	77	18	5
6	24 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	0.3 eq.	1:0.13:0.08	83	11	6
7	16 h.	r.t.	CH ₂ Cl ₂	5.0 eq.	0.3 eq.	1:0.20:0.06	79	16	5
8	16 h.	r.t.	CH ₂ Cl ₂	5.0 eq.	0.5 eq.	1:0.15:0.10	80	12	8
9	16 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	0.5 eq.	1:0.04:0.09	88	4	8

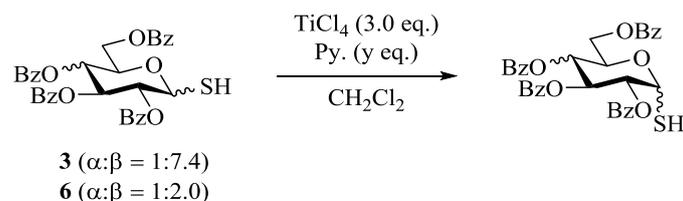
It can be seen here, that there is an enhancement in the α -selectivity when using the two reagents, TiCl₄ and pyridine, together.

This statement is based on the ratios observed for the anomerisation reactions where the Lewis acid, TiCl_4 , was used on its own over a 24 h reaction period (entry 5, Table 1.25 and 1.26), and when compared with the reaction carried out in the presence TiCl_4 and 0.3 eq of pyridine (entry 6, Table 1.25 and 1.26). The effect of increasing the co-promoter, pyridine, from 0.3 to 0.5 equivalents leads to another slight increase in $\alpha:\beta$ ratio (comparing entry 4 and 9, Table 1.25 and 1.26).

To this point, the reactions were generally run over a 16 h reaction, as such, it was sought to see what ratios of products could be obtained over a shorter reaction time, using 3.0 eq. of TiCl_4 and 0.5 eq. of pyridine.

The (2+2 h) reaction was where the anomerisation was carried out using 3.0 eq. of TiCl_4 with 0.3 eq. of pyridine for 2 h, then working up the reaction and taking the residue and subjecting it to the reaction conditions again for a further 2 h.

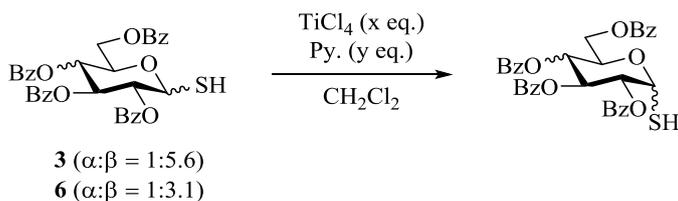
Table 1.27: TiCl_4 promoted anomerisation of **3** and **6** with pyridine as co-promoter over short reaction times, in CH_2Cl_2



Entry	Sugar	Time	Temp.	Solvent	TiCl_4	Py.	$\alpha:\beta:x$	% α	% β	%x
1	3	4 h.	r.t.	CH_2Cl_2	3.0 eq.	-	1:0.45:0.02	68	31	1
2	3	4 h.	r.t.	CH_2Cl_2	3.0 eq.	0.3 eq.	1:0.16:0.02	85	14	1
3	3	2+2 h.	r.t.	CH_2Cl_2	3.0 eq.	0.3 eq.	1:0.05:0.03	92	5	3
4	6	4 h.	r.t.	CH_2Cl_2	3.0 eq.	-	1:1.30:0.08	42	55	3
5	6	4 h.	r.t.	CH_2Cl_2	3.0 eq.	0.3 eq.	1:0.63:0.05	60	37	3
6	6	2+2 h.	r.t.	CH_2Cl_2	3.0 eq.	0.3 eq.	1:0.42:0.09	66	28	6

A comparison of entries 2 and 3, Table 1.27 (and 5 with 6, Table 1.27) indicates that the 2+2 approach led to an improved reaction. Also comparing entry 1 and 2 and comparing 4 and 5, Table 1.27, indicates that using pyridine is leading to an improvement in the anomerisation reactions. It can also be stated that a 16 h reaction is the optimum time need to achieve the greatest α -selectivity and as such anomerisations using these conditions should aim to be completed in or around that time.

A final set of studies were done to compare the anomerisation capability of the developed promoter-co-promoter system, 3.0 eq. of TiCl_4 and 0.5 eq. pyridine, versus the reagents when being used individually. Again the increase in the proportion of the alpha thiol is noted in the presence of pyridine.

Table 1.28: TiCl₄ and pyridine individual and co-operative promoted anomerisation of **3** and **6**, in CH₂Cl₂

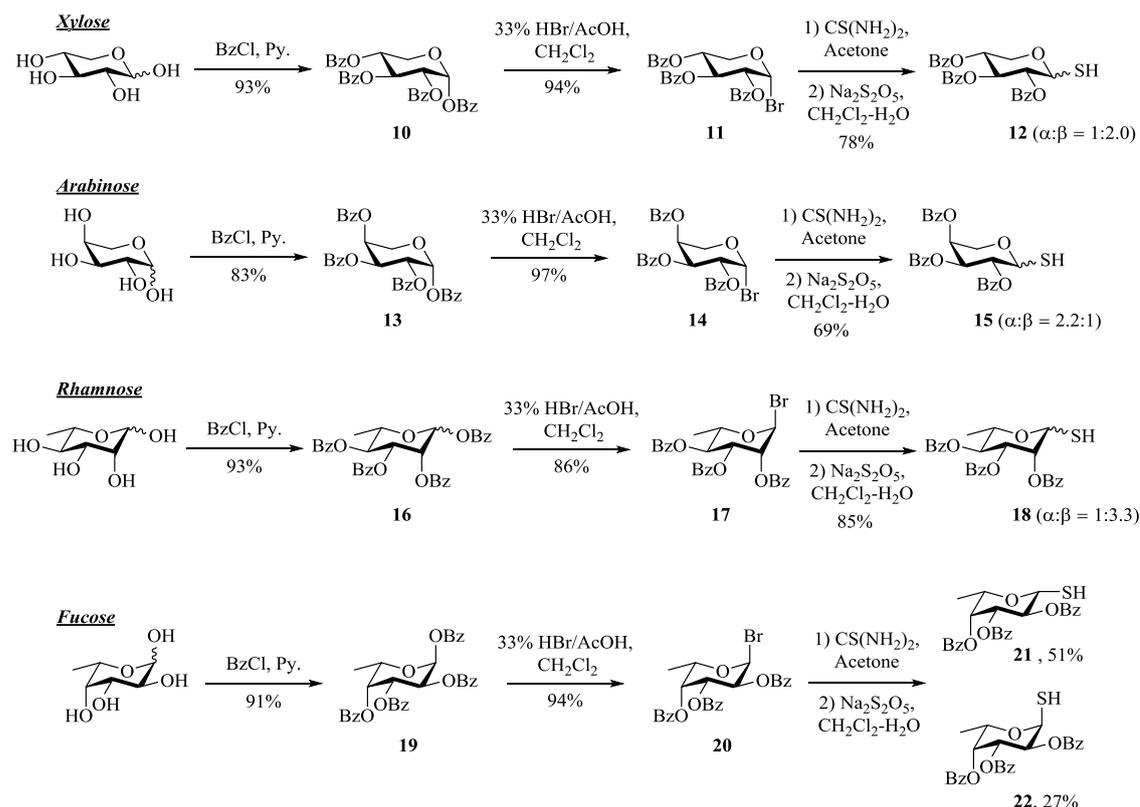
Sugar	Time	Temp.	Solvent	TiCl ₄	Py.	$\alpha:\beta:x$	% α	% β	% x
3	16 h.	r.t.	CH ₂ Cl ₂	-	0.5 eq.	1:5.12:-	16	84	-
3	16 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	-	1:0.08:0.18	79	7	14
3	16 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	0.5 eq.	1:0.05:0.05	91	5	4
6	16 h.	r.t.	CH ₂ Cl ₂	-	0.5 eq.	1:2.75:-	27	73	-
6	16 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	-	1:0.19:0.08	79	15	6
6	16 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	0.5 eq.	1:-:0.11	90	-	10

The tendency of pyridine to increase the proportion of the alpha anomer obtained could be explained by it acting as a Lewis base and donating electron density into the metal centre of the Lewis acid and thereby, contrary to what one might expect, could lead to increasing its electrophilicity and thereby enhancing the anomerisation of thiopyranoses **3** and **6**.

The scope of the anomerisation conditions developed was next tested with other thiopyranose derivatives.

1.3.3 Synthesis of further glycosyl thiols for anomerisation

Additional thiopyranoses were prepared, similar to those described previously. Those synthesised were from D-xylose L-arabinose, L-rhamnose and L-fucose. These were prepared by displacement of an anomeric bromide with thiourea to give the glycosyl thiouronium salt. This was subsequently hydrolysed under mildly basic conditions to give the thiopyranose **12**, **15**, **18**, **21** and **22** as displayed in Scheme 1.36.

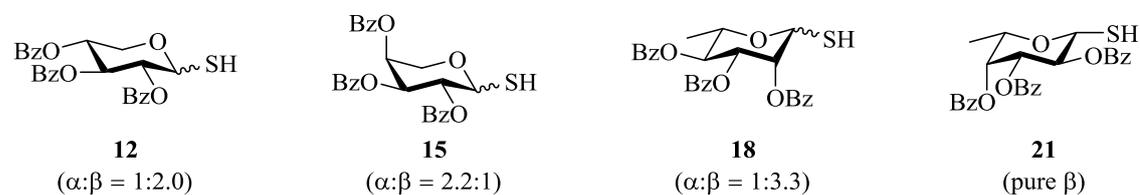


Scheme 1.36 The synthesis of further glycosyl thiols.

1.3.4 Anomerisation reactions

The anomerisation reactions of the above thiols were investigated under the conditions developed through the previously described studies, that is, under TiCl_4 and pyridine promoted anomerisation. The main objective was to extend the scope of thiopyranoses capable of undergoing anomerisation through Lewis acid promoted conditions. Herein the results of these investigations are presented and discussed.

Table 1.29: TiCl_4 promoted anomerisation of **12**, **15**, **18** and **21** with/without pyridine as co-promoter, in CH_2Cl_2



Sugar	Time	Temp.	Solvent	TiCl_4	Py.	$\alpha:\beta:x$	% α	% β	% x
12	16 h.	r.t.	CH_2Cl_2	3.0 eq.	-	1:0.10:0.04	88	9	3
12	16 h.	r.t.	CH_2Cl_2	3.0 eq.	0.5 eq.	1:0.07:0.16	81	6	13
15	16 h.	r.t.	CH_2Cl_2	3.0 eq.	-	-:1:0.12	-	89	11
15	16 h.	r.t.	CH_2Cl_2	3.0 eq.	0.5 eq.	0.07:1:0.17	5	81	14
18	16 h.	r.t.	CH_2Cl_2	3.0 eq.	-	1:-:0.48	68	-	32
18	16 h.	r.t.	CH_2Cl_2	3.0 eq.	0.5 eq.	1:0.03:0.42	69	2	29
21	16 h.	r.t.	CH_2Cl_2	3.0 eq.	-	1:-:1.34	43	-	57
21	16 h.	r.t.	CH_2Cl_2	3.0 eq.	0.5 eq.	1:-:1.95	34	-	66

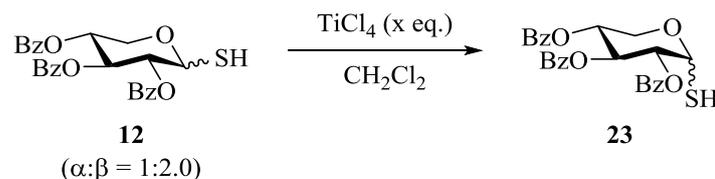
When using the novel conditions, developed herein, for anomerisation - TiCl_4 and pyridine, fair to good selectivity, towards the anomer of desired stereochemistry, was observed for the derivatives tested within this study - xylose, arabinose, rhamnose and fucose.

Anomerisation reactions, using just the Lewis acid, TiCl_4 , were also carried out which gave contrary results to those seen for the glucose and galactose derivatives, where an increase in α -selectivity of the sugars could be achieved through the co-operative anomerisation of the Lewis acid, TiCl_4 , and pyridine. The reactions within this study, where just the Lewis acid was used to facilitate the anomerisation, proved to be cleaner, with equal or enhanced selectivity of the anomer of desired stereochemistry.

1.3.4.1 Effect of independently promoted anomerisation of xylose **12** by TiCl_4

To see the effect of the Lewis acid, independently, a study was carried varying the equivalents of the TiCl_4 used in the anomerisation reaction of **12** over a 16 h reaction period.

Table 1.30: Varying equivalents of TiCl_4 promoted anomerisation of **12**, in CH_2Cl_2

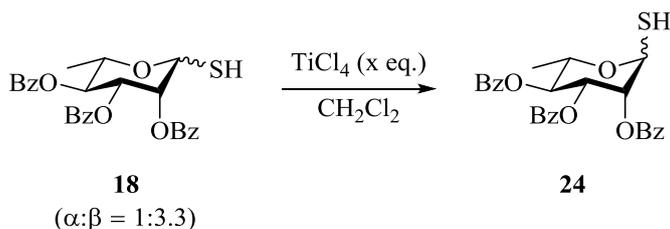


Time	Temp.	Solvent	TiCl_4	Py.	$\alpha:\beta:x$	% α	% β	% x
16 h.	r.t.	CH_2Cl_2	0.5 eq.	-	1:0.84:0.08	52	44	4
16 h.	r.t.	CH_2Cl_2	1.0 eq.	-	1:0.29:0.04	75	22	3
16 h.	r.t.	CH_2Cl_2	2.0 eq.	-	1:0.09:0.04	88	8	4
16 h.	r.t.	CH_2Cl_2	3.0 eq.	-	1:0.09:0.05	88	8	4
16 h.	r.t.	CH_2Cl_2	5.0 eq.	-	1:0.06:0.04	91	5	4

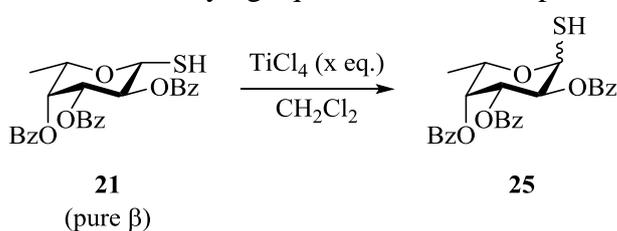
Improved selectivity for the α -anomer of **12** was achieved through the anomerisation reaction, as expected, by using increasing proportions of the Lewis acid.

1.3.4.2 Attempts to improve anomerisation of rhamnose and fucose thiols

From initial studies, as displayed in Table 1.29, it was noticed that work was needed to be done on improving the anomerisation reaction for the rhamnose and fucose thiols, **18** and **21**. To that end further studies were carried on these two substrates.

Table 1.31: Varying equivalents of TiCl_4 promoted anomerisation of **18**, in CH_2Cl_2 

Time	Temp.	Solvent	TiCl_4	Py.	$\alpha:\beta:x:z$	% α	% β	%x	%z
16 h.	r.t.	CH_2Cl_2	0.5 eq.	-	1:0.82:0.18:-	50	41	9	-
16 h.	r.t.	CH_2Cl_2	2.5 eq.	-	1:-:0.53:0.04	64	-	34	3
16 h.	r.t.	CH_2Cl_2	5.0 eq.	-	1:-:0.52:0.12	61	-	32	7

Table 1.32: Varying equivalents of TiCl_4 promoted anomerisation of **21**, in CH_2Cl_2 

Time	Temp.	Solvent	TiCl_4	Py.	$\alpha:\beta:x:z$	% α	% β	%x	%z
16 h.	r.t.	CH_2Cl_2	0.5 eq.	-	1:0.99:0.24:-	45	44	11	-
16 h.	r.t.	CH_2Cl_2	2.5 eq.	-	1:0.10:1.07:0.21	42	4	45	9
16 h.	r.t.	CH_2Cl_2	5.0 eq.	-	1:-:1.00:0.40	42	-	42	16

There was an excessive amount of side product being synthesised as part of the anomerisation reaction for both rhamnose and fucose derivatives **18** and **21**, increasing with increasing equivalents of the Lewis acid promoter. The main side product, labelled 'x' in the tables above as well as subsequent tables, is that of their respective glycosyl chloride derivative.

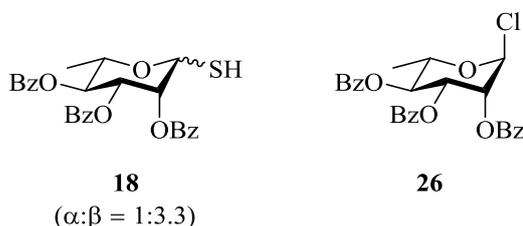


Fig. 1.30 Rhamnose thiol and its chloride by-product generated as part of the anomerisation reactions.

This was deduced from the NMR data for the rhamnose derivative, where literature data exists to compare to. The reported ^1H NMR data for **26**, 6.23(d, $J = 1.4$ Hz, 1H), corresponds well with those observed for the major by-product of the Lewis acid promoted anomerisation reaction of **18**, 6.23 (d, $J = 1.6$ Hz, 1H).

It can be speculated (as no experimental data exists), due to similar carbohydrate structure and signals in the NMR spectra that the major by-product for the anomerisation of fucose thiol **21** is also that of the chloride derivative, Fig. 1.31.

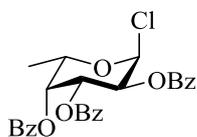


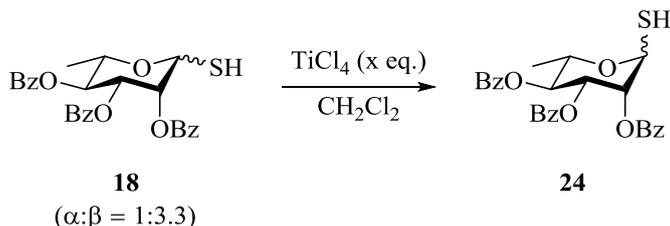
Fig. 1.31 Speculated chloride by-product being generated as part of the anomerisation of fucose thiol **21**.

It is also worth nothing that there appears to be another small, unidentified, by-product being generated during the anomerisation of these two sugars, labelled 'z' in the above and subsequent tables. It does not fit with reported data for a hemiacetal. Its peaks are very small with respect to the other peaks within the NMR spectra analysed.

Side product control investigations on rhamnose and fucose thiols

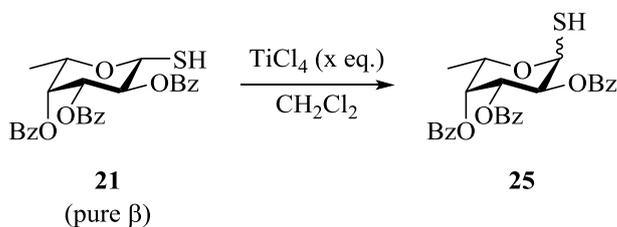
Studies were done to see if the anomerisation reaction of **18** and **21** could be controlled, with less side product production, i.e. to produce more of the desired anomerised thiopyranose product, with both time and temperature variations.

Table 1.33: Varying times of TiCl_4 promoted anomerisation of **18**, in CH_2Cl_2



Time	Temp.	Solvent	TiCl_4	Py.	$\alpha:\beta:x:z$	% α	% β	%x	%z
1 h.	r.t.	CH_2Cl_2	3.0 eq.	-	1:0.68:0.11:0.36	46	32	5	17
4 h.	r.t.	CH_2Cl_2	3.0 eq.	-	1:0.45:0.23:0.35	49	22	12	17
64 h.	4 °C	CH_2Cl_2	0.5 eq.	-	1:0.75:-:0.13	53	40	-	7

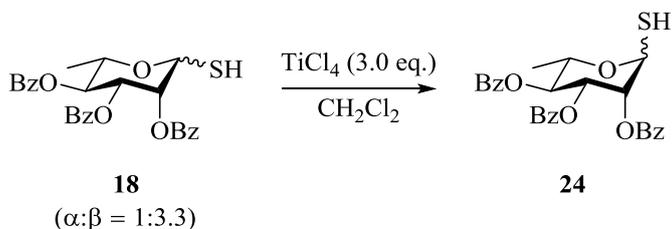
Table 1.34: Varying times of TiCl_4 promoted anomerisation of **21**, in CH_2Cl_2



Time	Temp.	Solvent	TiCl_4	Py.	$\alpha:\beta:x:z$	% α	% β	%x	%z
1 h.	r.t.	CH_2Cl_2	3.0 eq.	-	1:1.81:0.19:0.17	32	57	6	5
4 h.	r.t.	CH_2Cl_2	3.0 eq.	-	1:0.92:0.33:0.18	41	38	14	7
64 h.	4 °C	CH_2Cl_2	0.5 eq.	-	1:0.90:0.05:-	51	46	2	-

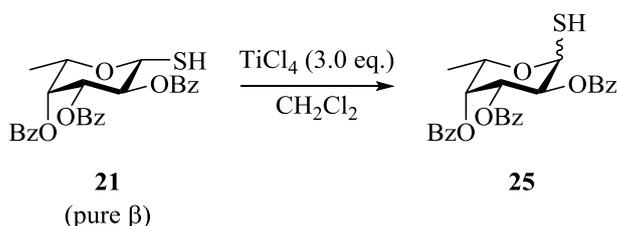
It would appear from these initial tests that the side product forming within the anomerisations of **18** and **21** could be controlled, to some degree, by using temperature control parameters. The next step was to see if the same control could be achieved while increasing the equivalents of TiCl_4 being used, to facilitate the anomerisation reaction, while also looking for an increase in the α -selectivity.

Table 1.35: Varying temperature and time of TiCl_4 promoted anomerisation of **18**, in CH_2Cl_2



Time	Temp.	Solvent	TiCl_4	Py.	$\alpha:\beta:x:z$	% α	% β	%x	%z
16 h.	4 °C	CH_2Cl_2	3.0 eq.	-	1:0.64:0.11:0.49	45	28	5	22
64 h.	4 °C	CH_2Cl_2	3.0 eq.	-	1:0.37:0.11:0.42	53	19	6	22
64 h.	-20 °C	CH_2Cl_2	3.0 eq.	-	1:1.99:0.05:0.20	31	61	2	6

Table 1.36: Varying temperature and time of TiCl_4 promoted anomerisation of **21**, in CH_2Cl_2



Time	Temp.	Solvent	TiCl_4	Py.	$\alpha:\beta:x:z$	% α	% β	%x	%z
16 h.	4 °C	CH_2Cl_2	3.0 eq.	-	1:1.10:0.17:0.06	43	47	7	3
64 h.	4 °C	CH_2Cl_2	3.0 eq.	-	1:0.58:0.21:0.05	54	32	11	3
64 h.	-20 °C	CH_2Cl_2	3.0 eq.	-	1:3.92:0.20:-	19	77	4	-

Side product control can be achieved, to some degree, through simple temperature change but this in itself directly affects the quantity of the, desired, anomerised product being synthesised. These preliminary studies give an insight into the anomerisation of rhamnose and fucose thiols, **18** and **21**. Further work on these two L-sugars is needed in order to try and increase both the selectivity and rate of their anomerisation. From this project, the work gives a good starting point for further investigations, with changes in the parameters discussed previously, such as solvent, a further screen of co-promoters, and a change of protecting groups, could potentially lead to a greater increase in the synthesis of the desired product.

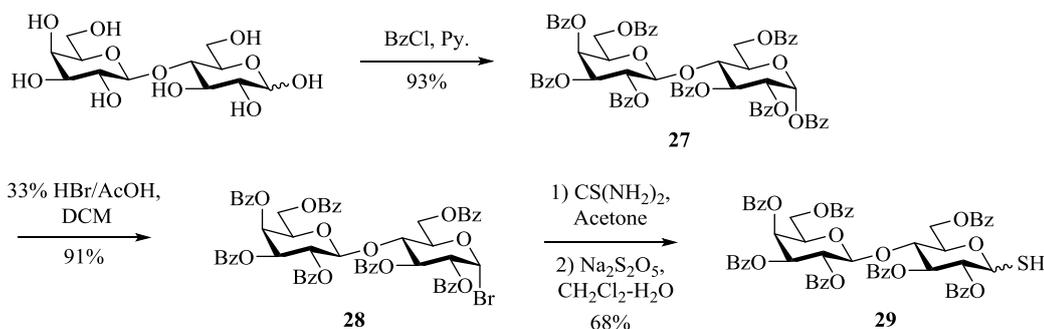
1.3.5 Synthesis of disaccharide thiols for anomerisation

The scope of the anomerisation reaction, being studied herein, was then tested with disaccharide derivatives. If the anomerisation of these sugars could be successful it would open the reaction to another possible group of chemists, those with a focus on or interest in polysaccharide chemistry.

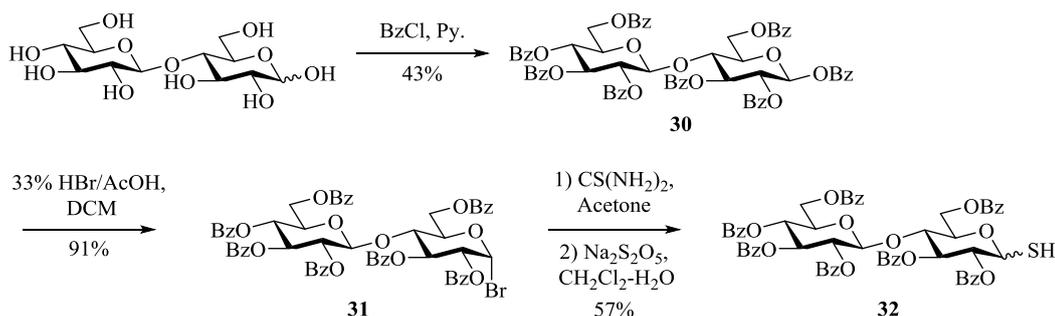
Not only that but if the anomerisation led to only a change in stereochemistry of the thiol and not the glycosidic linkage, it would show that the reaction is site specific.

The thio-disaccharides synthesised as part of the anomerisation study, herein, are synthesised from D-lactose and D-cellobiose. The synthesis of these is similar to those thiopyranoses described previously. They were prepared by displacement of an anomeric bromide with thiourea to give the glycosyl thiuronium salt which was subsequently hydrolysed under mildly basic conditions to give the thiopyranose **29** and **32** as displayed in Scheme 1.37.

Lactose



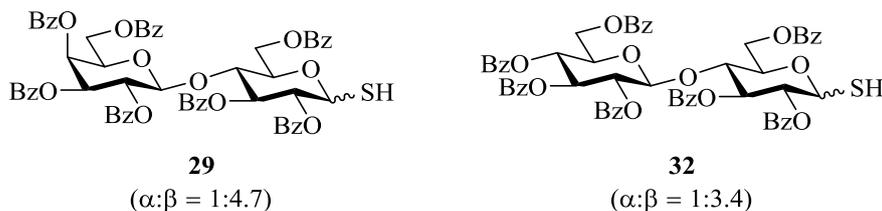
Cellobiose



Scheme 1.37 The synthesis of disaccharide thiols.

1.3.6 Anomerisation reactions

The anomerisation of these thiols were investigated using the conditions developed from the studies on **3** and **6**, as such they were subjected to an anomerisation reaction promoted by TiCl_4 and pyridine over a 16 h. period. The anomerisation reaction promoted by the Lewis acid independently was also tested, as a comparison and as a follow up to the pattern observed for thiopyranoses **12**, **15**, **18** and **21**.

Table 1.37: TiCl₄ promoted anomerisation of **29** and **32** with/without pyridine as co-promoter, in CH₂Cl₂

Sugar	Time	Temp.	Solvent	TiCl ₄	Py.	$\alpha:\beta:x$	% α	% β	% x
29	16 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	-	1:0.09:0.06	87	8	5
29	16 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	0.5 eq.	1:0.01:0.06	93	1	6
32	16 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	-	1:0.02:0.08	91	2	7
32	16 h.	r.t.	CH ₂ Cl ₂	3.0 eq.	0.5 eq.	1:0.01:0.05	94	1	5

Through the study of the anomerisation of these disaccharides we see a return to the patterns observed for the **3** and **6** thiols, in that there is an improvement in α -selectivity when using the co-promoter anomerisation conditions developed, as opposed to using the Lewis acid unaided.

The anomerisation is also shown to be regiospecific in this study, with only the thiol linkage, of both disaccharides, being anomerised to the desired α -derivative, leaving the glycosidic linkages, of both sugars, unchanged.

Examples of the patterns observed, for the anomerisations studied, are depicted in the stacked NMR spectra below.

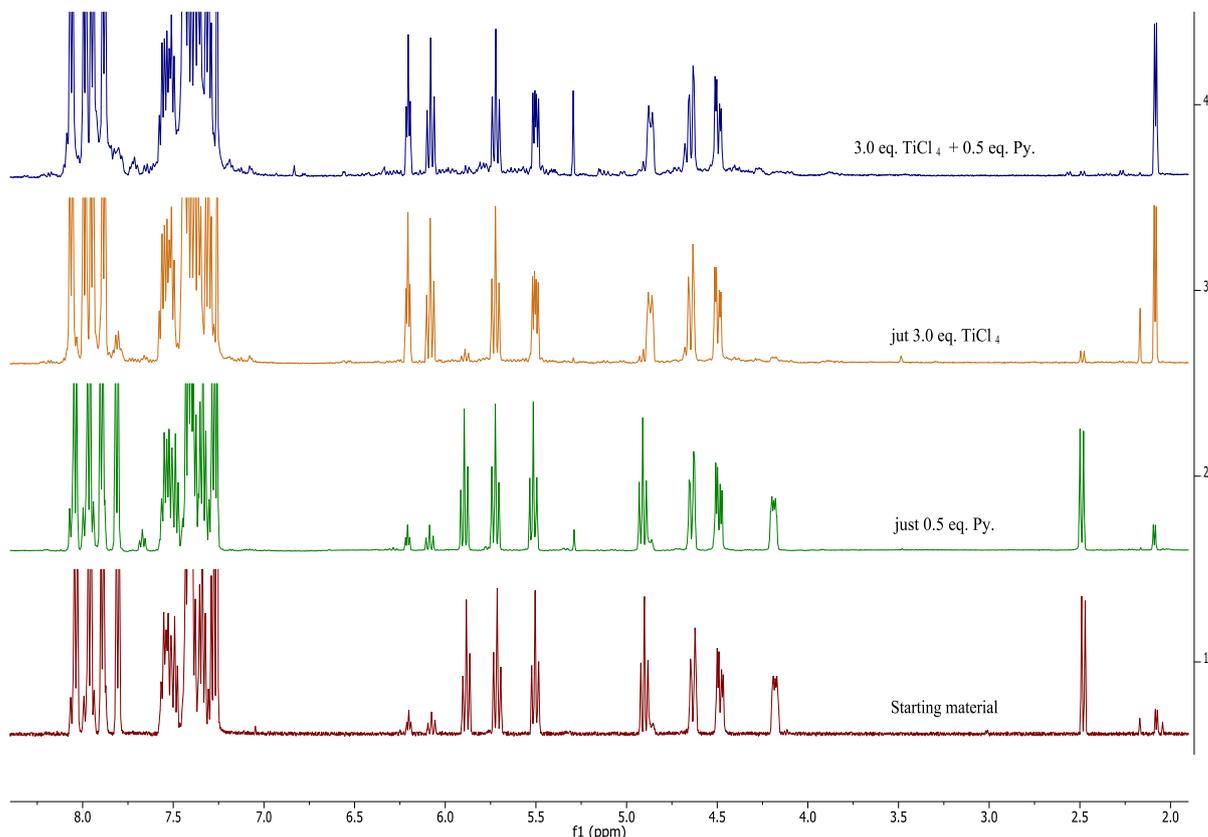
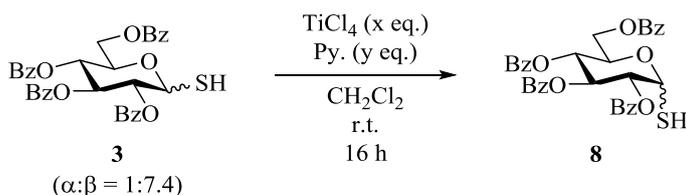
Example of glucose anomerisation NMRs

Fig. 1.32 The NMR spectra obtained for the anomerisation reactions of **3** using the promoters individually and co-operatively.

- The **red spectrum** is that of the starting material **3**, i.e. the sugar before any anomerisation reaction has been carried out.
- The **green spectrum** is for the reaction in which, only, 0.5 equivalents of pyridine was used to try and achieve an anomerisation.
- The **orange spectrum** is for the reaction in which, only, 3.0 equivalents of TiCl_4 was used and the anomerisation achieved in doing so.
- The **blue spectrum** is for the reaction in which both, 3.0 equivalents of TiCl_4 and 0.5 equivalents of pyridine were used and the anomerisation achieved in doing so.

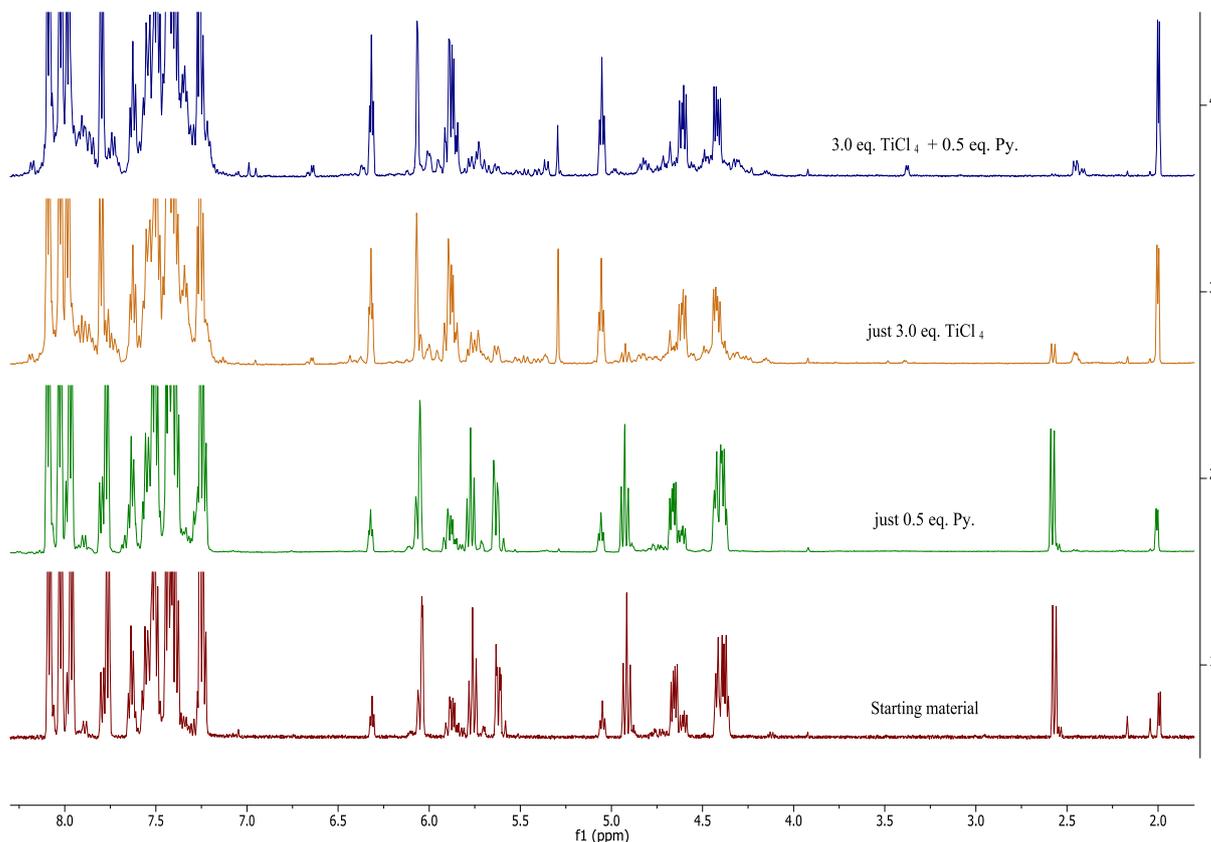
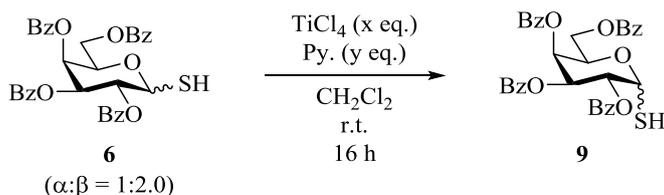
Example of galactose anomerisation NMRs

Fig. 1.33 The NMR spectra for the anomerisation reactions of **6** using the promoters individually and co-operatively.

- The **red spectrum** is that of the starting material **6**, i.e. the sugar before any anomerisation reaction has been carried out.
- The **green spectrum** is for the reaction in which, only, 0.5 equivalents of pyridine was used to try and achieve an anomerisation.
- The **orange spectrum** is for the reaction in which, only, 3.0 equivalents of TiCl_4 was used and the anomerisation achieved in doing so.
- The **blue spectrum** is for the reaction in which, both, 3.0 equivalents of TiCl_4 and 0.5 equivalents of pyridine were used and the anomerisation achieved in doing so.

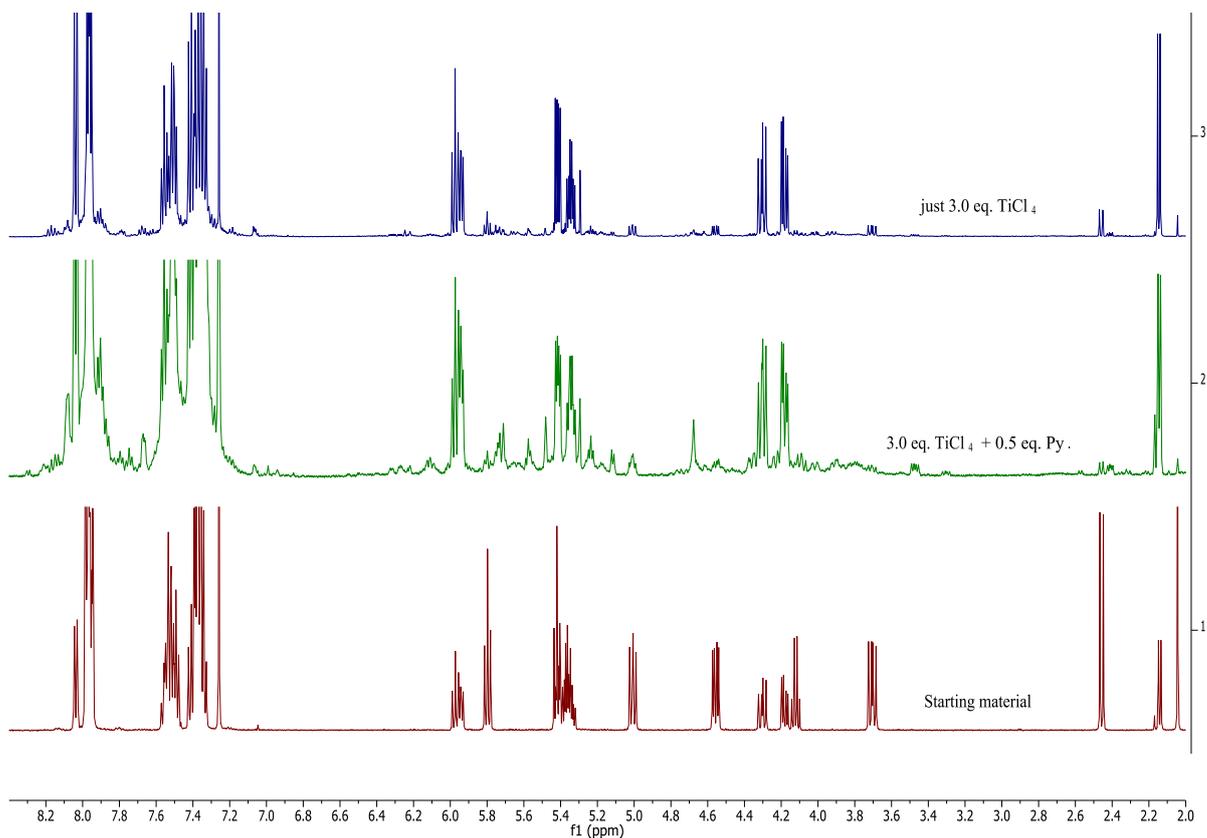
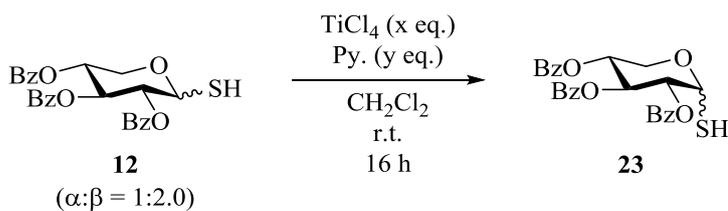
Example of xylose anomerisation NMRs

Fig. 1.34 The NMR spectra for the anomerisation reactions of **12** using the promoters individually and co-operatively.

- The **red spectrum** is that of the starting material **12**, i.e. the sugar before any anomerisation reaction has been carried out.
- The **green spectrum** is for the reaction in which, both, 3.0 equivalents of TiCl_4 and 0.5 equivalents of pyridine were used and the anomerisation achieved in doing so.
- The **blue spectrum** is for the reaction in which, only, 3.0 equivalents of TiCl_4 was used and the anomerisation achieved in doing so.

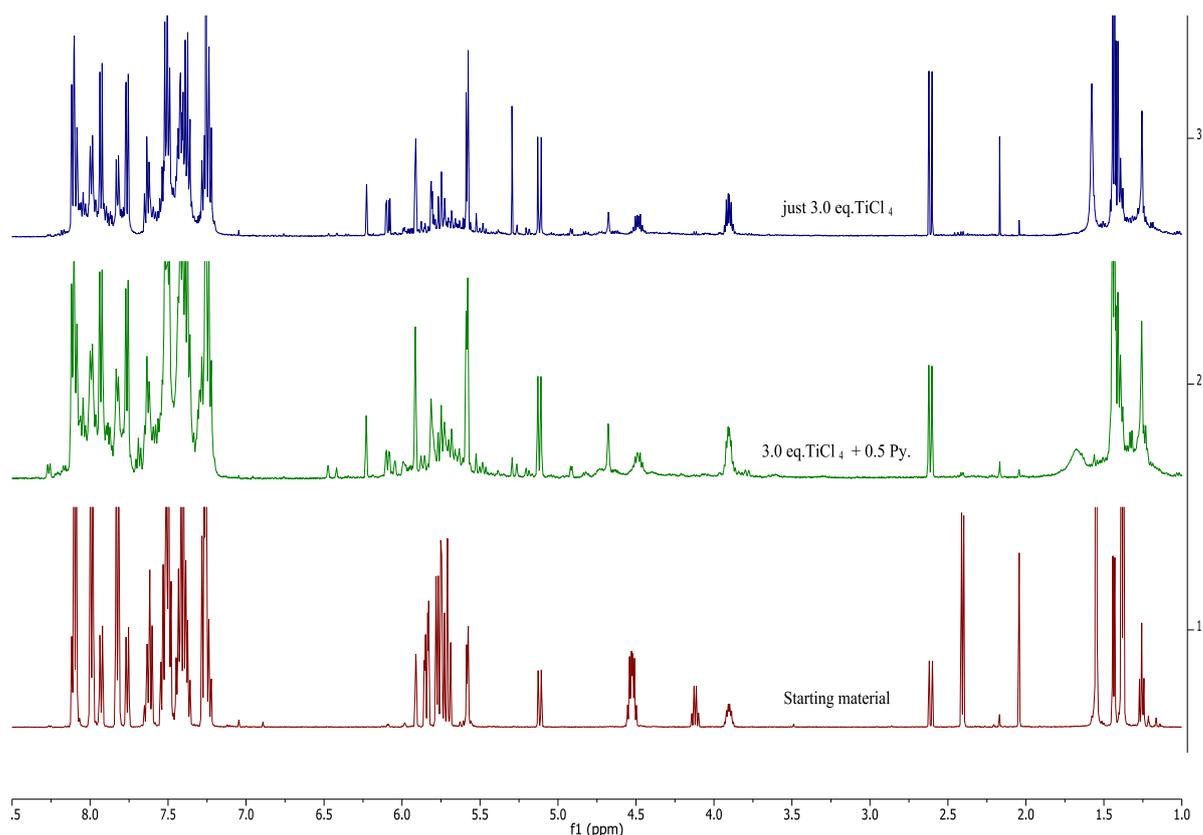
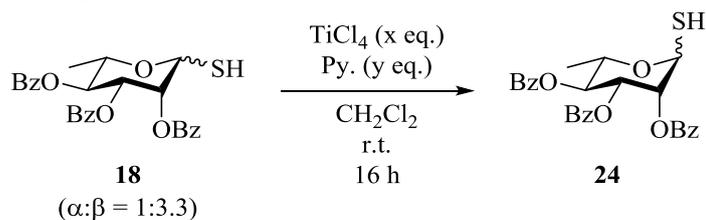
Example of rhamnose anomerisation NMRs

Fig. 1.35 The NMR spectra for the anomerisation reactions of **18** using the promoters individually and co-operatively.

- The **red spectrum** is that of the starting material **18**, i.e. the sugar before any anomerisation reaction has been carried out.
- The **green spectrum** is for the reaction in which, both, 3.0 equivalents of TiCl_4 and 0.5 equivalents of pyridine were used and the anomerisation achieved in doing so.
- The **blue spectrum** is for the reaction in which, only, 3.0 equivalents of TiCl_4 was used and the anomerisation achieved in doing so.

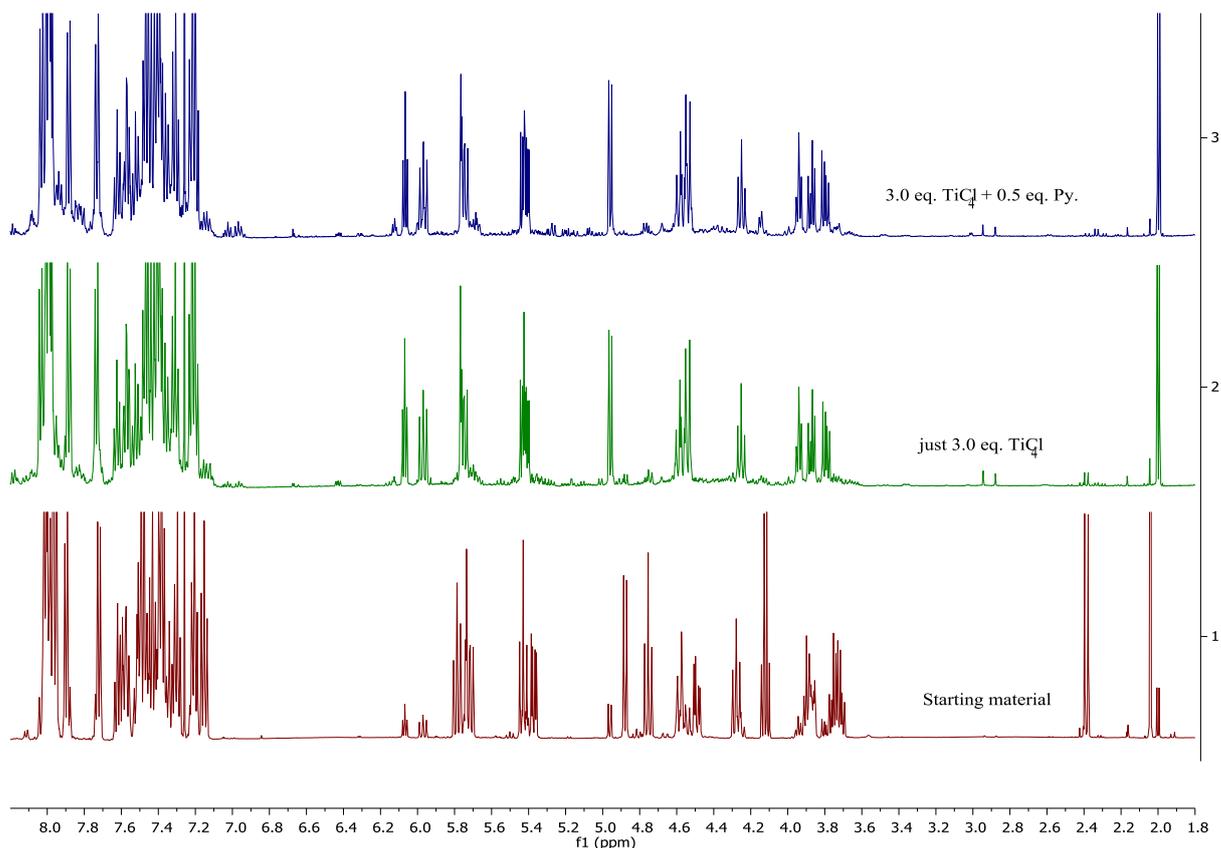
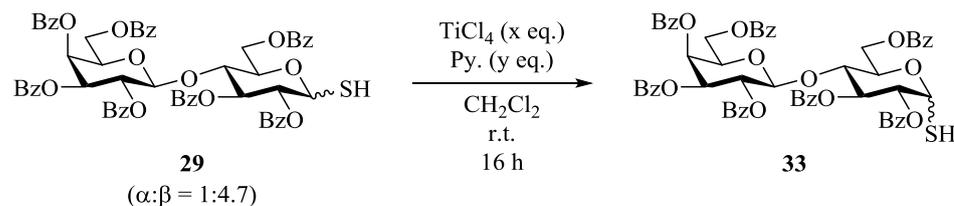
Example of disaccharide anomerisation NMRs

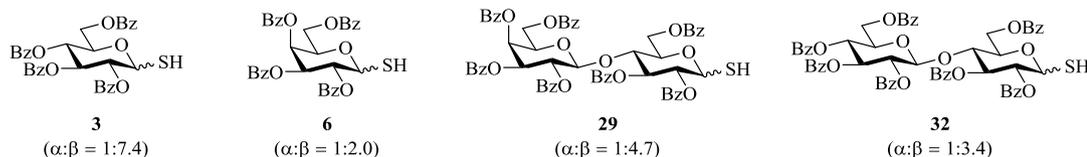
Fig. 1.36 The NMR spectra for the anomerisation reactions of disaccharide **29** using the promoters individually and co-operatively.

- The **red spectrum** is that of the starting material **29**, i.e. the sugar before any anomerisation reaction has been carried out.
- The **green spectrum** is for the reaction in which, only, 3.0 equivalents of TiCl_4 was used and the anomerisation achieved in doing so.
- The **blue spectrum** is for the in which both, 3.0 equivalents of TiCl_4 and 0.5 equivalents of pyridine were used and the anomerisation achieved in doing so.

Anomerisation have been carried out on eight different substrates under the conditions developed, TiCl_4 and pyridine promoted anomerisation. The best results, when using these novel conditions, were obtained for the sugars with a substituent at the C-6 position. For those thiopyranoses where this substituent doesn't exist, better reactions were achieved on using the Lewis acid, TiCl_4 , unaided.

Anomerisations of glycosyl thiols using TiCl_4 and pyridine

Starting Sugars:



Anomerised Sugars:

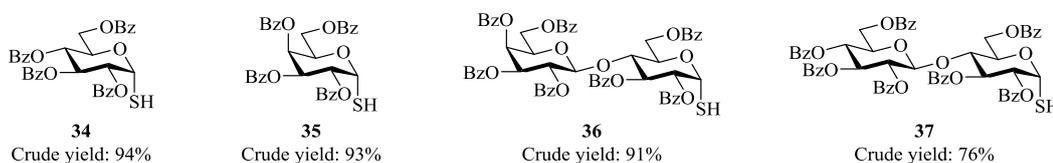
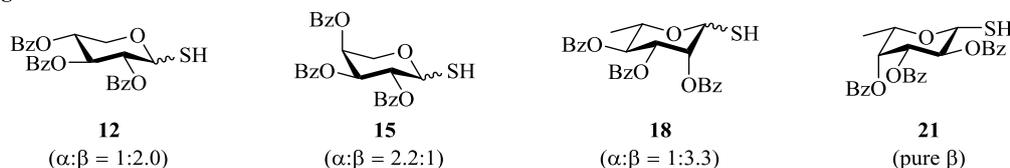


Fig. 1.37 Crude yields of sugars anomerised by TiCl_4 and pyridine.

Anomerisations of glycosyl thiols using just TiCl_4

Starting sugars:



Anomerised sugars:

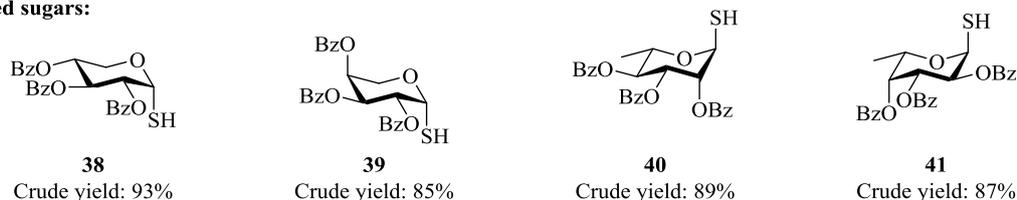


Fig. 1.38 Crude yields of sugars anomerised by just TiCl_4 .

In the above, Fig. 1.37 and 1.38, the yields reported are those for the crude (unpurified) anomerised sugars, post anomerisation reaction and subsequent work up (see experimental section for details). These crude yields are those obtained from the anomerisation reactions, reported in previous tables with illustrations of some of the products obtained shown through the blue spectra in Fig.1.32 to 1.36, of the best reaction conditions reported in these previous tables, i.e. 3.0 eq. of TiCl_4 and 0.5 eq. of pyridine for sugars **3**, **6**, **29** and **32**, while for sugars **12**, **15**, **18** and **21** just 3.0 eq. of TiCl_4 was used to obtained the crude yields shown in Fig. 1.38. For the anomeric distribution of these crude products, refer to appropriate previous tables.

Problems arose on trying to get isolated, clean, material which could be used for the analysis of those compounds synthesised through the, afore mentioned, anomerisations. It was observed that while the crude products of each of the anomerisation reactions indicated the presence of one major anomer, there was a significant decrease in isolated product yield being attained after attempts to purify the thiols by column chromatography.

1.3.7 Subsequent studies and reactions of anomerised glycosyl thiols

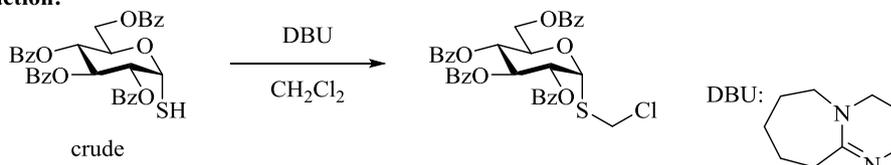
The loss of product, due to column chromatography, led to investigations on product purification, as well as the study of the use of the crude products without the need to carry out purification. This was done in an effort to try and retain the quantity of product achieved through the anomerisation reaction with that of the desired stereochemistry.

1.3.7.1 Reactions using crude glycosyl thiols

Three pathways, in which the crude sugars, synthesised through the anomerisation reactions, are used, are detailed below.

The first pathway uses an alkylation reaction with dichloromethane as the electrophile. Thus reaction of the crude anomeric mixture (predominately the α -anomer), from the anomerisation of the series of glycosyl thiol shown previously, in CH_2Cl_2 , was treated with DBU, leading to the 1-*S*-chloromethyl glycosyl thiols shown. The isolated yields of these products are provided in Fig. 1.39. Such chloromethyl derivatives can be used to prepare azide derivatives and for CuAAC reactions.

Example Reaction:



Yields:

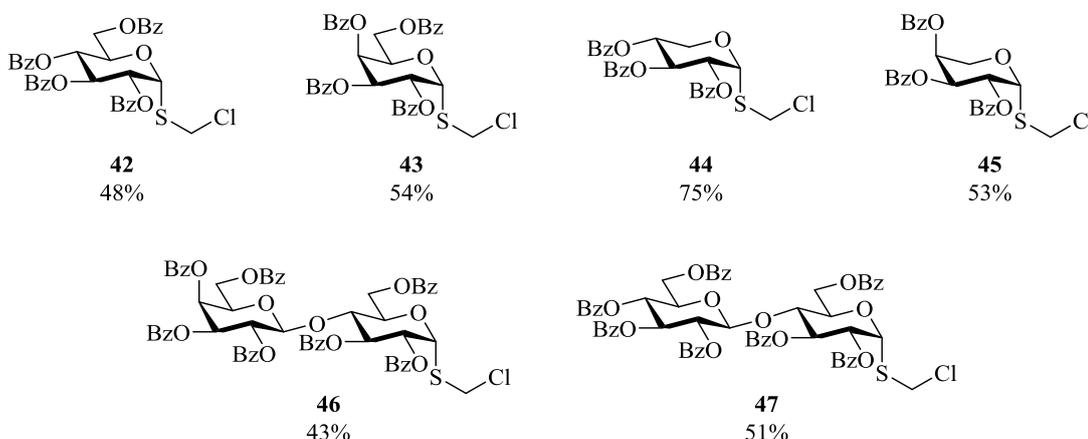
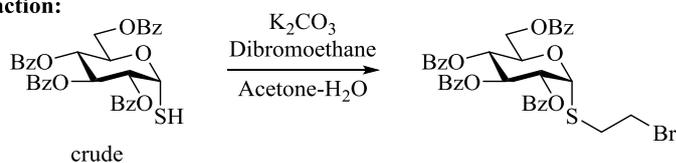


Fig. 1.39 The synthesis of 1-*S*-chloromethyl glycosyl thiols.

The second reaction investigated was the alkylation reaction of the glycosyl thiols with 1,2-dibromoethane in the presence of K_2CO_3 , while being stirred in an acetone- H_2O mixture.

Example Reaction:



Yields:

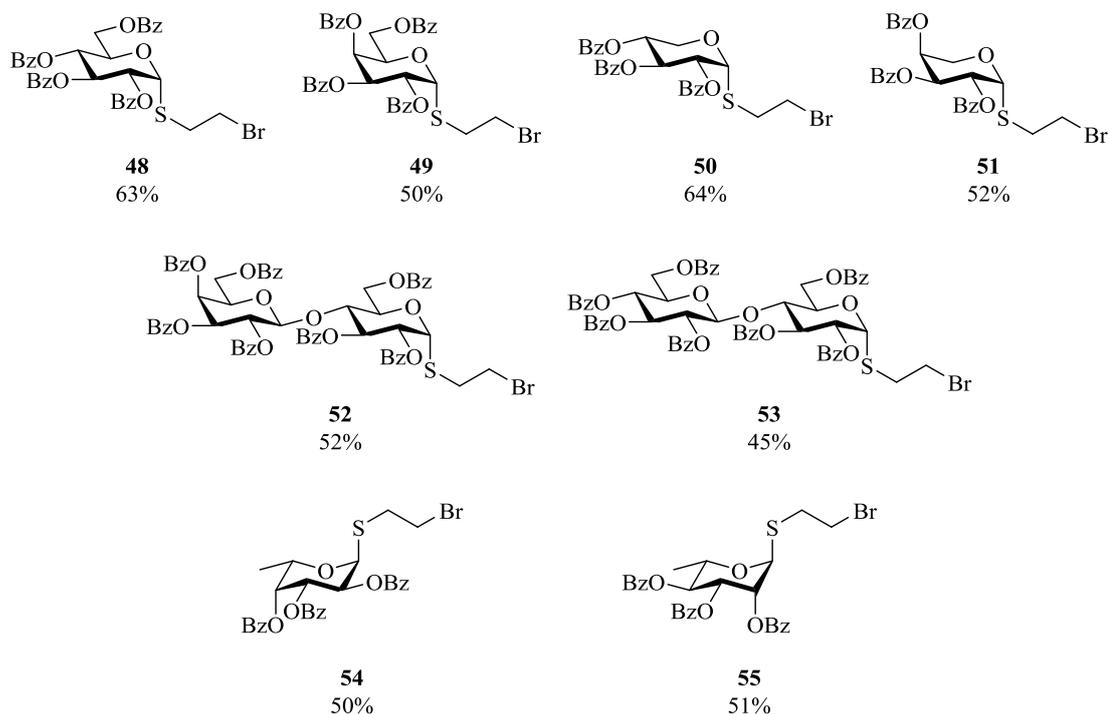
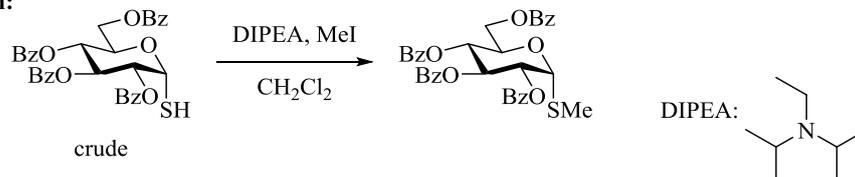


Fig. 1.40 The synthesis of 2-bromoethyl glycosyl thiols.

The third reaction that was investigated was the methylation of the crude anomerised thiols with Et₃N and iodomethane

Example Reaction:



Yields:

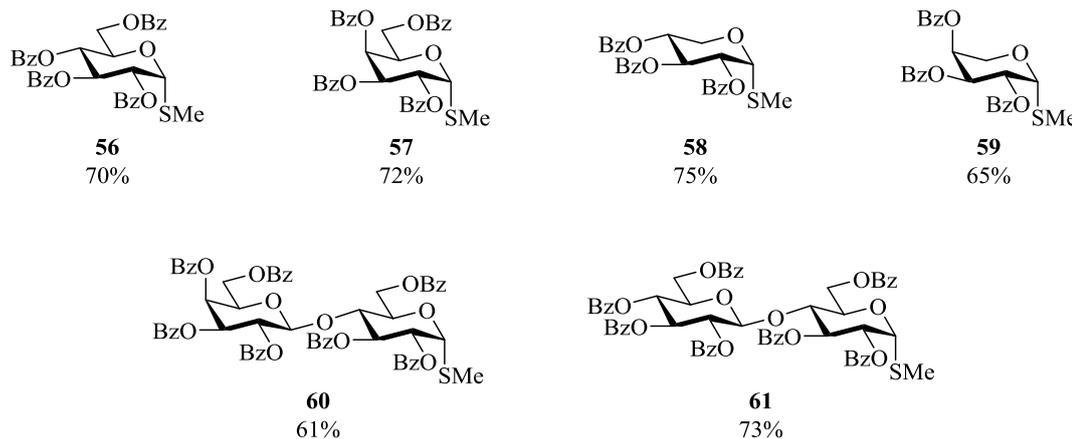


Fig. 1.41 The synthesis of methyl glycosyl thiols.

The results obtained from these three synthetic routes demonstrate the scope of these unpurified anomeric mixtures from the anomerisation reaction to be used in the synthesis of a variety of thioglycosides, with the anomeric substituent now having the less commonly found configuration. The yields reported are isolated yields.

A single reaction, in which the crude anomerised thiol **35** was protected with an acetyl group, was also carried out. This was a further illustration of the successful usage of these crude anomerised sugars, without the need for purification. This reaction was completed by stirring, crude, **35** in pyridine followed by the addition of Ac₂O, as per normal acetylation procedures, to give the thioacetyl **62**.

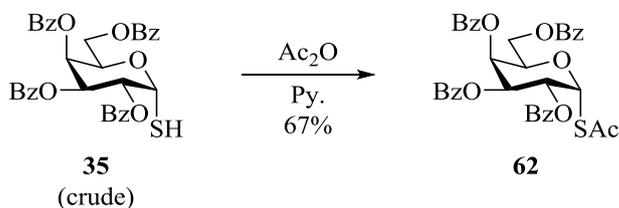


Fig. 1.42 The synthesis of 1-*S*-acetyl-2,3,4,6-tetra-*O*-benzoyl-1-thio- α -D-galactopyranose.

The success of these reactions illustrate that there isn't a necessity for purification of the anomerised sugars and that the crude products can be used efficiently in subsequent reactions.

1.3.7.2 Purification of anomerised glycosyl thiols

Attempts to improve the isolation of the thiols were also sought.

After extensive trialling of chromatography conditions, including investigation of gravity and flash methods using various solvent mixtures and adsorbents it was finally concluded that it is necessary to perform flash chromatography as quickly as possible using a short column of silica gel. The best isolated yields for the sugars synthesised through the anomerisations described previously after isolation by chromatography are shown below.

Purification of glycosyl thiols using $TiCl_4$ and pyridine promoted anomerisation

Anomerised Sugars:

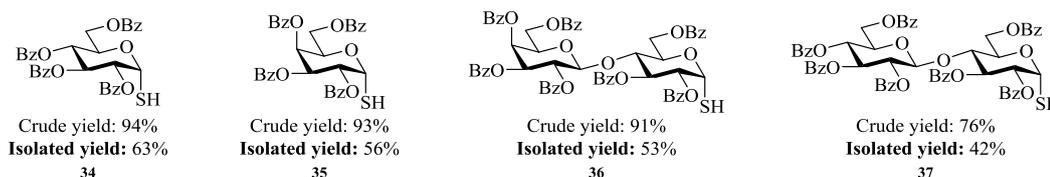


Fig. 1.43 Isolated, pure α -glycosyl thiol yields of sugars anomerised by $TiCl_4$ and pyridine.

Purification of glycosyl thiols using just $TiCl_4$ promoted anomerisation

Anomerised sugars:

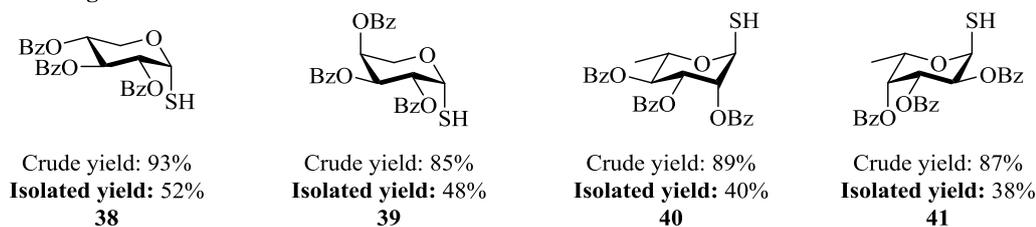


Fig. 1.44 Isolated, pure glycosyl thiol yields of sugars anomerised by just $TiCl_4$.

What has been shown, to this point, is that the anomerisation of thio-sugars is possible and the conditions described herein give moderate to high yields of products with the desired stereochemistry – that of the harder the synthesis configuration. Through the reduction of these products during purification by column chromatography it was found that the crude thiols can be used without the need to purify them, which can lead to useful products without a further loss in overall yield.

1.3.7.3 Application of anomerised thiols towards potential multivalent compounds

The potential application of the glycosyl thiol products synthesised through the work herein can be demonstrated through the lactose derivative. Previous work from the Murphy laboratory by Guan-Nan Wang⁵⁶ on glycoclusters as lectin inhibitors, with a focus on lactose derivatives, has been reported and will be discussed in more detail in chapter 3. For now it's suffice to say that the need for multivalency is important and the patterns observed within this publication showed that there was an increasing effect

with increasing multivalency, the biggest of which, in the article mentioned, was a tetravalent compound.

Thiol-yne click chemistry

A way to increase this multivalency would be to utilise the thiols synthesised herein, such as that of the lactose derivative **36**, and using either thiolene or thiol-yne click chemistry and a suitable linker, such as the trivalent linker **84**, synthesise a hexavalent derivative.

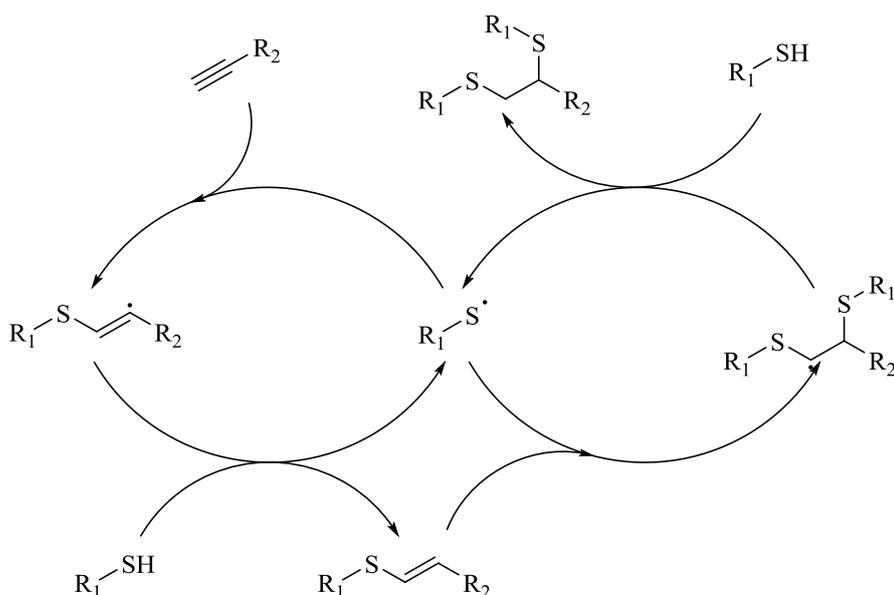
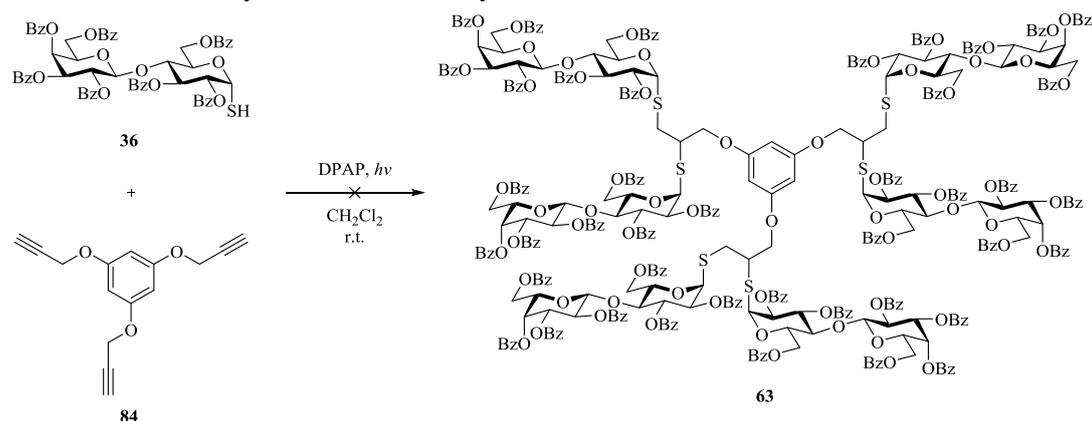


Fig. 1.45 Mechanism of thiol-yne click chemistry.

Preliminary studies were investigated as part of this thesis, nearing its completion.

Table 1.38: Thiol-yne click chemistry of **36** with **84**



Reaction	Reaction time	Sugar	DPAP	$h\nu$
1	3 h.	1 eq.	0.3 eq.	Sunlight
2	3 h.	1 eq.	0.3 eq.	365 nm
3	3 h.	1 eq.	1.3 eq.	365 nm
4	65 h.	1 eq.	0.3 eq.	Sunlight
5	65 h.	1 eq.	1.3 eq.	Sunlight

Although the synthesis of the hexavalent compound **63** wasn't achieved, these were only preliminary studies and this work has immense potential, as further research in this area could lead to a host of quickly and easily accessible multivalent compounds, with an α -configuration by use of the anomerisation conditions developed herein. The potential for these subsequently generated multivalent compounds to find activity as, say, lectin inhibitors, (chapter 3) are vast.

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Chapter 2: Synthesis of *N*-acetyl glucosamine glycoclusters

2.1 Background to *N*-acetyl glucosamine and multivalency

2.1.1 Introduction

N-Acetyl-D-glucosamine (GlcNAc) is a monosaccharide derivative of glucose differing in the substituent at the C-2 position, with the hydroxyl (OH) at C-2 of glucose replaced with an acetamide group (NHAc) in *N*-acetyl-D-glucosamine. This GlcNAc unit can be found in many biologically important oligosaccharides, glycoproteins and glycolipids. It can be found in, for example, part of the biopolymer peptidoglycan (murein) which is a mesh-like structure that makes up the cell wall of bacteria. It can also be found in the long chain polymer, chitin - the second-most abundant biopolymer in nature, which is made up solely of repeating units of GlcNAc. In nature chitin is the polymer which forms the exoskeletons of insects and crustaceans. The structurally similar chitosan, a polymer that is made up of repeating monosaccharide units D-glucosamine and *N*-acetyl-D-glucosamine, has become popular in wound treatment as surgical thread due to its strength and favorable biological attributes – with antimicrobial activity against a wide variety of bacteria, while also being able to enhance the healing process by re-epithelialization and the regeneration of the normal skin. It has been reported to help reduce scar formation during the healing process by preventing the construction of granulation tissue¹.

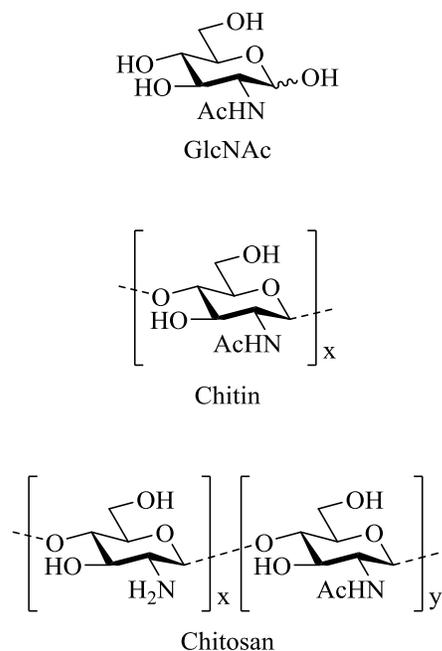


Fig. 2.1 The structure of GlcNAc and polymers consisting of the GlcNAc monosaccharide.

The monosaccharide, GlcNAc, itself, has also been found to have potential in the treatments of various diseases such as – osteoarthritis, where its use is to address the degenerative disorder (the problem) as opposed to the treatment of the associated pain (which is attained through the administration of steroids and does nothing to tackle the cause of the issues). This treatment with GlcNAc is believed to be beneficial by providing the body with a sustained released form of glucosamine which is the substrate used for glycosaminoglycan (GAG) biosynthesis. It can also stimulate GAG synthesis, inhibit its degradation, and appears to be directly involved in the repair of damaged cartilage², inflammatory bowel disease (such as Crohn's disease and ulcerative colitis)³ and gastritis. This monosaccharide offers an inexpensive and nontoxic treatment of these diseases. Herein the research is related to development of multivalent compounds, which present GlcNAc headgroups, which act as antibacterial agents against *Helicobacter pylori*.

The following sections summarise why GlcNAc compounds, as multivalent ligands, are attractive from a synthetic point of view, and why they have potential applications. In addition, the modes of interaction of these multivalent compounds, is also covered. The application of click chemistry is also briefly reviewed. The last section of this chapter deals with the area of interest, *Helicobacter pylori*, and the compounds synthesized as part of this project for evaluation against this stomach bacterium.

2.1.2 *N*-Acetyl glucosamine multivalent ligands

There exists a variety of different types of architecture by which multivalent ligands exist or can be made from. These include polymers, dendrimers, dimers and clusters to name but a few, with each and all capable of existing based on aliphatic or aromatic scaffolds. Within these, structurally different types of GlcNAc derivatives can be synthesized as multivalent ligands. Here we briefly discuss some of these, which show why this carbohydrate has potential as a biological tool.

Rheumatoid arthritis (RA) is a systemic autoimmune disease - an illness where the bodies own tissues are erroneously attacked by response of the immune system to what is believed to be a foreign invader. It, RA, is typified by chronic joint inflammation resulting in subsequent cartilage and bone deterioration/destruction, which can be observed as deformed and painful joints in a patient, which in turn can lead to loss of function. *N*-Acetyl glucosamine (GlcNAc) is widely used as a supplement in the treatment of osteoarthritis, as alluded to at the outset of this chapter. Many researchers have utilized this information by carrying out trials using pure GlcNAc, independently, for the treatment of RA, with positive results being obtained. All these studies, though, were performed using GlcNAc in its natural form, i.e. as a monosaccharide, which is known to have a low binding affinity to its specific receptors. Accordingly, a multivalent compound based on GlcNAc could potentially provide an even more effective therapeutic agent in the treatment of RA than the monosaccharide. To this end Richter et al.⁴ used a recognized experimental

model of human RA, collagen-induced arthritis (CIA), to test the effectiveness of some multivalent GlcNAc compounds. This model is set up/created through the introduction of either bovine or chicken type II collagen (CII) emulsified in complete Freund's adjuvant (CFA) into mice. The purpose of this experiment/model is to produce symptoms of RA, such as the aforementioned joint inflammation and swelling. This model, CIA, is then used as a way of studying the alterations of the functions of the immune system/response during the progression and development of the disease. Two glycodendrimers, Fig. 2.2, differing in their scaffold as well as size, bearing four or eight GlcNAc moieties, were used in the study. The researchers reported on a variety of responses such as the reduction of inflammation and the suppression of cells - T, B and APC (antigen-presenting cells) in the synovial, when using these glycodendrimers. A host of other responses and inhibitions, as a result of these GlcNAc-terminated glycoconjugates (GCs), Fig. 2.2, were also reported within the study. With RA known to affect areas of the body other than the joints, the authors also reported similar patterns in the spleen, with the glycodendrimers, Fig. 2.2, reported to have brought about a considerable decrease of NKG2D-expressing NK (natural killer) cells, without affecting their lytic function. A summary of what was found by Richter et al. was that the multivalent compounds tested either, successfully deferred the onset of arthritic symptoms, decreased the severity of these symptoms when present, and in 18% (**2A**, Fig. 2.2) and 31% (**2B**, Fig. 2.2) of cases completely prevented their appearance. This proves that multivalent compounds presenting GlcNAc moieties can have a very positive influence in prevention as well as possible cure to, in this instance, RA. The results observed by Richter et al. provide evidence and support to the use of multivalent glycoclusters as a treatment of rheumatoid arthritis (RA) and collagen-induced arthritis (CIA) and as such gives rise to further research in the development of other therapeutics of these multivalent forms.⁴

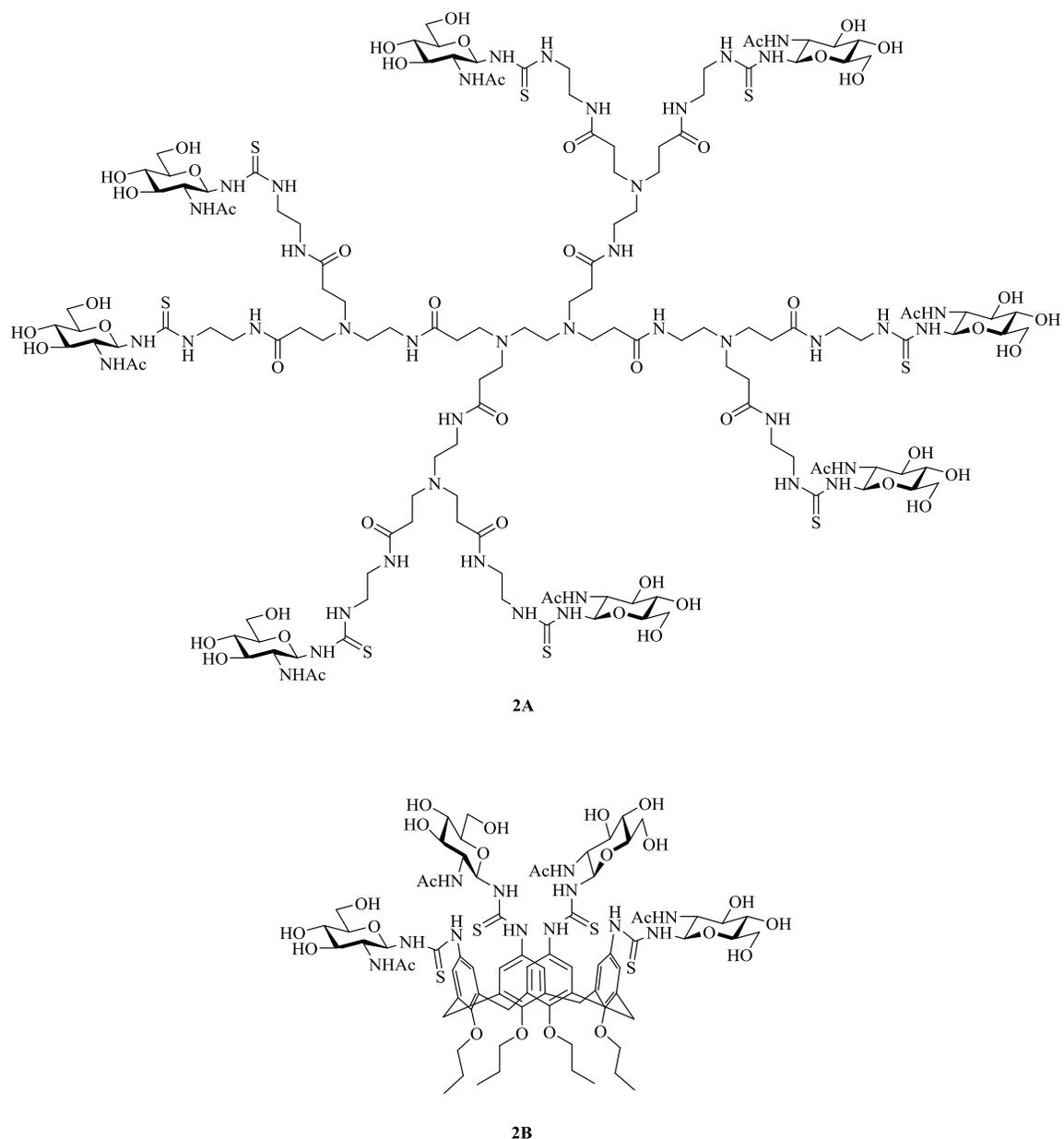


Fig. 2.2 Glycodendrimers tested for potential in RA treatment.

Schwefel et al. showed the importance of multivalency in regards to lectins, to be discussed later in chapter 3, with their studies on wheat germ agglutinin (WGA) ligands⁵. WGA is a plant type lectin that is augmented in the seeds of *Triticum Vulgaris* (wheat). Through the interaction with the fungal cell wall WGA can inhibit fungal growth and can also cause agglutination to occur, i.e. the clumping together of cells. Their initial screening studies identified a tetravalent neoglycopeptide, **2C** in Fig. 2.3, which was reported to have had an exceptionally strong increase in WGA binding. This tetravalent derivative had an increased potency factor of 1440, which equates to a factor of 360 per carbohydrate residue, when compared to binding of the monosaccharide GlcNAc. Subsequent work in the area, lead to

the synthesis of a cyclic neoglycopeptide where the spacer length was reduced by five bonds and where the glycosidic linkage had been change from a β -anomer in **2C**, to an α -linkage in **2D**, Fig. 2.3. This new ligand showed an improved IC_{50} value of 0.9 μ M, equating to a significant improvement in binding, being 25,500-fold lower than that of the monovalent GlcNAc. Within this same study they prepared a series of mono- to tri-valent GlcNAc derivatives to try and understand and reveal the structural parameters that allow for the enhanced WGA binding affinity of **2D** to be obtained. To that end they were able to synthesis a bivalent ligand, **2E** in Fig. 2.3 which itself had an even lower IC_{50} , 9.8 μ M, than that of the original tetraivalent glycopeptide **2C**.

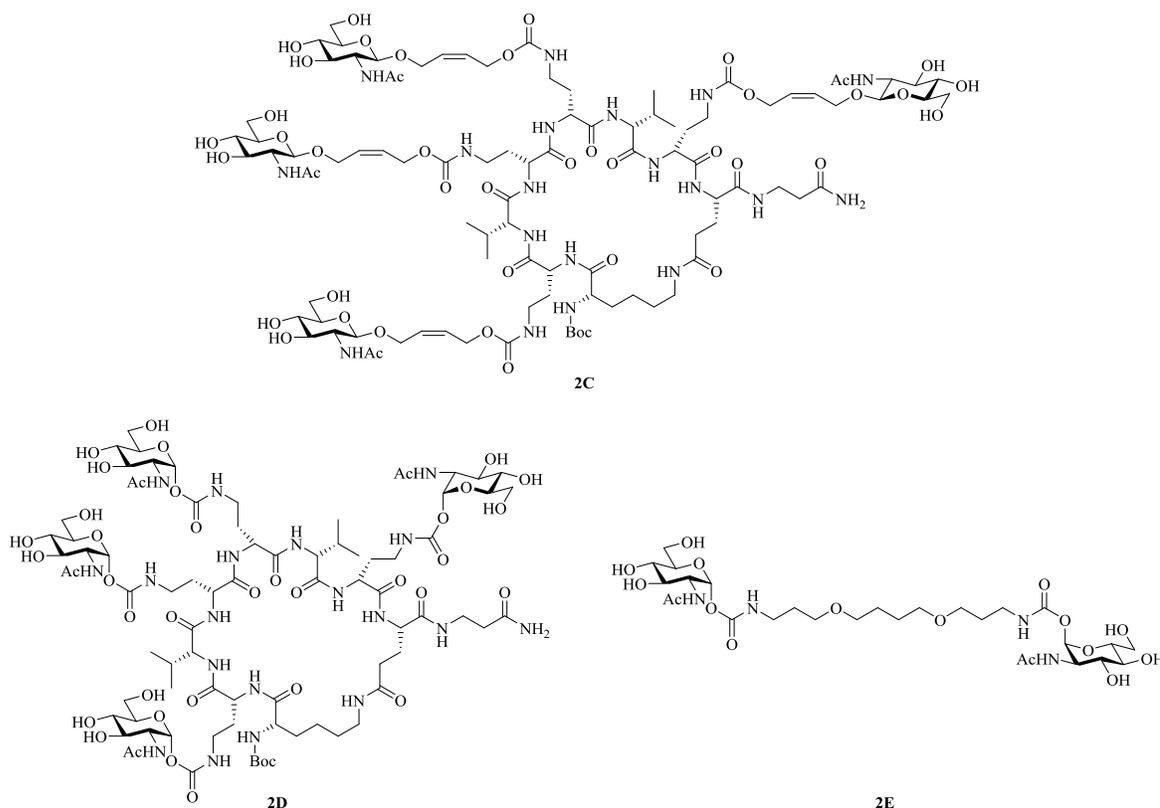


Fig. 2.3 Multivalent compounds tested for WGA binding.

These few examples show the potential of multivalent ligands and with respect to the examples shown - those with GlcNAc sugar heads as the binding element of interest, to be useful compounds and have possible clinical uses. Focus of the initial studies within this thesis were, in part, based on the potential of GlcNAc multivalent compounds, as well as other background which will be discussed in coming sections.

There also exists potential to develop the work herein through the synthesis of mimics of, for example, the potent bivalent compound **2E** in Fig. 2.3, with relative ease, using compounds synthesized as part of this project.

2.1.3 Multivalency

The environment of the surface of a cell is an intricate and dynamic one, with carbohydrates and proteins of varying shapes and sizes protruding from the lipid bilayer. These diverse molecules, the proteins and carbohydrates of the cell surface, are arranged heterogeneously, that is they can be dispersed evenly across the surface of a cell or concentrated within micro-domains. Regardless of their arrangement they act as a reporter - delivering messages to the cell. They communicate changes of the outside environment, such as the presence of toxins, nutrients, or foreign invaders. The surface of the cell also provides an area for the docking of other cells, the extracellular matrix, or pathogens⁶. The functions and communication of the external environment of the cell depend on the interactions or binding of specific ligands to their cell-surface receptors. The investigation and synthesis of natural and/or non-natural ligands that interfere with the recognition and response of cell-surface receptors to the binding of ligands is therefore an interesting and worthwhile one.

Compounds that are capable of displaying multiple copies of a recognition element (RE), i.e. the unit of the molecule capable of interaction with the cell receptor binding site, are termed multivalent. Multivalent compounds are interesting as they are potentially capable of elucidating a series of responses through their capability to undergo binding at a number of sites on the cell surface, through the presentation of a number of REs, as shown in the previous examples. As such it gives weight to the argument that the synthesis of multivalent molecules is a useful one. Synthetic multivalent ligands are useful tools in investigating multivalent cell-surface binding. They can be used, for example, to analyze the contributions of increasing the multivalency of compounds, in elucidating biological results/activities. In terms of complex biological/physiological multivalent ligands, such as those present on a cell or viral surfaces, they are often too scarce, structurally heterogeneous/complex to identify the relevant mode by which they may act, i.e. mechanism of action. It is worth noting that although it is the recognition element that is responsible for the actual binding and as such the main contributor to elucidating a function there are many other contributing features/elements to the initial binding. These include - the valency (number) and orientation of the receptor binding sites (how they are presented to incoming ligands, with this orientation possibly influencing the mode by which multivalent compounds can interact (see below)), as well as the flexibility/rigidity, size, and shape of the scaffold from which the recognition elements are attached. Synthetic multivalent ligands thereby become interesting tools to investigate these complex physiological multivalent ligands. They can be produced such that, the structure of the linker, i.e. the unit from which the REs are attached; the identity of said REs, i.e. the headgroups; the number of REs i.e. the valency of the multivalent compounds; and the spacing between the REs, can be varied systematically to try and understand the molecular mechanisms of the more complex physiological multivalent ligands⁶.

Synthetic multivalent ligands can be used through two pathways i.e. have two distinct modes of action: one way is by preventing the receptor–ligand binding/interaction – these are known as inhibitors. The other method is through the attachment of a multivalent ligand to a receptor which then stimulates a cellular response –these are known as effectors. Due to the multiple copies of an RE, multivalent ligands often have an increased functional affinity for their specific receptors when measure against that of the monovalent ligand. Through these multiple REs there are several different modes/mechanisms through which multivalent compounds can interact with receptors on the cell surface.

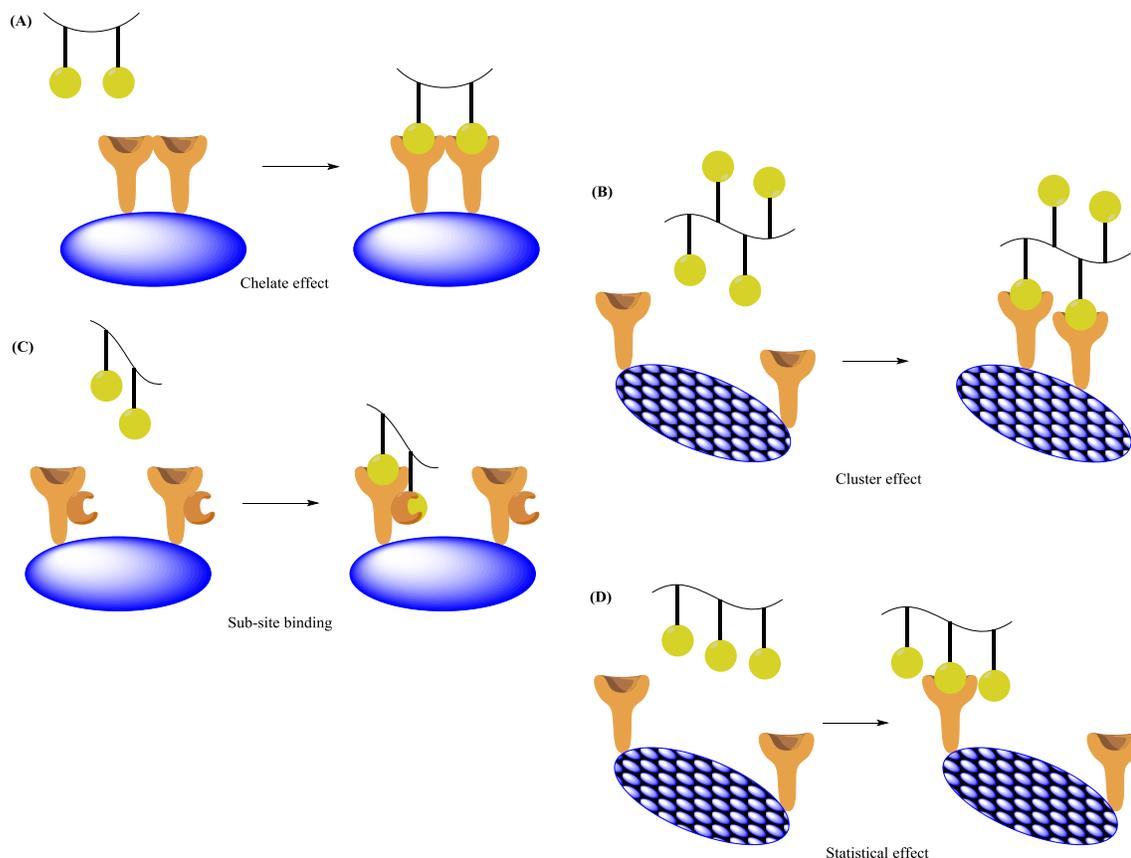


Fig. 2.4 Modes by which multivalent ligands can act to increase their potency.

Examples of the mechanisms/modes by which multivalent compounds can contribute to their potency are included in Fig. 2.4 - **(A)** shows the ability of multivalent ligands to attach to oligomeric receptors on the surface of the cell, also known as the chelate effect. Even with receptors that are not oligomeric, it is possible, through a process aided by the two dimensional diffusion of receptors in the lipid bilayer, for multivalent compounds to combine to multiple receptors **(B)**. This is known as the cluster effect and can lead to signaling pathways being activated. Some receptors, in addition to their primary binding sites, possess a secondary binding site that can be occupied by one of the REs of the multivalent ligand **(C)**, this is known as sub-site binding. Finally **(D)** - as multivalent

ligands can present a number of saccharides they can therefore display a higher local concentration of binding elements. Due to the enforced proximity of multiple unbound REs, multivalent ligands can have higher functional affinities, even when only one receptor of the cell surface is being occupied. This is known as the statistical effect.

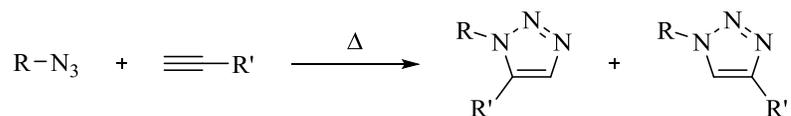
Another mode by which multivalent ligands may inhibit cell-surface interactions through binding to receptors, is by way of steric stabilization. This form of multivalent interaction makes use of the size of a particular multivalent ligand, such as a polymer, to inhibit the binding of other ligands through the steric effect. Even when only a few binding sites on a cell surface are engaged, the size of the multivalent ligand prevents any other binding on the surface of a cell with an opposing ligand, e.g. viral particle or cell.

Of the multivalent interactions discussed, the highest contribution is generally attributed to the chelate effect. Due to this, the nature of the linker between the binding elements, i.e. the carbohydrate derivatives of a multivalent compound, is important. The conformation and flexibility of the scaffold should therefore be considered when synthesizing multivalent compounds as they can strongly influence the ligands capability to participate in the chelate effect.

With the various modes of action possible for multivalent ligands to induce an effect, as either an inhibitor or an effector, these make the synthesis of multivalent compounds for biological testing a promising one⁶.

2.1.4 Click chemistry

The phrase ‘click chemistry’ was introduced by Sharpless in 2001.⁷ This type of chemistry describes reactions that are for a start, high yielding, simple to perform - can be carried out in solvents that are easily removed, and most importantly are stereospecific. These click chemistry reactions have their origin in the 1,3-dipolar cycloaddition (commonly referred to as the Huisgen cycloaddition). The pioneering work of these 1,3-dipolar cycloadditions, between an organic azide and an alkyne, was carried out by Rolf Huisgen during the 1960s⁸, hence the attribution of the name. The mechanism proposed, by Huisgen, that is now generally accepted, is that of a concerted pericyclic cycloaddition mechanism⁹.



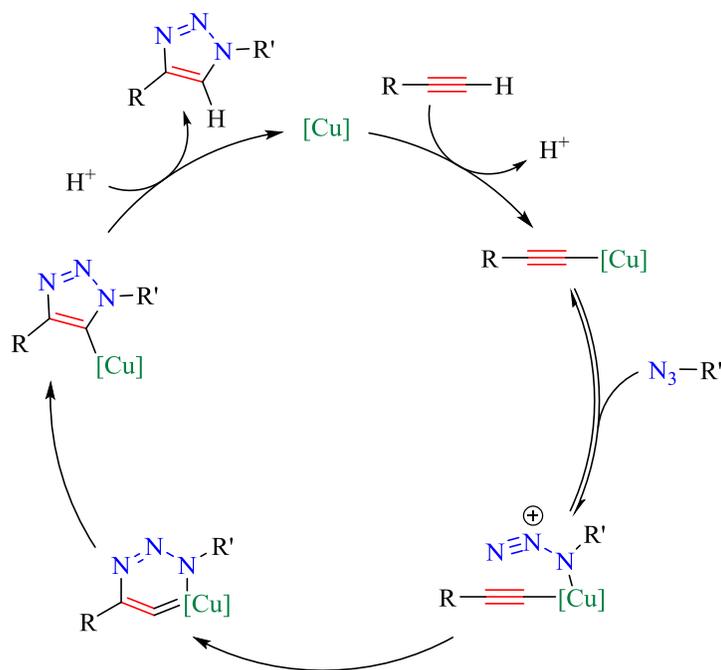
Scheme 2.1 Huisgen cycloaddition.

The issues with this 1,3-dipolar cycloaddition (Huisgen cycloaddition) are that the reaction of the azide and alkyne require elevated temperatures and often produce a mixture of the two regioisomers, depending on how the azide reacts. Due to these conditions and mixture

of products the Huisgen cycloaddition fails as a click reaction under the criteria stated by Sharpless.

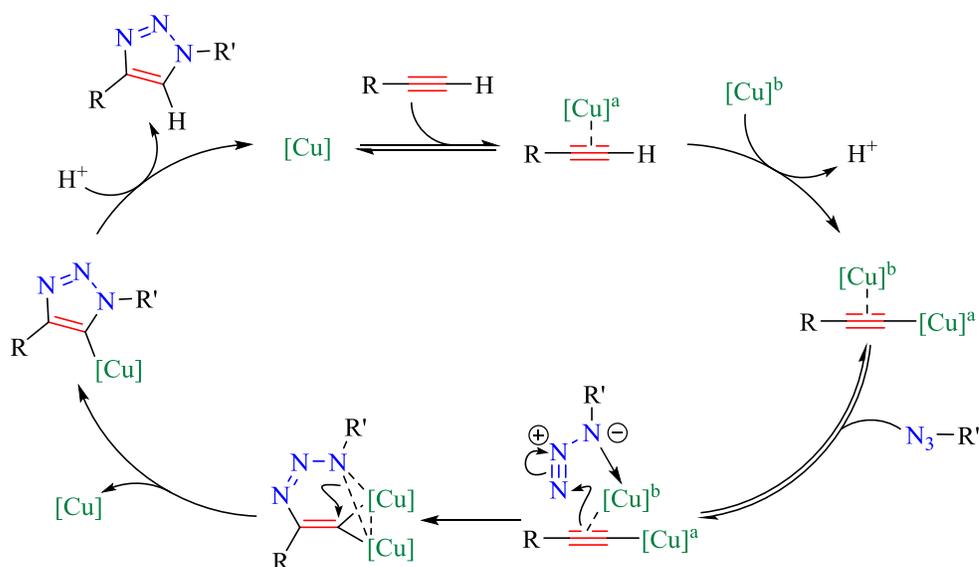
2.1.4.1 1,4-Click chemistry (CuAAC)

Meldal¹⁰ and Sharpless¹¹, working independently, developed a copper catalysed variant of the Huisgen cycloaddition, which gives rise to the 1,4-regioisomer specifically *via* a different mechanism.



Scheme 2.2 Originally proposed mechanism for 1,4-click chemistry.

The mechanism in Scheme 2.2 was what was believed to be the route of the copper-catalyzed azide-alkyne cycloaddition (CuAAC) until recently when a paper by Fokin et al.¹² showed evidence of a dinuclear copper intermediate in the CuAAC. Scheme 2.3 shows the new proposed scheme from the work by Fokin.



Scheme 2.3 New proposed mechanism for 1,4-click chemistry.

These 1,2,3-triazoles are also interesting as they can mimic properties of a peptide bond without having the same susceptibility to hydrolytic cleavage¹³, thereby increasing the stability of compounds they are incorporated into from chemical degradation or enzymatic cleavage.

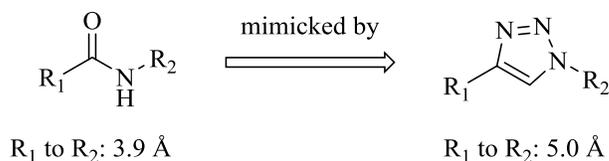


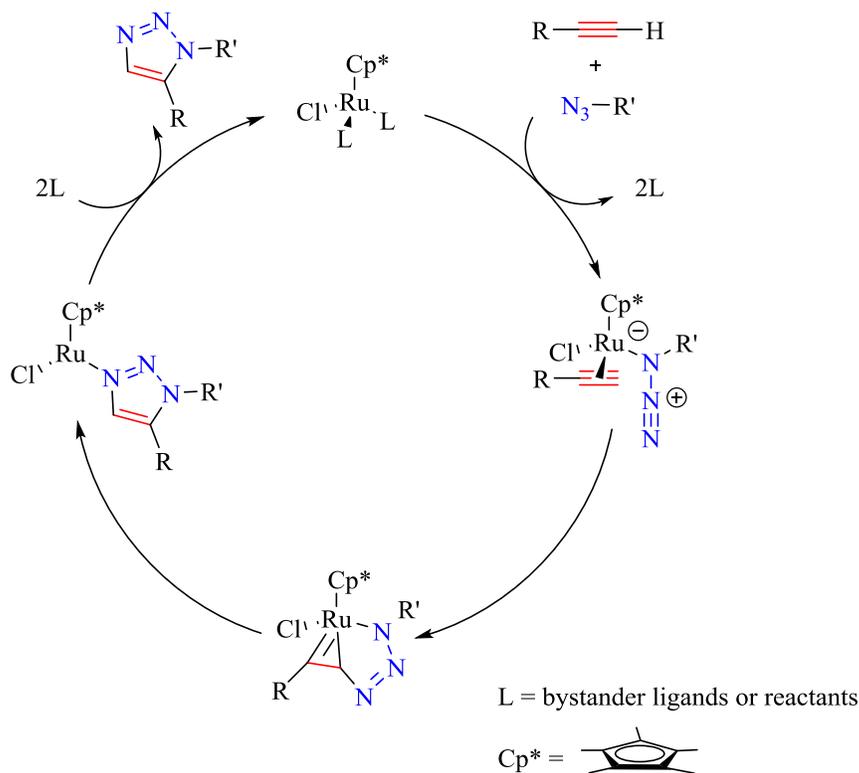
Fig. 2.4 Similarities between amides and 1,2,3-triazole.

These triazoles are also capable of active participation in hydrogen bonding as well as having possible hydrogen-bond acceptors in the N(2) and N(3) triazole atoms. In addition, the added dipole-dipole and π -stacking interactions, possible to these triazoles, could potentially increase the biological activity of any compound in which they are incorporated into¹³.

2.1.4.2 1,5-Click chemistry (RuAAC)

For access to the other regioisomer, usually synthesized as part of the Huisgen cycloaddition, i.e. the 1,5-disubstituted triazoles, through the idea of click chemistry, it is necessary to use a method similar to that of the CuAAC reaction but replacing the copper catalyst with a ruthenium catalyst, and in doing so this allows for the exclusive synthesis of the 1,5-regioisomer. This later developed method arose as part of a search for catalysts capable of promoting a click reaction. This search revealed that pentamethylcyclopentadienyl ruthenium chloride [Cp^*RuCl] complexes are able to

catalyze the reaction of an azide with an alkyne to give the 1,5-disubstituted 1,2,3-triazole selectively, Fig. 2.5. In contrast to CuAAC reactions, these ruthenium-catalyzed azide-alkyne cycloadditions (RuAAC) can also be utilized with internal alkynes as well as the more commonly used terminal alkynes. This allows for the generation of fully substituted 1,2,3-triazoles.



Scheme 2.5 Proposed mechanism for 1,5-click chemistry.

For the purposes of this project the focus of the glycoclusters to be synthesized were to be that of the more commonly used, and efficient, CuAAC reaction, i.e. the 1,4-regioisomers. The CuAAC reaction is one of the best click reactions used currently, owing in part to the enormous rate acceleration of 10^7 to 10^8 when compared to the uncatalyzed Huisgen cycloaddition. The active Cu(I) catalyst necessary for the CuAAC reaction can be obtained directly from Cu(I) salts or can be generated from Cu(II) salts using sodium ascorbate as a reducing agent. As part of the work in this thesis the conditions employed make use of this, using inexpensive copper (II) sulfate (the pentahydrate form) with sodium ascorbate to generate the catalyst needed to facilitate the synthesis, through click chemistry, of 1,4-disubstituted 1,2,3-triazoles.

2.2 *Helicobacter pylori*

2.2.1 Background

Barry J. Marshall and J. Robin Warren were jointly awarded the Nobel Prize in Physiology or Medicine in 2005 "for their discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease".

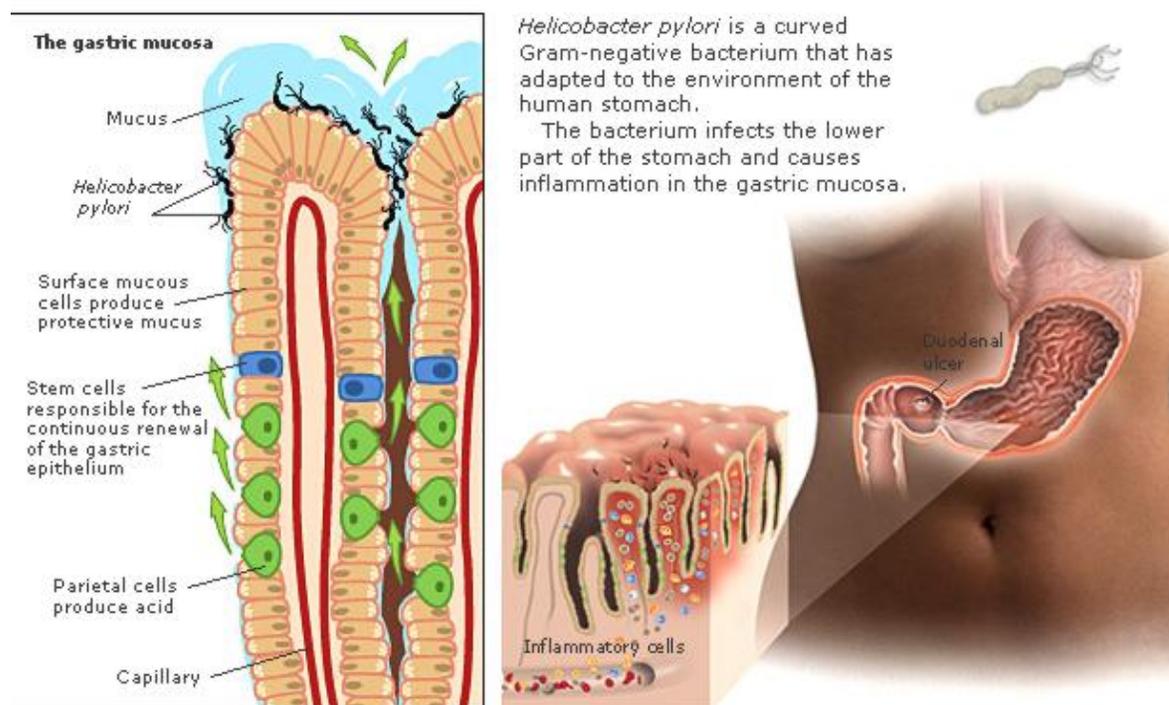


Fig. 2.6 Site of *Helicobacter pylori* infection. Copyright © The Nobel Assembly at Karolinska Institutet, <http://www.nobelprize.org/> Illustrations: Annika Röhl, Bengt Gullbing.

The work by these two in this field began in the early 1980s¹⁴ after near on 45 years of near discoveries by other investigating scientists¹⁵ only, for said early work and discoveries, to be forgotten due to either, further evidence not confirming initial results or for what was being observe being considered as being due to a contaminant. It wasn't until the work by Marshall and Warren that, first, led to the isolation of the spiral shaped bacterium, later named *Helicobacter pylori*. This was followed by the subsequent study of a group of patients presenting for gastroscopies. In this study biopsies were taken from areas of the antral mucosa, with the analysis of these samples giving rise to the deduction that this new species of bacilli, which appeared to be related to the genus *Campylobacter*, could in fact be the cause of a multitude of diseases, such as chronic gastritis, duodenal ulcer, gastric cancer and mucosa-associated lymphoma.

Marshall and Warren noted in this paper¹⁵ even though this new species closely resembled campylobacters, that their flagellar (hairlike protrusions on certain cells, with a primary function of acting like a propeller and give locomotion to said cell) morphology does not fit that of the genus *Campylobacter*. Campylobacters are reported to have a solitary unsheathed flagellum at either one or both ends of the cell while this newly discovered bacterium, *Helicobacter pylori*, has four to seven sheathed flagella¹⁶, to protect them from the disintegration in the gastric lumen, and all at one end. To that end they proposed the name "pyloric campylobacter" as a way of describing both the location where these bacteria are normally found, where the pylorus is the region of the stomach that connects to the duodenum, as well as to indicate the similarity to that of the species to the *Campylobacter* genus.

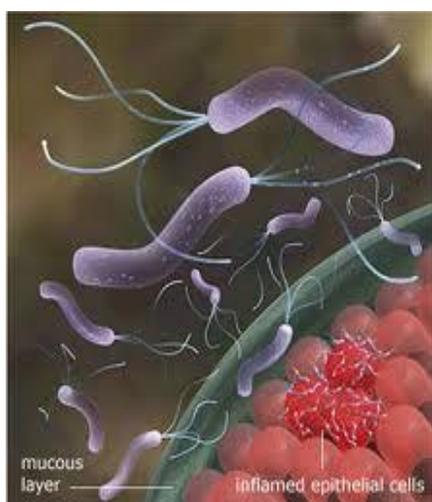


Fig. 2.7 *Helicobacter pylori*.



Fig. 2.8 *Campylobacter jejuni*.

Helicobacter pylori infects about half the world's population with infection rates differing from country to country. Fortunately though, even with such a vast infection number, the majority of infected individuals remain asymptomatic. Regardless, about 10-15% of those infected with *Helicobacter pylori* will experience an associated issue as a result of this stomach bacterium. This is generally seen in the form of peptic ulcer disease, leading, more commonly, to the formation of a duodenal ulcer than a peptic ulcer of the stomach itself. In some of these infected symptomatic cases, *Helicobacter pylori* can also infect the corpus (body) region of the stomach, leading to a more widespread and therefore more severe inflammation that not only can cause gastric ulcers but can also lead to stomach cancer.

2.2.2 Infection

During infection *Helicobacter pylori* enters the gastric lumen, the space into which gastric acid is secreted after being produced by the parietal cells, where it protects itself from this harsh acidic environment by producing urease which neutralizes the acid around it through the production of ammonia molecules. On reaching the mucus layer, the flagella of the *Helicobacter pylori* act as a propeller to allow the spiral shaped bacteria to bore through to

the gastric epithelial cells. Here it sticks to this single layer of epithelial cells using specialized adhesions and is now able to use the mucus layer, as well as its production of urease, to protect it from the gastric acid of the stomach.

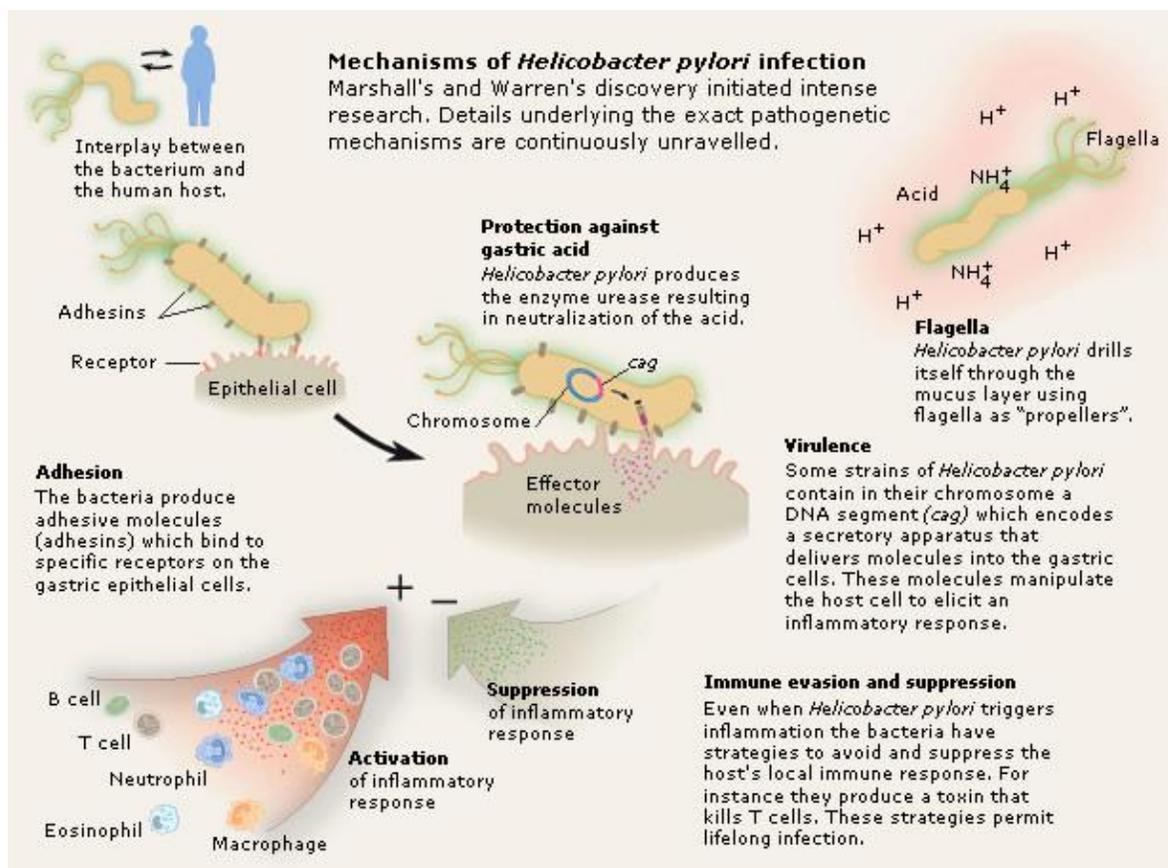


Fig. 2.9 Mechanisms of *Helicobacter pylori* infection. Copyright © The Nobel Assembly at Karolinska Institutet, <http://www.nobelprize.org/> Illustrations: Annika Röhl, Bengt Gullbing.

2.2.3 Antibiotics against *Helicobacter pylori* infection

With an infection rate of greater than 50% of the world population, this bacteria should be getting all the media attention of an pandemic but owing to the fact most individuals remain asymptomatic this is not the case.

Due to the small portion of symptomatic patients, it suggests the presence of a host defense mechanism against the organism, capable of limiting or preventing the otherwise present symptoms and diseases associated with *Helicobacter pylori* infection.

Mucins are produced by secretions of mucous membranes. They are a group of high molecular weight, protein glycoconjugates. There exists two types of gastric mucins: those secreted from surface mucous cells - the surface mucous cell-type mucin, and those secreted by gland mucous cells – these are found in deeper portions of the mucosa¹⁷.

Helicobacter pylori is hardly ever found in the deeper parts of the gastric mucosa, where these gland mucous cells are produced. These mucins, produced in the lower sections of the gastric mucosa, contain terminal α -1,4-linked *N*-acetyl glucosamine attached to core 2 branched *O*-glycans [GlcNAc α 1-4Gal β 1-4GlcNAc β 1-6 (GlcNAc α 1-4Gal β 1-3)GalNAc α -Ser/Thr]¹⁸.

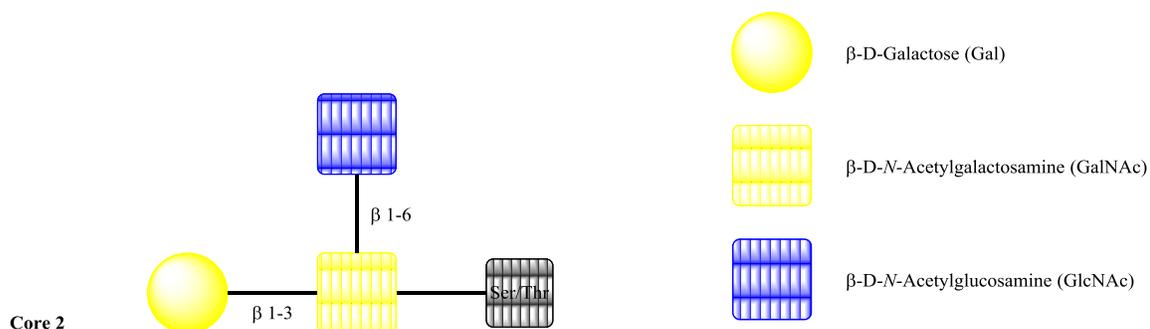


Fig. 2.10 Illustration of Core 2.

This lack of *Helicobacter pylori* in the lower portions of the gastric mucosa was a topic of research for Lee et al.¹⁹ In this article, they report that a gland mucin (MUC6), which is secreted in the lower/deeper portions of the gastric mucosa, contains α -1,4-*N*-acetyl glucosamine (α -1,4-GlcNAc) capped core 2-branched *O*-glycans. This mucin or rather the α -1,4-GlcNAc constituent of it was reported to inhibit the synthesis of α -glucosyl cholesterol, which is a key component of the *Helicobacter pylori* cell wall²⁰ and thus, through this inhibition, was able to suppress *Helicobacter pylori* growth.

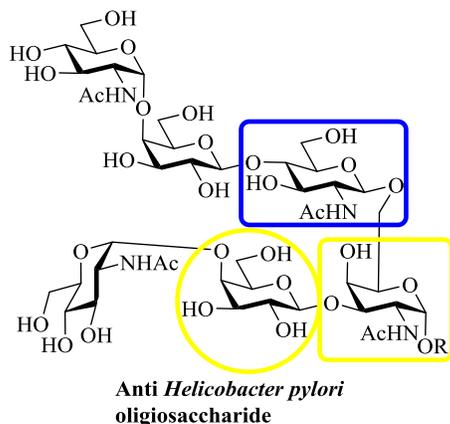


Fig. 2.11 Anti *Helicobacter pylori* oligosaccharide.

This growth inhibition, by means of inhibition the synthesis of α -glucosyl cholesterol, is not unique to this core 2-branched *O*-linked glycoprotein, as *p*-nitrophenyl α -*N*-acetyl glucosamine is also known to suppresses the growth of *Helicobacter pylori* in a dose dependent manner.²⁰ So it stands to reason that unique α -GlcNAc products could have

potential in inhibiting *Helicobacter pylori* infection and/or suppress *Helicobacter pylori* growth.

To that end it was hypothesized, by the Murphy laboratory, that multivalent glycoclusters based on α -GlcNAc headgroups could have probable activity against *Helicobacter pylori*. This is based on the structure of the anti *Helicobacter pylori* hexasaccharide which could be considered as being constructed of two α -GlcNAc residues (top and tail) grafted onto a core tetrasaccharide scaffold. This anti *Helicobacter pylori* hexasaccharide was, up until 2007, only available as a recombinant glycoprotein (CD43) form. It was synthesized using α -1,4-*N*-acetylglucosaminyl transferase in Chinese hamster ovary cells and it is because of the draw backs associated with enzymatic synthesis, such as the limitation in the amount of product that can be produced that lead Manabe et al. to investiage and report the first total synthesis of an anti *Helicobacter pylori* oligosaccharide²¹. This chemical synthesis and other developments in the field are important because strains of *Helicobacter pylori* resistant to antibiotics, such as one of the two recommended antibiotics, clarithromycin, which is part of a triple therapy in tandem with amoxicillin and a proton pump inhibitor, have been reported²².

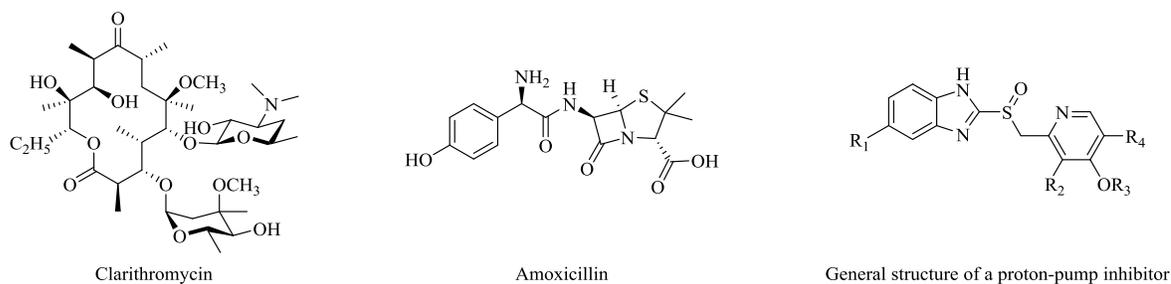


Fig. 2.12 Current triple therapy used against *Helicobacter pylori*.

Herein we described the design and synthesis of a series of multivalent GlcNAc derivatives where two or more of these monosaccharide residues are attached, by way of CuAAC, to a non carbohydrate scaffold to generate a series of glycocluster mimetics of the anti *Helicobacter pylori* hexasaccharide. Even though it is a terminal α -1,4-linked *N*-acetyl glucosamine, as in the native hexasaccharide, Fig. 2.13, that is believed to be the contributing factor necessary for the growth inhibition of *Helicobacter pylori*, compounds with GlcNAc residues containing β -linkages were also included.

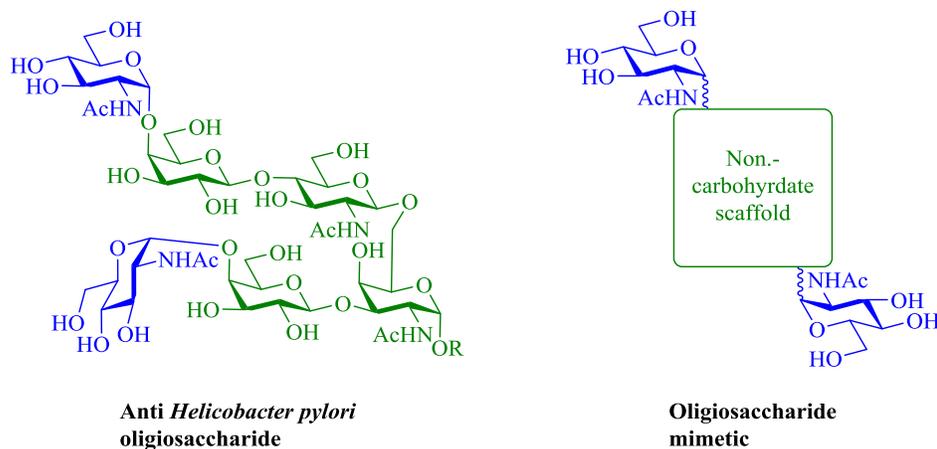


Fig. 2.13 Anti *Helicobacter pylori* oligosaccharide and mimetic idea.

2.2.4 Recent synthesis of bivalent glycoclusters containing GlcNAc as anti *Helicobacter Pylori* hexasaccharide mimetics

The Murphy group has recently reported the synthesis of bivalent α - and β -GlcNAc derivatives. Some of which have show bactericidal activity against *Helicobacter Pylori*.²³ The compounds tested returned positive results, in which two of the glycoclusters, Fig. 2.14, based on α -O-GlcNAc residues, selectively reduced the viability of two different strains *Helicobacter pylori* (Pu4 and P12).

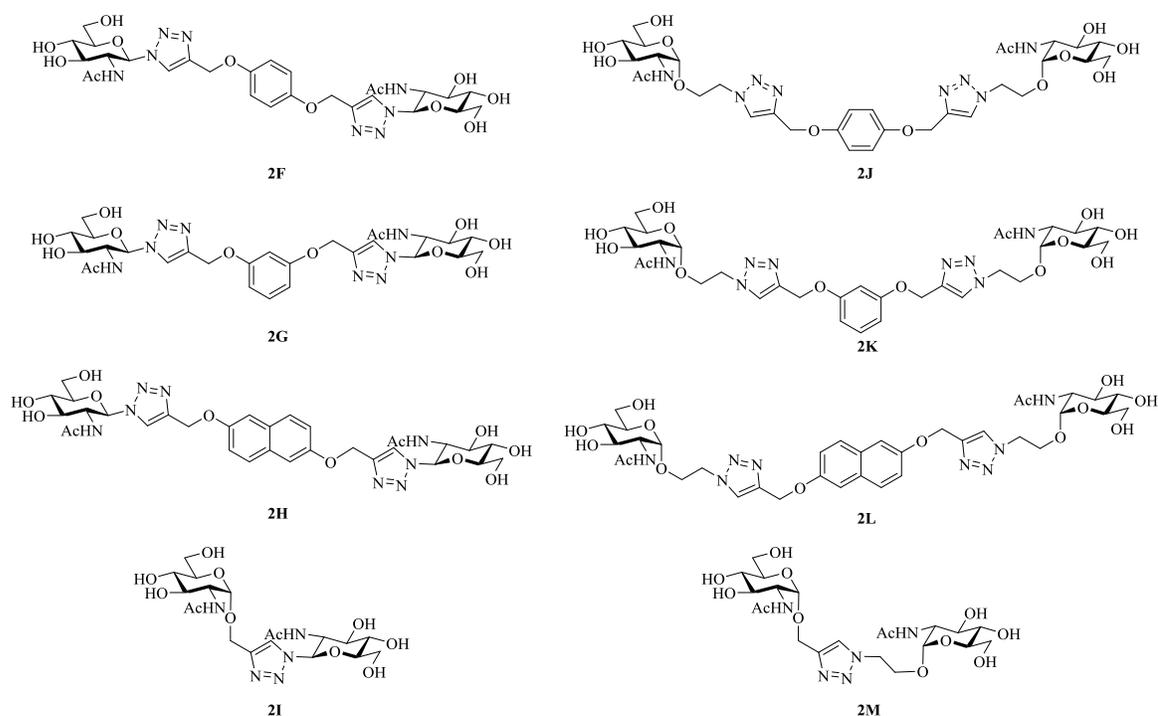


Fig. 2.14 Selection of bivalent compounds, based on different scaffolds, tested from the Murphy group for bactericidal activity against *Helicobacter Pylori*.

It was speculated that there could be a correlation between the anti-bactericidal activity of the anti *Helicobacter pylori* hexasaccharide and its mimetics, Fig. 2.13, and the distance between the GlcNAc residues. In the compounds tested this distance was most closely matched by derivatives **2J** and **2K**, i.e. those found to have activity. To investigate this, molecular modelling was used to generate a model of the anti *Helicobacter pylori* hexasaccharide, which was then overlapped with models generated for compounds **2J** and **2K**. It was shown in these models - of the bivalent compounds found to have activity against *Helicobacter pylori*, that the distances between the anomeric centres of the GlcNAc residues is ~ 20 Å. This, in principle, suggests that the core scaffolds, in these active compounds, can mimic the core tetrasaccharide unit in the native anti *Helicobacter pylori* hexasaccharide.

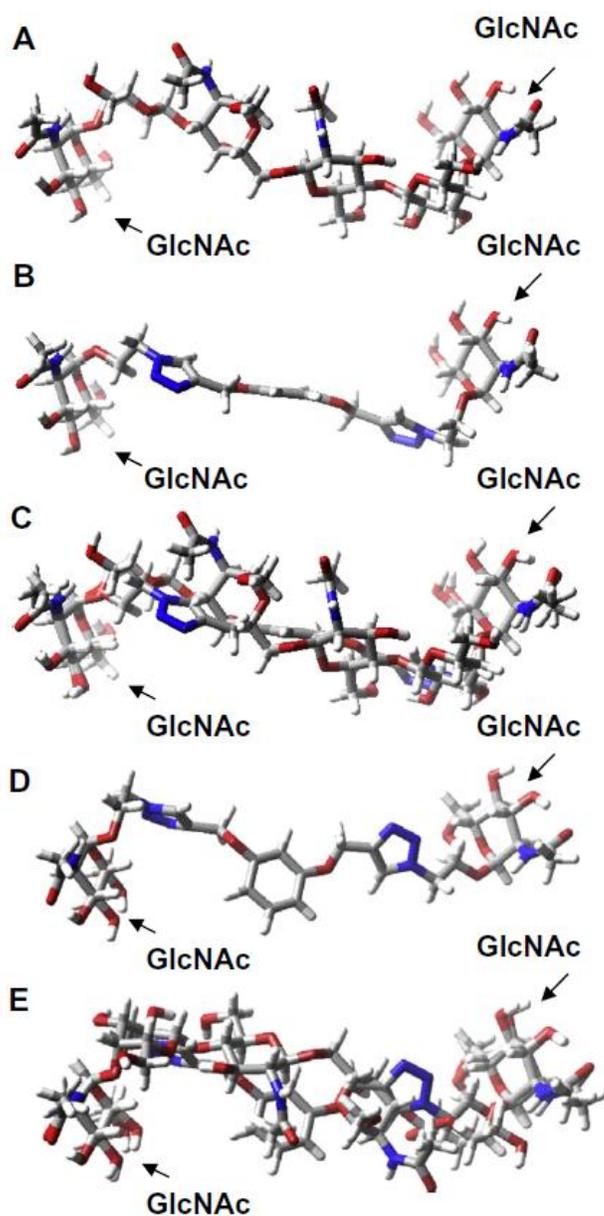


Fig. 2.15 Models of: (A) anti *Helicobacter pylori* hexasaccharide; (B) compound **2J**; (C) overlapped hexasaccharide and compound **2J**; (D) compound **2K**; (E) overlapped hexasaccharide and compound **2K**. Reprinted from Carbohydrate Research **2012**, 360, 1-7. © (2012) with permission from Elsevier.

If studies were done to provide information on the bioactive conformation of the anti *Helicobacter pylori* hexasaccharide it could potentially lead to more accurate and specific glycomimetic design, which, in theory, could give rise to more easily accessible antibiotics to be used in the treatment of *Helicobacter pylori*. As it is these investigations have yet to be studied, so design and synthesis has to be carried out on a trial and error basis, using positive results as a template for further design and studies.

To that end we use the positive results from this Yan et al. paper²³ to establish a front to continue our investigations. Herein we discuss the progress in the synthesis of analogues of these active compounds as well as further developments with the synthesis of tri- and tetra-valent derivatives based on α - and β -GlcNAc derivatives.

2.3 Results and discussion

2.3.1 Objectives of this work: To prepare analogues of bactericidal compounds for biological evaluation.

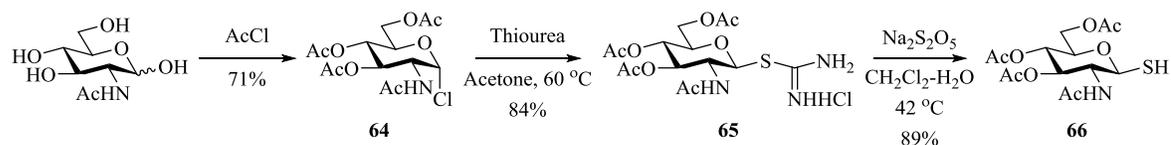
The compounds tested and found to be active to this point, against two different strains of *Helicobacter pylori*, were of the *O*-glycoside form, in addition to this both derivatives had an α -configuration. It was thus decided to prepare analogues of an *S*-glycoside form. It was an objective to prepare such compounds to evaluate their bactericidal activity against *Helicobacter pylori*. A reason for the change in the glycoside type would be to evaluate the effect of a slight change in the orientation of the headgroup and possibly distance, as outlined in section 1.2.5.2, that would result from using sulfur in the glycomimetics, due to atom size and electronegativity differences (between S and O), when compared with the corresponding, *O*-glycosides. These thioglycoside based compounds should also lead to an increased stability due to being less susceptible to chemical degradation and enzymatic cleavage as discussed in section 1.2.5.2.

Synthesis of both α and β configuration were once again considered as part of the investigations into these thioglycoside based glycoclusters. This was to evaluate whether once again only the α -derivatives proved to be active against the various strains of *Helicobacter pylori*.

The other parameter to be varied was that of the multivalency of the *S*-GlcNAc derivatives. All the compounds tested, to date, as part of the initial research by Yan et al²³, were bivalent compounds. As such, to extend the scope of compounds available for testing, linkers capable of forming tri-valent and tetra-valent compounds were synthesized to probe whether this would lead to improved biological activity through enhancement of the type of binding or allowing access to another type of multivalent bonding, as discussed in section 2.1.3.

2.3.1.1 The synthesis of α - and β -GlcNAc thiols

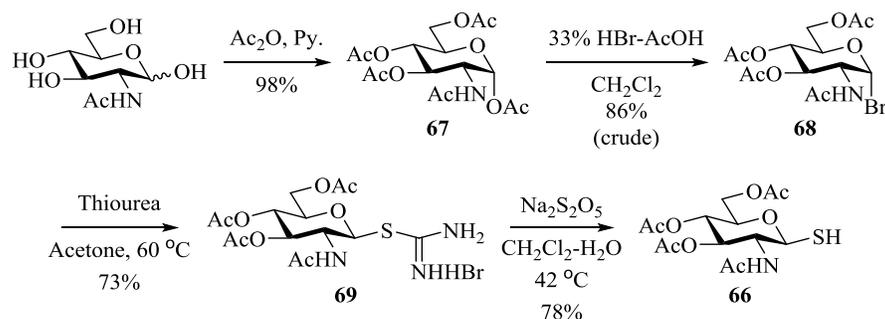
The synthesis of the β -GlcNAc thiol was achieved through two different glycosyl halide precursors. The first procedure involved synthesizing and isolating the GlcNAc chloride **64** starting from commercially available 2-acetamido-2-deoxy-D-glucopyranose, according to the procedure reported by Horton in *Organic Synthesis*²⁴. This halide was then reacted to give the thiourea intermediate **65** which in turn was converted to the desired β -thiol **66**.



Scheme 2.5 Synthesis of β -GlcNAc thiol via a glycosyl chloride.

It is essential that in order for this procedure to be successful that the conditions reported by Horton, for the chloride synthesis, are followed precisely, even in how the work up is carried out. Even with strict adherence to these conditions reproducibility of this reaction proved difficult with often a mixture of the desired chloride and the per-acetylated GlcNAc derivative being obtained. Due to this, occasional, problematic synthesis another method to give the β -thiol was also investigated, using the glycosyl bromide **68**.

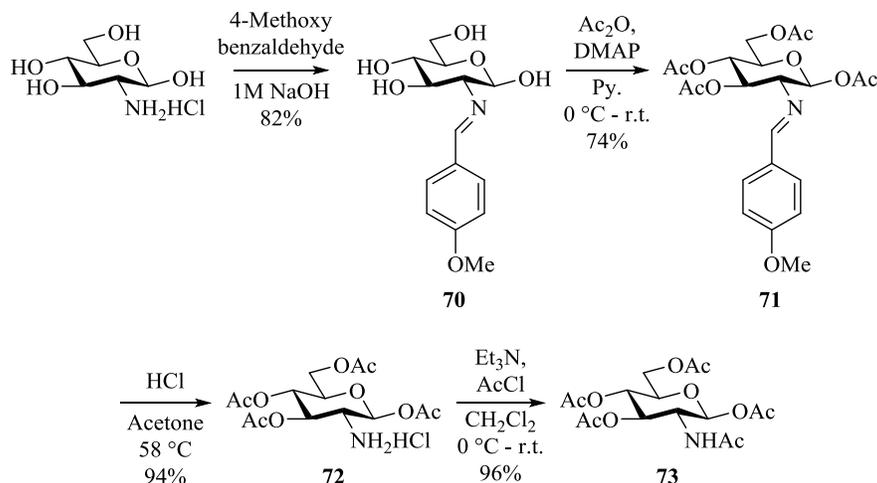
The procedures, as described in the literature, were followed. The first step, again, involved taking commercially available 2-acetamido-2-deoxy-D-glucopyranose which was fully acetylated by reacting it, in pyridine, with acetic anhydride. Treatment of this peracetylated glycoside **67** with 33% hydrogen bromide in acetic acid gave the glycosyl bromide **68**. There then followed a two-step reaction sequence involving the S_N2 substitution of the glycosyl halide, in acetone, with thiourea to give the intermediate **69** which then underwent hydrolysis and gave the desired β -glycosyl thiols **66** in good yields.



Scheme 2.6 Synthesis of β -GlcNAc thiol via a glycosyl bromide.

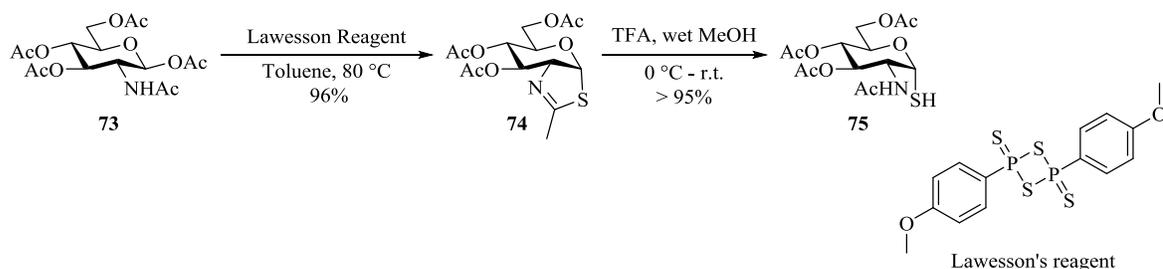
There were also issues with this route, which include the necessity to use the freshly prepared bromide derivative without delay, post work up. The reasons for this are the longer the bromide is allowed sit on the bench the further it degrades. It can be concluded that both routes, through either the glycosyl chloride or the glycosyl bromide, are usable, with each route having a drawback. Nevertheless each enabled the generation of the desired β -GlcNAc thiol in good yields.

The synthesis of the α -GlcNAc thiol followed a different synthetic path. It was first necessary to synthesize the β -GlcNAc acetate **73** as this allows for the later synthesis of the thiol of the desired stereochemistry. The synthesis of this derivative began with glucosamine hydrochloride, with the amine of the sugar being protected using 4-methoxybenzaldehyde, via stirring in a 1M NaOH solution. Compound **70**, was then acetylated, under standard conditions, using acetic anhydride, to give the acetate **71**. The amine protecting group was then removed using acidic conditions to give the free amine **72** which was then acetylated to give the acetamide **73** using acetyl chloride. All the reactions proceeded in good to excellent yields.



Scheme 2.7 Synthesis of β -OAc GlcNAc.

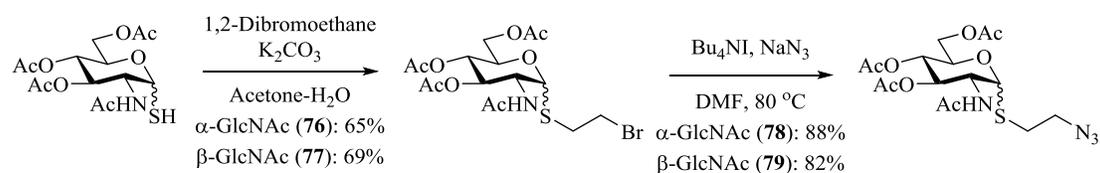
This protected sugar, where the anomeric acetate has a β -configuration, **73**, was then used in conditions as reported by Knapp et al.²⁵ This procedure involves reacting the sugar with Lawesson's reagent while heating to give the thiazoline **74**. This product then, under acidic conditions, underwent hydrolysis at the iminium carbon to give the α -GlcNAc thiol **75**, in a greater than 95% yield.



Scheme 2.8 Synthesis of α -GlcNAc thiol.

2.3.1.2 Synthesis of *S*-glycosides

Both thiols, **66** and **75**, were then used to give the desired thioglycosides. This involved reacting the thiols with 1,2-dibromoethane in an acetone-water mixture in the presence of potassium carbonate. These reactions proceeded in good yield to give the bromides of each derivative, **76** and **77**. Next each bromide was displaced through a reaction utilizing tetrabutylammonium iodide and sodium azide with when heated in DMF. This gave azido-sugars **78** and **79**, again, in good yields.



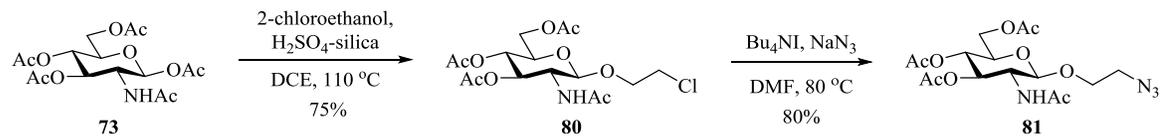
Scheme 2.9 Synthesis of both α - and β -GlcNAc thioglycosides.

The azido derivatives were then used as intermediates in the generation of a variety of glycoclusters, for evaluation as prospective agents which have bactericidal potential against *Helicobacter pylori*. These were achieved as described below using click-chemistry. Initial synthetic targets were based on the compounds found to be active within the studies by Yan et al.²³

2.3.1.3 Synthesis of *O*-glycosides

As well as the thioglycosides synthesized, the β -analogues of those compounds found to be active within the studies by Yan et al.²³ were also synthesized - for direct comparison, to make certain that it is the α -configuration of these bivalent compounds that is needed. To be able to synthesis the β -analogues of these compounds it was first necessary to synthesis the *O*-glycoside needed for the CuAAC reaction.

Microwave irradiation of β -OAc GlcNAc **73**, in 1,2-dichloroethane, with 2-chloroethanol in the presence of acidic silica gave the *O*-glycoside **80**, in good yields. This was transformed into the azido sugar **81** by a reaction in DMF with tetrabutylammonium iodide and sodium azide, giving the intermediate of interest, **81**, in an 80% yield.



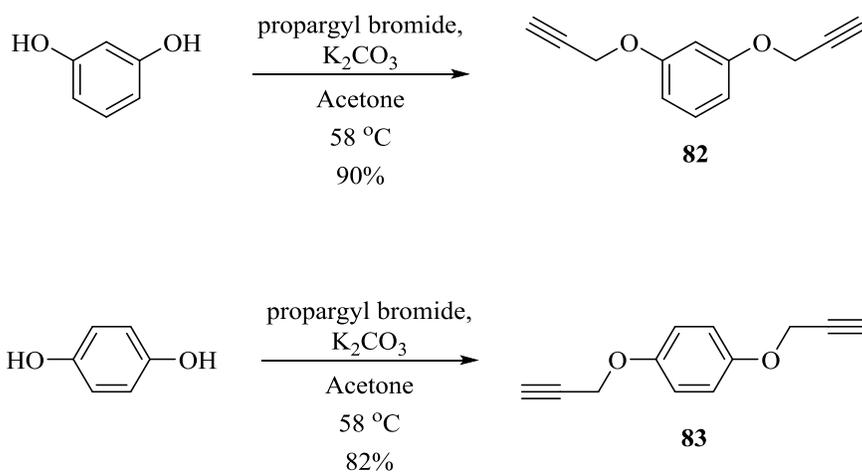
Scheme 2.10 Synthesis of β -GlcNAc *O*-glycoside.

2.3.1.4 Synthesis of bi-, tri- and tetra-alkynes

For the synthesis of the analogues, of the glycoclusters found to be active within the studies of Yan et al²³, it was necessary to synthesis the bi-valent linkers used as part of the click reaction towards these bi-valent glycoclusters.

Synthesis of bivalent linkers

These linkers were synthesised through reaction of benzene-1,4-diol (hydroquinone) or benzene-1,3-diol (resorcinol), with 80% propargyl bromide in toluene, in the presence of potassium carbonate with heating at reflux in acetone.

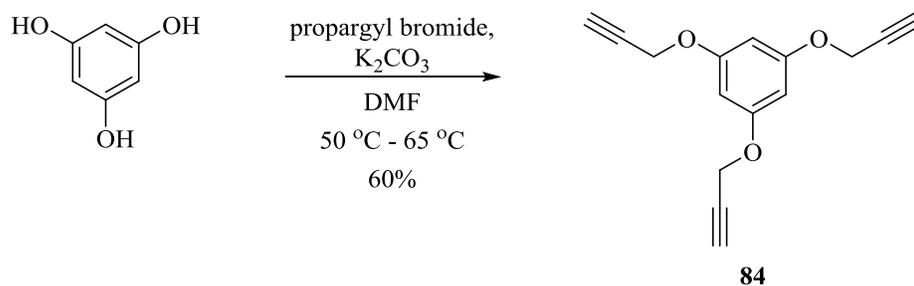


Scheme 2.11 Synthesis of bivalent linkers.

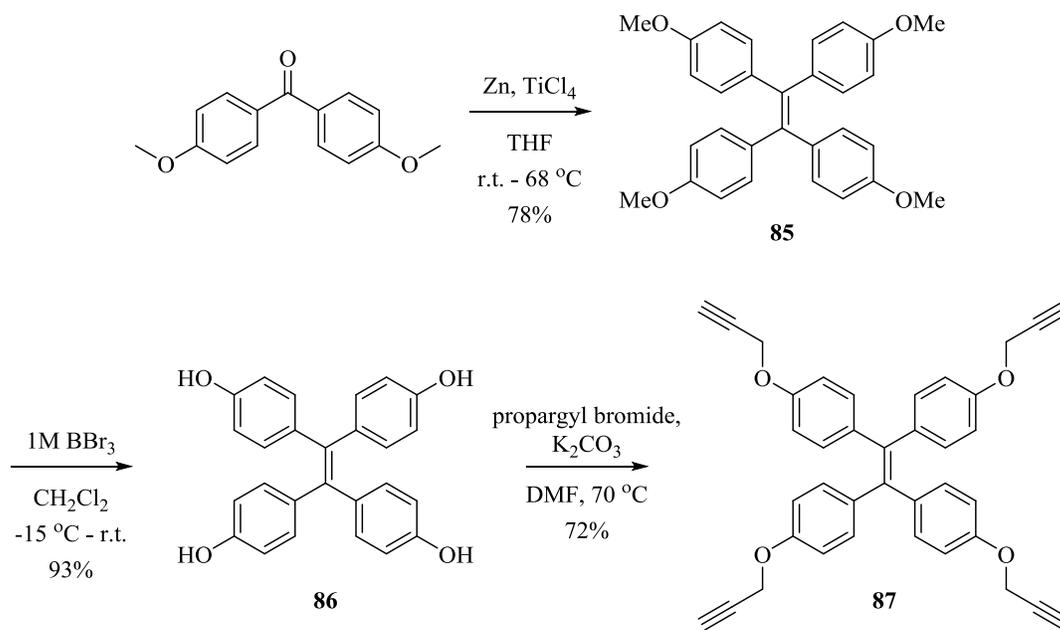
The linker/scaffold of the REs (recognition elements), which also can influence activity, must be attached to the binding elements in such a way that the receptor-ligand binding is not disrupted. The bivalent compounds synthesized herein are based on the same scaffolds as those in the bactericidal compounds **2J** and **2K**. The slight variation between scaffolds **82** and **83** allows for any deviation in the receptor-ligand binding of the different bivalent glycoclusters to be noted and, as such, the possible method of binding to be established.

Synthesis of trivalent linker

In previous work, only bivalent compounds were considered. Herein, the synthesis of trivalent compounds and a tetravalent derivative were carried out. This included the synthesis of a tri-valent linker based on benzene-1,3,5-triol (phloroglucinol) and a tetra-valent linker whose synthesis starts from 4,4'-dimethylbenzophenone. The trivalent linker synthesis was carried out under similar conditions to the two bivalent linkers already described. In the case of the synthesis of **84**, the reaction time and solvent were different.

**Scheme 2.12** Synthesis of trivalent linker.**Synthesis of tetravalent linker**

The synthesis of the fluorescent tetravalent linker first involved the McMurry reaction of 4,4'-dimethoxybenzophenone to give the tetra(4-anisyl)ethene, **85**. De-methylation of this using 1M boron tribromide in CH_2Cl_2 gave the free hydroxy compound, **86**. The reaction of this compound with propargyl bromide gave **87**.

**Scheme 2.13** Synthesis of tetravalent linker.

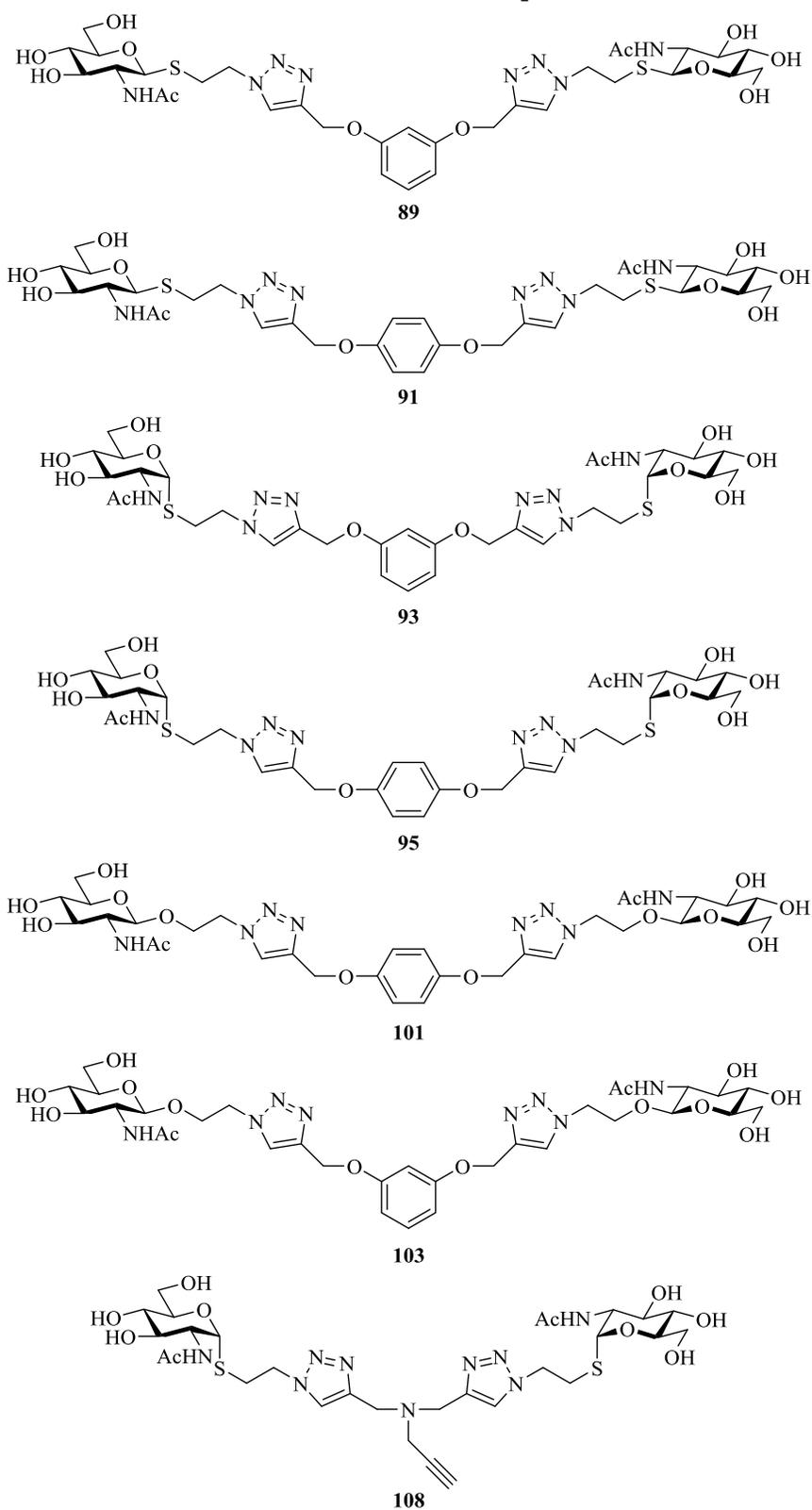
With these linkers in hand the click chemistry, as discussed in section 2.1.4.1, was then utilized to give a variety of compounds with the varying degrees of valency, bi-, tri- and tetra-valent.

2.3.2 New multivalent ligands for evaluation against *Helicobacter pylori*

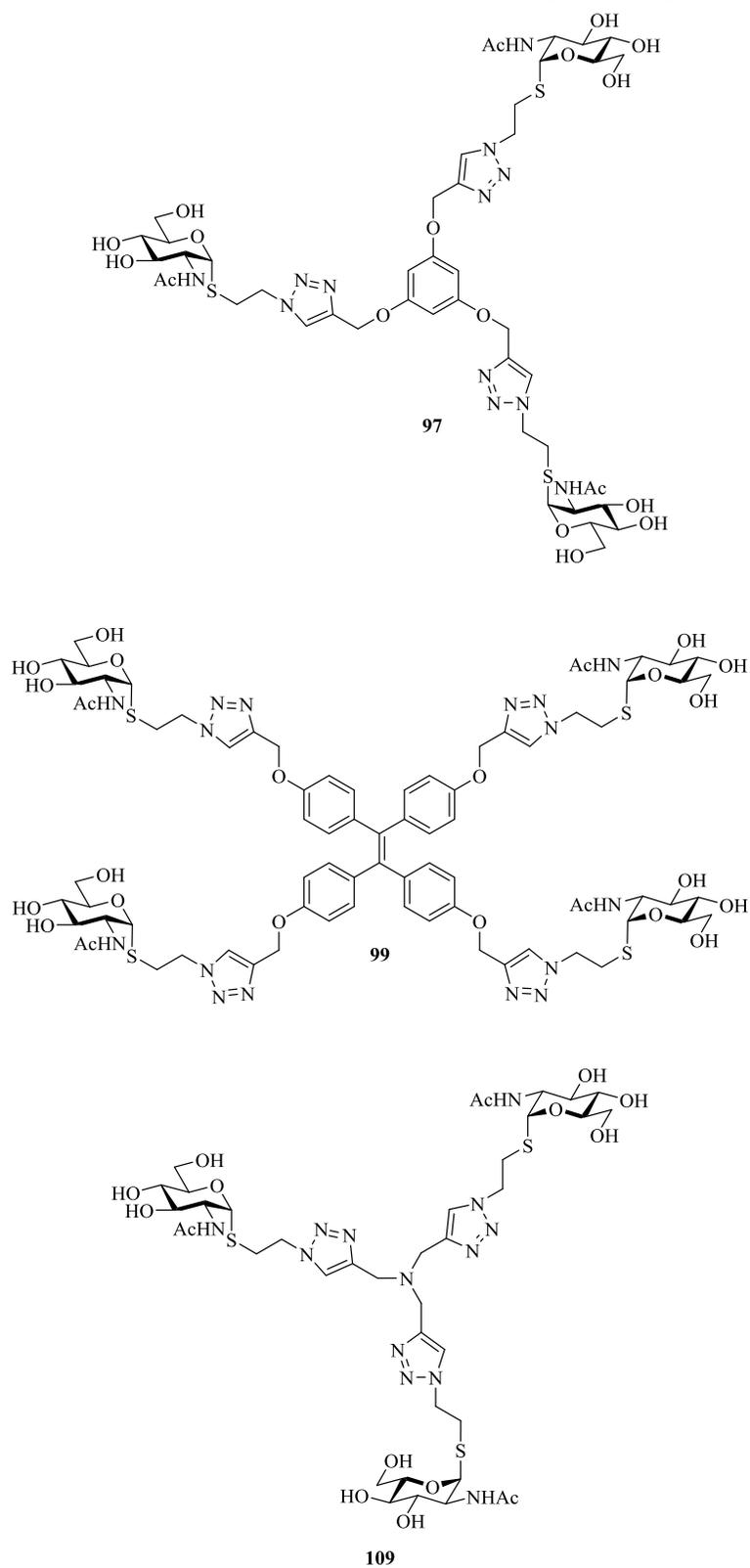
2.3.2.1 Summary of the conditions used for multivalent ligand synthesis

The CuAAC reaction, 1,4-click chemistry, was generally achieved by a reaction of the linker (as the limiting reagent) with a slight excess, per propargyl unit, of the sugar moiety in a 1:1 THF-H₂O mixture. The catalyst for the reaction was achieved by the reduction of Cu(II)SO₄·5H₂O by sodium ascorbate to the Cu(I) catalyst needed to facilitate the cycloaddition reaction. A typical procedure involved using 0.6 equivalents of Cu(II)SO₄·5H₂O and 0.65 equivalents, of sodium ascorbate. The reactions were carried out at room temperature for a period of 18 – 24 h. After purification by flash chromatography the various multivalent ligands were deprotected by Zemplén deacetylation conditions, this involved using, in most cases, a freshly prepared 1M sodium methoxide solution. Again, these reactions were carried out a room temperature but only for a period of 1 - 2.5 h. The purification of these various deprotected glycoclusters was achieved by reverse phase column chromatography, to give the desired multivalent ligands in good to excellent yields.

The glycoclusters prepared are shown in Fig. 2.16 and 2.17.

2.3.2.2 List of GlcNAc multivalent compounds**Fig. 2.16** List of bivalent GlcNAc multivalent compounds synthesised.

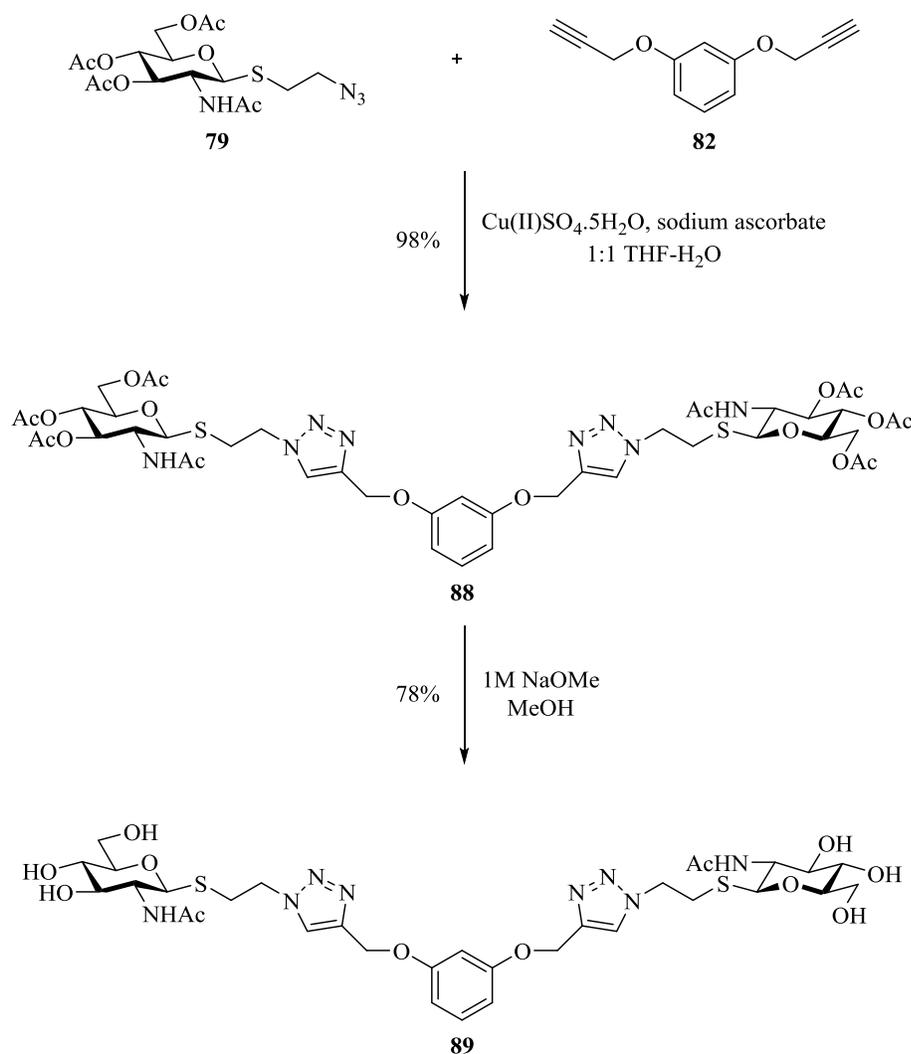
2.3.2.2 List of GlcNAc multivalent compounds (cont.)

**Fig. 2.17** List of tri- and tetra-valent GlcNAc multivalent compounds synthesized.

2.3.2.3 Synthesis of glycoclusters

Synthesis of 1,3-di[1-(ethyl 2-acetamido-2-deoxy-1-thio- β -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene

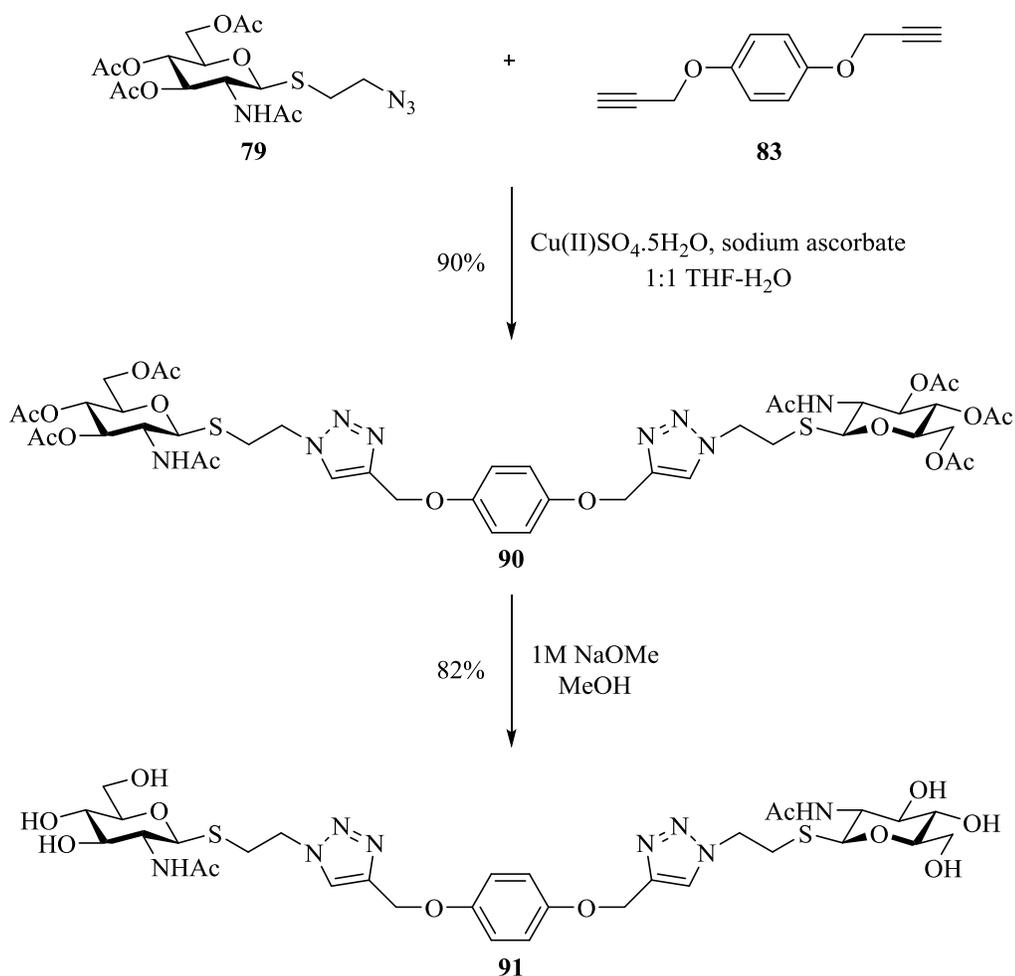
Meta-bispropargyloxybenzene **82** was reacted with the azide **79** by CuAAC, this involved using the *in situ* reduction of Cu(II)SO₄·5H₂O by sodium ascorbate in 1:1 THF-H₂O. The bispropargyl resorcinol was used as the limiting reagent. Column chromatography was used to separate the bivalent compound **88** from unreacted sugar **79**, and the product was isolated in high yields. The protecting groups were then removed by Zemplén deacetylation. This was achieved through the use of a catalytic amount of a freshly prepared 1M sodium methoxide solution, in methanol. Reverse phase column chromatography gave **89**, in a 78% yield.



Scheme 2.14 Synthesis of 1,3-di[1-(ethyl 2-acetamido-2-deoxy-1-thio- β -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene.

Synthesis of 1,4-di[1-(ethyl 2-acetamido-2-deoxy-1-thio- β -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene

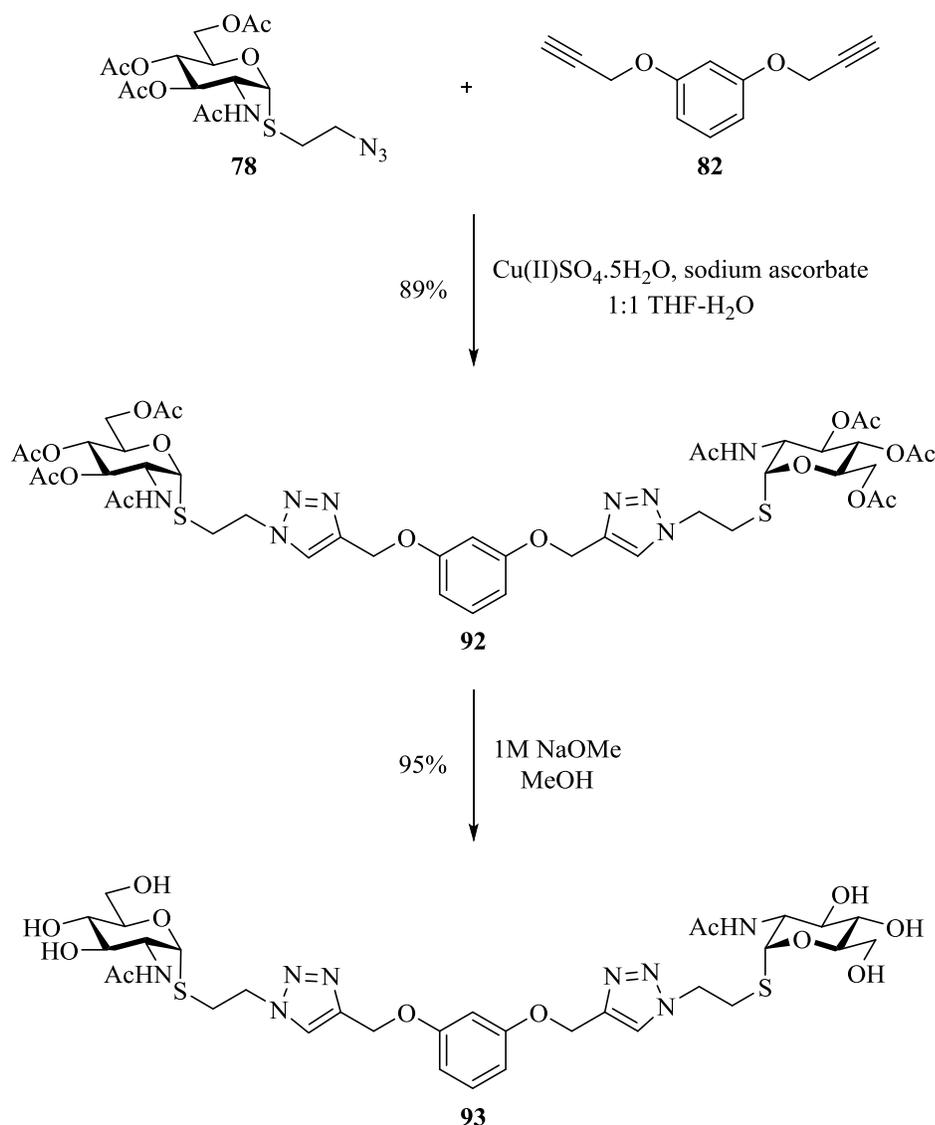
Para-bispropargyloxybenzene **83**, a structurally similar linker to that of the *m*-bispropargyloxybenzene **82**, used in the reaction of **88**, was coupled with the azide **79** through a similar procedure as that for **88** - by CuAAC, 1,4-click chemistry. This involved using the *in situ* reduction of Cu(II)SO₄·5H₂O by sodium ascorbate in 1:1 THF-H₂O. The bispropargyl hydroquinone linker was the limiting reagent. Again, column chromatography was used to separate the bivalent compound **90** from unreacted sugar **79**, and the product was isolated in high yields. The bivalent compound **90** was then deprotected by Zemplén deacetylation. This was achieved using a catalytic amount of a freshly prepared 1M sodium methoxide solution, in methanol. The compound was purified by reverse phase column chromatography to give **91**, in an 82% yield.



Scheme 2.15 Synthesis of 1,4-di[1-(ethyl 2-acetamido-2-deoxy-1-thio- β -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene.

Synthesis of 1,3-di[1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene

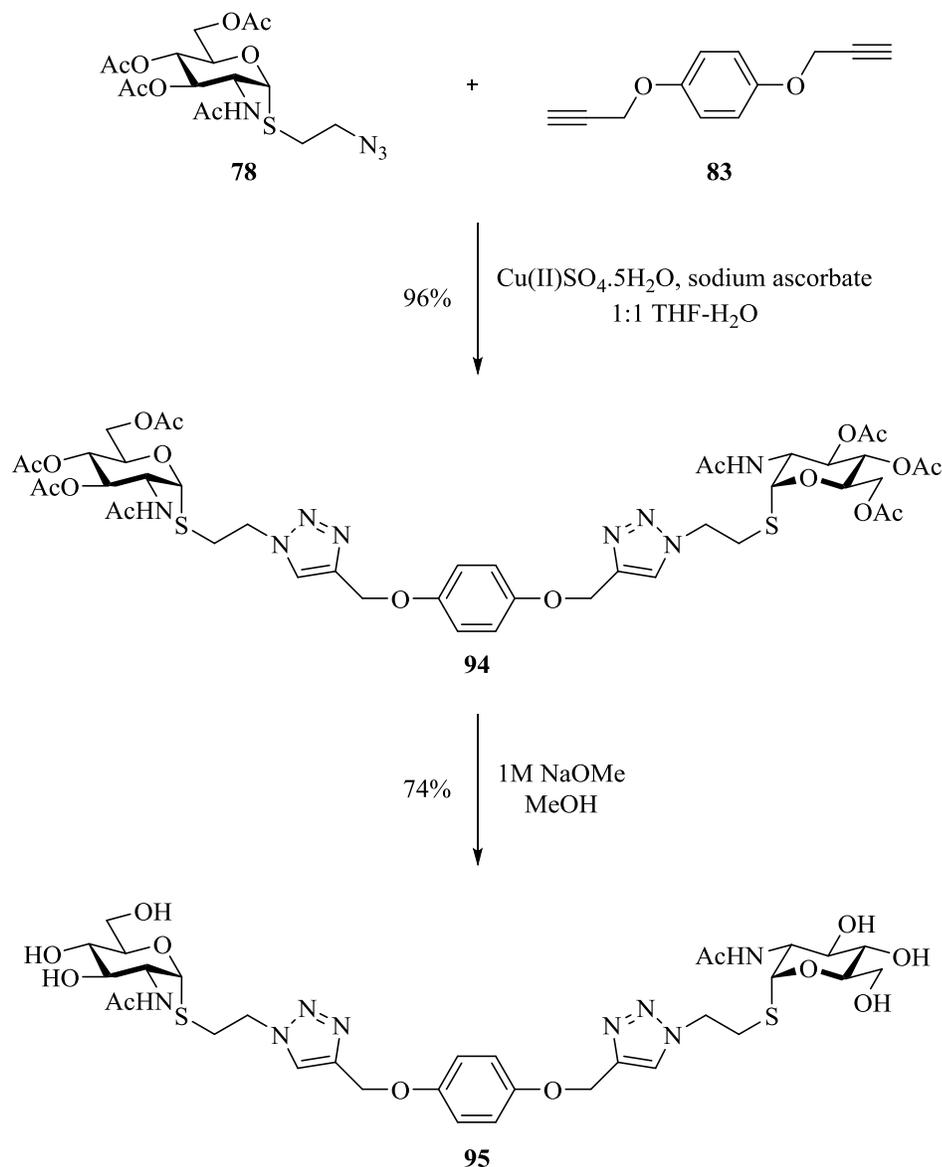
The synthesis of **93** followed a similar procedure to that used for the synthesis of **89**, using the azido sugar, of opposite anomeric configuration, **78**, to obtain the product. *Meta*-bispropargyloxybenzene, **82**, was reacted with the azide **78** by CuAAC, using Cu(II)SO₄·5H₂O which was reduced by sodium ascorbate in 1:1 THF-H₂O. Column chromatography was used to separate the bivalent compound **92** from unreacted sugar **78**, and gave the isolated product in high yields. The protecting groups were then removed by Zemplén deacetylation, followed by purification by reverse phase column chromatography, to give **93**, in a 95% yield.



Scheme 2.16 Synthesis of 1,3-di[1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene.

Synthesis of 1,4-di[1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene

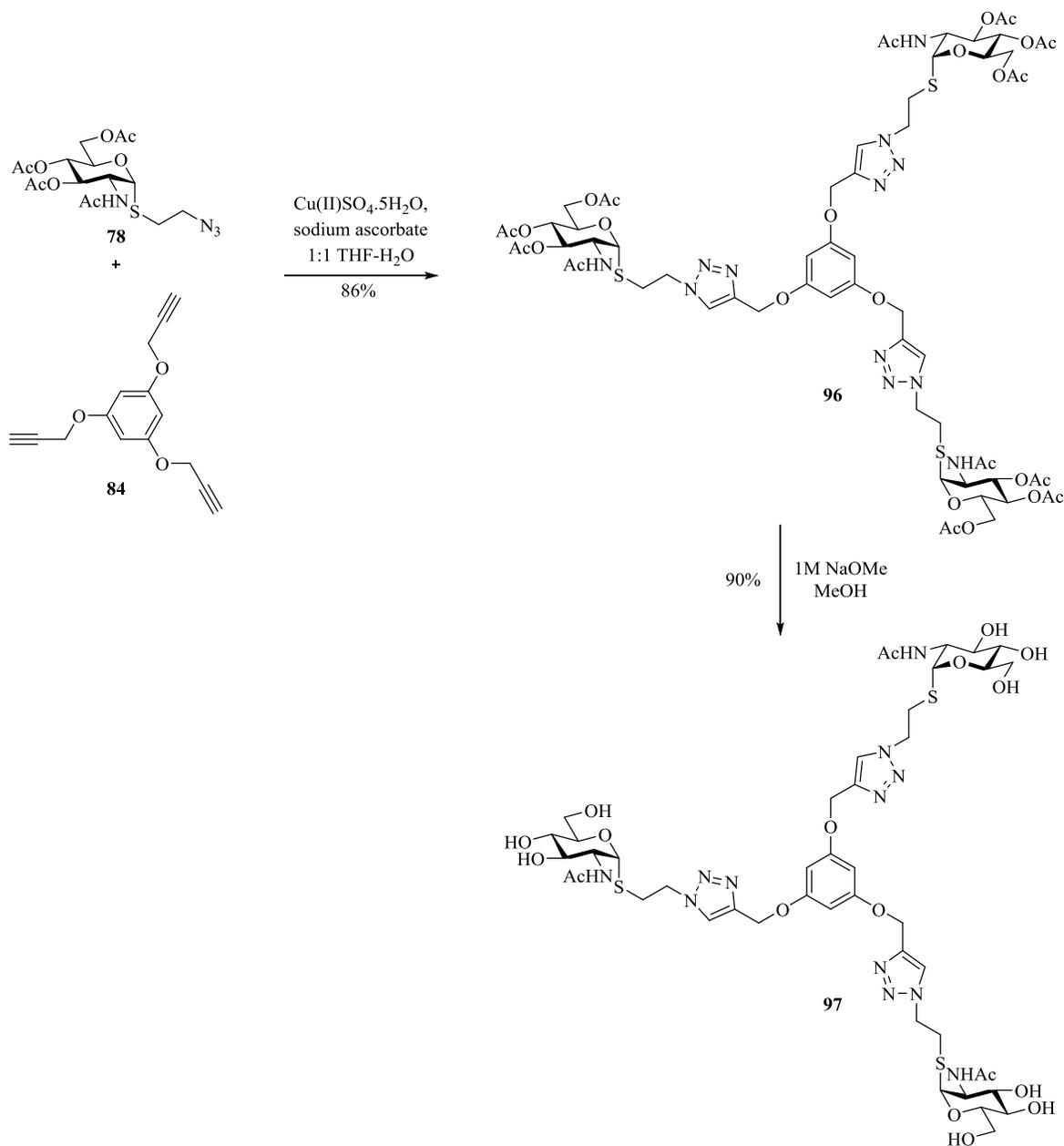
The synthesis of **94** was obtained by reacting the azide **78** with *p*-bispropargyloxybenzene, **83**, by CuAAC, using Cu(II)SO₄·5H₂O and sodium ascorbate, in 1:1 THF-H₂O. Column chromatography was used to separate the α -bivalent compound **94** from the unreacted sugar **78**, with the product isolated in high yields. The protecting groups were then removed by Zemplén deacetylation, using sodium methoxide. Purification by reverse phase column chromatography gave **95**, in a 95% yield.



Scheme 2.17 Synthesis of 1,4-di[1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene.

Synthesis of 1,3,5-tri[1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene

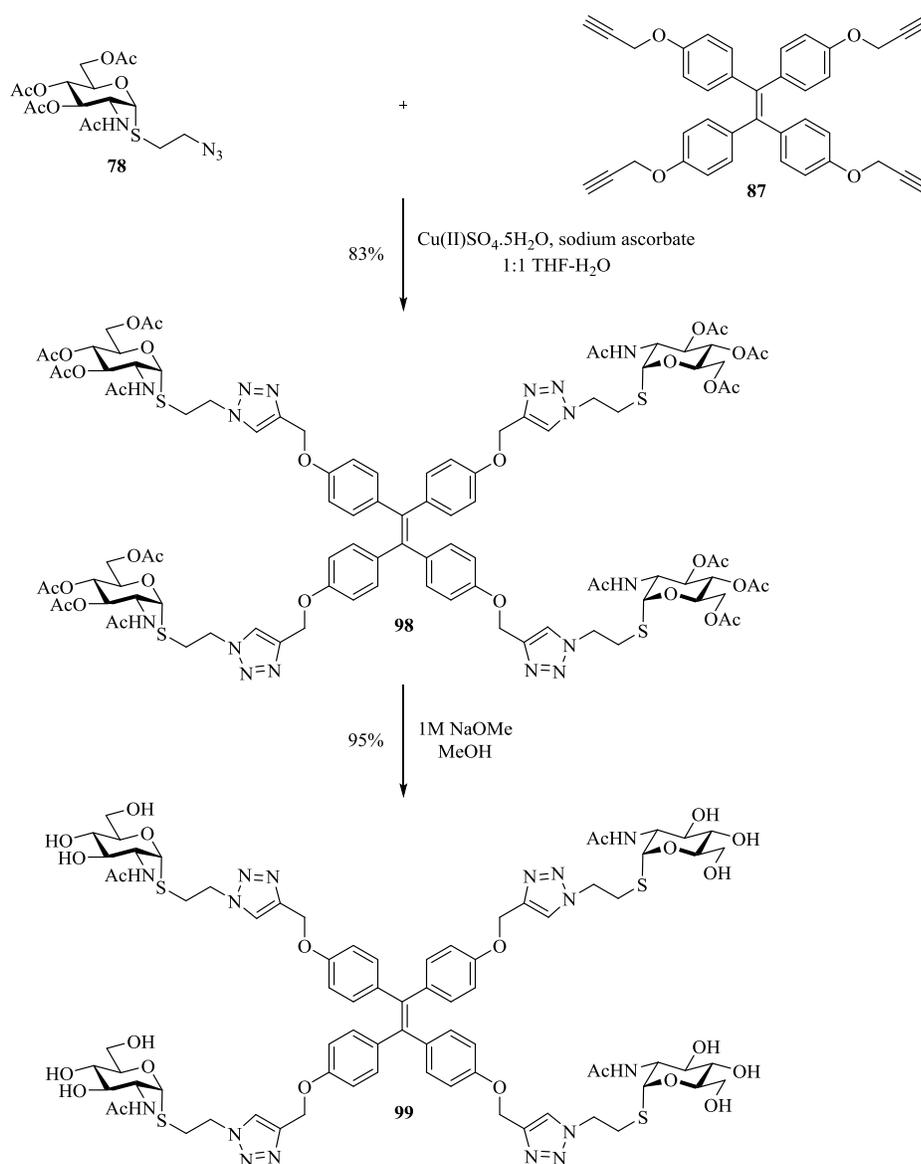
An increase in multivalency, was achieved by the reaction of the tripropargyl phloroglucinol compound **84**, with the azide **78** by the 1,4-copper catalysed click chemistry reaction. Column chromatography of **96**, gave the isolated product in high yields. The protecting groups were removed using sodium methoxide, in methanol, followed by purification of the trivalent compound **97**, by reverse phase column chromatography.



Scheme 2.18 Synthesis of 1,3,5-tri[1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene.

Synthesis of 1,1,2,2-tetrakis[4-(1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -*D*-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy)-phenyl]-ethene

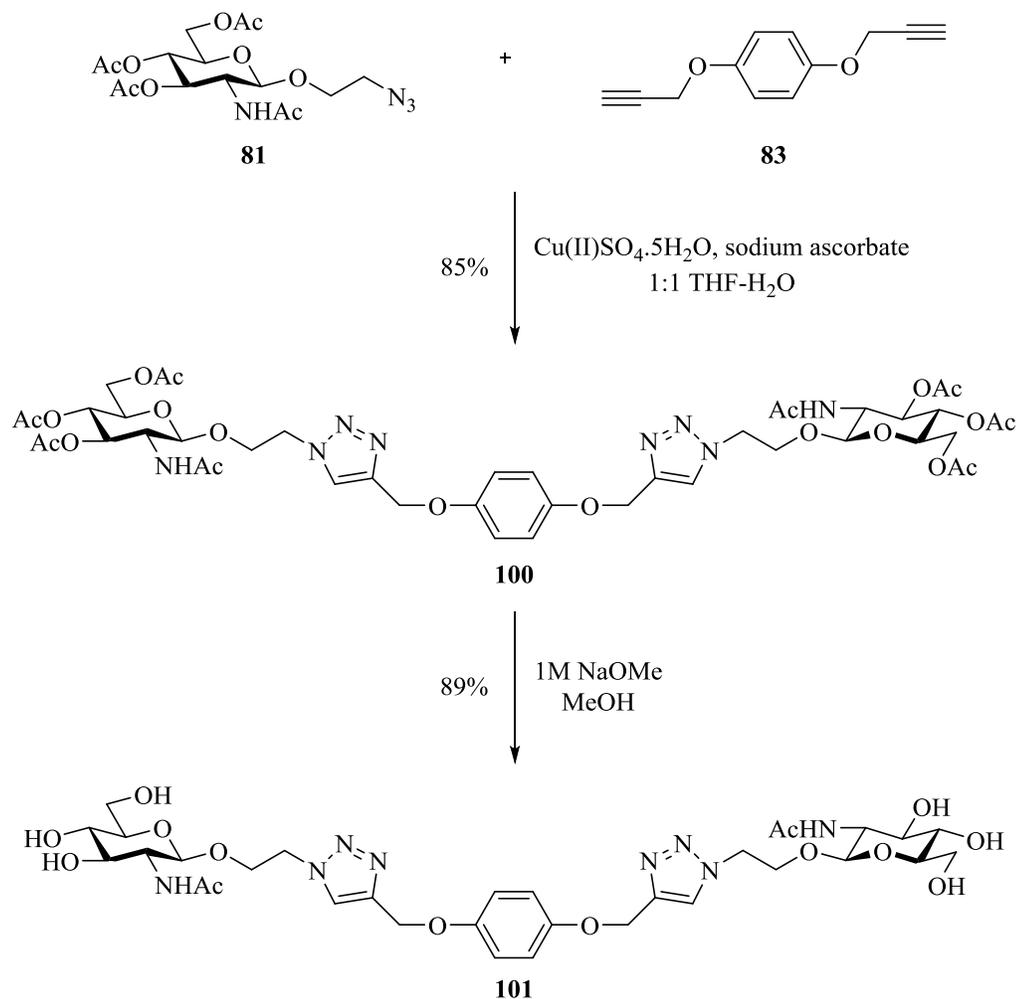
An additional increase of the multivalency was obtained by use of the fluorescent linker **87**. The procedure to obtain the tetravalent compound, **98**, followed the CuAAC described for previous multivalent compounds. The azide **78** was reacted with 1,1,2,2-tetrakis(4-prop-2-yn-1-yloxy benzene)-ethene, **87**, Cu(II)SO₄·5H₂O and sodium ascorbate, in 1:1 THF-H₂O. Column chromatography gave the tetravalent compound **98**, in, again, high yields. The protecting groups were then removed by Zemplén deacetylation, with purification of compound **99**, being achieved by reverse phase column chromatography, in excellent yields.



Scheme 2.19 Synthesis of 1,1,2,2-tetrakis[4-(1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -*D*-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy)-phenyl]-ethene.

Synthesis of 1,4-di[1-(ethyl 2-acetamido-2-deoxy- β -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene

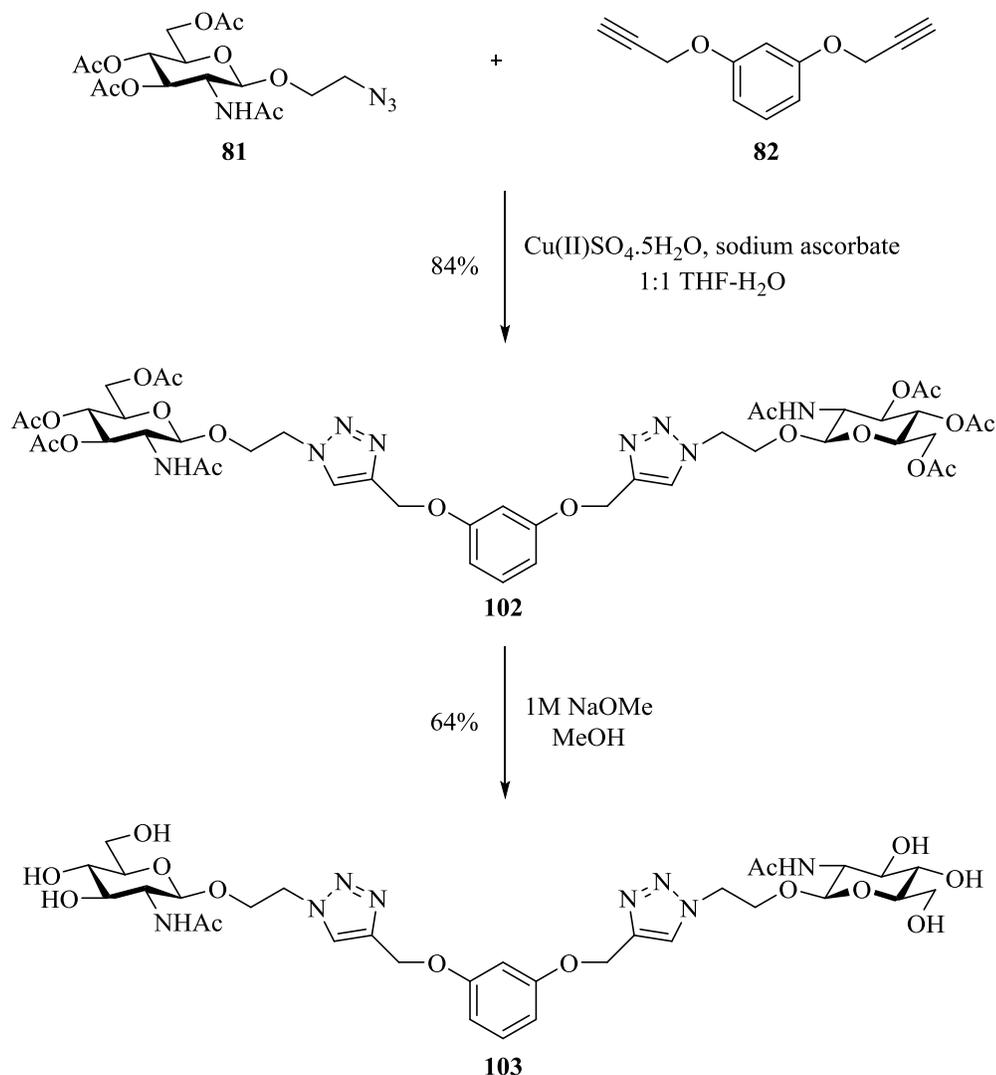
The β -*O*-analogues of the bactericidal compounds **2J** and **2K**, identified previously, were also synthesized as described above. The synthesis of bivalent **100** was obtained by the CuAAC reaction of *p*-bispropargyloxybenzene, **83**, and the azide, **81**. Column chromatography gave the isolated bivalent compound **100** in high yields. The protecting groups were removed using sodium methoxide in methanol. The product obtained was purified by reverse phase column chromatography to give **101**, in an 89% yield.



Scheme 2.20 Synthesis of 1,4-di[1-(ethyl 2-acetamido-2-deoxy- β -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene.

Synthesis of 1,3-di[1-(ethyl 2-acetamido-2-deoxy- β -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene

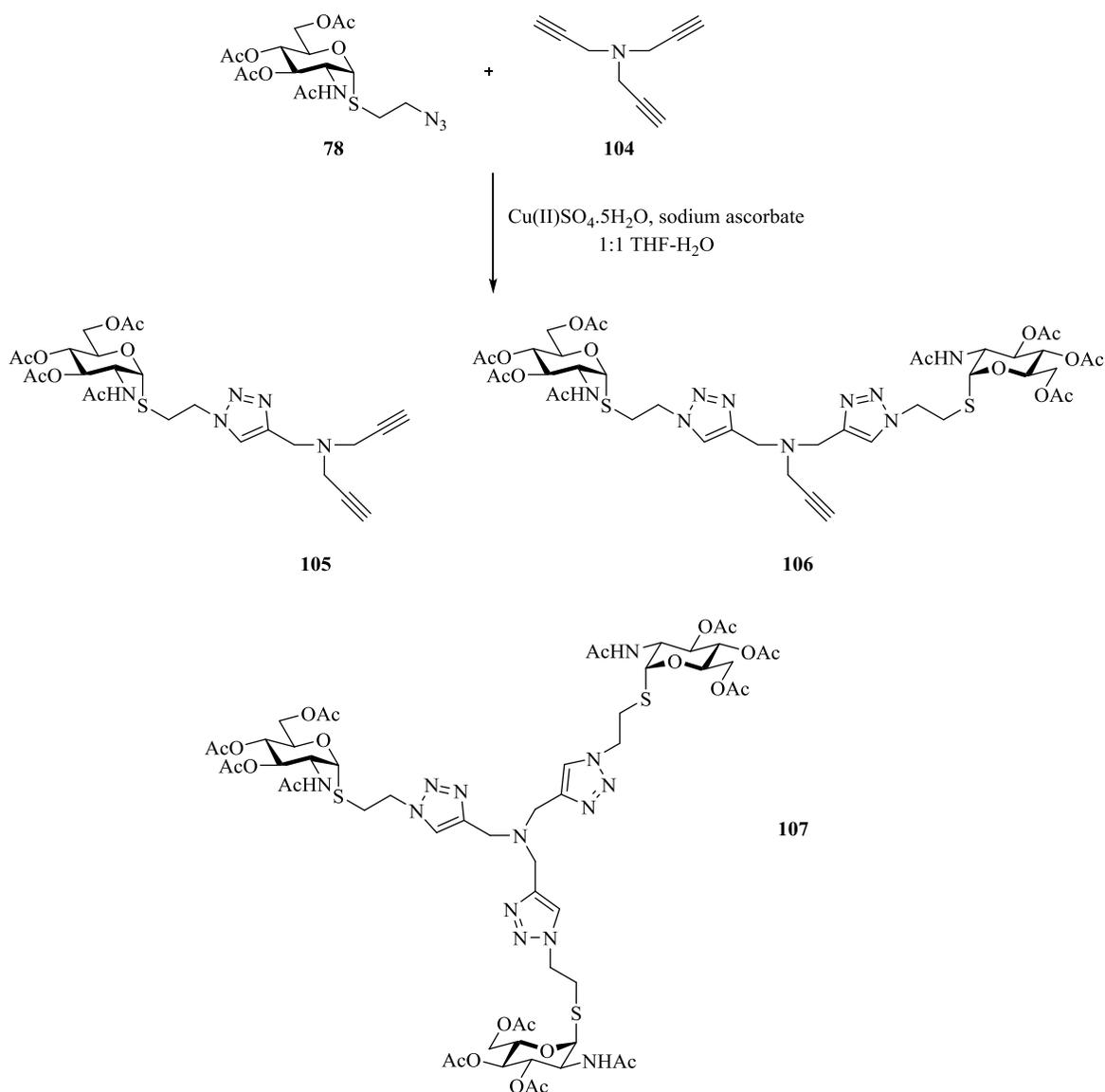
Meta-bispropargyloxybenzene **82**, was reacted with azide, **81**, using the *in situ* reduction of $\text{Cu(II)SO}_4 \cdot 5\text{H}_2\text{O}$ by sodium ascorbate in 1:1 THF- H_2O , to give the β -analogue of the bactericidal compound **2K**. Column chromatography gave the isolated bivalent compound **102**, in high yields. The protecting groups were then removed by Zemplén deacetylation, followed by purification of the obtained compound by reverse phase chromatography to give **103**, in a 64% yield.



Scheme 2.21 Synthesis of 1,3-di[1-(ethyl 2-acetamido-2-deoxy- β -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene.

Synthesis of mono/bis/tris[1-(1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-glucoopyranosyl)-1,2,3-triazol-4-ylmethyl)]-amine

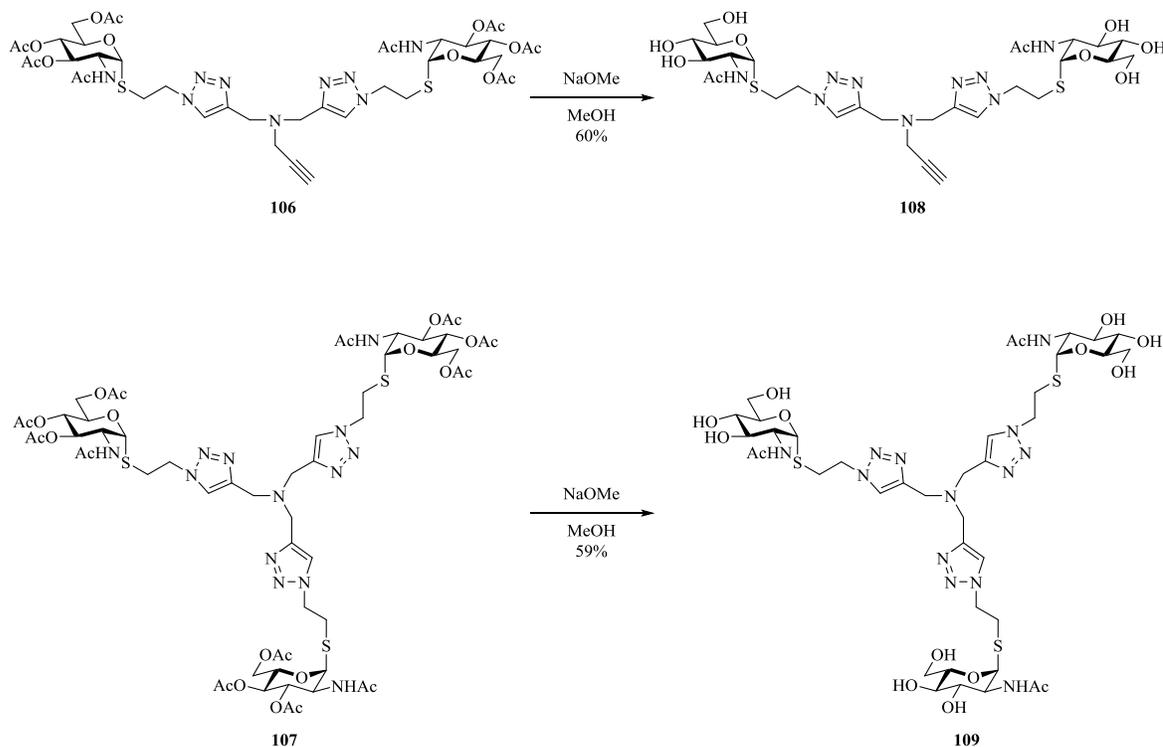
Commercially available tripropargyl amine, **104**, was used towards the attempted synthesis of *N,N,N*-tris[1-(1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-glucoopyranosyl)-1,2,3-triazol-4-ylmethyl)]-amine, **107**. The CuAAC reaction carried out, as described for the other glycoclusters, but led to a mixture of 1,4-clicked compounds - the mono-valent, **105**, the bi-valent, **106**, and the tri-valent, **107**. The reaction, to obtain these compounds, involved reacting azide, **78**, with tripropargylamine, **104**, by standard CuAAC conditions, in THF-H₂O, with Cu(II)SO₄·5H₂O and sodium ascorbate. Column chromatography of the crude mixture, gave the isolated compounds **105**, **106** and **107**.



Scheme 2.22 Synthesis of mono/bis/tris[1-(1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-glucoopyranosyl)-1,2,3-triazol-4-ylmethyl)]-amine.

Synthesis of *N,N*-bis/tris[1-(1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-glucoopyranosyl)-1,2,3-triazol-4-ylmethyl)]- *N*-prop-2-yn-1-amine

The protecting groups, of the bi- and tri-valent compounds, **106** and **107**, above, were removed by Zemplén deacetylation. Subsequent reverse phase column chromatography gave bivalent, **108**, in a 60% yield and the trivalent, **109**, in a 59% yield. Yields, in these particular instances, may be reduced, when compared to the yields obtained for the other multivalent ligands synthesized, as the sodium methoxide used was from an old stock solution.



Scheme 2.23 Synthesis of *N,N*-bis/tris[1-(1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-glucoopyranosyl)-1,2,3-triazol-4-ylmethyl)]- *N*-prop-2-yn-1-amine.

2.3.3 Biological evaluation

A series of GlcNAc based multivalent compounds have been sent to collaborating laboratories as part of the collaborative research group - the Alimentary Glycoscience Research Cluster (AGRC). These compounds have been provided for testing for the ability to inhibit *Helicobacter pylori* and/or suppress *Helicobacter pylori* growth. It was hoped, as the multivalent compounds synthesized herein bear structural similarities to those bactericidal compounds **2J** and **2K**, identified previously, that further progress in this area of research, as part of the AGRC, could have been made. However, recent communications state they have not shown bactericidal activity at 1 mM concentration. As such, other applications are currently being investigated for these compounds.

One potential route is the evaluation of their prospective WGA binding (section 2.1.2). This line of investigation is currently being carried out by our collaborators at the Ludwig-Maximilians-University Munich - Han-Joachim Gabius and Sabine André.

Further progress could possibly be made in the area of *Helicobacter pylori* research by returning to the *O*-glycoside based glycomimetics that have been previously found to have anti-bacterial activity. The scope of this work could be extended by increasing the valency of the α -*O*-GlcNAc based structures to tri- and tetra-valent compounds based on the scaffolds synthesized herein or on other linkers that could mimic the tetra-saccharide core 2 structure, as outlined in section 2.2.3.

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Chapter 3: Synthesis of *N*-acetyl galactoamine glycoclusters

3.1 Background to *N*-acetyl galactoamine

3.1.1 Introduction

N-Acetyl-D-galactosamine (GalNAc) is a monosaccharide derivative of galactose differing in the substituent at the C-2 position. The hydroxyl group (OH) of the galactose residue is replaced with an acetamido group (NHAc) in the GalNAc species. In addition to the structural similarities with galactose, GalNAc differs from the GlcNAc monosaccharide discussed in section 2.1.1 in the stereochemistry at C-4, with the hydroxyl group, at this position, axial (up) in GalNAc but is equatorial (down) for GlcNAc, in the commonly found 4C_1 conformation. However the isolation and purification of GalNAc and galactosamine (GalNH₂) from natural sources is difficult, when compared to that of GlcNAc, which can be readily obtained by the hydrolysis of chitin (the second most abundant natural biopolymer in the world¹). Thereby both GalNAc and GalNH₂ are both more expensive than their counterparts – GlcNAc and GlcNH₂.

The GalNAc monosaccharide is one of the main constituents of glycosaminoglycans (GAGs). These GAGs are a group of polysaccharides made of recurring disaccharide units of D-glucuronic acid or L-iduronic acid and GalNAc or GlcNAc residues, linked by a β -1-4 or β -1-3 linkage. These GAGs are primarily found in animal tissues with many of the polysaccharides attached to a single protein chain to give a proteoglycan². An example of a GAG, and the only one that is exclusively non-sulfated, is hyaluronic acid (also called hyaluronan or HA). HA consists of the repeating disaccharide unit [\rightarrow 4)- β -D-glucuronic acid-(1 \rightarrow 3)-GlcNAc-(1 \rightarrow)]. It acts as a lubricating agent in synovial fluid, the fluid in between the most common and movable type of joint in a mammal, a synovial joint (e.g. hinge joint and ball and socket joint). Its principle role is in reducing friction between the cartilage on the bones of these joints. As well as providing this protection between joints, it was also found that cancer of the prostate stimulated HA synthesis, both in tumor stroma (stromal cells are the connective, functionally supportive framework of tissue cells of any organ) and in the surrounding normal, nonmalignant prostate, tissue. Multiple mechanisms are proposed by Josefsson et al.³ as to why HA is increased in prostate tumors and their surroundings, such as, HA is known to increase the recruitment of cancer-associated fibroblasts and macrophages, which stimulate prostate cancer growth. Along with this, they also proposed the mechanism that prostate cancers are hypoxic; hypoxia makes tumors more aggressive, with the unfortunate additional factor that hypoxia stimulates HA synthesis, owing to a very unfavorable cyclical problem. These complimentary mechanisms of action promote tumor growth and increase HA in the surrounding normal prostate and the magnitude of this is associated with tumor aggressiveness and an unfavorable outcome³.

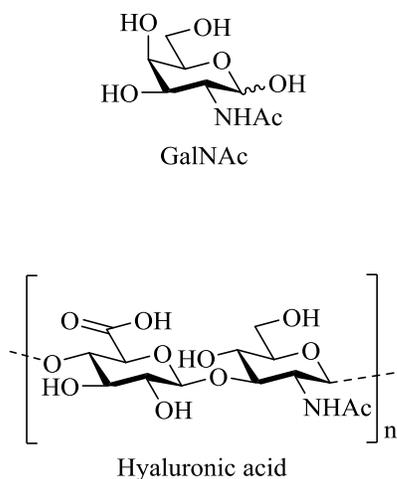


Fig. 3.1 The structure of GalNAc and Hyaluronic acid.

Hyaluronic acid is unique, in terms of the GAGs, in that it is nonsulfated. The other GAGs, those which comprise GalNAc residues, do fit the stereotypical structure of a GAG, i.e. are sulfated derivatives. The two GAGs where a GalNAc moiety can be found are - chondroitin sulfate (CS) and dermatan sulfate (DS).

Chondroitin is made of the recurring disaccharide [\rightarrow 4)- β -D-glucuronic acid-(1 \rightarrow 3)-GalNAc-(1 \rightarrow), so is structurally related to HA but with the GlcNAc moiety of HA replaced with a GalNAc residue in chondroitin. In addition to this saccharide difference chondroitin is also sulfated while HA is not. These sulfate groups are bonded to the C-4 or C-6 positions of the GalNAc residue in chondroitin. CS is an important constituent of the cartilage of various tissue such as that of the aorta, skin, cornea of the eye, and lung tissue, where it can be found between fibrous protein molecules, providing a supple quality to these tissues. CS is also reported by Baeurle et al.⁴ as being a key component of articular cartilage, which is the hydrated soft tissue in synovial joints, the principal purpose of which is to offer low friction and wear and thereby if it deteriorates or becomes damaged it can affect the mobility and flexibility of our joints in a significant way. It has been reported that CS has the potential to inhibit the structural progression of osteoarthritis, in tandem with glucosamine sulfate, in patients suffering from osteoarthritis of the knees and hands⁵. In addition to this it was found that CS and glucosamine, could be effective in reducing pain in patients with moderate-to-severe knee pain due to osteoarthritis⁶.

The epimer of chondroitin-4-sulfate, dermatan sulfate, differs through the orientation of the substituent at C-5 of the non-GalNAc residue. Dermatan sulfate consists of the repeating disaccharide [\rightarrow 4)- β -L-iduronic-(1 \rightarrow 3)-GalNAc-(1 \rightarrow] where the C-4 substituent, of the GalNAc residue, is sulfated. The DS polymer is found mostly in the skin and is also the predominant glycan found there, but is also expressed in many other mammalian tissues. Trowbridge et al.⁷ postulate with respect to heparan sulfate that DS should also be a chief

component in various cellular processes. This is illustrated in part with DS and DS proteoglycans reported to be likely to play a role in cardiovascular disease, tumorigenesis, infection, wound repair, and fibrosis.⁷

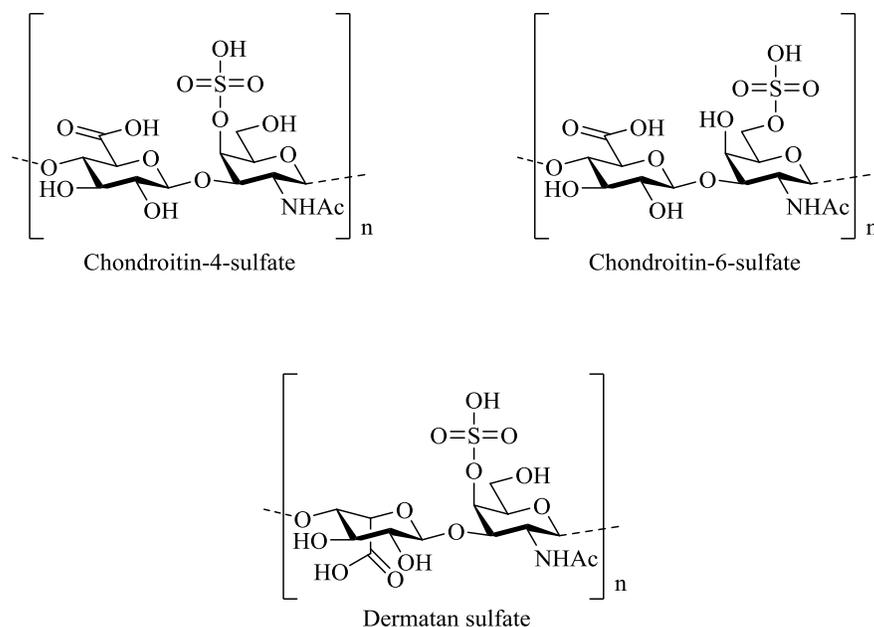


Fig. 3.2 The structure of polymers containing the GalNAc monosaccharide.

3.1.2 *N*-Acetyl galactosamine multivalent ligands

Asialoglycoprotein receptors are C-type lectins (see section 3.2.4.1) which bind asialoglycoprotein. These are glycoproteins from which a sialic acid, otherwise present, has been removed to expose galactose (Gal) or GalNAc residues. The receptors, which are located in large numbers on mammalian hepatocyte cell (liver cell) surfaces, remove target glycoproteins from circulation.

The liver is a very important organ for the regulation of the body and produces a multitude of biomolecules. It is also important due to the, afore mentioned presence of asialoglycoprotein receptors. These receptors are highly specific for galactose and *N*-acetylgalactosamine residues. The efficiency of these receptors, though, depends on the presence of at least three of these specific sugars - Gal or GalNAc residues, with the correct spatial composition. This necessity for multiple residues of a particular carbohydrate, to elucidate an action, make the synthesis of multivalent compounds an important an interesting one. The synthesis of multivalent ligands where the Gal residues are properly organized and laid out, to allow for correct and efficient binding, can produce bi- and tri-valent glycans which can exhibit affinity as high as ca. μM and nM (as K_D values).⁸ Within this study of asialoglycoprotein receptors Lee et al.⁸ reported on the synthesis of multivalent ligands containing terminal GalNAc or lactose (Lac). According to them it is a well established fact that asialoglycoprotein receptors, for all mammalian species, bind

GalNAc much better than Gal and Lac. For the Lac derivatives it can be speculated that this is due to size, as the spatial arrangement seems to be an important factor for binding. It was found, within this communication that, as expected, due to Lac residues being more weakly bound by asialoglycoprotein receptors than GalNAc residues, their trivalent Lac compound was in fact a much weaker ligand than the GalNAc counterpart, having an IC_{50} value higher than μM . They found that their trivalent GalNAc compound, **3A**, had the highest affinity of anything they had synthesized to that point. Interestingly, in addition to this, it was observed that the combining of two trivalent Lac molecules generated a hexavalent lactoside **3B** which possessed an IC_{50} in the nM range. This gives rise to an interesting increase in affinity, between the Lac derivatives, with increasing valency.

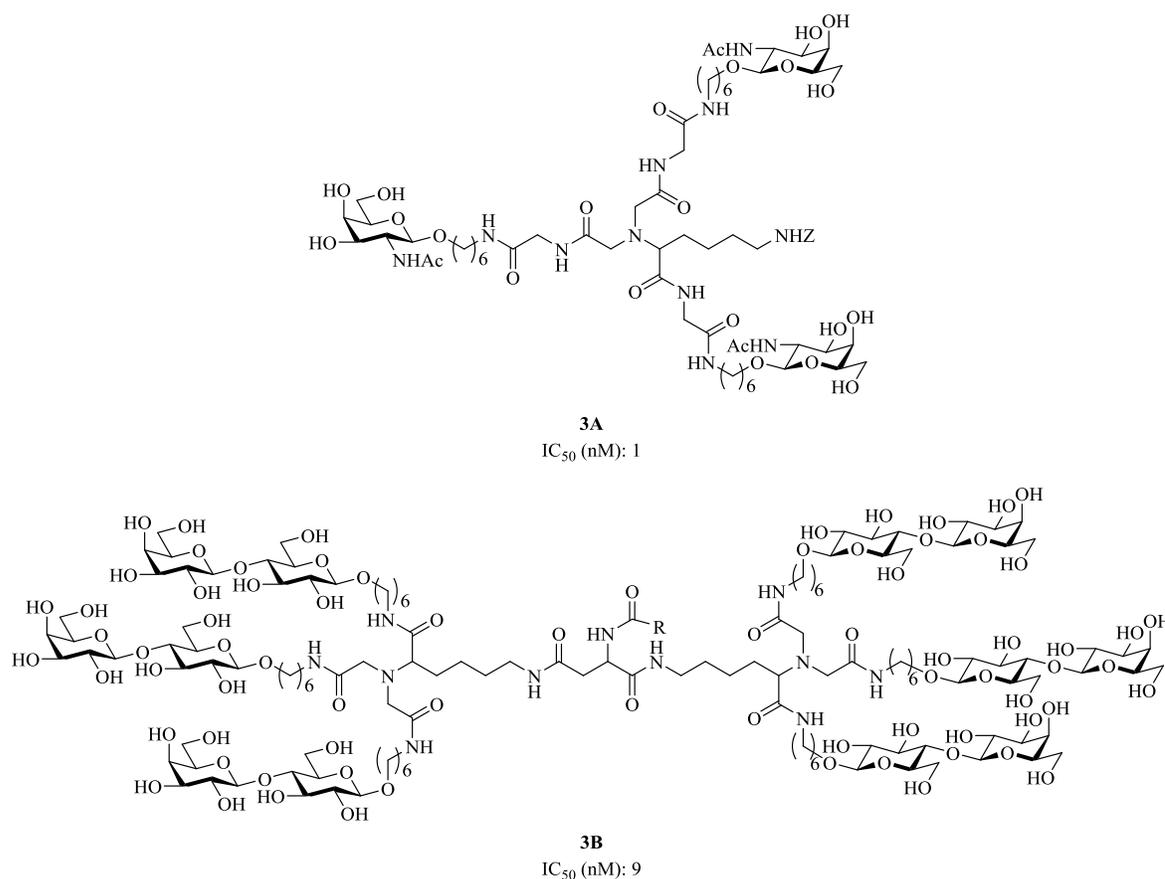


Fig. 3.3 Structures tested for their affinity to asialoglycoprotein receptors.

The attachment (adherence) of bacteria to host epithelial cell surfaces has been found to have an important role in the preliminary stages of pathogenesis (the mechanism that causes a disease/infection) of infection due to bacteria, in animals and humans. This attachment is brought about through the use of adhesions, which are constituents on microbial surfaces that allow for attachment/adherence of bacteria to mucosal surfaces, as mentioned in the mechanism of action for *Helicobacter pylori*, section 2.2.2. *Pseudomonas aeruginosa* – an opportunistic pathogen, utilizes adhesions, called fimbriae or pili, to

facilitate its attachment to host epithelial cells and once bound can instigate many infections and diseases.⁹ Research has suggested that the attachment of the pili of *P. aeruginosa* occurs with the disaccharide β -D-GalNAc-(1 \rightarrow 4)- β -D-Gal of the glycosphingolipid asialo-GM₁ [β -D-Gal-(1 \rightarrow 3)- β -D-GalNAc-(1 \rightarrow 4)- β -D-Gal-(1 \rightarrow 4)- β -D-Glc-OCer] receptor. To gain a better understanding, a study by Jiao et al.⁹ was carried out to investigate the interactions of these adhesions. With previous research having already been compiled on monovalent carbohydrates and their interactions with the pili, and the known multivalent character of *P. aeruginosa*, it was the view of Jiao et al. that the information from their study with “simple multivalent β -D-GalNAc-(1 \rightarrow 4)- β -D-Gal oligomers”, would provide, in tandem with what was known and had come before, information for the design of multivalent anti-adhesive therapeutics.

These studies give a brief insight into the importance of multivalency with respect to lectins and their potential application, through synthesis, in producing possible therapeutics.

3.2 Lectins

3.2.1 Background

Lectins (from the Latin *lectus* - chosen, picked, selected) are carbohydrate-binding proteins, distinct from both sugar-specific enzymes and antibodies, which exist in most living organisms. This term and the definition, for a lectin, was given by W.C. Boyd in 1954, during the authors work on blood group specific proteins. It was proposed as a way of distinguishing between actual antibodies and those proteins that combine specifically with certain antigens only but are not produced in response to an antigen.¹⁰

Originally it was believed that the initial description of a lectin, and thereby the origin/beginning of the field of lectin study – lectinology, was from a doctoral thesis from 1888, by Herman Stillmark, on the agglutination of red blood cells by isolated ricin, which was extracted from castor beans¹¹. It is now being reported that it was S. Weir Mitchell who first witnessed and described lectins when he observed rattlesnake venom lectin activity around 1860, with an article being published with the description, but not the terminology, of agglutination of red blood cells, by rattlesnake venom, in the following experiment: “*One drop of venom was put on a slide and a drop of blood from a pigeon’s wounded wing allowed to fall upon it. They were instantly mixed. Within three minute the mass had coagulated firmly, and within ten it was of arterial redness*”, this was published in 1860 within the Smithsonian contributions to knowledge journal, years before Stillmarks first description of plant lectin activity, and therefore it is now believed that it is S. Weir Mitchell who should be the researcher accredited for the first observation of lectin activity, whether of plant or animal origin¹².

Lectins bind, non-covalently, in a way that is typically reversible, to specific mono- or oligo-saccharides. With most lectins containing two or more ‘pockets’ for carbohydrate binding, their interaction with specific saccharides present on the surface of red blood cells (erythrocytes) leads to cell agglutination as a result of the cross-linking of several erythrocytes followed by their subsequent precipitation. Cell agglutination is a characteristic action of lectins and as such has and is used regularly for their detection and classification. Both, the agglutination and precipitation processes associated with lectins, as outlined previously, can be prevented/hindered by a carbohydrate for which the lectin is specific. It is the specificity that can prevent a foreign, undesirable lectin, through the use of monovalent or better yet multivalent ligands, from attaching to its target carbohydrate within the cell membrane. Lectins can be split into five groups, classified according to the monosaccharide derivative towards which they show the highest affinity, with specificity for these usually being high - mannose, galactose/*N*-acetyl galactosamine, *N*-acetyl glucosamine, fucose and *N*-acetyl neuraminic acid. Even though this is a useful way to classify the types of lectins it is more common, nowadays, to group them into families,

characterized by similar sequences and structural relatedness, e.g. C-type lectins, S-type lectins, P-type lectins and I-type lectins, these will be discussed presently.

3.2.2 Lectin type

Even though lectins were being described in excessive of 125 years ago in plants, it was not until the 1960s that they were recognized to be present throughout nature. With an ever increasing body of compounds, either native or born through synthetic methods/modulation, the traditional divisions of lectins, by their monosaccharide affinity, has been replaced by a more consistent categorization established on amino acid sequence homology (any characteristic of biological organisms that is derived from a common ancestor) and structural relatedness, i.e. where the sugar binding activities reside within these proteins. These classifications, of lectins, include - C-type lectins, S-type lectins, P-type lectins and I-type lectins.

3.2.3 Lectins in plants

During its early history and the brief period when the term lectin described non-immunoglobulin agglutinins (a substance that causes particles to coagulate and form a thickened mass), with the capability to differentiate between erythrocytes of different blood groups, most lectins were agglutinins from leguminous plants¹². This family of plants (legumes) includes lectins such as concanavalin A (ConA), which was originally extracted from the jack bean, and has been reported to exert a potent anti-hepatoma (where malignant hepatoma is the most common type of liver cancer) therapeutic effect via specific carbohydrate binding¹³, and the soybean lectin which has shown to inhibited the absorption of ferrous iron (Fe^{2+}), in rat models, with the introduction of monosaccharides allowing for competitive binding of the lectin and thereby inhibition, allowing the reduced absorption, as a cause of the soybean lectin, to be recovered, with significantly improvement in the uptake being observed when GalNAc is added¹⁴.

Even with plant lectins being the older of the two lectins (plant and animal), in terms of research, the purpose and role of lectins in plants is still not fully understood, though ideas have been put forward. Many lectins from leguminous plants are found in their seeds, fruit, etc. (storage tissues in plants), but the same lectins and/or homologous versions can also be found in other parts of the plant such as the leaves, stem and bark. Within the, so called, storage tissues, lectins account for a significant amount of the total protein matter found there. These lectins exhibit behaviors similar to other storage proteins such as aiding development as well as being important in providing defense to the plant. An example of these behaviors by lectins can be observed during germination - some lectins, in the storage tissues of a plant, are broken down to become important sources of nitrogen during the development process of a plant. Lectins, in general, are specific for certain carbohydrates, as outlined previously, and it is this very specificity, in this instance, of plant lectins for monosaccharides that do not seem to be contained within the plant itself, that has led some

to speculate that a number of lectins in the plant may also act as defense proteins against pathogenic attack. A further way in which these lectins provide a defense/protection for the plants can be illustrated by the leaves of mistletoe. These leaves contain three lectins that are Gal/GalNAc specific. What makes them interesting is two of these lectins have been reported to exhibit strong cryo-protective mechanisms during freezing and thawing processes¹⁵.

While the natural role/purpose of plant lectins still remains somewhat uncertain, as outlined above, they are now widely employed in routine assays. Various plant lectins are now commonly used, as biochemical tools, in the elucidation of the composition and functions of carbohydrate structures in animal cells.

3.2.4 Lectins in animals

With the research that has been carried out, to present, we now currently have a much more informed and detailed picture of the role and structure of animal lectins than we do of plant lectins. Lectins in animals account for a multitude of different biological functions. These roles can include the control of cell adhesion, as well as glycoprotein synthesis and through this later function, and other methods, the regulation of protein concentration in the blood. The importance of animal lectins can be demonstrated by those found on the surface of mammalian liver cells, asialoglycoprotein receptors (as discussed in section 3.1.2). These lectins are believed to be the receptors that allow for the facilitation of the removal of particular glycoproteins from the circulatory system. Lectins, in general, are also acknowledged as having an essential role in the immune system. This is so, as they are capable of identifying carbohydrates that are located exclusively on pathogens, or that are difficult to get to on host cells, and after such fact are able to elucidate an appropriate response. The four major groups, by which lectins are divided - C-type lectins, S-type lectins, P-type lectins and I-type lectins, are provided below in a bit more detail, followed by a table of the animal lectins (including these and others) classified according to known sequence homologies.

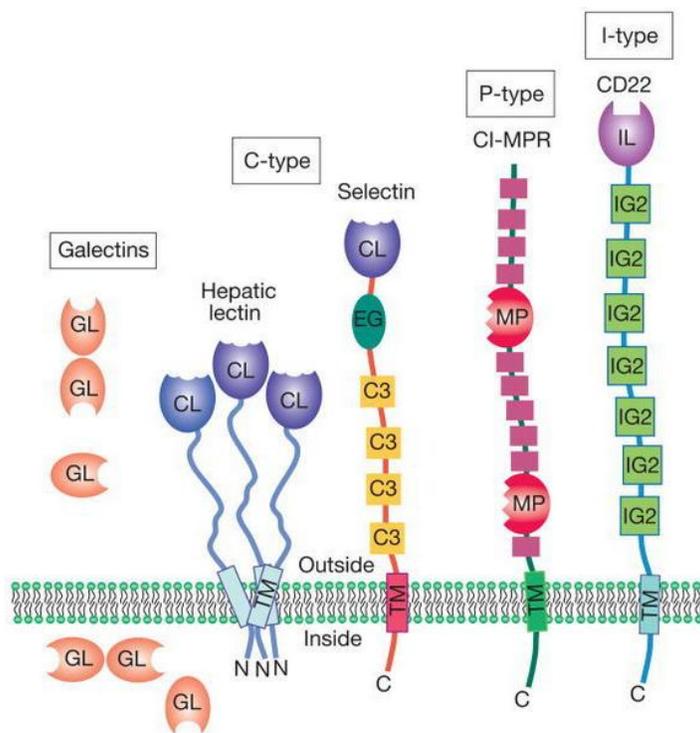


Fig. 3.4 An illustration of the four major groups of lectins. Reprinted from *Essentials of Glycobiology*, 2nd Edition 2009. © (2009) with permission from Cold Spring Harbor Laboratory Press.

3.2.4.1 C-type lectins

Drickamer, in 1988, proposed the organization of animal lectins into several distinct categories, one of these was the C-type lectin, so called due to the necessity for calcium ions for their recognition. He also proposed structural similarities, of the Ca^{2+} -dependent lectins, to the asialoglycoprotein receptor. These C-type lectins bind a variety of sugars and are characterized by an extracellular carbohydrate recognition domain (CRD). As with everything though, there are lectins, that fit the criteria of a C-type lectin, i.e. they are calcium requiring, but are not classified as C-type lectins, e.g. calnexin and calcireticulin.

3.2.4.2 S-type lectins

It is first worth noting that the term S-type lectin is now obsolete but for the sake of continuity it has been used. What was formerly known as the S-type lectin is now known as a galectin, due to their specificity for β -galactoside sugars. These galectins were originally named as S-type lectins, by Drickamer, due to their reliance on free thiols for complete activity. Owing to their galactoside specificity, galectins combine preferentially with GalNAc, lactose and *N*-acetyl lactosamine.

3.2.4.3 P- and I-type lectins

P-Type lectins differ from all the aforementioned lectins through their capability to identify phosphorylated mannose derivatives. The two components of the P-type lectin family are that of the cation-dependent mannose 6-phosphate receptor (CD-MPR) and the insulin-like growth factor II/mannose 6-phosphate receptor (IGF-II/MPR)¹⁶.

Those lectins of I-type family share a common immunoglobulin-like CRD and thus belong to the immunoglobulin super family (IgSF), excluding antibodies and T-cell receptors as these do not fall into the parameters of a lectin, as outlined in section 3.2.1. Bioinformatic analysis of mammalian genomes, predict more than 500 proteins – lectins, of the IgSF, other than antibodies and T-cell receptors. Only the siglec family, of sialic acid binding lectins, have been well characterized. As such there is considerable potential for assignment to the I-type lectins.

Table 3.1: Classification of animal lectins according to known sequence homologies²

Lectin class	Defining structural motif	Carbohydrate ligand	Calcium dependence
C-type (includes selectins, collectins, endocytic lectins)	conserved CRD	Variable	Yes (most)
Galectins (formerly S-type)	conserved CRD	β -galactosides	No
P-type	unique repeating motif	mannose 6-phosphate on high-mannose-type <i>N</i> -glycans	Variable
I -type (includes Siglec family)	immunoglobulin-like CRD	variable (Siglecs: sialic acids)	No
Calnexin, calcireticulin, calmeglin	homology with each other	glucosylated high-mannose-type <i>N</i> -glycans in the ER	Yes
Hyaluronan-binding proteins	homologue CRD	hyaluronan chains	No
Frog egg lectins	sequence homology		Yes

Abbreviations: CRD, carbohydrate recognition domain; ER, endoplasmic reticulum

3.2.5 Importance of multivalency

Although animal lectins can show a high degree of specificity for recognizing certain carbohydrate structures, the interactions/binding affinities of lectins with their specific monosaccharides are generally low. Thus, functional avidity (the accumulated strength of multiple affinities) is quite often attained by multivalency of CRDs. This is achieved either by means of the structure of the lectin (e.g. see galectins below) or via clustering in biological systems (e.g., at cell surfaces) – see section 2.1.3 on multivalent binding. The reason for the relatively weak interactions of lectins with their specific carbohydrates is due to the environment of the binding site of the lectin. These are shallow areas that allow for

few direct contacts and thus binding with the ligand is often weak for a monovalent derivative.

Even with these weak binding associations, lectins have been shown to demonstrate both high affinity and a high specificity for various saccharide structures on the surface of a cell. If these criteria didn't hold true, lectins would not be capable of acting as recognition molecules in the variety of biological processes that they do take part in, as has been discussed previously. As a result of their weak binding associations it has been proposed that numerous protein-carbohydrate interactions are involved in the recognition event. These multiple interactions allow for the necessary high affinity that is needed to elicit a response. It is through these observations and the aspiration to achieve these desired effects that multivalency is employed. An example of this can be seen in the work by Marikovsky et al. in which they discuss the clearance of senescent (biological ageing, i.e. the gradual deterioration of functional characteristic) erythrocytes¹⁷. In this article it is shown, or rather further evidence is added to the argument, that even though certain mechanisms of the process remain unclear, the clearance of erythrocytes by asialoglycoprotein receptors can only occur when the density of galactose residues reaches a significant level. Further to this and other beneficial outcomes of multivalent interactions, antibodies of all types possess several equivalent receptor sites. As such multivalency can be viewed as another positive attribute which leads to high affinity when binding to surfaces that show recurring epitopes, such what would be present on almost all invading pathogens.

With this background knowledge on lectins and their interactions and the importance of multivalency in, amongst other things, inducing an effect by increasing affinity, it makes the synthesis and evaluation of novel multivalent ligands an attractive and exciting one due to vast field of lectins where they could possibly be implemented.

3.2.6 Galectins

With lectins being involved in many varied biological processes, including but not limited to the elimination of glycoproteins for which they are specific for from the circulatory system, the adhesion of infectious bodies to host cells, recruitment of leukocytes to sites of inflammation, interactions of cells in the immune system and response, in malignancy and metastasis (see below), and all these associated processes occurring in many different species, they make for a very interesting area of study and research¹⁸. Of the lectins, already discussed, galectins have drawn the attention of the Murphy laboratory of late due to their diversity - being the most widely expressed class of lectins in all organisms. As such, opening compounds synthesized, as specific agents for galectins, to many possibilities.

Even with the study of lectins, and thereby galectins, still essentially in its infancy, in terms of scientific research, the field is expanding rapidly. A total of fifteen galectins have now

been identified in mammals, but only twelve of these galectins are reported to have been found in humans, of which there are two for the tandem repeat galectin-9. These various galectins have been classified into three major groups: prototypical, chimeric and tandem-repeat¹⁹.

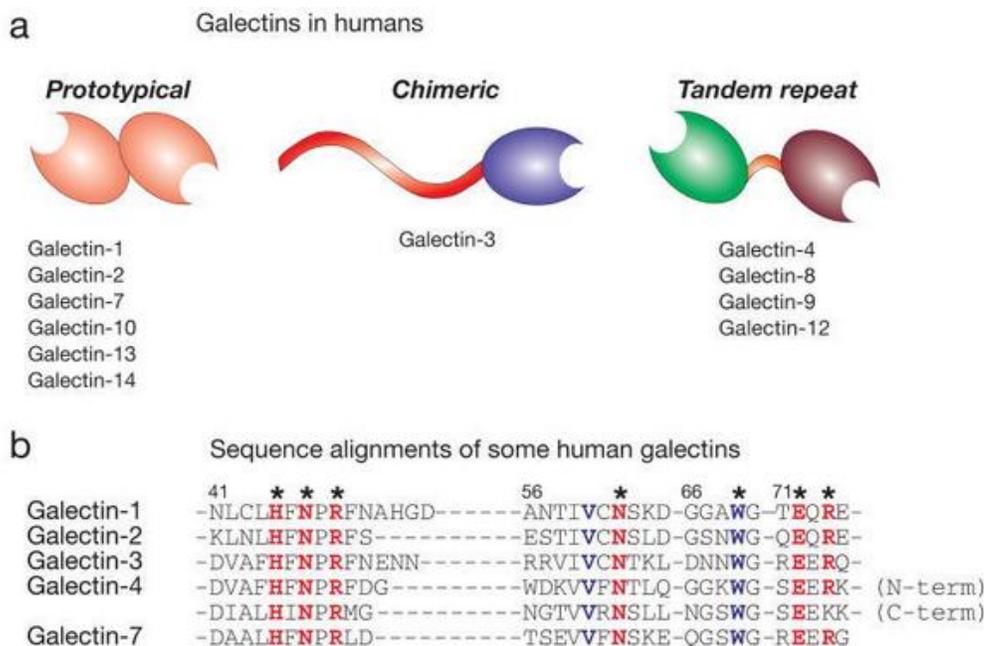


Fig. 3.5 The major groups of galectins found in humans. Reprinted from *Essentials of Glycobiology*, 2nd Edition 2009. © (2009) with permission from Cold Spring Harbor Laboratory Press.

Prototypical galectins: these galectins consist of a lone CRD (carbohydrate recognition domain) but may combine to form structures such as that illustrated in Fig. 3.5 - homodimers.

Chimeric galectins: This group of lectins are more commonly found in invertebrates. In humans only galectin-3 is known in the chimeric group. It is, as for the prototypical galectins, characterized by containing a sole CRD but differs from prototypical galectins by having an amino region, Fig. 3.5. This ‘tail’ can be plentiful in proline, glycine, and tyrosine residues.

Tandem-repeat galectins: These galectins have two CRDs, which are linked/connected by a small peptide chain. These peptide chains can vary from five to fifty, or more, amino acid residues in length.

It has been shown that tumour progression can be contributed to by galectins through a variety of different mechanisms and, with respect to normal tissues, have been found to be frequently over-expressed in various human solid tumours and blood malignancies.

Galectins have been reported to contribute to neoplastic transformation, the survival of tumour cells, tumour metastasis (the spread of the cancer) and angiogenesis (the formation of new blood vessels) Fig. 3.6.

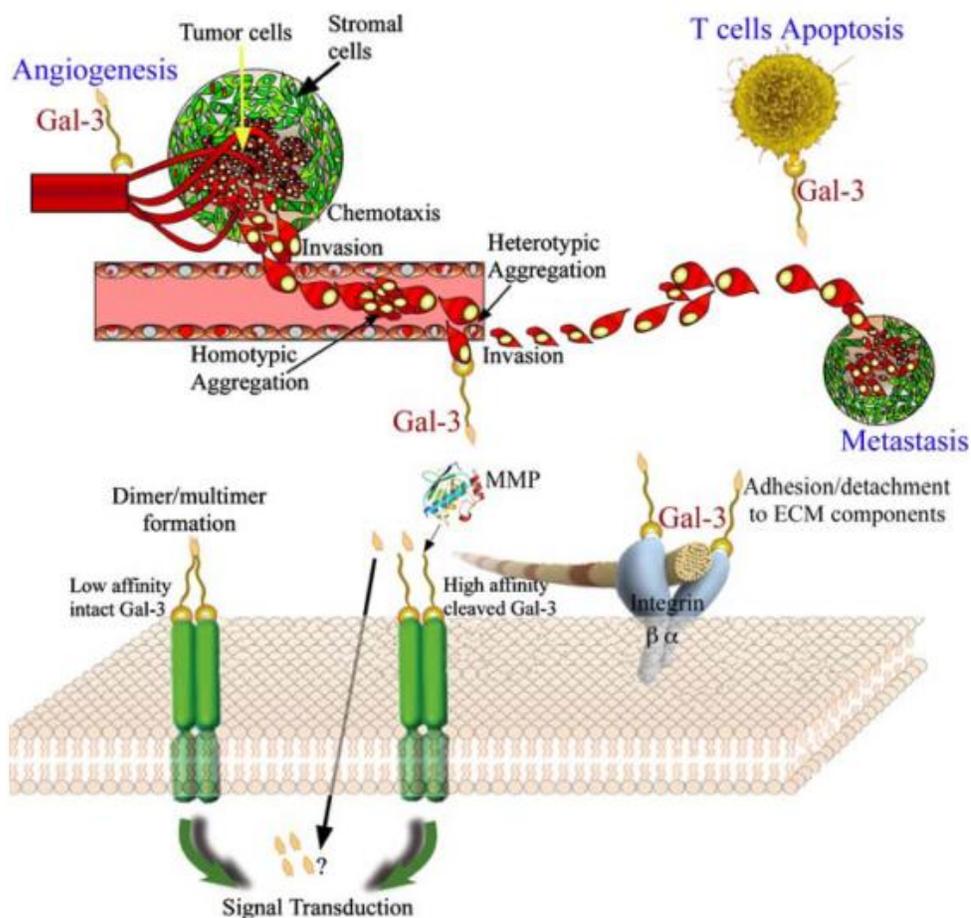


Fig. 3.6 Galectins contributing to tumour progression. Reprinted from *Cancer Microenvironment* **2008**, *1*, 43-51. © (2008) with permission from Springer.

Along with these tumour development and progression modulators, galectins can also ‘defend’ the tumour by altering the inflammatory and immune responses and as such might play a key role in helping tumours to escape natural immune system responses. Galectins can therefore be used as useful tools, such as diagnostic markers for specific cancers. In addition to this, due to all these processes by which galectins are involved in cancer, they can be viewed as potential targets for cancer treatment. Inhibitors of these tumour associated galectins have the potential to be used as both anti-tumour and anti-metastatic therapeutic agents.²⁰

3.2.7 Macrophage C-type lectin

Dendritic cells (DCs) are the most potent antigen presenting cells (APCs) (antigen being an abbreviation of *antibody generator*) of the immune system²¹. They express cell surface

lectins and through these and other types of receptors, ‘sense’ the microenvironment they exist in for environmental change - recognizing and eliminating pathogens. They are, thus, capable of activating and directing the immune response by means of the uptake of self and/or foreign pathogen-associated antigens²². One type of receptor present on these DCs is the C-type lectin receptor. The most important of which is the macrophage (Greek for big eaters, from *makros* "large" and *phagein* "eat") galactose type C-type lectin (MGL). It is reported as the sole galactose-type lectin among the C-type lectins expressed on DCs²³. Human MGL (hMGL) is a type II, possessing a single carbohydrate recognition domain, C-type lectin. It is specific for Gal/GalNAc residues, capable of recognition of either α - or β -GalNAc derivatives. These MGLs are involved in the detection of a host of different pathogens and are capable of activating T-cells, a type of lymphocyte (white blood cell) and, thus, activating an immune response, through the presentation of internalized antigens to these antigen specific T-cells. In terms of cancer research it has been reported that MGL enables DCs to ‘sense’ glycosylation and to selectively recognize tumour associated glycoproteins²². It is therefore reasonable that research exists in targeting these receptors as a means of delivering antigens in DC-based anticancer immunotherapy.

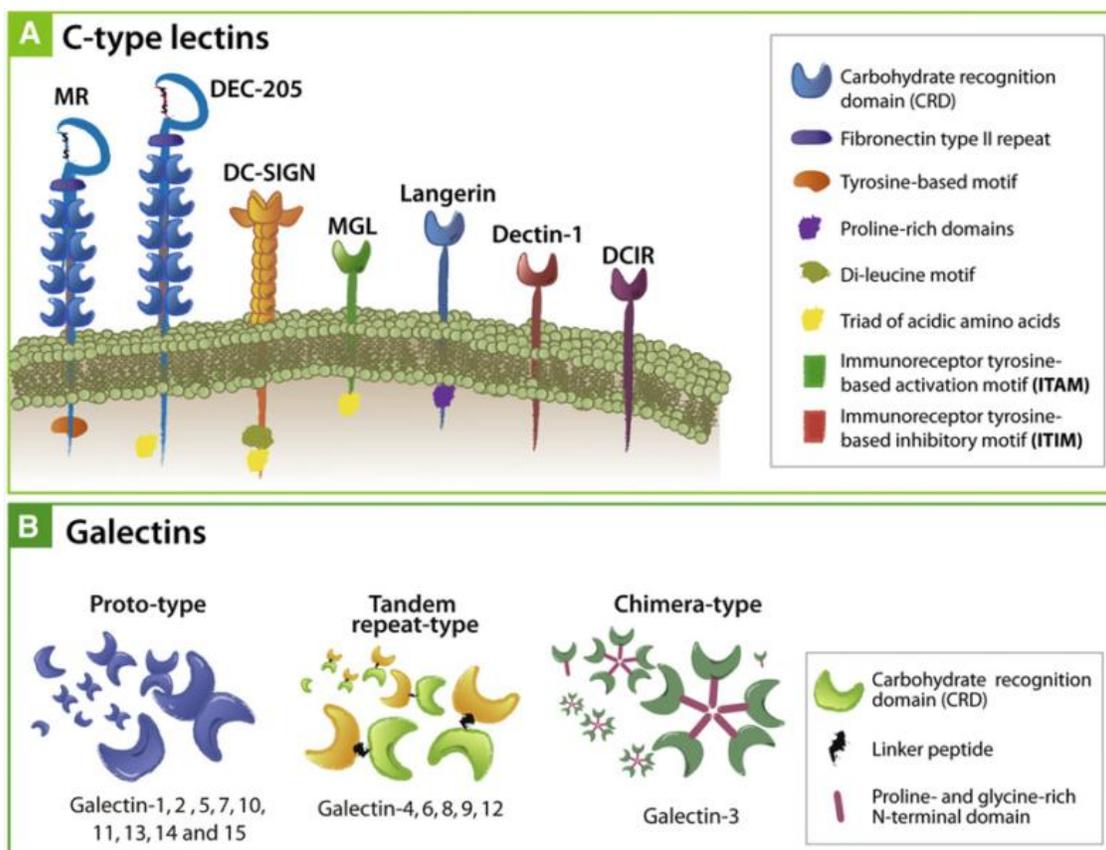


Fig. 3.7 Illustration of C-type lectins, including MGL, and another example of the major groups of galectins found in humans. Reprinted from *Immunity* **2012**, *36*, 322-335. © (2012) with permission from Elsevier.

3.2.8 Previous work by the Murphy laboratory

Galectins, as illustrated in Fig. 3.5 and 3.7, are either bivalent (prototypical or tandem repeat) or multivalent (chimeric), with regard to their carbohydrate-binding activities, as briefly outlined in section 3.2.6. Due to their multivalent nature, work in the area of lectin research, by the Murphy laboratory, initially focused on the synthesis of bivalent lactosides, on varying scaffolds, with subsequent assessment of their inhibitory capacities. Some of these lactose derivatives are included in Fig. 3.8.

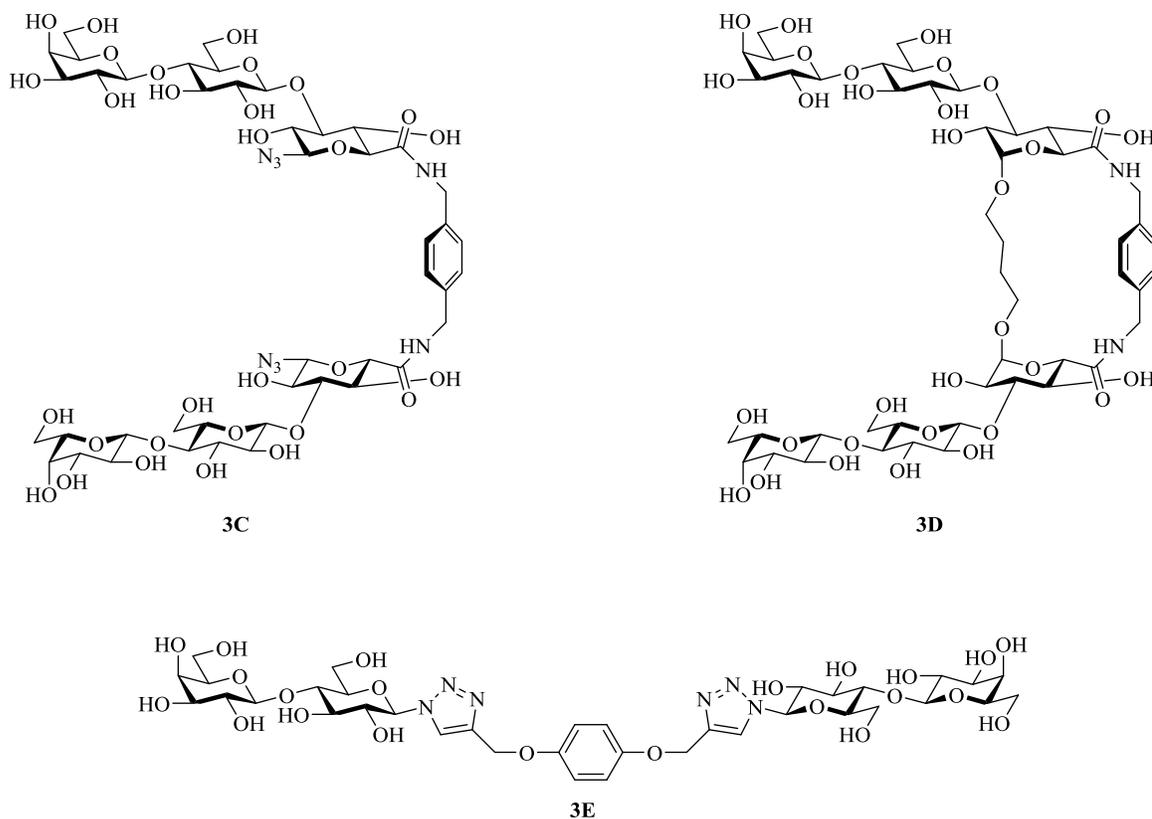


Fig. 3.8 Some examples of bivalent lactosides, from the Murphy laboratory, assessed for their lectin inhibitory capacities.

Initial studies were carried out to assess the ability of the glycoclusters to inhibit lectin-mediated heme-agglutination. Of all those tested, only **3E** could match the results obtained for that of lactose, with no inhibitory activity being observed for any of the other bivalent compounds. More involved and detailed studies were then carried out using a plant toxin (VAA: *Viscum album* (a species of mistletoe) agglutinin/toxin) and in three types of assay on human adhesion/growth regulatory galectins. Compounds **3C** and **3E** were found to be significantly more active than that of the free disaccharide, lactose, in blocking the plant toxin, VAA, binding to the cells. While good inhibition was also observed and detailed for the same compounds, for galectin-3, a proteolytically (see section 3.2.6) truncated form of

human galectin-3 and galectin-4. Thus, bivalent lactosides **3C** and **3E** were found to be particularly effective in reducing lectin association.²⁴

More recent research from the Murphy laboratory, by Wang et al.²⁵, continues the work on lactose derivatives while also investigating the effect of headgroup tailoring by evaluating glycoclusters with 2'-fucosyllactose. Further to this manipulation, an increase in valency was another parameter of review, with, in addition to a bivalent compound, tri- and tetra-valent derivatives being synthesized for testing against two plant agglutinins and adhesion/growth-regulatory lectins (galectins). A sample of the compounds tested as part of this study, are included in Fig. 3.9.

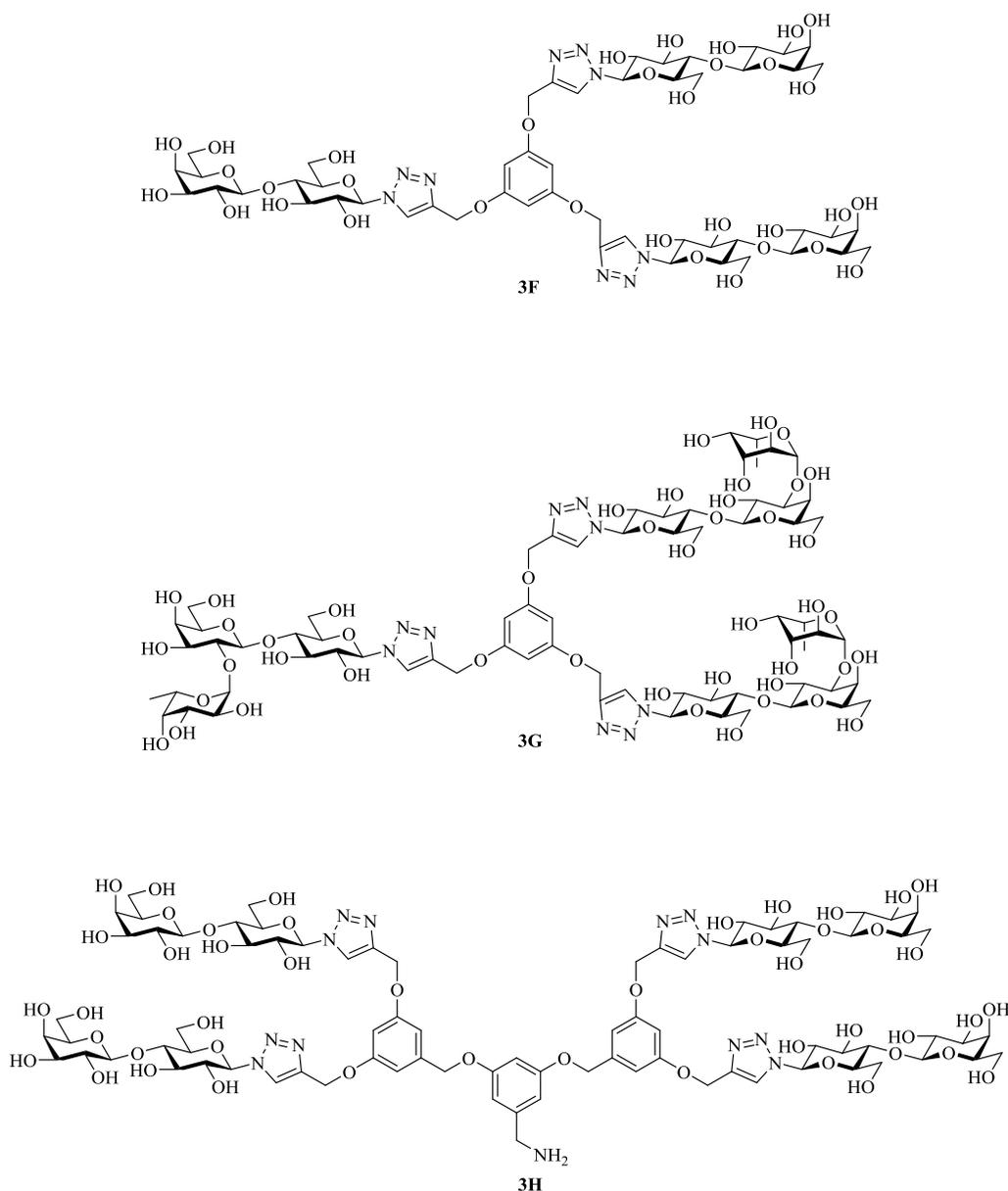


Fig. 3.9 Some of the multivalent compounds tested as part of the study by Wang et al.

The first assay carried out was on the inhibitory properties of these multivalent ligands on plant lectins. A note of interest as part of this study was that it is not just valency that matters but also the geometric mode of ligand presentation. IC₅₀-values were once again reported and with respect to VAA, when compared to free lactose, the inhibitory capacity of the multivalent compounds being tested here were, in most cases, only slightly improved. However, the tetravalent compound **3H**, was found to be the most potent inhibitor with an approximately a 20-fold enhancement, again, when compared to lactose. Assays were continued with the study of the inhibitory properties of the glycoclusters on chicken galectins (CG). Here it was observed that headgroup tailoring could produce positive results. Positive results were observed for both the tetravalent compound **3H**, and also the trivalent 2'-fucosyllactose (FucLac) **3G**. This trivalent FucLac, **3G**, showed the highest affinity of all the compounds with CG-3, providing support to further investigations in headgroup manipulation. The last of the assays were on the inhibitory properties on human galectins. Here the tetravalent compound **3H**, again, provides the best results in term of inhibition, showing the importance of valency in increasing avidity. It is also worth noting, from these human galectin assays, that for the trivalent compounds, bearing the same scaffold, i.e. **3F** and **3G**, it is the trivalent compound with the FucLac moieties, **3G**, that provides the best inhibition of the two, lending further weight to additional studies on headgroup tailoring²⁵.

3.3 Results and discussions

3.3.1 Headgroup tailoring on selectivity

As part of the work for this thesis, with respect to lectins, a variety of multivalent compounds were synthesized with GalNAc residues as the sugar moieties. These multivalent compounds were synthesized in a similar fashion to those synthesized as part of the *Helicobacter pylori* area of research, utilizing the same linker scaffolds synthesized previously in section 2.3.1.4.

The multivalency varied, from a series of bivalent compounds to a tri- and tetra-valent derivative, to see if the same pattern, as reported by Wang et al.²⁵ - that by increasing the valency of the compounds this leads to an increase in the inhibition, could be observed. In addition to this parameter, the variety of multivalent ligands bearing GalNAc residues synthesized herein could provide further evidence as to how multivalent ligands in general behave and present with respect to the lectins they are tested against, i.e. how they interact/bind e.g. through the cluster effect (see section 2.1.3). Further to this, the use of GalNAc as the headgroup could potentially allow for better results to be observed, than for analogous or similar compounds where lactose (Lac) sugars have been used as the headgroup. This should be the case for lectins with similar specificities to that of the asialoglycoprotein receptor, if patterns observed by Lee et al.⁸, that asialoglycoprotein receptors of all mammalian species bind GalNAc much better than Gal and Lac, arise.

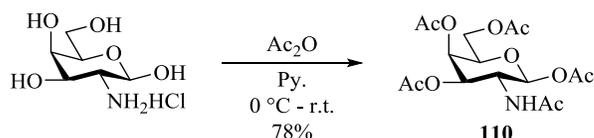
The multivalent compounds synthesized, herein, feature both α - and β -configurations as way of investigating whether the orientation of the sugar (the binding constituent of the multivalent ligand) has an effect on the affinity of those compounds. With proper spatial arrangement, with respect to the lectin, being shown to be an important parameter in efficacy, as illustrated in section 3.1.2.

Both *S*- and *O*-glycosides, as for the *Helicobacter pylori* study, were synthesized. The main compounds of interest were, again, speculated to be those of α -configuration. Though as discussed in the introduction of this chapter, section 3.2.6, galectins show specificity to β -galactosides, as such when it came to making analogues there was a tendency to make β -derivatives, so that these could be evaluated against galectins, with a view and hope that they would be found to be beneficial compounds.

3.3.1.1 The synthesis of α - and β -GalNAc thiols

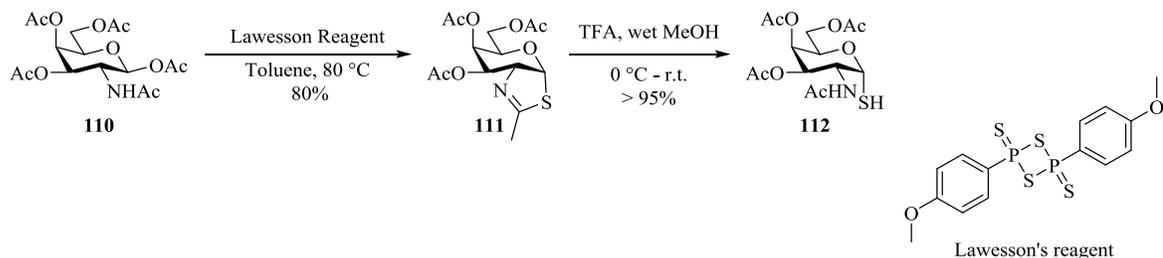
The importance of the synthesis of the β -OAc GalNAc, **110**, again arises, as a precursor for the synthesis of the α -GalNAc thiol, **112**. The synthetic route for producing the per-acetylated derivative, **110**, was, more, straight forward in the case of the galactosamine sugar, than when compared to the GlcNAc derivative, which needed to be subjected to a series of protection and deprotection procedures to get the protected sugar with the desired and necessary stereochemistry.

The β -OAc GalNAc precursor, **110**, was obtained through a simple and straightforward acetylation of the hydrochloride salt of D-galactosamine. This commercially available sugar was stirred in pyridine at 0 °C followed by the addition of acetic anhydride. When the reaction was completed, the solvents were efficiently removed by co-evaporation, a number of times, with toluene, with the subsequent solid being recrystallised from methanol to give the desired β -OAc GalNAc sugar, **110**, in very good yields.



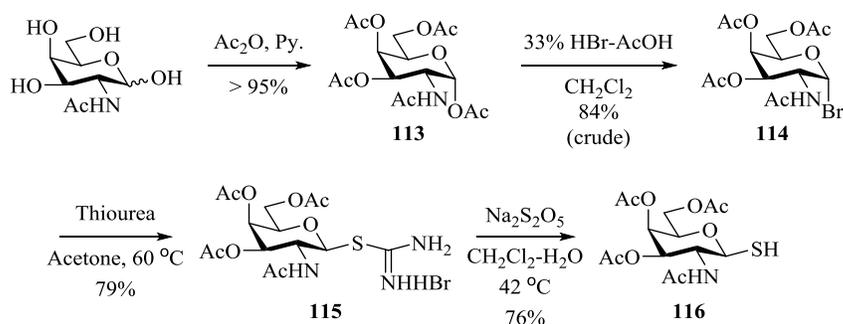
Scheme 3.1 The synthesis of β -OAc GalNAc.

Following a procedure, as reported by Knapp et al.²⁶, the protected sugar, **110**, was then reacted with Lawesson's reagent to first give the thiazoline derivative **111**, in very good yields. This was followed by the hydrolysis, under acidic conditions, to give the α -GalNAc thiol **112**, in a > 95% yield.



Scheme 3.2 Synthesis of α -GalNAc thiol.

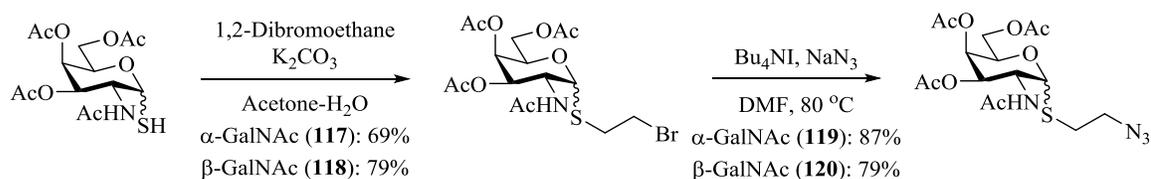
The β -GalNAc thiol was synthesized through a similar procedure to that of the GlcNAc derivative **73**, through a glycosyl bromide. This procedure starts out with the slightly cheaper, commercially available *N*-acetyl galactosamine sugar, where the amine is already protected, when compared to D-galactosamine hydrochloride. The protection of the free hydroxyl groups with acetic anhydride in pyridine is achieved through a similar manner to that of **110**, without the need for column chromatography or recrystallisation as for **110**. Treatment of this peracetylated derivative, **113**, with 33% hydrogen bromide in acetic acid gave the glycosyl bromide **114**. This was followed by a two-step reaction sequence, involving the S_N2 substitution of the glycosyl halide, in acetone, with thiourea to give the intermediate **115**, which then under goes mild hydrolysis to give the desired β -GalNAc thiol **116**, in good yields.



Scheme 3.3 Synthesis of β -GalNAc thiol via a glycosyl bromide.

3.3.1.2 Synthesis of *S*-glycosides

Both these α - and β -GalNAc thiols, **112** and **116**, were used in the synthesis of thioglycosides. This involved reacting the thiols with 1,2-dibromoethane in an acetone-water mixture in the presence of potassium carbonate. These reactions proceeded in good yields with the bromides of each derivative, **117** and **118**, then being displaced through a reaction utilizing tetrabutylammonium iodide and sodium azide, heated in DMF, to give azido-sugars **119** and **120**, again, in good yields.

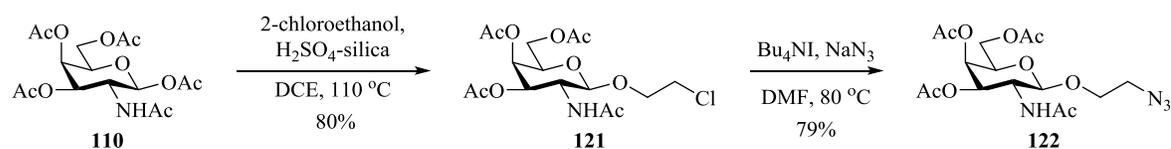


Scheme 3.4 Synthesis of both α - and β -GalNAc thioglycosides.

These azido sugars were then employed in a similar fashion to those synthesized in the *Helicobacter pylori* chapter. As such, the CuAAC reaction, section 2.1.4.1, was once again used to facilitate the generation of a variety of multivalent ligands, having bi-, tri- and tetra-valency.

3.3.1.3 Synthesis of *O*-glycosides

In addition to the thioglycosides synthesized, the β -*O*-glycoside analogue **122** was also synthesized, as another glycoside having the potential to generate multivalent compounds which could have promise in, the β -galactosides specific, galectins. The synthesis of this derivative was achieved by microwave irradiation of β -OAc GalNAc **110**, in 1,2-dichloroethane, with 2-chloroethanol in the presence of acidic silica to give **121**. This was then transformed into the azido sugar, **122**, by heating the reaction in DMF, with tetrabutylammonium iodide and sodium azide, to give the desired azido sugar, in good yields.



Scheme 3.5 Synthesis of β -GalNAc *O*-glycoside.

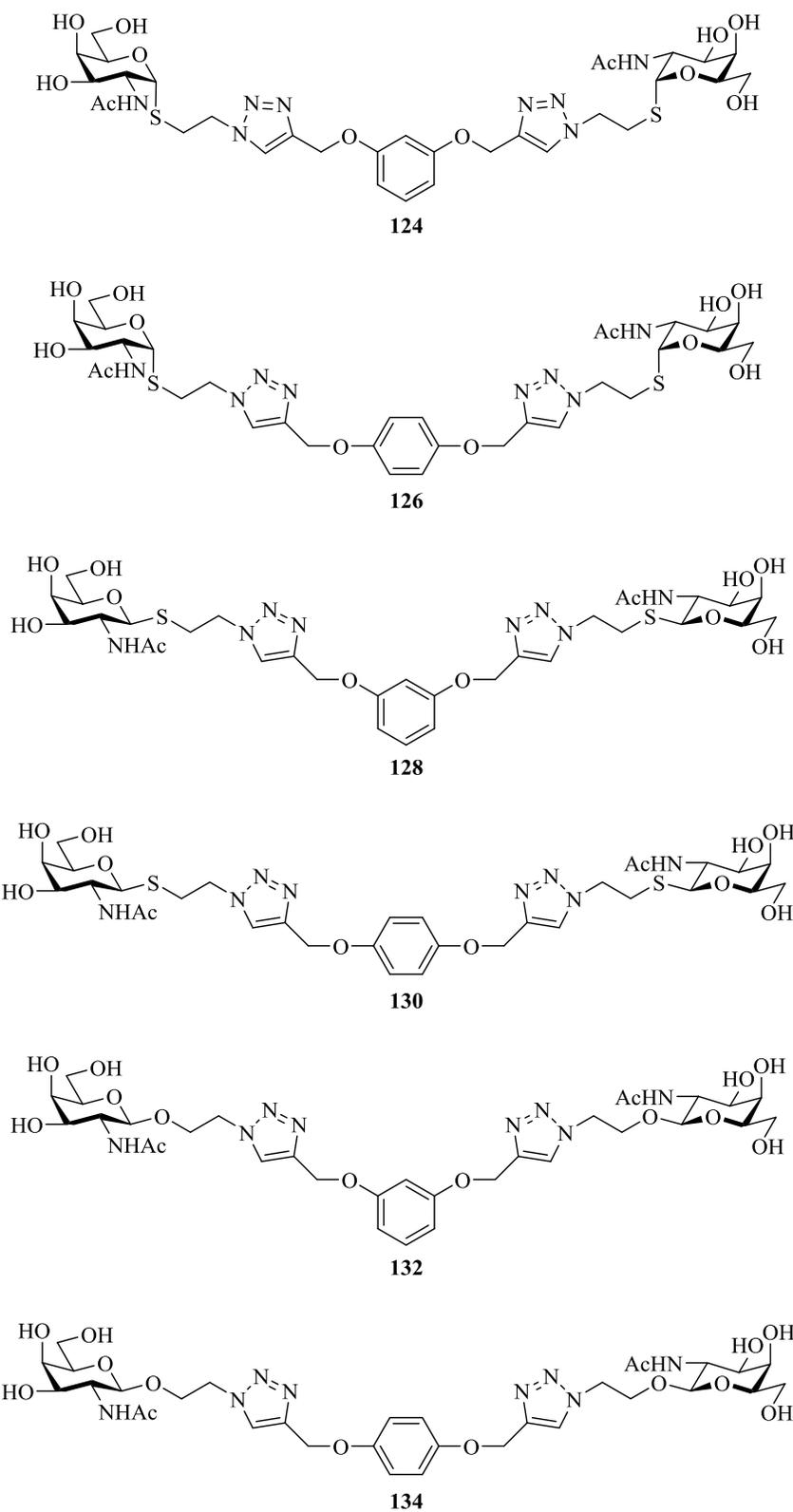
3.3.2 New multivalent ligands for evaluation as lectin inhibitors

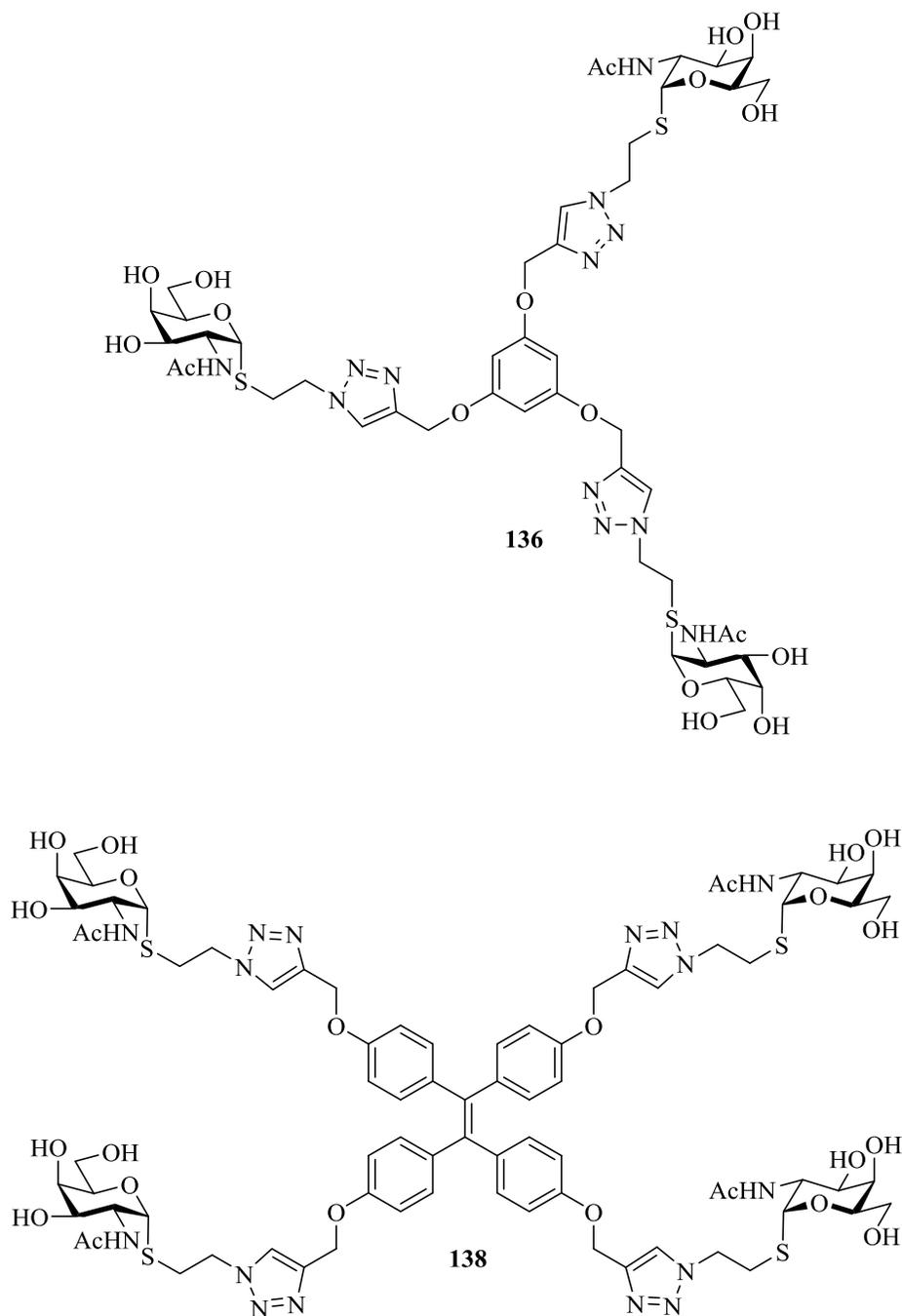
3.3.2.1 Summary of the conditions used for multivalent ligand synthesis

The CuAAC reaction, 1,4-click chemistry, was generally achieved by a reaction of the linker (as the limiting reagent) with a slight excess, per propargyl unit, of the sugar moiety in a 1:1 THF- H_2O mixture. The catalyst for the reaction was achieved by the reduction of $\text{Cu(II)SO}_4 \cdot 5\text{H}_2\text{O}$ by sodium ascorbate to the Cu(I) catalyst needed to facilitate the cycloaddition reaction. A typical procedure involved using 0.6 equivalents of $\text{Cu(II)SO}_4 \cdot 5\text{H}_2\text{O}$ and 0.65 equivalents, of sodium ascorbate. The reactions were carried out at room temperature for a period of 18 – 24 h. After purification by flash chromatography the various multivalent ligands were deprotected by Zemplén deacetylation conditions, this involved using, in most cases, a freshly prepared 1M sodium methoxide solution. Again, these reactions were carried out a room temperature but only for a period of 1 - 2.5 h. The purification of these various deprotected sugars was achieved by reverse phase column chromatography, to give the desired multivalent ligands in good to excellent yields.

The glycoclusters prepared are shown in Fig. 3.10 and 3.11

3.3.2.2 List of GalNAc multivalent compounds

**Fig. 3.10** List of bivalent GalNAc multivalent compounds synthesised.

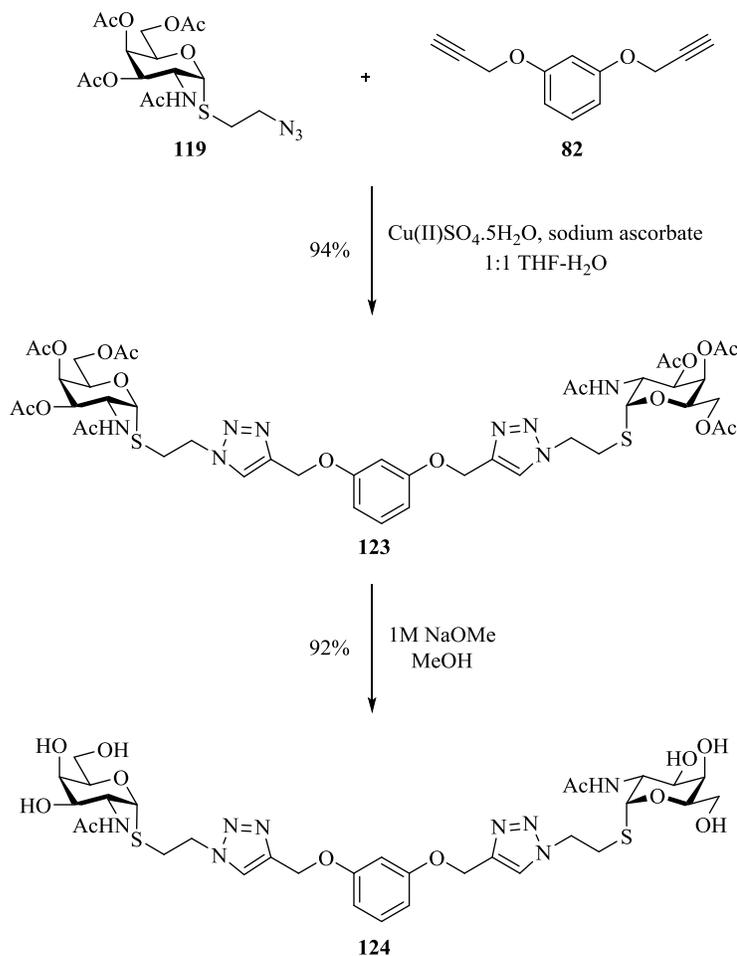
3.3.2.2 List of GalNAc multivalent compounds (cont.)**Fig. 3.11** List of tri- and tetra-valent GalNAc multivalent compounds synthesized.

3.3.2.3 Synthesis of glycoclusters

The synthesis of the multivalent compounds was achieved using CuAAC, as described, using the *S*- and *O*-glycosides synthesized herein along with the linkers described in section 2.3.1.4.

Synthesis of 1,3-di[1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene

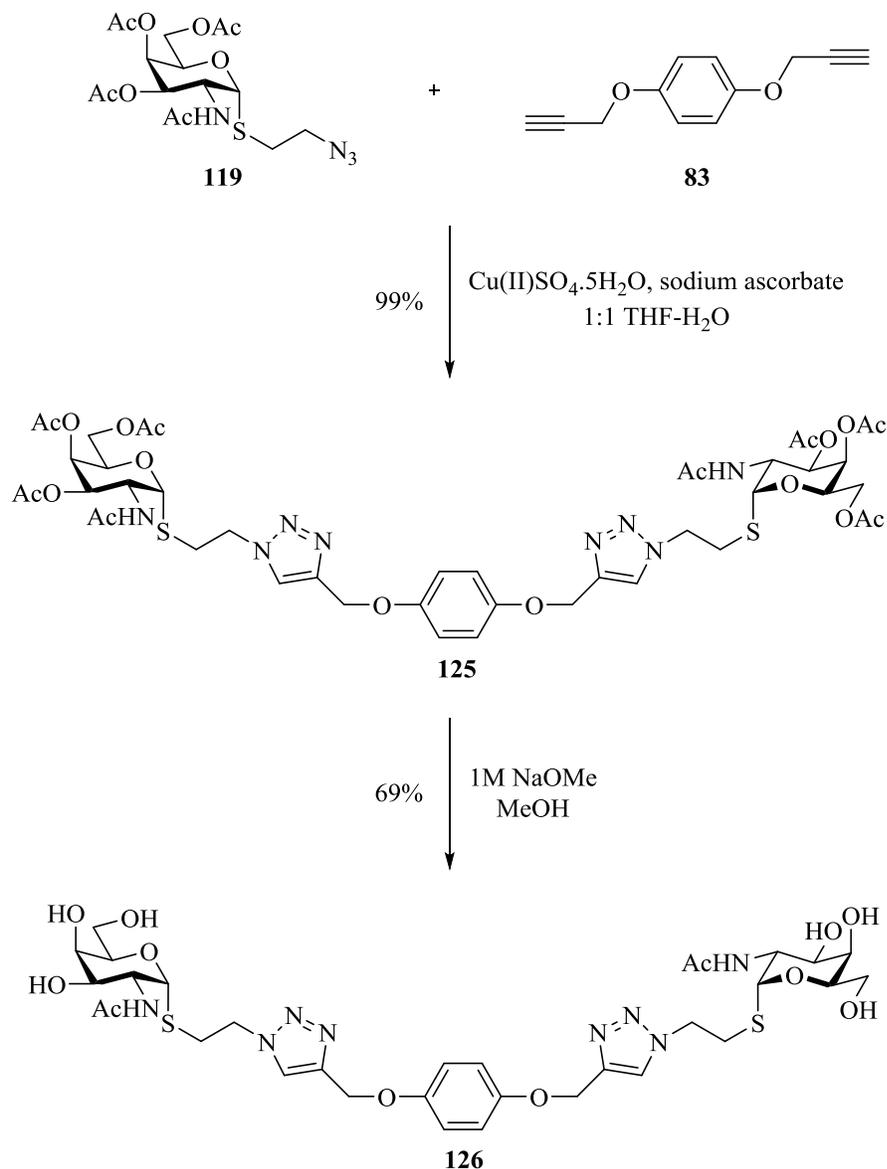
m-Bispropargyloxybenzene, **82**, was reacted with the α -GalNAc azide **119** through a CuAAC by means of the *in situ* reduction of Cu(II)SO₄·5H₂O by sodium ascorbate, in 1:1 THF-H₂O. The bispropargyl resorcinol, **82**, was the limiting reagent. Column chromatography was used to separate the bivalent compound **123** from unreacted sugar **119**, and the product was isolated in high yields. The acetyl, protecting, groups were then removed using a catalytic amount of a freshly prepared 1M sodium methoxide solution, in methanol. The bivalent compound was then purified by reverse phase column chromatography to give **124**, in a 92% yield.



Scheme 3.6 Synthesis of 1,3-di[1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene.

Synthesis of 1,4-di[1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene

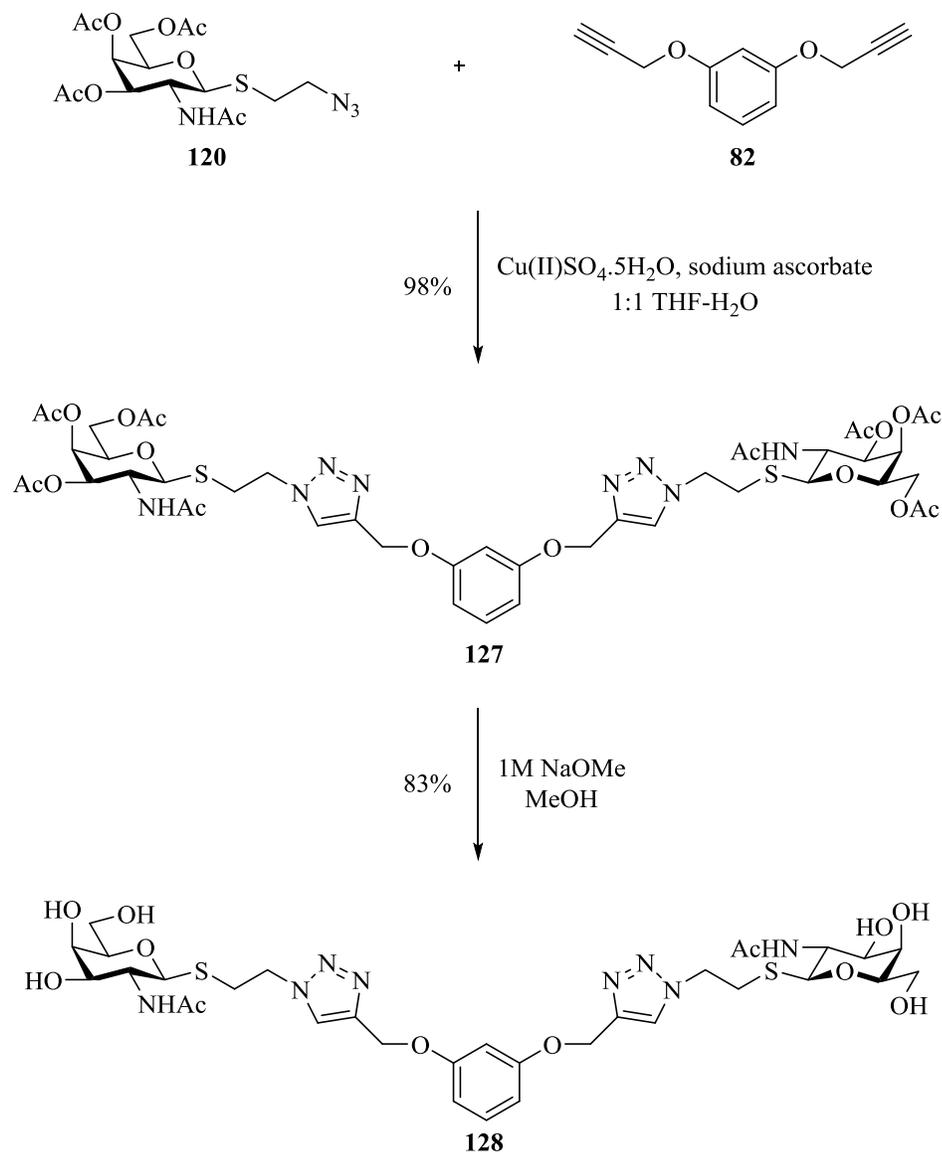
The α -azido compound, **119**, was reacted with *p*-bispropargyloxybenzene, **83**, with Cu(II)SO₄·5H₂O and sodium ascorbate, 1:1 THF-H₂O. Column chromatography was used to separate the desired bivalent compound **125** from unreacted thioglycoside **119**, and gave glycocluster in high yields. The protecting groups were then removed by Zemplén deacetylation. Reverse phase column chromatography of **126**, gave the product in a 69%, yield.



Scheme 3.7 Synthesis of 1,4-di[1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene.

Synthesis of 1,3-di[1-(ethyl 2-acetamido-2-deoxy-1-thio- β -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene

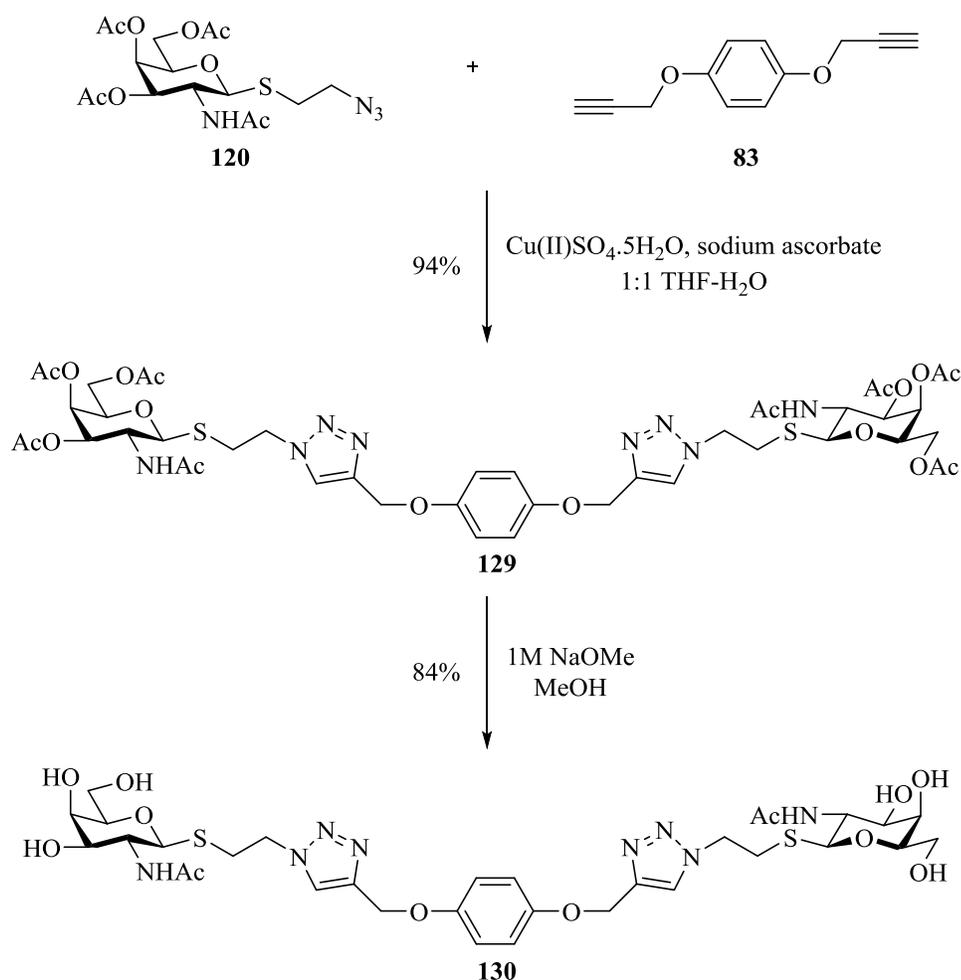
The β -azido GalNAc thioglycoside, **120**, was reacted with the *m*-bispropargyloxybenzene **82** by means of the copper catalysed click reaction described previously. Subsequent purification, by column chromatography, gave the bivalent compound **127**, in high yields. The protecting groups of this glycoclusters were removed using a 1M freshly prepared sodium methoxide solution. Reverse phase column chromatography gave the derivative, **128** in an 83% yield.



Scheme 3.8 Synthesis of 1,3-di[1-(ethyl 2-acetamido-2-deoxy-1-thio- β -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene.

Synthesis of 1,4-di[1-(ethyl 2-acetamido-2-deoxy-1-thio- β -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene

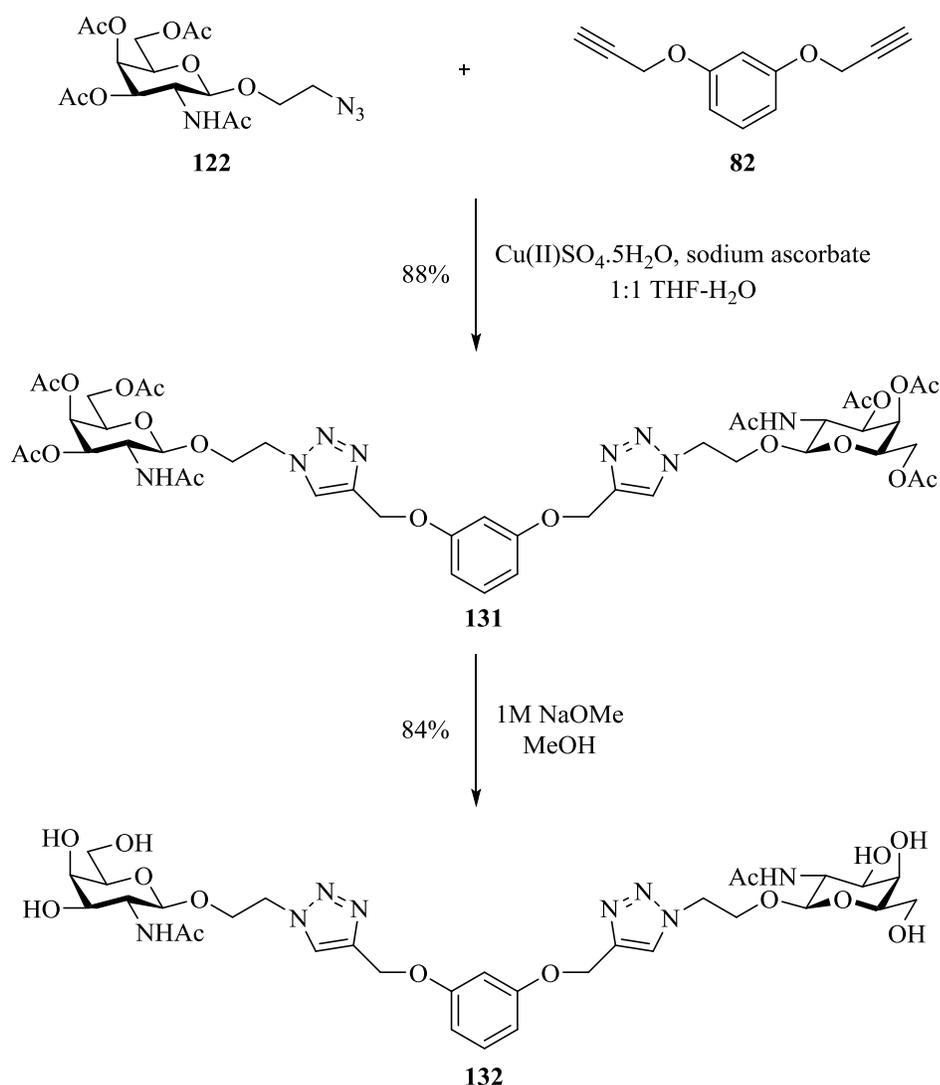
The analogue of **125**, with opposite configuration at the anomeric centres, was obtained by the reaction of the β -GalNAc azide thioglycoside, **120** with *p*-bispropargyloxybenzene, **83** by CuAAC using Cu(II)SO₄·5H₂O and sodium ascorbate, 1:1 THF-H₂O. Column chromatography, gave the triazole compound, **129**, in excellent yields. The deprotection of this compound was facilitated by using a catalytic amount of a freshly prepared 1M sodium methoxide solution. The bivalent compound was then purified by reverse phase chromatography to give, **130**, in an 84% yield.



Scheme 3.9 Synthesis of 1,4-di[1-(ethyl 2-acetamido-2-deoxy-1-thio- β -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene.

Synthesis of 1,3-di[1-(ethyl 2-acetamido-2-deoxy- β -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene

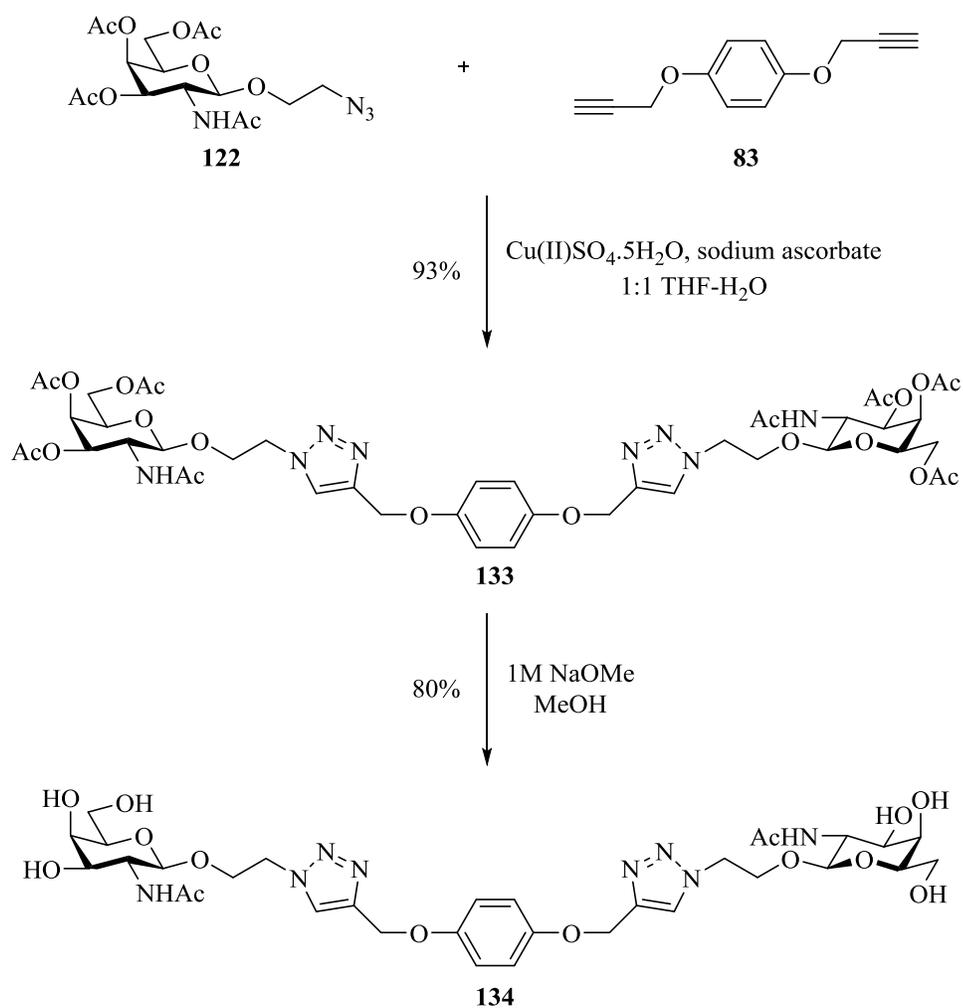
The synthesis of the bivalent compound, **132**, bearing *O*-glycoside headgroups was carried out next. The β -GalNAc azide, **122**, was reacted in the usual manner, as for the bivalent thio-glycoclusters - with *m*-bispropargyloxybenzene, **82**, Cu(II)SO₄·5H₂O and sodium ascorbate in 1:1 THF-H₂O, to give the compound, after column chromatography, **131**, in high yields. The bivalent compound was deprotected under Zemplén deacetylation conditions, followed by purification by reverse phase column chromatography, to give **132** in an 84% yield.



Scheme 3.10 Synthesis of 1,3-di[1-(ethyl 2-acetamido-2-deoxy- β -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene.

Synthesis of 1,4-di[1-(ethyl 2-acetamido-2-deoxy- β -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene

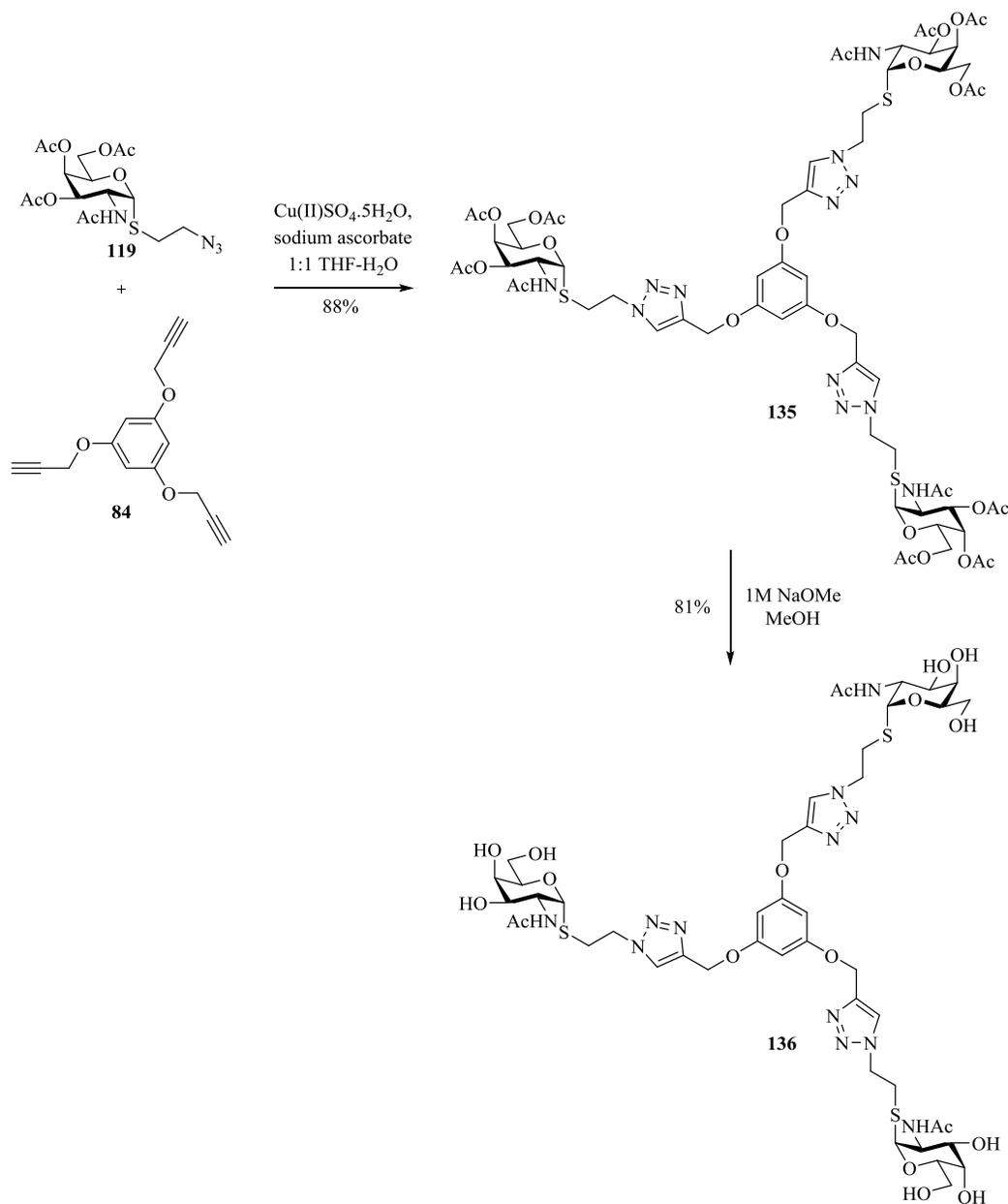
The alternative β -O-GalNAc bivalent compound, **133**, was prepared by the reaction of the β -azido GalNAc glycoside, **122**, with the propargyl hydroquinone linker, **83**, by the CuAAC reaction, described previously, for the synthesis of the other glycoclusters. The protected glycocluster, **133**, was obtained in excellent, 93%, yields, after isolation by column chromatography. Subsequent deacetylation of this derivative, using sodium methoxide, and purification by reverse phase chromatography gave the bivalent compound, **134**, in high yields.



Scheme 3.11 Synthesis of 1,4-di[1-(ethyl 2-acetamido-2-deoxy- β -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene.

Synthesis of 1,3,5-tri[1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene

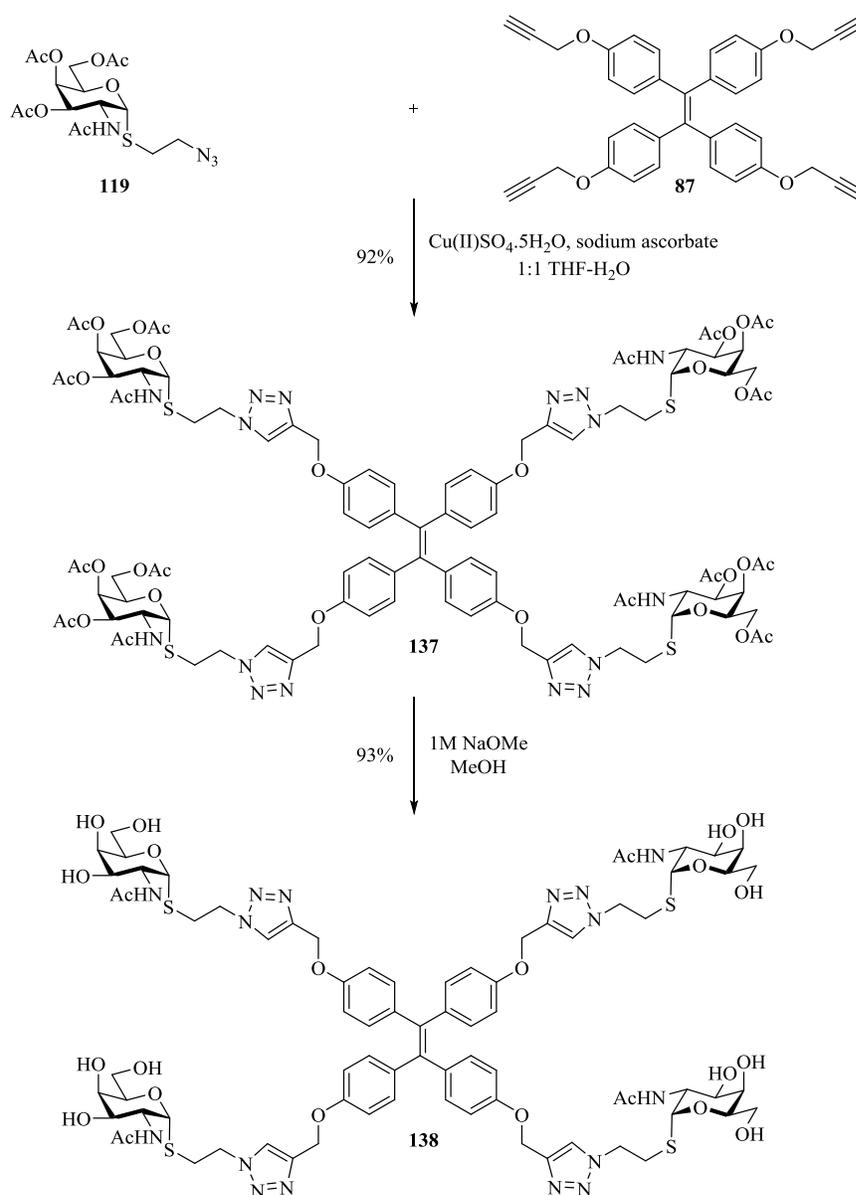
The preparation of a compound with an increase in valency was obtained by the reaction of the α -GalNAc azide **119** with 1,3,5-trispropargyloxybenzene, **84**, by the CuAAC reaction, using the same conditions described previously. Column chromatography gave **135**, in high yields. This trivalent compound was then deacetylated using freshly prepared 1M sodium methoxide solution. Purification of this deprotected multivalent ligand was carried out by reverse phase column chromatography, with good yields of **136** being attained.



Scheme 3.12 Synthesis of 1,3,5-tri[1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene.

Synthesis of 1,1,2,2-tetrakis[4-(1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -*D*-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy)-phenyl]-ethene

The preparation of a tetravalent compound was obtained by reacting the α -azido GalNAc thioglycoside, **119**, with the fluorescent tetra-linker **87**. The CuAAC reaction of α -GlcNAc azide **119** with 1,1,2,2-tetrakis(4-prop-2-yn-1-yloxy benzene)-ethene **87**, using Cu(II)SO₄·5H₂O and sodium ascorbate, in a 1:1 THF-H₂O mixture gave, after flash chromatography, the tetravalent compound, **137**, in high yields. This was then deprotected under Zemplén deacetylation conditions. Purification of the deprotected compound, **138**, was obtained by reverse phase column chromatography, in a 93% yield.



Scheme 3.13 Synthesis of 1,1,2,2-tetrakis[4-(1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -*D*-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy)-phenyl]-ethene

3.3.3 Biological evaluation

These GalNAc multivalent derivatives were provided to collaborators of the Murphy laboratory, Han-Joachim Gabius and Sabine André of the Ludwig-Maximilians-University Munich, to be evaluated as lectin inhibitors. These studies have now been completed with the biological data being compiled in addition with the work herein. This collaborative work has been published in *Organic and Biomolecular Chemistry* (*Org. Biomol. Chem.*, **2015**, *13*, 4190-4203).

Various levels of inhibition were obtained for the plant type lectins as well as macrophage galactose(-binding C)-type lectin (MGL). All the GalNAc derivatives, synthesized herein, were active against MGL, with the tetravalent compound **138** being the most potent. For the bivalent compounds, those with an α -configuration as the thioglycoside, **124** and **126**, gave the best results of that series with an improvement in inhibition being obtained by increasing the valency to the trivalent derivative **136**. The tetravalent tetraphenylethene **138** was shown to be highly potent, blocking binding of the lectin to a matrix and to cells in the nM range. It was over 400,000 fold more potent than GalNAc and considerably more potent than the bivalent and trivalent GalNAc derivatives.

The next step(s) could be to increase the valency of the compounds further than those synthesized to date - to carry out more detailed structure activity studies to determine the reasons for this major potency gain from using the tetraphenylethene derivative. An additional parameter that could be investigated is lengthening of the distances between the headgroups, to see if this variation in length and thereby possible access to further binding sites, as covered in section 2.1.3, would provide better multivalent compounds.

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Chapter 4: Experimental data

4.1 General experimental conditions

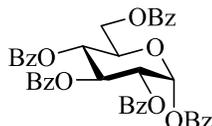
Compounds that are known in the literature already have been cited herein. Unless otherwise stated analytical data e.g. ^1H NMR and/or ^{13}C NMR, obtained during this thesis work has been found to be in agreement with previously published data.

NMR spectra were recorded with 500 & 600 MHz Varian spectrometers. Chemical shifts are reported relative to internal Me_4Si in CDCl_3 (δ 0.0), HOD for D_2O (δ 4.84) or CD_2HOD (δ 3.31) for ^1H and CDCl_3 (δ 77.16) or CD_3OD (δ 49.05) for ^{13}C . NMR spectra were processed and analysed using MestReNova software. ^1H NMR signals were assigned with the aid of gCOSY. ^{13}C NMR signals were assigned with the aid of DEPT, gHSQCAD and/or gHMBCAD. Coupling constants are reported in Hertz, with all J values reported uncorrected. Low and high resolution mass spectra were measured on a Waters LCT Premier XE Spectrometer, measuring in both positive and/or negative mode as, using MeCN, H_2O and/or MeOH as solvent. FT-IR spectra were recorded with a Perkin Elmer Spectrum 100 FTIR Spectrometer with a polarized UATR (Universal Attenuated Total Reflectance) accessory. Optical rotations were determined at the sodium D line at 20°C with a Schmidt & Haensch Unipol L 1000 polarimeter, using the solvents indicated (i.e. either CHCl_3 or DMSO). Thin layer chromatography (TLC) was performed on aluminium sheets precoated with silica gel 60 (HF_{254} , E. Merck) and spots visualized by UV and charring with H_2SO_4 -EtOH (1:20), or cerium molybdate. Flash chromatography was carried out with silica gel 60 (0.040-0.630 mm, E. Merck or Aldrich) and using a stepwise solvent polarity gradient (starting with the conditions indicated in each case and increasing the polarity as required). correlated with TLC mobility. Chromatography solvents, petroleum ether (fraction with b.p. $40 - 60^\circ\text{C}$), cyclohexane, EtOAc, CH_2Cl_2 and MeOH were used as obtained from suppliers (Fisher Scientific and Sigma-Aldrich). Reverse phase chromatography was carried out with C_{18} -reversed phase silica gel (100 Å pore size, Fluka) The MeCN used was HPLC grade and used as obtained from suppliers (Lab-Scan), while the H_2O used was distilled. Anhydrous pyridine was purchased from Sigma Aldrich with further reactions solvents, for anhydrous conditions, being obtained from a Pure Solv™ Solvent Purification System.

Note: H_2SO_4 -silica was prepared by stirring a slurry of silica gel (10 g) in dry Et_2O (50 ml), to which was added H_2SO_4 , for 10 mins. The solvent was then removed under reduced pressure after which the silica was dried in an oven, at 130°C , for 3h.

4.2 Experimental data – Chapter 1

1,2,3,4,6-Penta-*O*-benzoyl- α -D-glucopyranose (1)¹



D-Glucose (10.0 g, 55.5 mmol) was dissolved in pyridine (120 mL), and cooled to 0 °C. To this, benzoyl chloride (42 mL 362 mmol) was added slowly, portion wise, with the reaction being allowed to warm to room temperature overnight with stirring. After which point MeOH (50 mL) was added and stirred for 15 mins to decompose the excess benzoyl chloride. The reaction mixture was diluted with CH₂Cl₂ and washed with 1M HCl, water, brine, dried over MgSO₄ and the solvent removed under reduced pressure. Recrystallisation from EtOAc-hexane gave the title compound (30.7 g, 79%) as a colourless solid.

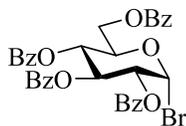
¹H NMR (500 MHz, CDCl₃) δ 8.17 (dd, J = 8.3, 1.4 Hz, 2H, Ar-H), 8.03 (dd, J = 8.3, 1.4 Hz, 2H, Ar-H), 7.95 (dd, J = 8.3, 1.4 Hz, 2H, Ar-H), 7.92 – 7.83 (m, 4H, Ar-H), 7.69 – 7.65 (m, 1H, Ar-H), 7.58 – 7.27 (m, 14H, Ar-H), 6.85 (d, J = 3.7 Hz, 1H, H-1), 6.32 (t, J = 10.0 Hz, 1H, H-3), 5.86 (t, J = 9.8 Hz, 1H, H-4), 5.68 (dd, J = 10.3, 3.8 Hz, 1H, H-2), 4.65 – 4.58 (m, 2H, H-5, H-6a), 4.52 – 4.45 (m, 1H, H-6b).

¹³C NMR (126 MHz, CDCl₃) δ ¹³C NMR (126 MHz, cdcl₃) δ 166.05, 165.87, 165.32, 165.09, 164.37 (each C=O), 133.89, 133.50, 133.46, 133.33, 133.11, 130.01, 129.86, 129.82, 129.76, 129.72, 129.51, 128.96, 128.80, 128.77, 128.67, 128.54, 128.42, 128.39, 128.36 (each Ar-C), 90.02 (C-1), 70.47 (C-3), 70.44 (C-5), 70.40 (C-2), 68.81 (C-4), 62.44 (C-6).

ES-HRMS calcd for C₄₁H₃₆N₁O₁₁ 718.2288, found m/z 718.2253 [M+NH₄]⁺

IR (ATR) cm⁻¹: 3065, 1728, 1451, 1262, 1092, 1068, 1020, 707

R_f: 0.54 (3:7 EtOAc-Pet ether)

2,3,4,6-Tetra-*O*-benzoyl- α -D-glucopyranosyl bromide (2)²

Compound **1** (30.3 g, 43.2 mmol) was dissolved in CH₂Cl₂ (190 mL) and cooled to 0 °C. To this stirring solution was added HBr (33% in AcOH, 90 mL). The reaction was allowed warm to r.t. overnight with stirring. The reaction mixture was then poured onto ice water, stirred for 15 mins and separated. The aqueous layer was re-extracted with CH₂Cl₂. The combined organic layers were washed with NaHCO₃ (sat.), brine, dried over MgSO₄. The solvent was removed under reduced pressure, to give the title compound (28.0 g, 98%) as a colourless solid.

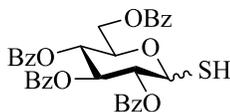
¹H NMR (500 MHz, CDCl₃) δ 8.10 – 8.04 (m, 2H, Ar-H), 8.02 – 7.98 (m, 2H, Ar-H), 7.98 – 7.93 (m, 2H, Ar-H), 7.90 – 7.85 (m, 2H, Ar-H), 7.61 – 7.49 (m, 2H, Ar-H), 7.48 – 7.34 (m, 8H, Ar-H), 7.34 – 7.27 (m, 2H, Ar-H), 6.87 (d, J = 4.0 Hz, 1H, H-1), 6.27 (t, J = 9.8 Hz, 1H, H-3), 5.83 (t, J = 10.0 Hz, 1H, H-4), 5.33 (dd, J = 10.0, 4.0 Hz, 1H, H-2), 4.78 – 4.71 (m, 1H, H-5), 4.67 (dd, J = 12.5, 2.7 Hz, 1H, H-6a), 4.52 (dd, J = 12.5, 4.5 Hz, 1H, H-6b).

¹³C NMR (126 MHz, CDCl₃) δ 165.99, 165.54, 165.28, 165.06 (each C=O), 133.78, 133.62, 133.32, 133.23, 130.07, 129.92, 129.82, 129.81, 129.73, 129.44, 128.79, 128.54, 128.51, 128.47, 128.44, 128.37, 128.34 (each Ar-C), 86.87 (C-1), 72.71 (C-5), 71.46 (C-2), 70.62 (C-3), 68.00 (C-4), 61.94 (C-6).

ES-HRMS calcd for C₃₄H₂₇O₉Br₁Na₁ 681.0736, found m/z 681.0750 [M+ Na]⁺

IR (ATR) cm⁻¹: 1723, 1602, 1451, 1260, 1091, 1068, 1026, 706

R_f: 0.41 (1:4 EtOAc-Pet ether)

2,3,4,6-Tetra-*O*-benzoyl-1-thio- α/β -D-glucopyranose (3)³

Compound **2** (18.2 g, 27.6 mmol) was dissolved in acetone (270 mL) and to this solution was added thiourea (3.60 g, 47.3 mmol). The reaction was heated to reflux (60 °C) and stirred at this temperature overnight. The clear solution was cooled to r.t. and concentrated under reduced pressure.

The salt was used without any purification. The glycosyl thiourea was suspended in a 3:2 CH₂Cl₂-H₂O mixture (300 mL) to which sodium metabisulfite (6.83 g, 35.9 mmol) was added. The reaction mixture was heated to reflux (42 °C) and stirred for 4 h. The solution was cooled to r.t. and separated. The aqueous layer was re-extracted with CH₂Cl₂. The combined organic layers were washed with H₂O, dried over MgSO₄, with the solvent then being removed under reduced pressure. Chromatography (EtOAc-Pet Ether 1:3) gave the title compound (14.9 g, 88%) as a colourless solid, as a mixture of anomers (α/β 1:5).

¹H NMR (500 MHz, CDCl₃) δ 8.08 – 8.02 (m, 4H, Ar-H), 8.01 – 7.93 (m, 4H, Ar-H), 7.91 – 7.87 (m, 4H, Ar-H), 7.83 – 7.79 (m, 4H, Ar-H), 7.58 – 7.47 (m, 6H, Ar-H), 7.46 – 7.26 (m, 18H, Ar-H), 6.20 (t, $J = 5.6$ Hz, 1H, H-1 α), 6.08 (t, $J = 9.9$ Hz, 1H, H-3 α), 5.89 (t, $J = 9.6$ Hz, 1H, H-3 β), 5.72 (t, $J_{3\beta/5\beta,4\beta} = 9.8$ Hz, 2H, H-4 α , H-4 β), 5.51 (t, $J_{1\beta/3\beta,2\beta} = 9.6$ Hz, 2H, H-2 α , H-2 β), 4.90 (t, $J_{SH\beta/2\beta,1\beta} = 9.6$ Hz, 2H, H-5 α , H-1 β), 4.63 (dd, $J_{5\beta/6a\beta,6a\beta} = 12.3$, 3.1 Hz, 2H, H-6 $\alpha\alpha$, H-6 $\alpha\beta$), 4.49 (dd, $J_{5\beta/6a\beta,6b\beta} = 12.3$, 4.9 Hz, 2H, H-6 $\beta\alpha$, H-6 $\beta\beta$), 4.18 (ddd, $J = 10.0$, 5.0, 3.0 Hz, 1H, H-5), 2.48 (d, $J = 9.5$ Hz, 1H, SH β), 2.08 (d, $J = 5.7$ Hz, 1H, SH α).

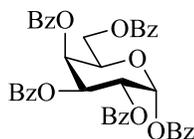
¹³C NMR (126 MHz, CDCl₃) δ 166.13, 165.74, 165.71, 165.67, 165.42, 165.23, 165.16, 165.10 (each C=O), 133.62, 133.48, 133.46, 133.27, 133.13, 129.96, 129.90, 129.86, 129.81, 129.79, 129.71, 129.70, 129.54, 128.93, 128.68, 128.51, 128.45, 128.42, 128.40, 128.34, 128.32, 128.29 (each Ar-C), 79.17 (C-1 β), 77.58 (C-1 α), 76.75 (C-5 β), 74.19 (C-2 β), 73.80 (C-3 β), 71.24 (C-2 α), 70.28 (C-3 α), 69.35 (C-4 β), 69.15 (C-4 α), 68.89 (C-5 α), 63.14 (C-6 β), 62.63 (C-6 α).

ES-HRMS calcd for C₃₄H₂₈O₉S₁Na₁ 635.1352, found m/z 635.1354 [M+ Na]⁺

IR (ATR) cm⁻¹: 1721, 1602, 1451, 1259, 1089, 1067, 707

R_f : 0.82 (3:7 EtOAc-Pet ether)

$[\alpha]_D^{20} +55.3$ (c 0.85, CHCl₃)

1,2,3,4,6-Penta-*O*-benzoyl- α -D-galactopyranose (4)⁴

D-Galactose (10.0 g, 55.5 mmol) was dissolved in pyridine (260 mL) and cooled to 0 °C. To this, benzoyl chloride (42 mL 362 mmol) was added slowly, portion wise, with the reaction being allowed to warm to room temperature overnight with stirring. After which point MeOH (50 mL) was added and stirred for 15 mins to decompose the excess benzoyl chloride. The reaction mixture was diluted with CH₂Cl₂ and washed with 1M HCl, water, brine, dried over MgSO₄ and the solvent removed under reduced pressure. Chromatography (EtOAc-Pet Ether 1:4) gave the title compound (35.2 g, 90%) as a colourless solid.

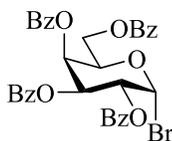
¹H NMR (500 MHz, CDCl₃) δ 8.16 – 8.09 (m, 4H, Ar-H), 7.96 (dd, J = 8.3, 1.4 Hz, 2H, Ar-H), 7.86 (dd, J = 8.4, 1.4 Hz, 2H, Ar-H), 7.82 (dd, J = 8.4, 1.4 Hz, 2H, Ar-H), 7.68 – 7.61 (m, 2H, Ar-H), 7.55 – 7.49 (m, 5H, Ar-H), 7.49 – 7.43 (m, 2H, Ar-H), 7.41 – 7.37 (m, 2H, Ar-H) 7.32 – 7.27 (m, 4H, Ar-H), 6.95 (d, J = 3.6 Hz, 1H, H-1), 6.19 (dd, J = 3.4, 1.3 Hz, 1H, H-4), 6.13 (dd, J = 10.7, 3.3 Hz, 1H, H-3), 6.03 (dd, J = 10.7, 3.7 Hz, 1H, H-2), 4.84 (t, J = 6.9 Hz, 1H, H-5), 4.63 (dd, J = 11.4, 6.4 Hz, 1H, H-6a), 4.42 (dd, J = 11.3, 6.9 Hz, 1H, H-6b).

¹³C NMR (126 MHz, CDCl₃) δ 165.88, 165.66, 165.52, 165.45, 164.50 (each C=O), 133.87, 133.70, 133.44, 133.36, 133.21, 130.56, 129.95, 129.92, 129.74, 129.73, 129.27, 128.99, 128.95, 128.86, 128.82, 128.76, 128.71, 128.69, 128.39, 128.38, 128.33 (each Ar-C), 90.65 (C-1), 69.43 (C-5), 68.51 (C-3), 68.45 (C-4), 67.67 (C-2), 61.81 (C-6).

ES-HRMS calcd for C₄₃H₃₅N₁O₁₁Na₁ 764.2108, found m/z 764.2104 [M+MeCN+Na]⁺

IR (ATR) cm⁻¹: 3063, 1724, 1452, 1259, 1093, 1068, 1023, 707

R_f: 0.56 (3:7 EtOAc-Pet ether)

2,3,4,6-Tetra-*O*-benzoyl- α -D-galactopyranosyl bromide (5)⁴

Compound **4** (34.4 g 49.1 mmol) was dissolved in CH_2Cl_2 (275 mL) and cooled to 0 °C. To this stirring solution was added HBr (33% in AcOH, 100 mL). The reaction was allowed warm to r.t. overnight, with stirring. The reaction mixture was then poured onto ice water, stirred for 15 mins and separated. The aqueous layer was re-extracted with CH_2Cl_2 . The combined organic layers were washed with NaHCO_3 (sat.), brine, dried over MgSO_4 . The solvent was removed under reduced pressure, to give the title compound (32.2 g, 99%) as a colourless solid.

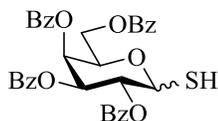
^1H NMR (500 MHz, CDCl_3) δ 8.09 – 8.04 (m, 2H), 8.03 – 7.99 (m, 4H), 7.81 – 7.78 (m, 2H), 7.66 – 7.61 (m, 1H), 7.58 – 7.52 (m, 2H), 7.52 – 7.46 (m, 3H), 7.46 – 7.38 (m, 5H), 7.30 – 7.23 (m, 1H), 6.98 (d, $J = 4.0$ Hz, 1H, H-1), 6.12 (dd, $J = 3.5, 1.3$ Hz, 1H, H-4), 6.05 (dd, $J = 10.4, 3.4$ Hz, 1H, H-3), 5.67 (dd, $J = 10.4, 4.0$ Hz, 1H, H-2), 4.92 (t, $J = 6.5$ Hz, 1H, H-5), 4.64 (dd, $J = 11.6, 6.8$ Hz, 1H, H-6), 4.47 (dd, $J = 11.6, 6.0$ Hz, 1H, H-6).

^{13}C NMR (126 MHz, CDCl_3) δ 165.89, 165.52, 165.31, 165.27 (each C=O), 133.76, 133.35, 133.30, 129.99, 129.92, 129.79, 129.73, 128.78, 128.70, 128.53, 128.43, 128.31 (each Ar-C), 88.24 (C-1), 71.81 (C-5), 68.86 (C-3), 68.58 (C-2), 68.05 (C-4), 61.65 (C-6)

ES-HRMS calcd for $\text{C}_{34}\text{H}_{27}\text{O}_9$ 579.1655, found m/z 579.1654 $[\text{M}-\text{Br}]^+$; ES-HRMS calcd for $\text{C}_{34}\text{H}_{27}\text{O}_9\text{Na}_1\text{Br}_1$ 681.0736, found m/z 681.0731 $[\text{M}+\text{Na}]^+$

IR (ATR) cm^{-1} : 1724, 1602, 1452, 1264, 1094, 1070, 708

R_f : 0.40 (1:4 EtOAc-Pet ether)

2,3,4,6-Tetra-*O*-benzoyl-1-thio- α/β -D-galactopyranose (6)¹

Compound **5** (20.1 g, 30.5 mmol) was dissolved in acetone (300 mL) and to this solution was added thiourea (3.95 g, 51.9 mmol). The reaction was heated to reflux (60 °C) and stirred overnight at this temperature. The clear solution was cooled to r.t. and concentrated under reduced pressure.

The salt was used without any purification. The solid was suspended in a 3:2 CH₂Cl₂-H₂O mixture (330 mL) to which sodium metabisulfite (7.53 g, 39.6 mmol) was added. The reaction mixture was heated to reflux (42 °C) and stirred for 4 h. The solution was cooled to r.t. and separated. The aqueous layer was re-extracted with CH₂Cl₂. The combined organic layers were washed with H₂O, dried over MgSO₄, with the solvent then being removed under reduced pressure. Chromatography (EtOAc-Pet Ether 1:3) gave the title compound (17.8 g, 95%) as a colourless solid, as a mixture of anomers (α/β 1:2).

¹H NMR (500 MHz, CDCl₃) δ 8.11 – 8.06 (m, 4H, Ar-H), 8.05 – 8.00 (m, 4H, Ar-H), 7.99 – 7.94 (m, 4H, Ar-H), 7.81 – 7.75 (m, 4H, Ar-H), 7.66 – 7.60 (m, 2H, Ar-H), 7.58 – 7.47 (m, 8H, Ar-H), 7.46 – 7.37 (m, 12H, Ar-H), 7.25 – 7.22 (m, 2H, Ar-H), 6.31 (t, J = 5.1 Hz, 1H, H-1 α), 6.06 (dd, J = 3.3, 1.2 Hz, 1H, H-4 α), 6.04 (dd, J = 3.4, 1.0 Hz, 1H, H-4 β), 5.94 – 5.82 (m, 2H, H-2 α , H-3 α), 5.76 (t, J = 9.8 Hz, 1H, H-2 β), 5.62 (dd, J = 10.0, 3.4 Hz, 1H, H-3 β), 5.09 – 5.01 (m, 1H, H-5 α), 4.92 (t, J = 9.7 Hz, 1H, H-1 β), 4.66 (dd, J = 11.0, 6.0 Hz, 1H, H-6 β), 4.61 (dd, J = 11.4, 6.7 Hz, 1H, H-6 α), 4.45 – 4.35 (m, 3H, H-5 β , H-6 β , H-6 α), 2.57 (d, J = 9.6 Hz, 1H, SH β), 2.00 (d, J = 5.1 Hz, 1H, SH α).

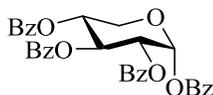
¹³C NMR (126 MHz, CDCl₃) δ 166.04, 165.99, 165.98, 165.59, 165.52, 165.46, 165.45, 165.43, 165.42 (each C=O), 133.66, 133.63, 133.48, 133.32, 133.31, 133.24, 129.98, 129.95, 129.91, 129.82, 129.78, 129.75, 129.74, 129.03, 129.00, 128.78, 128.67, 128.53, 128.45, 128.43, 128.30 (each Ar-C), 79.46 (C-1 β), 78.24 (C-1 α), 75.59 (C-5 β), 72.35 (C-3 β), 71.90 (C-2 β), 68.81 (C-4 α), 68.50 (C-3 α), 68.33 (C-2 α), 68.32 (C-4 β), 67.90 (C-5 α), 62.18 (C-6 α), 62.10 (C-6 β)

ES-HRMS calcd for C₃₄H₂₈O₉S₁Na₁ 635.1352, found m/z 635.1336 [M+ Na]⁺

IR (ATR) cm⁻¹: 1722, 1451, 1262, 1094, 1069, 1027, 707

R_f: Spot 1: 0.60; Spot 2: 0.70 (3:7 EtOAc-Pet ether)

$[\alpha]_D^{20}$ +129.1 (c 0.79, CHCl₃)

1,2,3,4-Tetra-*O*-benzoyl- α -D-xylopyranose (10)

D-Xylose (5.00 g, 33.3 mmol) was dissolved in pyridine (60 mL) and cooled to 0 °C. To this, benzoyl chloride (22 mL 189 mmol) was added slowly, portion wise, with the reaction being allowed to warm to room temperature overnight with stirring. After which point MeOH (20 mL) was added and stirred for 15 mins to decompose the excess benzoyl chloride. The reaction mixture was diluted with CH₂Cl₂ and washed with 1M HCl, water, brine, dried over MgSO₄ and the solvent removed under reduced pressure. Chromatography (EtOAc-Pet Ether 1:4) gave the title compound (17.6 g, 93%) as a colourless solid.

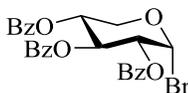
¹H NMR (500 MHz, CDCl₃) δ 8.15 (d, J = 7.7 Hz, 2H, Ar-H), 7.99 (d, J = 7.7 Hz, 2H, Ar-H), 7.95 (d, J = 7.8 Hz, 2H, Ar-H), 7.89 (d, J = 7.8 Hz, 2H, Ar-H), 7.67 – 7.28 (m, 12H, Ar-H), 6.76 (d, J = 2.8 Hz, 1H, H-1), 6.27 (t, J = 9.8 Hz, 1H, H-3), 5.63 (dd, J = 9.9, 2.8 Hz, 1H, H-2), 5.54 (td, J = 10.1, 6.1 Hz, 1H, H-4), 4.30 (dd, J = 11.3, 5.7 Hz, 1H, H-5a), 4.04 (t, J = 11.0 Hz, 1H, H-5b).

¹³C NMR (126 MHz, CDCl₃) δ ¹³C NMR (126 MHz, cdcl₃) δ 165.84, 165.49, 165.35, 164.58 (each C=O), 133.82, 133.51, 133.44, 133.37, 129.98, 129.96, 129.86, 129.81, 129.73, 129.02, 128.96, 128.84, 128.72, 128.62, 128.46, 128.40 (each Ar-C), 90.23 (C-1), 70.27 (C-2), 69.93 (C-3), 69.48 (C-4), 61.21 (C-5).

ES-HRMS calcd for C₃₃H₂₆O₉Na₁ 589.1475, found m/z 589.1461 [M+Na]⁺

IR (ATR) cm⁻¹: 1730, 1542, 1260, 1108, 1094, 1021, 707

R_f : 0.62 (3:7 EtOAc-Pet ether)

1,2,3,4-Tetra-*O*-benzoyl- α -D-xylopyranosyl bromide (11)

Compound **10** (17.5 g 30.9 mmol) was dissolved in CH_2Cl_2 (170 mL) and cooled to 0 °C. To this stirring solution was added HBr (33% in AcOH, 53 mL). The reaction was allowed warm to r.t. overnight with stirring. The reaction mixture was then poured onto ice water, stirred for 15 mins and separated. The aqueous layer was re-extracted with CH_2Cl_2 . The combined organic layers were washed with NaHCO_3 (sat.), brine, dried over MgSO_4 and the solvent removed under reduced pressure, to give the title compound (15.3 g, 94%) as a colourless solid.

^1H NMR (500 MHz, CDCl_3) δ 8.04 – 7.96 (m, 4H, Ar-H), 7.96 – 7.89 (m, 2H, Ar-H), 7.59 – 7.51 (m, 2H, Ar-H), 7.50 – 7.44 (m, 1H, Ar-H), 7.44 – 7.38 (m, 4H, Ar-H), 7.37 – 7.31 (m, 2H, Ar-H), 6.82 (d, J = 3.2 Hz, 1H, H-1), 6.23 (t, J = 9.8 Hz, 1H, H-3), 5.49 (td, J = 10.1, 6.2 Hz, 1H, H-4), 5.28 (dd, J = 10.0, 3.4 Hz, 1H, H-2), 4.36 (dd, J = 11.4, 5.8 Hz, 1H, H-5), 4.13 (t, J = 11.0 Hz, 1H, H-5)

^{13}C NMR (126 MHz, CDCl_3) δ 165.52, 165.48, 165.31 (each C=O), 133.74, 133.60, 133.34, 130.04, 129.89, 129.72, 128.53, 128.50, 128.37 (each Ar-C), 87.89 (C-1), 71.43 (C-2), 70.01 (C-3), 68.82 (C-4), 62.92 (C-5).

ES-HRMS calcd for $\text{C}_{26}\text{H}_{21}\text{O}_7$ 445.1287, found m/z 445.1284 $[\text{M}-\text{Br}]^+$

IR (ATR) cm^{-1} : 1721, 1601, 1452, 1247, 1091, 1068, 1026, 704

R_f : 0.56 (1:4 EtOAc-Pet ether)

2,3,4-Tri-*O*-benzoyl-1-thio- α/β -D-xylopyranose (12)

Sugar **11** (11.6 g, 22.1 mmol) was dissolved in acetone (170 mL) and to this solution was added thiourea (2.86 g, 37.6 mmol). The reaction was heated to reflux (60 °C) and stirred overnight. The clear solution was cooled to r.t. and concentrated under reduced pressure.

The salt was used without any purification. It was suspended in a 3:2 CH₂Cl₂-H₂O mixture (200 mL) to which sodium metabisulfite (5.46 g, 28.7 mmol) was added. The reaction mixture was heated to reflux (42 °C) and stirred for 4 h. The solution was cooled to r.t. and separated. The aqueous layer was re-extracted with CH₂Cl₂. The combined organic layers were washed with H₂O, dried over MgSO₄ and the solvent removed under reduced pressure. Chromatography (EtOAc-Pet Ether 1:3) gave the title compound (8.28 g, 78%) as a colourless solid, as a mixture of anomers (α/β 1:2).

¹H NMR (500 MHz, CDCl₃) δ 8.06 – 8.02 (m, 2H, Ar-H), 8.00 – 7.92 (m, 10H, Ar-H), 7.59 – 7.46 (m, 16H, Ar-H), 7.44 – 7.30 (m, 12H, Ar-H), 5.97 (t, J = 8.3 Hz, 1H, H-3 α), 5.94 (dd, J = 7.1, 5.1 Hz, 1H, H-1 α), 5.80 (t, J = 8.0 Hz, 1H, H-3 β), 5.44 – 5.40 (m, 2H, H-2 α , H-2 β), 5.39 – 5.31 (m, 2H, H-4 α , H-4 β), 5.01 (dd, J = 9.4, 7.7 Hz, 1H, H-1 β), 4.56 (dd, J = 11.9, 4.8 Hz, 1H, H-5 β), 4.30 (dd, J = 11.9, 8.5 Hz, 1H, H-5 α), 4.18 (dd, J = 11.9, 5.0 Hz, 1H, H-5 α), 3.70 (dd, J = 11.9, 8.4 Hz, 1H, H-5 β), 2.46 (d, J = 9.4 Hz, 1H, SH β), 2.14 (d, J = 6.7 Hz, 1H, SH α).

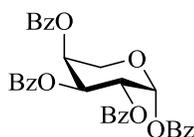
¹³C NMR (126 MHz, CDCl₃) δ 165.50, 165.44, 165.39, 165.37, 165.29, 165.27 (each C=O), 133.60, 133.44, 133.41, 130.00, 129.89, 129.85, 129.82, 129.75, 129.00, 128.96, 128.85, 128.75, 128.52, 128.43, 128.41, 128.38 (each Ar-C), 78.84 (C-1 β), 77.41 (C-1 α), 73.19 (C-2 β), 71.79 (C-3 β), 71.03 (C-2 α), 69.19 (C-4 β), 69.15 (C-3 α), 69.05 (C-4 α), 65.42 (C-5 β), 61.44 (C-5 α).

ES-HRMS calcd for C₂₆H₂₂O₇S₁Na₁ 501.0984, found m/z 501.0986 [M+ Na]⁺

IR (ATR) cm⁻¹: 1720, 1601, 1451, 1246, 1090, 1068, 706

R_f: Spot 1: 0.34; Spot 2: 0.45 (1:4 EtOAc-Pet ether)

$[\alpha]_D^{20}$ +9.2 (c 0.71, CHCl₃)

1,2,3,4-Tetra-*O*-benzoyl- β -L-arabinopyranose (13)⁵

L-Arabinose (5.00 g, 33.3 mmol) was dissolved in pyridine (75 mL) and cooled to 0 °C. To this, benzoyl chloride (21 mL 181 mmol) was added slowly, portion wise, with the reaction being allowed to warm to room temperature overnight with stirring. After which point MeOH (20 mL) was added and stirred for 15 mins to decompose the excess benzoyl chloride. The reaction mixture was diluted with CH₂Cl₂ and washed with 1M HCl, water, brine, dried over MgSO₄ and the solvent removed under reduced pressure. The product was washed thoroughly with MeOH through vacuum filtration to give the title compound (15.6 g, 83%) as a colourless solid.

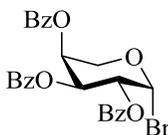
¹H NMR (500 MHz, CDCl₃) δ 8.15 – 8.09 (m, 4H, Ar-H), 7.90 – 7.86 (m, 4H, Ar-H), 7.68 – 7.59 (m, 2H, Ar-H), 7.55 – 7.44 (m, 6H, Ar-H), 7.33 – 7.28 (m, 4H), 6.86 (d, J = 1.6 Hz, 1H, H-1), 6.09 – 6.04 (m, 2H, H-2, H-3), 5.93 – 5.83 (m, 1H, H-4), 4.45 – 4.35 (m, 1H, H-5a), 4.18 (dd, J = 13.4, 2.0 Hz, 1H, H-5b).

¹³C NMR (126 MHz, CDCl₃) δ 165.74, 165.72, 165.56, 164.67 (each C=O), 133.82, 133.56, 133.43, 133.39, 129.90, 129.74, 129.34, 129.12, 128.92, 128.78, 128.73, 128.61, 128.40, 128.38 (each Ar-C), 91.08 (C-1), 69.48 (C-4), 68.18 (C-3), 67.76 (C-2), 63.01 (C-5).

ES-HRMS calcd for C₃₃H₂₆O₉Na₁ 589.1475, found m/z 589.1483 [M+Na]⁺

IR (ATR) cm⁻¹: 1721, 1602, 1451, 1245, 1090, 1011, 706

R_f : 0.62 (3:7 EtOAc-Pet ether)

2,3,4-Tri-*O*-benzoyl- β -L-arabinopyranosyl bromide (14)⁶

Sugar **13** (15.4 g, 27.2 mmol) was dissolved in CH₂Cl₂ (120 mL) and cooled to 0 °C. To this stirring solution was added HBr (33% in AcOH, 47 mL). The reaction was allowed warm to r.t. overnight with stirring. The reaction mixture was then poured onto ice water, stirred for 15 mins and separated. The aqueous layer was re-extracted with CH₂Cl₂. The combined organic layers were washed with NaHCO₃ (sat.), brine, dried over MgSO₄. The solvent was removed under reduced pressure, to give the title compound (13.9 g, 97%) as a colourless solid.

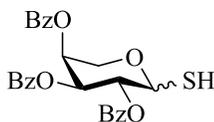
¹H NMR (500 MHz, CDCl₃) δ 8.12 – 8.07 (m, 2H, Ar-H), 8.04 – 8.00 (m, 2H, Ar-H), 7.87 – 7.83 (m, 2H, Ar-H), 7.65 – 7.60 (m, 1H, Ar-H), 7.57 – 7.53 (m, 1H, Ar-H), 7.52 – 7.46 (m, 3H, Ar-H), 7.43 – 7.39 (m, 2H, Ar-H), 7.32 – 7.27 (m, 2H, Ar-H), 6.92 (d, J = 3.8 Hz, 1H, H-1), 5.99 (dd, J = 10.5, 3.4 Hz, 1H, H-3), 5.82 (dt, J = 3.3, 1.6 Hz, 1H, H-4), 5.70 (dd, J = 10.4, 3.9 Hz, 1H, H-2), 4.47 (dd, J = 13.6, 1.8 Hz, 1H, H-5a), 4.23 (dd, J = 13.4, 1.9 Hz, 1H, H-5b).

¹³C NMR (126 MHz, CDCl₃) δ 165.55, 165.51, 165.39 (each C=O), 133.73, 133.61, 133.36, 129.99, 129.86, 129.72, 129.21, 128.89, 128.62, 128.60, 128.53, 128.35 (each Ar-C), 89.74 (C-1), 68.86 (C-4), 68.65 (C-2), 68.51 (C-3), 64.99 (C-5).

ES-HRMS calcd for C₂₆H₂₁O₇ 445.1287, found m/z 445.1295 [M-Br]⁺

IR (ATR) cm⁻¹: 1722, 1602, 1452, 1259, 1092, 1070, 709

R_f : 0.56 (1:4 EtOAc-Pet ether)

2,3,4-Tri-*O*-benzoyl-1-thio- α/β -L-arabinopyranose (15)

Compound **14** (9.67 g, 18.4 mmol) was dissolved in acetone (145 mL) and to this solution was added thiourea (2.38 g, 31.3 mmol). The reaction was heated to reflux (60 °C) and stirred at this temperature overnight. The clear solution was cooled to r.t. and concentrated under reduced pressure.

The salt was used without any purification. The urea intermediate was suspended in a 3:2 CH₂Cl₂-H₂O mixture (250 mL) to which sodium metabisulfite (4.55 g, 23.9 mmol) was added. The reaction mixture was heated to reflux (42 °C) and stirred for 4 h. The solution was cooled to r.t. and separated. The aqueous layer was re-extracted with CH₂Cl₂. The combined organic layers were washed with H₂O, dried over MgSO₄, with the solvent then being removed under reduced pressure. Chromatography (EtOAc-Pet Ether 1:3) gave the title compound (6.08 g, 69%) as a colourless solid, as a mixture of anomers (α/β 2:1).

¹H NMR (500 MHz, CDCl₃) δ 8.10 – 8.04 (m, 4H, Ar-H), 8.04 – 7.99 (m, 4H, Ar-H), 7.94 – 7.87 (m, 4H, Ar-H), 7.63 – 7.52 (m, 4H, Ar-H), 7.51 – 7.39 (m, 10H, Ar-H), 7.35 – 7.29 (m, 4H, Ar-H), 6.11 (dd, $J = 5.9, 3.6$ Hz, 1H, H-1 β), 5.88 – 5.81 (m, 2H, H-2 β , H-3 β), 5.78 – 5.70 (m, 3H, H-2 α , H-4 α , H-4 β), 5.62 (dd, $J = 8.9, 3.5$ Hz, 1H, H-3 α), 4.95 (t, $J = 9.0$ Hz, 1H, H-1 α), 4.57 (dd, $J = 13.2, 1.9$ Hz, 1H, H-5 $\alpha\beta$), 4.41 (dd, $J = 13.1, 3.6$ Hz, 1H, H-5 $\alpha\alpha$), 4.06 (dd, $J = 13.1, 3.3$ Hz, 1H, H-5 $\beta\beta$), 3.96 (dd, $J = 13.1, 1.9$ Hz, 1H, H-5 $\beta\alpha$), 2.52 (d, $J = 9.5$ Hz, 1H, SH α), 2.00 (d, $J = 5.8$ Hz, 1H, SH β).

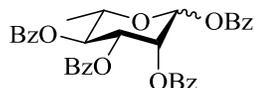
¹³C NMR (126 MHz, CDCl₃) δ 165.63, 165.60, 165.48, 165.44, 165.43, 165.36 (each C=O), 133.62, 133.50, 133.46, 133.45, 133.40, 133.36, 129.96, 129.92, 129.87, 129.84, 129.80, 129.40, 129.33, 129.05, 128.84, 128.82, 128.54, 128.53, 128.47, 128.40, 128.38 (each Ar-C), 79.03 (C-1 α), 78.14 (C-1 β), 72.19 (C-2 α), 71.33 (C-3 α), 69.15 (C-3 β , C-4 β), 68.77 (C-4 α), 67.89 (C-2 β), 66.60 (C-5 α), 61.91 (C-5 β)

ES-HRMS calcd for C₂₆H₂₂O₇S₁Na₁ 501.0984, found m/z 501.0966 [M+ Na]⁺

IR (ATR) cm⁻¹: 1720, 1602, 1451, 1276, 1247, 1087, 1069, 707

R_f: Spot 1: 0.59; Spot 2: 0.72 (3:7 EtOAc-Pet ether)

$[\alpha]_D^{20}$ +239.1 (c 0.85, CHCl₃)

1,2,3,4-Tetra-*O*-benzoyl- α/β -L-rhamnopyranose (16)⁷

L-Rhamnose monohydrate (5.00 g, 27.4 mmol) was dissolved in pyridine (65 mL) and cooled to 0 °C. To this, benzoyl chloride (21 mL 181 mmol) was added slowly, portion wise, with the reaction being allowed to warm to room temperature overnight with stirring. After which point MeOH (20 mL) was added and stirred for 15 mins to decompose the excess benzoyl chloride. The reaction mixture was diluted with CH₂Cl₂ and washed with 1M HCl, water, brine, dried over MgSO₄ and the solvent removed under reduced pressure. Chromatography (EtOAc-Pet Ether 1:4) gave the title compound (16.5 g, 93%), in an α/β ratio of 1:0.25, as a colourless solid.

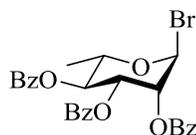
¹H NMR (500 MHz, CDCl₃) 8.23 – 8.16 (m, 4H, Ar-H), 8.15 – 8.10 (m, 4H, Ar-H), 8.01 – 7.92 (m, 4H, Ar-H), 7.87 – 7.81 (m, 4H Ar-H), 7.71 – 7.59 (m, 4H, Ar-H), 7.58 – 7.26 (m, 19H, Ar-H), 6.55 (d, *J* = 2.0 Hz, 1H, H-1 α), 6.35 (d, *J* = 1.4 Hz, 1H, H-1 β), 6.07 (dd, *J* = 2.7, 1.3 Hz, 1H, H-2 β), 5.99 (dd, *J* = 10.3, 3.3 Hz, 1H, H-3 α), 5.86 (dd, *J* = 3.4, 1.9 Hz, 1H, H-2 α), 5.80 (t, *J* = 10.0 Hz, 1H, H-4 α), 5.74 – 5.71 (m, 2H, H-3 β , H-4 β), 4.40 – 4.32 (m, 1H, H-5 α), 4.12 – 4.06 (m, 1H, H-5 β), 1.48 (d, *J* = 6.1 Hz, 3H, CH₃ β), 1.41 (d, *J* = 6.2 Hz, 3H, CH₃ α).

¹³C NMR (126 MHz, CDCl₃) δ 171.08, 165.72, 165.67, 165.65, 165.45, 165.31, 164.21, 164.00 (each C=O), 133.91, 133.71, 133.68, 133.64, 133.51, 133.46, 133.43, 133.29, 130.18, 130.11, 130.03, 130.00, 129.78, 129.74, 129.71, 129.41, 129.21, 129.09, 129.07, 129.05, 128.91, 128.81, 128.74, 128.63, 128.48, 128.47, 128.45, 128.41, 128.34, 128.31 (each Ar-C), 91.35 (C-1 α), 91.20 (C-1 β), 71.81 (C-5 β), 71.44 (C-3 β /C-4 β), 71.21(C-3 β /C-4 β), 71.19 (C-4 α), 69.87 (C-3 α), 69.76 (C-2 α), 69.63 (C-2 β), 69.34 (C-5 α), 17.72 (C-6 α), 17.72 (C-6 β).

ES-HRMS calcd for C₃₄H₂₈O₉Na₁ 603.1631, found *m/z* 603.1614 [M+Na]⁺

IR (ATR) cm⁻¹: 1728, 1602, 1452, 1261, 1093, 1068, 708

R_f: 0.76 (3:7 EtOAc-Pet ether)

2,3,4-Tri-*O*-benzoyl- α -L-rhamnopyranosyl bromide (17)⁷

Sugar **16** (16.1 g, 27.7 mmol) was dissolved in CH₂Cl₂ (160 mL) and cooled to 0 °C. To this stirring solution was added HBr (33% in AcOH, 48 mL). The reaction was allowed warm to r.t. overnight with stirring. The reaction mixture was then poured onto ice water, stirred for 15 mins and separated. The aqueous layer was re-extracted with CH₂Cl₂. The combined organic layers were washed with NaHCO₃ (sat.), brine, dried over MgSO₄. The solvent was removed under reduced pressure, to give the title compound (12.8 g, 86%) as a colourless solid.

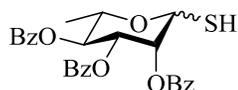
¹H NMR (500 MHz, CDCl₃) δ 8.11 – 8.06 (m, 2H, Ar-H), 8.03 – 7.98 (m, 2H, Ar-H), 7.85 – 7.81 (m, 2H, Ar-H), 7.66 – 7.61 (m, 1H, Ar-H), 7.57 – 7.48 (m, 3H, Ar-H), 7.46 – 7.38 (m, 3H, Ar-H), 7.30 – 7.25 (m, 2H, Ar-H), 6.55 (d, J = 1.5 Hz, 1H, H-1), 6.20 (dd, J = 10.3, 3.4 Hz, 1H, H-3), 5.87 (dd, J = 3.4, 1.6 Hz, 1H, H-2), 5.77 (t, J = 10.1 Hz, 1H, H-4), 4.43 (dq, J = 10.1, 6.2 Hz, 1H, H-5), 1.43 (d, J = 6.3 Hz, 3H, CH₃).

¹³C NMR (126 MHz, CDCl₃) δ 165.63, 165.32, 165.16 (each C=O), 133.76, 133.53, 133.27, 129.94, 129.79, 129.69, 128.93, 128.85, 128.84, 128.67, 128.50, 128.32 (each Ar-C), 83.84 (C-1), 73.40 (C-2), 71.46 (C-5), 70.97 (C-4), 68.88 (C-3), 17.21 (CH₃).

ES-HRMS calcd for C₂₇H₂₃O₇ 459.1444, found m/z 459.1455 [M-Br]⁺

IR (ATR) cm⁻¹: 1725, 1602, 1451, 1277, 1246, 1091, 1068, 706

R_f : 0.59 (1:4 EtOAc-Pet ether)

2,3,4-Tri-*O*-benzoyl-1-thio- α/β -L-rhamnopyranose (18)

Compound **17** (6.40 g, 11.9 mmol) was dissolved in acetone (95 mL) and to this solution was added thiourea (1.53 g, 20.1 mmol). The reaction was heated to reflux (60 °C) and stirred overnight. The clear solution was cooled to r.t. and concentrated under reduced pressure.

The salt was used without any purification. It was suspended in a 3:2 CH₂Cl₂-H₂O mixture (110 mL) to which sodium metabisulfite (2.93 g, 15.4 mmol) was added. The reaction mixture was heated to reflux (42 °C) and stirred for 4 h. The solution was then cooled to r.t. and separated. The aqueous layer was re-extracted with CH₂Cl₂. The combined organic layers were washed with H₂O, dried over MgSO₄, with the solvent then being removed under reduced pressure. Chromatography (EtOAc-Pet Ether 1:3) gave the title compound (4.98 g, 85%) as a colourless solid, as a mixture of anomers (α : β 1:3).

¹H NMR (500 MHz, CDCl₃) δ 8.13 – 8.08 (m, 4H, Ar-H), 8.02 – 7.97 (m, 2H, Ar-H), 7.95 – 7.91 (m, 2H, Ar-H), 7.85 – 7.81 (m, 2H, Ar-H), 7.79 – 7.75 (m, 2H, Ar-H), 7.66 – 7.58 (m, 2H, Ar-H), 7.56 – 7.47 (m, 6H, Ar-H), 7.46 – 7.35 (m, 5H, Ar-H), 7.29 – 7.21 (m, 5H, Ar-H), 5.94 – 5.89 (m, 1H, H-2 α), 5.84 (dd, J = 10.1, 3.4 Hz, 1H, H-3 β), 5.77 (dd, J = 6.9, 1.5 Hz, 1H, H-1 β), 5.75 (dt, J = 3.1, 1.3 Hz, 1H, H-2 β), 5.71 (t, J = 9.9 Hz, 1H, H-4 β), 5.59 – 5.57 (m, 2H, H-3 α , H-4 α), 5.12 (dd, J = 10.1, 1.2 Hz, 1H, H-1 α), 4.53 (dq, J = 12.3, 6.2 Hz, 1H, H-5 β), 3.90 (dq, J = 11.9, 5.9 Hz, 1H, H-5 α), 2.61 (d, J = 10.1 Hz, 1H, SH α), 2.40 (d, J = 6.9 Hz, 1H, SH β), 1.44 (d, J = 6.2 Hz, 3H, CH₃ α), 1.38 (d, J = 6.2 Hz, 3H, CH₃ β).

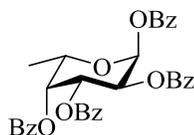
¹³C NMR (126 MHz, CDCl₃) δ 165.69, 165.58, 165.55, 165.49, 165.48, 165.47 (each C=O), 133.61, 133.56, 133.40, 133.23, 133.18, 130.03, 129.91, 129.74, 129.70, 129.69, 129.67, 129.24, 129.14, 128.92, 128.64, 128.60, 128.45, 128.43, 128.30, 128.23 (each Ar-C), 76.82 (C-1 β), 76.56 (C-1 α), 75.68 (C-5 α), 73.39 (C-2 β), 72.73 (C-2 α), 72.69 (C-3 α), 71.76 (C-4 β), 70.83 (C-4 α), 69.43 (C-3 β), 68.00 (C-5 β), 18.00 (CH₃ α), 17.54 (CH₃ β)

ES-HRMS calcd for C₂₉H₂₇O₇S₁Na₁N₁ 556.1406, found m/z 556.1404 [M+Na+MeCN]⁺

IR (ATR) cm⁻¹: 1722, 1602, 1451, 1279, 1247, 1091, 1068, 706

R_f : 0.71 (3:7 EtOAc-Pet ether)

$[\alpha]_D^{20}$ +155.8 (c 0.81, CHCl₃)

1,2,3,4-Tetra-*O*-benzoyl- α -L-fucopyranose (19)⁸

L-Fucose (1.00 g, 6.09 mmol) was dissolved in pyridine (17 mL) and cooled to 0 °C. To this, benzoyl chloride (3.60 mL, 31.0 mmol) was added slowly, portion wise, with the reaction being allowed to warm to room temperature overnight with stirring. After which point MeOH (15 mL) was added and stirred for 15 mins to decompose the excess benzoyl chloride. The reaction mixture was diluted with CH₂Cl₂ and washed with 1M HCl, water, brine, dried over MgSO₄ and the solvent removed under reduced pressure. Chromatography (EtOAc-Pet Ether 1:4→2:3→1:1) gave the title compound (3.23 g, 91%), as a colourless solid.

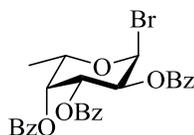
¹H NMR (500 MHz, CDCl₃) δ 8.15 – 8.09 (m, 4H, Ar-H), 7.87 – 7.80 (m, 4H, Ar-H), 7.67 – 7.62 (m, 2H, Ar-H), 7.55 – 7.49 (m, 4H, Ar-H), 7.47 – 7.42 (m, 2H, Ar-H), 7.32 – 7.23 (m, 4H, Ar-H), 6.87 (d, J = 3.6 Hz, 1H, H-1), 6.08 (dd, J = 10.8, 3.3 Hz, 1H, H-3), 5.99 (dd, J = 10.8, 3.7 Hz, 1H, H-2), 5.90 (dd, J = 3.4, 1.3 Hz, 1H, H-4), 4.64 (qd, J = 6.4, 1.2 Hz, 1H), 1.32 (d, J = 6.5 Hz, 3H, CH₃).

¹³C NMR (126 MHz, CDCl₃) δ 165.91, 165.78, 165.59, 164.67 (each C=O), 133.75, 133.56, 133.35, 133.28, 129.93, 129.89, 129.70, 129.25, 129.17, 128.97, 128.83, 128.71, 128.66, 128.36, 128.31 (each Ar-C), 90.84 (C-1), 71.40 (C-4), 68.96 (C-3), 67.93 (C-5), 67.63 (C-2), 16.22 (CH₃).

ES-HRMS calcd for C₃₄H₂₈O₉Na₁ 603.1631, found m/z 603.1630 [M+Na]⁺

IR (ATR) cm⁻¹: 1722, 1602, 1451, 1246, 1092, 1067, 1022, 706

R_f : 0.64 (3:7 EtOAc-Pet ether)

2,3,4-Tri-*O*-benzoyl- α -L-fucopyranosyl bromide (20)⁸

Sugar **19** (3.00 g, 5.17 mmol) was dissolved in CH₂Cl₂ (30 mL) and cooled to 0 °C. To this stirring solution was added HBr (33% in AcOH, 9 mL). The reaction was allowed warm to r.t. overnight with stirring. The reaction mixture was then poured onto ice water, stirred for 15 mins and separated. The aqueous layer was re-extracted with CH₂Cl₂. The combined organic layers were washed with NaHCO₃ (sat.), brine, dried over MgSO₄ and the solvent removed under reduced pressure, to give the title compound (2.63 g, 94%) as a colourless solid.

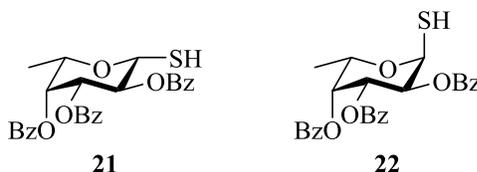
¹H NMR (500 MHz, CDCl₃) δ 8.15 – 8.05 (m, 2H, Ar-H), 8.02 – 7.97 (m, 2H, Ar-H), 7.82 – 7.77 (m, 2H, Ar-H), 7.66 – 7.61 (m, 1H, Ar-H), 7.56 – 7.48 (m, 3H, Ar-H), 7.47 – 7.42 (m, 1H, Ar-H), 7.42 – 7.37 (m, 2H, Ar-H), 7.28 – 7.24 (m, 2H, Ar-H), 6.94 (d, J = 3.9 Hz, 1H, H-1), 6.01 (dd, J = 10.5, 3.4 Hz, 1H, H-3), 5.84 (dd, J = 3.4, 1.3 Hz, 1H, H-4), 5.61 (dd, J = 10.5, 3.9 Hz, 1H, H-2), 4.69 (q, J = 6.5 Hz, 1H, H-5), 1.36 (d, J = 6.5 Hz, 3H, CH₃).

¹³C NMR (126 MHz, CDCl₃) δ 165.70, 165.60, 165.42 (each C=O), 133.67, 133.61, 133.26, 129.97, 129.89, 129.69, 129.03, 128.94, 128.66, 128.51, 128.29 (each Ar-C), 89.38 (C-1), 70.80 (C-4), 70.47 (C-5), 69.27 (C-3), 68.62 (C-2), 15.79 (CH₃).

ES-HRMS calcd for C₂₉H₂₆N₁O₇Na₁Br₁ 602.0790, found m/z 602.0776 [M+MeCN+Na]⁺

IR (ATR) cm⁻¹: 1722, 1602, 1452, 1548, 1090, 1068, 1025, 706

R_f : 0.81 (3:7 EtOAc-Pet ether)

2,3,4-Tri-*O*-benzoyl-1-thio- α/β -L-fucopyranose (21+22)

Compound **20** (2.80 g, 5.19 mmol) was dissolved in acetone (50 mL) and to this solution was added thiourea (677 mg, 8.89 mmol). The reaction was heated to reflux (70 °C) and stirred for 16 h. The clear solution was cooled to r.t. and concentrated under reduced pressure.

The salt was used without any purification. The glycosyl intermediate was suspended in a 3:2 CH₂Cl₂-H₂O mixture (50 mL) to which sodium metabisulfite (1.28 g, 6.73 mmol) was added. The reaction mixture was heated to reflux (42 °C) and stirred for 5 h. The solution was cooled to r.t. and separated. The aqueous layer was re-extracted with CH₂Cl₂. The combined organic layers were washed with H₂O, dried over MgSO₄, with the solvent then being removed under reduced pressure. Chromatography (EtOAc-Pet Ether 1:4→2:3→1:1) gave the title compounds (β -anomer (**21**): 1.39 g, 51%; α -anomer (**22**): 742 mg, 27%) as colourless solids.

¹H NMR (500 MHz, CDCl₃) β -anomer (**21**): δ 8.14 – 8.07 (m, 2H, Ar-H), 7.98 – 7.93 (m, 2H, Ar-H), 7.79 – 7.75 (m, 2H, Ar-H), 7.66 – 7.60 (m, 1H, Ar-H), 7.55 – 7.46 (m, 3H, Ar-H), 7.45 – 7.36 (m, 3H, Ar-H), 7.28 – 7.21 (m, 2H, Ar-H), 5.76 (dd, J = 3.4, 1.2 Hz, 1H, H-4), 5.71 (t, J = 9.9 Hz, 1H, H-2), 5.56 (dd, J = 10.1, 3.4 Hz, 1H, H-3), 4.84 (t, J = 9.7 Hz, 1H, H-1), 4.17 – 4.07 (m, 1H, H-5), 2.50 (d, J = 9.8 Hz, 1H, SH), 1.36 (d, J = 6.4 Hz, 3H, CH₃).

α -anomer (**22**): δ 8.13 – 8.08 (m, 2H, Ar-H), 7.99 – 7.96 (m, 2H, Ar-H), 7.81 – 7.77 (m, 2H, Ar-H), 7.66 – 7.58 (m, 1H, Ar-H), 7.54 – 7.47 (m, 3H, Ar-H), 7.46 – 7.42 (m, 1H, Ar-H), 7.41 – 7.36 (m, 2H, Ar-H), 7.28 – 7.23 (m, 2H, Ar-H), 6.23 (t, J = 5.2 Hz, 1H, H-1), 5.85 (dd, J = 10.7, 3.1 Hz, 1H, H-3), 5.81 (dd, J = 10.7, 5.1 Hz, 1H, H-2), 5.77 (dd, J = 3.1, 1.3 Hz, 1H, H-4), 4.84 – 4.73 (m, 1H, H-5), 1.95 (d, J = 5.1 Hz, 1H, SH), 1.30 (d, J = 6.5 Hz, 3H, CH₃).

¹³C NMR (126 MHz, CDCl₃) β -anomer (**21**): δ 165.91, 165.64, 165.53 (each C=O), 133.49, 133.38, 133.23, 129.94, 129.77, 129.70, 129.20, 129.15, 128.82, 128.59, 128.41, 128.26 (each Ar-C), 79.03 (C-1), 74.41 (C-5), 72.75 (C-3), 71.99 (C-2), 71.19 (C-4), 16.66 (CH₃).

α -anomer (**22**): δ 165.88, 165.58, 165.53 (EachC=O), 133.53, 133.47, 133.20, 129.90, 129.86, 129.68, 129.27, 129.05, 128.90, 128.60, 128.60, 128.48, 128.26 (each Ar-C), 78.08 (C-1), 71.62 (C-4), 68.72 (C-3), 68.51 (C-2), 66.15 (C-5), 16.13 (CH₃).

ES-HRMS β -anomer (**21**): calcd for C₂₉H₂₇N₁O₇S₁Na₁ 556.1406, found m/z 556.1403 [M+MeCN+Na]⁺

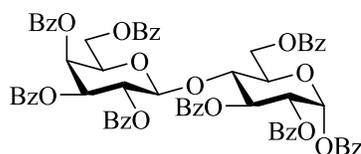
ES-HRMS α -anomer (**22**): calcd for C₂₇H₂₄O₇S₁Na₁ 515.1140, found m/z 515.1155 [M+Na]⁺

IR (ATR) cm⁻¹: β -anomer (**21**): 1723, 1602, 1451, 1280, 1260, 1094, 1070, 707

IR (ATR) cm⁻¹: α -anomer (**22**): 1721, 1602, 1452, 1280, 1259, 1095, 1069, 1026, 709.

R_f: β -anomer (**21**): 0.63, α -anomer (**22**): 0.75; (3:7 EtOAc-Pet ether)

$[\alpha]_D^{20}$ -255.5 (c 1.19, CHCl₃); $[\alpha]_D^{20}$ -229.8 (c 1.12, CHCl₃)

Octa-*O*-benzoyl- α -D-lactose (27)⁹

D-Lactose (5.00 g, 14.6 mmol) was suspended in pyridine (55 mL) and to this DMAP (150 mg, 1.23 mmol) was added, with the reaction flask then cooled to 0 °C. To this suspension, benzoyl chloride (20 mL 172 mmol) was added slowly, portion wise. The reaction was allowed to warm to room temperature overnight with stirring. After which point MeOH (50 mL) was added and stirred for 15 mins to decompose the excess benzoyl chloride. The reaction mixture was diluted with CH₂Cl₂ and washed with 1M HCl, water, brine, dried over MgSO₄ and the solvent removed under reduced pressure. Column chromatography (EtOAc-Pet. Ether 1:5→1:1) gave the title compound (16.1 g, 93%) as a colourless solid.

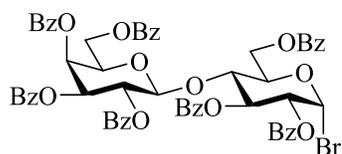
¹H NMR (500 MHz, CDCl₃) δ 8.15 – 8.10 (m, 2H, Ar-H), 8.06 – 7.95 (m, 8H, Ar-H), 7.91 – 7.84 (m, 4H, Ar-H), 7.76 – 7.71 (m, 2H, Ar-H), 7.66 – 7.27 (m, 20H, Ar-H), 7.24 – 7.16 (m, 4H, Ar-H), 6.74 (d, J = 3.8 Hz, 1H, H-1), 6.20 (dd, J = 10.3, 9.1 Hz, 1H, H-3), 5.80 – 5.73 (m, 2H, H-2', H-4'), 5.61 (dd, J = 10.3, 3.8 Hz, 1H, H-2), 5.37 (dd, J = 10.3, 3.4 Hz, 1H, H-3'), 4.94 (d, J = 7.9 Hz, 1H, H-1'), 4.59 – 4.52 (m, 2H, H-6a, H-6b), 4.38 (dd, J = 10.1, 9.1 Hz, 1H, H-4), 4.29 (dt, J = 10.1, 2.7 Hz, 1H, H-5), 3.90 (ddd, J = 7.4, 6.4, 1.1 Hz, 1H, H-5'), 3.79 (dd, J = 11.3, 6.4 Hz, 1H, H-6'a), 3.73 (dd, J = 11.3, 7.1 Hz, 1H, H-6'b).

¹³C NMR (126 MHz, CDCl₃) δ 171.13, 165.76, 165.51, 165.41, 165.39, 165.17, 164.84, 164.46 (each C=O), 133.84, 133.51, 133.43, 133.41, 133.39, 133.29, 133.24, 130.13, 130.05, 129.96, 129.82, 129.77, 129.74, 129.64, 129.62, 129.61, 129.53, 129.40, 129.37, 128.85, 128.74, 128.62, 128.58, 128.55, 128.52, 128.46, 128.39, 128.32, 128.23 (each Ar-C), 101.23 (C-1'), 89.85 (C-1), 75.63 (C-4), 72.02 (C-3'), 71.38 (C-5'), 71.16 (C-5), 70.40 (C-3), 70.21 (C-2), 69.88 (C-2'), 67.46 (C-4'), 61.81 (C-6), 60.97 (C-6')

ES-HRMS calcd for C₆₈H₅₄O₁₉Na₁ 1197.3157, found m/z 1197.3131 [M+ Na]⁺

IR (ATR) cm⁻¹: 1725, 1602, 1451, 1260, 1092, 1068, 1021, 706

R_f: 0.30 (3:7 EtOAc-Pet ether)

Hepta-*O*-benzoyl- α -D-lactosyl bromide (28)¹⁰

Sugar **27** (15.2 g, 12.9 mmol) was dissolved in CH₂Cl₂ (160 mL) and cooled to 0 °C. To this stirring solution was added HBr (33% in AcOH, 40 mL). The reaction was allowed warm to r.t. overnight with stirring. The reaction mixture was then poured onto ice water, stirred for 15 mins and separated. The aqueous layer re-extracted with CH₂Cl₂. The combined organic layers were washed with NaHCO₃ (sat.), brine, dried over MgSO₄. The solvent was removed under reduced pressure, to give the title compound (13.3 g, 91%) as a colourless solid.

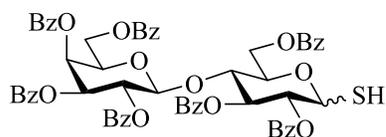
¹H NMR (500 MHz, CDCl₃) δ 8.05 – 7.95 (m, 10H, Ar-H), 7.91 – 7.88 (m, 2H, Ar-H), 7.75 – 7.71 (m, 2H, Ar-H), 7.65 – 7.51 (m, 53H, Ar-H), 7.50 – 7.29 (m, 14H, Ar-H), 7.24 – 7.17 (m, 4H, Ar-H), 6.74 (d, J = 4.1 Hz, 1H, H-1), 6.14 (t, J = 9.57 Hz, 1H, H-3), 5.79 – 5.70 (m, 2H, H-2', H-4'), 5.40 (dd, J = 10.3, 3.4 Hz, 1H, H-3'), 5.26 (dd, J = 10.0, 4.1 Hz, 1H, H-2), 4.95 (d, J = 7.9 Hz, 1H, H-1'), 4.66 – 4.54 (m, 2H, H-6a, H-6b), 4.43 (dt, J = 10.3, 2.6 Hz, 1H, H-5), 4.34 (dd, J = 10.2, 9.1 Hz, 1H, H-4), 3.94 – 3.90 (m, 1H, H-5'), 3.85 (dd, J = 11.3, 6.3 Hz, 1H, H-6a'), 3.75 (dd, J = 11.3, 7.0 Hz, 1H, H-6b').

¹³C NMR (126 MHz, CDCl₃) δ 165.68, 165.53, 165.43, 165.37, 165.20, 165.07, 164.75 (each C=O), 133.74, 133.53, 133.48, 133.42, 133.37, 133.30, 133.26, 130.06, 129.96, 129.75, 129.65, 129.63, 129.61, 129.46, 129.34, 129.30, 128.79, 128.63, 128.61, 128.57, 128.55, 128.52, 128.41, 128.31, 128.24 (each Ar-C), 101.05 (C-1'), 86.73 (C-1), 74.84 (C-4), 73.35 (C-5), 71.86 (C-3'), 71.42 (C-5'), 71.32 (C-2), 70.51 (C-3), 69.83 (C-2'), 67.43 (C-4'), 61.47 (C-6), 61.02 (C-6').

ES-HRMS calcd for C₆₁H₄₉O₁₇Na₁Br₁ 1155.2051, found m/z 1155.2064 [M+ Na]⁺

IR (ATR) cm⁻¹: 1722, 1062, 1451, 1259, 1091, 1068, 1026, 703

R_f : 0.39 (3:7 EtOAc-Pet ether)

Hepta-*O*-benzoyl-1-thio- α/β -D-lactose (29)¹¹

Compound **28** (7.76 g, 6.84 mmol) was dissolved in acetone (95 mL) and to this solution was added thiourea (900 mg, 11.8 mmol). The reaction was heated to reflux (70 °C) and stirred for 26 h. The clear solution was cooled to r.t. and concentrated under reduced pressure.

The salt was used without any purification. The glycosyl thiourea intermediate was suspended in a 3:2 CH₂Cl₂-H₂O mixture (100 mL) to which sodium metabisulfite (1.76 g, 9.26 mmol) was added. The reaction mixture was heated to reflux (42 °C) and stirred for 7 h. The solution was cooled to r.t. and separated. The aqueous layer was re-extracted with CH₂Cl₂. The combined organic layers were washed with H₂O, dried over MgSO₄, with the solvent then being removed under reduced pressure. Chromatography (EtOAc-Pet Ether 1:4→2:3→1:1) gave the title compound (5.04 g, 68%) as a colourless solid, as a mixture of anomers (α : β 1:4).

¹H NMR (500 MHz, CDCl₃) δ 8.05 – 7.94 (m, 20H, Ar-H), 7.91 – 7.87 (m, 4H, Ar-H), 7.75 – 7.70 (m, 4H, Ar-H), 7.64 – 7.55 (m, 6H, Ar-H), 7.54 – 7.27 (m, 28H, Ar-H), 7.24 – 7.13 (m, 8H, Ar-H), 6.07 (t, J = 5.9 Hz, 1H, H-1 α), 5.97 (t, J = 9.5 Hz, 1H, H-3 α), 5.79 (t, J = 9.3 Hz, 1H, H-3 β), 5.76 – 5.69 (m, 4H, H-2' α , H-2' β , H-4' α , H-4' β), 5.43 (t, J = 9.6 Hz, 1H, H-2 β), 5.45 – 5.39 (m, 2H, H-2 α , H-3' α), 5.37 (dd, J = 10.3, 3.4 Hz, 1H, H-3' β), 4.96 (d, J = 7.9 Hz, 1H, H-1' α), 4.87 (d, J = 7.9 Hz, 1H, H-1' β), 4.75 (t, J = 9.7 Hz, 1H, H-1 β), 4.58 (dd, J = 12.3, 1.8 Hz, 1H, H-6 $\alpha\beta$), 4.61 – 4.52 (m, 3H, H-5 α , H-6 $\alpha\alpha$, H-6 $\beta\alpha$), 4.49 (dd, J = 12.3, 4.3 Hz, 1H, H-6 $\beta\beta$), 4.28 (t, J = 9.6 Hz, 1H, H-4 β), 4.27 – 4.22 (m, 1H, H-4 α), 3.94 (t, J = 6.6 Hz, 1H, H-5' α), 3.91 – 3.84 (m, 3H, H-5 β , H-5' β , H-6' $\alpha\alpha$), 3.81 – 3.68 (m, 3H, H-6' $\beta\alpha$, H-6' $\alpha\beta$, H-6' $\beta\beta$), 2.39 (d, J = 9.7 Hz, 1H, SH β), 2.00 (d, J = 6.0 Hz, 1H, SH α).

¹³C NMR (126 MHz, CDCl₃) δ 171.11, 165.82, 165.80, 165.56, 165.54, 165.53, 165.43, 165.37, 165.33, 165.31, 165.23, 165.23, 165.20, 164.80 (each C=O), 133.58, 133.52, 133.50, 133.42, 133.39, 133.37, 133.35, 133.24, 133.21, 129.96, 129.89, 129.86, 129.81, 129.75, 129.72, 129.65, 129.63, 129.58, 129.56, 129.52, 129.49, 129.48, 129.40, 128.99, 128.83, 128.70, 128.63, 128.59, 128.56, 128.54, 128.49, 128.46, 128.42, 128.38, 128.30, 128.25, 128.23 (each Ar-C), 101.07 (C-1' α), 100.89 (C-1' β), 78.90 (C-1 β), 77.51 (C-5 β), 77.43 (C-1 α), 75.87 (C-4 α), 75.70 (C-4 β), 74.10 (C-2 β), 73.69 (C-3 β), 71.88 (C-3' α), 71.75

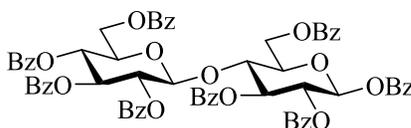
(C-3'β), 71.40 (C-5'α), 71.38 (C-5'β), 71.09 (C-2α), 70.22 (C-3α), 69.90 (C-2'α), 69.86 (C-2'β), 69.60 (C-5α), 67.52 (C-4'α), 67.49 (C-4'β), 62.53 (C-6β), 62.13 (C-6α), 61.14 (C-6'α), 61.01 (C-6'β)

ES-HRMS calcd for C₆₁H₅₀O₁₇Na₁S₁ 1109.2666, found m/z 1109.2660 [M+ Na]⁺

IR (ATR) cm⁻¹: 1723, 1602, 1451, 1261, 1089, 1067, 1026, 706

R_f: 0.32 (3:7 EtOAc-Pet ether)

[α]_D²⁰ +70.0 (c 0.97, CHCl₃)

Octa-*O*-benzoyl- β -D-cellobiose (30)¹²

D-Cellobiose (5.00 g, 14.6 mmol) was suspended in pyridine (55 mL), and to this DMAP (190 mg, 1.56 mmol) was added, with the reaction flask then cooled to 0 °C. To this suspension, benzoyl chloride (20 mL 172 mmol) was added slowly, portion wise. The reaction was allowed to warm to room temperature overnight with stirring. After which point MeOH (50 mL) was added and stirred for 15 mins to decompose the excess benzoyl chloride. The reaction mixture was diluted with CH₂Cl₂ and washed with 1M HCl, water, brine, dried over MgSO₄ and the solvent removed under reduced pressure. Column chromatography (EtOAc-Pet. Ether 1:5→1:1) gave the title compound (7.42 g, 43%) as a colourless solid.

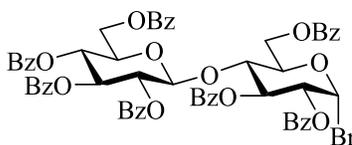
¹H NMR (500 MHz, CDCl₃) δ 8.02 – 7.92 (m, 10H, Ar-H), 7.89 – 7.86 (m, 2H, Ar-H), 7.78 – 7.73 (m, 4H, Ar-H), 7.57 – 7.51 (m, 2H, Ar-H), 7.47 – 7.35 (m, 12H, Ar-H), 7.34 – 7.27 (m, 6H, Ar-H), 7.26 – 7.21 (m, 4H, Ar-H), 6.11 (d, J = 8.0 Hz, 1H, H-1), 5.92 (t, J = 9.2 Hz, 1H, H-3), 5.78 – 5.67 (m, 2H, H-2, H-3'), 5.53 (dd, J = 9.8, 7.9 Hz, 1H, H-2'), 5.39 (t, J = 9.6 Hz, 1H, H-4'), 4.95 (d, J = 7.9 Hz, 1H, H-1'), 4.60 (dd, J = 12.4, 2.0 Hz, 1H, H-6), 4.49 (dd, J = 12.4, 4.0 Hz, 1H, H-6), 4.37 (t, J = 9.4 Hz, 1H, H-4), 4.05 (m, 2H, H-5, H-6'), 3.85 – 3.76 (m, 2H, H-5', H-6').

¹³C NMR (126 MHz, CDCl₃) δ 165.68, 165.64, 165.58, 165.21, 165.19, 164.94, 164.72, 164.45 (each C=O), 133.69, 133.42, 133.36, 133.33, 133.29, 133.23, 133.18, 133.16, 130.14, 130.10, 129.78, 129.72, 129.69, 129.68, 129.63, 129.60, 129.49, 129.45, 129.30, 128.73, 128.63, 128.59, 128.50, 128.47, 128.43, 128.41, 128.36, 128.30, 128.28, 128.22 (each Ar-C), 101.01 (C-1'), 92.46 (C-1), 75.97 (C-4), 73.80 (C-5), 72.76 (C-3), 72.73 (C-3'), 72.40 (C-5'), 71.82 (C-2'), 70.81 (C-2), 69.37 (C-4'), 62.63 (C-6'), 62.09 (C-6)

ES-HRMS calcd for C₆₈H₅₄O₁₉Na₁ 1197.3157, found m/z 1197.3173 [M+ Na]⁺

IR (ATR) cm⁻¹: 1722, 1602, 1451, 1246, 1090, 1064, 1025, 704

R_f: 0.30 (3:7 EtOAc-Pet ether)

Hepta-*O*-benzoyl- α -D-cellobiosyl bromide (31)¹⁰

Compound **30** (6.20 g, 5.28 mmol) was dissolved in CH₂Cl₂ (75 mL) and cooled to 0 °C. To this stirring solution was added HBr (33% in AcOH, 20 mL). The reaction was allowed warm to r.t. overnight with stirring. The reaction mixture was then poured onto ice water, stirred for 15 mins and separated. The aqueous layer was re-extracted with CH₂Cl₂. The combined organic layers were washed with NaHCO₃ (sat.), brine, dried over MgSO₄ and the solvent removed under reduced pressure, to give the title compound (5.45 g, 91%) as a colourless solid.

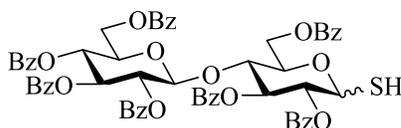
¹H NMR (500 MHz, CDCl₃) δ 8.02 – 7.98 (m, 4H, Ar-H), 7.98 – 7.89 (m, 6H, Ar-H), 7.80 – 7.71 (m, 4H, Ar-H), 7.60 – 7.49 (m, 3H, Ar-H), 7.46 – 7.35 (m, 11H, Ar-H), 7.30 – 7.20 (m, 7H, Ar-H), 6.72 (d, J = 4.1 Hz, 1H, H-1), 6.13 (t, J = 9.5 Hz, 1H, H-3), 5.76 (t, J = 9.6 Hz, 1H, H-3'), 5.54 (dd, J = 9.8, 7.9 Hz, 1H, H-2'), 5.42 (t, J = 9.6 Hz, 1H, H-4'), 5.19 (dd, J = 9.9, 4.1 Hz, 1H, H-2), 5.03 (d, J = 7.9 Hz, 1H, H-1'), 4.64 (dd, J = 12.6, 1.9 Hz, 1H, H-6a), 4.54 (dd, J = 12.5, 3.7 Hz, 1H, H-6b), 4.45 – 4.40 (m, 1H, H-5), 4.33 (t, J = 9.7 Hz, 1H, H-4), 4.09 (dd, J = 11.9, 3.1 Hz, 1H, H-6a'), 3.90 (dd, J = 11.9, 5.2 Hz, 1H, H-6b'), 3.87 – 3.82 (m, 1H, H-5').

¹³C NMR (126 MHz, CDCl₃) δ 165.66, 165.63, 165.62, 165.35, 165.06, 164.94, 164.72 (each C=O), 133.73, 133.38, 133.36, 133.34, 133.20, 133.17, 130.03, 129.76, 129.73, 129.69, 129.64, 129.62, 129.58, 129.41, 129.39, 129.28, 128.60, 128.59, 128.52, 128.50, 128.45, 128.38, 128.34, 128.30, 128.23 (each Ar-C), 100.86 (C-1'), 86.54 (C-1), 75.20 (C-4), 73.34 (C-5), 72.87 (C-3'), 72.46 (C-5'), 71.91 (C-2'), 71.53 (C-2), 70.30 (C-3), 69.31 (C-4'), 62.64 (C-6'), 61.46 (C-6).

ES-HRMS calcd for C₆₁H₄₉O₁₇Na₁Br₁ 1155.2051, found m/z 1155.2069 [M+ Na]⁺

IR (ATR) cm⁻¹: 1721, 1602, 1452, 1258, 1090, 1067, 1026, 706

R_f : 0.41 (3:7 EtOAc-Pet ether)

Hepta-*O*-benzoyl-1-thio- α/β -D-cellobiose (32)

Compound **31** (3.77 g, 3.32 mmol) was dissolved in acetone (100 mL) and to this solution was added thiourea (430 mg, 5.65 mmol). The reaction was heated to reflux (70 °C) and stirred for 36 h. The clear solution was cooled to r.t. and concentrated under reduced pressure.

The salt was used without purification. The glycosyl thiourea intermediate was suspended in a 3:2 CH₂Cl₂-H₂O mixture (60 mL) to which sodium metabisulfite (853 mg, 4.49 mmol) was added. The reaction mixture was heated to reflux (42 °C) and stirred for 7 h. The solution was cooled to r.t. and separated. The aqueous layer was re-extracted with CH₂Cl₂. The combined organic layers were washed with H₂O, dried over MgSO₄, with the solvent then being removed under reduced pressure. Chromatography (EtOAc-Pet Ether 1:4→2:3→1:1) gave the title compound (2.06 g, 57%) as a colourless solid, as a mixture of anomers (α : β 1:3).

¹H NMR (500 MHz, CDCl₃) δ 8.02 – 7.97 (m, 6H, Ar-H), 7.96 – 7.89 (m, 16H, Ar-H), 7.79 – 7.72 (m, 8H, Ar-H), 7.59 – 7.48 (m, 6H, Ar-H), 7.46 – 7.34 (m, 22H, Ar-H), 7.30 – 7.19 (m, 12H, Ar-H), 6.03 (t, J = 5.9 Hz, 1H, H-1 α), 5.95 (t, J = 9.4 Hz, 1H, H-3 α), 5.80 – 5.74 (m, 1H, H-3' α), 5.76 (t, J = 9.3 Hz, 1H, H-3 β), 5.72 (t, J = 9.7 Hz, 1H, H-3' β), 5.53 (dd, J = 9.8, 7.9 Hz, 1H, H-2' α), 5.50 (dd, J = 9.8, 7.9 Hz, 1H, H-2' β), 5.43 – 5.34 (m, 4H, H-2 α , H-2 β , H-4' α , H-4' β), 5.02 (d, J = 7.9 Hz, 1H, H-1' α), 4.94 (d, J = 7.9 Hz, 1H, H-1' β), 4.70 (t, J = 9.7 Hz, 1H, H-1 β), 4.64 – 4.57 (m, 1H, H-6 $\alpha\alpha$), 4.59 (dd, J = 12.3, 1.9 Hz, 1H, H-6 $\alpha\beta$), 4.54 – 4.48 (m, 2H, H-5 α , H-6 $\beta\alpha$), 4.45 (dd, J = 12.2, 4.4 Hz, 1H, H-6 $\beta\beta$), 4.25 (t, J = 9.5 Hz, 1H, H-4 β), 4.23 (t, J = 9.5 Hz, 1H, H-4 α), 4.12 (dd, J = 11.8, 2.9 Hz, 1H, H-6' $\alpha\alpha$), 4.07 – 4.02 (m, 1H, H-6' $\alpha\beta$), 3.90 (dd, J = 11.7, 5.4 Hz, 1H, H-6' $\beta\alpha$), 3.91 – 3.86 (m, 1H, H-5' α), 3.85 (ddd, J = 9.8, 4.3, 1.8 Hz, 1H, H-5' β), 3.83 – 3.77 (m, 2H, H-5' β , H-6' $\beta\beta$), 2.35 (d, J = 9.6 Hz, 1H, SH β), 1.97 (d, J = 6.0 Hz, 1H, SH α).

¹³C NMR (126 MHz, CDCl₃) δ 165.76, 165.74, 165.69, 165.62, 165.61, 165.56, 165.52, 165.30, 165.30, 165.20, 164.97, 164.96, 164.75, 164.73 (each C=O), 133.56, 133.39, 133.34, 133.29, 133.24, 133.20, 133.17, 133.14, 129.94, 129.82, 129.76, 129.73, 129.68, 129.67, 129.62, 129.57, 129.54, 129.45, 129.39, 129.29, 128.92, 128.63, 128.62, 128.58, 128.51, 128.47, 128.45, 128.42, 128.38, 128.34, 128.32, 128.29, 128.21 (each Ar-C), 100.94 (C-1' α), 100.72 (C-1' β), 78.76 (C-1 β), 77.48 (C-5 β), 77.20 (C-1 α), 76.26 (C-4 α),

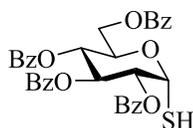
76.11 (C-4 β), 74.24 (C-2 β), 73.50 (C-3 β), 72.90 (C-3' α), 72.79 (C-3' β), 72.41 (C-5' α), 72.38 (C-5' β), 71.94 (C-2' α), 71.89 (C-2' β), 71.27 (C-2 α), 69.99 (C-3 α), 69.58 (C-5 α), 69.41 (C-4' β), 69.39 (C-4' α), 62.73 (C-6' α), 62.64 (C-6 β), 62.54 (C-6' β), 62.10 (C-6 α)

ES-HRMS calcd for C₆₁H₅₀O₁₇Na₁S₁ 1109.2666, found m/z 1109.2668 [M+ Na]⁺

IR (ATR) cm⁻¹: 1722, 1602, 1451, 1260, 1087, 1067, 1026, 706

R_f: 0.32 (3:7 EtOAc-Pet ether)

[α]_D²⁰ +50.9 (c 0.94, CHCl₃)

2,3,4,6-Tetra-*O*-benzoyl-1-thio- α -D-glucopyranose (34)

Compound **3** (1.00 g, 1.63 mmol) was dissolved in CH₂Cl₂ (15 mL) and to this, pyridine was added (66 μ L, 0.819 mmol). A 1M solution of TiCl₄ in CH₂Cl₂ (4.9 mL, 4.90 mmol) was then added to the reaction flask. The reaction was stirred at r.t. for 16 h. The deep coloured solution lightened in appearance during the course of the reaction.

The reaction mixture was diluted with CH₂Cl₂ and transferred to a separation funnel. This solution was washed with NH₄Cl_(sat.). The organic layer was separated, with the aqueous layer re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with NaHCO₃, brine, dried over MgSO₄ and the solvent removed under diminished pressure. Flash chromatography (Pet ether-CH₂Cl₂-Et₂O 14:10:1 or CH-EtOAc 7:3) gave the title compound (629 mg, 63%) as a colourless solid.

Crude yield: 94%

Isolated yield 63%

¹H NMR (500 MHz, CDCl₃) δ 8.08 – 8.04 (m, 2H, Ar-H), 8.01 – 7.97 (m, 2H, Ar-H), 7.96 – 7.92 (m, 2H, Ar-H), 7.89 – 7.86 (m, 2H, Ar-H), 7.59 – 7.48 (m, 3H, Ar-H), 7.47 – 7.34 (m, 7H, Ar-H), 7.34 – 7.28 (m, 2H, Ar-H), 6.20 (t, *J* = 5.7 Hz, 1H, H-1), 6.08 (t, *J* = 9.9 Hz, 1H H-3), 5.72 (t, *J* = 9.9 Hz, 1H, H-4), 5.50 (dd, *J* = 10.2, 5.6 Hz, 1H, H-2), 4.86 (ddd, *J* = 10.1, 4.6, 2.6 Hz, 1H, H-5), 4.64 (dd, *J* = 12.4, 2.8 Hz, 1H, H-6a), 4.49 (dd, *J* = 12.4, 4.6 Hz, 1H, H-6b), 2.08 (d, *J* = 5.7 Hz, 1H, SH).

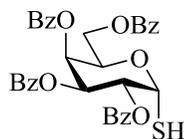
¹³C NMR (126 MHz, CDCl₃) δ 166.12, 165.67, 165.23, 165.16 (each C=O), 133.62, 133.48, 133.26, 133.13, 129.96, 129.86, 129.78, 129.71, 129.59, 128.89, 128.73, 128.63, 128.51, 128.42, 128.39, 128.32 (each Ar-C), 77.57 (C-1), 71.24 (C-2), 70.27(C-3), 69.15 (C-4), 68.89 (C-5), 62.63(C-6).

ES-HRMS calcd for C₃₄H₂₈O₉S₁Na₁ 635.1352, found *m/z* 635.1349 [M+Na]⁺

IR (ATR) cm⁻¹: 1721, 1602, 1452, 1260, 1090, 1069, 1027, 707

*R*_f: 0.53 (3:7 EtOAc-Pet ether)

$[\alpha]_D^{20}$ +102.0 (*c* 0.79, CHCl₃)

2,3,4,6-Tetra-*O*-benzoyl-1-thio- α -D-galactopyranose (35)

Sugar **6** (1.00 g, 1.63 mmol) was dissolved in CH_2Cl_2 (15 mL) and to this pyridine was added (66 μL , 0.819 mmol). A 1M solution of TiCl_4 in CH_2Cl_2 (4.9 mL, 4.90 mmol) was then added to the reaction flask. The reaction was stirred at r.t. for 16 h. The deep coloured solution lightened in appearance during the course of the reaction.

The reaction mixture was diluted with CH_2Cl_2 and transferred to a separation funnel. This solution was washed with $\text{NH}_4\text{Cl}_{(\text{sat.})}$. The organic layer was separated, with the aqueous layer re-extracted with a further portion of CH_2Cl_2 . The combined organic layers were then washed with NaHCO_3 , brine, dried over MgSO_4 and the solvent removed under diminished pressure. Flash chromatography (Pet ether- CH_2Cl_2 - Et_2O 14:10:1 or CH - EtOAc 7:3) gave the title compound (560 mg, 56%) as a colourless solid.

Crude yield: 93%

Isolated yield 56%

^1H NMR (500 MHz, CDCl_3) δ 8.13 – 8.07 (m, 2H, Ar-H), 8.05 – 8.00 (m, 2H, Ar-H), 8.00 – 7.96 (m, 2H, Ar-H), 7.82 – 7.77 (m, 2H, Ar-H), 7.65 – 7.60 (m, 1H, Ar-H), 7.57 – 7.46 (m, 4H, Ar-H), 7.46 – 7.37 (m, 5H, Ar-H), 7.29 – 7.23 (m, 2H, Ar-H), 6.31 (t, $J = 5.1$ Hz, 1H, H-1), 6.06 (dd, $J = 3.1, 1.5$ Hz, 1H, H-4), 5.90 (dd, $J = 10.7, 3.1$ Hz, 1H, H-3), 5.86 (dd, $J = 10.7, 5.1$ Hz, 1H, H-2), 5.05 (t, $J = 6.5$ Hz, 1H, H-5), 4.61 (dd, $J = 11.5, 6.7$ Hz, 1H, H-6a), 4.42 (dd, $J = 11.5, 6.3$ Hz, 1H, H-6b), 2.00 (d, $J = 4.9$ Hz, 1H, SH).

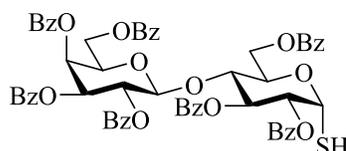
^{13}C NMR (126 MHz, CDCl_3) δ 165.98, 165.50, 165.45, 165.42 (each C=O), 133.61, 133.28, 133.22, 129.93, 129.89, 129.77, 129.72, 129.40, 129.03, 128.89, 128.76, 128.65, 128.51, 128.41, 128.28 (each Ar-C), 78.22 (C-1), 68.79 (C-4), 68.48 (C-3), 68.30 (C-2), 67.88 (C-5), 62.16 (C-6).

ES-HRMS calcd for $\text{C}_{34}\text{H}_{28}\text{O}_9\text{S}_1\text{Na}_1$ 635.1352, found m/z 635.1340 $[\text{M}+\text{Na}]^+$.

IR (ATR) cm^{-1} : 1719, 1602, 1451, 1258, 1092, 1068, 1026, 707

R_f : 0.51 (3:7 EtOAc-Pet ether)

$[\alpha]_{\text{D}}^{20} +164.7$ (c 0.84, CHCl_3)

Hepta-*O*-benzoyl-1-thio- α -D-lactose (36)

Sugar **29** (1.00 g, 0.920 mmol) was dissolved in CH_2Cl_2 (7 mL) and to this was added pyridine (37.1 μL , 0.460 mmol). A 1M solution of TiCl_4 in CH_2Cl_2 (2.76 mL, 2.76 mmol) was then added to the reaction flask. The reaction was stirred at r.t. for 16 h. The deep coloured solution lightened in appearance during the course of the reaction.

The reaction mixture was diluted with CH_2Cl_2 and transferred to a separation funnel. This solution was washed with $\text{NH}_4\text{Cl}_{(\text{sat.})}$. The organic layer was separated, with the aqueous layer re-extracted with a further portion of CH_2Cl_2 . The combined organic layers were then washed with NaHCO_3 , brine, dried over MgSO_4 and the solvent removed under diminished pressure. This gave the title compound (911 mg, 91%), as a crude, unpurified, yellow-ish solid.

Flash chromatography (Pet ether- CH_2Cl_2 - Et_2O 14:10:1 or CH - EtOAc 6:4) of a portion of the crude material (100 mg) gave the title compound (58 mg, 58%) as a colourless solid.

Therefore 58% of 911 mg crude material = 528 mg = 53% isolated yield

Crude yield: 91%

Isolated yield 53%

^1H NMR (500 MHz, CDCl_3) δ 8.05 – 8.01 (m, 2H, Ar-H), 8.01 – 7.95 (m, 8H, Ar-H), 7.89 – 7.85 (m, 2H, Ar-H), 7.74 – 7.71 (m, 2H, Ar-H), 7.65 – 7.60 (m, 1H, Ar-H), 7.59 – 7.55 (m, 1H, Ar-H), 7.54 – 7.50 (m, 1H, Ar-H), 7.49 – 7.33 (m, 12H, Ar-H), 7.33 – 7.28 (m, 2H, Ar-H), 7.24 – 7.17 (m, 4H, Ar-H), 6.06 (t, $J = 5.9$ Hz, 1H, H-1), 5.96 (dd, $J = 10.1, 9.0$ Hz, 1H, H-3), 5.77 – 5.71 (m, 2H, H-2', H-4'), 5.44 – 5.41 (m, 1H, H-2), 5.40 (dd, $J = 7.5, 2.9$ Hz, 1H, H-3'), 4.94 (d, $J = 7.9$ Hz, 1H, H-1'), 4.60 – 4.56 (m, 1H, H-6a), 4.55 – 4.51 (m, 2H, H-5, H-6b), 4.24 (t, $J = 9.2$ Hz, 1H, H-4), 3.96 – 3.91 (m, 1H, H-5'), 3.86 (dd, $J = 11.3, 6.3$ Hz, 1H, H-6'a), 3.78 (dd, $J = 11.3, 7.0$ Hz, 1H, H-6'b), 1.99 (d, $J = 6.0$ Hz, 1H, SH).

^{13}C NMR (126 MHz, CDCl_3) δ 165.81, 165.56, 165.43, 165.34, 165.21, 165.20, 164.78 (each C=O), 133.58, 133.49, 133.36, 133.25, 129.97, 129.96, 129.75, 129.64, 129.59, 129.56, 129.49, 129.39, 128.83, 128.71, 128.69, 128.61, 128.56, 128.55, 128.51, 128.50, 128.30, 128.24 (each Ar-C), 101.07 (C-1'), 77.43 (C-1), 75.86 (C-4), 71.89 (C-3'), 71.39

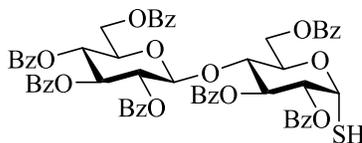
(C-5'), 71.09 (C-2), 70.20 (C-3), 69.87 (C-2'), 69.59 (C-5), 67.50 (C-4'), 62.11 (C-6), 61.12 (C-6').

ES-HRMS calcd for $C_{61}H_{49}O_{17}S_1$ 1085.2690, found m/z 1085.2716 $[M-H]^-$

IR (ATR) cm^{-1} : 1723, 1602, 1451, 1262, 1090, 1069, 1027, 908, 707

R_f : 0.36 (4:6 EtOAc-Pet ether)

$[\alpha]_D^{20} +86.9$ (c 0.97, $CHCl_3$)

Hepta-*O*-benzoyl-1-thio- α -D-cellobiose (37)

Sugar **32** (1.00 g, 0.92 mmol) was dissolved in CH_2Cl_2 (7 mL) and to this was added pyridine (37.1 μL , 0.460 mmol). A 1M solution of TiCl_4 in CH_2Cl_2 (2.76 mL, 2.76 mmol) was then added to the reaction flask. The reaction was stirred at r.t. for 16 h. The deep coloured solution lightened in appearance during the course of the reaction.

The reaction mixture was diluted with CH_2Cl_2 and transferred to a separation funnel. This solution was washed with $\text{NH}_4\text{Cl}_{(\text{sat.})}$. The organic layer was separated, with the aqueous layer re-extracted with a further portion of CH_2Cl_2 . The combined organic layers were then washed with NaHCO_3 , brine, dried over MgSO_4 and the solvent removed under diminished pressure. This gave the title compound (755 mg, 76%), as a crude, unpurified, yellow-ish solid.

Flash chromatography (Pet ether- CH_2Cl_2 - Et_2O 14:10:1 or CH-EtOAc 6:4) of a portion of the crude material (100 mg) gave the title compound (56 mg, 56%) as a colourless solid.

Therefore 56% of 755 mg crude material = 423 mg = 42% isolated yield

Crude yield: 76%

Isolated yield 42%

^1H NMR (500 MHz, CDCl_3) δ 8.03 – 7.98 (m, 4H, Ar-H), 7.98 – 7.91 (m, 6H, Ar-H), 7.81 – 7.73 (m, 4H, Ar-H), 7.59 – 7.49 (m, 3H, Ar-H), 7.47 – 7.43 (m, 1H, Ar-H), 7.43 – 7.36 (m, 10H, Ar-H), 7.31 – 7.22 (m, 7H, Ar-H), 6.04 (t, $J = 5.8$ Hz, 1H, H-1), 5.96 (t, 1H, 9.5 Hz, H-3), 5.77 (t, $J = 9.7$ Hz, 1H, H-3'), 5.54 (dd, $J = 9.8, 7.9$ Hz, 1H, H-2'), 5.42 (t, $J = 9.6$ Hz, 1H, H-4'), 5.36 (dd, $J = 10.0, 5.7$ Hz, 1H, H-2), 5.03 (d, $J = 7.9$ Hz, 1H, H-1'), 4.65 – 4.58 (m, 1H, H-6a), 4.57 – 4.45 (m, 2H H-5, H-6b), 4.23 (t, $J = 9.4$ Hz, 1H, H-4), 4.15 – 4.08 (m, 1H, H-6'a), 3.94 – 3.84 (m, 2H, H-5', H-6'b), 1.97 (d, $J = 6.0$ Hz, 1H, SH).

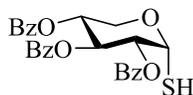
^{13}C NMR (126 MHz, CDCl_3) δ 165.76, 165.69, 165.63, 165.31, 165.20, 164.98, 164.76 (each C=O), 133.58, 133.35, 133.30, 133.25, 133.19, 133.15, 129.95, 129.77, 129.74, 129.70, 129.62, 129.58, 128.64, 128.62, 128.59, 128.48, 128.47, 128.45, 128.38, 128.33, 128.31, 128.23 (each Ar-C), 100.95 (C-1'), 77.39 (C-1) 76.27 (C-4), 72.91 (C-3'), 72.42 (C-5'), 71.93 (C-2'), 71.28 (C-2), 69.99 (C-3), 69.58 (C-5), 69.39 (C-4'), 62.73 (C-6'), 62.10 (C-6).

ES-HRMS calcd for $C_{61}H_{49}O_{17}S_1$ 1085.2690, found m/z 1085.2706 $[M-H]^-$

IR (ATR) cm^{-1} : 1725, 1602, 1452, 1267, 1091, 1069, 1033, 707

R_f : 0.43 (4:6 EtOAc-Pet ether)

$[\alpha]_D^{20}$ +63.4 (c 1.28, $CHCl_3$)

2,3,4-Tri-*O*-benzoyl-1-thio- α -D-xylopyranose (38)

Sugar **12** (500 mg, 1.04 mmol) was dissolved in CH₂Cl₂ (10 mL). A solution of 1M TiCl₄ in CH₂Cl₂ (3.1 mL, 3.10 mmol) was then added. The reaction was stirred at r.t. for 16 h. The deep coloured solution lightened in appearance during the course of the reaction.

The reaction mixture was diluted with CH₂Cl₂ and transferred to a separation funnel. This solution was washed with NH₄Cl_(sat.). The organic layer was separated, with the aqueous layer re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with NaHCO₃, brine, dried over MgSO₄ and the solvent removed under diminished pressure. Flash chromatography (Pet ether-CH₂Cl₂-Et₂O 14:10:1 or CH-EtOAc 8:2) gave the title compound (260 mg, 52%) as a colourless solid.

Crude yield: 93%

Isolated yield 52%

¹H NMR (500 MHz, CDCl₃) δ 8.09 – 8.00 (m, 2H, Ar-H), 7.98 – 7.94 (m, 4H, Ar-H), 7.60 – 7.48 (m, 3H, Ar-H), 7.43 – 7.32 (m, 6H, Ar-H), 5.97 (t, J = 8.4 Hz, 1H, H-3), 5.94 (dd, J = 6.8, 4.9 Hz, 1H, H-1), 5.41 (dd, J = 8.5, 4.7 Hz, 1H, H-2), 5.34 (td, J = 8.3, 4.9 Hz, 1H, H-4), 4.30 (dd, J = 11.9, 8.5 Hz, 1H, H-5a), 4.18 (dd, J = 11.9, 5.0 Hz, 1H, H-5b), 2.14 (d, J = 6.7 Hz, 1H, SH).

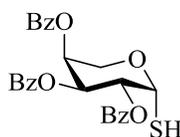
¹³C NMR (126 MHz, CDCl₃) δ 165.50, 165.30, 165.27 (each C=O), 133.60, 133.42, 133.41, 130.00, 129.85, 129.75, 128.99, 128.96, 128.75, 128.52, 128.43, 128.41, 128.39 (each Ar-C), 77.41 (C-1), 71.03 (C-2), 69.15 (C-3), 69.05 (C-4), 61.44 (C-5).

ES-HRMS calcd for C₂₈H₂₅O₇S₁Na₁N₁ 542.1249, found m/z 542.1230 [M+MeCN+Na]⁺

IR (ATR) cm⁻¹: 1722, 1602, 1452, 1315, 1259, 1094, 1094, 1070, 707

R_f : 0.61 (3:7 EtOAc-Pet ether)

$[\alpha]_D^{20}$ +45.6 (c 0.92, CHCl₃)

2,3,4-Tri-*O*-benzoyl-1-thio- β -L-arabinopyranose (39)

Sugar **15** (1.00 g, 2.09 mmol) was dissolved in CH_2Cl_2 (10 mL). A 1M solution of TiCl_4 in CH_2Cl_2 (6.3 mL, 6.30 mmol) was then added. The reaction was stirred at r.t. for 16 h. The deep coloured solution lightened in appearance during the course of the reaction.

The reaction mixture was diluted with CH_2Cl_2 and transferred to a separation funnel. This solution was washed with $\text{NH}_4\text{Cl}_{(\text{sat.})}$. The organic layer was separated, with the aqueous layer re-extracted with a further portion of CH_2Cl_2 . The combined organic layers were then washed with NaHCO_3 , brine, dried over MgSO_4 and the solvent removed under diminished pressure. This gave the title compound (854 mg, 85%), as a crude, unpurified, yellow-ish solid.

Flash chromatography (Pet ether- CH_2Cl_2 - Et_2O 14:10:1 or CH-EtOAc 8:2) of a portion of the crude material (100 mg) gave the title compound (56 mg, 56%) as a colourless solid.

Therefore 56% of 854 mg crude material = 478 mg = 48% isolated yield

Crude yield: 85%

Isolated yield 48%

^1H NMR (500 MHz, CDCl_3) δ 8.08 – 8.04 (m, 2H, Ar-H), 8.04 – 8.01 (m, 2H, Ar-H), 7.91 – 7.85 (m, 2H, Ar-H), 7.62 – 7.57 (m, 1H, Ar-H), 7.57 – 7.53 (m, 1H, Ar-H), 7.51 – 7.40 (m, 5H, Ar-H), 7.34 – 7.29 (m, 2H, Ar-H), 6.10 (dd, $J = 5.9, 3.6$ Hz, 1H, H-1), 5.88 – 5.79 (m, 2H, H-2, H-3), 5.73 (td, $J = 3.0, 1.8$ Hz, 1H, H-4), 4.57 (dd, $J = 13.2, 1.9$ Hz, 1H, H-5a), 4.06 (dd, $J = 13.1, 3.3$ Hz, 1H, H-5b), 2.00 (d, $J = 5.8$ Hz, 1H, SH).

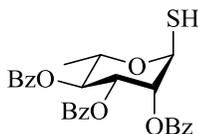
^{13}C NMR (126 MHz, CDCl_3) δ 165.61, 165.44, 165.37 (each C=O), 133.62, 133.45, 133.36, 129.92, 129.84, 129.72, 129.40, 129.03, 128.81, 128.54, 128.38 (each Ar-C), 78.13 (C-1), 69.15 (C-3, C-4), 67.89 (C-2), 61.91 (C-5).

ES-HRMS calcd for $\text{C}_{28}\text{H}_{25}\text{O}_7\text{S}_1\text{N}_1\text{Na}_1$ 542.1249, found m/z 542.1241 [$\text{M}+\text{Na}+\text{MeCN}$] $^+$

IR (ATR) cm^{-1} : 1720, 1602, 1451, 1249, 1106, 1087, 1068, 1025, 706

R_f : 0.56 (3:7 EtOAc-Pet ether)

$[\alpha]_{\text{D}}^{20} +252.5$ (c 0.57, CHCl_3)

2,3,4-Tri-*O*-benzoyl-1-thio- α -L-rhamnopyranose (40)

Sugar **18** (500 mg, 1.02 mmol) was dissolved in CH₂Cl₂ (10 mL). A 1M solution of TiCl₄ in CH₂Cl₂ (3 mL, 3.00 mmol) was then added to the reaction. The reaction was stirred at r.t. for 16 h. The deep coloured solution lightened in appearance during the course of the reaction.

The reaction mixture was diluted with CH₂Cl₂ and transferred to a separation funnel. This solution was washed with NH₄Cl_(sat.). The organic layer was separated, with the aqueous layer re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with NaHCO₃, brine, dried over MgSO₄ and the solvent removed under diminished pressure. This gave the title compound (446 mg, 89%), as a crude, unpurified, yellow solid.

Flash chromatography (Pet ether-CH₂Cl₂-Et₂O 14:10:1 or CH-EtOAc 7:3) of a portion of the crude material (100 mg) gave the title compound (45 mg, 45%) as a colourless solid.

Therefore 45% of 446 mg crude material = 201 mg = 40% isolated yield

Crude yield: 89%

Isolated yield 40%

¹H NMR (500 MHz, CDCl₃) δ 8.14 – 8.08 (m, 2H, Ar-H), 7.96 – 7.90 (m, 2H, Ar-H), 7.79 – 7.73 (m, 2H, Ar-H), 7.66 – 7.61 (m, 1H, Ar-H), 7.54 – 7.48 (m, 3H, Ar-H), 7.45 – 7.40 (m, 1H, Ar-H), 7.40 – 7.35 (m, 2H, Ar-H), 7.26 – 7.21 (m, 3H, Ar-H), 5.95 – 5.85 (m, 1H, H-2), 5.61 – 5.56 (m, 2H, H-3, H-4), 5.12 (dd, *J* = 10.1, 1.2 Hz, 1H, H-1), 3.97 – 3.84 (m, 1H, H-5), 2.61 (d, *J* = 10.1 Hz, 1H, SH), 1.44 (d, *J* = 6.2 Hz, 3H, CH₃).

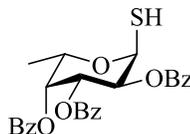
¹³C NMR (126 MHz, CDCl₃) δ 165.59, 165.56, 165.50 (each C=O), 133.61, 133.39, 133.19, 130.03, 129.70, 129.67, 128.84, 128.65, 128.43, 128.23 (each Ar-C), 76.56 (C-1), 75.68 (C-5 α), 72.73 (C-2 α), 72.69 (C-3 α), 70.82 (C-4 α), 18.00 (CH₃).

ES-HRMS calcd for C₂₉H₂₇O₇S₁Na₁N₁ 556.1406, found *m/z* 556.1415 [M+Na+MeCN]⁺

IR (ATR) cm⁻¹: 1722, 1602, 1451, 1278, 1247, 1089, 1067, 1026, 704

R_f: 0.54 (3:7 EtOAc-Pet ether)

[α]_D²⁰ +133.8 (*c* 0.40, CHCl₃)

2,3,4-Tri-*O*-benzoyl-1-thio- α -L-fucopyranose (41)

Sugar **21** (500 mg, 1.02 mmol) was dissolved in CH_2Cl_2 (8 mL). A solution of 1M TiCl_4 in CH_2Cl_2 (3 mL, 3.00 mmol) was then added. The reaction was stirred at r.t. for 16 h. The deep coloured solution lightened in appearance during the course of the reaction.

The reaction mixture was diluted with CH_2Cl_2 and transferred to a separation funnel. This solution was washed with $\text{NH}_4\text{Cl}_{(\text{sat.})}$. The organic layer was separated, with the aqueous layer re-extracted with a further portion of CH_2Cl_2 . The combined organic layers were then washed with NaHCO_3 , brine, dried over MgSO_4 and the solvent removed under diminished pressure. This gave the title compound (437 mg, 87%), as a crude, unpurified, yellow solid.

Flash chromatography (Pet ether- CH_2Cl_2 - Et_2O 14:10:1 or CH - EtOAc 7:3) of a portion of the crude material (80 mg) gave the title compound (34 mg, 43%) as a colourless solid.

Therefore 43% of 437 mg crude material = 188 mg = 38% isolated yield

Crude yield: 87%

Isolated yield 38%

^1H NMR (500 MHz, CDCl_3) δ 8.13 – 8.09 (m, 2H, Ar-H), 8.00 – 7.95 (m, 2H, Ar-H), 7.83 – 7.72 (m, 2H, Ar-H), 7.65 – 7.59 (m, 1H, Ar-H), 7.54 – 7.48 (m, 3H, Ar-H), 7.46 – 7.42 (m, 1H, Ar-H), 7.41 – 7.35 (m, 2H, Ar-H), 7.29 – 7.22 (m, 2H, Ar-H), 6.23 (t, $J = 5.1$ Hz, 1H, H-1), 5.86 (dd, $J = 10.7, 3.2$ Hz, 1H, H-3), 5.81 (dd, $J = 10.6, 5.1$ Hz, 1H, H-2), 5.78 (d, $J = 3.2$ Hz, 1H, H-4), 4.80 (q, $J = 6.5$ Hz, 1H, H-5), 1.95 (d, $J = 4.8$ Hz, 1H, SH), 1.30 (d, $J = 6.4$ Hz, 3H, CH_3).

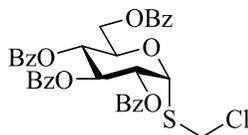
^{13}C NMR (126 MHz, CDCl_3) δ 165.88, 165.57, 165.53 (each C=O), 133.53, 133.46, 133.19, 129.90, 129.86, 129.68, 129.28, 129.06, 128.90, 128.59, 128.51, 128.48, 128.26 (each Ar-C), 78.08 (C-1), 71.62 (C-4), 68.71 (C-3), 68.51 (C-2), 66.15 (C-5), 16.13 (CH_3).

ES-HRMS calcd for $\text{C}_{27}\text{H}_{24}\text{O}_7\text{S}_1\text{Na}_1$ 515.1140, found m/z 515.1144 $[\text{M}+\text{Na}]^+$

IR (ATR) cm^{-1} : 1721, 1602, 1452, 1316, 1280, 1259, 1094, 1069, 1026, 754, 708

R_f : 0.33 (1:5 EtOAc -Pet ether)

$[\alpha]_{\text{D}}^{20}$ -222.9 (c 0.54, CHCl_3)

Chloromethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio- α -D-glucofuranoside (42)

The crude anomerised sugar **34** (50 mg, 0.082 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL). To this solution was added DBU (14.7 μL , 0.098 mmol). The reaction was stirred at r.t. overnight. The reaction was then concentrated *in vacuo*. The resultant residue was purified by flash chromatography (Pet ether-EtOAc 5:1) and gave the title compound (26 mg, 48%) as a colourless solid.

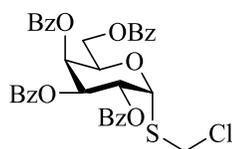
^1H NMR (500 MHz, CDCl_3) δ 8.07 – 8.04 (m, 2H, Ar-H), 8.00 – 7.93 (m, 4H, Ar-H), 7.90 – 7.86 (m, 2H, Ar-H), 7.59 – 7.29 (m, 12H), 6.21 (d, $J = 5.8$ Hz, 1H, H-1), 6.03 (t, $J = 9.9$ Hz, 1H, H-3), 5.75 (t, $J = 9.8$ Hz, 1H, H-4), 5.65 (dd, $J = 10.2, 5.8$ Hz, 1H, H-2), 4.88 (d, $J = 11.8$ Hz, 1H, CH_2Cl), 4.77 (ddd, $J = 10.1, 5.2, 2.8$ Hz, 1H, H-5), 4.69 – 4.63 (m, 2H, H-6a, CH_2Cl), 4.53 (dd, $J = 12.3, 5.2$ Hz, 1H, H-6b)

^{13}C NMR (126 MHz, CDCl_3) δ 166.07, 165.59, 165.17, 165.13 (each C=O), 133.65, 133.53, 133.31, 133.21, 130.00, 129.93, 129.88, 129.84, 129.72, 129.70, 129.68, 129.53, 128.83, 128.64, 128.52, 128.51, 128.46, 128.44, 128.41, 128.34, 128.31 (each Ar-C), 81.35 (C-1), 70.92 (C-2), 70.84 (C-3), 69.24 (C-5), 69.20 (C-4), 62.77 (C-6), 45.20 (CH_2Cl).

ES-HRMS calcd for $\text{C}_{35}\text{H}_{29}\text{O}_9\text{S}_1\text{Na}_1\text{Cl}_1$ 683.1119, found m/z 683.1116 $[\text{M}+\text{Na}]^+$

IR (ATR) cm^{-1} : 1721, 1602, 1451, 1257, 1088, 1068, 1026, 706, 686

R_f : 0.68 (1:2 EtOAc-Pet ether)

Chloromethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio- α -D-galactopyranoside (43)

The crude anomerised sugar **35** (50 mg, 0.082 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL). To this solution was added DBU (14.7 μL , 0.098 mmol). The reaction was stirred at r.t. overnight. The reaction was concentrated *in vacuo*. The resultant residue was purified by flash chromatography (Pet ether-EtOAc 5:1) and gave the title compound (29 mg, 54%) as a colourless solid.

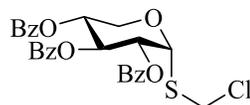
^1H NMR (500 MHz, CDCl_3) δ 8.12 – 8.09 (m, 2H, Ar-H), 8.03 – 8.00 (m, 2H, Ar-H), 7.99 – 7.95 (m, 2H, Ar-H), 7.82 – 7.78 (m, 2H, Ar-H), 7.67 – 7.62 (m, 1H, Ar-H), 7.59 – 7.24 (m, 11H, Ar-H), 6.31 (d, $J = 5.7$ Hz, 1H, H-1), 6.07 (dd, $J = 3.5, 1.2$ Hz, 1H, H-4), 6.01 (dd, $J = 10.7, 5.7$ Hz, 1H, H-2), 5.81 (dd, $J = 10.7, 3.4$ Hz, 1H, H-3), 4.92 – 4.86 (m, 1H, H-5), 4.89 (d, $J = 11.8$ Hz, 1H, CH_2Cl), 4.63 (dd, $J = 11.5, 7.1$ Hz, 1H, H-6a), 4.66 (d, $J = 11.7$ Hz, 1H, CH_2Cl), 4.49 (dd, $J = 11.5, 5.7$ Hz, 1H, H-6b).

^{13}C NMR (126 MHz, CDCl_3) δ 165.95, 165.42, 165.38, 165.38 (each C=O), 133.71, 133.63, 133.33, 130.01, 129.96, 129.94, 129.86, 129.75, 129.73, 129.72, 129.68, 129.33, 128.94, 128.83, 128.70, 128.67, 128.66, 128.51, 128.48, 128.44, 128.31 (each Ar-C), 81.38 (C-1), 69.04 (C-3), 68.68 (C-4), 68.31 (C-5), 68.14 (C-2), 62.29 (C-6), 45.02 (CH_2Cl).

ES-HRMS calcd for $\text{C}_{35}\text{H}_{29}\text{O}_9\text{S}_1\text{Na}_1\text{Cl}_1$ 683.1119, found m/z 683.1104 $[\text{M}+\text{Na}]^+$

IR (ATR) cm^{-1} : 1721, 1602, 1451, 1259, 1092, 1068, 1026, 706, 686

R_f : 0.68 (1:2 EtOAc-Pet ether)

Chloromethyl 2,3,4-tri-*O*-benzoyl-1-thio- α -D-xylopyranoside (44)

The crude anomerised sugar **38** (50 mg, 0.100 mmol) was dissolved in anhydrous CH_2Cl_2 (4 mL). To this solution was added DBU (18.8 μL , 0.125 mmol). The reaction was stirred at r.t. overnight. The reaction was then concentrated *in vacuo*. The resultant residue was purified by flash chromatography (Pet ether-EtOAc 5:1) and gave the title compound (41 mg, 75%) as a colourless solid.

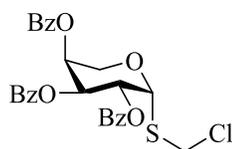
^1H NMR (500 MHz, CDCl_3) δ 8.04 – 7.92 (m, 6H, Ar-H), 7.58 – 7.33 (m, 9H Ar-H), 6.04 (d, $J = 5.2$ Hz, 1H, H-1), 5.94 (t, $J = 8.9$ Hz, 1H, H-3), 5.57 (dd, $J = 9.1, 5.2$ Hz, 1H, H-2), 5.43 (t, $J = 8.0$ Hz, 1H, H-4), 4.88 (d, $J = 11.8$ Hz, 1H, CH_2Cl), 4.67 (d, $J = 11.8$ Hz, 1H, CH_2Cl), 4.20 (d, $J = 7.3$ Hz, 2H, H-5a, H-5b).

^{13}C NMR (126 MHz, CDCl_3) δ 165.48, 165.39, 165.18 (each C=O), 133.59, 133.46, 133.44, 133.40, 130.02, 129.98, 129.92, 129.85, 129.75, 128.96, 128.89, 128.67, 128.49, 128.42, 128.40 (each Ar-C), 81.24 (C-1), 70.55 (C-2), 69.84 (C-3), 69.38 (C-4), 61.01 (C-5), 45.41 (CH_2Cl).

ES-HRMS calcd for $\text{C}_{29}\text{H}_{26}\text{O}_7\text{S}_1\text{Na}_1\text{Cl}_1\text{N}_1$ 590.1016, found m/z 590.1017 [$\text{M}+\text{MeCN}+\text{Na}$] $^+$

IR (ATR) cm^{-1} : 1723, 1602, 1452, 127, 1258, 1093, 1070, 1027, 707

R_f : 0.77 (1:2 EtOAc-Pet ether)

Chloromethyl 2,3,4-tri-*O*-benzoyl-1-thio- β -L-arabinopyranoside (45)

The crude anomersed sugar **39** (50 mg, 0.100 mmol) was dissolved in anhydrous CH_2Cl_2 (4 mL). To this solution was added DBU (18.8 μL , 0.125 mmol). The reaction was stirred at r.t. overnight. The reaction was then concentrated *in vacuo*. The resultant residue was purified by flash chromatography (Pet ether-EtOAc 5:1) and gave the title compound (29 mg, 53%) as a colourless solid.

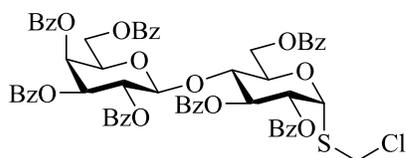
^1H NMR (500 MHz, CDCl_3) δ 8.14 – 8.08 (m, 2H, Ar-H), 8.04 – 7.97 (m, 2H, Ar-H), 7.91 – 7.86 (m, 2H, Ar-H), 7.65 – 7.28 (m, 9H, Ar-H), 6.18 (d, $J = 5.4$ Hz, 1H, H-1), 6.01 (dd, $J = 10.0, 5.4$ Hz, 1H, H-2), 5.79 – 5.73 (m, 2H, H-3, H-4), 4.88 (d, $J = 11.8$ Hz, 1H, CH_2Cl), 4.69 (d, $J = 11.7$ Hz, 1H, CH_2Cl), 4.46 (dd, $J = 13.3, 1.6$ Hz, 1H, H-5a), 4.08 (dd, $J = 13.2, 2.5$ Hz, 1H, H-5b).

^{13}C NMR (126 MHz, CDCl_3) δ 165.62, 165.41, 165.39 (each C=O), 133.60, 133.52, 133.49, 133.46, 133.37, 129.95, 129.93, 129.86, 129.85, 129.73, 129.38, 128.96, 128.77, 128.59, 128.51, 128.46, 128.37 (each Ar-C), 81.75 (C-1), 69.40 (C-4), 68.57 (C-3), 68.40 (C-2), 61.86 (C-5), 45.44 (CH_2Cl).

ES-HRMS calcd for $\text{C}_{29}\text{H}_{26}\text{O}_7\text{S}_1\text{Na}_1\text{Cl}_1\text{N}_1$ 590.1016, found m/z 590.1016 $[\text{M}+\text{MeCN}+\text{Na}]^+$

IR (ATR) cm^{-1} : 1720, 1602, 1451, 1247, 1085, 1068, 1025, 706, 686

R_f : 0.71 (1:2 EtOAc-Pet ether)

Chloromethyl hepta-*O*-benzoyl-1-thio- α -D-lactoside (46)

The crude anomerised sugar **36** (100 mg, 0.092 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL). To this solution was added DBU (16.5 μL , 0.110 mmol). The reaction was stirred at r.t. overnight. The reaction was then concentrated *in vacuo*. The resultant residue was purified by flash chromatography (Pet ether-EtOAc 4:1) and gave the title compound (48 mg, 46%) as a colourless solid.

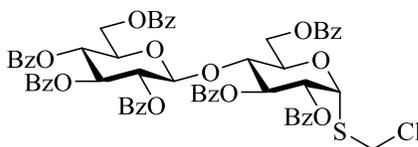
^1H NMR (500 MHz, CDCl_3) δ 8.04 – 7.95 (m, 10H, Ar-H), 7.89 – 7.85 (m, 2H, Ar-H), 7.75 – 7.70 (m, 2H, Ar-H), 7.65 – 7.27 (m, 17H, Ar-H), 7.24 – 7.18 (m, 4H, Ar-H), 6.07 (d, $J = 5.9$ Hz, 1H, H-1), 5.91 (dd, $J = 10.0, 8.8$ Hz, 1H, H-3), 5.76 (dd, $J = 3.5, 1.0$ Hz, 1H, H-4'), 5.73 (dd, $J = 10.3, 7.9$ Hz, 1H, H-2'), 5.57 (dd, $J = 10.0, 5.9$ Hz, 1H, H-2), 5.40 (dd, $J = 10.3, 3.5$ Hz, 1H, H-3'), 4.94 (d, $J = 7.9$ Hz, 1H, H-1), 4.76 (d, $J = 11.9$ Hz, 1H, CH_2Cl), 4.57 (d, $J = 12.0$ Hz, 1H, CH_2Cl), 4.55 (dd, $J = 8.3, 3.2$ Hz, 2H, H-6a, H-6b), 4.45 (ddd, $J = 10.1, 4.2, 2.1$ Hz, 1H, H-5), 4.27 (dd, $J = 10.0, 8.9$ Hz, 1H, H-4), 3.97 – 3.93 (m, 1H, H-5'), 3.87 (dd, $J = 11.3, 6.4$ Hz, 1H, H-6a'), 3.77 (dd, $J = 11.4, 7.0$ Hz, 1H, H-6b').

^{13}C NMR (126 MHz, CDCl_3) δ 165.78, 165.58, 165.42, 165.22, 165.22, 165.16, 164.78 (Each C=O), 133.59, 133.51, 133.40, 133.37, 133.29, 133.25, 130.01, 129.97, 129.95, 129.76, 129.74, 129.66, 129.64, 129.52, 129.42, 129.38, 128.81, 128.68, 128.60, 128.57, 128.55, 128.50, 128.48, 128.31, 128.24 (each Ar-C), 101.11 (C-1'), 81.06 (C-1), 76.02 (C-4), 71.87 (C-3'), 71.39 (C-5'), 70.78 (C-3), 70.65 (C-2), 69.90 (C-5), 69.87 (C-2'), 67.50 (C-4'), 62.29 (C-6), 61.13 (C-6'), 45.23 (CH_2Cl).

ES-HRMS calcd for $\text{C}_{62}\text{H}_{51}\text{O}_{17}\text{Na}_1\text{S}_1\text{Cl}_1$ 1157.2433, found m/z 1157.2435 $[\text{M}+\text{Na}]^+$

IR (ATR) cm^{-1} : 1724, 1452, 1266, 1092, 1070, 906, 727, 708

R_f : 0.41 (1:2 EtOAc-Pet ether)

Chloromethyl hepta-*O*-benzoyl-1-thio- α -D-cellobioside (47)

The crude anomerised sugar **37** (100 mg, 0.092 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL). To this solution was added DBU (16.5 μL , 0.110 mmol). The reaction was stirred at r.t. overnight. The reaction was then concentrated *in vacuo*. The resultant residue was purified by flash chromatography (Pet ether-EtOAc 4:1) and gave the title compound (53 mg, 51%) as a colourless solid.

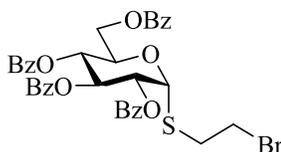
^1H NMR (500 MHz, CDCl_3) δ 8.03 – 7.90 (m, 11H, Ar-H), 7.81 – 7.71 (m, 4H, Ar-H), 7.59 – 7.50 (m, 3H, Ar-H), 7.46 – 7.35 (m, 12H, Ar-H), 7.32 – 7.22 (m, 5H, Ar-H), 6.05 (d, $J = 5.8$ Hz, 1H, H-1), 5.91 (dd, $J = 9.8, 8.7$ Hz, 1H, H-3), 5.76 (t, $J = 9.6$ Hz, 1H, H-3'), 5.55 – 5.49 (m, 2H, H-2, H-2'), 5.41 (t, $J = 9.7$ Hz, 1H, H-4'), 5.02 (d, $J = 7.9$ Hz, 1H, H-1'), 4.75 (d, $J = 11.9$ Hz, 1H, CH_2Cl), 4.58 (dd, $J = 12.1, 1.9$ Hz, 1H, H-6a), 4.55 (d, $J = 11.8$ Hz, 1H, CH_2Cl), 4.50 (dd, $J = 12.1, 4.6$ Hz, 1H, H-6b), 4.45 (ddd, $J = 10.2, 4.6, 1.9$ Hz, 1H, H-5), 4.25 (dd, $J = 9.9, 8.7$ Hz, 1H, H-4), 4.17 – 4.09 (m, 1H, H-6a'), 3.94 – 3.84 (m, 2H, H-5', H-6b').

^{13}C NMR (126 MHz, CDCl_3) δ 165.72, 165.69, 165.61, 165.19, 165.15, 164.97, 164.73 (each C=O), 133.59, 133.35, 133.34, 133.32, 133.28, 133.19, 133.15, 129.99, 129.89, 129.77, 129.74, 129.69, 129.62, 129.60, 129.58, 129.55, 129.52, 129.46, 129.32, 128.64, 128.61, 128.58, 128.52, 128.49, 128.47, 128.42, 128.38, 128.35, 128.31, 128.29, 128.23 (each Ar-C), 100.94 (C-1'), 80.87 (C-1), 76.43 (C-4), 72.90 (C-3'), 72.40 (C-5'), 71.93 (C-2'), 70.83 (C-2), 70.51 (C-3), 69.88 (C-5), 69.33 (C-4'), 62.67 (C-6'), 62.32 (C-6), 45.18 (CH_2Cl).

ES-HRMS calcd for $\text{C}_{62}\text{H}_{51}\text{O}_{17}\text{Na}_1\text{S}_1\text{Cl}_1$ 1157.2433, found m/z 1157.2444 $[\text{M}+\text{Na}]^+$

IR (ATR) cm^{-1} : 1722, 1602, 1451, 1088, 1068, 1026, 908, 730, 706

R_f : 0.42 (1:2 EtOAc-Pet ether)

Bromoethyl 2,3,4,6-Tetra-*O*-benzoyl-1-thio- α -D-glucopyranoside (48)

The crude anomersed sugar **34** (200 mg, 0.330 mmol) was dissolved in an acetone-H₂O mixture (2:1, 3 mL). To this solution was added K₂CO₃ (54 mg, 0.390 mmol) and then 1,2-dibromoethane (0.35 mL, 4.06 mmol). The reaction was stirred at r.t. for 3 h. The solution was then diluted with CH₂Cl₂. The organic layer was separated. The aqueous layer was then re-extracted with a further portion of CH₂Cl₂. The combined organic phase was dried over MgSO₄ and the solvent removed under diminished pressure. The resultant residue was purified by flash chromatography (Pet ether-EtOAc 3:1) and gave the title compound (148 mg, 63%) as a colourless solid.

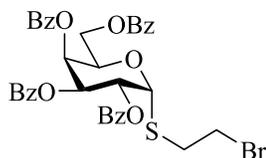
¹H NMR (500 MHz, CDCl₃) δ 8.07 – 8.03 (m, 2H, Ar-H), 7.99 – 7.94 (m, 4H, Ar-H), 7.90 – 7.86 (m, 2H, Ar-H), 7.59 – 7.49 (m, 3H, Ar-H), 7.46 – 7.35 (m, 7H, Ar-H), 7.32 – 7.27 (m, 2H), 6.04 (t, *J* = 9.9 Hz, 1H, H-3), 5.98 (d, *J* = 5.7 Hz, 1H, H-1), 5.67 (t, *J* = 9.9 Hz, 1H, H-4), 5.50 (dd, *J* = 10.2, 5.7 Hz, 1H, H-2), 4.86 (ddd, *J* = 10.2, 6.0, 2.6 Hz, 1H, H-5), 4.62 (dd, *J* = 12.3, 2.7 Hz, 1H, H-6a), 4.52 (dd, *J* = 12.3, 6.0 Hz, 1H, H-6b), 3.50 (dtd, *J* = 28.6, 10.0, 5.9 Hz, 2H, CH₂CH₂Br), 3.12 (ddd, *J* = 13.8, 10.3, 5.9 Hz, 1H, CH₂CH₂Br), 3.01 (ddd, *J* = 13.9, 10.3, 5.8 Hz, 1H, CH₂CH₂Br).

¹³C NMR (126 MHz, CDCl₃) δ 166.12, 165.58, 165.36, 165.27 (each C=O), 133.62, 133.54, 133.26, 133.23, 133.22, 130.03, 129.99, 129.93, 129.90, 129.87, 129.84, 129.77, 129.74, 129.71, 129.69, 129.44, 128.90, 128.65, 128.51, 128.50, 128.45, 128.42, 128.34, 128.33, 128.30 (each Ar-C), 83.06 (C-1), 71.52 (C-2), 70.58 (C-3), 69.32 (C-4), 68.72 (C-5), 63.05 (C-6), 32.76 (CH₂CH₂Br), 30.07 (CH₂CH₂Br).

ES-HRMS calcd for C₃₆H₃₁O₉Na₁S₁Br₁ 741.0770, found *m/z* 741.0767 [M+Na]⁺

IR (ATR) cm⁻¹: 1721, 1602, 1451, 1260, 1090, 1069, 1026, 707

R_f: 0.31 (2:8 EtOAc-Pet ether)

Bromoethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio- α -D-galactopyranoside (49)

The crude anomerised sugar **35** (200 mg, 0.330 mmol) was dissolved in an acetone-H₂O mixture (2:1, 3 mL). To this solution was added K₂CO₃ (55 mg, 0.400 mmol) and then 1,2-dibromoethane (0.35 mL, 4.06 mmol). The reaction was stirred at r.t. for 3 h. The solution was then diluted with CH₂Cl₂. The organic layer was separated. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic phase was dried over MgSO₄ and the solvent removed under diminished pressure. The resultant residue was purified by flash chromatography (Pet ether-EtOAc 3:1) and gave the title compound (118 mg, 50%) as a colourless solid.

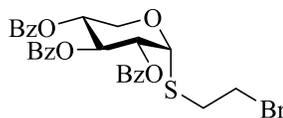
¹H NMR (500 MHz, CDCl₃) δ 8.12 – 8.08 (m, 2H, Ar-H), 8.06 – 8.02 (m, 2H, Ar-H), 7.99 – 7.95 (m, 2H, Ar-H), 7.81 – 7.77 (m, 2H, Ar-H), 7.66 – 7.61 (m, 1H, Ar-H), 7.58 – 7.54 (m, 1H, Ar-H), 7.54 – 7.48 (m, 3H, Ar-H), 7.47 – 7.42 (m, 3H, Ar-H), 7.42 – 7.37 (m, 2H, Ar-H), 7.28 – 7.22 (m, 2H, Ar-H), 6.09 (d, J = 4.9 Hz, 1H, H-1), 6.04 (dd, J = 3.0, 1.3 Hz, 1H, H-4), 5.88 – 5.81 (m, 2H, H-2, H-3), 5.00 (ddd, J = 7.5, 4.9, 1.4 Hz, 1H, H-5), 4.59 (dd, J = 11.6, 7.5 Hz, 1H, H-6a), 4.49 (dd, J = 11.7, 4.9 Hz, 1H, H-6b), 3.50 (dtd, J = 32.4, 10.1, 5.7 Hz, 2H, CH₂CH₂Br), 3.13 (ddd, J = 13.8, 10.6, 5.7 Hz, 1H, CH₂CH₂Br), 3.00 (ddd, J = 13.8, 10.6, 5.7 Hz, 1H, CH₂CH₂Br).

¹³C NMR (126 MHz, CDCl₃) δ 166.06, 165.63, 165.44, 165.34 (each C=O), 133.69, 133.60, 133.31, 133.29, 129.99, 129.94, 129.92, 129.78, 129.75, 129.73, 129.71, 129.28, 128.97, 128.90, 128.78, 128.69, 128.54, 128.51, 128.31, 128.29 (each Ar-C), 83.32 (C-1), 68.96 (C-4), 68.78 (C-3), 68.68 (C-2), 67.87 (C-5), 62.77 (C-6), 32.41 (CH₂CH₂Br), 30.01 (CH₂CH₂Br).

ES-HRMS calcd for C₃₆H₃₁O₉Na₁S₁Br₁ 741.0770, found m/z 741.0766 [M+Na]⁺

IR (ATR) cm⁻¹: 1720, 1602, 1451, 1258 1092, 1068, 1026, 706

R_f : 0.31 (2:8 EtOAc-Pet ether)

Bromoethyl 2,3,4-tri-*O*-benzoyl-1-thio- α -D-xylopyranoside (50)

The crude anomerised sugar **38** (150 mg, 0.310 mmol) was dissolved in an acetone-H₂O mixture (2:1, 3 mL). To this solution was added K₂CO₃ (52 mg, 0.380 mmol) and then 1,2-dibromoethane (0.34 mL, 3.95 mmol). The reaction was stirred at r.t. for 3 h. The solution was then diluted with CH₂Cl₂. The organic layer was separated and the aqueous layer re-extracted with a further portion of CH₂Cl₂. The combined organic phase was dried over MgSO₄ and the solvent removed under diminished pressure. The resultant residue was purified by flash chromatography (Pet ether-EtOAc 5:1) and gave the title compound (117 mg, 64%) as a colourless solid.

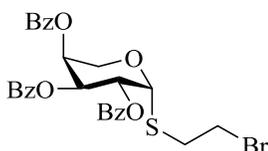
¹H NMR (500 MHz, CDCl₃) δ 8.01 – 7.93 (m, 6H, Ar-H), 7.57 – 7.45 (m, 2H, Ar-H), 7.43 – 7.31 (m, 7H, Ar-H), 5.96 (t, J = 9.2 Hz, 1H, H-3), 5.84 (d, J = 5.3 Hz, 1H, H-1), 5.43 (dd, J = 9.5, 5.3 Hz, 1H, H-2), 5.39 (td, J = 9.5, 5.6 Hz, 1H, H-4), 4.26 (dd, J = 11.4, 9.7 Hz, 1H, H-5a), 4.14 (dd, J = 11.4, 5.5 Hz, 1H, H-5b), 3.50 (pd, J = 10.0, 6.0 Hz, 2H, CH₂CH₂Br), 3.10 (ddd, J = 13.9, 10.2, 6.2 Hz, 1H, CH₂CH₂Br), 3.01 (ddd, J = 13.9, 10.1, 6.0 Hz, 1H, CH₂CH₂Br).

¹³C NMR (126 MHz, CDCl₃) δ 165.52, 165.43, 165.41 (each C=O), 133.58, 133.49, 133.45, 133.34, 130.00, 129.93, 129.90, 129.87, 129.85, 129.72, 129.05, 128.92, 128.76, 128.51, 128.45, 128.43, 128.40, 128.39 (each Ar-C), 83.44 (C-1), 71.27 (C-2), 69.77 (C-3), 69.55 (C-4), 60.12 (C-5), 32.88 (CH₂CH₂Br), 30.27 (CH₂CH₂Br).

ES-HRMS calcd for C₃₀H₂₈N₁O₇Na₁S₁Br₁ 648.0668, found m/z 648.0689 [M+MeCN+Na]⁺

IR (ATR) cm⁻¹: 1723, 1452, 1258, 1092, 1069, 906, 729, 707

*R*_f: 0.43 (2:8 EtOAc-Pet ether)

Bromoethyl 2,3,4-tri-*O*-benzoyl-1-thio- β -L-arabinopyranoside (51)

The crude anomerised sugar **39** (150 mg, 0.310 mmol) was dissolved in an acetone-H₂O mixture (2:1, 3 mL). To this solution was added K₂CO₃ (52 mg, 0.380 mmol) and then 1,2-dibromoethane (0.34 mL, 3.95 mmol). The reaction was stirred at r.t. for 3 h. The solution was then diluted with CH₂Cl₂. The organic layer was separated and the aqueous layer re-extracted with a further portion of CH₂Cl₂. The combined organic phase was dried over MgSO₄ and the solvent removed under diminished pressure. The resultant residue was purified by flash chromatography (Pet ether-EtOAc 5:1) and gave the title compound (96 mg, 52%) as a colourless solid.

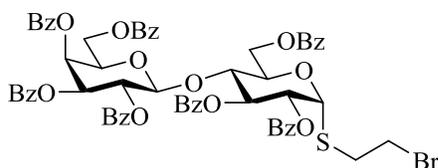
¹H NMR (500 MHz, CDCl₃) δ 8.13 – 8.06 (m, 2H, Ar-H), 8.04 – 7.96 (m, 2H, Ar-H), 7.90 – 7.83 (m, 2H, Ar-H), 7.65 – 7.57 (m, 1H, Ar-H), 7.55 – 7.52 (m, 1H, Ar-H), 7.50 – 7.44 (m, 3H, Ar-H), 7.43 – 7.38 (m, 2H, Ar-H), 7.32 – 7.28 (m, 2H, Ar-H), 5.96 (d, J = 5.3 Hz, 1H, H-1), 5.87 (dd, J = 9.7, 5.3 Hz, 1H, H-2), 5.78 – 5.74 (m, 2H, H-3, H-4), 4.54 (dd, J = 13.1, 1.5 Hz, 1H, H-5a), 4.02 (dd, J = 13.2, 2.3 Hz, 1H, H-5b), 3.57 – 3.42 (m, 2H, CH₂CH₂Br), 3.10 (ddd, J = 13.9, 10.1, 6.1 Hz, 1H, CH₂CH₂Br), 3.01 (ddd, J = 13.9, 10.0, 6.1 Hz, 1H, CH₂CH₂Br).

¹³C NMR (126 MHz, CDCl₃) δ 165.63, 165.62, 165.38 (each C=O), 133.57, 133.47, 133.31, 129.93, 129.89, 129.86, 129.84, 129.72, 129.71, 129.44, 129.03, 128.61, 128.57, 128.53, 128.51, 128.42, 128.34 (each Ar-C), 83.81 (C-1), 69.53 (C-4), 69.07 (C-2), 68.25 (C-3), 61.25 (C-5), 32.63 (CH₂CH₂Br), 30.24 (CH₂CH₂Br).

ES-HRMS calcd for C₃₀H₂₈N₁O₇Na₁S₁Br₁ 648.0668, found m/z 648.0646 [M+MeCN+Na]⁺

IR (ATR) cm⁻¹: 1722, 1259, 1108, 1085, 1069, 905, 727, 707

R_f : 0.44 (2:8 EtOAc-Pet ether)

Bromoethyl hepta-*O*-benzoyl-1-thio- α -D-lactoside (52)

The crude anomersed sugar **36** (120 mg, 0.110 mmol) was dissolved in an acetone-H₂O mixture (2:1, 3 mL). To this solution was added K₂CO₃ (18 mg, 0.130 mmol) and then 1,2-dibromoethane (0.12 mL, 1.39 mmol). The reaction was stirred at r.t. for 3 h. The solution was then diluted with CH₂Cl₂. The organic layer was separated, with the aqueous layer re-extracted with a further portion of CH₂Cl₂. The organic phase was dried over MgSO₄ and the solvent removed under diminished pressure. The resultant residue was purified by flash chromatography (Pet ether-EtOAc 3:1) and gave the title compound (69 mg, 52%) as a colourless solid.

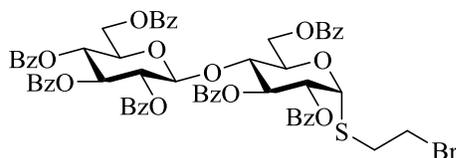
¹H NMR (500 MHz, CDCl₃) δ 8.05 – 7.94 (m, 10H, Ar-H), 7.90 – 7.87 (m, 2H, Ar-H), 7.76 – 7.71 (m, 2H, Ar-H), 7.65 – 7.50 (m, 3H, Ar-H), 7.49 – 7.34 (m, 12H, Ar-H), 7.30 – 7.26 (m, 2H, Ar-H), 7.25 – 7.17 (m, 4H, Ar-H), 5.92 (dd, *J* = 10.2, 9.0 Hz, 1H, H-3), 5.85 (d, *J* = 5.9 Hz, 1H, H-1), 5.77 (dd, *J* = 3.4, 1.0 Hz, 1H, H-4'), 5.74 (dd, *J* = 10.3, 7.8 Hz, 1H, H-2'), 5.42 (dd, *J* = 10.2, 5.7 Hz, 1H, H-2), 5.42 (dd, *J* = 10.3, 3.5 Hz, 1H, H-3'), 4.94 (d, *J* = 7.9 Hz, 1H, H-1'), 4.58 – 4.52 (m, 3H, H-5, H-6a, H-6b), 4.18 (t, *J* = 9.4 Hz, 1H, H-4), 3.99 – 3.94 (m, 1H, H-5'), 3.88 (dd, *J* = 11.3, 6.3 Hz, 1H, H-6a'), 3.76 (dd, *J* = 11.3, 7.1 Hz, 1H, H-6b'), 3.41 (dtd, *J* = 22.4, 10.0, 5.9 Hz, 2H, CH₂CH₂Br), 3.01 (ddd, *J* = 13.9, 10.5, 5.9 Hz, 1H, CH₂CH₂Br), 2.91 (ddd, *J* = 13.8, 10.4, 5.9 Hz, 1H, CH₂CH₂Br).

¹³C NMR (126 MHz, CDCl₃) δ 165.86, 165.56, 165.46, 165.43, 165.22, 165.13, 164.79 (each C=O), 133.58, 133.50, 133.41, 133.35, 133.25, 129.99, 129.96, 129.74, 129.65, 129.63, 129.57, 129.37, 129.36, 128.82, 128.70, 128.64, 128.60, 128.57, 128.54, 128.51, 128.47, 128.42, 128.31, 128.26, 128.24 (each Ar-C), 101.18 (C-1'), 82.87 (C-1), 76.32 (C-4), 71.87 (C-3'), 71.36 (C-5'), 71.31 (C-2), 70.53 (C-3), 69.90 (C-2'), 69.35 (C-5), 67.49 (C-4'), 62.56 (C-6), 61.08 (C-6'), 32.56 (CH₂CH₂Br), 29.95 (CH₂CH₂Br).

ES-HRMS calcd for C₆₃H₅₃O₁₇Na₁S₁Br₁ 1215.2085, found *m/z* 1215.2080 [M+Na]⁺

IR (ATR) cm⁻¹: 1722, 1451, 1262, 1091, 1068, 1026, 907, 731, 706

R_f: 0.39 (1:2 EtOAc-Pet ether)

Bromoethyl hepta-*O*-benzoyl-1-thio- α -D-cellobioside (53)

The crude anomerised sugar **37** (120 mg, 0.110 mmol) was dissolved in an acetone-H₂O mixture (2:1, 3 mL). To this solution was added K₂CO₃ (19 mg, 0.140 mmol) and then 1,2-dibromoethane (0.12 mL, 1.39 mmol). The reaction was stirred at r.t. for 3 h. The solution was then diluted with CH₂Cl₂. The organic layer was separated. The aqueous layer was then re-extracted with a further portion of CH₂Cl₂. The combined organic phase was dried over MgSO₄ and the solvent removed under diminished pressure. The resultant residue was purified by flash chromatography (Pet ether-EtOAc 3:1) and gave the title compound (59 mg, 45%) as a colourless solid.

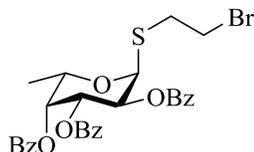
¹H NMR (500 MHz, CDCl₃) δ 8.02 – 7.98 (m, 2H, Ar-H), 7.97 – 7.91 (m, 8H, Ar-H), 7.80 – 7.72 (m, 4H, Ar-H), 7.58 – 7.49 (m, 3H, Ar-H), 7.47 – 7.32 (m, 12H, Ar-H), 7.30 – 7.20 (m, 6H, Ar-H), 5.91 (dd, *J* = 10.0, 8.9 Hz, 1H, H-3), 5.81 (d, *J* = 5.9 Hz, 1H, H-1), 5.77 (t, *J* = 9.7 Hz, 1H, H-3'), 5.53 (dd, *J* = 9.8, 7.9 Hz, 1H, H-2'), 5.43 (t, *J* = 9.5 Hz, 1H, H-4'), 5.35 (dd, *J* = 10.0, 5.8 Hz, 1H, H-2), 5.00 (d, *J* = 7.9 Hz, 1H, H-1'), 4.59 – 4.48 (m, 3H, H-5, H-6a, H-6b), 4.16 (t, *J* = 9.3 Hz, 1H, H-4), 4.10 (dd, *J* = 11.7, 2.8 Hz, 1H, H-6a'), 3.94 – 3.86 (m, 2H, H-5', H-6b'), 3.39 (dtd, *J* = 24.1, 10.1, 5.9 Hz, 2H, CH₂CH₂Br), 2.99 (ddd, *J* = 13.8, 10.5, 5.9 Hz, 1H, CH₂CH₂Br), 2.89 (ddd, *J* = 13.8, 10.5, 5.9 Hz, 1H, CH₂CH₂Br).

¹³C NMR (126 MHz, CDCl₃) δ 165.81, 165.69, 165.62, 165.43, 165.12, 164.95, 164.75 (each C=O), 133.56, 133.34, 133.30, 133.25, 133.18, 133.13, 129.97, 129.73, 129.69, 129.65, 129.63, 129.60, 129.56, 129.43, 129.38, 128.64, 128.62, 128.59, 128.56, 128.49, 128.48, 128.46, 128.42, 128.38, 128.35, 128.32, 128.30, 128.22 (each Ar-C), 100.99 (C-1'), 82.76 (C-1), 76.75 (C-4) 72.89 (C-3'), 72.39 (C-5'), 71.94 (C-2'), 71.50 (C-2), 70.26 (C-3), 69.34 (C-5), 69.30 (C-4'), 62.63 (C-6), 62.58 (C-6'), 32.58 (CH₂CH₂Br), 29.96. (CH₂CH₂Br)

ES-HRMS calcd for C₆₃H₅₃O₁₇Na₁S₁Br₁ 1215.2085, found *m/z* 1215.2092 [M+Na]⁺

IR (ATR) cm⁻¹: 1722, 1451, 1261, 1091, 1068, 1027, 706

*R*_f: 0.41 (1:2 EtOAc-Pet ether)

Bromoethyl 2,3,4-tri-*O*-benzoyl-1-thio- α -L-fucopyranoside (54)

The crude anomerised sugar **41** (100 mg, 0.203 mmol) was dissolved in an acetone-H₂O mixture (2:1, 6 mL). To this solution was added K₂CO₃ (36 mg, 0.260 mmol) and then 1,2-dibromoethane (0.22 mL, 2.55 mmol). The reaction was stirred at r.t. for 3 h. The solution was then diluted with CH₂Cl₂. The organic layer was separated. The aqueous layer was then re-extracted with a further portion of CH₂Cl₂. The combined organic phase was dried over MgSO₄ and the solvent removed under diminished pressure. The resultant residue was purified by flash chromatography (Pet ether-EtOAc 5:1) and gave the title compound (61 mg, 50%) as a colourless solid

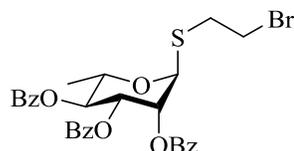
¹H NMR (500 MHz, CDCl₃) δ 8.13 – 8.07 (m, 2H, Ar-H), 8.00 – 7.93 (m, 2H, Ar-H), 7.81 – 7.75 (m, 2H, Ar-H), 7.65 – 7.60 (m, 1H, Ar-H), 7.52 – 7.47 (m, 3H, Ar-H), 7.46 – 7.42 (m, 1H, Ar-H), 7.41 – 7.34 (m, 2H, Ar-H), 7.28 – 7.23 (m, 2H, Ar-H), 5.99 (d, J = 4.8 Hz, 1H, H-), 5.85 – 5.75 (m, 3H, H-2, H-3, H-4), 4.75 (p, J = 6.1, 5.7 Hz, 1H, H-5), 3.57 – 3.42 (m, 2H, CH₂CH₂Br), 3.10 (ddd, J = 13.9, 9.8, 6.5 Hz, 1H, CH₂CH₂Br), 3.01 (ddd, J = 13.9, 9.6, 6.4 Hz, 1H, CH₂CH₂Br), 1.31 (d, J = 6.5 Hz, 3H, CH₃).

¹³C NMR (126 MHz, CDCl₃) δ 165.84, 165.71, 165.45 (each C=O), 133.51, 133.48, 133.18, 129.88, 129.67, 128.65, 128.61, 128.49, 128.47, 128.28, 128.25 (each Ar-C), 83.52 (C-1), 71.57 (C-4), 69.12 (C-3), 68.85 (C-2), 65.81 (C-5), 32.79 (CH₂CH₂Br), 30.33 (CH₂CH₂Br), 16.12 (CH₃).

ES-HRMS calcd for C₂₉H₂₇O₇Na₁S₁Br₁ 621.0559, found m/z 621.0583 [M+Na]⁺

IR (ATR) cm⁻¹: 1724, 1451, 1316, 1281, 1259, 1178, 1095, 1069, 1026, 709

R_f : 0.45 (1:5 EtOAc-Pet ether)

Bromoethyl 2,3,4-tri-*O*-benzoyl-1-thio- α -L-rhamnopyranoside (55)

The crude anomersed sugar **40** (400 mg, 0.812 mmol) was dissolved in an acetone-H₂O mixture (2:1, 15 mL). To this solution was added K₂CO₃ (146 mg, 1.06 mmol) and then 1,2-dibromoethane (0.9 mL, 10.4 mmol). The reaction was stirred at r.t. for 3 h. The solution was then diluted with CH₂Cl₂. The organic layer was separated. The aqueous layer was then re-extracted with a further portion of CH₂Cl₂. The combined organic phase was dried over MgSO₄ and the solvent removed under diminished pressure. The resultant residue was purified by flash chromatography (Pet ether-EtOAc 5:1) and gave the title compound (248 mg, 51%) as a colourless solid.

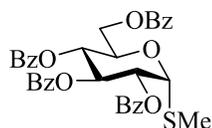
¹H NMR (500 MHz, CDCl₃) δ 8.09 – 8.05 (m, 2H, Ar-H), 7.96 – 7.91 (m, 2H, Ar-H), 7.78 – 7.74 (m, 2H, Ar-H), 7.63 – 7.58 (m, 1H, Ar-H), 7.53 – 7.46 (m, 2H, Ar-H), 7.44 – 7.34 (m, 4H, Ar-H), 7.25 – 7.20 (m, 2H, Ar-H), 5.97 (dd, $J = 3.5, 1.2$ Hz, 1H, H-2), 5.62 (t, $J = 9.7$ Hz, 1H, H-4), 5.56 (dd, $J = 10.2, 3.5$ Hz, 1H, H-3), 5.08 (d, $J = 1.1$ Hz, 1H, H-1), 3.91 (dq, $J = 9.3, 6.1$ Hz, 1H, H-5), 3.66 – 3.58 (m, 1H, CH₂CH₂Br), 3.54 (td, $J = 10.3, 5.8$ Hz, 1H, CH₂CH₂Br), 3.21 (ddd, $J = 13.9, 10.7, 5.8$ Hz, 1H, CH₂CH₂Br), 3.14 (ddd, $J = 13.9, 10.8, 5.7$ Hz, 1H, CH₂CH₂Br), 1.45 (d, $J = 6.1$ Hz, 3H, CH₃).

¹³C NMR (126 MHz, CDCl₃) δ 165.59, 165.54, 165.53 (each C=O), 133.40, 133.21, 130.06, 129.71, 128.81, 128.54, 128.44, 128.24 (each Ar-C), 83.02 (C-1), 75.44 (C-5), 72.47 (C-3) 71.32 (C-2), 71.05 (C-4), 33.69 (CH₂CH₂Br), 30.48 (CH₂CH₂Br), 18.04 (CH₃).

ES-HRMS calcd for C₃₁H₃₀N₁O₇Na₁S₁Br₁ 662.0824, found m/z 662.0867 [M+MeCN+Na]⁺

IR (ATR) cm⁻¹: 1726, 1602, 1451, 1279, 1261, 1177, 1091, 1069, 1026, 906, 710

*R*_f: 0.33 (1:5 EtOAc-Pet ether)

Methyl 2,3,4,6-tetra-O-benzoyl-1-thio- α -D-glucopyranoside (56)

The crude anomerised sugar **34** (200 mg, 0.326 mmol) was dissolved in CH_2Cl_2 (5 mL). To this was added DIPEA (0.12 mL, 0.689 mmol), followed by methyl iodide (91.5 μL , 1.47 mmol). The reaction was stirred at r.t. for 2 h.

The reaction was concentrated *in vacuo*. The resultant residue was purified by flash chromatography (CH-EtOAc 7:3) and gave the title compound (143 mg, 70%) as a colourless solid.

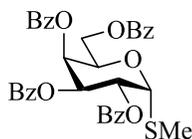
^1H NMR (500 MHz, CDCl_3) δ 8.10 – 8.03 (m, 2H, Ar-H), 8.03 – 7.98 (m, 2H, Ar-H), 7.98 – 7.94 (m, 2H, Ar-H), 7.91 – 7.85 (m, 2H, Ar-H), 7.59 – 7.55 (m, 1H, Ar-H), 7.55 – 7.50 (m, 2H, Ar-H), 7.46 – 7.35 (m, 8H, Ar-H), 7.33 – 7.28 (m, 1H, Ar-H), 6.11 (t, $J = 9.8$ Hz, 1H, H-3), 5.83 (d, $J = 5.8$ Hz, 1H, H-1), 5.70 (t, $J = 9.8$ Hz, 1H, H-4), 5.55 (dd, $J = 10.1$, 5.7 Hz, 1H, H-2), 4.85 (ddd, $J = 10.2$, 5.5, 2.8 Hz, 1H, H-5), 4.62 (dd, $J = 12.2$, 2.8 Hz, 1H, H-6a), 4.54 (dd, $J = 12.2$, 5.5 Hz, 1H, H-6b), 2.13 (s, 3H, SMe).

^{13}C NMR (126 MHz, CDCl_3) δ 166.12, 165.63, 165.38, 165.28 (each C=O), 133.51, 133.46, 133.18, 133.13, 129.99, 129.89, 129.73, 129.71, 129.04, 128.80, 128.79, 128.48, 128.44, 128.42, 128.40, 128.30 (each Ar-C), 83.25 (C-1), 71.71 (C-2), 70.88 (C-3), 69.54 (C-4), 68.05 (C-5), 63.09 (C-6), 12.51 (SMe).

ES-HRMS calcd for $\text{C}_{35}\text{H}_{30}\text{O}_9\text{S}_1\text{Na}_1$ 649.1508, found m/z 649.1488 $[\text{M}+\text{Na}]^+$

IR (ATR) cm^{-1} : 1725, 1602, 1451, 1316, 1265, 1092, 1069, 1027, 707

R_f : 0.69 (1:2 EtOAc-Pet ether)

Methyl 2,3,4,6-tetra-*O*-benzoyl-1-thio- α -D-galactopyranoside (57)

The crude anomerised sugar **35** (200 mg, 0.326 mmol) was dissolved in CH_2Cl_2 (5 mL). To this was added DIPEA (0.12 mL, 0.689 mmol), followed by methyl iodide (91.5 μL , 1.47 mmol). The reaction was stirred at r.t. for 2 h.

The reaction was concentrated *in vacuo*. The resultant residue was purified by flash chromatography (CH-EtOAc 7:3) and gave the title compound (147 mg, 72%) as a colourless solid.

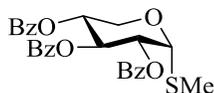
^1H NMR (500 MHz, CDCl_3) δ 8.13 – 8.09 (m, 2H, Ar-H), 8.05 – 8.01 (m, 2H, Ar-H), 8.01 – 7.97 (m, 2H, Ar-H), 7.82 – 7.79 (m, 2H, Ar-H), 7.66 – 7.61 (m, 1H, Ar-H), 7.59 – 7.48 (m, 4H, Ar-H), 7.45 – 7.37 (m, 6H, Ar-H), 7.29 – 7.22 (m, 1H, Ar-H), 6.08 – 6.03 (m, 1H, H-2), 5.93 (d, $J = 2.7$ Hz, 1H, H-1), 5.92 – 5.89 (m, 2H, H-3, H-4), 5.00 (ddd, $J = 7.0, 5.4, 1.3$ Hz, 1H, H-5), 4.63 (dd, $J = 11.5, 7.3$ Hz, 1H, H-6a), 4.47 (dd, $J = 11.5, 5.4$ Hz, 1H, H-6b), 2.13 (s, 3H, SMe).

^{13}C NMR (126 MHz, CDCl_3) δ 166.00, 165.65, 165.52, 165.41 (each C=O), 133.60, 133.50, 133.23, 129.99, 129.96, 129.93, 129.92, 129.77, 129.76, 129.75, 129.73, 129.71, 129.69, 129.48, 129.11, 129.02, 128.94, 128.68, 128.66, 128.48, 128.45, 128.44, 128.32, 128.28, 128.26 (each Ar-C), 83.58 (C-1), 69.06 (C-4), 68.99 (C-2), 68.94 (C-3), 67.20 (C-5), 62.69 (C-6), 12.44 (SMe).

ES-HRMS calcd for $\text{C}_{35}\text{H}_{30}\text{O}_9\text{S}_1\text{Na}_1$ 649.1508, found m/z 649.1516 $[\text{M}+\text{Na}]^+$

IR (ATR) cm^{-1} : 1722, 1602, 1451, 1316, 1261, 1094, 1069, 1026, 708

R_f : 0.69 (1:2 EtOAc-Pet ether)

Methyl 2,3,4-tri-*O*-benzoyl-1-thio- α -D-xylopyranoside (58)

The crude anomerised sugar **38** (150 mg, 0.313 mmol) was dissolved in CH₂Cl₂ (5 mL). To this was added DIPEA (0.12 mL, 0.689 mmol), followed by methyl iodide (87.9 μ L, 1.41 mmol). The reaction was stirred at r.t. for 2 h.

The reaction was concentrated *in vacuo*. The resultant residue was purified by flash chromatography (CH-EtOAc 7:3) and gave the title compound (116 mg, 75%) as an off colourless solid.

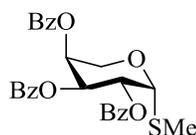
¹H NMR (500 MHz, CDCl₃) δ 8.04 – 7.92 (m, 6H, Ar-H), 7.57 – 7.45 (m, 3H, Ar-H), 7.42 – 7.32 (m, 6H, Ar-H), 6.03 (t, J = 9.2 Hz, 1H, H-3), 5.69 (d, J = 5.3 Hz, 1H, H-1), 5.48 (dd, J = 9.5, 5.3 Hz, 1H, H-2), 5.40 (ddd, J = 9.7, 8.9, 5.5 Hz, 1H, H-4), 4.26 (dd, J = 11.3, 9.8 Hz, 1H, H-5a), 4.12 (dd, J = 11.3, 5.5 Hz, 1H, H-5b), 2.13 (s, 3H, SMe)

¹³C NMR (126 MHz, CDCl₃) δ 165.58, 165.48, 165.43 (each C=O), 133.46, 133.38, 133.24, 130.00, 129.91, 129.87, 129.84, 129.71, 129.18, 129.03, 128.92, 128.47, 128.43, 128.41, 128.39, 128.37, 128.35 (each Ar-C), 83.74 (C-1), 71.43 (C-2), 69.99 (C-3), 69.85 (C-4), 59.60 (C-5), 12.90 (SMe).

ES-HRMS calcd for C₂₉H₂₇O₇S₁N₁Na₁ 556.1406, found m/z 556.1394 [M+MeCN+Na]⁺

IR (ATR) cm⁻¹: 1721, 1602, 1451, 1256, 1092, 1069, 1027, 706

R_f : 0.77 (1:2 EtOAc-Pet ether)

Methyl 2,3,4-tri-*O*-benzoyl-1-thio- β -L-arabinopyranoside (59)

The crude anomerised sugar **39** (110 mg, 0.23 mmol) was dissolved in CH₂Cl₂ (4 mL). To this was added DIPEA (87 μ L, 0.500 mmol), followed by methyl iodide (64.4 μ L, 1.03 mmol). The reaction was stirred at r.t. for 2 h.

The reaction was concentrated *in vacuo*. The resultant residue was purified by flash chromatography (CH-EtOAc 7:3) and gave the title compound (76 mg, 67%) as an off colourless solid.

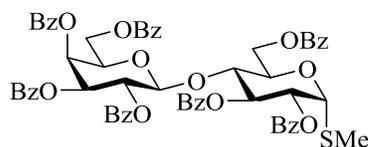
¹H NMR (500 MHz, CDCl₃) δ 8.12 – 8.08 (m, 2H, Ar-H), 8.02 – 7.99 (m, 2H, Ar-H), 7.88 – 7.84 (m, 2H, Ar-H), 7.63 – 7.58 (m, 1H Ar-H), 7.55 – 7.51 (m, 1H, Ar-H), 7.50 – 7.44 (m, 3H, Ar-H), 7.42 – 7.37 (m, 2H, Ar-H), 7.31 – 7.27 (m, 2H, Ar-H), 5.91 (dd, J = 10.3, 5.3 Hz, 1H, H-2), 5.82 (dd, J = 10.3, 3.5 Hz, 1H, H-3), 5.79 (d, J = 5.3 Hz, 1H, H-1), 5.75 (dt, J = 3.6, 1.9 Hz, 1H, H-4), 4.53 (dd, J = 13.2, 1.5 Hz, 1H, H-5a), 3.99 (dd, J = 13.1, 2.5 Hz, 1H, H-5b), 2.13 (s, 3H, SMe).

¹³C NMR (126 MHz, CDCl₃) δ 165.69, 165.65, 165.43 (each C=O), 133.46, 133.40, 133.23, 129.92, 129.85, 129.72, 129.70, 129.14, 129.03, 128.53, 128.47, 128.31 (each Ar-C), 84.17 (C-1), 69.79 (C-4), 69.21 (C-2), 68.44 (C-3), 60.79 (C-5), 12.82 (SMe).

ES-HRMS calcd for C₂₉H₂₇O₇S₁N₁Na₁ 556.1406, found m/z 556.1387 [M+MeCN+Na]⁺

IR (ATR) cm⁻¹: 1722, 1602, 1452, 1259, 1108, 1086, 1070, 1026, 707

R_f : 0.44 (2:8 EtOAc-Pet ether)

Methyl hepta-*O*-benzoyl-1-thio- α -D-lactoside (60)

The crude anomerised sugar **36** (100 mg, 0.092 mmol) was dissolved in CH_2Cl_2 (2.5 mL). To this was added DIPEA (34.5 μL , 0.198 mmol), followed by methyl iodide (25.8 μL , 0.414 mmol). The reaction was stirred at r.t. for 2 h.

The reaction was concentrated *in vacuo*. The resultant residue was purified by flash chromatography (CH-EtOAc 7:3) and gave the title compound (62 mg, 61%) as an off colourless solid.

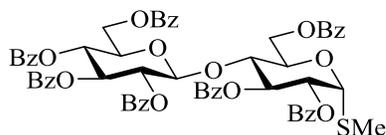
^1H NMR (500 MHz, CDCl_3) δ 8.06 – 7.96 (m, 10H, Ar-H), 7.91 – 7.86 (m, 2H, Ar-H), 7.76 – 7.71 (m, 2H, Ar-H), 7.67 – 7.17 (m, 21H, Ar-H), 5.99 (t, $J = 9.6$ Hz, 1H, H-3), 5.78 – 5.72 (m, 2H, H-2', H-4'), 5.70 (d, $J = 5.8$ Hz, 1H, H-1), 5.48 (dd, $J = 10.1, 5.9$ Hz, 1H, H-2), 5.40 (dd, $J = 10.4, 3.4$ Hz, 1H, H-3'), 4.94 (d, $J = 7.9$ Hz, 1H, H-1'), 4.59 – 4.52 (m, 3H, H-5, H-6a, H-6b), 4.22 (t, $J = 9.3$ Hz, 1H, H-4), 3.94 (t, $J = 6.8$ Hz, 1H, H-5'), 3.86 (dd, $J = 11.3, 6.3$ Hz, 1H, H-6'a), 3.77 (dd, $J = 11.3, 7.0$ Hz, 1H, H-6'b), 2.03 (s, 3H, SMe).

^{13}C NMR (126 MHz, CDCl_3) δ 165.86, 165.57, 165.49, 165.44, 165.23, 165.16, 164.73 (each C=O), 133.49, 133.47, 133.35, 133.32, 133.29, 133.23, 133.16, 129.99, 129.97, 129.78, 129.75, 129.71, 129.65, 129.64, 129.61, 129.53, 129.41, 128.85, 128.84, 128.75, 128.63, 128.59, 128.56, 128.53, 128.50, 128.47, 128.27, 128.23 (each Ar-C), 101.12 (C-1'), 83.26 (C-1), 76.32 (C-4), 71.94 (C-3'), 71.55 (C-2), 71.35 (C-5'), 70.82 (C-3), 69.91 (C-2'), 68.71 (C-5), 67.50 (C-4'), 62.56 (C-6), 61.11 (C-6'), 12.61 (SMe).

ES-HRMS calcd for $\text{C}_{62}\text{H}_{52}\text{O}_{17}\text{S}_1\text{Na}_1$ 1123.2823, found m/z 1123.2834 $[\text{M}+\text{Na}]^+$

IR (ATR) cm^{-1} : 1726, 1602, 1452, 1267, 1093, 1069, 1027, 707

R_f : 0.37 (1:2 EtOAc-Pet ether)

Methyl hepta-*O*-benzoyl-1-thio- α -D-cellobioside (61)

The crude anomerised sugar **37** (100 mg, 0.092 mmol) was dissolved in CH₂Cl₂ (2.5 mL). To this was added DIPEA (34.5 μ L, 0.198 mmol), followed by methyl iodide (25.8 μ L, 0.414 mmol). The reaction was stirred at r.t. for 2 h.

The reaction was concentrated *in vacuo*. The resultant residue was purified by flash chromatography (CH-EtOAc 7:3) and gave the title compound (74 mg, 73%) as an off colourless solid.

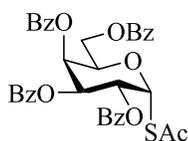
¹H NMR (500 MHz, CDCl₃) δ 8.04 – 7.91 (m, 10H, Ar-H), 7.80 – 7.74 (m, 4H, Ar-H), 7.59 – 7.22 (m, 21H, Ar-H), 5.97 (t, J = 9.5 Hz, 1H, H-3), 5.76 (t, J = 9.6 Hz, 1H, H-3'), 5.67 (d, J = 5.8 Hz, 1H, H-1), 5.54 (dd, J = 9.9, 7.9 Hz, 1H, H-2'), 5.45 – 5.42 (m, 1H, H-4'), 5.41 (dd, J = 5.7, 4.3 Hz, 1H, H-2), 5.01 (d, J = 7.9 Hz, 1H, H-1'), 4.60 – 4.52 (m, 3H, H-5, H-6a, H-6b), 4.20 (t, J = 9.4 Hz, 1H, H-4), 4.10 (dd, J = 11.6, 2.8 Hz, 1H, H-6'a) 3.92 – 3.85 (m, 2H, H-5', H-6'b), 2.00 (s, 3H, SMe).

¹³C NMR (126 MHz, CDCl₃) δ 165.80, 165.69, 165.63, 165.46, 165.16, 164.96, 164.70 (each C=O), 133.45, 133.33, 133.25, 133.20, 133.17, 133.14, 129.97, 129.78, 129.75, 129.73, 129.70, 129.63, 129.62, 129.56, 129.54, 129.47, 128.78, 128.66, 128.64, 128.48, 128.44, 128.42, 128.40, 128.37, 128.34, 128.29, 128.27, 128.22 (each Ar-C), 100.96 (C-1'), 83.09 (C-1), 76.75 (C-4), 72.98 (C-3'), 72.37 (C-5'), 71.96 (C-2'), 71.75 (C-2), 70.58 (C-3), 69.36 (C-4'), 68.71 (C-5), 62.67 (C-6'), 62.56 (C-6), 12.55 (SMe).

ES-HRMS calcd for C₆₂H₅₂O₁₇S₁Na₁ 1123.2823, found m/z 1123.2787 [M+Na]⁺

IR (ATR) cm⁻¹: 1722, 1602, 1452, 1261, 1090, 1068, 1027, 909, 706

R_f : 0.46 (1:2 EtOAc-Pet ether)

1-S-Acetyl-2,3,4,6-tetra-O-benzoyl-1-thio- α -D-galactopyranose (62)

The crude anomerised sugar **35** (100 mg, 0.160 mmol) was dissolved in pyridine (2 mL). To this solution was added Ac₂O (1.5 mL, 15.9 mmol). The reaction was stirred at r.t. overnight. The solvents were removed by co-evaporation with toluene (x5). The resultant residue was purified by flash chromatography (Pet ether-EtOAc 9:1-3:1) and gave the title compound (72 mg, 67%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 8.12 – 8.08 (m, 2H, Ar-H), 8.01 – 7.98 (m, 2H, Ar-H), 7.95 – 7.92 (m, 2H, Ar-H), 7.81 – 7.78 (m, 2H, Ar-H), 7.67 – 7.61 (m, 1H, Ar-H), 7.57 – 7.31 (m, 10H, Ar-H), 7.29 – 7.24 (m, 1H, Ar-H), 6.65 (d, J = 5.6 Hz, 1H, H-1), 6.04 (dd, J = 10.8, 5.6 Hz, 1H, H-2), 6.04 (dd, J = 3.3, 1.3 Hz, 1H, H-4), 5.67 (dd, J = 10.8, 3.4 Hz, 1H, H-3), 4.65 – 4.57 (m, 2H, H-5, H-6a), 4.41 (dd, J = 11.0, 6.2 Hz, 1H, H-6b), 2.37 (s, 3H, SAc)

¹³C NMR (126 MHz, CDCl₃) δ 191.53(C=O of SAc), 165.92, 165.41, 165.40, 165.22 (each C=O), 133.68, 133.54, 133.34, 133.24, 129.96, 129.93, 129.85, 129.83, 129.82, 129.76, 129.73, 129.71, 129.36, 128.95, 128.79, 128.76, 128.69, 128.67, 128.46, 128.44, 128.41, 128.39, 128.31, 128.28 (Ar-C), 81.60 (C-1), 70.51 (C-5), 69.74 (C-3), 68.30 (C-4), 67.48 (C-2), 61.86 (C-6), 31.54 (SAc)

ES-HRMS calcd for C₃₈H₃₃N₁O₁₀Na₁S₁ 718.1723, found m/z 718.1719 [M+MeCN+Na]⁺

IR (ATR) cm⁻¹: 1724, 1602, 1452, 1262, 1094, 1070, 1026, 708

R_f : 0.51 (1:2 EtOAc-Pet ether)

General conditions for co-promoter studies

Note: All glycosyl thiols were dried on a vacuum line for at least 3 hours prior to experiments.

A typical reaction involved dissolving the substrate (~ 0.070 mmol) in CH_2Cl_2 (1 mL) in a pre-dried sample vial, followed by the addition of the co-promoter of interest (see Tables in Chapter 1) (of appropriate concentration) and then, either, stock Lewis acid (TiCl_4) solution, of appropriate concentration, made up in CH_2Cl_2 , or commercially available 1M TiCl_4 , in CH_2Cl_2 .

These were then stirred or shaken for the appropriate time (see Tables in Chapter 1) at varying temperatures (generally room temperature).

The reactions were, during early studies, worked up by dilution with CH_2Cl_2 and quenched through addition of solid and aqueous NaHCO_3 . The resulting emulsion was filtered through a Pasteur pipette plugged with cotton wool and Celite, before the organic layer was washed with a further portion of $\text{NaHCO}_{3(\text{sat.})}$. This solution was then dried over either MgSO_4 or NaSO_4 and then separated into a pre-weighed sample vial. The alternative, and more efficient, work up method involved dilution of the reaction with CH_2Cl_2 followed by the successive washings of this organic solution with $\text{NH}_4\text{Cl}_{(\text{sat.})}$ and $\text{NaHCO}_{3(\text{sat.})}$. This solution was then dried over either MgSO_4 or NaSO_4 and then separated into a pre-weighed sample vial.

In both work up methods the solvent was then removed under reduced pressure, before drying on vacuum line prior to NMR analysis.

The relative $\alpha:\beta$ ratios, reported in the Tables 1.4 to 1.37, were determined by integration of well isolated, well defined signals of each derivative by ^1H NMR. This integration provided the anomeric distribution, of each carbohydrate tested, subsequent to its anomerisation reaction. In addition, in the majority of cases, a small amount of α -chloride, example shown in Fig. 4.1, was formed as a by-product (labelled x in the tables mentioned above) of the Lewis acid promoted anomerisation. This by-product was also noted through the integration procedure described. The ratios were also reported as a percentage, based on the relative integration of ^1H NMR signals, for ease of comparison.

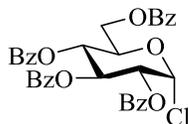
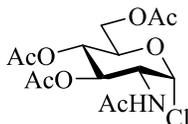


Fig. 4.1 An example of the chloride by-product that is being observed from the Lewis acid promoted anomerisation of glycosyl thiols, in this instance that of the glucose derivative.

4.3 Experimental data – Chapter 2

2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- α -D-glucopyranosyl chloride (64)¹³



Acetyl chloride (15 mL, 211mmol) was added to reaction vessel and to this *N*-acetyl-D-glucosamine (5.00 g, 22.6 mmol) was added portionwise over ~2 mins with continuous stirring. The reaction vessel was equipped with a condenser and then heated to 24 °C. The reaction was then stirred at this heated temperature for 24 h. Dichloromethane (40 mL) was then added to reaction which was then pored over ice (40 g) and H₂O (10 mL). This organic layer was separated into iced NaHCO_{3(sat.)} (40 mL), this mixture was shaken until neutralisation was complete, separated and dried over NaSO₄. (Note: this work up phase should be completed as quickly as possible). The solution is then concentrated at 50 °C to a heavy syrup (~7 mL). This syrup should not be allowed to crystallise during concentration phase. Crystallisation is achieved by the addition of Et₂O (50 mL) to the warm solution with swirling, to give the title compound (5.85 g, 71%) as a clear solid.

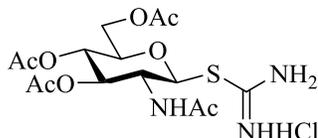
¹H NMR (500 MHz, CDCl₃): δ 6.19 (d, J = 3.7 Hz, 1H, H-1), 5.82 (d, J = 8.8 Hz, 1H, NH), 5.32 (dd, J = 10.7, 9.4 Hz, 1H, H-3), 5.22 (t, J = 9.9 Hz, 1H, H-4), 4.54 (ddd, J = 10.7, 8.8, 3.8 Hz, 1H, H-2), 4.40 – 4.24 (m, 2H, H-5, H-6a) 4.24 – 4.07 (m, 1H, H-6b), 2.11 (s, 3H), 2.06 (s, 3H), 2.06 (s, 3H) (each OAc), 1.99 (s, 3H, NHAc).

¹³C NMR (126MHz, CDCl₃): δ 171.51, 170.58, 170.09, 169.13 (each C=O) 93.62 (C-1), 70.91 (C-5), 70.15 (C-3), 66.94 (C-4), 61.15 (C-6), 53.52 (C-2), 23.11 (NHAc), 20.69, 20.69, 20.55 (each OAc)

ES-HRMS calcd for C₁₆H₂₃N₁O₁₀Cl₁ 424.1010, found m/z 424.1029 [M+AcOH-H]⁻

IR cm⁻¹: 1745, 1641, 1538, 1369, 1213, 1033, 1014, 976

R_f: 0.52 (1:19 MeOH-CH₂Cl₂)

2-Acetamido-3,4,6-tri-*O*-acetyl- β -D-glucopyranosyl-1-isothiuronium chloride (65)¹³

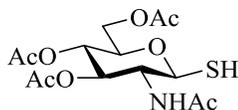
Compound **64** (5.00 g, 13.7 mmol) was dissolved in acetone (80 mL) to which was added thiourea (1.88 g, 24.7 mmol). The reaction mixture was then heated to reflux (60 °C) and stirred for 2 h. The solid obtained was then filtered off with the filtrate returned to the reaction vessel and heated for an additional 2 h to ensure completion of reaction. The precipitates were combined and recrystallised from acetone-pet ether. This gave the title compound (5.07 g, 84%) as a colourless solid.

¹H NMR (500 MHz, DMSO) δ 9.36 (s, 2H, NH₂), 9.16 (s, 2H, NH₂), 8.39 (d, J = 9.2 Hz, 1H, NH), 5.65 (d, J = 10.5 Hz, 1H, H-1), 5.13 (t, J = 9.8 Hz, 1H, H-3), 4.94 (t, J = 9.6 Hz, 1H, H-4), 4.23 – 4.16 (m, 2H, H-5, H-6a), 4.10 – 4.00 (m, 2H, H-2, H-6b), 2.02 (s, 3H), 1.99 (s, 3H), 1.95 (s, 3H) (each OAc), 1.81 (s, 3H, NHAc).

¹³C NMR (126 MHz, DMSO) δ 170.42, 170.24, 170.01, 169.67 (each C=O), 167.62 (C=NH₂Cl), 81.09 (C-1), 75.18 (C-5), 73.06 (C-3), 68.32 (C-4), 61.95 (C-6), 51.65 (C-2), 22.97 (NHAc), 21.01, 20.85, 20.74 (each OAc).

ES-HRMS calcd for calcd for C₁₅H₂₄N₃O₈S₁ 406.1284, found m/z 406.1269 [M-Cl]⁺

IR cm⁻¹: 3038, 1749, 1648, 1542, 1367, 1223, 1206, 1096, 1026, 908

2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- β -D-glucopyranose (66)¹³

Compound **65** (5.00 g, 11.3 mmol) and sodium metabisulphite (2.80 g, 14.7 mmol) were added to a reaction pot and stirred in a $\text{CH}_2\text{Cl}_2\text{-H}_2\text{O}$ (3:2, 50 mL) mixture. The reaction was heated to reflux and stirred at this temperature overnight. The reaction mixture was allowed to cool and separated. The aqueous layer was re-extracted with CH_2Cl_2 . The combined organic layers were then washed with H_2O , separated and dried over MgSO_4 . The solvent was then removed *in vacuo*. The resulting colourless solid was crystallized from EtOAc-Pet ether to give the title compound (3.65 g, 89%) as a colourless solid.

^1H NMR (500 MHz, CDCl_3): δ 5.63 (d, $J = 9.5$ Hz, 1H, NH), 5.13 (t, $J = 9.4$ Hz, 1H, H-4), 5.08 (t, $J = 9.6$ Hz, 1H, H-3), 4.58 (t, $J = 9.7$ Hz, 1H, H-1), 4.24 (dd, $J = 12.4, 4.8$ Hz, 1H, H-6a), 4.16 – 4.09 (m, 2H, H-2, H-6b), 3.69 (ddd, $J = 9.7, 4.9, 2.3$ Hz, 1H, H-5), 2.57 (d, $J = 9.4$ Hz, 1H, SH), 2.10 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H) (each OAc), 1.99 (s, 3H, NHAc).

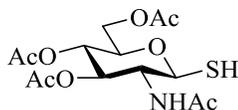
^{13}C NMR (126 MHz, CDCl_3): δ 171.26, 170.73, 170.37, 169.20 (each C=O), 80.39 (C-1), 76.33 (C-5), 73.52 (C-3), 68.03 (C-4), 62.16 (C-6), 56.85 (C-2), 23.32 (NHAc), 20.79, 20.68, 20.60 (each OAc)

ES-HRMS calcd for $\text{C}_{14}\text{H}_{21}\text{N}_1\text{O}_8\text{Na}_1\text{S}_1$ 386.0886, found m/z 386.0903 $[\text{M}+\text{Na}]^+$

IR cm^{-1} : 3285, 1743, 1662, 1542, 1370, 1229, 1045

R_f : 0.36 (1:19 MeOH- CH_2Cl_2)

$[\alpha]_D^{20}$ -22.8 (c 0.33, CHCl_3)

2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- β -D-glucopyranose (66)¹³

Compound **65** (9.04 g, 18.6 mmol) and sodium metabisulphite (4.27 g, 22.5 mmol) were stirred in a CH₂Cl₂-H₂O (3:2, 90 mL) mixture. This reaction solution was heated to reflux and stirred at this temperature for 3 h. The reaction mixture was allowed to cool and separated. The aqueous layer was re-extracted with CH₂Cl₂. The combined organic layers were then washed with H₂O, separated and dried over MgSO₄. The solvent was removed *in vacuo* to give the title compound (5.28 g, 78%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃): δ 5.60 (d, J = 9.5 Hz, 1H, NH), 5.12 (t, J = 9.5 Hz, 1H, H-4), 5.07 (t, J = 9.7 Hz, 1H, H-3), 4.57 (t, J = 9.7 Hz, 1H, H-1), 4.24 (dd, J = 12.4, 4.8 Hz, 1H, H-6a), 4.16 – 4.09 (m, 2H, H-2, H-6b), 3.68 (ddd, J = 9.7, 4.8, 2.3 Hz, 1H, H-5), 2.57 (d, J = 9.4 Hz, 1H, SH), 2.10 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H) (each OAc), 1.98 (s, 3H, NHAc).

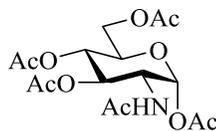
¹³C NMR (126 MHz, CDCl₃): δ 171.25, 170.70, 170.35, 169.18 (each C=O), 80.39 (C-1), 76.31 (C-5), 73.49 (C-3), 67.97 (C-4), 62.12 (C-6), 56.82 (C-2), 23.29 (NHAc), 20.77, 20.65, 20.57 (each OAc)

ES-HRMS calcd for C₁₄H₂₁N₁O₈Na₁S₁ 386.0886, found m/z 386.0880 [M+Na]⁺

IR cm⁻¹: 1741, 1661, 1545, 1368, 1219, 1034, 733

R_f : 0.36 (1:19 MeOH-CH₂Cl₂)

$[\alpha]_D^{20}$ -17.3 (c 0.40, CHCl₃)

2-Acetamido-2-deoxy-1,3,4,6-tetra-*O*-acetyl- α -D-glucopyranose (67)¹⁴

N-Acetyl-D-glucosamine (10.0 g, 45.2 mmol) was suspended in pyridine (46 mL), and at r.t. acetic anhydride (44 mL 466 mmol) was added slowly, portion wise. The reaction was then stirred at r.t. overnight. The solvents were then removed by co-evaporation with toluene, a number of times, until it gave the title compound (17.3 g, 98%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 6.17 (d, J = 3.6 Hz, 1H, H-1), 5.54 (d, J = 9.0 Hz, 1H, NH), 5.30 – 5.15 (m, 2H, H-3, H-4), 4.48 (tdd, J = 8.9, 3.6, 1.8 Hz, 1H, H-3), 4.25 (dd, J = 12.5, 4.1 Hz, 1H, H-6a), 4.06 (dd, J = 12.5, 2.4 Hz, 1H, H-6b), 3.99 (ddd, J = 9.9, 4.1, 2.3 Hz, 1H, H-5), 2.19 (s, 3H), 2.09 (s, 4H), 2.05 (s, 3H), 2.04 (s, 3H) (each OAc), 1.94 (s, 3H, HNAc).

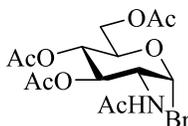
¹³C NMR (126 MHz, CDCl₃) δ 171.74, 170.67, 169.86, 169.05, 168.56 (each C=O), 90.68 (C-1), 70.67 (C-3), 69.70 (C-5), 67.43 (C-4), 61.50 (C-6), 51.06 (C-2), 23.05 (NHAc), 20.92, 20.71, 20.67, 20.55 (each OAc).

ES-HRMS calcd for C₁₈H₂₆N₂O₁₀Na₁ 453.1485, found m/z 453.1483 [M+MeCN+Na]⁺

IR (ATR) cm⁻¹: 1744, 1664, 1368, 1215, 1036, 1012, 916, 728

R_f : 0.34 (1:19 MeOH-CH₂Cl₂)

$[\alpha]_D^{20}$ 75.9 (c 0.22, CHCl₃)

2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- α -D-glucopyranosyl bromide (68)

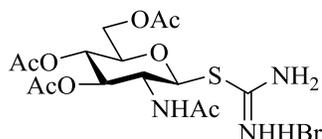
Compound **67** (1.67 g, 4.29 mmol) was dissolved in CH_2Cl_2 (25 mL) and cooled to 0 °C. To this solution was added, slowly, a 30% HBr-AcOH (6 mL) solution. The reaction was allowed to warm to r.t. and stirred for 3.5 h. The reaction mixture was then poured onto iced water with stirring and separated, washed with iced $\text{NaHCO}_3(\text{sat.})$, dried over NaSO_4 and concentrated under reduced pressure, which involved maintaining a rotary evaporator water bath temp < 30 °C. This gave the title compound (1.51 g, 86%) as a crude slightly yellow solid. This unpurified solid should be used as soon as possible after preparation, so as to avoid degradation and thereby low yields in subsequent reactions.

^1H NMR (500 MHz, CDCl_3): δ 6.52 (d, $J = 3.7$ Hz, 1H, H-1), 5.79 (d, $J = 8.6$ Hz, 1H, NH), 5.32 (dd, $J = 10.4, 9.8$ Hz, 1H, H-3), 5.25 (t, $J = 9.8$ Hz, 1H, H-4), 4.36 (ddd, $J = 10.5, 8.6, 3.7$ Hz, 1H, H-2), 4.30 (dd, $J = 12.6, 4.0$ Hz, 1H, H-6a), 4.26 – 4.19 (m, 1H, H-5), 4.13 (dd, $J = 12.5, 2.2$ Hz, 1H, H-6b), 2.10 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H) (each OAc), 1.99 (s, 3H, NHAc).

^{13}C NMR (126MHz, CDCl_3): δ 171.49, 170.54, 170.09, 169.10 (each C=O), 91.56 (C-1), 72.65 (C-5), 70.93 (C-3), 66.63 (C-4), 60.95 (C-6), 53.64 (C-2), 23.11 (NHAc), 20.66, 20.66, 20.53 (each OAc).

ES-HRMS calcd for $\text{C}_{14}\text{H}_{19}\text{N}_1\text{O}_8\text{Br}_1$ 408.0294, found m/z 408.0277 [M-H] $^-$

IR cm^{-1} : 1738, 1662, 1534, 1368, 1213, 1108, 1038, 1014, 913, 729

2-Acetamido-3,4,6-tri-*O*-acetyl- β -D-glucopyranosyl-1-isothiuronium bromide (69)

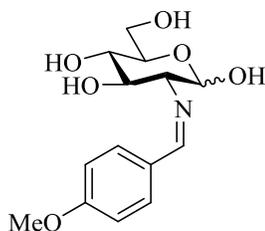
Compound **68** (10.8 g, 26.4 mmol) was dissolved in acetone (160 mL) to which was added thiourea (3.42 g, 44.9 mmol). The reaction mixture was then heated to reflux (60 °C) and stirred for 2 h. The solid was then filtered off with the filtrate returned to the reaction vessel and heated for an additional 2 h to ensure completion of reaction. The precipitate was dried under diminished pressure to give the title compound (9.39 g, 73%) as a colourless solid.

^1H NMR (500 MHz, DMSO) δ 9.35 (s, 2H, NH_2), 9.15 (s, 2H, NH_2), 8.37 (d, $J = 9.2$ Hz, 1H, NH), 5.63 (d, $J = 10.5$ Hz, 1H, H-1), 5.12 (t, $J = 9.8$ Hz, 1H, H-3), 4.93 (t, $J = 9.6$ Hz, 1H, H-4), 4.21 – 4.14 (m, 2H, H-5, H-6a), 4.08 – 3.97 (m, 2H, H-2, H-6b), 2.00 (s, 3H), 1.97 (s, 3H), 1.93 (s, 3H) (each OAc), 1.79 (s, 3H, NHAc).

^{13}C NMR (126 MHz, DMSO) δ 170.42, 170.24, 170.01, 169.67 (each C=O), 167.63 (C= NH_2Cl), 81.10 (C-1), 75.18 (C-5), 73.06 (C-3), 68.32 (C-4), 61.95 (C-6), 51.68 (C-2), 22.98 (NHAc), 21.01, 20.85, 20.74 (each OAc).

ES-HRMS calcd for $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}_8\text{S}_1\text{Br}_1$ 484.0389 found m/z 484.0403 [$\text{M}-\text{H}$] $^-$

IR cm^{-1} : 3056, 1747, 1637, 1545, 1368, 1215, 1088, 1055, 907

2-*p*-Methoxybenzylideneamino-D-glucosamine (70)¹⁵

D-Glucosamine hydrochloride (15.3 g, 71.0 mmol) was added to and stirred in 1M NaOH (80 mL) and then under intense stirring anisaldehyde (8.70 mL, 71.5 mmol) was added. Precipitate forms after a short period of time with the reaction then placed in the freezer overnight, to ensure completion of reaction. The solid was then filtered and washed with water (2 x 100 mL) and a MeOH-Et₂O (1:1, 2 x 100 mL) mixture. The solid was then dried under diminished pressure to give the title compound (17.3 g, 82%) as a colourless solid.

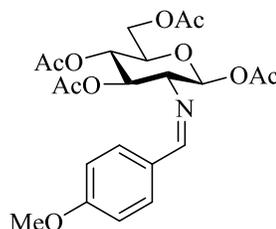
¹H NMR (500 MHz, DMSO-*d*₆) δ 8.10 (s, 1H, ArCH=N), 7.67 (d, *J* = 8.7 Hz, 2H, Ar-H), 6.97 (d, *J* = 8.7 Hz, 2H, Ar-H), 6.50 (d, *J* = 6.7 Hz, 1H, OH-1), 4.88 (d, *J* = 5.3 Hz, 1H, OH-4), 4.78 (d, *J* = 5.6 Hz, 1H, OH-3), 4.68 (dd, *J* = 7.7, 6.7 Hz, 1H, H-1), 4.51 (t, *J* = 5.8 Hz, 1H, OH-6), 3.79 (s, 3H, OMe), 3.71 (ddd, *J* = 11.6, 5.6, 2.1 Hz, 1H, H-6a), 3.47 (dt, *J* = 11.8, 6.0 Hz, 1H, H-6b), 3.41 (td, *J* = 9.0, 5.7 Hz, 1H, H-3), 3.22 (ddd, *J* = 9.8, 6.0, 2.1 Hz, 1H, H-5), 3.13 (ddd, *J* = 9.6, 8.6, 5.4 Hz, 1H, H-4), 2.77 (dd, *J* = 9.3, 7.7 Hz, 1H, H-2).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 161.63 (ArCH=N), 161.48, 130.05, 129.55, 114.33 (each Ar-C), 96.07 (C-1), 78.63 (C-2), 77.30 (C-5), 75.04 (C-3), 70.81 (C-4), 61.72 (C-6), 55.72 (OMe).

ES-HRMS calcd for C₁₄H₂₀N₁O₆ 298.1291, found *m/z* 298.1278 [M+H]⁺

IR (ATR) cm⁻¹: 3487, 3324, 1604, 1516, 1268, 1104, 1062, 1029, 88, 834

***N*-((*p*-Methoxyphenyl)methyliden)-1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-amino- β -D-glucopyranose (**71**)¹⁵**



Compound **70** (17.1 g, 57.5 mmol) was dissolved in pyridine (92 mL) and cooled to 0 °C. To this solution was added 4-dimethylaminopyridine (172 mg, 1.41 mmol) and acetic anhydride (52 mL, 550 mmol). Reaction was allowed warm to r.t. with the solid slowly going back into solution and then stirred overnight. Solution poured into iced water (300 mL). Solid filtered and washed with water (2 x 20 mL) and Et₂O (2 x 20 mL), then dried under diminished pressure to give the title compound (19.7 g, 74%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 8.16 (s, 1H, (ArCH=N)), 7.66 (d, *J* = 8.7 Hz, 2H, Ar-H), 6.92 (d, *J* = 8.7 Hz, 2H, Ar-H), 5.94 (d, *J* = 8.3 Hz, 1H, H-1), 5.43 (t, *J* = 9.6 Hz, 1H, H-3), 5.14 (t, *J* = 9.8 Hz, 1H, H-4), 4.38 (dd, *J* = 12.4, 4.6 Hz, 1H, H-6a), 4.13 (dd, *J* = 12.5, 2.1 Hz, 1H, H-6b), 3.97 (ddd, *J* = 10.1, 4.6, 2.1 Hz, 1H, H-5), 3.84 (s, 3H, OMe), 3.45 (dd, *J* = 9.8, 8.3 Hz, 1H, H-2), 2.10 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.88 (s, 3H) (each OAc).

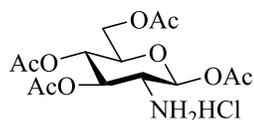
¹³C NMR (126 MHz, CDCl₃) δ 170.66, 169.86, 169.51, 168.74 (each C=O), 164.23 (ArCH=N), 162.29, 130.24, 128.32, 114.05 (each Ar-C), 93.17 (C-1), 73.27 (C-3), 72.95 (C-2), 72.77 (C-5), 68.06 (C-4), 61.84 (C-6), 55.40 (OMe), 20.81, 20.76, 20.68, 20.51 (each OAc).

ES-HRMS calcd for C₂₂H₂₈N₁O₁₀ 466.1713, found *m/z* 466.1711 [M+H]⁺

IR (ATR) cm⁻¹: 1747, 1605, 1514, 1365, 1247, 1213, 1078, 1028, 834

*R*_f: 0.64 (1:19 MeOH-CH₂Cl₂)

[α]_D²⁰ 95.1 (*c* 0.27, CHCl₃)

1,3,4,6-Tetra-*O*-acetyl- β -D-glucosamine hydrochloride (72)¹⁵

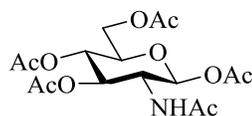
Compound **71** (18.3 g, 47.6 mmol) was dissolved in acetone (92 mL) and heated to reflux. To this solution was added, dropwise, 5M HCl (9 mL). A colourless precipitate is formed after 5 mins with the reaction then allowed to cool to r.t. The precipitate was then filtered. It was then washed with acetone (25 mL) and Et₂O (2 x 60 mL), then dried under diminished pressure to give the title compound (14.2 g, 94%) as a colourless solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.70 (s, 3H, NH₃⁺), 5.89 (d, J = 8.6 Hz, 1H, H-1), 5.34 (dd, J = 10.4, 9.2 Hz, 1H, H-3), 4.92 (dd, J = 10.1, 9.2 Hz, 1H, H-4), 4.18 (dd, J = 12.5, 4.5 Hz, 1H, H-6a), 4.04 (ddd, J = 10.1, 4.5, 2.2 Hz, 1H, H-5), 3.98 (dd, J = 12.5, 2.2 Hz, 1H, H-6b), 3.56 (dd, J = 10.4, 8.6 Hz, 1H, H-2), 2.16 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.96 (s, 3H) (each OAc).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 170.38, 170.22, 169.73, 169.07 (each C=O), 90.56 (C-1), 72.04 (C-5), 70.78 (C-), 68.22 (C-4), 61.69 (C-6), 52.54 (C-2), 21.36, 21.28, 20.94, 20.79 (each OAc).

ES-HRMS calcd for C₁₄H₂₂N₁O₉ 348.1295, found m/z 348.1290 [M+H]⁺

IR (ATR) cm⁻¹: 2828, 1757, 1366, 1246, 1205, 1081, 1059, 1038, 898

2-Acetamido-2-deoxy-1,3,4,6-tetra-*O*-acetyl- β -D-glucopyranose (73)^{16,17}

Compound **72** (13.2 g, 34.3 mmol) was dissolved in CH₂Cl₂ (135 mL) and cooled to 0 °C. Triethylamine (10.5 mL, 75.3 mmol) was added and the solution was stirred until everything had dissolved. Acetyl chloride (2.9 mL, 40.8 mmol) was then added slowly to the cooled solution. The reaction allowed warm to r.t. and stirred for 1 h. The reaction was then washed with water and brine, dried over Na₂SO₄, with the solvent removed under diminished pressure to give the title compound (12.8 g, 96%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 5.69 (d, J = 8.7 Hz, 1H, H-1), 5.52 (d, J = 9.5 Hz, 1H, NH), 5.20 – 5.06 (m, 2H, H-3, H-4), 4.33 – 4.27 (m, 1H, H-2), 4.26 (dd, J = 12.5, 4.6 Hz, 1H, H-6a), 4.13 (dd, J = 12.5, 2.3 Hz, 1H, H-6b), 3.79 (ddd, J = 9.5, 4.6, 2.3 Hz, 1H, H-5), 2.12 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H) (each OAc), 1.93 (s, 3H, NHAc).

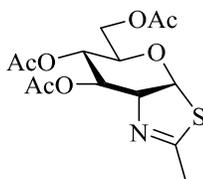
¹³C NMR (126 MHz, CDCl₃) δ 171.18, 170.64, 170.02, 169.53, 169.18 (each C=O), 92.62 (C-1), 72.95 (C-5), 72.57 (C-3), 67.63 (C-4), 61.60 (C-6), 53.06 (C-2), 23.19 (NHAc), 20.88, 20.71, 20.61, 20.56 (each OAc).

ES-HRMS calcd for C₁₆H₂₃N₁O₁₀Na₁ 412.1220, found m/z 412.1230 [M+Na]⁺

IR (ATR) cm⁻¹: 1742, 1664, 1368, 1217, 1069, 1034, 908, 735

R_f : 0.34 (1:19 MeOH-CH₂Cl₂)

$[\alpha]_D^{20}$ 15.8 (c 0.11, CHCl₃)

(3aR,5R,6S,7R,7aR)-5-(Acetoxymethyl)-6,7-diacetoxy-2-methyl-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole (74)¹⁸

Compound **73** (2.00 g, 5.13 mmol) was dissolved in toluene (21 mL), and to this solution was added Lawesson's reagent (1.76 mg, 4.35 mmol). The reaction mixture was heated to 80 °C and then stirred at this temperature for 2.5 h. The reaction mixture was then cooled to r.t. and neutralised by the addition of NaHCO₃ (210 mg). Chromatography of the residue (3:7-1:1 EtOAc-CH₂Cl₂) gave the title compound (1.70 g, 96%) as a yellow solid.

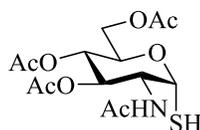
¹H NMR (500 MHz, CDCl₃) δ 6.25 (d, *J* = 7.1 Hz, 1H, H-1), 5.58 (dd, *J* = 3.4, 1.8 Hz, 1H, H-3), 4.96 (dt, *J* = 9.5, 1.5 Hz, 1H, H-4), 4.48 (dddd, *J* = 7.1, 3.5, 2.3, 1.2 Hz, 1H, H-2), 4.12 (dd, *J* = 5.3, 3.6 Hz, 2H, H-6a, H-6b), 3.62 – 3.49 (m, 1H, H-5), 2.32 (d, *J* = 2.3 Hz, 3H, Thiaz CH₃), 2.14 (s, 3H), 2.09 (s, 4H), 2.09 (s, 3H) (each OAc).

¹³C NMR (126 MHz, CDCl₃) δ 170.61, 169.59, 169.31 (each C=O), 88.85 (C-1), 76.70 (C-2), 70.75 (C-3), 69.33 (C-4), 68.46 (C-5), 63.31 (C-6), 20.98, 20.90, 20.77 (each OAc), 20.72 (Thiaz CH₃).

ES-HRMS calcd for C₁₄H₁₉N₁O₇Na₁S₁ 368.0780, found *m/z* 368.0772 [M+Na]⁺

IR (ATR) cm⁻¹: 1738, 1664, 1537, 1369, 1219, 1040, 733

R_f: 0.46 (1:19 MeOH-CH₂Cl₂)

2-Acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-1-thio- α -D-glucopyranose (75)¹⁹

Compound **74** (1.59 g, 4.60 mmol) was dissolved in MeOH (16 mL) and cooled to 0 °C. To this stirring solution was added TFA (32 drops) and H₂O (32 drops). The reaction was then allowed to come to room temperature and stirred for 2 h. The reaction was then concentrated under diminished pressure to give the title compound (1.67 g, > 95%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 5.90 (d, J = 8.4 Hz, 1H, NH), 5.78 (dd, J = 7.1, 5.2 Hz, 1H, H-1), 5.14 (t, J = 9.4 Hz, 1H, H-4), 5.10 (dd, J = 10.6, 9.3 Hz, 1H, H-3), 4.49 (ddd, J = 10.6, 8.4, 5.2 Hz, 1H, H-2), 4.31 (ddd, J = 9.5, 4.3, 2.2 Hz, 1H, H-5), 4.26 (dd, J = 12.3, 4.3 Hz, 1H, H-6a), 4.12 (dd, J = 12.4, 2.2 Hz, 1H, H-6b), 2.11 (s, 3H), 2.06 (s, 3H), 2.06 (s, 3H) (each OAc), 2.03 (d, J = 7.2 Hz, 1H, SH), 2.00 (s, 3H, NHAc).

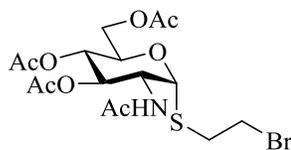
¹³C NMR (126 MHz, CDCl₃) δ 170.76, 170.63, 169.23 (each C=O), 78.75 (C-1), 70.67 (C-3), 69.03 (C5), 67.81 (C4), 61.74 (C-6), 52.71 (C-2), 23.11 (NHAc), 20.74, 20.72, 20.60 (each OAc).

ES-HRMS calcd for C₁₄H₂₁N₁O₈Na₁S₁ 386.0886, found m/z 386.0888 [M+Na]⁺

IR (ATR) cm⁻¹: 3297, 1723, 1659, 1545, 1374, 1236, 1200, 1136, 1035, 734

R_f : 0.45 (2:23 MeOH-CH₂Cl₂)

$[\alpha]_D^{20}$ -0.7 (c 0.55, CHCl₃)

2-Bromoethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-glucopyranoside (76)

Compound **75** (3.12 g, 8.59 mmol) was dissolved in an acetone-H₂O (2:1, 36 mL) mixture and to this solution was added potassium carbonate (1.40 g, 10.1 mmol) and 1,2 dibromoethane (6 mL, 69.3 mmol). This mixture was stirred at r.t. for 3 h after which point it was diluted with CH₂Cl₂. The layers were separated, with the aqueous layer being re-extracted with a further portion of CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and then concentrated under diminished pressure. Chromatography (EtOAc-Pet Ether, 1:3) gave the title compound (2.61 g, 65%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃): δ 5.74 (d, J = 8.4 Hz, 1H, NH), 5.52 (d, J = 5.4 Hz, 1H, H-1), 5.10 (t, J = 9.5 Hz, 1H, H-4), 5.05 (dd, J = 10.8, 9.3 Hz, 1H, H-3), 4.48 (ddd, J = 10.8, 8.4, 5.4 Hz, 1H, H-2), 4.37 (ddd, J = 9.8, 5.4, 2.2 Hz, 1H H-5), 4.24 (dd, J = 12.3, 5.4 Hz, 1H, H-6a), 4.10 (dd, J = 12.3, 2.2 Hz, 1H, H-6b), 3.58 (td, J = 9.8, 5.8 Hz, 1H, SCH₂CH₂Br), 3.49 (td, J = 9.9, 6.3 Hz, 1H, SCH₂CH₂Br), 3.10 (ddd, J = 14.0, 9.7, 6.3 Hz, 1H, SCH₂CH₂Br), 3.03 (ddd, J = 13.9, 9.6, 5.8 Hz, 1H, SCH₂CH₂Br), 2.11 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H) (each OAc), 1.96 (s, 3H, NHAc).

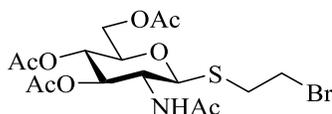
¹³C NMR (126 MHz, CDCl₃): δ 171.69, 170.56, 169.95, 169.23 (each C=O), 85.09 (C-1), 71.02 (C-3), 68.71 (C-5), 68.06 (C-4), 62.10 (C-6), 52.62 (C-2), 33.92 (SCH₂CH₂Br), 30.28 (SCH₂CH₂Br), 23.20 (NHAc), 20.72, 20.70, 20.58 (each OAc).

ES-HRMS calcd for C₁₆H₂₄N₁O₈Na₁S₁Br₁ 492.0304, found m/z 492.0296 [M+Na]⁺

IR cm⁻¹: 1744, 1665, 1535, 1367, 1229, 1088, 912

R_f : 0.60 (3:47 MeOH-CH₂Cl₂)

$[\alpha]_D^{20}$ 138.8 (c 0.63, CHCl₃)

2-Bromoethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- β -D-glucopyranoside (77)

Compound **66** (1.00 g, 2.75 mmol) was dissolved in an acetone-H₂O (2:1, 15 mL) mixture and to this was added potassium carbonate (450 mg, 3.26 mmol) and 1,2 dibromoethane (2 mL, 23.2 mmol). This mixture was stirred at r.t. overnight after which point it was diluted with CH₂Cl₂. The layers were separated, with the aqueous layer being re-extracted with a further portion of CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and then concentrated under diminished pressure. Chromatography (CH₂Cl₂-MeOH, 95:5-93:7) gave the title compound (898 mg, 69%) as a clear solid.

¹H NMR (500 MHz, CDCl₃): δ 5.67 (d, J = 9.2 Hz, 1H, NH), 5.18 (dd, J = 10.3, 9.3 Hz, 1H, H-3), 5.06 (t, J = 9.7 Hz, 1H, H-4), 4.69 (d, J = 10.4 Hz, 1H, H-1), 4.16 (d, J = 4.0 Hz, 2H, H-6a, H-6b), 4.06 (td, J = 10.3, 9.1 Hz, 1H, H-2), 3.72 (dt, J = 10.0, 4.0 Hz, 1H, H-5), 3.60 (ddd, J = 10.9, 9.8, 5.6 Hz, 1H, SCH₂CH₂Br), 3.51 (ddd, J = 10.9, 9.7, 5.6 Hz, 1H, SCH₂CH₂Br), 3.19 (ddd, J = 14.0, 11.0, 5.6 Hz, 1H, SCH₂CH₂Br), 2.99 (ddd, J = 14.0, 11.0, 5.6 Hz, 1H, SCH₂CH₂Br), 2.11 (s, 3H), 2.03 (s, 4H), 2.03 (s, 3H) (each OAc), 1.95 (s, 3H, NHAc).

¹³C NMR (126 MHz, CDCl₃): δ 171.06, 170.65, 170.14, 169.26 (C=O), 85.11 (C-1), 76.02 (C-5), 73.40 (C-3), 68.30 (C-4), 62.29 (C-6), 53.40 (C-2), 32.90 (SCH₂CH₂Br), 30.95 (SCH₂CH₂Br), 23.24 (NHAc), 20.76, 20.65, 20.58 (each OAc).

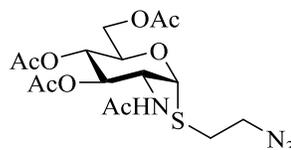
ES-HRMS calcd for C₁₆H₂₅N₁O₈S₁Br₁ 470.0484, found m/z 470.0471 [M+H]⁺

IR cm⁻¹: 3288, 1746, 1661, 1543, 1373, 1233, 1047, 946, 735

R_f : 0.46 (2:23 MeOH-CH₂Cl₂)

$[\alpha]_D^{20}$ -42.5 (c 0.48, CHCl₃)

2-Azidoethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-glucopyranoside (78)



Compound **76** (2.52 g, 5.36 mmol) was dissolved in DMF (40 mL) and to this was added tetrabutylammonium iodide (1.99 g, 5.39 mmol) and sodium azide (1.40 g, 21.5 mmol). The reaction was heated to 80 °C and stirred overnight at this temperature. The reaction was then allowed to cool, after which it was diluted with CH₂Cl₂ and washed a number of times with H₂O, to remove the DMF. The organic layer was dried over Na₂SO₄ and then concentrated under diminished pressure. Chromatography (EtOAc-Pet Ether, 1:3-1:1) gave the title compound (2.05 g, 88%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃): δ 5.74 (d, *J* = 8.5 Hz, 1H, NH), 5.52 (d, *J* = 5.4 Hz, 1H, H-1), 5.12 (t, *J* = 9.6 Hz, 1H, H-4), 5.06 (dd, *J* = 11.0, 9.3 Hz, 1H, H-3), 4.50 (ddd, *J* = 11.0, 8.5, 5.4 Hz, 1H, H-2), 4.35 (ddd, *J* = 9.9, 4.7, 2.3 Hz, 1H, H-5), 4.26 (dd, *J* = 12.4, 4.8 Hz, 1H, H-6a), 4.10 (dd, *J* = 12.4, 2.3 Hz, 1H, H-6b), 3.53 (dt, *J* = 11.3, 5.7 Hz, 1H, SCH₂CH₂N₃), 3.50 – 3.45 (m, 1H, SCH₂CH₂N₃), 2.87 (dt, *J* = 13.6, 6.8 Hz, 1H, SCH₂CH₂N₃), 2.81 – 2.75 (m, 1H, SCH₂CH₂N₃), 2.10 (s, 3H), 2.04 (s, 3H), 2.04 (s, 3H) (each OAc), 1.96 (s, 3H, NHAc).

¹³C NMR (126 MHz, CDCl₃): δ 171.68, 170.56, 169.98, 169.23 (each C=O), 84.86 (C-1), 71.08 (C-3), 68.65 (C-5), 67.99 (C-4), 61.98 (C-6), 52.56 (C2), 50.80 (SCH₂CH₂N₃), 30.99 (SCH₂CH₂N₃), 23.19 (NHAc), 20.69, 20.69, 20.58 (each OAc).

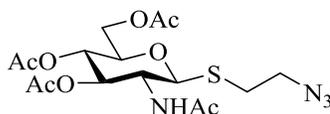
ES-HRMS calcd for C₁₆H₂₄N₄O₈Na₁S₁ 455.1213, found *m/z* 455.1228 [M+Na]⁺

IR cm⁻¹: 2962, 2104, 1741, 1666, 1535, 1367, 1225, 1088, 1034, 734

*R*_f: 0.64 (3:47 MeOH-CH₂Cl₂)

[α]_D²⁰ 130.5 (*c* 0.44, CHCl₃)

2-Azidoethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- β -D-glucopyranoside (79)



Compound **77** (1.24 g, 2.64 mmol) was dissolved in DMF (20 mL) and to this was added tetrabutylammonium iodide (1.12 g, 3.03 mmol) and sodium azide (705 mg, 10.8 mmol). The reaction was heated to 80 °C and stirred overnight at this temperature. The reaction was then allowed to cool, after which it was diluted with CH₂Cl₂ and washed a number of times with H₂O, to remove the DMF. The organic layer was dried over Na₂SO₄ and then concentrated under diminished pressure. Chromatography (EtOAc-Pet Ether, 1:3-1:1) gave the title compound (934 mg, 82%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃): δ 5.56 (d, J = 9.3 Hz, 1H, NH), 5.16 (dd, J = 10.3, 9.3 Hz, 1H, H-3), 5.09 (t, J = 9.7 Hz, 1H, H-4), 4.65 (d, J = 10.3 Hz, 1H, H-1), 4.22 (dd, J = 12.4, 5.1 Hz, 1H, H-6a), 4.15 (dd, J = 12.4, 2.4 Hz, 1H, H-6b), 4.10 (td, J = 10.3, 9.2 Hz, 1H, H-2), 3.70 (ddd, J = 9.9, 5.0, 2.4 Hz, 1H, H-5), 3.56 (dt, J = 13.2, 6.7 Hz, 1H, SCH₂CH₂N₃), 3.48 (dt, J = 12.6, 6.9 Hz, 1H, SCH₂CH₂N₃), 2.99 (dt, J = 13.9, 6.9 Hz, 1H, (SCH₂CH₂N₃), 2.79 (dt, J = 13.8, 6.7 Hz, 1H, SCH₂CH₂N₃), 2.09 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H) (each OAc), 1.96 (s, 3H, NHAc).

¹³C NMR (126 MHz, CDCl₃): δ 171.08, 170.62, 170.12, 169.24 (each C=O), 84.69 (C-1), 76.09 (C-5), 73.55 (C-3), 68.19 (C-4), 62.18 (C-6), 53.21 (C-2), 51.60 (SCH₂CH₂N₃), 29.64 (SCH₂CH₂N₃), 23.26 (NHAc), 20.71, 20.65, 20.58 (each OAc).

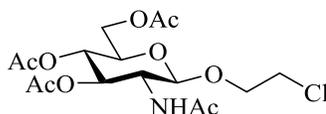
ES-HRMS calcd for C₁₆H₂₄N₄O₈Na₁S₁ 455.1213, found m/z 455.1210 [M+Na]⁺

IR cm⁻¹: 2099, 1742, 1659, 1543, 1371, 1223, 1036, 916

*R*_f: 0.57 (3:47 MeOH-CH₂Cl₂)

[α]_D²⁰ -60.5 (*c* 0.44, CHCl₃)

2-Chloroethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- β -D-glucopyranoside (80)²⁰



Sugar **73** (1.00 g, 2.57 mmol) was dissolved in 1,2-dichloroethane (5 mL) in a microwave vial equipped with a stir bar. To this mixture was added H₂SO₄-silica (18 mg) and 2-chloroethanol (0.21 mL, 3.13 mmol). This mixture was then heated and stirred under microwave conditions at 110 °C for 15 mins. The reaction was then filtered through Celite, with the plug being flushed clear with CH₂Cl₂, to ensure complete recovery of product. The filtrate was then washed with NaHCO₃(sat.), brine, dried over NaSO₄ and concentrated under reduced pressure. Column chromatography (EtOAc-Pet Ether, 1:3-1:1-2:1-100% EtOAc) gave the title compound (784 mg, 75%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃-*d*) δ 5.52 (d, *J* = 8.7 Hz, 1H, NH), 5.30 (dd, *J* = 10.7, 9.3 Hz, 1H, H-3), 5.07 (t, *J* = 9.7 Hz, 1H, H-4), 4.77 (d, *J* = 8.4 Hz, 1H, H-1), 4.26 (dd, *J* = 12.3, 4.8 Hz, 1H, H-6a), 4.14 (dd, *J* = 12.3, 2.5 Hz, 1H, H-6b), 4.10 (dd, *J* = 10.7, 5.6 Hz, 1H, OCH₂CH₂Cl), 3.86 (dt, *J* = 10.6, 8.5 Hz, 1H, H-2), 3.78 (dt, *J* = 11.4, 6.4 Hz, 1H, OCH₂CH₂Cl), 3.71 (ddd, *J* = 10.0, 4.8, 2.4 Hz, 1H, H-5), 3.64 (dd, *J* = 6.3, 5.0 Hz, 2H, OCH₂CH₂Cl), 2.09 (s, 3H), 2.03 (s, 3H), 2.03 (s, 3H) (each OAc), 1.96 (s, 3H, NHAc).

¹³C NMR (126 MHz, CDCl₃): δ 170.81, 170.66, 170.40, 169.36 (C=O), 101.06 (C-1), 72.09 (C-3), 71.97 (C-5), 69.67 (OCH₂CH₂Cl), 68.48 (C-4), 62.00 (C-6), 54.70 (C-2), 42.98 (OCH₂CH₂Cl), 23.35 (NHAc), 20.73, 20.67, 20.61 (each OAc).

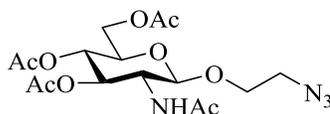
ES-HRMS calcd for C₁₆H₂₄Cl₁N₁O₉Na₁ 432.1037, found *m/z* 432.1023 [M+Na]⁺

IR cm⁻¹: 1742, 1659, 1556, 1432, 1368, 1223, 1120, 1039, 907

*R*_f: 0.51 (1:19 MeOH-CH₂Cl₂)

[α]_D²⁰ -4.0 (*c* 0.10, CHCl₃)

2-Azidoethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- β -D-glucopyranoside (81)²⁰



Sugar **80** (1.36 g, 3.32 mmol) was dissolved in DMF (22 mL) and to this tetrabutylammonium iodide (1.29 g, 3.49 mmol) and sodium azide (863 mg, 13.3 mmol) were added. The reaction was then heated to 80 °C and stirred at this temperature overnight. The reaction was cooled, diluted with CH₂Cl₂ and washed with water. Aqueous layer re-extracted with a portion of CH₂Cl₂. The combined organic layers were then washed with successive portions of water, with no re-extraction of any of these aqueous layers. The organic layer was then washed with brine, dried over NaSO₄ and the solvent then removed under diminished pressure. Chromatography (EtOAc-Pet Ether, 1:3-1:1-2:1-100% EtOAc) gave the title compound (1.10 g, 80%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃-*d*) δ 5.50 (d, *J* = 8.6 Hz, 1H, NH), 5.36 (dd, *J* = 10.6, 9.3 Hz, 1H, H-3), 5.08 (dd, *J* = 10.0, 9.3 Hz, 1H, H-4), 4.83 (d, *J* = 8.3 Hz, 1H, H-1), 4.26 (dd, *J* = 12.3, 4.7 Hz, 1H, H-6a), 4.15 (dd, *J* = 12.3, 2.4 Hz, 1H, H-6b), 4.05 (ddd, *J* = 10.8, 4.7, 3.2 Hz, 1H, OCH₂CH₂N₃), 3.80 (dt, *J* = 10.7, 8.5 Hz, 1H, H-2), 3.74 – 3.66 (m, 2H, H-5, OCH₂CH₂N₃), 3.51 (ddd, *J* = 13.5, 8.6, 3.3 Hz, 1H, OCH₂CH₂N₃), 3.26 (ddd, *J* = 13.4, 4.7, 3.1 Hz, 1H, OCH₂CH₂N₃), 2.09 (s, 3H), 2.03 (s, 3H), 2.03 (s, 3H) (each OAc), 1.96 (s, 3H, NHAc).

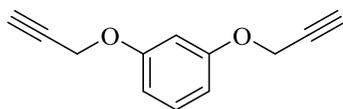
¹³C NMR (126 MHz, CDCl₃): δ 170.74, 170.65, 170.40, 169.38 (each C=O), 100.46 (C-1), 72.04 (C-4), 71.97 (C-5), 68.55 (C-3), 68.41 (OCH₂CH₂N₃), 61.97 (C-6), 54.93 (C-2), 50.60 (OCH₂CH₂N₃), 23.37 (NHAc), 20.74, 20.66, 20.62 (each OAc).

ES-HRMS calcd for C₁₆H₂₄N₄O₉Na₁ 439.1441, found *m/z* 439.1429 [M+Na]⁺

IR cm⁻¹: 2106, 1744, 1656, 1566, 1436, 1368, 1225, 1170, 1125, 1033, 910

*R*_f: 0.41 (1:19 MeOH-CH₂Cl₂)

[α]_D²⁰ -22.8 (*c* 0.36, CHCl₃)

1,3-Bis(prop-2-yn-1-yloxy)benzene (82)²¹

Resorcinol (2.00 g, 18.2 mmol) was dissolved in acetone (50 mL). To this solution was added anhydrous K_2CO_3 (15.0 g, 109 mmol) and the reaction heated to reflux for 30 mins. Propargyl bromide (80% in toluene, 4.45 mL, 40.0 mmol) was added dropwise, very slowly, to this mixture. The reaction mixture was then refluxed overnight. The reaction mixture was then cooled to r.t. and the solution diluted with CH_2Cl_2 , washed with water, dried over $MgSO_4$ and the solvents then removed under reduced pressure. Column chromatography (EtOAc-Pet ether 1:9) gave the title compound (3.05 g, 90%) as a beige solid.

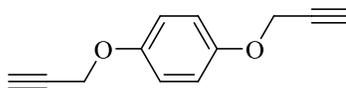
1H NMR (500 MHz, $CDCl_3$) δ 7.22 (t, $J = 8.5$ Hz, 1H, Ar-H), 6.63 (d, $J = 6.5$ Hz, 3H, Ar-H), 4.68 (d, $J = 2.4$ Hz, 4H, $ArOCH_2$), 2.52 (t, $J = 2.4$ Hz, 2H, CCH).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.72 (Ar-C), 129.93 (Ar-CH), 107.89 (Ar-CH), 102.45 (Ar-CH), 78.41 (CCH), 75.56 (CCH), 55.86 ($ArOCH_2$).

ES-HRMS calcd for $C_{12}H_{11}O_2$ 187.0759, found m/z 187.0768 $[M+H]^+$

IR (ATR) cm^{-1} : 3288, 1591, 1489, 1454, 1281, 1257, 1175, 1144, 1044, 1027, 835, 763, 681

R_f : 0.28 (1:9 EtOAc-Pet ether)

1,4-Bis(prop-2-yn-1-yloxy)benzene (83)²¹

Hydroquinone (2.00 g, 18.2 mmol) was dissolved in acetone (40 mL). To this solution was added anhydrous K_2CO_3 (15.0 g, 109 mmol) and the reaction heated to reflux for 30 mins. To this mixture propargyl bromide (80% in toluene, 4.45 mL, 40.0 mmol) was added dropwise, very slowly. The reaction mixture was then refluxed overnight. Following this it was cooled to r.t. and the solution diluted with CH_2Cl_2 and washed with water, dried over $MgSO_4$ and the solvents then removed under reduced pressure. Column chromatography (EtOAc-Pet ether 1:9) gave the title compound (2.77 g, 82%) as a brown solid.

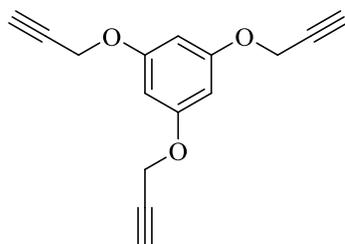
1H NMR (500 MHz, $CDCl_3$) δ 6.93 (s, 4H, Ar-H), 4.64 (d, $J = 2.4$ Hz, 4H, $ArOCH_2$), 2.51 (t, $J = 2.4$ Hz, 2H, CCH).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.38 (Ar-C), 116.02 (Ar-CH), 78.77 (CCH), 75.37 (CCH), 56.50 ($ArOCH_2$).

ES-HRMS calcd for $C_{12}H_{11}O_2$ 187.0759, found m/z 187.0755 $[M+H]^+$

IR (ATR) cm^{-1} : 3288, 1502, 1454, 1374, 1267, 1198, 1027, 923, 823

R_f : 0.44 (1:9 EtOAc-Pet ether)

1,3,5-Tri(prop-2-yn-1-yloxy)benzene (84)²²

Phloroglucinol (1.26 g, 9.99 mmol) was dissolved in dry DMF (30 mL) and anhydrous potassium carbonate (5.52 g, 39.9 mmol) was added and heated to 50°C for 1 h under a nitrogen atmosphere. Propargyl bromide (80% in toluene, 4.46 mL, 40.0 mmol) was then added to the reaction mixture and stirred for 38 h at 65°C. The reaction was then cooled to r.t. and diluted with chloroform, washed with water and dried over Na₂SO₄. The solvent was removed under diminished pressure. Column chromatography (1:9-1:4 EtOAc-Pet ether) gave the title compound (1.43 g, 60%) as a cream-coloured solid.

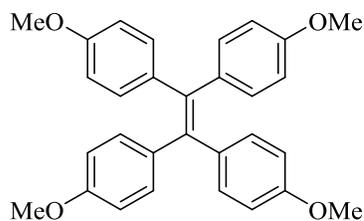
¹H NMR (500 MHz, CDCl₃) δ 6.20 (s, 3H, Ar-H), 4.58 (d, *J* = 2.4 Hz, 6H, ArOCH₂), 2.46 (t, *J* = 2.4 Hz, 3H, CCH).

¹³C NMR (126 MHz, CDCl₃) δ 159.33 (Ar-C), 95.46 (Ar-CH), 78.22 (CCH), 75.70 (CCH), 55.95 (ArOCH₂).

ES-HRMS calcd for C₁₅H₁₃O₃ 241.0865, found *m/z* 241.0875 [M+H]⁺

IR (ATR) cm⁻¹: 3288, 1597, 1471, 1455, 1371, 1268, 1148, 1064, 1033, 821

*R*_f: 0.31 (1:9 EtOAc-Pet ether)

1,1,2,2-Tetrakis(4-methoxy-phenyl)ethane (85)²³

4,4'-dimethylbenzophenone (5 g, 20.6 mmol) was dissolved in dry THF (100 mL) and to this was added zinc powder (6.60 g, 101 mmol). To this stirring suspension titanium tetrachloride (7.50 mL, 68.4 mmol) was added dropwise, slowly and carefully, at r.t. The mixture was then stirred at reflux for 16 h. The solution was then cooled. Water (100 mL) was added slowly to the reaction flask, with the mixture then diluted with CH₂Cl₂ and separated. The aqueous layer was extracted a further 3 times with CH₂Cl₂. The combined organic layers were dried over NaSO₄ and the solvent removed under reduced pressure. Column chromatography (CH₂Cl₂-Pet ether 1:1) gave the title compound (3.63 g, 78%) as a colourless solid

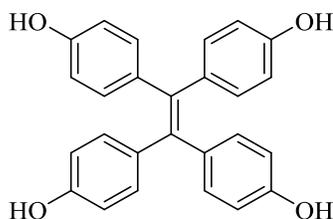
¹H NMR (500 MHz, CDCl₃) δ 6.93 (d, *J* = 8.8 Hz, 8H, Ar-H), 6.64 (d, *J* = 8.8 Hz, 8H, Ar-H), 3.74 (s, 12H, OCH₃).

¹³C NMR (126 MHz, CDCl₃) δ 157.74 (Ar-C-OMe), 138.34 (Ar₂-C=C-Ar₂), 136.86 (Ar-C), 132.50 (Ar-CH), 112.99 (Ar-CH), 55.06 (OCH₃).

ES-HRMS calcd for C₃₀H₂₉O₄ 453.2066, found *m/z* 453.2047 [M+H]⁺

IR (ATR) cm⁻¹: 1641, 1508, 1463, 1292, 1243, 1173, 1033, 830

R_f: 0.35 (1:9 EtOAc-Pet ether)

1,1,2,2-Tetrakis(4-hydroxy-phenyl)ethane (86)²⁴

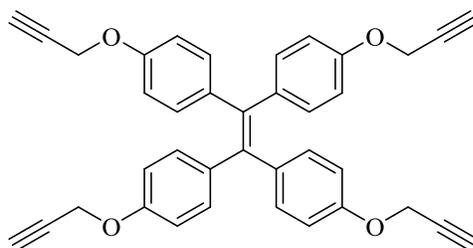
To a solution of **85** (3.63 g, 8.02 mmol) in CH_2Cl_2 (30 mL), cooled with an ice-salt bath, was added, dropwise, a 1M boron tribromide solution in CH_2Cl_2 (39 mL, 39.0 mmol). The ice bath was then removed and the solution was allowed warm to r.t. and stirred overnight. Water (35 mL) was then added slowly, dropwise, with stirring. The precipitate was collected by filtration, with the solid washed with clean portions of water. Recrystallisation of this solid from acetone-water (1:1, 100 mL) gave the title compound (2.96 g, 93%) as a colourless solid.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.19 (s, 4H, OH), 6.68 (d, $J = 8.5$ Hz, 8H, Ar-H), 6.46 (d, $J = 8.5$ Hz, 8H, Ar-H).

^{13}C NMR (126 MHz, DMSO) δ 155.78 (Ar-C-OH), 138.12 ($\text{Ar}_2\text{-C}=\text{C-Ar}_2$), 135.49 (Ar-C), 132.37 (Ar-CH), 114.92 (Ar-CH).

ES-HRMS calcd for $\text{C}_{26}\text{H}_{19}\text{O}_4$ 395.1283, found m/z 395.1277 [M-H]⁻

IR (ATR) cm^{-1} : 3383, 1608, 1507, 1434, 1344, 1252, 1216, 1167, 1104, 829, 817, 795

1,1,2,2-Tetrakis[4-(prop-2-yn-1-yloxy)benzene]ethane (87)²³

To a solution of **86** (2.96 g, 7.47 mmol) in DMF (240 mL) was added anhydrous potassium carbonate (8.34 g, 60.3 mmol). Propargyl bromide (80% in toluene, 3.70 mL, 33.2 mmol) was then added to the reaction mixture and stirred for 14 h at 70 °C under a nitrogen atmosphere. The reaction was then cooled to r.t. and diluted with CH₂Cl₂. This solution was washed with water, with the aqueous layer being re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water and dried over Na₂SO₄. The solvent was removed under diminished pressure. Column chromatography (1:1 CH₂Cl₂-Pet ether) gave the title compound (2.95 g, 72%) as yellow solid.

¹H NMR (500 MHz, CDCl₃) δ 6.93 (d, *J* = 8.8 Hz, 8H, Ar-H), 6.70 (d, *J* = 8.8 Hz, 8H, Ar-H), 4.62 (d, *J* = 2.4 Hz, 8H, ArOCH₂), 2.50 (t, *J* = 2.4 Hz, 4H, CCH).

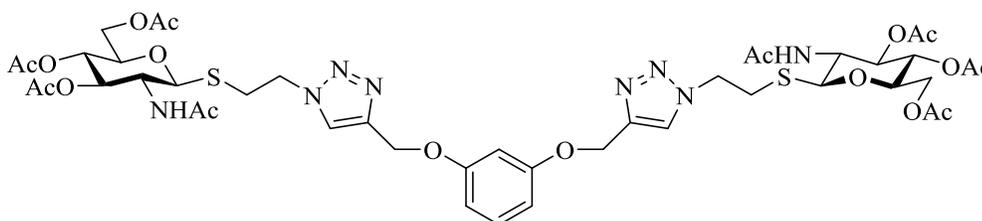
¹³C NMR (126 MHz, CDCl₃) δ 155.96 (Ar-C-O-propargyl), 138.56 (Ar₂-C=C-Ar₂), 137.41 (Ar-C), 132.49 (Ar-CH), 113.99 (Ar-CH), 78.60 (CCH), 75.37 (CCH), 55.77 (ArOCH₂).

ES-HRMS calcd for C₃₈H₂₉O₈ 549.2066, found *m/z* 549.2063 [M+H]⁺

IR (ATR) cm⁻¹: 3283, 1603, 1505, 1452, 1215, 1174, 1111, 1025, 924, 831, 808

R_f: 0.77 (3:7 EtOAc-Pet ether)

1,3-Di[1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- β -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (88)



To a mixture of sugar **79** (350 mg, 0.809 mmol) and *meta*-bispropargyloxybenzene **82** (63 mg, 0.338 mmol) in a THF-H₂O (1:1, 12 mL) mixture was added sodium ascorbate (41 mg, 0.207 mmol) and copper sulphate pentahydrate (51 mg, 0.204 mmol). The mixture was stirred at r.t. for 18 h. Tetrahydrofuran was then removed under diminished pressure followed by the dilution of the solution with CH₂Cl₂. This mixture was then washed with water. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water, dried over NaSO₄ and the solvent removed *in vacuo*. Chromatography of the crude material (95:5 CH₂Cl₂-MeOH) gave the title compound (350 mg, 98%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 7.76 (s, 2H, CCH, triazole), 7.20 (t, J = 8.3 Hz, 1H, Ar-H), 6.65 – 6.61 (m, 3H, Ar-H), 6.01 (d, J = 9.3 Hz, 2H, NH), 5.20 (s, 4H, ArOCH₂), 5.17 (dd, J = 10.3, 9.4 Hz, 2H, H-3), 5.05 (dd, J = 10.1, 9.3 Hz, 2H, H-4), 4.67 (dt, J = 13.1, 6.4 Hz, 2H, SCH₂CH₂triazole), 4.61 – 4.55 (m, 2H, SCH₂CH₂triazole), 4.53 (d, J = 10.4 Hz, 2H, H-1), 4.19 – 4.13 (m, 4H, H-6a, H-6b), 4.05 (td, J = 10.3, 9.2 Hz, 2H, H-2), 3.67 (ddd, J = 10.1, 4.6, 3.0 Hz, 2H, H-5), 3.30 (dt, J = 14.6, 6.7 Hz, 2H, SCH₂CH₂triazole), 3.08 (dt, J = 14.6, 6.4 Hz, 2H, SCH₂CH₂triazole), 2.05 (s, 6H), 2.03 (s, 6H), 2.03 (s, 6H) (each OAc), 1.93 (s, 6H, NHAc).

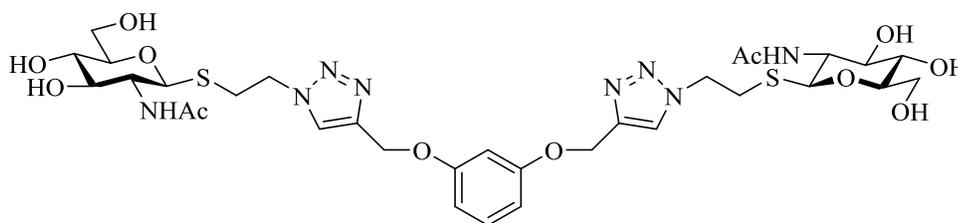
¹³C NMR (126 MHz, CDCl₃) δ 170.88, 170.56, 170.40, 169.31 (each C=O), 159.30 (Ar-C), 143.60 (CCH, triazole), 130.40 (Ar-CH), 124.22 (CCH, triazole), 108.26 (Ar-CH), 102.45 (Ar-CH), 84.48 (C-1), 76.08 (C-5), 73.34 (C-3), 68.25 (C-4), 62.04 (C-6), 62.04 (CH₂OAr), 53.15 (C-2), 50.38 (SCH₂CH₂triazole), 30.44 (SCH₂CH₂triazole), 23.19 (NHAc), 20.72, 20.65, 20.59 (each OAc)

ES-HRMS calcd for C₄₄H₅₈N₈O₁₈S₂Na₁ 1073.3208, found m/z 1073.3201 [M+Na]⁺

IR (ATR) cm⁻¹: 1743, 1660, 1525, 1371, 1221, 1035, 733, 703

*R*_f: 0.44 (2:23 MeOH-CH₂Cl₂)

1,3-Di[1-(ethyl 2-acetamido-2-deoxy-1-thio- β -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (89)



Compound **88** (350 mg, 0.333 mmol) was stirred in methanol (30 mL) and to this was added a catalytic amount of a freshly prepared 1M NaOMe solution in MeOH (0.17 mL, 0.170 mmol). The resulting mixture was stirred for 2 h at r.t. at which point Amberlite IR-120 H⁺ was added and stirred gently for 10 mins, to neutralize (pH = 7) the solution. The resin was removed by filtration and washed with water and acetonitrile. The solvents were removed to a minimal amount of water. Reverse phase column chromatography was then carried out. The compound, in a minimal amount of water (made acidic and slightly heated, if solid crashes out, to return it to solution), was loaded onto the column, with the elution carried out as follows: 3 volumes of water were flushed through the column, to ensure salt removal, followed by a 1:1 MeCN-H₂O mixture. This gave the title compound (207 mg, 78%) as a colourless solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.20 (s, 2H, CCH, triazole), 7.72 (d, *J* = 9.3 Hz, 2H, NH), 7.18 (t, *J* = 8.2 Hz, 1H, Ar-H), 6.71 (t, *J* = 2.3 Hz, 1H, Ar-H), 6.62 (dd, *J* = 8.3, 2.3 Hz, 2H, Ar-H), 5.09 (s, 4H, ArOCH₂), 5.04 (d, *J* = 5.3 Hz, 2H, OH-4), 4.99 (d, *J* = 5.4 Hz, 2H, OH-3), 4.67 – 4.52 (m, 6H, SCH₂CH₂triazole, OH-6), 4.40 (d, *J* = 10.3 Hz, 2H, H-1), 3.71 (ddd, *J* = 11.8, 5.4, 2.0 Hz, 2H, H-6a), 3.53 (q, *J* = 9.8 Hz, 2H, H-2), 3.44 (dt, *J* = 11.9, 6.1 Hz, 2H, H-6b), 3.29 – 3.23 (m, 2H, H-3), 3.20 – 3.13 (m, 4H, H-5, SCH₂CH₂triazole), 3.09 (td, *J* = 9.1, 5.2 Hz, 2H, H-4), 2.97 (dt, *J* = 13.9, 6.9 Hz, 2H, SCH₂CH₂triazole), 1.78 (s, 6H, NHAc).

¹³C NMR (126 MHz, DMSO) δ 169.52 (C=O), 159.75 (Ar-C), 142.62 (CCH, triazole), 130.45 (Ar-CH), 125.60 (CCH, triazole), 107.67 (Ar-CH), 102.01 (Ar-CH), 85.03 (C-1), 81.60 (C-5), 75.81 (C-3), 70.90 (C-4), 61.68 (C-6), 61.60 (CH₂OAr), 54.70 (C-2), 50.14 (SCH₂CH₂triazole), 30.50 (SCH₂CH₂triazole), 23.46 (NHAc).

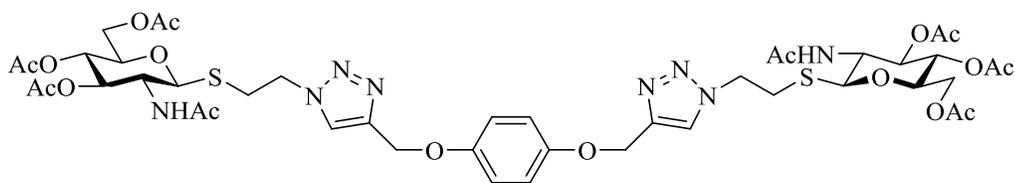
ES-HRMS calcd for C₃₂H₄₆N₈O₁₂S₂Na₁ 821.2574, found *m/z* 821.2573 [M+Na]⁺

IR (ATR) cm⁻¹: 3269, 1645, 1551, 1373, 1264, 1153, 1048, 1027, 820

*R*_f: 0.61 (1:1 MeCN-H₂O) reverse phase

[α]_D²⁰ -26.9 (*c* 0.26, DMSO)

1,4-Di[1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- β -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (90)



To a solution of sugar **79** (350 mg, 0.809 mmol) and *para*-bispropargyloxybenzene **83** (63 mg, 0.338 mmol) in a THF-H₂O (1:1, 12 mL) mixture was added sodium ascorbate (41 mg, 0.207 mmol) and copper sulphate pentahydrate (51 mg, 0.204 mmol). The mixture was stirred at r.t. for 18 h. Tetrahydrofuran was then removed under diminished pressure followed by the dilution of the solution with CH₂Cl₂. This mixture was then washed with water. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water, dried over NaSO₄ and the solvent removed *in vacuo*. Chromatography of the crude material (95:5 CH₂Cl₂-MeOH) gave the title compound (319 mg, 90%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 7.72 (s, 2H, CCH, triazole), 6.91 (s, 4H, Ar-H), 5.92 (d, *J* = 9.3 Hz, 2H, H-1), 5.16 (s, 4H, ArOCH₂), 5.14 (t, *J* = 10.0 Hz, 2H, H-3), 5.06 (t, *J* = 9.7 Hz, 2H, H-4), 4.67 (dt, *J* = 12.9, 6.2 Hz, 2H, SCH₂CH₂triazole), 4.56 (dt, *J* = 13.7, 6.6 Hz, 2H, SCH₂CH₂triazole), 4.43 (d, *J* = 10.4 Hz, 2H, NH), 4.25 – 4.14 (m, 4H, H-6a, H-6b), 4.06 (q, *J* = 9.9 Hz, 2H, H-2), 3.67 (ddd, *J* = 10.1, 4.8, 2.6 Hz, 2H, H-5), 3.30 (dt, *J* = 13.8, 6.7 Hz, 2H, SCH₂CH₂triazole), 3.06 (dt, *J* = 14.6, 6.3 Hz, 2H, SCH₂CH₂triazole), 2.06 (s, 6H), 2.03 (s, 6H), 2.02 (s, 6H) (each OAc), 1.93 (s, 6H, NHAc).

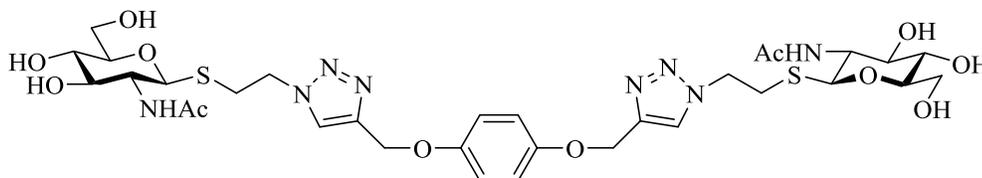
¹³C NMR (126 MHz, CDCl₃) δ 170.91, 170.56, 170.34, 169.30 (each C=O), 152.70 (Ar-C), 143.86 (CCH, triazole), 124.18 (CCH, triazole), 116.20 (Ar-CH), 84.54 (C-1), 76.08 (C5), 73.39 (C-3), 68.21 (C-4), 62.68 (CH₂OAr), 62.06 (C-6), 53.02 (C-2), 50.45 (SCH₂CH₂triazole), 30.37 (SCH₂CH₂triazole), 23.17 (NHAc), 20.72, 20.64, 20.58 (each OAc).

ES-HRMS calcd for C₄₄H₅₈N₈O₁₈S₂Na₁ 1073.3208, found *m/z* 1073.3193 [M+Na]⁺

IR (ATR) cm⁻¹: 1743, 1661, 1536, 1508, 1372, 1221, 1043, 915, 731

R_f: 0.34 (2:23 MeOH-CH₂Cl₂)

1,4-Di[1-(ethyl 2-acetamido-2-deoxy-1-thio- β -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (91)



Compound **90** (315 mg, 0.300 mmol) was stirred in methanol (30 mL) and to this was added a catalytic amount of a freshly prepared 1M NaOMe solution in MeOH (0.15 mL, 0.150 mmol). The resulting mixture was stirred for 2 h at r.t. at which point Amberlite IR-120 H⁺ was added and stirred gently for 10 mins, to neutralize (pH = 7) the solution. The resin was removed by filtration and washed with water and acetonitrile. The solvents were removed to a minimal amount of water. Reverse phase column chromatography was then carried out. The compound, in a minimal amount of water (made acidic and slightly heated, if solid crashes out, to return it to solution), was loaded onto the column, with the elution carried out as follows: 3 volumes of water were flushed through the column, to ensure salt removal, followed by a 1:1 MeCN-H₂O mixture. This gave the title compound (196 mg, 82%) as a colourless solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.18 (s, 2H, CCH, triazole), 7.71 (d, *J* = 9.3 Hz, 2H, NH), 6.95 (s, 4H, Ar-H), 5.05 (d, *J* = 1.4 Hz, 4H, ArOCH₂), 5.04 (d, *J* = 3.9 Hz, 2H, OH-4), 4.99 (d, *J* = 5.5 Hz, 2H, OH-3), 4.63 – 4.54 (m, 6H, SCH₂CH₂triazole, OH-6), 4.40 (d, *J* = 10.3 Hz, 2H, H-1), 3.71 (ddd, *J* = 11.9, 5.6, 2.0 Hz, 2H, H-6), 3.53 (q, *J* = 9.8 Hz, 2H, H-2), 3.44 (dt, *J* = 11.9, 6.1 Hz, 2H, H-6b), 3.30 – 3.21 (m, 2H, H-3), 3.20 – 3.13 (m, 4H, H-5, SCH₂CH₂triazole), 3.09 (td, *J* = 9.1, 5.3 Hz, 2H, H-4), 2.97 (dt, *J* = 13.9, 6.9 Hz, 2H, SCH₂CH₂triazole), 1.78 (s, 6H, NHAc).

¹³C NMR (126 MHz, DMSO) δ 169.51 (C=O), 152.81 (Ar-C), 142.91 (CCH, triazole), 125.48 (CCH, triazole), 116.03 (Ar-CH), 85.03 (C-1), 81.61 (C-5), 75.81 (C-3), 70.90 (C-4), 62.07 (CH₂OAr), 61.68 (C-6), 54.70 (C-2), 50.11 (SCH₂CH₂triazole), 30.51 (SCH₂CH₂triazole), 23.46 (NHAc).

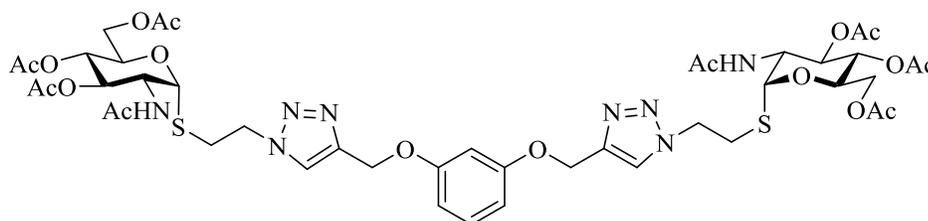
ES-HRMS calcd for C₃₂H₄₆N₈O₁₂S₂Na₁ 821.2574, found *m/z* 821.2584 [M+Na]⁺

IR (ATR) cm⁻¹: 3267, 1644, 1552, 1508, 1374, 1216, 1052, 1027, 1007, 822

*R*_f: 0.62 (1:1 MeCN-H₂O) reverse phase

[α]_D²⁰ -24.0 (c 0.27, DMSO)

1,3-Di[1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (92)



To a mixture of sugar **78** (335 mg, 0.775 mmol) and *meta*-bispropargyloxybenzene **82** (65 mg, 0.349 mmol) in a THF-H₂O (1:1, 14 mL) mixture was added sodium ascorbate (42 mg, 0.212 mmol) and copper sulphate pentahydrate (52 mg, 0.208 mmol). The mixture was stirred at r.t. for 20 h. Tetrahydrofuran was then removed under diminished pressure followed by the dilution of the solution with CH₂Cl₂. This mixture was then washed with water. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water, dried over NaSO₄ and the solvent removed *in vacuo*. Chromatography of the crude material (95:5 CH₂Cl₂-MeOH) gave the title compound (327 mg, 89%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 7.68 (s, 2H, CCH, triazole), 7.23 – 7.17 (m, 1H, Ar-H), 6.65 – 6.59 (m, 3H, Ar-H), 5.88 (d, *J* = 8.0 Hz, 2H, NH), 5.58 (d, *J* = 5.4 Hz, 2H, H-1), 5.20 (s, 4H, CH₂OAr), 5.11 (t, *J* = 9.6 Hz, 2H, H-4), 5.02 (dd, *J* = 11.1, 9.3 Hz, 2H, H-3), 4.59 (t, *J* = 6.7 Hz, 4H, SCH₂CH₂triazole), 4.46 (ddd, *J* = 11.1, 8.0, 5.4 Hz, 2H, H-2), 4.30 (ddd, *J* = 9.9, 4.9, 2.2 Hz, 2H, H-5), 4.25 (dd, *J* = 12.3, 4.8 Hz, 2H, H-6a), 4.12 (dd, *J* = 12.3, 2.2 Hz, 2H, H-6b), 3.18 (dt, *J* = 13.6, 6.7 Hz, 2H, SCH₂CH₂triazole), 3.09 (dt, *J* = 14.0, 6.8 Hz, 2H, SCH₂CH₂triazole), 2.06 (s, 6H), 2.04 (s, 6H), 2.04 (s, 6H) (each OAc), 1.97 (s, 6H, NHAc).

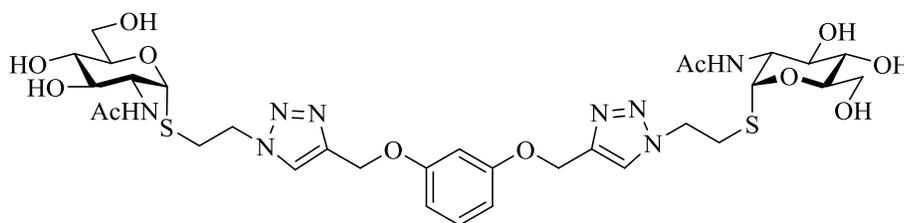
¹³C NMR (126 MHz, CDCl₃) δ 171.72, 170.52, 170.20, 169.24 (each C=O), 159.37 (Ar-C), 144.26 (CCH, triazole), 130.13 (Ar-CH) 123.05 (CCH, triazole), 107.78 (Ar-CH), 102.13 (Ar-CH), 84.63 (C-1), 70.96 (C-3), 68.75 (C-5), 67.98 (C-4), 62.07 (CH₂OAr), 62.01 (C-6), 52.75 (C-2), 49.52 (SCH₂CH₂triazole), 31.44 (SCH₂CH₂triazole), 23.18 (NHAc), 20.70, 20.68, 20.58 (each OAc).

ES-HRMS calcd for C₄₄H₅₈N₈O₁₈S₂Na₁ 1073.3208, found *m/z* 1073.3237 [M+Na]⁺

IR (ATR) cm⁻¹: 3286, 1742, 1540, 1369, 1227, 1150, 1086, 1039, 734

R_f: 0.47 (2:23 MeOH-CH₂Cl₂)

1,3-Di[1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (93)



Compound **92** (314 mg, 0.299 mmol) was stirred in methanol (30 mL) and to this was added a catalytic amount of a freshly prepared 1M NaOMe solution in MeOH (0.15 mL, 0.150 mmol). The resulting mixture was stirred for 2 h at r.t. at which point Amberlite IR-120 H⁺ was added and stirred gently for 10 mins, to neutralize (pH = 7) the solution. The resin was removed by filtration and washed with water and acetonitrile. The solvents were removed to a minimal amount of water. Reverse phase column chromatography was then carried out. The compound, in a minimal amount of water (made acidic and slightly heated, if solid crashes out, to return it to solution), was loaded onto the column, with the elution carried out as follows: 3 volumes of water were flushed through the column, to ensure salt removal, followed by a 1:1 MeCN-H₂O mixture. This gave the title compound (226 mg, 95%) as a colourless solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.20 (s, 2H, CCH, triazole), 7.83 (d, *J* = 7.0 Hz, 2H, NH), 7.19 (t, *J* = 8.2 Hz, 1H, Ar-H), 6.70 (t, *J* = 2.4 Hz, 1H, Ar-H), 6.62 (dd, *J* = 8.3, 2.3 Hz, 2H, Ar-H), 5.44 (d, *J* = 5.3 Hz, 2H, H-1), 5.11 (d, *J* = 5.6 Hz, 2H, OH-4), 5.09 (s, 4H, CH₂OAr), 4.82 (d, *J* = 5.7 Hz, 2H, OH-3), 4.64 (t, *J* = 5.8 Hz, 2H, OH-6), 4.59 (dt, *J* = 13.7, 6.8 Hz, 2H, SCH₂CH₂triazole), 4.52 (dt, *J* = 13.9, 7.0 Hz, 2H, SCH₂CH₂triazole), 3.79 (ddd, *J* = 11.0, 7.0, 5.3 Hz, 2H, H-2), 3.75 – 3.67 (m, 4H, H-5, H-6a), 3.48 (dt, *J* = 11.9, 6.2 Hz, 2H, H-6b), 3.34 (ddd, *J* = 10.4, 8.4, 5.4 Hz, 2H, H-3), 3.11 (td, *J* = 9.3, 5.6 Hz, 2H, H-4), 3.05 (dt, *J* = 13.9, 7.0 Hz, 2H, SCH₂CH₂triazole), 2.96 (dt, *J* = 13.8, 6.8 Hz, 2H, SCH₂CH₂triazole), 1.81 (s, 6H, NHAc).

¹³C NMR (126 MHz, DMSO) δ 170.03 (C=O), 159.74 (Ar-C), 142.87 (CCH, triazole), 130.47 (Ar-CH), 125.15 (CCH, triazole), 107.68 (Ar-CH), 102.03 (Ar-CH), 84.47 (C-1), 74.19 (C-5), 71.42 (C-4), 71.08 (C-3), 61.61 (CH₂OAr), 61.31 (C-6), 54.60 (C-2), 49.74 (SCH₂CH₂triazole), 30.54 (SCH₂CH₂triazole), 23.03 (NHAc).

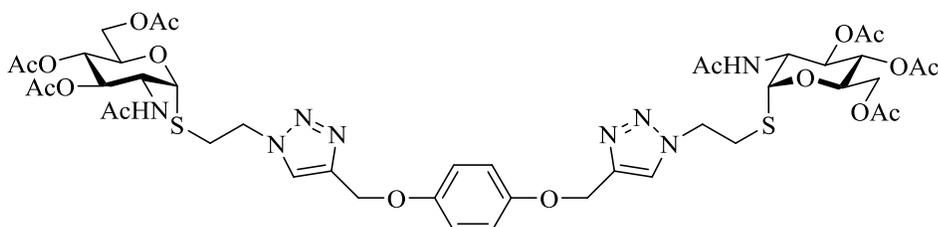
ES-HRMS calcd for C₃₂H₄₆N₈O₁₂S₂Na₁ 821.2574, found *m/z* 821.2585 [M+Na]⁺

IR (ATR) cm⁻¹: 3278, 1644, 1594, 1547, 1283, 1150, 1041, 1028, 763

*R*_f: 0.57 (1:1 MeCN-H₂O) reverse phase

[α]_D²⁰ +114.6 (*c* 0.42, DMSO)

1,4-Di[1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-glucoopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (94)



To a solution of sugar **78** (335 mg, 0.775 mmol) and *para*-bispropargyloxybenzene **83** (65 mg, 0.349 mmol) in a THF-H₂O (1:1, 12 mL) mixture was added sodium ascorbate (42 mg, 0.212 mmol) and copper sulphate pentahydrate (51 mg, 0.208 mmol). The mixture was stirred at r.t. for 20 h. Tetrahydrofuran was then removed under diminished pressure followed by the dilution of the solution with CH₂Cl₂. This mixture was then washed with water. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water, dried over NaSO₄ and the solvent removed *in vacuo*. Chromatography of the crude material (95:5 CH₂Cl₂-MeOH) gave the title compound (353 mg, 96%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 7.65 (s, 2H, CCH, triazole), 6.92 (s, 4H, Ar-H), 5.83 (d, *J* = 8.0 Hz, 2H, NH), 5.57 (d, *J* = 5.4 Hz, 2H, H-1), 5.17 (s, 4H, CH₂OAr), 5.12 (t, *J* = 9.6 Hz, 2H, H-4), 5.02 (dd, *J* = 11.1, 9.3 Hz, 2H, H-3), 4.59 (t, *J* = 6.7 Hz, 4H, SCH₂CH₂triazole), 4.46 (ddd, *J* = 11.1, 7.9, 5.5 Hz, 2H, H-2), 4.30 (ddd, *J* = 10.0, 4.9, 2.1 Hz, 2H, H-5), 4.26 (dd, *J* = 12.3, 4.8 Hz, 2H, H-6a), 4.12 (dd, *J* = 12.3, 2.1 Hz, 2H, H-6b), 3.18 (dt, *J* = 13.6, 6.7 Hz, 2H, SCH₂CH₂triazole), 3.09 (dt, *J* = 13.9, 6.8 Hz, 2H, SCH₂CH₂triazole), 2.06 (s, 6H), 2.04 (s, 6H), 2.04 (s, 6H) (each OAc), 1.97 (s, 6H, NHAc).

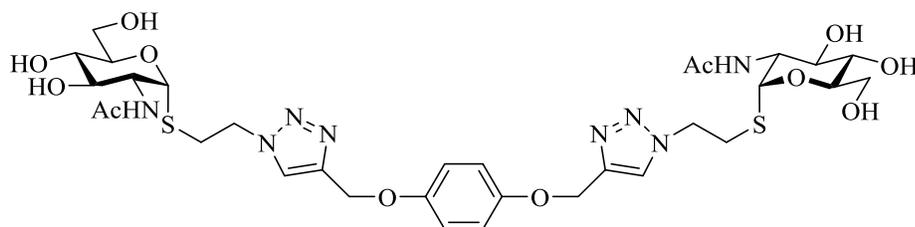
¹³C NMR (126 MHz, CDCl₃) δ 172.87, 171.77, 170.52, 170.18 (each C=O), 152.75 (Ar-C), 144.55 (CCH, triazole), 122.96 (CCH, triazole), 115.88 (Ar-CH), 84.64 (C-1), 70.99 (C-3), 68.76 (C-5), 67.93 (C-4), 62.66 (CH₂OAr), 62.01 (C-6), 52.77 (C-2), 49.50 (SCH₂CH₂triazole), 31.46 (SCH₂CH₂triazole), 23.18 (NHAc), 20.70, 20.69, 20.58 (each OAc).

ES-HRMS calcd for C₄₄H₅₈N₈O₁₈S₂Na₁ 1073.3208, found *m/z* 1073.3203 [M+Na]⁺

IR (ATR) cm⁻¹: 3278, 1744, 1635, 1547, 1376, 1228, 1085, 1043, 1027, 800

R_f: 0.47 (2:23 MeOH-CH₂Cl₂)

1,4-Di[1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (95)



Compound **94** (349 mg, 0.332 mmol) was stirred in methanol (32 mL) and to this was added a catalytic amount of a freshly prepared 1M NaOMe solution in MeOH (0.17 mL, 0.170 mmol). The resulting mixture was stirred for 1.5 h at r.t. at which point Amberlite IR-120 H⁺ was added and stirred gently for 10 mins, to neutralize (pH = 7) the solution. The resin was removed by filtration and washed with water and acetonitrile. The solvents were removed to a minimal amount of water. Reverse phase column chromatography was then carried out. The compound, in a minimal amount of water (made acidic and slightly heated, if solid crashes out, to return it to solution), was loaded onto the column, with the elution carried out as follows: 3 volumes of water were flushed through the column, to ensure salt removal, followed by a 1:1 MeCN-H₂O mixture. This gave the title compound (196 mg, 74%) as a colourless solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.17 (s, 2H, CCH, triazole), 7.83 (d, *J* = 7.0 Hz, 2H, NH), 6.95 (s, 4H, Ar-H), 5.44 (d, *J* = 5.2 Hz, 2H, H-1), 5.12 (d, *J* = 5.6 Hz, 2H, OH-4), 5.04 (s, 4H, CH₂OAr), 4.82 (d, *J* = 5.7 Hz, 2H, OH-3), 4.64 (t, *J* = 5.7 Hz, 2H, OH-6), 4.58 (dt, *J* = 13.7, 6.8 Hz, 2H, SCH₂CH₂triazole), 4.51 (dt, *J* = 13.9, 7.0 Hz, 2H, SCH₂CH₂triazole), 3.79 (ddd, *J* = 11.0, 7.0, 5.2 Hz, 2H, H-2), 3.74 – 3.67 (m, 4H, H-5, H-6a), 3.48 (dt, *J* = 12.0, 6.2 Hz, 2H, H-6b), 3.34 (ddd, *J* = 11.1, 8.7, 5.8 Hz, 2H, H-3), 3.10 (ddd, *J* = 9.9, 8.6, 5.6 Hz, 2H, H-4), 3.04 (dt, *J* = 13.9, 7.0 Hz, 2H, SCH₂CH₂triazole), 2.96 (dt, *J* = 13.8, 6.8 Hz, 2H, SCH₂CH₂triazole), 1.81 (s, 6H, NHAc).

¹³C NMR (126 MHz, DMSO) δ 170.02 (C=O), 152.80 (Ar-C), 143.15 (CCH, triazole), 125.03 (CCH, triazole), 116.04 (Ar-CH), 84.48 (C-1), 74.19 (C-5), 71.42 (C-4), 71.08 (C-3), 62.09 (CH₂OAr), 61.32 (C-6), 54.61 (C-2), 49.72 (SCH₂CH₂triazole), 30.57 (SCH₂CH₂triazole), 23.03 (NHAc).

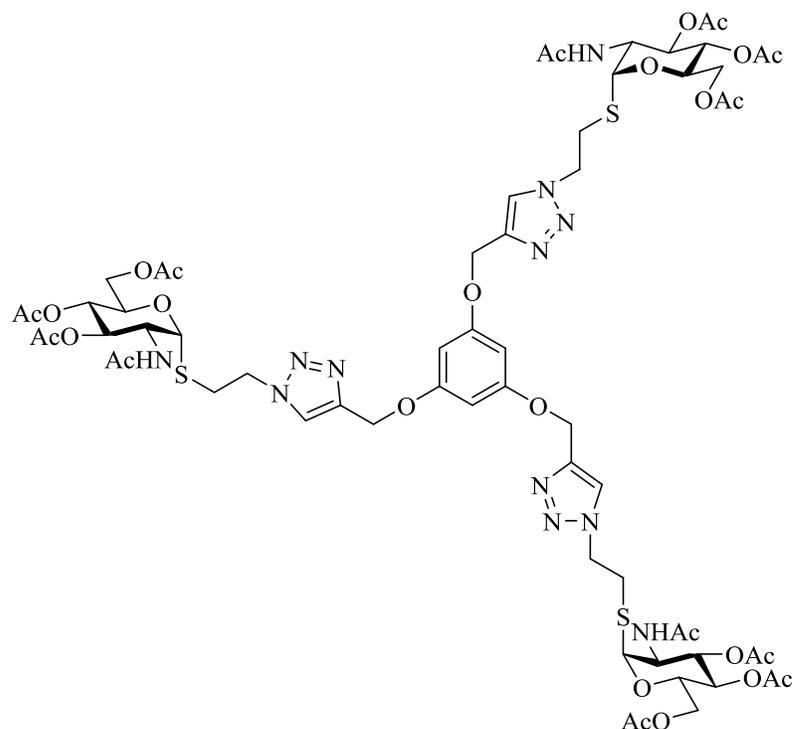
ES-HRMS calcd for C₃₂H₄₆N₈O₁₂S₂Na₁ 821.2574, found *m/z* 821.2578 [M+Na]⁺

IR (ATR) cm⁻¹: 3283, 1644, 1543, 1508, 1215, 1064, 1039, 1007, 823

*R*_f: 0.61 (1:1 MeCN-H₂O) reverse phase

[α]_D²⁰ +146.4 (*c* 0.39, DMSO)

1,3,5-Tri[1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (96)



To a solution of sugar **78** (348 mg, 0.805 mmol) and tripropargyl phloroglucinol ether **84** (62 mg, 0.258 mmol) in a THF-H₂O (1:1, 14 mL) mixture was added sodium ascorbate (31 mg, 0.156 mmol) and copper sulphate pentahydrate (39 mg, 0.156 mmol). The mixture was stirred at r.t. for 20 h. Tetrahydrofuran was then removed under diminished pressure followed by the dilution of the solution with CH₂Cl₂. This mixture was then washed with water. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water, dried over NaSO₄ and the solvent removed *in vacuo*. Chromatography of the crude material (95:5-93:7 CH₂Cl₂-MeOH) gave the title compound (343 mg, 86%) as a colourless solid.

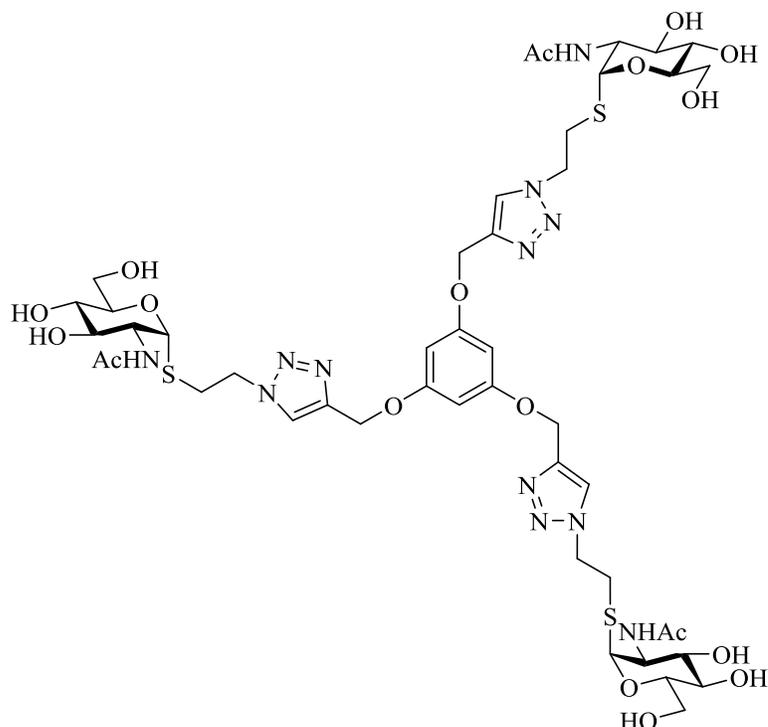
¹H NMR (500 MHz, CDCl₃-*d*) δ 7.71 (s, 3H, CCH, triazole), 6.28 (s, 3H, Ar-H), 5.99 (d, *J* = 8.0 Hz, 3H, NH), 5.59 (d, *J* = 5.4 Hz, 3H, H-1), 5.17 (s, 6H, CH₂OAr), 5.11 (t, *J* = 9.6 Hz, 3H, H-4), 5.02 (dd, *J* = 11.1, 9.3 Hz, 3H, H-3), 4.60 (t, *J* = 6.7 Hz, 6H, SCH₂CH₂triazole), 4.47 (ddd, *J* = 11.2, 8.0, 5.4 Hz, 3H, H-2), 4.31 (ddd, *J* = 10.0, 4.8, 2.2 Hz, 3H, H-5), 4.26 (dd, *J* = 12.3, 4.9 Hz, 3H, H-6a), 4.12 (dd, *J* = 12.3, 2.2 Hz, 3H, H-6b), 3.18 (dt, *J* = 13.6, 6.7 Hz, 3H, SCH₂CH₂triazole), 3.10 (dt, *J* = 13.9, 6.8 Hz, 3H, SCH₂CH₂triazole), 2.05 (s, 9H), 2.04 (s, 9H), 2.04 (s, 9H) (each OAc), 1.97 (s, 9H, NHAc).

^{13}C NMR (126 MHz, CDCl_3) δ 171.65, 170.53, 170.25, 169.28 (each C=O), 160.02 (Ar-C), 143.99 (CCH, triazole), 123.21 (CCH, triazole), 95.38 (Ar-CH), 84.64 (C-1), 70.92 (C-3), 68.73 (C-5), 68.05 (C-4), 62.03 (CH_2OAr), 62.03 (C-6), 52.71 (C-2), 49.53 ($\text{SCH}_2\text{CH}_2\text{triazole}$), 31.43 ($\text{SCH}_2\text{CH}_2\text{triazole}$), 23.17 (NHAc), 20.70, 20.69, 20.59 (each OAc).

ES-HRMS calcd for $\text{C}_{63}\text{H}_{84}\text{N}_{12}\text{O}_{27}\text{S}_3\text{Na}_1$ 1559.4629, found m/z 1559.4636 $[\text{M}+\text{Na}]^+$

IR (ATR) cm^{-1} : 3276, 1744, 1635, 1541, 1509, 1376, 1230, 1152, 1118, 1044, 827, 803

R_f : 0.40 (2:23 MeOH- CH_2Cl_2)

1,3,5-Tri[1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (97)

Compound **96** (330 mg, 0.215 mmol) was stirred in methanol (20 mL) and to this was added a catalytic amount of a freshly prepared 1M NaOMe solution in MeOH (0.11 mL, 0.110 mmol). The resulting mixture was stirred for 1.5 h at r.t. at which point Amberlite IR-120 H⁺ was added and stirred gently for 10 mins, to neutralize (pH = 7) the solution. The resin was removed by filtration and washed with water and acetonitrile. The solvents were removed to a minimal amount of water. Reverse phase column chromatography was then carried out. The compound, in a minimal amount of water (made acidic and slightly heated, if solid crashes out, to return it to solution), was loaded onto the column, with the elution carried out as follows: 3 volumes of water were flushed through the column, to ensure salt removal, followed by a 1:1 MeCN-H₂O mixture. This gave the title compound (224 mg, 90%) as a colourless solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.20 (s, 3H, CCH, triazole), 7.83 (d, J = 7.0 Hz, 3H, NH), 6.33 (s, 3H, Ar-H), 5.45 (d, J = 5.3 Hz, 3H, H-1), 5.11 (d, J = 5.7 Hz, 3H, OH-4), 5.07 (s, 6H, CH₂OAr), 4.81 (d, J = 5.3 Hz, 3H, OH-3), 4.66 – 4.63 (m, 3H, OH-6), 4.59 (dt, J = 13.7, 6.9 Hz, 3H, SCH₂CH₂triazole), 4.52 (dt, J = 14.0, 7.0 Hz, 3H, SCH₂CH₂triazole), 3.79 (ddd, J = 10.9, 7.0, 5.2 Hz, 3H, H-2), 3.71 (td, J = 12.4, 11.1, 5.2 Hz, 6H, H-5. H-6a),

3.48 (dt, $J = 11.4, 5.3$ Hz, 3H, H-6b), 3.38 – 3.33 (m, 3H, H-3), 3.11 (dt, $J = 9.6, 4.7$ Hz, 3H, H-4), 3.05 (dt, $J = 14.0, 7.2$ Hz, 3H, SCH₂CH₂triazole), 2.96 (dt, $J = 13.9, 6.9$ Hz, 3H, SCH₂CH₂triazole), 1.81 (s, 9H, NHAc).

¹³C NMR (126 MHz, DMSO) δ 170.04 (C=O), 160.36 (OAr-C), 142.77 (CCH, triazole), 125.18 (CCH, triazole), 94.91 (Ar-CH), 84.47 (C-1), 74.18 (C-5), 71.42 (C-4), 71.08 (C-3), 61.68 (ArOCH₂), 61.31 (C-6), 54.60 (C-2), 49.75 (SCH₂CH₂triazole), 30.53 (SCH₂CH₂triazole), 23.03 (NHAc).

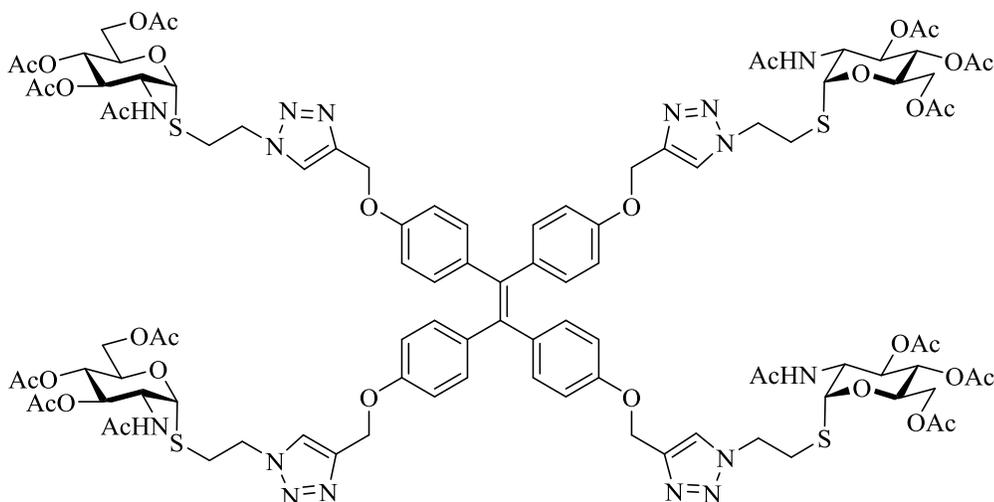
ES-HRMS calcd for C₄₅H₆₆N₁₂O₁₈S₃Na₁ 1181.3678, found m/z 1181.3660 [M+Na]⁺

IR (ATR) cm⁻¹: 3286, 1641, 1543, 1376, 1168, 1099, 1066, 1004, 943, 810, 757

R_f : 0.71 (1:1 MeCN-H₂O) reverse phase

$[\alpha]_D^{20}$ +142.2 (c 0.45, DMSO)

1,1,2,2-Tetrakis[4-(1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy)-phenyl]ethane (98)



To a solution of sugar **78** (333 mg, 0.770 mmol) and tetrapropargyl tetraphenylethene ether **87** (104 mg, 0.190 mmol) in a THF-H₂O (1:1, 20 mL) mixture was added sodium ascorbate (23 mg, 0.116 mmol) and copper sulphate pentahydrate (28 mg, 0.112 mmol). The mixture was stirred at r.t. for 20 h. Tetrahydrofuran was then removed under diminished pressure followed by the dilution of the solution with CH₂Cl₂. This mixture was then washed with water. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water, dried over NaSO₄ and the solvent removed *in vacuo*. Chromatography of the crude material (95:5-93:7 CH₂Cl₂-MeOH) gave the title compound (357 mg, 83%) as a yellow solid.

¹H NMR (500 MHz, CDCl₃-*d*) δ δ 7.66 (s, 4H, CCH, triazole), 6.93 (d, *J* = 8.7 Hz, 8H, Ar-H), 6.72 (d, *J* = 8.8 Hz, 8H, Ar-H), 5.89 (d, *J* = 8.0 Hz, 4H, NH), 5.58 (d, *J* = 5.4 Hz, 4H, H-1), 5.14 (s, 8H, CH₂OAr), 5.11 (t, *J* = 9.8 Hz, 4H, H-4), 5.02 (dd, *J* = 11.1, 9.3 Hz, 4H, H-3), 4.60 (t, *J* = 6.8 Hz, 8H, SCH₂CH₂triazole), 4.47 (ddd, *J* = 11.1, 8.0, 5.5 Hz, 4H, H-2), 4.31 (ddd, *J* = 10.1, 4.8, 2.0 Hz, 4H, H-5), 4.26 (dd, *J* = 12.3, 4.8 Hz, 4H, H-6a), 4.13 (dd, *J* = 12.4, 2.2 Hz, 4H, H-6b), 3.18 (dt, *J* = 13.7, 6.7 Hz, 4H, SCH₂CH₂triazole), 3.10 (dt, *J* = 14.0, 6.9 Hz, 4H, SCH₂CH₂triazole), 2.06 (s, 12H), 2.04 (s, 12H), 2.04 (s, 12H) (each OAc), 1.96 (s, 12H, NHAc).

¹³C NMR (126 MHz, , CDCl₃) δ 171.71, 170.54, 170.23, 169.25 (each C=O), 156.56 (OAr-C), 144.35 (CCH, triazole), 138.73 (Ar₂-C=C-Ar₂), 137.20 (Ar-C), 132.56 (Ar-CH), 123.01 (CCH, triazole), 113.88 (Ar-CH), 84.60 (C-1), 70.97 (C-3), 68.76 (C-5), 68.00 (C-4), 62.01

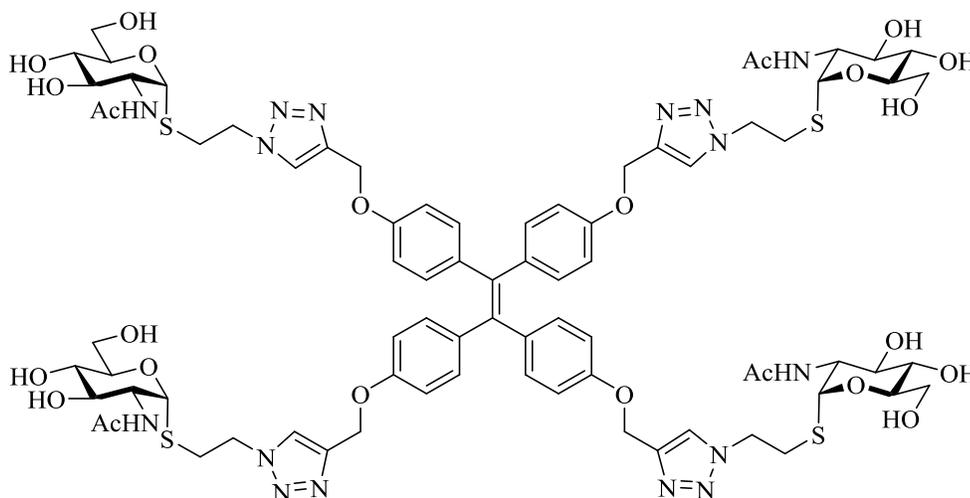
(CH₂OAr), 62.01 (C-6), 52.71 (C-2), 49.52 (SCH₂CH₂triazole), 31.38 (SCH₂CH₂triazole), 23.17 (NHAc), 20.70, 20.70, 20.58 (each OAc).

ES-HRMS calcd for C₁₀₂H₁₂₄N₁₆O₃₆S₄Cl₁ 2311.6936, found m/z 2311.6877 [M+Cl]⁻

IR (ATR) cm⁻¹: 1741, 1669, 1508, 1367, 1225, 1039, 734

R_f: 0.39 (2:23 MeOH-CH₂Cl₂)

1,1,2,2-Tetrakis[4-(1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy-phenyl)]ethane (99)



Compound **98** (355 mg, 0.311 mmol) was stirred in methanol (25 mL) and to this was added a catalytic amount of a freshly prepared 1M NaOMe solution in MeOH (0.08 mL, 0.080 mmol). The resulting mixture was stirred for 2 h at r.t. at which point Amberlite IR-120 H⁺ was added and stirred gently for 10 mins, to neutralize (pH = 7) the solution. The resin was removed by filtration and washed with water and acetonitrile. The solvents were removed to a minimal amount of water. Reverse phase column chromatography was then carried out. The compound, in a minimal amount of water (made acidic and slightly heated, if solid crashes out, to return it to solution), was loaded onto the column, with the elution carried out as follows: 3 volumes of water were flushed through the column, to ensure salt removal, followed by a 1:1 AC MeCN-H₂O mixture. This gave the title compound (263 mg, 95%) as a yellow solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.18 (s, 4H, CCH, triazole), 7.83 (d, *J* = 7.0 Hz, 4H, NH), 6.87 (d, *J* = 8.7 Hz, 8H, Ar-H), 6.80 (d, *J* = 8.8 Hz, 8H, Ar-H), 5.44 (d, *J* = 5.3 Hz, 4H, H-1), 5.11 (d, *J* = 5.6 Hz, 4H, OH-4), 5.03 (s, 8H, CH₂OAr), 4.81 (d, *J* = 5.8 Hz, 4H, OH-3), 4.64 (t, *J* = 5.8 Hz, 4H, OH-6), 4.58 (dt, *J* = 13.7, 6.8 Hz, 4H, SCH₂CH₂triazole), 4.51 (dt, *J* = 14.0, 7.0 Hz, 4H, SCH₂CH₂triazole), 3.79 (ddd, *J* = 10.9, 7.0, 5.2 Hz, 4H, H-2), 3.75 – 3.67 (m, 8H, H5, H-6a), 3.48 (dt, *J* = 12.0, 6.2 Hz, 4H, H-6b), 3.37 – 3.31 (m, 4H, H-3), 3.11 (td, *J* = 9.1, 5.9 Hz, 4H, H-4), 3.04 (dt, *J* = 13.9, 7.0 Hz, 4H, SCH₂CH₂triazole), 2.96 (dt, *J* = 13.8, 6.8 Hz, 4H, SCH₂CH₂triazole), 1.80 (s, 12H, NHAc).

^{13}C NMR (126 MHz, DMSO) δ 170.03 (C=O), 156.89 (OAr-C), 142.86 (CCH, triazole), 138.51 (Ar₂-C=C-Ar₂), 136.95 (Ar-C), 132.46 (Ar-CH), 125.15 (CCH, triazole), 114.33 (Ar-CH), 84.49 (C-1), 74.19 (C-5), 71.42 (C-4), 71.08 (C-3), 61.46 (CH₂OAr), 61.31 (C-6), 54.60 (C-2), 49.76 (SCH₂CH₂triazole), 30.56 (SCH₂CH₂triazole), 23.03 (NHAc).

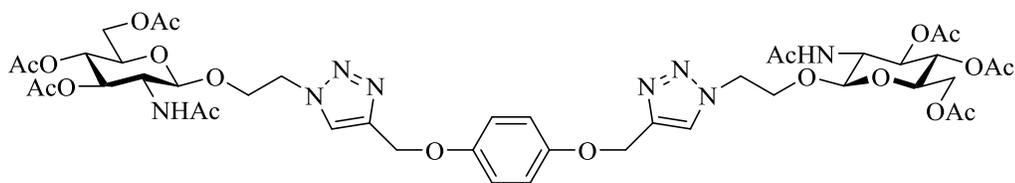
ES-HRMS calcd for C₇₈H₁₀₀N₁₆O₂₄S₄Na₁ 1795.5877, found m/z 1795.5903 [M+Na]⁺

IR (ATR) cm⁻¹: 3279, 1644, 1506, 1235, 1175, 1051, 1004, 830, 761

R_f: 0.62 (1:1 MeCN-H₂O) reverse phase

$[\alpha]_{\text{D}}^{20}$ +132.6 (*c* 0.33, DMSO)

1,4-Di[1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- β -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (100)



To a solution of sugar **81** (320 mg, 0.769 mmol) and *para*-bispropargyloxybenzene **83** (68 mg, 0.365 mmol) in a THF-H₂O (1:1, 12 mL) mixture was added sodium ascorbate (44 mg, 0.222 mmol) and copper sulphate pentahydrate (54 mg, 0.216 mmol). The mixture was stirred at r.t. for 18 h. Tetrahydrofuran was then removed under diminished pressure followed by the dilution of the solution with CH₂Cl₂. This mixture was then washed with water. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water, dried over NaSO₄ and the solvent removed *in vacuo*. Chromatography of the crude material (95:5 CH₂Cl₂-MeOH) gave the title compound (315 mg, 85%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 7.74 (s, 2H, CCH, triazole), 6.92 (s, 4H, Ar-H), 5.68 (d, *J* = 8.9 Hz, 2H, NH), 5.16 (dd, *J* = 10.7, 9.3 Hz, 2H, H-3), 5.13 (d, *J* = 2.5 Hz, 4H, ArOCH₂), 5.06 (t, *J* = 9.6 Hz, 2H, H-4), 4.62 (ddd, *J* = 14.5, 4.5, 2.9 Hz, 2H, OCH₂CH₂triazole), 4.55 (d, *J* = 8.4 Hz, 2H, H-1), 4.50 (ddd, *J* = 14.5, 9.0, 3.2 Hz, 2H, OCH₂CH₂triazole), 4.27 – 4.23 (m, 2H, OCH₂CH₂triazole), 4.23 (dd, *J* = 12.3, 4.7 Hz, 2H, H-6a), 4.13 (dd, *J* = 12.3, 2.4 Hz, 2H, H-6b), 3.94 (dt, *J* = 10.6, 8.6 Hz, 2H, H-2), 3.92 – 3.87 (m, 2H, OCH₂CH₂triazole), 3.67 (ddd, *J* = 10.0, 4.7, 2.4 Hz, 2H, H-5), 2.08 (s, 6H), 2.02 (s, 6H), 2.01 (s, 6H) (each OAc), 1.84 (s, 6H, NHAc).

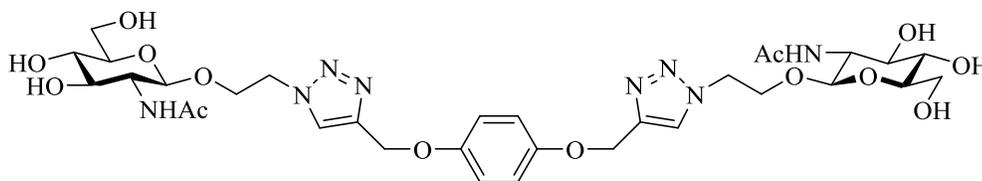
¹³C NMR (126 MHz, CDCl₃) δ 170.93, 170.62, 170.42, 169.30 (each C=O), 152.72 (Ar-C), 143.91 (CCH, triazole), 124.43 (CCH, triazole), 115.87 (Ar-CH), 100.73 (C-1), 72.17 (C-3), 71.98 (C-5), 68.28 (C-4), 67.32 (OCH₂CH₂triazole), 62.40 (CH₂OAr), 61.87 (C-6), 54.21 (C-2), 50.10 (OCH₂CH₂triazole), 23.18 (NHAc), 20.74, 20.63, 20.59 (each OAc).

ES-HRMS calcd for C₄₄H₅₈N₈O₂₀Na₁ 1041.3665, found *m/z* 1041.3674 [M+Na]⁺

IR (ATR) cm⁻¹: 1742, 1662, 1592, 1508, 1490, 1374, 1231, 1219, 1039, 1003, 734

R_f: 0.43 (2:23 MeOH-CH₂Cl₂)

1,4-Di[1-(ethyl 2-acetamido-2-deoxy- β -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (101)



Compound **100** (310 mg, 0.304 mmol) was stirred in methanol (30 mL) and to this was added a catalytic amount of a freshly prepared 1M NaOMe solution in MeOH (0.15 mL, 0.150 mmol). The resulting mixture was stirred for 1.5 h at r.t. at which point Amberlite IR-120 H⁺ was added and stirred gently for 10 mins, to neutralize (pH = 7) the solution. The resin was removed by filtration and washed with water and acetonitrile. The solvents were removed to a minimal amount of water. Reverse phase column chromatography was then carried out. The compound, in a minimal amount of water (made acidic and slightly heated, if solid crashes out, to return it to solution), was loaded onto the column, with the elution carried out as follows: 3 volumes of water were flushed through the column, to ensure salt removal, followed by a 1:1 MeCN-H₂O mixture. This gave the title compound (207 mg, 89%) as a colourless solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.05 (s, 2H, CCH, triazole), 7.62 (d, *J* = 9.0 Hz, 2H, NH), 6.97 (s, 4H, Ar-H), 5.03 (s, 4H, ArOCH₂), 4.55 (ddd, *J* = 14.5, 5.8, 3.8 Hz, 2H, OCH₂CH₂triazole), 4.49 (ddd, *J* = 14.5, 7.4, 3.8 Hz, 2H, OCH₂CH₂triazole), 4.31 (d, *J* = 8.5 Hz, 2H, H-1), 4.06 (ddd, *J* = 11.2, 5.8, 3.8 Hz, 2H, OCH₂CH₂triazole), 3.79 (ddd, *J* = 11.1, 7.4, 3.7 Hz, 2H, OCH₂CH₂triazole), 3.68 (dd, *J* = 11.9, 2.0 Hz, 2H, H-6a), 3.46 – 3.40 (m, 4H, H-2, H-6b), 3.25 (dd, *J* = 10.2, 8.3 Hz, 2H, H-3), 3.10 (ddd, *J* = 10.0, 5.9, 2.0 Hz, 2H, H-5), 3.05 (dd, *J* = 9.7, 8.3 Hz, 2H, H-4), 1.74 (s, 6H, NHAc).

¹³C NMR (126 MHz, DMSO) δ 169.67 (C=O), 152.80 (Ar-C), 143.07 (CCH, triazole), 125.40 (CCH, triazole), 115.97 (Ar-CH), 101.15 (C-1), 77.53 (C-5), 74.56 (C-3), 71.00 (C-4), 66.97 (OCH₂CH₂triazole), 62.01 (CH₂OAr), 61.48 (C-6), 55.55 (C-2), 49.96 (OCH₂CH₂triazole), 23.45 (NHAc).

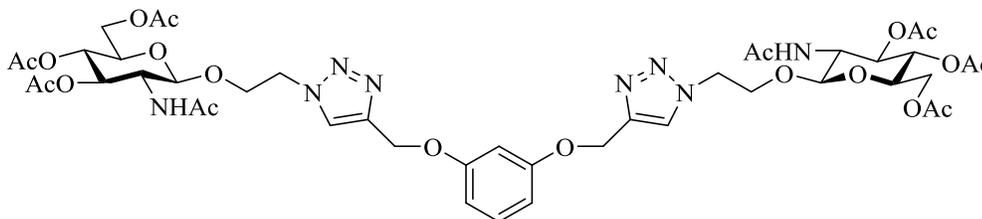
ES-HRMS calcd for C₃₂H₄₆N₈O₁₄Na₁ 789.3031, found *m/z* 789.3014 [M+Na]⁺

IR (ATR) cm⁻¹: 3283, 644, 1549, 1512, 1375, 1236, 1226, 1101, 1055, 1030, 822, 806, 708

*R*_f: 0.70 (1:1 MeCN-H₂O) reverse phase

[α]_D²⁰ -32.1 (*c* 0.41, DMSO)

1,3-Di[1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- β -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (102)



To a solution of sugar **81** (320 mg, 0.769 mmol) and *meta*-bispropargyloxybenzene **82** (68 mg, 0.365 mmol) in a THF-H₂O (1:1, 12 mL) mixture was added sodium ascorbate (44 mg, 0.222 mmol) and copper sulphate pentahydrate (54 mg, 0.216 mmol). The mixture was stirred at r.t. for 18 h. Tetrahydrofuran was then removed under diminished pressure followed by the dilution of the solution with CH₂Cl₂. This mixture was then washed with water. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water, dried over NaSO₄ and the solvent removed *in vacuo*. Chromatography of the crude material (95:5 CH₂Cl₂-MeOH) gave the title compound (311 mg, 84%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 7.76 (s, 2H, CCH, triazole), 7.21 (t, *J* = 8.2 Hz, 1H, Ar-H), 6.63 (dd, *J* = 8.2, 2.3 Hz, 2H, Ar-H), 6.58 (t, *J* = 2.4 Hz, 1H, Ar-H), 6.01 (d, *J* = 8.8 Hz, 2H, NH), 5.21 (dd, *J* = 10.6, 9.3 Hz, 2H, H-3), 5.20 – 5.12 (m, 4H, ArOCH₂), 5.03 (dd, *J* = 10.0, 9.3 Hz, 2H, H-4), 4.65 (d, *J* = 8.4 Hz, 2H, H-1), 4.64 – 4.59 (m, 2H, OCH₂CH₂triazole), 4.50 (ddd, *J* = 14.5, 9.0, 3.2 Hz, 2H, OCH₂CH₂triazole), 4.26 – 4.23 (m, 2H, OCH₂CH₂triazole), 4.21 (dd, *J* = 12.4, 4.8 Hz, 2H, H-6a), 4.12 (dd, *J* = 12.3, 2.4 Hz, 2H, H-6b), 3.91 (ddd, *J* = 11.2, 9.1, 2.9 Hz, 2H, OCH₂CH₂triazole), 3.87 (dt, *J* = 10.7, 8.6 Hz, 2H, H-2), 3.68 (ddd, *J* = 10.0, 4.8, 2.4 Hz, 2H, H-5), 2.08 (s, 6H), 2.01 (s, 6H), 2.01 (s, 6H) (each OAc), 1.84 (s, 6H, NHAc).

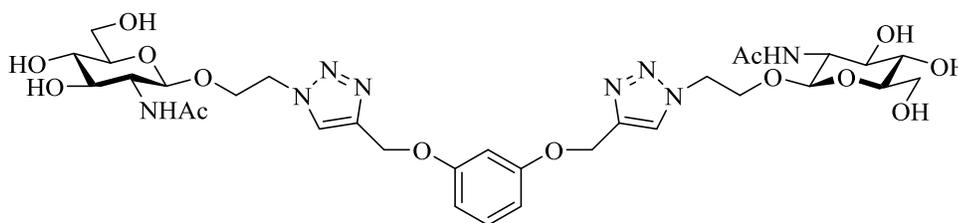
¹³C NMR (126 MHz, CDCl₃) δ 170.82, 170.61, 170.61, 169.33 (each C=O), 159.28 (Ar-C), 143.57 (CCH, triazole), 130.24 (Ar-CH), 124.54 (CCH, triazole), 107.88 (Ar-CH), 102.20 (Ar-CH), 100.59 (C-1), 72.09 (C-3), 71.92 (C-5), 68.43 (C-4), 67.30 (OCH₂CH₂triazole), 61.92 (CH₂OAr), 61.76 (C-6), 54.34 (C-2), 50.14 (OCH₂CH₂triazole), 23.16 (NHAc), 20.74, 20.64, 20.60 (each OAc).

ES-HRMS calcd for C₄₄H₅₈N₈O₂₀Na₁ 1041.3665, found *m/z* 1041.3691 [M+Na]⁺

IR (ATR) cm⁻¹: 1740, 1659, 1369, 1256, 1153, 1038, 733

R_f: 0.43 (2:23 MeOH-CH₂Cl₂)

1,3-Di[1-(ethyl 2-acetamido-2-deoxy- β -D-glucopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (103)



Compound **102** (303 mg, 0.297 mmol) was stirred in methanol (30 mL) and to this was added a catalytic amount of a freshly prepared 1M NaOMe solution in MeOH (0.15 mL, 0.150 mmol). The resulting mixture was stirred for 1 h at r.t. at which point Amberlite IR-120 H⁺ was added and stirred gently for 10 mins, to neutralize (pH = 7) the solution. The resin was removed by filtration and washed with water and acetonitrile. The solvents were removed to a minimal amount of water. Reverse phase column chromatography was then carried out. The compound, in a minimal amount of water (made acidic and slightly heated, if solid crashes out, to return it to solution), was loaded onto the column, with the elution carried out as follows: 3 volumes of water were flushed through the column, to ensure salt removal, followed by a 1:1 MeCN-H₂O mixture. This gave the title compound (146 mg, 64%) as a colourless solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.07 (s, 2H, CCH, triazole), 7.62 (d, *J* = 9.0 Hz, 2H NH), 7.20 (t, *J* = 8.2 Hz, 1H, Ar-H), 6.71 (t, *J* = 2.4 Hz, 1H, Ar-H), 6.63 (dd, *J* = 8.2, 2.3 Hz, 2H, Ar-H), 5.08 (s, 4H, ArOCH₂), 4.56 (ddd, *J* = 14.5, 5.8, 3.8 Hz, 2H, OCH₂CH₂triazole), 4.50 (ddd, *J* = 14.4, 7.4, 3.8 Hz, 2H, OCH₂CH₂triazole), 4.31 (d, *J* = 8.5 Hz, 2H, H-1), 4.06 (ddd, *J* = 11.2, 5.8, 3.8 Hz, 2H, OCH₂CH₂triazole), 3.80 (ddd, *J* = 11.1, 7.4, 3.8 Hz, 2H, OCH₂CH₂triazole), 3.68 (dd, *J* = 11.9, 2.0 Hz, 2H, H-6a), 3.46 – 3.39 (m, 4H, H-2, H-6b), 3.24 (dd, *J* = 10.3, 8.4 Hz, 2H, H-3), 3.10 (ddd, *J* = 9.8, 5.9, 2.0 Hz, 2H, H-5), 3.08 – 3.01 (m, 2H, H-4), 1.74 (s, 6H, NHAc).

¹³C NMR (126 MHz, DMSO) δ 169.68 (C=O), 159.74 (Ar-C), 142.79 (CCH, triazole), 130.47 (Ar-CH), 125.51 (CCH, triazole), 107.62 (Ar-CH), 102.00 (Ar-CH), 101.14 (C-1), 77.53 (C-5), 74.56 (C-3), 71.00 (C-4), 66.96 (OCH₂CH₂triazole), 61.59 (CH₂OAr), 61.49 (C-6), 55.55 (C-2), 49.98 (OCH₂CH₂triazole), 23.45 (NHAc).

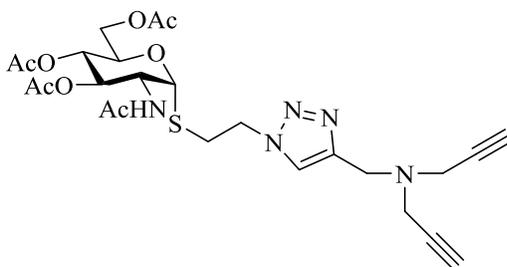
ES-HRMS calcd for C₃₂H₄₆N₈O₁₄Na₁ 789.3031, found *m/z* 789.3037 [M+Na]⁺

IR (ATR) cm⁻¹: 3269, 1644, 1605, 1547, 1294, 1185, 1161, 1054, 1028, 825, 765

*R*_f: 0.61 (1:1 MeCN-H₂O) reverse phase

[α]_D²⁰ -30.0 (*c* 0.34, DMSO)

***N*-[1-(1-(Ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-glucoopyranosyl)-1,2,3-triazol-4-ylmethyl)]-*N,N*-diprop-2-yn-1-amine (105)**



To a solution of sugar **78** (251 mg, 0.580 mmol) in a THF-H₂O (1:1, 10 mL) mixture was added sodium ascorbate (22 mg, 0.111 mmol) and copper sulphate pentahydrate (27 mg, 0.108 mmol) and tripropargylamine (26.5 μ l, 0.187 mmol). The mixture was stirred at r.t. for 18 h. Tetrahydrofuran was then removed under diminished pressure followed by the dilution of the solution with CH₂Cl₂. This mixture was then washed with water. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water, dried over NaSO₄ and the solvent removed *in vacuo*. Chromatography of the crude material (95:5 CH₂Cl₂-MeOH) gave three distinct compounds, the **mono-clicked** product, **105**, (52 mg, 49%) as a colourless solid, the di-clicked product (102 mg, 55%) as a colourless solid and the tri-clicked product (113 mg, 42%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 7.57 (s, 1H, CCH, triazole), 5.85 (d, *J* = 8.1 Hz, 1H, NH), 5.55 (d, *J* = 5.4 Hz, 1H, H-1), 5.11 (t, *J* = 9.6 Hz, 1H, H-4), 5.01 (dd, *J* = 11.2, 9.3 Hz, 1H, H-3), 4.57 (td, *J* = 6.8, 1.5 Hz, 2H, SCH₂CH₂triazole), 4.46 (ddd, *J* = 11.1, 8.1, 5.4 Hz, 1H, H-2), 4.30 (ddd, *J* = 9.9, 4.7, 2.1 Hz, 1H, H-5), 4.26 (dd, *J* = 12.2, 4.7 Hz, 1H, H-6a), 4.12 (dd, *J* = 12.3, 2.1 Hz, 1H, H-6b), 3.86 (s, 2H, NCH₂triazole), 3.46 (d, *J* = 2.4 Hz, 4H, NCH₂CCH), 3.16 (dt, *J* = 13.6, 6.7 Hz, 1H, SCH₂CH₂triazole), 3.07 (dt, *J* = 14.0, 6.9 Hz, 1H, SCH₂CH₂triazole), 2.27 (t, *J* = 2.4 Hz, 2H, NCH₂CCH), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H) (each OAc), 1.97 (s, 3H, NHAc).

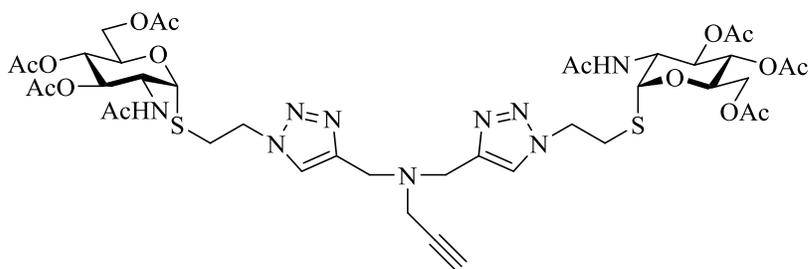
¹³C NMR (126 MHz, CDCl₃) δ 171.74, 170.54, 170.23, 169.22 (each C=O), 144.76 (CCH, triazole), 123.18 (CCH, triazole), 84.62 (C-1), 78.47 (NCH₂CCH), 73.49 (NCH₂CCH), 70.99 (C-3), 68.74 (C-5), 67.92 (C-4), 61.98 (C-6), 52.69 (C-2), 49.44 (SCH₂CH₂triazole), 47.99 (NCH₂triazole), 41.97 (NCH₂CCH), 31.48 (SCH₂CH₂triazole), 23.19 (NHAc), 20.70, 20.69, 20.57 (each OAc).

ES-HRMS calcd for C₂₅H₃₄N₅O₈S₁ 564.2128, found *m/z* 564.2116 [M+H]⁺

IR (ATR) cm⁻¹: 3280, 1742, 1665, 1367, 1227, 1090, 1040, 910, 729

R_f: 0.35 (1:19 MeOH-CH₂Cl₂)

***N,N*-Bis[1-(1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-glucoopyranosyl)-1,2,3-triazol-4-ylmethyl)]-*N*-prop-2-yn-1-amine (106)**



To a solution of sugar **78** (251 mg, 0.580 mmol) in a THF-H₂O (1:1, 10 mL) mixture was added sodium ascorbate (22 mg, 0.111 mmol) and copper sulphate pentahydrate (27 mg, 0.108 mmol) and tripropargylamine (26.5 μ l, 0.187 mmol). The mixture was stirred at r.t. for 18 h. Tetrahydrofuran was then removed under diminished pressure followed by the dilution of the solution with CH₂Cl₂. This mixture was then washed with water. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water, dried over NaSO₄ and the solvent removed *in vacuo*. Chromatography of the crude material (95:5 CH₂Cl₂-MeOH) gave three distinct compounds, the mono-clicked product (52 mg, 49%) as a colourless solid, the **di-clicked** product, **106**, (102 mg, 55%) as a colourless solid and the tri-clicked product (113 mg, 42%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 7.66 (s, 2H, CCH, triazole), 6.13 (d, J = 8.1 Hz, 2H, NH), 5.55 (d, J = 5.4 Hz, 2H, H-1), 5.10 (t, J = 9.6 Hz, 2H, H-4), 5.00 (dd, J = 11.2, 9.3 Hz, 2H, H-3), 4.64 – 4.51 (m, 4H, SCH₂CH₂triazole), 4.47 (ddd, J = 11.2, 8.1, 5.4 Hz, 2H, H-2), 4.30 (ddd, J = 9.9, 4.7, 2.2 Hz, 2H, H-5), 4.26 (dd, J = 12.2, 4.6 Hz, 2H, H-6a), 4.12 (dd, J = 12.2, 2.1 Hz, 2H, H-6b), 3.85 (d, J = 2.1 Hz, 4H, NCH₂triazole), 3.35 (dd, J = 6.7, 2.4 Hz, 2H, NCH₂CCH), 3.16 (dt, J = 14.2, 6.4 Hz, 2H, SCH₂CH₂triazole), 3.07 (dt, J = 14.0, 6.9 Hz, 2H, SCH₂CH₂triazole), 2.31 (t, J = 2.2 Hz, 1H, NCH₂CCH), 2.07 (s, 6H), 2.03 (s, 6H), 2.02 (s, 6H) (each OAc), 1.97 (s, 6H, NHAc).

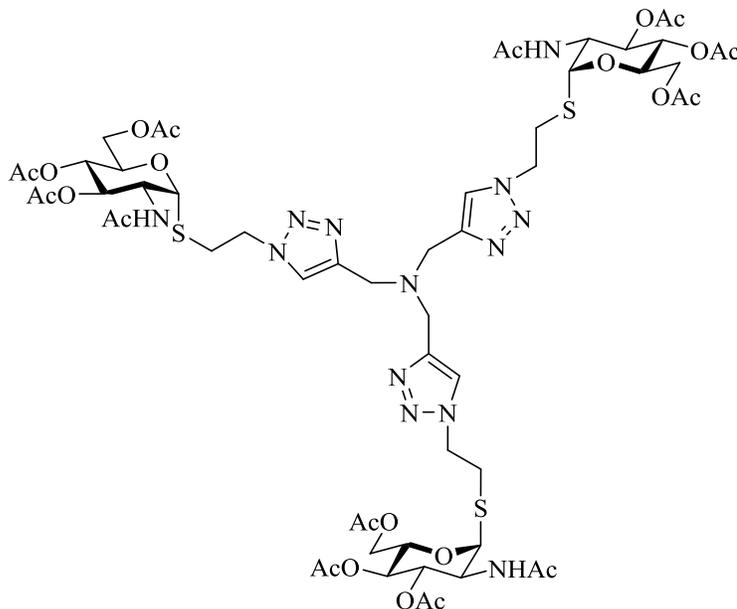
¹³C NMR (126 MHz, CDCl₃) δ 171.59, 170.57, 170.34, 169.26 (each C=O), 144.45 (CCH, triazole), 123.67 (CCH, triazole), 84.51 (C-1), 78.25 (NCH₂CCH), 73.96 (NCH₂CCH), 70.90 (C-3), 68.70 (C-5), 68.09 (C-4), 61.96 (C-6), 52.57 (C-2), 49.37 (SCH₂CH₂triazole), 47.76 (NCH₂triazole), 42.28 (NCH₂CCH), 31.40 (SCH₂CH₂triazole), 23.13 (NHAc), 20.71, 20.71, 20.58 (each OAc).

ES-HRMS calcd for C₄₁H₅₇N₉O₁₆S₂Na₁ 1018.3262, found m/z 1018.3289 [M+Na]⁺

IR (ATR) cm⁻¹: 1742, 1665, 1535, 1367, 1227, 1090, 1040, 910, 729

*R*_f: 0.25 (1:19 MeOH-CH₂Cl₂)

***N,N,N*-Tris[1-(1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-glucoopyranosyl)-1,2,3-triazol-4-ylmethyl)amine] (107)**



To a solution of sugar **78** (251 mg, 0.580 mmol) in a THF-H₂O (1:1, 10 mL) mixture was added sodium ascorbate (22 mg, 0.111 mmol) and copper sulphate pentahydrate (27 mg, 0.108 mmol) and tripropargylamine (26.5 μ l, 0.187 mmol). The mixture was stirred at r.t. for 18 h. Tetrahydrofuran was then removed under diminished pressure followed by the dilution of the solution with CH₂Cl₂. This mixture was then washed with water. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water, dried over NaSO₄ and the solvent removed *in vacuo*. Chromatography of the crude material (95:5 CH₂Cl₂-MeOH) gave three distinct compounds, the mono-clicked product (52 mg, 49%) as a colourless solid, the di-clicked product (102 mg, 55%) as a colourless solid and the **tri-clicked** product, **107**, (113 mg, 42%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 7.85 (s, 3H, CCH, triazole), 6.29 (d, *J* = 8.2 Hz, 3H, NH), 5.54 (d, *J* = 5.4 Hz, 3H, H-1), 5.09 (t, *J* = 9.6 Hz, 3H, H-4), 5.01 (dd, *J* = 11.1, 9.2 Hz, 3H, H-3), 4.60 (ddq, *J* = 20.8, 13.9, 6.5 Hz, 6H, SCH₂CH₂triazole), 4.48 (ddd, *J* = 11.1, 8.2, 5.4 Hz, 3H, H-2), 4.30 (ddd, *J* = 9.9, 4.6, 2.2 Hz, 3H, H-5), 4.26 (dd, *J* = 12.3, 4.6 Hz, 3H, H-6a), 4.12 (dd, *J* = 12.4, 2.2 Hz, 3H, H-6b), 3.74 (q, *J* = 14.2 Hz, 6H, NCH₂triazole), 3.18 (dt, *J* = 14.2, 6.3 Hz, 3H, SCH₂CH₂triazole), 3.09 (dt, *J* = 13.9, 6.8 Hz, 3H, SCH₂CH₂triazole), 2.07 (s, 9H), 2.02 (s, 9H), 2.00 (s, 9H) (each OAc), 1.97 (s, 9H, NHAc).

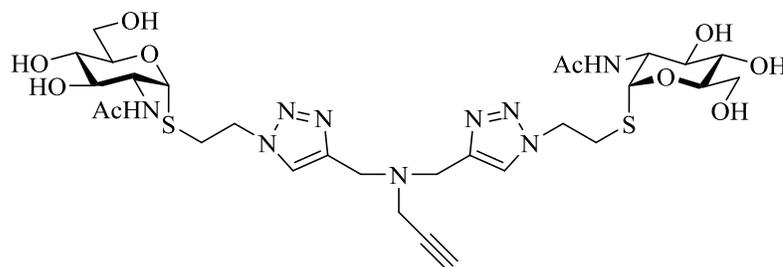
^{13}C NMR (126 MHz, CDCl_3) δ 171.48, 170.60, 170.42, 169.28 (each C=O), 143.65 (CCH, triazole), 124.44 (CCH, triazole), 84.55 (C-1), 70.84 (C-3), 68.67 (C-5), 68.20 (C-4), 61.97 (C-6), 52.47 (C-2), 49.47 ($\text{SCH}_2\text{CH}_2\text{triazole}$), 47.12 ($\text{NCH}_2\text{triazole}$), 31.40 ($\text{SCH}_2\text{CH}_2\text{triazole}$), 23.11 (NHAc), 20.72, 20.71 20.57 (each OAc) .

ES-HRMS calcd for $\text{C}_{57}\text{H}_{82}\text{N}_{13}\text{O}_{24}\text{S}_3$ 1428.4758, found m/z 1428.4789 $[\text{M}+\text{H}]^+$

IR (ATR) cm^{-1} : 1742, 1665, 1535, 1367, 1227, 1090, 1042, 912, 730

R_f : 0.18 (1:19 MeOH- CH_2Cl_2)

***N,N*-Bis[1-(1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-glucoopyranosyl)-1,2,3-triazol-4-ylmethyl)]-*N*-prop-2-yn-1-amine (108)**



Compound **106** (117 mg, 0.117 mmol) was stirred in methanol (15 mL) and to this a portion of a 1M NaOMe solution in MeOH (0.1 mL, 0.100 mmol) was added. The resulting mixture was stirred for 2 h at r.t. at which point Amberlite IR-120 H⁺ was added and stirred gently for 10 mins, to neutralize (pH = 7) the solution. The resin was removed by filtration and washed with water and acetonitrile. The solvents were removed to a minimal amount of water. Reverse phase column chromatography was then carried out. The compound, in a minimal amount of water (made acidic and slightly heated, if solid crashes out, to return it to solution), was loaded onto the column, with the elution carried out as follows: 3 volumes of water were flushed through the column, to ensure salt removal, followed by a 1:1 MeCN-H₂O mixture. This gave the title compound (52 mg, 60%) as an off-white solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 7.98 (s, 2H, CCH, triazole), 7.82 (d, *J* = 7.0 Hz, 2H, NH), 5.43 (d, *J* = 5.3 Hz, 2H, H-1), 5.11 (br s, 2H, OH), 4.80 (br s, 2H, OH), 4.63 (br s, 2H, OH), 4.56 (dt, *J* = 13.8, 6.9 Hz, 2H, SCH₂CH₂triazole), 4.48 (dt, *J* = 14.0, 7.1 Hz, 2H, SCH₂CH₂triazole), 3.79 (ddd, *J* = 11.7, 7.0, 5.2 Hz, 2H, H-2), 3.74 – 3.66 (m, 8H, H-5, H-6a, NCH₂triaz), 3.48 (dd, *J* = 12.0, 6.3 Hz, 2H, H-6b), 3.31 (m, 4H, H-3, NCH₂CCH), 3.11 (t, *J* = 9.3 Hz, 2H, H-4), 3.03 (dt, *J* = 13.9, 7.0 Hz, 2H, SCH₂CH₂triazole), 2.94 (dt, *J* = 13.8, 6.9 Hz, 2H, SCH₂CH₂triazole), 2.48 (m, 1H, NCH₂CCH) 1.80 (s, 6H, NHAc).

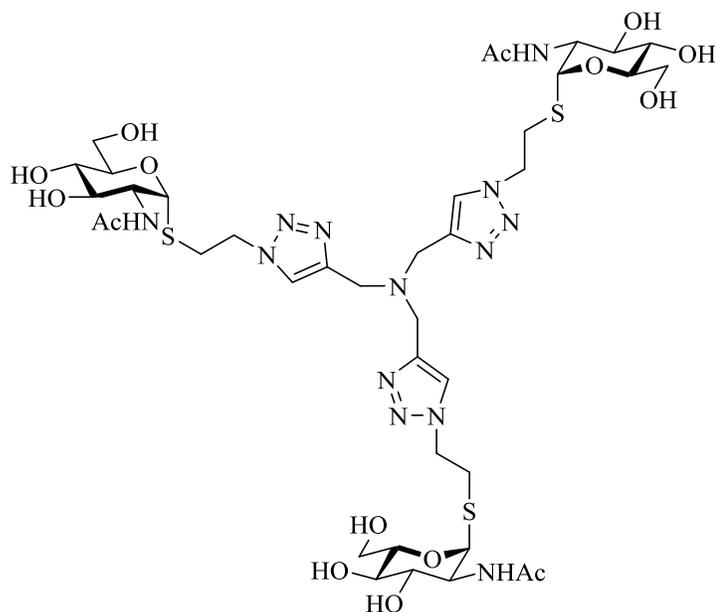
¹³C NMR (126 MHz, DMSO) δ 170.04 (C=O), 143.53 (CCH, triazole), 124.58 (CCH, triazole), 84.36 (C-1), 74.13 (C-5), 71.38 (C-4), 71.06 (C-3), 61.28 (C-6), 54.57 (C-2), 49.64 (SCH₂CH₂triazole), 47.78 (NCH₂triaz), 41.38 (NCH₂CCH), 40.49 (NCH₂CCH) 30.50 (SCH₂CH₂triazole), 23.01 (NHAc).

ES-HRMS calcd for C₂₉H₄₆N₉O₁₀S₂ 744.2809, found *m/z* 744.2811 [M+H]⁺

IR (ATR) cm⁻¹: 3278, 1645, 1544, 1431, 1373, 1299, 1097, 1051, 1030, 1005, 848, 761

[α]_D²⁰ 165.9 (*c* 0.14, DMSO)

***N,N,N*-Tris[1-(1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-glucoopyranosyl)-1,2,3-triazol-4-ylmethyl)]amine (109)**



Compound **107** (100 mg, 0.070 mmol) was stirred in methanol (12 mL) and to this a portion of a 1M NaOMe solution in MeOH (0.08 mL, 0.080 mmol) was added. The resulting mixture was stirred for 2 h at r.t. at which point Amberlite IR-120 H⁺ was added and stirred gently for 10 mins, to neutralize (pH = 7) the solution. The resin was removed by filtration and washed with water and acetonitrile. The solvents were removed to a minimal amount of water. Reverse phase column chromatography was then carried out. The compound, in a minimal amount of water (made acidic and slightly heated, if solid crashes out, to return it to solution), was loaded onto the column, with the elution carried out as follows: 3 volumes of water were flushed through the column, to ensure salt removal, followed by a 1:1 MeCN-H₂O mixture. This gave the title compound (44 mg, 59%) as a colourless solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.02 (s, 3H, CCH, triazole), 7.83 (d, *J* = 7.0 Hz, 3H, NH), 5.44 (d, *J* = 5.2 Hz, 3H, H-1), 5.11 (d, *J* = 5.6 Hz, 3H, OH-4), 4.81 (d, *J* = 5.7 Hz, 3H, OH-3), 4.65 (t, *J* = 5.8 Hz, 3H, OH-6), 4.58 (dt, *J* = 13.8, 6.9 Hz, 3H, SCH₂CH₂triazole), 4.50 (dt, *J* = 14.0, 7.1 Hz, 3H, SCH₂CH₂triazole), 3.79 (ddd, *J* = 11.8, 7.0, 5.3 Hz, 3H, H-2), 3.75 – 3.66 (m, 6H, H-5, H-6a), 3.61 (s, 6H, NCH₂triaz), 3.49 (dt, *J* = 11.9, 6.2 Hz, 3H, H-6b), 3.34 (ddd, *J* = 10.8, 8.7, 5.8 Hz, 3H, H-3), 3.11 (ddd, *J* = 9.9, 8.4, 5.6 Hz, 3H, H-4),

3.04 (dt, $J = 14.0, 7.1$ Hz, 3H, SCH₂CH₂triazole), 2.96 (dt, $J = 13.8, 7.0$ Hz, 3H, SCH₂CH₂triazole), 1.78 (s, 9H, NHAc).

¹³C NMR (126 MHz, DMSO) δ 170.04 (C=O), 143.67 (CCH, triazole), 124.58 (CCH, triazole), 84.41 (C-1), 74.15 (C-5), 71.39 (C-4), 71.08 (C-3), 61.29 (C-6), 54.59 (C-2), 49.68 (SCH₂CH₂triazole), 47.39 (NCH₂triaz), 30.55 (SCH₂CH₂triazole), 23.00 (NHAc).

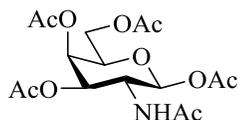
ES-HRMS calcd for C₄₀H₆₄N₁₃O₁₇S₃ 1094.3705, found m/z 1094.3727 [M+FA-H]⁻

IR (ATR) cm⁻¹: 3277, 1645, 1544, 1432, 1373, 1300, 1221, 1097, 1051, 1028, 1005, 848, 762

$[\alpha]_D^{20}$ 191.5 (*c* 0.14, DMSO)

4.4 Experimental data – Chapter 3

2-Acetamido-2-deoxy-1,3,4,6-tetra-*O*-acetyl- β -D-galactopyranose (110)²⁵



D-Galactosamine hydrochloride (8.00 g, 37.1 mmol) was stirred in pyridine (120 mL), and cooled to 0 °C. To this, acetic anhydride (30 mL, 317 mmol) was added slowly, portion wise. The reaction was allowed warm to room temperature and stirred overnight. The solvents were then removed by co-evaporation with toluene, which was carried out a number of times, until a colourless solid was formed. Recrystallisation of this solid from MeOH gave the title compound (11.2 g, 78%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 5.70 (d, J = 8.8 Hz, 1H, H-1), 5.37 (dd, J = 3.6, 1.2 Hz, 1H, H-4), 5.38 (d, J = 9.4 Hz, 1H, NH) 5.08 (dd, J = 11.3, 3.3 Hz, 1H, H-3), 4.45 (dt, J = 11.4, 9.2 Hz, 1H, H-2), 4.17 (dd, J = 11.4, 6.6 Hz, 1H, H-6a), 4.11 (dd, J = 11.3, 6.5 Hz, 1H, H-6b), 4.01 (td, J = 6.5, 1.2 Hz, 1H, H-5), 2.17 (s, 3H), 2.13 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), (each OAc) 1.94 (s, 3H, NHAc).

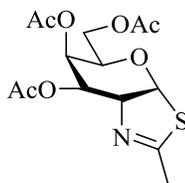
¹³C NMR (126 MHz, CDCl₃) δ 170.71, 170.36, 170.19, 170.12, 169.53 (each C=O), 93.04 (C-1), 71.88 (C-5), 70.30 (C-3), 66.31 (C-4), 61.27 (C-6), 49.83 (C-2), 23.31 (NHAc), 20.88, 20.65, 20.65, 20.62 (each OAc).

ES-HRMS calcd for C₁₆H₂₃N₁O₁₀Na₁ 412.1220, found m/z 412.1240 [M+Na]⁺

IR (ATR) cm⁻¹: 3256, 1752, 1738, 1645, 1215, 1077, 1041

R_f : 0.28 (1:19 MeOH-CH₂Cl₂)

$[\alpha]_D^{20}$ 22.2 (c 0.11, CHCl₃)

(3aR,5R,6R,7R,7aR)-5-(Acetoxymethyl)-6,7-diacetoxy-2-methyl-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole (111)²⁶

Compound **110** (1.00 g, 2.57 mmol) was dissolved in toluene (12 mL), and to this solution was added Lawessons reagent (890 mg, 2.20 mmol). The reaction flask was heated to 80 °C and then stirred at this temperature for 2.5 h. The reaction mixture was then cooled to r.t. and neutralised by the addition of NaHCO₃ (120 mg). Chromatography of the residue (3:7-1:1 EtOAc-CH₂Cl₂) gave the title compound (708 mg, 80%) as a yellow solid.

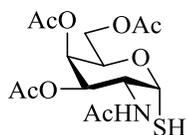
¹H NMR (500 MHz, CDCl₃) δ 6.25 (d, *J* = 6.3 Hz, 1H, H-1), 5.52 (t, *J* = 3.3 Hz, 1H, H-4), 5.21 (dd, *J* = 7.9, 3.3 Hz, 1H, H-3), 4.39 (ddq, *J* = 7.9, 6.3, 1.6 Hz, 1H, H-2), 4.30 (ddd, *J* = 7.4, 5.6, 3.4 Hz, 1H, H-5), 4.23 (dd, *J* = 11.5, 7.4 Hz, 1H, H-6a), 4.10 (dd, *J* = 11.3, 5.5 Hz, 1H, H-6b), 2.27 (d, *J* = 1.6 Hz, 3H, Thiaz CH₃), 2.14 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H) (each OAc).

¹³C NMR (126 MHz, CDCl₃) δ 170.54, 170.21, 169.80 (each C=O), 89.04 (C-1), 74.46 (C-2), 70.69 (C-3), 70.56 (C-5), 66.29 (C-4), 60.88 (C-6), 21.47 (Thiaz CH₃), 20.91, 20.71, 20.62 (each OAc).

ES-HRMS calcd for C₁₄H₂₀N₁O₇S₁ 346.0960, found *m/z* 346.0970 [M+H]⁺

IR (ATR) cm⁻¹: 1743, 1661, 1370, 1217, 1083, 1048, 1034, 733

R_f: 0.39 (1:19 MeOH-CH₂Cl₂)

2-Acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-1-thio- α -D-galactopyranose (112)²⁶

Compound **111** (545 mg, 1.58 mmol) was dissolved in MeOH (6 mL) and cooled to 0 °C. To this stirring solution was added TFA (12 drops) and H₂O (12 drops). The reaction was then allowed to come to r.t. and stirred for 2 h. The reaction was then concentrated under diminished pressure to give the title compound (573 mg, > 95%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 5.87 (dd, J = 6.4, 5.4 Hz, 1H, H-1), 5.70 (d, J = 8.5 Hz, 1H, NH), 5.41 (dd, J = 3.4, 1.3 Hz, 1H, H-4), 5.08 (dd, J = 11.7, 3.3 Hz, 1H, H-3), 4.75 (ddd, J = 11.6, 8.5, 5.1 Hz, 1H, H-2), 4.55 – 4.51 (m, 1H, H-5), 4.17 (dd, J = 11.3, 6.4 Hz, 1H, H-6a), 4.06 (dd, J = 11.3, 6.6 Hz, 1H, H-6b), 2.17 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.96 (d, J = 6.6 Hz, 1H, SH).

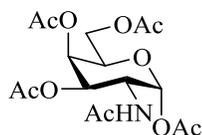
¹³C NMR (126 MHz, CDCl₃) δ 171.20, 170.63, 170.44, 170.19 (each C=O), 79.58 (C-1), 67.89 (C-3/C-5), 67.83 (C-3/C-5), 67.09 (C-4), 61.57 (C-6), 48.59 (C-2), 23.25 (NHAc), 20.75, 20.70, 20.68 (each OAc).

ES-HRMS calcd for C₁₄H₂₁N₁O₈Na₁S₁ 386.0886, found m/z 386.0883 [M+Na]⁺

IR (ATR) cm⁻¹: 3282, 2924, 1637, 1541, 1373, 1238, 1201, 1037, 701

R_f : 0.40 (2:23 MeOH-CH₂Cl₂)

$[\alpha]_D^{20}$ 97.4 (c 0.37, CHCl₃)

2-Acetamido-2-deoxy-1,3,4,6-tetra-*O*-acetyl- α -D-galactopyranose (113)²⁷

N-Acetyl-D-galactosamine (1.00 g, 4.52 mmol) was stirred in pyridine (25 mL), and cooled to 0 °C. To this, acetic anhydride (25 mL 264 mmol) was added slowly, portion wise. The reaction was allowed warm to room temperature and stirred overnight. The solvents were then removed by co-evaporation with toluene, a number of times, until it gave the title compound (1.76 g, > 95%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 6.22 (d, J = 3.6 Hz, 1H, H-1), 5.42 (dd, J = 3.4, 1.3 Hz, 1H, H-4), 5.39 (d, J = 9.3 Hz, 1H, NH), 5.22 (dd, J = 11.5, 3.2 Hz, 1H H-3), 4.73 (ddd, J = 11.6, 9.2, 3.7 Hz, 1H, H-2), 4.28 – 4.21 (m, 1H, H-5), 4.11 (dd, J = 11.3, 6.9 Hz, 1H, H-6a), 4.06 (dd, J = 11.3, 6.6 Hz, 1H, H-6b), 2.18 (s, 6H), 2.03 (s, 6H) (each OAc), 1.95 (s, 3H, NHAc).

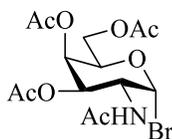
¹³C NMR (126 MHz, CDCl₃) δ 171.20, 170.35, 170.19, 169.97, 168.74 (each C=O), 91.35 (C-1), 68.54 (C-5), 67.82 (C-3), 66.68 (C-4), 61.27 (C-6), 46.99 (C-2), 23.19 (NHAc), 20.95, 20.74, 20.67, 20.63 (each OAc).

ES-HRMS calcd for C₁₈H₂₆N₂O₁₀Na₁ 453.1485, found m/z 453.1485 [M+MeCN+Na]⁺

IR (ATR) cm⁻¹: 1742, 1661, 1371, 1215, 1010, 913, 728

R_f : 0.29 (1:19 MeOH-CH₂Cl₂)

$[\alpha]_D^{20}$ 85.7 (c 0.11, CHCl₃)

2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- α -D-galactopyranosyl bromide (114)

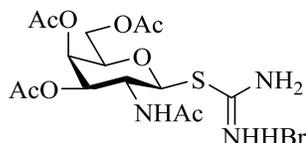
Compound **113** (1.76 g, 4.52 mmol) was dissolved in CH_2Cl_2 (25 mL) and cooled to 0 °C. To this solution was added, slowly, a 30% HBr-AcOH (6.5 mL) solution. The reaction was allowed to warm to r.t. and stirred for 3.5 h. The reaction mixture was then poured onto iced water with stirring and separated, washed with iced $\text{NaHCO}_3(\text{sat.})$, dried over NaSO_4 and concentrated under reduced pressure, which involved maintaining a rotary evaporator water bath temp < 30 °C. This gave the title compound (1.55 g, 84%) as a crude colourless solid. This unpurified solid should be used as soon as possible after preparation, so as to avoid degradation and thereby low yields in subsequent reactions.

^1H NMR (500 MHz, CDCl_3): δ 6.62 (d, $J = 3.6$ Hz, 1H, H-1), 5.75 (d, $J = 8.7$ Hz, 1H, NH), 5.47 (dd, $J = 3.3, 1.4$ Hz, 1H, H-4), 5.28 (dd, $J = 11.2, 3.3$ Hz, 1H, H-3), 4.60 (ddd, $J = 11.1, 8.8, 3.6$ Hz, 1H, H-2), 4.46 (t, $J = 6.6$ Hz, 1H, H-5), 4.21 (dd, $J = 11.5, 6.3$ Hz, 1H, H-6a), 4.10 (dd, $J = 11.4, 6.8$ Hz, 1H, H-6b), 2.16 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H) (each OAc), 2.02 (s, 3H, NHAc).

^{13}C NMR (126MHz, CDCl_3): δ 170.86, 170.42, 170.31, 169.94 (each C=O), 93.37 (C-1), 71.68 (C-5), 68.29 (C-3), 66.30 (C-4), 60.91 (C-6), 49.58 (C-2), 23.19 (NHAc), 20.69, 20.61, 20.61 (each OAc).

ES-HRMS calcd for $\text{C}_{14}\text{H}_{19}\text{N}_1\text{O}_8\text{Br}_1$ 408.0294, found m/z 408.0283 $[\text{M}-\text{H}]^-$

IR cm^{-1} : 1743, 1656, 1370, 1212, 1079, 1046, 913, 728

2-Acetamido-3,4,6-tri-*O*-acetyl- β -D-galactopyranosyl-1-isothiuronium bromide (115)

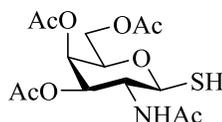
Compound **114** (1.30 g, 3.17 mmol) was dissolved in acetone (20 mL) to which was added thiourea (415 mg, 5.45 mmol). The reaction mixture was then heated to reflux (60 °C) and stirred for 2 h. The solid obtained was then filtered off with the filtrate returned to the reaction vessel and heated for an additional 2 h to ensure completion of reaction. The precipitate was dried under diminished pressure to give the title compound (1.22 g, 79%) as a colourless solid.

^1H NMR (500 MHz, DMSO) δ 9.15 (s, 2H, NH_2), 8.99 (s, 2H, NH_2), 8.27 (d, $J = 9.0$ Hz, 1H, NH), 5.45 (d, $J = 10.5$ Hz, 1H, H-1), 5.34 (d, $J = 3.1$ Hz, 1H, H-4), 5.00 (dd, $J = 10.9$, 3.2 Hz, 1H, H-3), 4.33 (t, $J = 6.2$ Hz, 1H, H-5), 4.13 (q, $J = 10.2$ Hz, 1H, H-2), 4.04 (t, $J = 5.9$ Hz, 2H, H-6a, H-6b), 2.11 (s, 3H), 1.99 (s, 3H), 1.92 (s, 3H) (each OAc), 1.81 (s, 3H, NHAc).

^{13}C NMR (126 MHz, DMSO) δ 170.55, 170.36, 170.32, 169.91 (each C=O), 167.81 (C= NH_2Br), 82.22 (C-1), 74.43 (C-5), 70.76 (C-3), 66.78 (C-4), 61.86 (C-6), 47.49 (C-2), 23.04 (NHAc), 21.02, 20.87, 20.86 (each OAc).

ES-HRMS calcd for calcd for $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}_8\text{S}_1\text{Br}_1$ 484.0389 found m/z 484.0399 $[\text{M-H}]^-$

IR cm^{-1} : 3056, 1747, 1640, 1551, 1374, 1224, 1213, 1080, 1035, 913

2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- β -D-galactopyranose (116)²⁸

Compound **115** (1.12 g, 2.30 mmol) and sodium metabisulphite (485 mg, 2.55 mmol) were stirred in a CH₂Cl₂-H₂O (3:2, 15 mL) mixture. This reaction solution was heated to reflux and stirred at this temperature for 3 h. The reaction mixture was allowed to cool and separated. The aqueous layer was re-extracted with CH₂Cl₂. The combined organic layers were then washed with H₂O, separated and dried over MgSO₄. The solvent was removed *in vacuo* to give the title compound (640 mg, 76%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃): δ 5.47 (d, J = 9.5 Hz, 1H, NH), 5.38 (dd, J = 3.5, 1.2 Hz, 1H, H-4), 5.05 (dd, J = 10.9, 3.3 Hz, 1H, H-3), 4.59 (dd, J = 10.0, 9.3 Hz, 1H, H-1), 4.28 (dt, J = 10.8, 9.7 Hz, 1H, H-2), 4.13 (dd, J = 6.6, 1.1 Hz, 2H, H-6a, H-6b), 3.91 (td, J = 6.6, 1.2 Hz, 1H, H-5), 2.61 (d, J = 9.2 Hz, 1H, SH), 2.17 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H) (each OAc), 1.99 (s, 3H, HNAc).

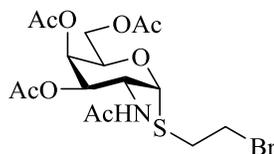
¹³C NMR (126 MHz, CDCl₃): δ 170.77, 170.52, 170.41, 170.19 (each C=O), 80.78 (C-1), 74.93 (C-5), 71.01 (C-3), 66.76 (C-4), 61.63 (C-6), 53.22 (C-2), 23.40 (NHAc), 20.71, 20.69, 20.66 (each OAc).

ES-HRMS calcd for C₁₄H₂₁N₁O₈Na₁S₁ 386.0886, found m/z 386.0889 [M+Na]⁺

IR cm⁻¹: 3286, 1743, 1661, 1542, 1370, 1227, 1083, 1049, 732

R_f : 0.33 (1:19 MeOH-CH₂Cl₂)

$[\alpha]_D^{20}$ -1.2 (c 0.68, CHCl₃)

2-Bromoethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-galactopyranoside (117)

Compound **112** (2.50 g, 6.88 mmol) was dissolved in an acetone-H₂O (2:1, 30 mL) mixture and to this was added potassium carbonate (1.13 g, 8.18 mmol) and 1,2 dibromoethane (4.8 mL, 55.5 mmol). This mixture was stirred at r.t. for 3 h after which point it was diluted with CH₂Cl₂. The layers were separated, with the aqueous layer being re-extracted with a further portion of CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and then concentrated under diminished pressure. Chromatography (EtOAc-Pet Ether, 1:3) gave the title compound (2.25 g, 69%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃): 5.60 (d, *J* = 5.3 Hz, 1H, H-1), 5.60 (d, *J* = 8.5 Hz, 1H, NH), 5.38 (dd, *J* = 3.3, 1.3 Hz, 1H, H-4), 5.03 (dd, *J* = 11.8, 3.3 Hz, 1H, H-3), 4.75 (ddd, *J* = 11.8, 8.5, 5.3 Hz, 1H, H-2), 4.60 – 4.50 (m, 1H, H-5), 4.13 (dd, *J* = 11.5, 5.3 Hz, 1H, H-6a), 4.09 (dd, *J* = 11.5, 7.4 Hz, 1H, H-6b), 3.59 (td, *J* = 10.0, 5.7 Hz, 1H, SCH₂CH₂Br), 3.48 (td, *J* = 10.0, 6.1 Hz, 1H, SCH₂CH₂Br), 3.10 (ddd, *J* = 13.9, 10.1, 6.1 Hz, 1H, SCH₂CH₂Br), 3.01 (ddd, *J* = 13.9, 10.1, 5.7 Hz, 1H, SCH₂CH₂Br), 2.16 (s, 3H), 2.07 (s, 3H), 2.01 (s, 3H) (each OAc), 1.97 (s, 3H, NHAc).

¹³C NMR (126 MHz, CDCl₃): δ 171.05, 170.37, 170.17, 170.14 (each C=O), 85.60 (C-1), 68.21 (C-3), 67.69 (C-5), 67.29 (C-4), 62.16 (C-6), 48.50 (C-2), 33.60 (SCH₂CH₂Br), 30.28 (SCH₂CH₂Br), 23.29 (NHAc), 20.72, 20.70, 20.66 (each OAc).

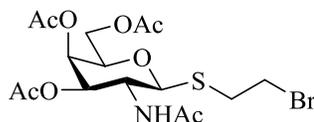
ES-HRMS calcd for C₁₆H₂₄N₁O₈Na₁S₁Br₁ 492.0304, found *m/z* 492.0321 [M+Na]⁺

IR cm⁻¹: 1746, 1663, 1543, 1371, 1230, 1083, 1049

*R*_f: 0.48 (3:47 MeOH-CH₂Cl₂)

[α]_D²⁰ 126.1 (*c* 0.19, CHCl₃)

2-Bromoethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- β -D-galactopyranoside (118)



Compound **116** (802 mg, 2.21 mmol) was dissolved in an acetone-H₂O (2:1, 15 mL) mixture. To this solution was added potassium carbonate (361 mg, 2.61 mmol) and 1,2-dibromoethane (1.6 mL, 18.6 mmol). This mixture was stirred at r.t. overnight after which point it was diluted with CH₂Cl₂. The layers were separated, with the aqueous layer being re-extracted with a further portion of CH₂Cl₂. The combined organic layers were washed with water and dried over Na₂SO₄ and then concentrated under diminished pressure. Chromatography (MeOH-CH₂Cl₂: 5:95-7:93) gave the title compound (817 mg, 79%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃): δ 5.42 – 5.38 (m, 2H, NH, H-4), 5.14 (dd, J = 10.8, 3.3 Hz, 1H, H-3), 4.70 (d, J = 10.3 Hz, 1H, H-1), 4.23 (td, J = 10.5, 9.2 Hz, 1H, H-2), 4.13 – 4.11 (m, 2H, H-6a, H-6b), 3.93 (ddd, J = 7.1, 6.0, 1.2 Hz, 1H, H-5), 3.62 (ddd, J = 11.0, 9.8, 5.6 Hz, 1H, SCH₂CH₂Br), 3.54 (ddd, J = 11.0, 9.8, 5.6 Hz, 1H, SCH₂CH₂Br), 3.23 (ddd, J = 14.0, 11.0, 5.6 Hz, 1H, SCH₂CH₂Br), 3.01 (ddd, J = 14.0, 11.0, 5.6 Hz, 1H, SCH₂CH₂Br), 2.17 (s, 3H), 2.08 (s, 3H), 2.01 (s, 3H) (each OAc), 1.97 (s, 3H, NHAc).

¹³C NMR (126 MHz, CDCl₃): δ 170.63, 170.46, 170.24, 170.15 (each C=O), 85.64 (C-1), 74.78 (C-5), 70.96 (C-3), 66.90 (C-4), 61.90 (C-6), 49.75 (C-2), 33.03 (SCH₂CH₂Br), 30.90 (SCH₂CH₂Br), 23.37 (NHAc), 20.71, 20.71, 20.65 (each OAc).

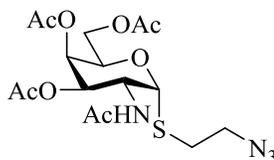
ES-HRMS calcd for C₁₆H₂₄BrN₁O₈S₁Na₁ 492.0304, found m/z 492.0300 [M+Na]⁺

IR cm⁻¹: 1743, 1656, 1547, 1435, 1370, 1225, 1082, 1047, 1034, 920

R_f : 0.42 (1:19 MeOH-CH₂Cl₂)

$[\alpha]_D^{20}$ -26.9 (c 0.19, CHCl₃)

2-Azidoethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-galactopyranoside (119)



Compound **117** (2.20 g, 4.68 mmol) was dissolved in DMF (35 mL) and to this was added tetrabutylammonium iodide (1.75 g, 4.74 mmol) and sodium azide (1.23 g, 18.9 mmol). The reaction was heated to 80 °C and stirred overnight at this temperature. The reaction was then allowed to cool, after which it was diluted with CH₂Cl₂ and washed a number of times with H₂O, to remove the DMF. The organic layer was dried over Na₂SO₄ and then concentrated under diminished pressure. Chromatography (EtOAc-Pet Ether, 1:3-1:1) gave the title compound (1.76 g, 87%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃): 5.66 (d, *J* = 8.5 Hz, 1H, NH), 5.60 (d, *J* = 5.3 Hz, 1H, H-1), 5.39 (dd, *J* = 3.5, 1.2 Hz, 1H, H-4), 5.05 (dd, *J* = 11.7, 3.2 Hz, 1H, H-3), 4.76 (ddd, *J* = 11.7, 8.5, 5.3 Hz, 1H, H-2), 4.57 – 4.52 (m, 1H, H-5), 4.14 (dd, *J* = 11.4, 5.8 Hz, 1H, H-6a), 4.08 (dd, *J* = 11.4, 7.0 Hz, 1H, H-6b), 3.53 (dt, *J* = 13.4, 6.8 Hz, 1H, SCH₂CH₂N₃), 3.50 – 3.44 (m, 1H, SCH₂CH₂N₃), 2.87 (dt, *J* = 13.7, 6.8 Hz, 1H, SCH₂CH₂N₃), 2.77 (dt, *J* = 13.6, 6.6 Hz, 1H, SCH₂CH₂N₃), 2.15 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H) (each OAc), 1.97 (s, 3H, NHAc).

¹³C NMR (126 MHz, CDCl₃): δ ¹³C NMR (126 MHz, cdcl₃) δ 171.02, 170.32, 170.23, 170.16 (each C=O), 85.29 (C-1), 68.23 (C-3), 67.56 (C-5), 67.25 (C-4), 61.95 (C-6), 50.86 (SCH₂CH₂N₃), 48.44 (C-2), 30.64 (SCH₂CH₂N₃), 23.27 (NHAc), 20.72, 20.66, 20.65 (each OAc).

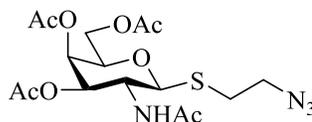
ES-HRMS calcd for C₁₆H₂₄N₄O₈Na₁S₁ 455.1213, found *m/z* 455.1222 [M+Na]⁺

IR cm⁻¹: 2103, 1744, 1661, 1537, 1369, 1217, 1081, 1046, 734

R_f: 0.57 (3:47 MeOH-CH₂Cl₂)

[α]_D²⁰ 156.6 (*c* 0.35, CHCl₃)

2-Azidoethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- β -D-galactopyranoside (120)



Compound **118** (190 mg, 0.404 mmol) was dissolved in DMF (5 mL) and to this was added tetrabutylammonium iodide (164 mg, 0.444 mmol) and sodium azide (105 mg, 1.62 mmol). The reaction was heated to 80 °C and stirred at this temperature overnight. The reaction was then allowed to cool, after which it was diluted with CH₂Cl₂ and washed, a number of times, with H₂O, to remove the DMF. The organic layer was dried over Na₂SO₄ and then concentrated under diminished pressure. Chromatography (EtOAc-Pet Ether, 1:3-1:1) gave the title compound (138 mg, 79%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃): δ 5.40 (dd, $J = 3.2, 1.0$ Hz, 1H, H-4), 5.38 (d, $J = 9.5$ Hz, 1H, NH), 5.14 (dd, $J = 10.8, 3.3$ Hz, 1H, H-3), 4.68 (d, $J = 10.3$ Hz, 1H, H-1), 4.26 (q, $J = 10.4$ Hz, 1H, H-2), 4.19 – 4.05 (m, 2H, H-6a, H-6b), 3.93 (td, $J = 6.5, 1.2$ Hz, 1H, H-5), 3.56 (dt, $J = 13.5, 6.8$ Hz, 1H, SCH₂CH₂N₃), 3.50 (dt, $J = 12.6, 7.0$ Hz, 1H, SCH₂CH₂N₃), 3.02 (dt, $J = 14.0, 7.0$ Hz, 1H, SCH₂CH₂N₃), 2.81 (ddd, $J = 13.8, 7.2, 6.3$ Hz, 1H, SCH₂CH₂N₃), 2.17 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H) (each OAc), 1.98 (s, 3H, NHAc).

¹³C NMR (126 MHz, CDCl₃): δ 170.64, 170.40, 170.27, 170.15 (each C=O), 85.14 (C-1), 74.76 (C-5), 71.07 (C-3), 66.88 (C-4), 61.71 (C-6), 51.62 (SCH₂CH₂N₃), 49.62 (C-2), 29.66 (SCH₂CH₂N₃), 23.39 (NHAc), 20.72, 20.66, 20.66 (each OAc).

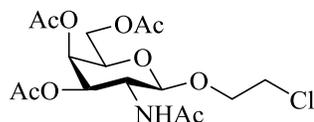
ES-HRMS calcd for C₁₆H₂₄N₄O₈S₁Na₁ 455.1213, found m/z 455.1201 [M+Na]⁺

IR cm⁻¹: 2102, 1743, 1659, 1542, 1370, 1300, 1225, 1081, 1034, 919

R_f : 0.42 (1:19 MeOH-CH₂Cl₂)

$[\alpha]_D^{20}$ -48.5 (c 0.17, CHCl₃)

2-Chloroethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- β -D-galactopyranoside (121)



Sugar **110** (2.00 g, 5.14 mmol) was dissolved in 1,2-dichloroethane (10 mL) in a microwave vial equipped with a stir bar and to this mixture was added H₂SO₄-silica (37 mg) and 2-chloroethanol (0.43 mL, 6.41 mmol). This mixture was then heated and stirred under microwave conditions at 110 °C for 15 mins. The reaction was then filtered through Celite, with the plug being flushed clear with CH₂Cl₂, to ensure complete recovery of product. The filtrate was then washed with NaHCO₃(sat.), brine, dried over NaSO₄ and concentrated under reduced pressure. Column chromatography (EtOAc-Pet Ether, 1:3-1:1-2:1-100% EtOAc) gave the title compound (1.69 g, 80%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃): δ 5.41 (d, J = 8.7 Hz, 1H, NH), 5.37 (dd, J = 3.5, 1.1 Hz, 1H, H-4), 5.31 (dd, J = 11.2, 3.4 Hz, 1H, H-3), 4.81 (d, J = 8.4 Hz, 1H H-1), 4.24 – 4.06 (m, 3H, H-6a, H-6b, OCH₂CH₂Cl), 3.97 (dt, J = 11.2, 8.5 Hz, 1H, H-2), 3.92 (dd, J = 6.5, 1.3 Hz, 1H, H-5), 3.79 (dt, J = 11.4, 6.3 Hz, 1H, OCH₂CH₂Cl), 3.65 (dd, J = 6.3, 4.9 Hz, 2H, OCH₂CH₂Cl), 2.15 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H) (each OAc), 1.98 (s, 3H, NHAc).

¹³C NMR (126 MHz, CDCl₃): δ 170.54, 170.38, 170.38, 170.16 (each C=O), 101.26 (C-1), 70.84 (C-5), 69.70 (C-3), 69.65 (OCH₂CH₂Cl), 66.70 (C-4), 61.40 (C-6), 51.63 (C-2), 43.01 (OCH₂CH₂Cl), 23.50 (NHAc), 20.68, 20.67, 20.65 (each OAc).

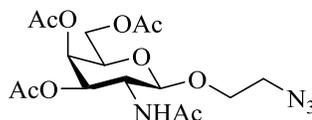
ES-HRMS calcd for C₁₆H₂₄Cl₁N₁O₉Na₁ 432.1037, found m/z 432.1024 [M+Na]⁺

IR cm⁻¹: 1744, 1662, 1556, 1370, 1227, 1168, 1136, 1080, 1046, 923

R_f : 0.48 (1:19 MeOH-CH₂Cl₂)

$[\alpha]_D^{20}$ -17.1 (c 0.13, CHCl₃)

2-Azidoethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- β -D-galactopyranoside (122)



Sugar **121** (1.68 g, 4.10 mmol) was dissolved in DMF (25 mL) and to this tetrabutylammonium iodide (1.59 g, 4.30 mmol) and sodium azide (1.07 g, 16.5 mmol) was added. The reaction was then heated to 80 °C and stirred at this temperature overnight. The reaction was cooled, diluted with CH₂Cl₂ and washed with water. Aqueous layer re-extracted with a portion of CH₂Cl₂. The combined organic layers were then washed with successive portions of water, with no re-extraction of any of these aqueous layers. The organic layer was then washed with brine, dried over NaSO₄ and the solvent then removed under diminished pressure. Chromatography (EtOAc-Pet Ether, 1:3-1:1-2:1-100% EtOAc) gave the title compound (1.35 g, 79%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃-*d*) δ 5.59 (d, *J* = 8.5 Hz, 1H, NH), 5.41 – 5.33 (m, 2H, H-3, H-4), 4.86 (d, *J* = 8.4 Hz, 1H, H-1), 4.16 (dd, *J* = 11.2, 6.6 Hz, 1H, H-6a), 4.12 (dd, *J* = 11.3, 6.7 Hz, 1H, H-6b), 4.07 (ddd, *J* = 10.8, 4.7, 3.4 Hz, 1H, OCH₂CH₂N₃), 3.95 (t, *J* = 6.4 Hz, 2H, H-5), 3.94 – 3.88 (m, 1H, H-2), 3.71 (ddd, *J* = 11.2, 8.6, 3.1 Hz, 1H, OCH₂CH₂N₃), 3.52 (ddd, *J* = 13.5, 8.6, 3.3 Hz, 1H, OCH₂CH₂N₃), 3.27 (ddd, *J* = 13.5, 4.7, 3.1 Hz, 1H, OCH₂CH₂N₃), 2.14 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H) (each OAc), 1.96 (s, 3H, NHAc).

¹³C NMR (126 MHz, CDCl₃): δ 170.63, 170.41, 170.33, 170.19 (each C=O), 100.61 (C-1), 70.81 (C-5), 69.54 (C-3), 68.36 (OCH₂CH₂N₃), 66.80 (C-4), 61.44 (C-6), 51.76 (C-2), 50.62 (OCH₂CH₂N₃), 23.47 (NHAc).

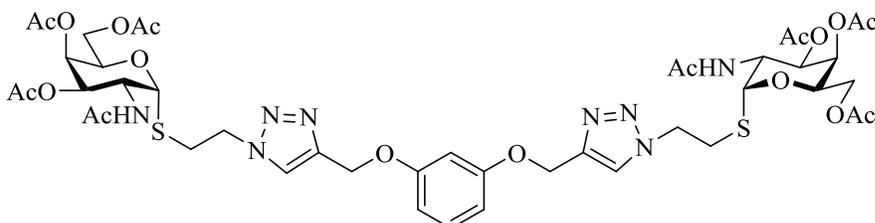
ES-HRMS calcd for C₁₆H₂₄N₄O₉Na₁ 439.1441, found *m/z* 439.1431 [M+Na]⁺

IR cm⁻¹: 2105, 1742, 1661, 1548, 1433, 1369, 1223, 1167, 1136, 1046, 932

R_f: 0.38 (1:19 MeOH-CH₂Cl₂)

[α]_D²⁰ -28.4 (*c* 0.36, CHCl₃)

1,3-Di[1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (123)



To a solution of sugar **119** (335 mg, 0.775 mmol) and *meta*-bispropargyloxybenzene **82** (65 mg, 0.349 mmol) in a THF-H₂O (1:1, 12 mL) mixture was added sodium ascorbate (42 mg, 0.212 mmol) and copper sulphate pentahydrate (52 mg, 0.208 mmol). The mixture was stirred at r.t. for 18 h. Tetrahydrofuran was then removed under diminished pressure followed by the dilution of the solution with CH₂Cl₂. This mixture was then washed with water. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water, dried over NaSO₄ and the solvent removed *in vacuo*. Chromatography of the crude material (95:5 CH₂Cl₂-MeOH) gave the title compound (344 mg, 94%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 7.70 (s, 2H, CCH, triazole), 7.18 (t, *J* = 8.2 Hz, 1H, Ar-H), 6.62 (dd, *J* = 8.2, 2.3 Hz, 2H, Ar-H), 6.58 (t, *J* = 2.3 Hz, 1H, Ar-H), 5.96 (d, *J* = 8.0 Hz, 2H, NH), 5.67 (d, *J* = 5.4 Hz, 2H, H-1), 5.38 (dd, *J* = 3.3, 1.3 Hz, 2H, H-4), 5.21 (s, 4H, CH₂OAr), 4.99 (dd, *J* = 11.8, 3.2 Hz, 2H, H-3), 4.73 (ddd, *J* = 11.8, 8.0, 5.3 Hz, 2H, H-2), 4.65 – 4.53 (m, 4H, SCH₂CH₂triazole), 4.45 (td, *J* = 6.4, 1.5 Hz, 2H, H-5), 4.10 (dd, *J* = 6.3, 1.8 Hz, 4H, H-6a, H-6b), 3.18 (dt, *J* = 13.6, 6.7 Hz, 2H, SCH₂CH₂triazole), 3.07 (dt, *J* = 13.8, 6.7 Hz, 2H, SCH₂CH₂triazole), 2.16 (s, 6H), 2.01 (s, 6H), 1.98 (s, 6H) (each OAc), 1.98 (s, 6H, NHAc).

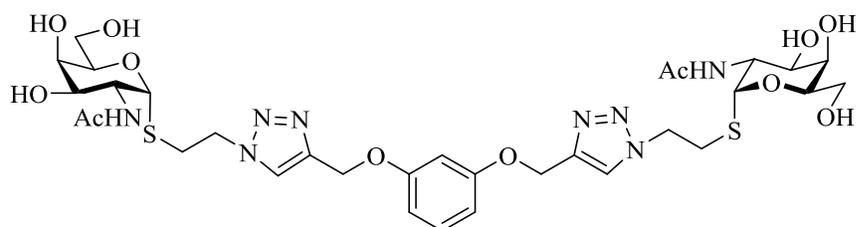
¹³C NMR (126 MHz, CDCl₃) δ 170.96, 170.53, 170.35, 170.12 (each C=O), 159.28 (Ar-C), 144.16 (CCH, triazole), 130.11 (Ar-CH), 123.27 (CCH, triazole), 108.17 (Ar-CH), 102.03 (Ar-CH), 85.24 (C-1), 68.14 (C-3), 67.61 (C-5), 67.11 (C-4), 62.09 (C-6), 62.09 (CH₂OAr), 49.67 (SCH₂CH₂triazole), 48.53 (C-2), 31.38 (SCH₂CH₂triazole), 23.22 (NHAc), 20.73, 20.66, 20.62 (each OAc).

ES-HRMS calcd for C₄₄H₅₇N₈O₁₈S₂, found *m/z* 1049.3232 [M-H]⁻

IR (ATR) cm⁻¹: 1745, 1664, 1542, 1370, 1227, 1152, 1083, 1050, 1033, 735

R_f: 0.52 (2:23 MeOH-CH₂Cl₂)

1,3-Di[1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (124)



Compound **123** (327 mg, 0.311 mmol) was stirred in methanol (30 mL) and to this was added a catalytic amount of a freshly prepared 1M NaOMe solution in MeOH (0.16 mL, 0.160 mmol). The resulting mixture was stirred for 1.5 h at r.t. at which point Amberlite IR-120 H⁺ was added and stirred gently for 10 mins, to neutralize (pH = 7) the solution. The resin was removed by filtration and washed with water and acetonitrile. The solvents were removed to a minimal amount of water. Reverse phase column chromatography was then carried out. The compound, in a minimal amount of water (made acidic and slightly heated, if solid crashes out, to return it to solution), was loaded onto the column, with the elution carried out as follows: 3 volumes of water were flushed through the column, to ensure salt removal, followed by a 1:1 MeCN-H₂O mixture. This gave the title compound (230 mg, 92%) as a colourless solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.20 (s, 2H, CCH, triazole), 7.74 (d, *J* = 7.1 Hz, 2H, NH), 7.18 (t, *J* = 8.2 Hz, 1H, Ar-H), 6.70 (t, *J* = 2.4 Hz, 1H, Ar-H), 6.62 (dd, *J* = 8.3, 2.3 Hz, 2H, Ar-H), 5.50 (d, *J* = 5.3 Hz, 2H, H-1), 5.09 (s, 4H, CH₂OAr), 4.69 (d, *J* = 5.6 Hz, 2H, OH-6), 4.67 (d, *J* = 4.7 Hz, 2H, OH-4), 4.61 – 4.56 (m, 4H, OH-3, SCH₂CH₂triazole), 4.52 (td, *J* = 13.9, 13.5, 6.5 Hz, 2H, SCH₂CH₂triazole), 4.17 (ddd, *J* = 11.9, 6.9, 5.5 Hz, 2H, H-2), 3.90 (t, *J* = 6.0 Hz, 2H, H-5), 3.73 – 3.69 (m, 2H, H-4), 3.53 (td, *J* = 5.7, 1.3 Hz, 4H, H-6a, H-6b), 3.48 (ddd, *J* = 10.8, 6.8, 3.0 Hz, 2H, H-3), 3.03 (dt, *J* = 13.9, 7.0 Hz, 2H, SCH₂CH₂triazole), 2.93 (dt, *J* = 13.8, 6.9 Hz, 2H, SCH₂CH₂triazole), 1.79 (s, 6H, NHAc).

¹³C NMR (126 MHz, DMSO) δ 170.21 (C=O), 159.73 (Ar-C), 142.83 (CCH, triazole), 130.45 (Ar-CH), 125.22 (CCH, triazole), 107.69 (Ar-CH), 102.04 (Ar-CH), 84.82 (C-1), 72.69 (C-5), 68.55 (C-4), 67.93 (C-3), 61.61 (CH₂OAr), 61.37 (C-6), 50.47 (C-2), 49.77(SCH₂CH₂triazole), 30.34 (SCH₂CH₂triazole), 23.09 (NHAc).

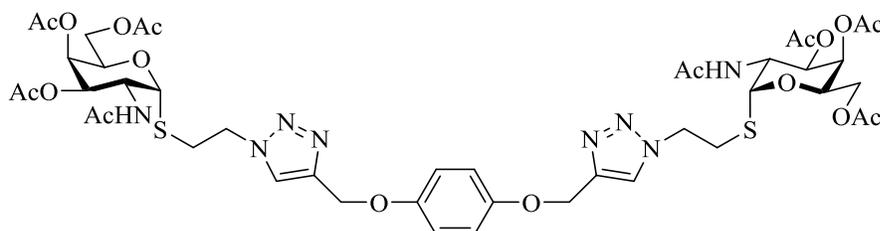
ES-HRMS calcd for C₃₂H₄₆N₈O₁₂S₂Na₁ 821.2574, found *m/z* 821.2555 [M+Na]⁺

IR (ATR) cm⁻¹: 3279, 1637, 1596, 1548, 1491, 1283, 1150, 1116, 1044, 1023, 801

*R*_f: 0.60 (1:1 MeCN-H₂O) reverse phase

[α]_D²⁰ +176.4 (*c* 0.25, DMSO)

1,4-Di[1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (125)



To a solution of sugar **119** (335 mg, 0.775 mmol) and *para*-bispropargyloxybenzene **83** (65 mg, 0.349 mmol) in a THF-H₂O (1:1, 12 mL) mixture was added sodium ascorbate (42 mg, 0.212 mmol) and copper sulphate pentahydrate (51 mg, 0.208 mmol). The mixture was stirred at r.t. for 20 h. Tetrahydrofuran was then removed under diminished pressure followed by the dilution of the solution with CH₂Cl₂. This mixture was then washed with water. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water, dried over NaSO₄ and the solvent removed *in vacuo*. Chromatography of the crude material (95:5 CH₂Cl₂-MeOH) gave the title compound (363 mg, 99%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 7.66 (s, 2H, CCH, triazole), 6.90 (s, 4H, Ar-H), 5.75 (d, *J* = 8.1 Hz, 2H, NH), 5.65 (d, *J* = 5.3 Hz, 2H, H-1), 5.38 (dd, *J* = 3.4, 1.3 Hz, 2H, H-4), 5.18 (s, 4H, CH₂OAr), 5.00 (dd, *J* = 11.8, 3.2 Hz, 2H, H-3), 4.73 (ddd, *J* = 11.8, 8.0, 5.3 Hz, 2H, H-2), 4.61 (dt, *J* = 13.7, 6.8 Hz, 2H, SCH₂CH₂triazole), 4.55 (dt, *J* = 13.8, 6.8 Hz, 2H, SCH₂CH₂triazole), 4.47 (td, *J* = 6.1, 1.2 Hz, 2H, H-5), 4.11 (dd, *J* = 6.3, 2.2 Hz, 4H, H-6a, H-6b), 3.18 (dt, *J* = 13.7, 6.8 Hz, 2H, SCH₂CH₂triazole), 3.06 (dt, *J* = 13.9, 6.7 Hz, 2H, SCH₂CH₂triazole), 2.16 (s, 6H), 2.01 (s, 6H), 1.99 (s, 6H) (each OAc), 1.98 (s, 6H, NHAc).

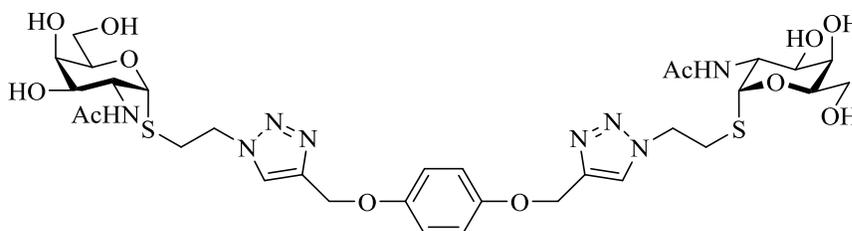
¹³C NMR (126 MHz, CDCl₃) δ 171.03, 170.42, 170.35, 170.11 (each C=O), 152.67 (Ar-C), 144.46 (CCH, triazole), 123.11 (CCH, triazole), 115.99 (Ar-CH), 85.22 (C-1), 68.16 (C-3), 67.66 (C-5), 67.11 (C-4), 62.65 (CH₂OAr), 62.03 (C-6), 49.67 (SCH₂CH₂triazole), 48.60 (C-2), 31.32 (SCH₂CH₂triazole), 23.25 (NHAc), 20.72, 20.66, 20.63 (each OAc).

ES-HRMS calcd for C₄₄H₅₈N₈O₁₈S₂Na₁ 1073.3208, found *m/z* 1073.3217 [M+Na]⁺

IR (ATR) cm⁻¹: 3279, 1747, 1541, 1507, 1373, 1229, 1083, 1047, 1024, 828

*R*_f: 0.47 (2:23 MeOH-CH₂Cl₂)

1,3-Di[1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (126)



Compound **125** (354 mg, 0.337 mmol) was stirred in methanol (35 mL) and to this was added a catalytic amount of a freshly prepared 1M NaOMe solution in MeOH (0.17 mL, 0.170 mmol). The resulting mixture was stirred for 1 h at r.t. at which point Amberlite IR-120 H⁺ was added and stirred gently for 10 mins, to neutralize (pH = 7) the solution. The resin was removed by filtration and washed with water and acetonitrile. The solvents were removed to a minimal amount of water. Reverse phase column chromatography was then carried out. The compound, in a minimal amount of water (made acidic and slightly heated, if solid crashes out, to return it to solution), was loaded onto the column, with the elution carried out as follows: 3 volumes of water were flushed through the column, to ensure salt removal, followed by a 1:1 MeCN-H₂O mixture. This gave the title compound (186 mg, 69%) as a colourless solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.17 (s, 2H, CCH, triazole), 7.74 (d, *J* = 7.0 Hz, 2H, NH), 6.95 (s, 4H, Ar-H), 5.50 (d, *J* = 5.3 Hz, 2H, H-1), 5.05 (s, 4H, CH₂OAr), 4.65 (br s, 4H, OH), 4.57 (dt, *J* = 13.7, 6.8 Hz, 2H, SCH₂CH₂triazole), 4.51 (dt, *J* = 13.9, 7.0 Hz, 2H, SCH₂CH₂triazole), 4.17 (ddd, *J* = 11.9, 7.0, 5.2 Hz, 2H, H-2), 3.90 (t, *J* = 6.0 Hz, 2H, H-5), 3.71 (d, *J* = 3.2 Hz, 2H, H-4), 3.54 (d, *J* = 6.0 Hz, 4H, H-6a, H-6b), 3.48 (dd, *J* = 11.2, 3.1 Hz, 2H, H-3), 3.31 (br s, 2H, OH), 3.02 (dt, *J* = 13.9, 6.9 Hz, 2H, SCH₂CH₂triazole), 2.93 (dt, *J* = 13.8, 6.8 Hz, 2H, SCH₂CH₂triazole), 1.79 (s, 6H, NHAc)

¹³C NMR (126 MHz, DMSO) δ 170.20 (C=O), 152.79 (Ar-C), 143.12 (CCH, triazole), 125.09 (CCH, triazole), 116.04 (Ar-CH), 84.81 (C-1), 72.69 (C-5), 68.55 (C-4), 67.94 (C-3), 62.07 (CH₂OAr), 61.36 (C-6), 50.46 (C-2), 49.74 (SCH₂CH₂triazole), 30.34 (SCH₂CH₂triazole), 23.09 NHAc).

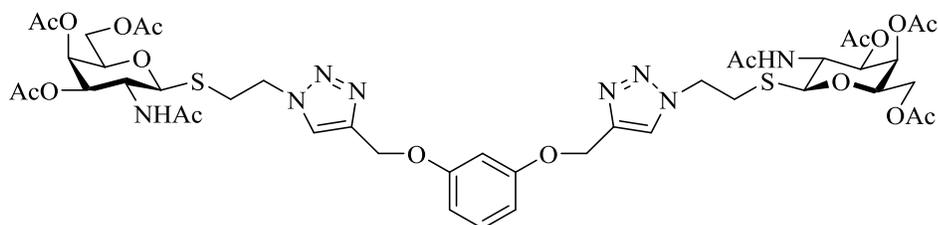
ES-HRMS calcd for C₃₂H₄₆N₈O₁₂S₂Na₁ 821.2574, found *m/z* 821.2562 [M+Na]⁺

IR (ATR) cm⁻¹: 3279, 1635, 1546, 1508, 1212, 1115, 1045, 1011, 827, 802

*R*_f: 0.67 (1:1 MeCN-H₂O) reverse phase

[α]_D²⁰ +223.8 (*c* 0.27, DMSO)

1,3-Di[1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- β -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (127)



To a solution of sugar **120** (96 mg, 0.222 mmol) and *meta*-bispropargyloxybenzene **82** (20 mg, 0.107 mmol) in a THF-H₂O (1:1, 4 mL) mixture was added sodium ascorbate (14 mg, 0.071 mmol) and copper sulphate pentahydrate (16 mg, 0.064 mmol). The mixture was stirred at r.t. for 18 h. Tetrahydrofuran was then removed under diminished pressure followed by the dilution of the solution with CH₂Cl₂. This mixture was then washed with water. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water, dried over NaSO₄ and the solvent removed *in vacuo*. Chromatography of the crude material (95:5 CH₂Cl₂-MeOH) gave the title compound (111 mg, 98%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 7.78 (s, 2H, CCH, triazole), 7.20 (t, J = 8.1 Hz, 1H, Ar-H), 6.63 (dd, J = 8.2, 2.3 Hz, 2H, Ar-H), 6.60 (t, J = 2.3 Hz, 1H, Ar-H), 5.93 (d, J = 9.3 Hz, 2H, NH), 5.38 (dd, J = 3.3, 1.1 Hz, 2H, H-4), 5.20 (s, 4H, ArOCH₂), 5.04 (dd, J = 10.6, 3.3 Hz, 2H, H-3), 4.72 (dt, J = 14.0, 6.2 Hz, 2H, SCH₂CH₂triazole), 4.57 (dt, J = 13.8, 6.8 Hz, 2H, SCH₂CH₂triazole), 4.34 (d, J = 10.4 Hz, 2H, H-1), 4.27 (q, J = 10.4 Hz, 2H, H-2), 4.13 – 4.07 (m, 4H, H-6a, H-6b), 3.86 (td, J = 6.4, 1.2 Hz, 2H, H-5), 3.33 (dt, J = 13.8, 6.7 Hz, 2H, SCH₂CH₂triazole), 3.09 (dt, J = 14.5, 6.2 Hz, 2H, SCH₂CH₂triazole), 2.16 (s, 6H), 2.02 (s, 6H), 1.99 (s, 6H) (each OAc), 1.93 (s, 6H, NHAc).

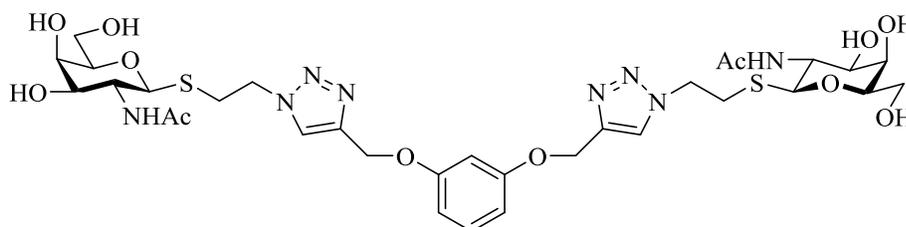
¹³C NMR (126 MHz, CDCl₃) δ 170.59, 170.52, 170.44, 170.20 (each C=O), 159.28 (Ar-C), 143.57 (CCH, triazole), 130.26 (Ar-CH), 124.21 (CCH, triazole), 107.97 (Ar-CH), 102.63 (Ar-CH), 84.93 (C-1), 74.73 (C-5), 71.15 (C-3), 66.84 (C-4), 62.01 (CH₂OAr), 61.81 (C-6), 50.51 (SCH₂CH₂triazole), 49.09 (C-2), 30.27 (SCH₂CH₂triazole), 23.25 (NHAc), 20.73, 20.68, 20.66 (each OAc).

ES-HRMS calcd for C₄₄H₅₈N₈O₁₈S₂Na₁ 1073.3208, found m/z 1073.3213 [M+Na]⁺

IR (ATR) cm⁻¹: 1742, 1663, 1593, 1553, 1492, 1370, 1223, 1150, 1081, 1034, 919, 732

R_f: 0.42 (2:23 MeOH-CH₂Cl₂)

1,3-Di[1-(ethyl 2-acetamido-2-deoxy-1-thio- β -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (128)



Compound **127** (107 mg, 0.102 mmol) was stirred in methanol (10 mL) and to this was added a catalytic amount of a freshly prepared 1M NaOMe solution in MeOH (0.06 mL, 0.060 mmol). The resulting mixture was stirred for 2 h at r.t. at which point Amberlite IR-120 H⁺ was added and stirred gently for 10 mins, to neutralize (pH = 7) the solution. The resin was removed by filtration and washed with water and acetonitrile. The solvents were removed to a minimal amount of water. Reverse phase column chromatography was then carried out. The compound, in a minimal amount of water (made acidic and slightly heated, if solid crashes out, to return it to solution), was loaded onto the column, with the elution carried out as follows: 3 volumes of water were flushed through the column, to ensure salt removal, followed by a 1:1 MeCN-H₂O mixture. This gave the title compound (67 mg, 83%) as a colourless solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.19 (s, 2H, CCH, triazole), 7.64 (d, *J* = 9.5 Hz, 2H, NH), 7.19 (t, *J* = 8.2 Hz, 1H, Ar-H), 6.71 (t, *J* = 2.4 Hz, 1H, Ar-H), 6.62 (dd, *J* = 8.2, 2.3 Hz, 2H, Ar-H), 5.09 (s, 4H, ArOCH₂), 4.71 (d, *J* = 6.2 Hz, 2H, OH-3), 4.63 (d, *J* = 5.2 Hz, 2H, OH-6), 4.62 – 4.58 (m, 6H, OH-4, SCH₂CH₂triazole), 4.34 (d, *J* = 10.3 Hz, 2H, H-1), 3.89 (q, *J* = 10.0 Hz, 2H H-2), 3.71 – 3.67 (m, 2H, H-4), 3.57 – 3.48 (m, 4H, H-6a, H-6b), 3.44 – 3.36 (m, 4H, H-3, H-5), 3.20 (dt, *J* = 13.7, 6.8 Hz, 2H, SCH₂CH₂triazole), 2.95 (dt, *J* = 14.1, 7.1 Hz, 2H, SCH₂CH₂triazole), 1.78 (s, 6H, NHAc).

¹³C NMR (126 MHz, DMSO) δ 169.77 (C=O), 159.75 (Ar-C), 142.66 (CCH, triazole), 130.45 (Ar-CH), 125.49 (CCH, triazole), 116.03 (Ar-CH), 107.67 (Ar-CH), 102.61 (Ar-CH), 85.15 (C-1), 79.90 (C-5), 72.77 (C-3), 68.16 (C-4), 61.60 (CH₂OAr), 61.25 (C-6), 50.79 (C-2), 50.14 (SCH₂CH₂triazole), 30.24 (SCH₂CH₂triazole), 23.51 (NHAc).

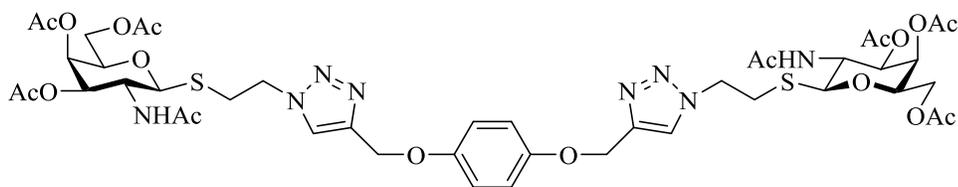
ES-HRMS calcd for C₃₂H₄₆N₈O₁₂S₂Na₁ 821.2574, found *m/z* 821.2571 [M+Na]⁺

IR (ATR) cm⁻¹: 3266, 1642, 1596, 1553, 1373, 1286, 1180, 1153, 1119, 1078, 1037, 1023, 864, 759

*R*_f: 0.64 (1:1 MeCN-H₂O) reverse phase

[α]_D²⁰ -18.5 (*c* 0.28, DMSO)

1,4-Di[1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- β -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (129)



To a solution of sugar **120** (215 mg, 0.497 mmol) and *para*-bispropargyloxybenzene **83** (44 mg, 0.236 mmol) in a THF-H₂O (1:1, 10 mL) mixture was added sodium ascorbate (30 mg, 0.151 mmol) and copper sulphate pentahydrate (33 mg, 0.132 mmol). The mixture was stirred at r.t. for 18 h. Tetrahydrofuran was then removed under diminished pressure followed by the dilution of the solution with CH₂Cl₂. This mixture was then washed with water. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water, dried over NaSO₄ and the solvent removed *in vacuo*. Chromatography of the crude material (95:5 CH₂Cl₂-MeOH) gave the title compound (232 mg, 94%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 7.72 (s, 2H, CCH, triazole), 6.91 (s, 4H, Ar-H), 5.81 (d, *J* = 8.7 Hz, 2H, NH), 5.37 (dd, *J* = 3.4, 1.2 Hz, 2H, H-4), 5.17 (s, 4H, ArOCH₂), 5.04 (dd, *J* = 10.2, 3.2 Hz, 2H, H-3), 4.70 (dt, *J* = 13.0, 6.2 Hz, 2H, SCH₂CH₂triazole), 4.57 (dt, *J* = 13.8, 6.7 Hz, 2H, SCH₂CH₂triazole), 4.30 – 4.24 (m, 4H, H-1, H-2), 4.11 (dd, *J* = 6.5, 2.5 Hz, 4H, H-6a, H-6b), 3.87 (td, *J* = 6.2, 1.1 Hz, 2H, H-5), 3.33 (dt, *J* = 14.6, 6.4 Hz, 2H, SCH₂CH₂triazole), 3.07 (dt, *J* = 14.5, 6.3 Hz, 2H, SCH₂CH₂triazole), 2.16 (s, 6H), 2.03 (s, 6H), 1.99 (s, 6H) (each OAc), 1.94 (s, 6H, NHAc).

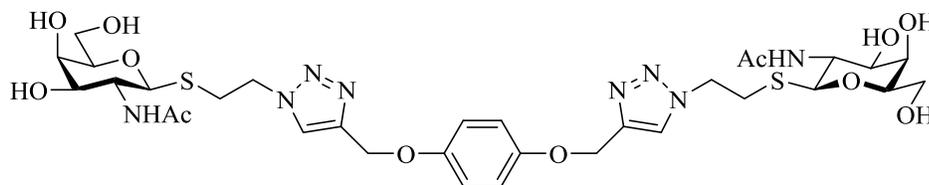
¹³C NMR (126 MHz, CDCl₃) δ 170.52, 170.45, 170.40, 170.15 (each C=O), 152.71 (Ar-C), 143.83 (CCH, triazole), 124.14 (CCH, triazole), 116.16 (Ar-CH), 84.98 (C-1), 74.77 (C-5), 71.11 (C-3), 66.82 (C-4), 62.70 (CH₂OAr), 61.74 (C-6), 50.54 (SCH₂CH₂triazole), 49.10 (C-2), 30.28 (SCH₂CH₂triazole), 23.26 (NHAc), 20.72, 20.66, 20.65 (each OAc).

ES-HRMS calcd for C₄₄H₅₈N₈O₁₈S₂Na₁ 1073.3208, found *m/z* 1073.3197 [M+Na]⁺

IR (ATR) cm⁻¹: 1746, 1663, 1508, 1371, 1234, 1054, 1032, 1016, 749

R_f: 0.38 (2:23 MeOH-CH₂Cl₂)

1,4-Di[1-(ethyl 2-acetamido-2-deoxy-1-thio-β-D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (130)



Compound **129** (25 mg, 0.024 mmol) was stirred in methanol (3 mL) and to this was added a catalytic amount of a freshly prepared 1M NaOMe solution in MeOH (0.02 mL, 0.020 mmol). The resulting mixture was stirred for 2 h at r.t. at which point Amberlite IR-120 H⁺ was added and stirred gently for 10 mins, to neutralize (pH = 7) the solution. The resin was removed by filtration and washed with water and acetonitrile. The solvents were removed to a minimal amount of water. Reverse phase column chromatography was then carried out. The compound, in a minimal amount of water (made acidic and slightly heated, if solid crashes out, to return it to solution), was loaded onto the column, with the elution carried out as follows: 3 volumes of water were flushed through the column, to ensure salt removal, followed by a 1:1 MeCN-H₂O mixture. This gave the title compound (16 mg, 84%) as a colourless solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.17 (s, 2H, CCH, triazole), 7.64 (d, *J* = 9.5 Hz, 2H, NH), 6.96 (s, 4H, Ar-H), 5.05 (s, 4H, ArOCH₂), 4.71 (d, *J* = 6.2 Hz, 2H, OH-3), 4.63 (d, *J* = 5.5 Hz, 1H, OH-6), 4.61 (d, *J* = 4.5 Hz, 1H, OH-4), 4.61 – 4.56 (m, 4H, SCH₂CH₂triazole), 4.35 (d, *J* = 10.3 Hz, 2H, H-1), 3.89 (q, *J* = 10.0 Hz, 2H, H-2), 3.69 (t, *J* = 3.6 Hz, 2H, H-4), 3.52 (t, *J* = 5.4 Hz, 4H, H-6a, H-6b), 3.47 – 3.36 (m, 4H, H-3, H-5), 3.20 (dt, *J* = 13.7, 6.7 Hz, 2H, SCH₂CH₂triazole), 2.94 (dt, *J* = 14.1, 7.1 Hz, 2H, SCH₂CH₂triazole), 1.78 (s, 6H, NHAc).

¹³C NMR (126 MHz, DMSO) δ 169.74 (C=O), 152.80 (Ar-C), 142.94 (CCH, triazole), 125.37 (CCH, triazole), 116.03 (Ar-CH), 85.16 (C-1), 79.91 (C-5), 72.77 (C-3), 68.16 (C-4), 62.07 (CH₂OAr), 61.25 (C-6), 50.80 (C-2), 50.13 (SCH₂CH₂triazole), 30.24 (SCH₂CH₂triazole), 23.51 (NHAc).

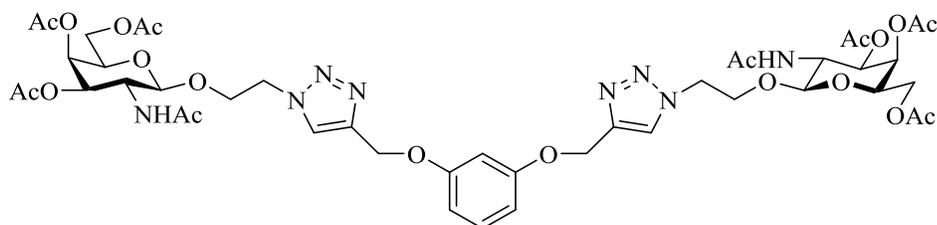
ES-HRMS calcd for C₃₂H₄₆N₈O₁₂S₂Na₁ 821.2574, found *m/z* 821.2551 [M+Na]⁺

IR (ATR) cm⁻¹: 3271, 1635, 1549, 1507, 1372, 1312, 1225, 1115, 1041, 1016, 978, 864, 820, 705

*R*_f: 0.68 (1:1 MeCN-H₂O) reverse phase

[α]_D²⁰ 8.3 (*c* 0.17, DMSO)

1,3-Di[1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- β -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (131)



To a solution of sugar **122** (350 mg, 0.841 mmol) and *meta*-bispropargyloxybenzene **82** (74 mg, 0.397 mmol) in a THF-H₂O (1:1, 12 mL) mixture was added sodium ascorbate (49 mg, 0.247 mmol) and copper sulphate pentahydrate (59 mg, 0.236 mmol). The mixture was stirred at r.t. for 18 h. Tetrahydrofuran was then removed under diminished pressure followed by the dilution of the solution with CH₂Cl₂. This mixture was then washed with water. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water, dried over NaSO₄ and the solvent removed *in vacuo*. Chromatography of the crude material (95:5 CH₂Cl₂-MeOH) gave the title compound (355 mg, 88%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃) δ 7.77 (s, 2H, CCH, triazole), 7.23 (t, J = 8.3 Hz, 1H, Ar-H), 6.65 (dd, J = 8.3, 2.4 Hz, 2H, Ar-H), 6.47 (t, J = 2.3 Hz, 1H, Ar-H), 6.02 (d, J = 9.1 Hz, 2H, NH), 5.34 (dd, J = 3.4, 1.2 Hz, 2H, H-4), 5.19 d, J = 11.7 Hz, 2H, ArOCH₂), 5.12 (d, J = 11.7 Hz, 2H, ArOCH₂), 5.06 (dd, J = 11.3, 3.4 Hz, 2H, H-3), 4.67 (dt, J = 14.5, 3.3 Hz, 2H, OCH₂CH₂triazole), 4.50 (ddd, J = 14.5, 9.7, 3.1 Hz, 2H, OCH₂CH₂triazole), 4.36 (d, J = 8.4 Hz, 2H, H-1), 4.29 (dt, J = 10.9, 3.5 Hz, 2H, OCH₂CH₂triazole), 4.17 – 4.08 (m, 2H, H-2), 4.13 (dd, J = 7.8, 6.5 Hz, 4H, H-6a, H-6b), 3.90 (dd, J = 6.5, 1.3 Hz, 2H, H-5), 3.89 – 3.83 (m, 2H, OCH₂CH₂triazole), 2.14 (s, 6H), 2.05 (s, 6H), 1.91 (s, 6H) (each OAc), 1.83 (s, 6H, NHAc).

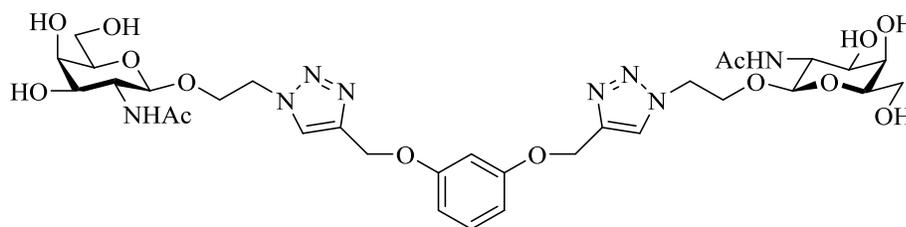
¹³C NMR (126 MHz, CDCl₃) δ 170.75, 170.71, 170.43, 170.29 (each C=O), 159.22 (Ar-C), 143.15 (CCH, triazole), 130.42 (Ar-CH), 124.91 (CCH, triazole), 107.04, (Ar-CH) 102.78 (Ar-CH), 101.10 (C-1), 70.81 (C-5), 70.07 (C-3), 67.21 (OCH₂CH₂triazole), 66.61 (C-4), 61.61 (CH₂OAr), 61.52 (C-6), 50.45 (C-2), 50.27 (OCH₂CH₂triazole), 23.15 (NHAc), 20.70, 20.69, 20.64 (each OAc).

ES-HRMS calcd for C₄₄H₅₈N₈O₂₀Na₁ 1041.3665, found m/z 1041.3655 [M+Na]⁺

IR (ATR) cm⁻¹: 1743, 1664, 1593, 1555, 1370, 1224, 1152, 1047, 1032, 733

R_f : 0.39 (2:23 MeOH-CH₂Cl₂)

1,3-Di[1-(ethyl 2-acetamido-2-deoxy- β -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (132)



Compound **131** (330 mg, 0.324 mmol) was stirred in methanol (30 mL) and to this was added a catalytic amount of a freshly prepared 1M NaOMe solution in MeOH (0.17 mL, 0.170 mmol). The resulting mixture was stirred for 2 h at r.t. at which point Amberlite IR-120 H⁺ was added and stirred gently for 10 mins, to neutralize (pH = 7) the solution. The resin was removed by filtration and washed with water and acetonitrile. The solvents were removed to a minimal amount of water. Reverse phase column chromatography was then carried out. The compound, in a minimal amount of water (made acidic and slightly heated, if solid crashes out, to return it to solution), was loaded onto the column, with the elution carried out as follows: 3 volumes of water were flushed through the column, to ensure salt removal, followed by a 1:1 MeCN-H₂O mixture. This gave the title compound (208 mg, 84%) as a colourless solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.08 (s, 2H, CCH, triazole), 7.56 (d, *J* = 9.1 Hz, 2H, NH), 7.20 (t, *J* = 8.2 Hz, 1H, Ar-H), 6.71 (t, *J* = 2.4 Hz, 1H, Ar-H), 6.63 (dd, *J* = 8.2, 2.3 Hz, 2H, Ar-H), 5.07 (s, 4H, ArOCH₂), 4.59 (d, *J* = 6.5 Hz, 2H, OH-3), 4.58 (d, *J* = 5.5 Hz, 2H, OH-6), 4.55 (td, *J* = 6.0, 5.6, 2.6 Hz, 2H, OCH₂CH₂triazole), 4.50 (d, *J* = 4.4 Hz, 2H, OH-4), 4.49 – 4.45 (m, 2H, OCH₂CH₂triazole), 4.27 (d, *J* = 8.4 Hz, 2H, H-1), 4.05 (ddd, *J* = 11.1, 5.8, 3.7 Hz, 2H, OCH₂CH₂triazole), 3.81 – 3.72 (m, 4H, H-2, OCH₂CH₂triazole), 3.63 (t, *J* = 4.1 Hz, 2H, H-4), 3.51 (tt, *J* = 11.0, 5.4 Hz, 4H, H-6a, H-6b), 3.40 (ddd, *J* = 10.2, 6.4, 3.2 Hz, 2H H-3), 3.34 – 3.32 (m, 2H, H-5), 1.74 (s, 6H, NHAc)

¹³C NMR (126 MHz, DMSO) δ 170.01 (C=O), 159.75 (Ar-C), 142.80 (CCH, triazole), 130.47 (Ar-CH), 125.46 (CCH, triazole), 107.62 (Ar-CH), 102.00 (Ar-CH), 101.52 (C-1), 75.92 (C-5), 71.77 (C-3), 67.93 (C-4), 66.68 (OCH₂CH₂triazole), 61.60 (CH₂OAr), 60.94 (C-6), 52.11 (C-2), 50.03 (OCH₂CH₂triazole), 23.47 (NHAc).

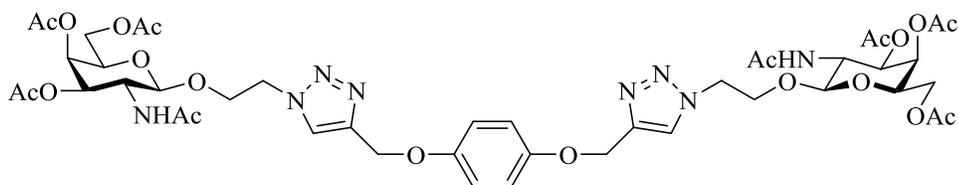
ES-HRMS calcd for C₃₂H₄₆N₈O₁₄Na₁ 789.3031, found *m/z* 789.3011 [M+Na]⁺

IR (ATR) cm⁻¹: 3272, 1637, 1598, 1554, 1494, 1375, 1278, 1264, 1181, 1152, 1117, 1047, 1032, 1005, 891, 786, 759

*R*_f: 0.70 (1:1 MeCN-H₂O) reverse phase

[α]_D²⁰ -5.5 (*c* 0.48, DMSO)

1,4-Di[1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- β -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (133)



To a solution of sugar **122** (351 mg, 0.843 mmol) and *para*-bispropargyloxybenzene **83** (74 mg, 0.397 mmol) in a THF-H₂O (1:1, 14 mL) mixture was added sodium ascorbate (49 mg, 0.247 mmol) and copper sulphate pentahydrate (59 mg, 0.236 mmol). The mixture was stirred at r.t. for 18 h. Tetrahydrofuran was then removed under diminished pressure followed by the dilution of the solution with CH₂Cl₂. This mixture was then washed with water. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water, dried over NaSO₄ and the solvent removed *in vacuo*. Chromatography of the crude material (95:5 CH₂Cl₂-MeOH) gave the title compound (378 mg, 93%) as a colourless solid.

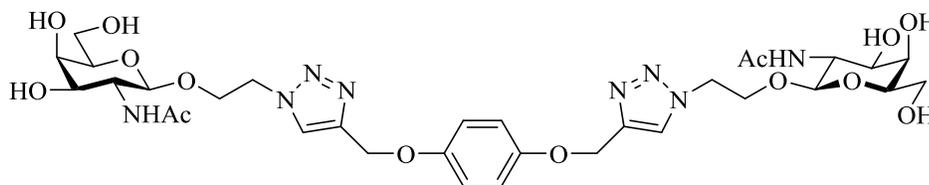
¹H NMR (500 MHz, CDCl₃) δ 7.75 (s, 2H, CCH, triazole), 6.92 (s, 4H, Ar-H), 5.60 (d, *J* = 9.0 Hz, 2H, NH), 5.34 (dd, *J* = 3.5, 1.2 Hz, 2H, H-4), 5.14 (d, *J* = 3.0 Hz, 4H, ArOCH₂), 5.10 (dd, *J* = 11.3, 3.4 Hz, 2H, H-3), 4.63 (ddd, *J* = 14.6, 4.4, 2.9 Hz, 2H, OCH₂CH₂triazole), 4.56 – 4.47 (m, 2H, OCH₂CH₂triazole), 4.51 (d, *J* = 8.4 Hz, 2H, H-1), 4.27 (ddd, *J* = 10.7, 4.4, 3.3 Hz, 2H, OCH₂CH₂triazole), 4.13 (dd, *J* = 6.6, 5.8 Hz, 4H, H-6a, H-6b), 4.11 – 4.07 (m, 2H, H-2), 3.93 – 3.89 (m, 2H, OCH₂CH₂triazole), 3.87 (dd, *J* = 6.6, 1.3 Hz, 2H, H-5), 2.15 (s, 6H), 2.05 (s, 6H), 1.99 (s, 6H) (each OAc), 1.85 (s, 6H, NHAc).

¹³C NMR (126 MHz, CDCl₃) δ 170.58, 170.54, 170.39, 170.16 (each C=O), 152.74 (Ar-C), 143.88 (CCH, triazole), 124.46 (CCH, triazole), 115.90 (Ar-CH), 101.02 (C-1), 70.86 (C-5), 69.86 (C-3), 67.18 (OCH₂CH₂triazole), 66.55 (C-4), 62.44 (CH₂OAr), 61.39 (C-6), 50.81 (C-2), 50.17 (OCH₂CH₂triazole), 23.28 (NHAc), 20.68, 20.67, 20.64 (each OAc).

ES-HRMS calcd for C₄₄H₅₈N₈O₂₀Na₁ 1041.3665, found *m/z* 1041.3674 [M+Na]⁺

IR (ATR) cm⁻¹: 1744, 1663, 1548, 1507, 1371, 1223, 1137, 1050, 1033, 830, 733

R_f: 0.36 (2:23 MeOH-CH₂Cl₂)

1,4-Di[1-(ethyl 2-acetamido-2-deoxy- β -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (134)

Compound **133** (374 mg, 0.367 mmol) was stirred in methanol (30 mL) and to this was added a catalytic amount of a freshly prepared 1M NaOMe solution in MeOH (0.18 mL, 0.180 mmol). The resulting mixture was stirred for 2 h at r.t. at which point Amberlite IR-120 H⁺ was added and stirred gently for 10 mins, to neutralize (pH = 7) the solution. The resin was removed by filtration and washed with water and acetonitrile. The solvents were removed to a minimal amount of water. Reverse phase column chromatography was then carried out. The compound, in a minimal amount of water (made acidic and slightly heated, if solid crashes out, to return it to solution), was loaded onto the column, with the elution carried out as follows: 3 volumes of water were flushed through the column, to ensure salt removal, followed by a 1:1 MeCN-H₂O mixture. This gave the title compound (224 mg, 80%) as a colourless solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.06 (s, 2H, CCH, triazole), 7.56 (d, *J* = 9.2 Hz, 2H, NH), 6.97 (s, 4H, Ar-H), 5.03 (s, 4H, ArOCH₂), 4.59 (d, *J* = 6.4 Hz, 2H, OH-3), 4.58 (d, *J* = 5.9 Hz, 2H, OH-6), 4.53 (dd, *J* = 5.8, 3.6 Hz, 2H, OCH₂CH₂triazole), 4.51 (d, *J* = 4.4 Hz, 2H, OH-4), 4.48 (dd, *J* = 7.1, 3.8 Hz, 2H, OCH₂CH₂triazole), 4.26 (d, *J* = 8.4 Hz, 2H, H-1), 4.05 (ddd, *J* = 11.0, 5.9, 3.7 Hz, 2H, OCH₂CH₂triazole), 3.83 – 3.70 (m, 4H, H-2, OCH₂CH₂triazole), 3.65 – 3.62 (m, 2H, H-4), 3.51 (tt, *J* = 11.1, 5.6 Hz, 4H, H-6a, H-6b), 3.40 (ddd, *J* = 9.9, 6.4, 3.2 Hz, 2H, H-3), 3.34 – 3.32 (m, 2H, H-5), 1.74 (s, 6H, NHAc).

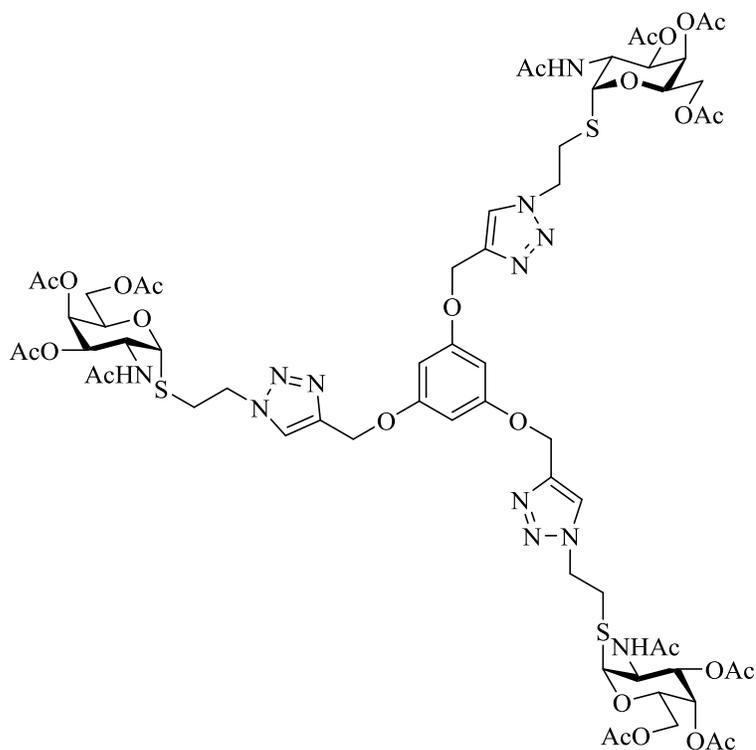
¹³C NMR (126 MHz, DMSO) δ 170.00 (C=O), 152.81 (Ar-C), 143.08 (CCH, triazole), 125.35 (CCH, triazole), 115.98 (Ar-CH), 101.53 (C-1), 75.92 (C-5), 71.78 (C-3), 67.93 (C-4), 66.70 (OCH₂CH₂triazole), 62.03 (CH₂OAr), 60.94 (C-6), 52.12 (C-2), 50.01 (OCH₂CH₂triazole), 23.48 (NHAc).

ES-HRMS calcd for C₃₂H₄₆N₈O₁₄Na₁ 789.3031, found *m/z* 789.3026 [M+Na]⁺

IR (ATR) cm⁻¹: 3276, 1637, 1556, 1511, 1372, 1310, 1224, 1109, 1046, 1033, 980, 822, 782

*R*_f: 0.72 (1:1 MeCN-H₂O) reverse phase

[α]_D²⁰ -7.8 (*c* 0.48, DMSO)

1,3,5-Tri[1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (135)

To a solution of sugar **119** (345 mg, 0.798 mmol) and tripropargyl phloroglucinolyl ether **84** (62 mg, 0.258 mmol) in a THF-H₂O (1:1, 14 mL) mixture was added sodium ascorbate (31 mg, 0.156 mmol) and copper sulphate pentahydrate (39 mg, 0.156 mmol). The mixture was stirred at r.t. for 20 h. Tetrahydrofuran was then removed under diminished pressure followed by the dilution of the solution with CH₂Cl₂. This mixture was then washed with water. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water, dried over NaSO₄ and the solvent removed *in vacuo*. Chromatography of the crude material (95:5-93:7 CH₂Cl₂-MeOH) gave the title compound (349 mg, 88%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃-*d*) δ 7.74 (s, 3H, CCH, triazole), 6.25 (s, 3H, Ar-H), 6.22 (d, *J* = 7.8 Hz, 3H, NH), 5.71 (d, *J* = 5.4 Hz, 3H, H-1), 5.39 (dd, *J* = 3.4, 1.3 Hz, 3H, H-4), 5.17 (s, 6H, CH₂OAr), 4.99 (dd, *J* = 11.8, 3.2 Hz, 3H, H-3), 4.73 (ddd, *J* = 12.5, 7.8, 5.3 Hz, 3H, H-2), 4.62 (dt, *J* = 13.4, 6.5 Hz, 3H, SCH₂CH₂triazole), 4.57 (dt, *J* = 13.8, 6.6 Hz, 3H, SCH₂CH₂triazole) 4.45 (t, *J* = 6.3 Hz, 3H, H-5), 4.10 (dd, *J* = 6.4, 2.2 Hz, 6H, H-6a, H-6b),

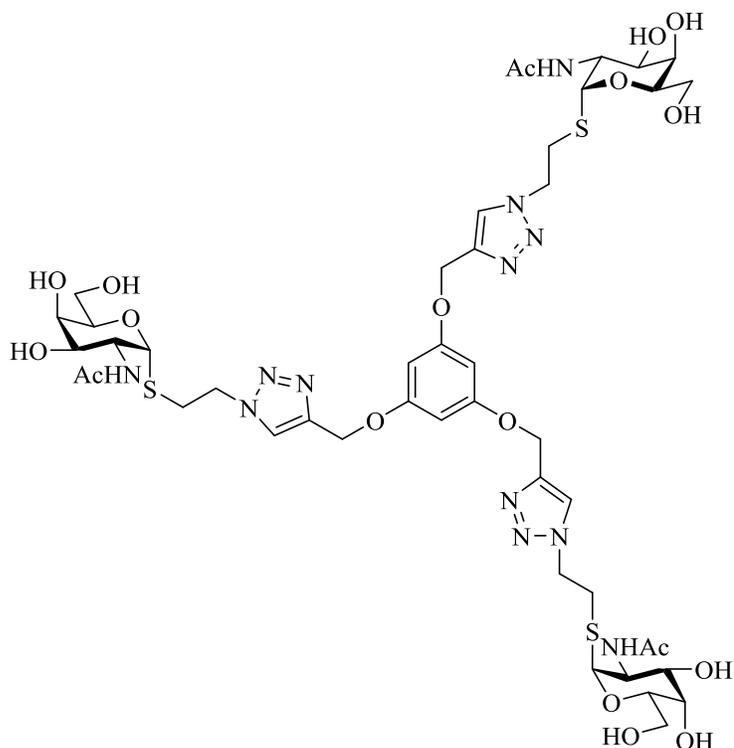
3.18 (dt, $J = 13.5, 6.6$ Hz, 3H, SCH₂CH₂triazole), 3.06 (dt, $J = 13.8, 6.6$ Hz, 3H, SCH₂CH₂triazole), 2.16 (s, 9H), 2.00 (s, 9H), 1.99 (s, 9H) (each OAc), 1.97 (s, 9H, NHAc).

¹³C NMR (126 MHz, , CDCl₃) δ 170.89, 170.69, 170.40, 170.18 (each C=O), 159.88 (Ar-C), 143.88 (CCH, triazole), 123.52 (CCH, triazole), 95.83 (Ar-CH), 85.20 (C-1), 68.16 (C-3), 67.55 (C-5), 67.11 (C-4), 62.18 (C-6), 62.04 (CH₂OAr), 49.68 (SCH₂CH₂triazole), 48.46 (C-2), 31.38 (SCH₂CH₂triazole), 23.17 (NHAc), 20.75, 20.67, 20.62 (each OAc).

ES-HRMS calcd for C₆₃H₈₄N₁₂O₂₇S₃Na₁ 1559.4629, found m/z 1559.4656 [M+Na]⁺

IR (ATR) cm⁻¹: 1745, 1664, 1601, 1542, 1452, 1231, 1156, 1083, 1052, 712

R_f : 0.40 (2:23 MeOH-CH₂Cl₂)

1,3,5-Tri[1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy]benzene (136)

Compound **135** (343 mg, 0.223 mmol) was stirred in methanol (22 mL) and to this was added a catalytic amount of a freshly prepared 1M NaOMe solution in MeOH (0.11 mL, 0.110 mmol). The resulting mixture was stirred for 2 h at r.t. at which point Amberlite IR-120 H⁺ was added and stirred gently for 10 mins, to neutralize (pH = 7) the solution. The resin was removed by filtration and washed with water and acetonitrile. The solvents were removed to a minimal amount of water. Reverse phase column chromatography was then carried out. The compound, in a minimal amount of water (made acidic and slightly heated, if solid crashes out, to return it to solution), was loaded onto the column, with the elution carried out as follows: 3 volumes of water were flushed through the column, to ensure salt removal, followed by a 1:1 MeCN-H₂O mixture. This gave the title compound (211 mg, 81%) as a colourless solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.21 (s, 3H, CCH, triazole), 7.74 (d, *J* = 7.1 Hz, 3H, NH), 6.33 (s, 3H, Ar-H), 5.51 (d, *J* = 5.2 Hz, 3H, H-1), 5.07 (s, 6H, CH₂OAr), 4.58 (dt, *J* = 13.7, 6.8 Hz, 3H, SCH₂CH₂triazole), 4.52 (dt, *J* = 13.9, 7.0 Hz, 3H, SCH₂CH₂triazole), 4.17 (ddd, *J* = 11.9, 7.0, 5.3 Hz, 3H, H-2), 3.90 (t, *J* = 6.1 Hz, 3H, H-5), 3.71 (d, *J* = 3.1

Hz, 3H, H-4), 3.54 (d, $J = 6.0$ Hz, 6H, H-6a, H-6b), 3.48 (dd, $J = 11.3, 3.0$ Hz, 3H, H-3), 3.03 (dt, $J = 13.9, 7.0$ Hz, 3H, SCH₂CH₂triazole), 2.93 (dt, $J = 13.8, 6.9$ Hz, 3H, SCH₂CH₂triazole), 1.80 (s, 9H, NHAc).

¹³C NMR (126 MHz, DMSO) δ 170.23 (C=O), 160.34 (OAr-C), 142.73 (CCH, triazole), 125.25 (CCH, triazole), 94.92 (Ar-CH), 84.83 (C-1), 72.69 (C-5), 68.55 (C-4), 67.94 (C-3), 61.68 (ArOCH₂) 61.37 (C-6), 50.47 (C-2), 49.78 (SCH₂CH₂triazole), 30.34 (SCH₂CH₂triazole), 23.10 (NHAc).

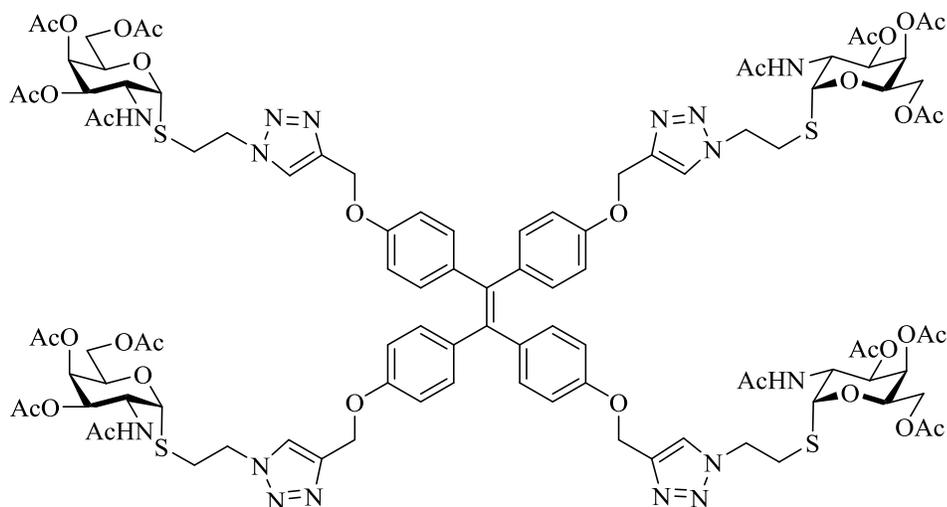
ES-HRMS calcd for C₄₅H₆₅N₁₂O₁₈S₃ 1157.3702, found m/z 1157.3733 [M-H]⁻

IR (ATR) cm⁻¹: 3282, 1634, 1546, 1374, 1151, 1116, 1052, 881, 802

R_f : 0.70 (1:1 MeCN-H₂O) reverse phase

$[\alpha]_D^{20} +169.3$ (c 0.46, DMSO)

1,1,2,2-Tetrakis[4-(1-(ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio- α -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy-phenyl)]ethane (137)



To a solution of sugar **119** (149 mg, 0.345 mmol) and tetrapropargyl tetraphenylethene ether **87** (46 mg, 0.084 mmol) in a THF-H₂O (1:1, 210 mL) mixture was added sodium ascorbate (10 mg, 0.050 mmol) and copper sulphate pentahydrate (12 mg, 0.048 mmol). The mixture was stirred at r.t. for 20 h. Tetrahydrofuran was then removed under diminished pressure followed by the dilution of the solution with CH₂Cl₂. This mixture was then washed with water. The aqueous layer was re-extracted with a further portion of CH₂Cl₂. The combined organic layers were then washed with water, dried over NaSO₄ and the solvent removed *in vacuo*. Chromatography of the crude material (95:5-93:7 CH₂Cl₂-MeOH) gave the title compound (175 mg, 92%) as a colourless solid.

¹H NMR (500 MHz, CDCl₃-*d*) δ 7.66 (s, 4H, CCH, triazole), 6.92 (d, *J* = 8.5 Hz, 8H, Ar-H), 6.71 (d, *J* = 8.7 Hz, 8H, Ar-H), 5.91 (d, *J* = 8.2 Hz, 4H, NH), 5.67 (d, *J* = 5.4 Hz, 4H, H-1), 5.41 – 5.39 (m, 4H, H-4), 5.15 (s, 8H, CH₂OAr), 5.01 (dd, *J* = 11.8, 3.2 Hz, 4H, H-3), 4.74 (ddd, *J* = 12.6, 8.0, 5.3 Hz, 4H, H-2), 4.59 (hept, *J* = 6.9 Hz, 8H, SCH₂CH₂triazole), 4.52 (t, *J* = 6.4 Hz, 4H, H-5), 4.15 (dd, *J* = 11.5, 5.9 Hz, 4H, H-6a), 4.11 (dd, *J* = 11.5, 7.0 Hz, 4H, H-6b), 3.18 (dt, *J* = 13.8, 6.8 Hz, 4H, SCH₂CH₂triazole), 3.08 (dt, *J* = 14.0, 6.9 Hz, 4H, SCH₂CH₂triazole), 2.17 (s, 12H), 2.01 (s, 12H), 2.00 (s, 12H) (each OAc), 1.97 (s, 12H, NHAc).

¹³C NMR (126 MHz, , CDCl₃) δ 170.99, 170.53, 170.39, 170.15(each C=O), 156.52 (OAr-C), 144.28 (CCH, triazole), 138.60 (Ar₂-C=C-Ar₂), 137.18 (Ar-C), 132.53 (Ar-CH), 123.12 (CCH, triazole), 113.93 (Ar-CH), 85.11 (C-1), 68.17 (C-3), 67.65 (C-5), 67.11 (C-4), 61.98

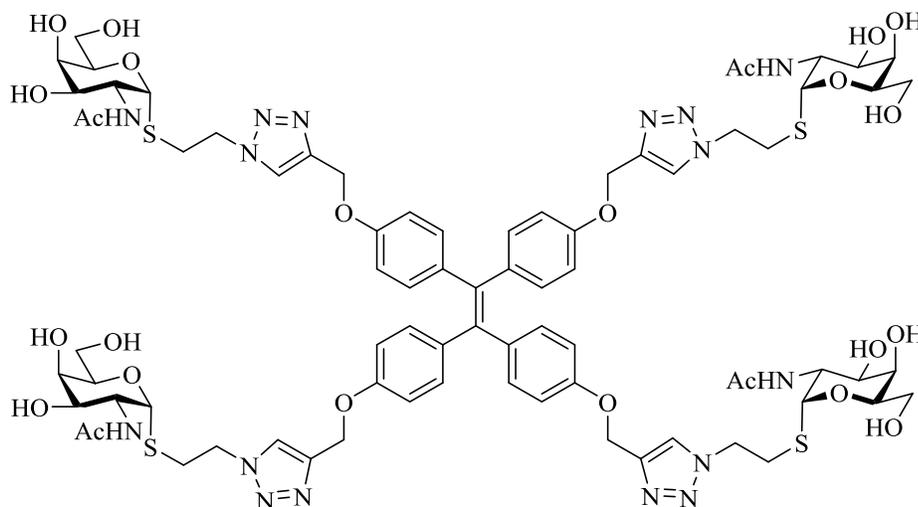
(C-6), 61.88 (CH₂OAr), 49.64 (SCH₂CH₂triazole), 48.52 (C-2), 31.14 (SCH₂CH₂triazole), 23.21 (NHAc), 20.73, 20.66, 20.66 (each OAc).

ES-HRMS calcd for C₅₁H₆₂N₈O₁₈S₂Na₁ 1161.3521, found m/z 1161.3503 [M/2+Na]⁺

IR (ATR) cm⁻¹: 2923, 1747, 1667, 1455, 1372, 1235, 1085, 1032, 1054, 710

R_f: 0.39 (2:23 MeOH-CH₂Cl₂)

1,1,2,2-Tetrakis[4-(1-(ethyl 2-acetamido-2-deoxy-1-thio- α -D-galactopyranosyl)-1,2,3-triazol-4-ylmethoxy-phenyl)]ethene (138)



Compound **137** (220 mg, 0.097 mmol) was stirred in methanol (20 mL) and to this was added a catalytic amount of a freshly prepared 1M NaOMe solution in MeOH (0.05 mL, 0.050 mmol). The resulting mixture was stirred for 2 h at r.t. at which point Amberlite IR-120 H⁺ was added and stirred gently for 10 mins, to neutralize (pH = 7) the solution. The resin was removed by filtration and washed with water and acetonitrile. The solvents were removed to a minimal amount of water. Reverse phase column chromatography was then carried out. The compound, in a minimal amount of water (made acidic and slightly heated, if solid crashes out, to return it to solution), was loaded onto the column, with the elution carried out as follows: 3 volumes of water were flushed through the column, to ensure salt removal, followed by a 1:1 MeCN-H₂O mixture. This gave the title compound (159 mg, 93%) as a yellow solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.18 (s, 4H, CCH, triazole), 7.74 (d, *J* = 7.1 Hz, 4H, NH), 6.87 (d, *J* = 8.4 Hz, 8H, Ar-H), 6.80 (d, *J* = 8.8 Hz, 8H, Ar-H), 5.50 (d, *J* = 5.3 Hz, 4H, H-1), 5.03 (s, 8H, CH₂OAr), 4.67 (br s, OH), 4.58 (dt, *J* = 13.8, 6.8 Hz, 4H, SCH₂CH₂triazole), 4.51 (dt, *J* = 13.9, 7.0 Hz, 4H, SCH₂CH₂triazole), 4.17 (ddd, *J* = 11.8, 7.0, 5.2 Hz, 4H, H-2), 3.91 (t, *J* = 6.1 Hz, 4H, H-5), 3.75 – 3.67 (br d, *J* = 3.0 Hz, 4H, H-4), 3.54 (d, *J* = 6.0 Hz, 8H, H-6a, H-6b), 3.48 (dd, *J* = 11.3, 3.0 Hz, 4H, H-3), 3.02 (dt, *J* = 13.9, 7.0 Hz, 4H, SCH₂CH₂triazole), 2.93 (dt, *J* = 13.8, 6.9 Hz, 4H, SCH₂CH₂triazole), 1.79 (s, 12H, NHAc).

^{13}C NMR (126 MHz, dmsO) δ 170.22 (C=O), 156.89 (OAr-C), 142.83 (CCH, triazole), 138.51 (Ar₂-C=C-Ar₂), 136.94 (Ar-C), 132.46 (Ar-CH), 125.21 (CCH, triazole), 114.33 (Ar-CH), 84.82 (C-1), 72.70 (C-5), 68.55 (C-4), 67.94 (C-3), 61.46 (CH₂OAr), 61.36 (C-6), 50.47 (C-2), 49.78 (SCH₂CH₂triazole), 30.33 (SCH₂CH₂triazole), 23.09 (NHAc).

ES-HRMS calcd for C₇₈H₁₀₀N₁₆O₂₄S₄Na₁ 1795.5877, found m/z 1795.5940 [M+Na]⁺

IR (ATR) cm⁻¹: 3277, 1638, 1545, 507, 1224, 1175, 1114, 1048, 1009, 830, 802

R_f: 0.48 (1:1 MeCN-H₂O) reverse phase

$[\alpha]_{\text{D}}^{20}$ +150.0 (*c* 0.28, DMSO)

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