Synthesis towards new C-glycoside derivatives of multivalent carbohydrates

A Thesis submitted to The University Manchester for the degree of Master of Philosophy in the Faculty of Engineering and Physical Sciences

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## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>10</td>
</tr>
<tr>
<td>DECLARATION</td>
<td>11</td>
</tr>
<tr>
<td>COPYRIGHT STATEMENT</td>
<td>12</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>13</td>
</tr>
<tr>
<td>ABBREVIATIONS</td>
<td>14</td>
</tr>
</tbody>
</table>

### 1. INTRODUCTION

1.1. Carbohydrates Chemistry and Biology                                | 17   |

1.2. Occurrence of Carbohydrates                                        | 18   |

1.3. Conformational Analysis of Carbohydrates                          | 19   |

1.3.1. Conformational Study of Monosaccharides                         | 19   |

1.3.2. Conformational Study of Disaccharides                           | 25   |

1.4. Biological Roles                                                  | 26   |

1.5. Glycoconjugates                                                   | 32   |

1.6. Chemistry of the C-Glycosidic Bonds                               | 34   |

1.6.1. C-Glycoside Bonds in Natural Products and Medicinal Chemistry   | 34   |

1.6.2. C-Nucleoside Bonds in Natural Products and Medicinal Chemistry  | 38   |

1.7. Multivalent Carbohydrates                                          | 38   |

1.7.1. Multivalent Carbohydrate Ligands                                | 43   |

1.7.2. Molecular Recognition in Carbohydrates                          | 47   |

1.7.2.1. Human Immunodeficiency Virus (HIV)                            | 47   |

1.7.2.2. Heparin                                                       | 48   |

1.7.2.3. Bacterial Adhesion and Multivalent Carbohydrates              | 48   |
1.8. Sulfur-linked and Sulfur-containing Carbohydrates 49
1.9. C- Allylation Reactions 54
1.10. Thiol-ene Click Chemistry 56
1.11. Aim of the Project 61

2. Results and Discussion
2.1. Synthesis of the C- Glycosidic Bond 64
2.2. Thiol-ene Click Chemistry 71
   2.2.1. Synthesis of Thioether Sugar 71
   2.2.2. Synthesis of Organosulfur Compound as a Model 75
   2.2.3. Synthesis of Free Thiol-containing Sugars 82
2.3. Conclusions 92
2.4. Future work 93

3. EXPERIMENTAL
3.1. General Experimental 96
3.2. Experimental Procedures and Data 97
3.2.1. 1-(α,β-D- Mannopyanosyl)-2-propene 141 97
3.2.2. Methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside 142 98
3.2.3. 3-(2,3,4,6-Tetra-O-acetyl-α,β-D-mannopyranosyl) propene 135 99
3.2.4. 6-(Acetyltiho) hexanoic acid 149 100
3.2.5. S-(6-(Benzylamino)-6-oxohexyl) ethanethioate 150 101
3.2.6. N-Benzyl-6- mercaptohexanamide 134 102
3.2.7. α/β-(2R,3S,4R,5R,6R)-2-(Acetoxymethyl)-6-(3-(6-(benzylamino)-
   6-oxohexyl)thio)propyl tetrahydro-2H-pyran-3,4,5-triyl triacetate 136 103
3.2.8. α/β-(2R,3S,4R,5R,6R)-2-(Acetoxymethyl)-6-(3-(2-hydroxyethyl)thio)propyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate 147  

3.2.9. 1-C-(2,3,4,6-Tetra-O-acetyl-(α,β-D-mannopyranosyl)-3-iodopropan-2-ol 143  

3.2.10. α/β-(2R,3S,4R,5R,6R)-2-(Acetoxymethyl)-6-(3-(acetylthio)propyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate 137  

3.2.11. α/β-(2R,3S,4R,5R,6R)-2-(Acetoxymethyl)-6-(3-mercaptpropyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate 138  

3.2.12. 1,2-Bis(3-(2,3,4,6-tetra-O-acetyl-α,β-D-mannopyranosyl)propyl)disulfane 151  

3.2.13. Methyl 2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside 64  

3.2.14. 3-(2,3,4,6-Tetra-O-benzyl-α-D-mannopyranosyl) propene 65  

3.2.15. S-(3-((2R,3R,4R,5S,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)propyl)ethanethioate 139  

3.2.16. 3-((2R,3R,4R,5S,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)propane-1-thiol 140  

4. BIBLIOGRAPHY AND APPENDIX

4.1. References  

4.2. Appendix  

List of Figures, Schemes and Tables:

**Figure 1.1**: Representation of carbohydrates illustrated by α-D-mannopyranose and β-D-mannopyranose: Fischer projection 1; Chair conformations 2, 3; Haworth projections 4, 5.
Figure 1.2: Chair conformations of β-D-glucopyranose (1C₁ & 1C₄).

Figure 1.3: Representation of the geometries of the lone pair-lone pair (lp-lp) orbitals on oxygen atoms at the anomeric centre.

Figure 1.4: Conformation of glycosides: Exo- and Endo-anomeric effects.

Figure 1.5: The working hypothesis for kinetic anomeric effect for controlling both α- or β stereoselectivity in C-glycosidation reaction.

Figure 1.6: An Efficient construction of β-C-glycoside on the basis of the conformation restriction restriction strategy.

Figure 1.7: Conformationally 1C₄-restricted glucose derivatives as the anomeric radical reaction substrates.

Figure 1.8: Definition of torsional angles (ϕ, ψ and ω) for methyl β-D-galactopyranosyl-(1→6)-β-D-glucopyranoside.

Figure 1.9: Schematic model for targeting glycoproteins on the cell surface.

Figure 1.10: Structure of Tₐ antigen.

Figure 1.11: Structure of sulfated N-linked oligosaccharides on luteinizing hormone.

Figure 1.12: One-pot protein glycosylation with reducing sugars isolated from natural sources.

Figure 1.13: Natural products containing C-glycoside bonds.

Figure 1.14: C-Glycosidic β-glucosidase inhibitors.

Figure 1.15: Axial-C-glucosides exist in a gauche arrangement rather than its anti-arrangement.

Figure 1.16: Natural products containing C-nucleoside bonds.
**Figure 1.17:** Different modes of multivalence in many normal and pathological processes observed in biological systems (not to scale).

**Figure 1.18:** The general approach to immobilised sugar supports.

**Figure 1.19:** Mode of action and *in vivo* results of lectin-directed enzyme activated prodrug therapy.

**Figure 1.20:** The structure of Heparin (n = 5-50).

**Figure 1.21:** Bacterial infection and the role of multivalent carbohydrates.

**Figure 1.22:** Interaction of aromatic mannosyl disulfide ligand with concanavalin A.

**Figure 1.23:** Graphical representation of the key step of the synthesis of glycodendrimers involving thio-ene reaction.

**Figure 2.1:** COSY spectrum of 142.

**Figure 2.2:** $^1$H NMR spectrum of 135.

**Figure 2.3:** Partial $^1$H NMR spectrum of 135.

**Figure 2.4:** X-ray structure of 135: ORTEP plot of the molecule and molecular cell (containing two mannosides).

**Figure 2.5:** $^1$H NMR spectrum of 147.

**Figure 2.6:** Mass spectrum of 147.

**Figure 2.7:** IR spectrum of 147.

**Figure 2.8:** $^1$H NMR spectrum of 136.

**Figure 2.9:** Partial $^1$H NMR spectrum of 136.

**Figure 2.10:** $^{13}$C NMR spectrum of 136.

**Figure 2.11:** Partial $^{13}$C NMR spectrum of 136.
Figure 2.12: Accurate mass spectrum of 136.

Figure 2.13: IR spectrum of 136.

Figure 2.14: Partial $^1$H NMR spectrum of 137.

Figure 2.15: Partial $^{13}$C NMR spectrum of 137.

Figure 2.16: $^1$H NMR spectrum of 138.

Figure 2.17: Partial $^1$H NMR spectrum of 138.

Figure 2.18: $^{13}$C NMR spectrum of 138.

Figure 2.19: Partial $^{13}$C NMR spectrum of 138.

Figure 2.20: IR spectrum of 138.

Figure 2.21: Partial $^1$H NMR spectrum of 65.

Figure 2.22: Partial $^1$H NMR spectrum of 139.

Figure 2.23: Partial $^{13}$C NMR spectrum of 139.

Figure 2.24: Partial $^1$H NMR spectrum of 140.

Figure 2.25: Graphical representation of the key step of the synthesis of glycodendrimers involving thio-ene reaction using free thiol-containing dendrimers.

Figure 2.26: Graphical representation of the key step of the synthesis of glycodendrimers involving thio-ene reaction using alkene cores.

Scheme 1.1: Synthesis of thioacetic glycoside.

Scheme 1.2: Synthesis of lacto-$N$-neotetraose clusters.

Scheme 1.3: Direct thionation of $\alpha$-$D$-mannopyranose using Lawesson’s reagent.

Scheme 1.4: Direct thionation of 2,3,4,6-tetra-$O$-benzyl-$\alpha$-$D$-mannopyranose using Lawesson’s reagent.
**Scheme 1.5:** *C-*glycosidic ligands for *E. Coli* receptors.

**Scheme 1.6:** Synthesis of trivalent glyocluster.

**Scheme 1.7:** Synthesis of multivalent tuberculosis and *Leishmania* capping structures on latex beads.

**Scheme 1.8:** Synthesis of trivalent *C-*mannoside.

**Scheme 1.9:** Synthesis of thiosugars.

**Scheme 1.10:** Synthesis of sulfide spacer-arm glycoside.

**Scheme 1.11:** Synthesis of organosulfur glycosides.

**Scheme 1.12:** Synthesis of a free thiol group-containing glycopyranoside.

**Scheme 1.13:** Synthesis of 4-deoxy-(1→5)-5-*C*-thiodisaccharides.

**Scheme 1.14:** Synthesis of 4-**S**-(β-*D*-glucopyranose-4-thio-*D*-glucopyranose.

**Scheme 1.15:** Synthesis of *C-*glycosidic bond.

**Scheme 1.16:** Synthesis of *C*-allyl glycosides.

**Scheme 1.17:** Synthesis of *S*-disaccharides.

**Scheme 1.18:** Synthesis of azido-functionalised pDVB80 microspheres (pDVB-*N*₃) *via* the thiol-ene reaction.

**Scheme 1.19:** Synthesis of highly branched glycopolymers.

**Scheme 1.20:** Synthesis of amide bond formation and deprotection of thioacetate to generate free thiol group.

**Scheme 2.1:** Synthesis of *C-*mannoside bond.

**Scheme 2.2:** Synthesis of methyl glycoside derivatives.

**Scheme 2.3:** Synthesis of *C*-allyl mannopyranosides.

**Scheme 2.4:** Synthesis of 1-*C*-(2,3,4,6-Tetra-*O*-acetyl-(α,β-*D*-mannopyanosyl)
-3-iodopropan-2-ol.

**Scheme 2.5**: Synthesis of sulfide spacer-arm glycoside.

**Scheme 2.6**: Thiol-ene Click chemistry.

**Scheme 2.7**: Synthesis of thiosugars.

**Scheme 2.8**: Synthesis of protected C-allyl mannopyranoside.

**Scheme 2.9**: Synthesis of free thiol group-containing sugar.

**Table 2.1**: Diastereoselectivity, yield and reaction conditions for C-1-allylation.
Abstract

C-Allyl mannopyranosides, 3-(2,3,4,6-tetra-O-acetyl-α,β-D-mannopyranosyl) propene and 3-(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl) propene, were successfully synthesised from α-D-methyl mannopyranoside. In this manner, C-allyl mannopyranosides were obtained in 39-60% yields, with α:β 4:1 anomeric selectivity for 3-(2,3,4,6-tetra-O-acetyl-α,β-D-mannopyranosyl) propene, while 3-(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl) propene was produced exclusively as the α-anomer.

Sulfur-linked carbohydrates were successfully synthesised [in the presence of 1,1′-azobis(cyclohexanecarbonitrile) as radical initiator] via the thiol-ene click reaction. Each reaction afforded the corresponding sulfide spacer-arm glycosides in good yields.

An efficient two-step methodology has been developed for the synthesis of the novel primary thiol group-containing sugars, (2R,3S,4R,5R,6R)-2-(acetoxymethyl)-6-(3-mercaptopropyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate and 3-((2R,3R,4R,5S,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)propane-1-thiol. In this way, free thiol group-containing sugars were obtained in 73% and 60% yields respectively, with an anomeric ratio of α:β 2.5:1 for (2R,3S,4R,5R,6R)-2-(acetoxymethyl)-6-(3-mercaptopropyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate and 3-((2R,3R,4R,5S,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)propane-1-thiol being obtained as the α-anomer only.

The thiol-ene click reaction was thus shown to be a viable method to obtain novel free thiol-containing C-glycosides. These compounds are suitable for future applications towards as multivalent saccharides via the use of the primary thiol function for click thiol-ene conjugations, or other S-based conjugation chemistry.
DECLARATION

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## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
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<td>ASn</td>
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<tr>
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<td>Aromatic</td>
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<td>BSTFA</td>
<td>Bis(trimethylsilyl)trifluoroacetamide</td>
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<tr>
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<td>WGA</td>
<td>Wheat-germ agglutinin</td>
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CHAPTER 1

INTRODUCTION
1. Introduction

1.1. Carbohydrates Chemistry and Biology

The term carbohydrate was originally used in the nineteenth century to describe the family of compounds which have the empirical formula $C_n(H_2O)_m$, are also known as the hydrates of carbon. However, carbohydrates can be defined in a broader sense as “all those substances composed of polyhydroxy aldehydes and ketones and their derivatives”. The purely chemical aspects of these compounds had fascinated chemists through the ages due to the multi-functionality of carbohydrates. Carbohydrates are important biologically where they serve as:

a) energy sources (starch, glycogen);

b) structural components including cellulose and chitin;

c) important parts of building blocks of nucleotides (RNA, DNA);

d) key roles in immune systems, important for blood clotting, cellular interaction and communication glycoconjugates, where they are covalently linked to proteins (glyco-proteins) or lipids (glycolipids).

Fischer and Haworth projections are the best known methods to represent the configuration of carbohydrates (Figure 1.1). The Haworth projection shows clearly the cyclic nature of carbohydrates. However, carbohydrate structures are more realistically represented by the chair forms 2 and 3.
1.2. Occurrence of Carbohydrates

Annually around 400 billion tons of carbohydrates are produced by photosynthesis. Around 60% of our diet consists of carbohydrates and cellulose is one of the most abundant sources of carbohydrates on earth. The specificity of the major blood types is determined by carbohydrates and both types of erythrocytes from the blood stream were cleared by the spleen. These are only some of the fascinating and remarkable properties of carbohydrates.

Most of the carbohydrates belong to the D-family of carbohydrate stereoisomers. The stereochemistry of the chiral carbon furthest from the anomeric carbon is distinguished according to the two prefixes, D and L. If the hydroxyl group, on this carbon is positioned to
the right in the Fischer projection, then this is represented as a D-series and if the hydroxyl group is on the left, it is represented as an L-series. D-Glucose is important as it serves as an immediate source of energy for mammals. Naturally occurring D-xylose is found in hemi-celluloses, whilst D-ribose plays an important role in metabolic processes. In addition, D-ribose-5-phosphate is present in ribonucleotides and polyribonucleotides (RNA), whilst 2-deoxyribose is part of polydeoxyribonucleotides (DNA).\(^5\)

1.3. Conformational Analysis of Carbohydrates

1.3.1. Conformational Study of Monosaccharides

Monosaccharides typically exist in two forms, as the six-membered pyranose ring or as the five-membered furanose ring. Both pyranose and furanose forms adopt puckered shapes to minimise eclipsing interactions.\(^6\) Pyranose and its derivatives mostly exist in a stable chair conformation. The other conformational forms that can be adopted are boat, skew, twist boat and half chair.

![Figure 1.2: Chair conformations of β-D-glucopyranose (\(^4\)C\(_1\) & \(^1\)C\(_4\)).](image)

The most stable conformation of \(β\)-glucopyranose, represented by 6, is the \(^4\)C\(_1\) conformation. The conformer 7 (Figure 1.2) is less stable, this being attributed to an axial hydroxymethyl group at C-5 and the resultant unfavourable 1,3-diaxial interactions with substituents at C-1 and C-3. Furanose derivatives are normally present as a mixture of twist and envelope conformations, as determined by the interactions between the substituents.\(^7\)
The reactivity of carbohydrates is strongly influenced by their conformations and therefore the conformational analysis of sugars is important in the study of their chemical and biological activity. In 1950, Reeves reported on the conformation of fifty two glycopyranosides in solution. He concluded that pyranose rings occurred mostly in their chair form rather than the boat-form, but both are structurally possible depending on substituents. Boat-form pyranose rings are unstable due to the large repulsions that occur between the adjacent groups as well as within the ring. In chair form, the relative thermodynamic stability increases when the substituent at C-1 is in the axial position rather than the equatorial position. The increased stability of the axial orientation over that of the equatorial conformer can be explained by an additional factor known as the anomeric effect, which occurs when an electron-withdrawing group, such as a halo or alkoxy group, is present at C-1 of the pyranose ring.

Electrostatic, steric and stereoelectronic factors are important considerations when trying to explain the anomeric effect. There have been many explanations given to account for the origins of the anomeric effect. More recently, evidence has supported two theories contributing to the effect: i) unfavourable dipole-dipole interactions and ii) a favourable interaction between the ring heteroatom lone pair and the σ* (antibonding) orbital of the C-O bond. Edward et al. conclude that the pyranose ring with axial substituent at C-1 is more stable than the equatorial case due to smaller dipole-dipole interactions and the unshared pair of electrons, which stabilise the adjacent electron-deficient carbon by hyperconjugation. The explanation for the anomeric effect involves destabilising dipole-dipole repulsion between the two oxygen atoms and their lone pairs (Figure 1.3).
Figure 1.3: Representation of the geometries of the lone pair-lone pair ($l_p$-$l_p$) orbitals on oxygen atoms at the anomeric centre.

In the equatorial conformer 8, the lone pair orbital on the exocyclic oxygen atom (O-7) is parallel with one lone-pair orbital on the endocyclic oxygen atom (O-1), while another lone-pair orbital on the exocyclic oxygen atom (O-7) is parallel with another lone pair orbital on the endocyclic oxygen atom (O-1), leading to repulsive destabilisation. In the axial conformer 9, on the other hand, only one pair of orbitals is parallel, leading to less repulsion. Thus, the geometry of the $\alpha$-amomer changed simultaneously in order to minimise the possible lone pair-lone pair interactions.

The anomeric effect also involves a stabilising interaction between the lone pair of electrons on the ring oxygen atom and the $\sigma^*$ (antibonding) orbital of the anomeric carbon-oxygen bond. This interaction is known as the endo-anomeric effect, as in (10, Figure 1.4).

Figure 1.4: Conformation of glycosides: Exo- and Endo-anomeric effects.
Additionally, an exo-anomeric effect is observed, through the donation of an electron pair from the exo-cyclic oxygen atom to the σ* orbital of the bond between the anomeric carbon and the ring oxygen, as in 11 and 12. It is to be noted that the equatorial conformation is stabilised by the exo-anomeric effect. This is due to the lack of any important competition for delocalisation of electrons from the glycosidic oxygen that, in the sterically most favourable orientation, has an unshared pair of electrons anti-periplanar to the C-1-ring oxygen bond. However, for the axial conformations, competition exists between the endo- and exo-anomeric effects, as in 10 and 12, for the electron deficiency at the anomeric carbon. The endo-anomeric effect is inherently stronger than the exo-anomeric effect for axial conformations.\textsuperscript{13}

Tamura \textit{et al.}\textsuperscript{14} reported that the kinetic anomeric effect was used effectively for controlling both α- or β-stereoselectivity in glycosidation reactions. As shown in Figure 1.5, the S\textsubscript{N}1-type C-glycosidation reaction of substrate 13, which is conformationally restricted in the \textsuperscript{4}C\textsubscript{1}-chair form 14 as a result of conformational restriction of the pyranose backbone, where the kinetic anomeric effect promotes selective formation of the α-product 15. Similarly, when the conformation of the radical intermediate is restricted to the unusual \textsuperscript{1}C\textsubscript{4}-chair form 16, the corresponding β-product 18 should be selectively obtained due to the kinetic anomeric effect via the β-axial attack transition state 17.
Figure 1.5: The working hypothesis for kinetic anomeric effect for controlling both α- or β stereoselectivity in C-glycosidation reaction.\textsuperscript{14}

The anomeric effect is influenced by the conformation of the sugar molecule, because it is the stereoelectronic effect on the anomeric position due to the nonbonding electron pair on the ring oxygen. Both the transition states, 14 (\textsuperscript{4}C\textsubscript{1}-form) and 17 (\textsuperscript{1}C\textsubscript{4}-form) can be effectively stabilised by the interaction between the σ\textsuperscript{*} (antibonding) orbital of the newly forming anomeric bond and the \(p\)-orbital of a nonbonded electron pair on the ring oxygen, because of the periplanar arrangement, which is the kinetic anomeric effect in anomeric radical reactions.\textsuperscript{15} Therefore, depending on the specific substrate conformation, which is restricted to the \textsuperscript{4}C\textsubscript{1}- or the \textsuperscript{1}C\textsubscript{4}-form, the α- or β-products can be obtained in a highly stereoselectively way \textit{via} anomeric radical reactions.

Thus, Abe \textit{et al.}\textsuperscript{16} reported the high dependence on the anomeric effect of α- and β-selective anomeric radical reactions based on the conformational restriction of the pyranose ring. For example, the conformation of the pyranose ring of the substrate 19, bearing a 3,4-\(O\)-cyclic-
diketal group, was restricted to the $^4C_1$-form due to its *trans*-decalin-type ring system. The reduction of substrate 19 having an anomeric carbon substituent by Et$_3$SiH/TMSOTf proceeded with complete stereoselectivity to produce the corresponding $\beta$-$C$-glycoside 20 when the substrate was conformationally restricted in the $^4C_1$-chair form.

**Figure 1.6:** An Efficient construction of $\beta$-$C$-glycoside on the basis of the conformation restriction strategy.

It is known that introducing a quite bulky protecting group at the 3,4-*trans*-hydroxy groups of pyranoses causes a flip in their conformation leading to the $^1C_4$-form, in which the bulky substituents are in axial positions due to mutual steric repulsion. Therefore, phenyl 1-seleno-2,3,4-tris-$O$-triisopropylsilyl-$\beta$-$D$-glucopyranoside 21 adopted a $^1C_4$-conformation due to the steric effect of the bulky silyl groups and were significantly sterically hindered due to the 1,3- and 1,5-diaxial repulsion. Abe *et al.* investigated the deuteration of the anomeric glucosyl radicals produced from unrestricted substrates, the $^4C_1$-restricted substrates, and the $^1C_4$-restricted substrates with Bu$_3$SnD/AIBN. Such deuterium-labeling experiments would be useful in estimating the stereoselectivity, leading to a clarification of the influence of the steric hindrance and the anomeric effect in anomeric radical reactions.

**Figure 1.7:** Conformationally $^1C_4$-restricted glucose derivatives as the anomeric radical reaction substrates.
However, when the \(^1\text{C}_4\)-restricted substrate 21 was used, no deuterium was incorporated at the anomeric position in the corresponding reduction product, which was produced in high yield. This result showed that significant 1,5-steric repulsion occurred in the \(^1\text{C}_4\)-restricted substrate due to the tetrahedral carbon structure (-CH\(_2\)) at the 5-position to prevent the approach of Bu\(_3\)SnD to the anomeric \(\beta\)-side. The radical reaction product from 21 was then treated with NaBH\(_4\), which readily converted it into the corresponding glucose derivative 22. The radical deuteration with the 6-aldehyde substrate 22, which has a formyl group attached at the 5-position instead of the hydroxymethyl group in 21, gave the \(\beta\)-deuterated product highly selectively as expected (\(\alpha:\beta\) 0:100). Thus, depending on the conformation of the substrates restricted to the \(^1\text{C}_1\)- or the \(^1\text{C}_4\)-form, the \(\alpha\)- or \(\beta\)-products would be obtained highly stereoselectively via anomeric radical reactions.\(^{14}\)

1.3.2. Conformational Study of Disaccharides

The monosaccharide units in a disaccharide are free to rotate around the glycosidic bonds. The relative orientations between the two participating monosaccharide units are defined by two torsion angles, \(\phi\) and \(\psi\), about the glycosidic bonds. When the glycosidic linkage is formed between C-1 of one monosaccharide unit and C-6 of the other, there is an extra torsion angle, \(\omega\) (23, Figure 1.8). The conformations of disaccharides are mainly determined by the torsional angles across the glycosidic linkage, starting from the anomeric centre.\(^{18}\) Therefore, studies of the conformations of disaccharides mainly focus on these glycosidic torsional angles. For example, torsional angles, \(\phi\) (H-1′–C-1′–O-1′–C-6) 24, \(\psi\) (C-1′–O-1′–C-6–C-5) 25 and \(\omega\) (O-1′–C-6–C-5–H-5) 26 are illustrated in the case of a (1→6)-linkage (23, Figure 1.8).\(^{7}\)
**Figure 1.8:** Definition of torsional angles ($\phi$, $\psi$ and $\omega$) for methyl $\beta$-$D$-galactopyranosyl-(1→6)-$\beta$-$D$-glucopyranoside.

### 1.4. Biological Roles

There is an ongoing effort to study the biological activity and function of carbohydrates. Multivalent interactions are now understood to be a ubiquitous strategy that has evolved in nature for a wide range of applications.\(^{19}\) These multivalent interactions, such as carbohydrate-recognition receptors on cell surfaces, peptide and hormone-recognition receptors on cell surfaces, enzymes, $G$-protein-coupled receptors, ion channels, lectins, toxins, viruses and bacteria, are more potent and selective than the analogous monovalent interactions. Several semi-synthetic glycopeptide derivatives, which act against resistant Gram-positive *cocci*, are currently in clinical development. Like vancomycin, these agents act by binding terminal acyl-$D$-alanyl-$D$-alanine residues in peptidoglycan precursors. The prevention of the transglycosylation and transpeptidation reactions is essential for production of the mature bacterial cell wall. Telavancin is a synthetic derivative of vancomycin under development by Theravance as a parenteral glycopeptide antibiotic for the treatment of severe
Gram-positive infections, which is more effective than vancomycin against Gram-positive cocci.\textsuperscript{20}

Bertozzi \textit{et al.}\textsuperscript{21} have reported the use of \(C\)-glycosyl compounds to inhibit the attachment of pathogenic organisms to cells. They demonstrated their ability to target the molecules to an infectious agent \textit{via} its cell-surface carbohydrate receptor. Biotin-linked \(C\)-glycoside derivatives of mannose derived, containing sugars have been used to attach avidin and streptavidin to the bacterial cell surface (\textbf{Figure 1.9}).

\begin{center}
\begin{tikzpicture}
\node (n1) at (0,0) {Pathogen};
\node (n2) at (1.5,0) {Avidin or Streptavidin};
\node (n3) at (1.5,-2) {Biotin};
\node (n4) at (-2,-2) {Carbohydrate receptor};
\node (n5) at (0,-4) {Carbohydrate};
\draw[->] (n1) -- (n2);
\draw[->] (n1) -- (n3);
\draw[->] (n1) -- (n4);
\end{tikzpicture}
\end{center}

\textbf{Figure 1.9:} Schematic model for targeting glycoproteins on the cell surface.\textsuperscript{21}

Brocke \textit{et al.}\textsuperscript{22} reported that \(T_N\) tumour-associated glycopeptide antigens represent important structures for the design of immunogens. The \(T_N\) antigen is linked to serine or threonine \textit{via} \(\alpha\)-\(O\)-glycosidic linkage (27, \textbf{Figure 1.10}). Such structures are of interest for the diagnosis of tumours.
Thiosugars are being explored as potential receptors for carbohydrate-based therapeutics and in the treatment of different pathological conditions including cancer and infectious diseases. The lacto-N-neotetraose clusters (Schemes 1.1 and 1.2) have been synthesised using thioacetyl tetrasaccharide 33 with fan, ball and dumbbell shaped carbosilane dendrimers.
Scheme 1.1: Synthesis of thioacetate glycoside 33.24 Reagents and reaction conditions: i) BzCl, pyridine, rt, 3 h ii) 50% CF₃CO₂H aq, CH₂Cl₂, rt, 3 h, 77% for 29 iii) AgOTf, MS 4Å powder, CH₃NO₂, rt, 15 h, 76% iv) n-BuNH₂, MeOH, reflux, 24 h v) Ac₂O, pyridine, 79% for 32 vi) AcSH, AIBN, 1,4-dioxane, 80 °C, 2 h, 98% for 33.
Scheme 1.2: Synthesis of lacto-N-neotetraose clusters.25 Reagents and reaction conditions: i) NaOMe, MeOH, DMF, 11 h, rt ii) Ac₂O, DMAP, pyridine, 30 °C, 3 h iii) NaOMe, MeOH, rt, aq. NaOH, rt, 0.5 h, 68% for 41, 96% for 45 and quant. yield for 37.

These lacto-N-neotetraose clusters were expected to be used as an artificial dengue virus receptor.24 In 2006, Aoki et al.25 discovered that the dengue virus preferentially adheres to lacto-N-neotetraose (Galβ1-4GlcNAcβ1-3Galβ1-4Glcβ1) located on the surface of eukaryotic cells. They found that lacto-N-neotetraose clusters act as a competitive inhibitor against the binding of dengue-2 virus to the host cell surface, using a TLC/virus binding assay. In 2007, Yamada26 described the specific binding properties of lactotriose dendrimers. Their biological activities with respect to wheat-germ agglutinin (WGA) were evaluated using fluorescence methods.
Organosulfur compounds are very significant in the field of biological science where they are widely used as intermediate compounds in the synthesis of medicines and are also important in agriculture and many other industries. S-Linked oligosaccharides are also very important in biological studies as hydrolytically stable probes for enzymatic action. Sulfated carbohydrates are significant in the control of the circulating half-life of luteinizing hormone. The function of GalNAc-4-SO₄-bearing oligosaccharides almost certainly extends beyond rapid clearance of luteinizing hormone from the bloodstream, which removed from the circulation four to fivefold more rapidly than recombinant luteinizing hormone bearing oligosaccharides which terminate with Gal-Sia (Figure 1.11). Also, thioglycosides have been used as competitive inhibitors of oligosaccharide processing enzymes.
1.5. Glycoconjugates

Over the last 15 years, there have been considerable efforts to synthesise well-defined multivalent glycoconjugates due to their importance in studying polyvalent interactions between proteins and carbohydrates. Glycoconjugates are essential for investigating such biological processes and they play an important role in cell signalling, regulation, cellular differentiation and the immune response. Recently, a lot of research has been carried out on the synthesis of glycoconjugate containing glycosyl thiols in order that they may be compared to glycopeptides and glycoproteins. In 2006, Bernardes et al. reported a one-pot protein glycoconjugation following the formation of glycosyl thiols from reducing sugars. They speculated that a direct synthesis of glycosyl thiols in combination with selenenylsulfide-mediated protein glycoconjugation would lead to a one-pot protein glycosylation method that could use reducing sugars isolated from natural sources. The free thiol of the side chain of the cysteine is converted into the corresponding (phenylselenenyl)sulfide following exposure to phenylselenenyl bromide. This activated protein, upon the addition of a 1-thio oligosaccharide, is directly converted into the corresponding glycoprotein (Figure 1.12).
Figure 1.12: One-pot protein glycosylation with reducing sugars isolated from natural sources.\textsuperscript{37}

They optimised the reaction conditions with respect to solvent system, temperature, reaction time and equivalents of Lawesson’s reagent\textsuperscript{39} for direct thionation of fully protected sugars (Scheme 1.3 and 1.4).\textsuperscript{37,40}

Scheme 1.3: Direct thionation of $\alpha$-D-mannopyranose using Lawesson’s reagent. Reagents and reaction conditions: \textit{i)} Lawesson’s reagent (1.5 equiv.), anhydrous dioxane, 110 °C \textit{ii)} Ac$_2$O, pyridine \textit{iii)} NaOMe, MeOH, 48 h, 48\% for 46.
Scheme 1.4: Direct thionation of 2,3,4,6-tetra-O-benzyl-α-D-mannopyranose using Lawesson’s reagent. Reagents and reaction conditions: Lawesson’s reagent (1.2 equiv.), anhydrous dioxane, 80 °C, 2 h, 80% for 48.

1.6. Chemistry of the C-Glycosidic Bonds

In biology, most important carbohydrate structures have sugars linked together or to other molecules via glycosidic bonds. When the oxygen atom of the glycosidic bond is replaced with a carbon atom, it is known as a C-glycosidic bond (See, for example, structures 49 and 50). The most significant difference between O- and C-glycosides is the absence of anomic and exo-anomeric effects in C-glycosides, which are unique features of saccharides and play an important role in the chemical and structural behaviour of O-glycosides. Additionally, C-glycosides are unable to form hydrogen bonds at the anomeric position due to the absence of a hydrogen-bonding acceptor. A major difference between C- and O-glycosides is found in their chemical reactivity. The anomeric atom of O-glycosides is susceptible to both acidic and enzymatic cleavage, whereas C-glycosides are resistant to hydrolysis.

1.6.1. C-Glycoside Bonds in Natural Products and Medicinal Chemistry

In 1984, Takashi et al. isolated the yellow pigment 51 (Figure 1.13) from the petals of Carthamus tinctorius and this was found to contain a C-glycoside moiety. In 1986, the C-
glycoside lignin 52 (Figure 1.13) was first isolated from *Tracheospermum asiaticum*.\textsuperscript{44} *Citreoviridin* 53 (Figure 1.13) was considered as a naturally occurring C-glycoside.\textsuperscript{45}

![Figure 1.13: Natural products containing C-glycoside bonds.](image)

In pharmaceutical synthesis and design, C-glycosides are considered as stable pharmacophores and can be used to synthesise enzyme inhibitors. In 1991, Schmidt et al.\textsuperscript{46} prepared 54 and 55 which were shown to be β-glucosidase inhibitors.

![Figure 1.14: C-Glycosidic β-glucosidase inhibitors.](image)

Experimental studies on the conformation of C-glycosides have been reported by Kishi and co-workers.\textsuperscript{47} From their findings, they proposed that axial and equatorial C-glycosides exist
in a gauche arrangement 56 rather than the anti-arrangement 57 due to 1,3-diaxial-like interactions in the latter conformer (Figure 1.15).

![Figure 1.15: Axial-C-glucosides exist in a gauche arrangement rather than its anti-arrangement.](image)

In 1993, H. N. Houk et al.\textsuperscript{48} investigated the predominancy of gauche O-C-1-C\textsubscript{exo} arrangement 56 over the anti-arrangement 57 by ab initio quantum mechanics and were in close agreement with Kishi’s experimental results. Kishi studied the conformational similarity between C- and O-glycosides. The (type II group O) trisaccharide 58 and its carbon analogue 59 are ideally suited for this purpose.\textsuperscript{49} He predicted that four different conformers of the blood group determinant trisaccharide can thus be accessed through the use of small, but strategically chosen structural modifications. The human blood group antigen 58 is ideal for this study because both the C-5 hydroxymethyl and the C-3’ hydroxyl group are available for the structural modification. Experimentally, Kishi has been demonstrated the conformational similarity of carbon- and oxygen-linked trisaccharides. To test this experimentally, he developed an efficient and flexible synthesis of this class of C-trisaccharides 60-63, which were predicted to exhibit four different conformational behaviours.
In 1992, Bertozzi et al.\textsuperscript{21} reported C-mannoside ligands that bind to \textit{Esherichia Coli} receptors. These biotin-linked C-linked mannosides were used to attach avidin and streptavidin to the bacterial cell surface (Scheme 1.5).

\textbf{Scheme 1.5:} C-glycosidic ligands for \textit{E. Coli} receptors. Reagents and reaction conditions: \textit{i)} Allyl-TMS, TMSOTf, MeCN, 0 °C then rt, 20 h, 91%, \(\alpha:\beta\) 15:1 \textit{ii)} 9-BBN, 30% \(\text{H}_2\text{O}_2\), THF, reflux then rt, 3 h, 95% \textit{iii)} \(\text{MsCl, Et}_3\text{N}\) \textit{iv)} \(\text{Bu}_3\text{NN}_{3}\), \(\text{CH}_3\text{CN}\) \textit{v)} \(\text{H}_2/\text{Pd(OH)}_2\), DMF, rt, 24 h, 56% \textit{vi)} NHS-Biotin, \(\text{Et}_3\text{N}\), MeOH, rt, 24 h, 71%.
1.6.2. C-Nucleoside Bonds in Natural Products and Medicinal Chemistry

C-Nucleosides are a class of C-glycosylated heterocyclic compounds in which position 1 is attached to a heterocycle by a C-C bond. The naturally occurring C-nucleosides show medicinal properties such as antibacterial, antiviral and antitumour activity. The modified C-nucleosides 69-74 are particularly designed for the treatment of viral infectious diseases such as the human immunodeficiency virus (HIV), hepatitis B virus (HBV) and the herpes viruses (Figure 1.16).

![Chemical Structures](image)

**Figure 1.16:** Natural products containing C-nucleoside bonds.

1.7. Multivalent Carbohydrates

The interaction between monovalent carbohydrate and receptor proteins is typically of low affinity. Therefore, multivalency plays a vital and functional role in carbohydrate-protein interactions, which is known as the cluster effect or glycoside cluster effect. Multivalency is defined as “the atom or molecule, macromolecule, material, protein or indeed a cell having multiple binding sites which bind to a number of ligands, presenting multiple interactions between them”. It has been reported that these global interactions are stronger than the sum of the individual monovalent interactions for many normal biological systems and
pathological processes where multivalency occurs. The lectins, such as the adhesins, which are membrane-tethered and consist of a lectin structure which presents only one CRD (carbohydrate-recognition domain), are attached to flagella bound to the cell surface. Many fimbrial structures clustered together at the cell surface would also give a multivalent presentation of the lectins in the extracellular environment. The collectins (soluble lectins), are a group of mannose-binding lectins that associate together forming oligomers. Three subunits combine to form a trimer; the trimers attached together via a collagen-like α-helix which is bound to the cell membrane. Biological systems use various types of multivalency in many normal and pathological processes, depending on their position, function and status (Figure 1.17).

**Figure 1.17**: Different modes of multivalence in many normal and pathological processes observed in biological systems$^{53}$ (not to scale).
Multivalency is an important factor in numerous biological processes such as tissue differentiation, cell-cell communication, host interactions with pathogens, protein targeting and many other therapeutic applications. Multivalent carbohydrate interactions with other molecules, especially with proteins, play a very important role in biological systems where they strongly influence key recognition processes. Examples include the interaction of uropathogenic Escherichia coli strains to urethral endothelial cells, neutrophil-endothelium interactions during the inflammatory process, the adhesion of cholera toxin to gangliosides GM1 on cell surfaces, tools for the discovery of transcription factor multiple binding sites in DNA sequences and the adhesion of influenza viruses to bronchial epithelial cells. Recognition between carbohydrates and proteins is most importance in many biological systems, such as bacterial, viral, parasitic and mycoplasmal infections, targeting of cells, cancer metastasis, fertilisation and differentiation.

Wheat-germ agglutinin (WGA) is a plant lectin, which is enriched in seeds of Triticum vulgaris and is important for inhibition of fungal growth. In 2010, Schwefel et al. showed that WGA interacted with multivalent N-acetylglucosamine (GlcNAc) and its derivatives using an enzyme-linked lectin assay (ELLA). As part of this study, trivalent glycoclusters (Scheme 1.6) were prepared.
Scheme 1.6: Synthesis of trivalent glyocluster 78. Reagents and reaction conditions: 

i) NH₂CH₂CH₂NH₂, AcOH, THF, α:β 9:1, 92%

ii) p-Nitrophenyl chloroformate, Et₃N, CH₂Cl₂, 0 °C, 3 h, α only, 92%

iii) Tris(2-aminoethyl)amine, i-Pr₂EtN, CH₂Cl₂, 2.5 h, rt, α only, 88%.

In 2010 Osanya et al. synthesised multivalent *tuberculosis* and *Leishmania*-associated capped carbohydrates. They selected commercially available latex beads 79 (microspheres, 1 μm diameter and yellow-green fluorescent) derivatised with carboxylate groups because the size of these beads mimics the size of the *Leishmania* and multivalent *tuberculosis* pathogens and the FITC-label permits use of a common immunofluorescent assay for the observation of beads uptake by macrophages. In order to avoid the spatial proximity of sugars on the surface of beads and improve the availability of sugars to possible macrophage binding allies, an ethylenediamine spacer was attached to the carboxylated beads surface under standard peptide coupling conditions (Scheme 1.7).
Scheme 1.7: Synthesis of multivalent *tuberculosis* and *Leishmania* capping structures on latex beads.\(^6^2\) Reagents and reaction conditions: \(i\) NH\(_2\)CH\(_2\)CH\(_2\)NH\(_2\), EDC, water, 25 °C, 36 h \(ii\) Sugar (30-50 equiv.), EDC, water, 25 °C, 36 h.

Ting *et al.*\(^6^3\) synthesised glycopolymers and explained their multivalent interactions with lectins. A number of lectins have been reported and isolated from plants, animals and microorganisms, which in combination with carbohydrates, engage in sugar-lectin recognition, which is very important in biological systems.

Glycopolymers (including glycodendrimers, linear glycopolymers and spherical glycopolymers in the form of micelles, vesicles and micro/nano particles) also have the ability to form multivalent interactions with lectins.\(^6^4\) In 2007, Chen *et al.* prepared surface modified Wang resin for protein purification chromatography. Their work was mainly on the synthesis of supports bearing covalently immobilised carbohydrates. They prepared two distinct classes of immobilised carbohydrate. Firstly, mannose monosaccharide moieties were “clicked” on to alkyne-modified Wang resin; secondly, polyalkyne polymers were prepared from immobilised initiators and mannose-azide units were then “clicked” on to this macromolecular scaffold to give the desired glycopolymer-bead hybrid materials. It was proposed\(^6^5\) that this mannose-binding model had great potential application in chromatography, sensors and protein recognition/separation fields (Figure 1.18).
Recently, more attention has been focused on the synthesis of multivalent carbohydrate assemblies due to their ability to target multiple receptors simultaneously.

1.7.1. Multivalent Carbohydrate Ligands

The use of carbohydrate ligands with targeted proteins for recognition is useful in the improvement, distribution of medicines in biological systems and treatment of diseases such as cancer using cytotoxic chemotherapy or radiotherapy. In 1989, Sharon et al. investigated carbohydrate ligands, which exhibited high affinity for lectins as receptors. Recently, the Gardiner group has reported various multivalent systems involving the synthesis of the scaffolds/core units and their combination with C-glycosidic compounds to form anomerically stable carbohydrate C-glycosidic ligands (Scheme 1.8).
**Scheme 1.8:** Synthesis of trivalent C-mannoside.\(^6^7\) Reagents and reaction conditions:  

1. NaH (60% mineral oil dispersion), BnBr, DMF, rt, 6 h, 77%  
2. Allyl-TMS, TMSOTf, MeCN, 18 h, rt, 53%  
3. BH\(_3\)-THF, THF, 27% H\(_2\)O\(_2\), 6 M NaOH, 80 °C then rt, 5 h, 77%  
4. Cr(III), H\(_2\)SO\(_4\), H\(_2\)O, Me\(_2\)CO, rt, 1.5 h, 76%  
5. TBTU, HOBt, DIPEA, DMF, 4 °C, 22 h, 60%.

Targeted drug delivery is extremely important in drug therapeutics. Over the last decade, attention has focused on the synthesis of glycopolymers and glycoproteins employing covalent conjugation of drugs to the carbohydrate ligands.\(^6^8\) Controlling the dose on such scaffolds is problematic. However, this can be solved by the introduction of lectin-directed enzyme activated prodrug therapy (LEAPT).\(^6^9\) The LEAPT is designed to exploit endogenous carbohydrate-lectin binding by combining it with biocatalysis through the construction of novel glycosylated enzymes and prodrugs. After administration of the appropriate prodrug,
the active drug molecule is released by the enzyme, resulting in a potential reduction in selectivity due to the diffusion and uptake of active drug into non-targeted bystander cells. However, several specific and potent binding mechanisms are present in nature and may be exploited in drug delivery. Among these mechanisms, the interaction of carbohydrate-binding protein lectins with carbohydrates is one of potential utility that has been chiefly highlighted by serum-clearance studies of glycoproteins by the asialoglycoprotein receptor (ASGPR) and the mannose receptor. The asialoglycoprotein receptor was first exploited in carbohydrate-mediated macromolecular drug delivery in 1983, but various examples have since been demonstrated. The targeting of enzymes by carbohydrate receptors has been demonstrated, but only when the enzyme itself is the therapeutic agent. To exploit such natural carbohydrate-binding mechanisms, the LEAPT approach uses two components: firstly, a glycosylated enzyme (α-rhamnosidase) is delivered to specific cell types within the body that are predetermined by the selected carbohydrate ligand; Secondly, the delivery of a L-rhamnopyranose-capped prodrug that is cleaved only by the delivery of glycosylated rhamnosidase. When these two steps are combined, activation of the prodrug results in site-selective release of the parent drug (Figure 1.19).
In 2000, Baek synthesised glycopolythiophenes containing mannose ligands by oxidative copolymerisation of thiophene-carbohydrate monomers with methyl 2-(thiophene-3-yl)acetate. These glycopolythiophenes were used for the detection of lectins, influenza virus and *E. coli* by visible absorption spectrometry.

In 2010, Vico *et al.* studied the kinetics of multivalent lectin-carbohydrate interactions. Each lectin-carbohydrate interaction showed a unique kinetic response, which varied depending on the carbohydrate, the surface density of carbohydrate and the lectin.
1.7.2. Molecular Recognition in Carbohydrates

Carbohydrate-specific cell surface receptors play essential roles in various biological recognition processes, for example, liver parenchymal cells have cell surface receptors that are specific for galactose and phagocytic to mannose. In 2001, David et al.\textsuperscript{73} studied the synthesis of novel $N$-(2-hydroxypropyl)methacrylamide (HPMA) copolymers containing multivalent carbohydrates side-chains, as potential drug carriers to achieve optimal targeting to hepatocarcinoma cells. The incorporation of sugar moieties in HPMA copolymers resulted in effective bio-recognition.

1.7.2.1. Human Immunodeficiency Virus (HIV)

The human immunodeficiency virus (HIV) has infected 35 million people worldwide.\textsuperscript{74} Vaccines to neutralise the antibodies and T-cell responses are considered potential preventive measures against HIV. The CD4 glycoprotein molecules are considered as the primary cellular receptor for the HIV-1 virus and are involved in switching on the human immune system.\textsuperscript{46} In 2004, Kesinger et al.\textsuperscript{52} studied the interaction of HIV-1 gp120 with GalCer and SGalCer and developed potential carbohydrate-based inhibitors to block this interaction. Glycosphingolipids (GSLs), GalCer \textbf{86} and its 3'-sulfated derivative, sulfatide (SGalCer), are alternative receptors, which may interact with HIV-1 gp120 in the absence of CD4.

The multivalent carbohydrates have also been identified as a potential class of HIV-1 inhibitors. Borges \textit{et al.}\textsuperscript{75} investigated multivalent carbohydrates in which glycosphingolipids (GSL) covalently bound to a dendrimer core inhibited HIV-1 infection. Recently, Kabanova
et al.\textsuperscript{26} studied four and eight valent sugar clusters of HIV-1 related oligomannose carbohydrates and synthesised neoglycoconjugates to target these carbohydrates.

\textbf{1.7.2.2. Heparin}

Heparin is a mixed polymer of \textit{D}-glucosamine, \textit{D}-glucuronic acid and \textit{L}-iduronic acid joined by glycosidic linkages. It is widely used in anti-coagulative therapy (\textbf{Figure 1.20}).\textsuperscript{5}

\begin{center}
\textbf{Figure 1.20:} The structure of Heparin (n = 5-50).
\end{center}

The flexible structure and high anionic charge of heparin permit electrostatic interactions with a variety of different molecules. Heparin has been used largely for its anticoagulant effects, such as anti-inflammatory, antiangiogenic, antimetastatic and wound healing abilities. Angiogenesis regulation, lipoprotein lipase modulation, maintenance of endothelial competence and inhibition of vascular smooth muscle proliferation after injury, are all clinical uses of heparin.

\textbf{1.7.2.3. Bacterial Adhesion and Multivalent Carbohydrates}

Infection at the tissue cell surface is often preceded by bacterial adhesion and the interaction between proteins and carbohydrates plays an important role in governing this process. Treatment of bacterial infection at an early stage is more attractive than using conventional antibiotics that are prone to the development of resistance. Synthetic efforts have been made
to design glycodendrimer and glycopolymer inhibitors that show high affinity in controlling these infections (Figure 1.21).\textsuperscript{77}

![Figure 1.21: Bacterial infection and the role of multivalent carbohydrates.\textsuperscript{77}](image)

Lindhorst \textit{et al.}\textsuperscript{78} prepared a number of multivalent carbohydrate compounds targeted against \textit{E. coli} interactions and studied their efficacy. It was found that the relative inhibition potencies of \(\alpha\)-mannosyl residues attached to a multivalent core were 100 times more effective than that of methyl \(\alpha-D\)-mannoside alone.

\textbf{1.8. Sulfur-linked and Sulfur-containing Carbohydrates}

Disaccharides in which the interglycosidic oxygen bond has been replaced by a disulfide bond are a relatively new approach to obtaining novel glycomimetics.\textsuperscript{79} Several synthetic multivalent glycomimetics have been prepared from multiple scaffolds.\textsuperscript{80} In 2009, Murthy \textit{et
prepared aromatic mannosyl disulfide 87 and its derivatives and studied their interactions with concanavalin-A (Figure 1.22).

![Figure 1.22: Interaction of aromatic mannosyl disulfide ligand with concanavalin A.](image)

Thiosugars have attracted much attention among chemists due to their unique physiochemical properties. Many functionalised thiosugars occur naturally and these are considered convenient probes for enzyme inhibition studies. Thiosugars are also used as potential targets for carbohydrate-based therapeutics and in the treatment of different pathological conditions, including cancer and infectious diseases. In 2001, Yu et al. reported the efficient synthesis of the biologically important methyl and heptyl 1-thio-β-mannopyranosides, which employed simple nucleophilic displacement reactions (Scheme 1.9).

![Scheme 1.9: Synthesis of thiosugars. Reagents and reaction conditions: i) AcSH, t-BuO’K+, DMF, rt, 4 h, 63% ii) NaOMe/MeOH iii) Iodomethane (R =-CH₃) or 1-Iodoheptane (R = -(CH₂)₆CH₃), MeOH, rt, 1 h, 91% or 97%.](image)

In 1997, Seeventer et al. reported the elongation of protected allyl α- or β-glycosides 92 via a radical addition reaction in the presence of the radical initiator azobisisobutyronitrile (AIBN), to prepare a functionalised sulfide spacer-arm glycoside 93 (Scheme 1.10).
Scheme 1.10: Synthesis of sulfide spacer-arm glycoside. Reagents and reaction conditions: AIBN, 2-mercaptoethanol, 1,4-dioxane, 75 ºC, 2 h, 75%.

In 2007, Sidamonidze et al.\textsuperscript{27} prepared organosulfur compounds by reacting 1-\textit{O}-allyl-2,3,4,6-tetra-\textit{O}-acetyl-\textit{D}-glactopyranose 92 with free thiol group-containing compounds in the presence of a radical initiator, \textit{i.e.} benzoyl peroxide (Scheme 1.11).

\begin{align*}
\text{Scheme 1.11: Synthesis of organosulfur glycosides. Reagents and reaction conditions:} & \\
\text{Benzoyl peroxide, CHCl}_3, \text{HSR (where R = -C}_2\text{H}_5 \text{ or -C}_3\text{H}_7 \text{ or -C}_4\text{H}_9), 75-80 \text{ ºC, 5 h, 62% for 94, 55% for 95 and 52% for 96.} & \\
\text{In 2008, D. Ellis et al.\textsuperscript{28} synthesised sulfur-linked carbohydrates using Ferrier reaction conditions. The per-\textit{O}-acetate protected derivative 98 was prepared by deprotection of the thioacetate in the presence of acetate groups 97 using hydrazine hydrate (Scheme 1.12).} & \\
\end{align*}

Scheme 1.12: Synthesis of a free thiol group-containing glycopyranoside. Reagents and reaction conditions: N\textsubscript{2}H\textsubscript{4} H\textsubscript{2}O, H\textsubscript{2}O, acetic acid, DMF, rt, 0.5 h, 86%.
In 2007, Witczak et al. prepared sulfur-linked products by reacting the 1-thiosugar, 2,3,4,6-tetra-O-acetyl-β-D-glucopyranose with the highly reactive enone 4-deoxy-1,2-O-isopropylidene-L-glyceropent-4-enopyranos-3-ulose. Reduction followed by in situ acetylation and then de-O-acetylation gave an anomic mixture of methyl 4-deoxy-5-C-(β-D-glucopyranosyl)-thio-α/β-L-ribo-pyranoside as stable and biologically important glycomimetic (Scheme 1.13).

**Scheme 1.13:** Synthesis of 4-deoxy-(1→5)-5-C-thiodisaccharides. Reagents and reaction conditions: i) Et$_3$N, CH$_3$CN, rt, 24 h, 89% ii) L-Selectride/THF, Ac$_2$O/Py, THF, −78 ºC to rt, 12 h, 82% iii) p-TSA/MeOH, MeOH, Et$_3$N/MeOH/H$_2$O, rt, 12 h, 89%.
Thiodisaccharides are used as potential inhibitors of glycosidases for the treatment of various metabolic diseases. Witczak et al.\textsuperscript{85} proposed a stereoselective approach towards the synthesis of $\beta$-(1$\rightarrow$4)-3-deoxythiodisaccharides (3-deoxytocellubiose) \textbf{109} from 2,3,4,6-tetra-$O$-acetyl-1-thio-$\beta$-$D$-glucopyranose \textbf{99} (Scheme 1.14).

\textbf{Scheme 1.14:} Synthesis of 4-$S$-(\textit{$\beta$}-$D$-glucopyranose-4-thio-$D$-glucopyranose. Reagents and reaction conditions: i) CH$_2$Cl$_2$, Et$_3$N or CH$_3$CN, Et$_3$N, 24 h, 89% ii) $L$-Selectride\textsuperscript{®}, THF, Py/\acs{Ac$_2$O}, $-78$ °C then rt, 15 h, 91% for \textbf{106} and 3% for \textbf{107} or DIBAH/THF, THF, Py/Toluene, $-78$ °C then rt, 25 h, traces for \textbf{106} and 63% for \textbf{107} iii) Et$_3$SiOSO$_2$CF$_3$/\acs{Ac$_2$O}, 4 °C, 12 h, $\alpha$:$\beta$ 1:5, 91% iv) MeOH/H$_2$O/Et$_3$N, rt, 6 h, $\alpha$:$\beta$ 1:6, 89%.
1.9. C- Allylation Reactions

Given the current research in C-glycosides and their numerous applications, which range from foodstuffs to components of nucleic acids, the synthesis of compounds containing the glycoside bonds is of particular interest. Many examples of the preparation of C-glycoside compounds have been reported in the literature. These types of reactions are usually carried out in the presence of Lewis acids, such as TMSOTf (trimethylsilyl trifluoromethanesulphonate), BF$_3$OEt$_2$ (boron trifluoride etherate) or tin chloride. In 1982, Kishi et al.\textsuperscript{86} studied highly stereoselective approaches to α- and β-glycopyranosides. They described the stereochemical control of the nucleophilic addition to the oxonium ion derived from tetra- O-benzyl- D-pyranose derivatives. The oxonium ion accepts nucleophiles from the α-axial side due to the anomeric effect from the oxygen in the ring. They treated 2,3,4,6-tetra- O-benzyl- D-glucopyranose with allyltrimethylsilane and boron trifluoride etherate in acetonitrile generating the product with high stereoselectivity.

In 1984, Hosomi et al.\textsuperscript{87} reported stereoselective synthesis of functionalised C-glycosides in good yield. They obtained stereoselective C-allylated glycopyranosides by reacting methyl α- D-gluco- and mannopyranosides with allyl silanes in the presence of trimethylsilyl triflate or iodotrimethylsilane. In 1987, Benneand et al.\textsuperscript{88} prepared allyl C-glycosides in good yields using silylation with bis(trimethylsilyl)acetamide (BSA) and bis(trimethylsilyl)trifluoroacetamide (BSTFA), followed by reductive cleavage in the presence of allyltrimethylsilane and TMSOTf. In 2006, Mari et al.\textsuperscript{89} prepared two novel galactose-derived bicyclic acetamides. They prepared 1- (α-D-galactopyranosyl)-2-propene as a single diastereomer by reaction of methyl α-D-galactopyranoside in the presence of bis(trimethylsilyl)trifluoroacetamide (BSTFA).
Horton et al.\textsuperscript{90} have reported the synthesis of 3-(2,3,4,6-tetra-O-acetyl-\(\alpha,\beta\)-D-glucopyranosyl) propene 111 and 112 in 23% combined yield with \(\alpha:\beta\) 5:1 (Scheme 1.15).

![Scheme 1.15: Synthesis of C-glycosidic bond. Reagents and reaction conditions: Allyl-TMS, BF\textsubscript{3}Et\textsubscript{2}O, MeCN, 80 °C, 48 h, \(\alpha:\beta\) 5:1, 23%.](image)

The Gardiner group also prepared C-glycoside analogues of monosaccharide sugars (Gal, Man, Glc), through allylation of the benzyl ethers with TMSOTf and allytrimethylsilane after benzylation. Subsequent chromatographic separation of the crude mixtures of C-galactoside 115, C-glucoside 118 and C-mannoside 65 yielded the diastereomers in the ratio \(\alpha:\beta\) 10:90 for 115, \(\alpha:\beta\) 12:88 for 118 and \(\alpha:\beta\) 97:3 for 65, respectively (Scheme 1.16).\textsuperscript{66}

![Scheme 1.16: Synthesis of C-allyl glycosides. Reaction and reaction conditions: i) NaH (60% dispersion in mineral oil), BnBr, DMF, rt, 6 h, 87% for 114, 93% for 117 and 77% for 64 ii) Allyl-TMS, TMSOTf, MeCN, rt, 18 h, 65% for 115 (\(\alpha:\beta\) 10:90), 57% for 118 (\(\alpha:\beta\) 12:88), 58% for 65 (\(\alpha:\beta\) 97:3).](image)

In 2002, Palomo et al.\textsuperscript{91} reported the synthesis of gluco-, galacto- and mannopyranosides through allylation with TMSOTf and trimethylsilane after benzylation. In 1992, Bertozzi et al.\textsuperscript{21} prepared a mixture of \(\alpha\)- and \(\beta\)-C-glycosyl compounds in good yield, with the \(\alpha\)-C-
glycosyl compound being the major compound. They reported that the ratio of $\alpha$- and $\beta$-glycosyl compounds were 15:1.

In 2008, McGarvey et al.\textsuperscript{92} investigated the stereoselectivity of C-allyl glucose under specific reaction conditions. They obtained the $\alpha$-allylated product in good yield with allyltrimethylsilane and boron trifluoride etherate in acetonitrile. They tried to find conditions that favoured $\beta$-formation of the allylated product selectively, but this proved to be less successful.

1.10. Thiol-ene Click Chemistry

Click chemistry is an advanced modular approach for synthesising macromolecular prototypes and it is a very useful tool in polymer science. In 2001, Kolb et al.\textsuperscript{93} introduced the concept of click chemistry to generate substances quickly by joining small units together.

The characteristics of modular click reactions\textsuperscript{94} include:

a) reactions are highly regiospecific and stereospecific;

b) reaction conditions are mild and aqueous;

c) yields of the reactions are high;

d) easy to remove impurities and side products;

e) availability of inexpensive starting material;

f) orthogonality with functional groups;

In 2002, Rostovtsev et al.\textsuperscript{95} studied copper-catalysed azide-alkyne cycloaddition click chemistry and applied it to the preparation of macromolecular constructs such as glycodendrimers and glycopolymers.

Recently, much research has been carried out on the well-known addition of a S-H group across a double or triple bond by either a free radical or ionic mechanism. This is known as thiol-ene click chemistry,\textsuperscript{96} which has wide applications in the chemical, biological, physical,
material and engineering fields. Thiol compounds react with a vast range of chemical species under optimised conditions and give excellent yields due to their high reactivity. The photochemically/thermally-induced version of the thiol-ene coupling (TEC) reaction proceeds by a radical mechanism to give an anti-Markovnikov-type stable thioether linkage. Reported examples of TEC applications in biochemistry include neoglycoconjugates, sulfide spacer glycosides, amino-terminated thioether spacers, neoglycopeptides, glycodendrimers containing mannose as fragments, tumour-associated glycopeptides and antitumour vaccines. Thiol-ene coupling reactions, in the absence of any metal catalyst, are very useful for bioconjugation since CuACC cannot be used due to the toxicity of copper metal for living cells. The reversibility of the thioalkyl radical addition to the alkene double is a known drawback, which may vary depending upon the structures of both the thiol and alkene reagents, the concentration of the thiol and the reaction temperature. This problem of reversibility can be overcome by employing an irreversible “locking step”, wherein the thioalkyl radical captures hydrogen a radical from another thiol to give the target stable thioether linkage. The nucleophilicity of the thiol component is an important factor in determining the rate of reaction in the thiol-ene click reaction. This coupling reaction has served as an important tool used for polymerisation and vulcanisation chemistry and to modify polymers.

In 2009, Fiore et al. prepared the photoinduced thiol-ene coupled thiodisaccharide 120 (Scheme 1.17) in good to excellent yields (76-92%) with high diastereoselectivities (up to 99%) of the α- and β-diastereomers.
Scheme 1.17: Synthesis of S-disaccharides. Reagents and reaction conditions: 2,2'-Dimethoxy-2-phenylethanone, DCM, hv (365 nm), rt, 15 min, 89%.

In 2004, Gao et al.\textsuperscript{103} reported the synthesis of a photoinduced glycocluster (Figure 1.23) based on polyhedral oligosilsesquioxanes. The bonds were made by employing a TEC reaction.

Figure 1.23: Graphical representation of the key step of the synthesis of glycodendrimers involving thio-ene reactions.\textsuperscript{103}

In 2009, Goldmann et al.\textsuperscript{104} used sequential reaction methodology for the functionalisation of cross-linked poly(divinylbenzene) microspheres (pDVB80). The (pDVB80) microspheres \textbf{122} (diameters of 1.3 µm) were prepared by distillation-precipitation polymerisation, in which the commercially available divinylbenzene monomer is polymerised and precipitated.
during the distillation of acetonitrile solvent from the reaction system. These poly(divinylbenzene) microspheres have a thin surface layer consisting of lightly cross-linked and swellable poly (divinyl benzene) and containing vinyl groups on their surfaces, which are approachable for modification. Here, poly(divinylbenzene) azidomicrospheres (pDVB-N$_3$) 123 were synthesised by treating the poly(divinylbenzene) microspheres 122 with 1-azidoundecan-11-thiol in a photoinitiated thiol-ene radical process (Scheme 1.18).

**Scheme 1.18:** Synthesis of azido-functionalised pDVB80 microspheres (pDVB-N$_3$) via the thiol-ene reaction. Reagents and reaction conditions: 1-Azidoundecan-11-thiol, AIBN, acetonitrile, 48 h, 70 °C.

In 2010, Semsarilar *et al.*$^{105}$ studied the use of RAFT polymerisation in combination with postpolymerisation by click chemistry to synthesise densely functionalised hyperbranched glycopolymers (Scheme 1.19). These glycopolymers with their unique structure have potential biomedical applications.
Scheme 1.19: Synthesis of highly branched glycopolymers. Reagents and reaction Conditions: i) PABTC, AIBN, toluene, 60 °C, 24 h, 93% ii) CH₃COOH, TBAF, THF, rt, 12 h, 100% iii) Azidoethyl galactose, Cu(PPh₃)₃Br, DIPEA, DMF, rt, 72 h, 85% iv) Glucothiose, HCl, DMPA, DMF, rt, 8 h, > 90%.

Ekeroth et al.¹⁰⁶ synthesised phosphorylated amino acid analogues of serine, threonine and tyrosine based on 3-mercaptopropionic acid and then assembled them onto gold surfaces.
Scheme 1.20: Synthesis of the amide bond formation and deprotection of thioacetate to generate free thiol group. Reagents and reaction conditions: 

1. Hydroxy benzotriazole, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, Et<sub>3</sub>N, DCM, 0 °C, 12 h, 83%

2. CH<sub>3</sub>OH, CH<sub>3</sub>O<sup>−</sup>Na<sup>+</sup>, rt, 20 min, quant. yield

3. Tetrazole, N,N-Diisopropyl-di-tert-butyl phosphoramidite, mCPBA, DCM, 0 °C, 2.5 h, 62%

4. Trifluoroacetic acid, CH<sub>3</sub>OH, CH<sub>3</sub>O<sup>−</sup>Na<sup>+</sup>, DCM, rt, 1.5 h, quant. yield.

1.11. Aim of the Project

Initially, the yield for 3-(2,3,4,6-tetra-O-acetyl-α,β-D-mannopyranosyl) propene improved by optimisation of the reaction conditions through allylation of 2,3,4,5-tetra-O-acetyl mannopyranoside.

The aim of this project is also to investigate the thiol-ene click coupling reaction by reacting N-benzyl-6-mercaptohexanamide with allyl sugar.

We also aimed to investigate to optimise reaction conditions for the synthesis of free thiol-containing carbohydrates in two steps. The first step involved the addition of thioacetic acid to the C-allyl protected sugars (using a radical initiator) via the
thiol-ene click reaction. The second step involved the deprotection of the resulting thioacetates 137 and 139 using hydrazine hydrate at rt and the generate of a free thiol group.
CHAPTER 2

RESULTS AND DISCUSSION
The main aspect of this research was to synthesise intermediates, which could be used to prepare multivalent carbohydrates.

2.1. Synthesis of the C-Glycosidic Bond

When the oxygen atom of the glycosidic bond is replaced with a carbon atom, it is known as a C-glycosidic bond. The initial reactions described herein involved the introduction of the C-glycosidic bond through allylation. The first allylation conditions evaluated were those reported in literature\textsuperscript{88,109} involving treatment of the unprotected methyl-\(\alpha\)-D-mannopyranoside 49 with BSTFA followed by allyltrimethylsilane and TMSOTf (Scheme 2.1). This reaction successfully provided the C-allylic glycoside 141 (\(\alpha/\beta\)) in a combined yield of 74%, with the \(\alpha\)-anomer isolated as the major product. This reaction required the transient protection of all hydroxyls using BSTFA but due to the high cost of this reagent, we decided to evaluate alternative C-allylation methods.

\begin{center}
\textbf{Scheme 2.1:} Synthesis of C-mannoside bond. Reagents and reaction conditions: BSTFA, allyltrimethylsilane, TMSOTf, acetonitrile, H\textsubscript{2}O, 80 °C then rt, 25 h, \(\alpha/\beta\) 9:1, 74% for 141 (\(\alpha/\beta\)).
\end{center}

A carbohydrate protection strategy was designed for acquiring the desired glycoside derivatives via the use of acetylation and benzylolation. According to a published procedure, the commercially available methyl-\(\alpha\)-D-mannopyranoside 49 reacted with acetic anhydride, producing the target compound 142 in 86% yield. Furthermore, the methyl 2,3,4,6-tetra-O-benzyl-\(\alpha\)-D-mannopyranoside 64 was synthesised in 60% yield by treating the methyl-\(\alpha\)-D-mannopyranoside 49 with benzyl bromide in the presence of sodium hydride (Scheme 2.2).
Scheme 2.2: Synthesis of methyl glycoside derivatives. Reagents and reaction conditions: 

(i) Acetic anhydride, 0 °C to rt then 25 °C, pyridine, 4 h, 86% for 142

(ii) (a) Sodium hydride (60% mineral oil dispersion), DMF, 25 °C, 1 h (b) Benzyl bromide in DMF, 70 °C, 15 h, 60% for 64.

The structure of 142 was established by $^1$H NMR, $^{13}$C NMR, DEPT-135, COSY, HMQC, MS and IR experiments. The spectral data collected for compound 142 matched those reported in the literature. The $^1$H NMR spectrum of 142 showed a double doublet of doublets ($J = 9, 5$ and 2.5 Hz) for H-5 at 3.96 ppm and a doublet of doublets for H-6a and H-6b at 4.11 and 4.28 ppm with coupling constants $J_{5,6a}$ and $J_{5,6b}$ of 2.5 and 5 Hz, respectively. The peak for H-1 appeared as a doublet at 4.71 ppm and H-2 as a doublet of doublets at 5.23 ppm with $J_{1,2}$ of 2 Hz. The H-3 and H-4 protons showed multiplet peaks at 5.27 and 5.32 ppm, respectively.

Two-dimensional correlated spectroscopy (COSY) is used for measurements of the proton-proton coupling constants. Thus, this spectrum indicates which protons are coupled in a molecule in a fairly unambiguous way. The COSY spectrum of compound 142 revealed the coupling of H-1 to H-2, while H-2 also showed coupling with H-3. The H-5 was coupled to H-6a, H-6b and H-4, while H-4 also showed coupling with H-3 (Figure 2.1).
Subsequently, TMSOTf was employed as the Lewis acid for \( C \)-allylation with allyl-TMS as the \( C \)-nucleophile (Scheme 2.3). On treatment of methyl tetra-\( O \)-acetyl-\( \alpha \)-\( D \)-mannopyranoside 142 in acetonitrile with allyltrimethylsilane and TMSOTf at room temperature, no reaction was observed. However, on elevation of the temperature, the reaction was found to proceed (Table 2.1).

Scheme 2.3: Synthesis of \( C \)-allyl mannopyranosides. Reagents and reaction conditions: \( i \) Allyltrimethylsilane, TMSOTf, 80 °C, acetonitrile, 8 h, 39% for 135 or 24 h, 42% for 135 or 48 h, 54% for 135 \( ii \) Allyltrimethylsilane, TMSOTf, 50 °C, acetonitrile, 16 h, 54% for 65.
After purification and analysis, the α-anomer of 135 was observed as the major diastereomer. This inversion of selectivity of the α-anomer of 135 was thought to be due to the presence of the axial -OAc group at C-2 in 142. This may facilitate nucleophilic attack on the opposite face of the intermediate oxonium ion. Attempts were made to separate the mixture of anomers by flash chromatography, but these were found to be unsuccessful. From Table 2.1, it can be seen that the diastereoselectivity of the C-1-allylation for compound 135 did not change on increasing the reaction time, but it did have a slight effect on the yield of the product.

**Table 2.1:** Diastereoselectivity, yield and reaction conditions for C-1-allylation

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Conditions</th>
<th>Yield</th>
<th>α:β anomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>135</td>
<td>Acetyl</td>
<td>Allyltrimethylsilane, TMSOTf, 25 °C, acetonitrile, 48 h</td>
<td>No Reaction</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allyltrimethylsilane, TMSOTf, 80 °C, acetonitrile, 8 h</td>
<td>39%</td>
<td>4:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allyltrimethylsilane, TMSOTf, 80 °C, acetonitrile, 24 h</td>
<td>42%</td>
<td>4:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allyltrimethylsilane, TMSOTf, 80 °C, acetonitrile, 48 h</td>
<td>54%</td>
<td>4:1</td>
</tr>
<tr>
<td>65</td>
<td>Benzyl</td>
<td>Allyltrimethylsilane, TMSOTf, 50 °C, acetonitrile, 24 h</td>
<td>60%</td>
<td>Only α-anomer</td>
</tr>
</tbody>
</table>

The 1H NMR spectrum of 135 showed the signals for the allyl CH₂ protons between 5.17 and 5.23 ppm and for the allyl CH proton between 5.69 and 5.82 ppm, while peaks for the methylene protons appeared between 2.35 and 2.56 ppm (m, CH₂). The 1H signals for the acetate groups of 135 were observed between 1.98 and 2.18 ppm (Figure 2.3). The signals for the acetate groups of the α-diastereomer were observed at 2.03, 2.07, 2.09 and 2.13 ppm whereas those for the β-diastereomer were at 1.98, 2.04, 2.09 and 2.18 ppm. The proton peak for H-1 appeared as a doublet of doublets at 4.03 ppm, while peaks for H-2 and H-2', H-3 and
H-3′ and H-4 and H-4′ were observed between 5.02 and 5.34 ppm (Figure 2.2). The ¹H NMR spectrum recorded for 135 showed a doublet of doublets for H-6 and H-6b at 4.09 ppm and 4.30 ppm, respectively. The proton signal for H-5′ of the β-anomer appeared as a multiplet between 3.59 and 3.64 ppm while the proton signal for H-5 of the α-anomer showed as a double doublet of doublets at 3.88 ppm, clearly separated from the H-5′ signal (Figure 2.2). The ¹H NMR spectrum recorded showed that both the α- and β-diastereomers were present in the mixture in a 4:1 ratio with the α-anomer being the major diastereomer.

The ¹³C NMR spectrum recorded for 135 was assigned with the help of HMOC and DEPT-135. The formation of the C-allyl mannopyranoside 135 was confirmed by the disappearance of the carbon signal for the methoxy group at 55.3 ppm that had been present in the spectrum recorded for 142, and by the emergence of carbon signals for the allyl CH at 132 ppm and allyl CH₂ at 118 ppm.

Figure 2.2: ¹H NMR spectrum of 135.
Figure 2.3: Partial $^1$H NMR spectrum of 135.

The COSY NMR spectrum recorded for 135 was crucial for assigning the sugar ring and allyl protons. Proton H-5 showed coupling to H-6a and H-6a’, while H-5’ was coupled to 6b and 6b’. Proton H-8 was coupled to H-7 and H-9, while H-7 also showed coupling to H-1.

Finally, crystals of 135 were obtained upon crystallisation from the solvent mixture acetone:hexane (1:15), hence single X-ray crystallography was conducted. Disorder was observed in the X-ray crystallographic structure due to the presence of the minor β-diastereomer of 135 in the crystal lattice. The X-ray crystal structure provided evidence that the pyranose ring of the α-diastereomer of 135 adopted a $^4$C$_1$-chair conformation.
**Figure 2.4:** X-ray structure of 135: ORTEP plot of the molecule and molecular cell (containing two mannoses).

Following allylation, we obtained the addition product 143 in quantitative yield by treating C-allyl mannopyranoside 135 with N-iodosuccinimide (Scheme 2.4).

**Scheme 2.4:** Synthesis of 1-C-(2,3,4,6-tetra-O-acetyl-(α,β-D-mannopyranosyl)-3-iodopropan-2-ol 143. Reagents and reaction conditions: N-Iodosuccinimide, DMSO, Na$_2$S$_2$O$_3$, rt, 12 h, 65%.

The $^1$H NMR studies showed the disappearance of the allyl CH and CH$_2$ signals, which had been present in the $^1$H NMR spectrum recorded for 135, and the emergence of a methylene signal for the group directly attached to iodine at 3.27 ppm and the emergence of a CH signal for the group attached to OH at 3.95 ppm. The proton signal for the OH group appeared as two broad peaks at 3.77 and 3.50 ppm due to the presence of both the $R$- and $S$-isomers of
respectively. The $^{13}$C spectrum recorded for 143 showed two carbon signals for the CH$_2$ group attached to iodine at 13.0 and 13.6 ppm, respectively, for the two isomers of 143 while only a single carbon signal at 72.1 ppm was observed for the CH group attached to the OH. The structure of the novel compound 143 was further established from the MS (m/z 539 [M + Na$^+$, 100%]) and HRMS data. Finally, an IR spectrum recorded for 143 (3484 cm$^{-1}$ broad stretch for O-H) was also consistent with this preparation.

Initially, we decided to perform the synthesis of compound 145 from the C-allyl sugar 135 (Scheme 2.4). Hence, the title compound 143 was synthesised. However, we then changed our focus towards the aim of developing a two-step methodology (Scheme 2.7) rather than a three-step methodology (Scheme 2.4) for the synthesis of a free thiol group-containing novel sugar, which is similar to compound 145. Towards this end, no further reaction of 144 was carried out. However, the title compound 143 suggested that the free thiol group-containing sugar 145 could be produced by OH oxidation followed by nucleophilic displacement reactions respectively (Scheme 2.4).

2.2. Thiol-ene Click Chemistry

2.2.1. Synthesis of Thioether Sugar

Thiol compounds were selected because of their high reactivity, broad range of availability and low cost. However, a significant disadvantage of thiols is their odour but this can be overcome by appropriate handling and stabiliser selection. 2-Mercaptoethanol was chosen for the thiol-ene click reaction with C-allyl glycoside 135 as it is commercially available, inexpensive and exhibits both hydrophilic and hydrophobic characters. It is noteworthy that the primary hydroxyl function of 3-(2-hydroxyethyl-thio)-propyl glycosides (see, for example, compound 147) was transformed into an azide function. It is currently recognised that these azides are suitable substrates for performing further synthetic elaboration via click
copper-catalysed azide-alkyne cycloaddition (CuAAC). Similar reactions would be carried out between allyl sugar and thiols with different functional groups. For example, thioglycolic acid would be chosen for its ability to make carboxylic acid functionality instead of double bonds, which results in a significant change in solubility and the associated increase in capability to bind to the surface of nanoparticles, an indication of possible use for biomedical applications.  

Compound 147 was synthesised by treating the C-allyl sugar 135 with 2-mercaptoethanol in the presence of a radical initiator. Initially, benzoyl peroxide was selected as the radical initiator. However, it did not produce the desired target molecule 147 and only the starting material 135 was observed in the $^1$H NMR spectrum recorded of the material isolated. Subsequently, 1,1'-azobis(cyclohexanecarbonitrile) was used as the radical initiator. This gave the novel target compound 147 in good yield (57%), in the anomeric ratio $\alpha:\beta$ 5:1. The product 147 was fully characterised using an IR, $^1$H NMR, $^{13}$C NMR, COSY and DEPT-135 spectroscopy and both low- and high-resolution mass spectrometry.

Scheme 2.5: Synthesis of sulfide spacer-arm glycoside. Reagents and reaction conditions: 1,1'-Azobis(cyclohexanecarbonitrile), 1,4-dioxane, 80 °C, 10 h, 57%, $\alpha:\beta$ 5:1.
Figure 2.5: $^1$H NMR spectrum of 147.

The $^1$H NMR spectrum of 147 showed the disappearance of the signals for the CH and CH$_2$ protons of the allyl moiety, which had been present in the $^1$H NMR spectrum recorded for 135. Furthermore, proton signals for the -CH$_2$-S-CH$_2$- group appeared as a multiplet peak between 2.5 and 2.8 ppm. The proton signal for the CH$_2$ group directly attached to the OH group of 147 appeared as a triplet ($J = 6$ Hz) at 3.73 ppm. The proton signal for the OH group was observed as a singlet peak at 3.7 ppm. The H-5$'$ signal for the $\beta$-anomer was observed at 3.6 ppm. The $^{13}$C NMR spectrum recorded for 147 showed carbon signals for the -CH$_2$-S-CH$_2$-CH$_2$-OH moiety at 30.6, 34.7 and 60.1 ppm. The C-5$'$ carbon appeared as a signal at 75.9 ppm, which was assigned with the help of the corresponding HMQC spectrum.

The structure of the compound 147 was also confirmed with the help of mass spectrometry MS ($m/z$ 473 [M + Na$^+$, 100%]) and HRMS (Figure 2.6). Finally, an IR spectrum recorded for 145 (3472 cm$^{-1}$ broad stretch for O-H) was also consistent with the formation of 147 (Figure 2.7).
Figure 2.6: Mass spectrum of 147.

Figure 2.7: IR spectrum of 147.
2.2.2. Synthesis of Organosulfur Compound as a Model

Organosulfur compounds have considerable importance in the field of biological science. They are widely used in agriculture and as intermediate compounds in medicines.\textsuperscript{16} S-Glycosides have also been used in the treatment of different pathological conditions including cancer and infectious diseases.\textsuperscript{23,27}

The synthesis of organosulfur sugar 136 proceeded with the reaction of a solution of 6-bromohexanoic acid 148 with potassium thioacetate in methanol. This gave the target compound 149, as reported in the literature.\textsuperscript{108} The -COOH function of 149 was then protected as an amide by treating 149 with benzylamine in the presence of a coupling reagent, either \(O-(7\text{-azabenzotriazol-1-yl})-N,N,N',N'-\text{tetramethyluronium hexafluorophosphate (HATU)}\) or \(N,N,N',N'-\text{tetramethyl-O-(1H-benzotriazol-1-yl)uranium hexafluorophosphate (HBTU)}\) and 1-hydroxybenzotriazole hydrate. Finally, the thioacetate group of 150 was deprotected to give the novel free thiol group-containing compound 134. The conversion of the thioacetate group into the free thiol group was first attempted using sodium ethoxide but this did not give the target free thiol compound 134, while mass spectra revealed that dimerisation had occurred instead. Another attempt was made using aqueous \(K_2\text{CO}_3\) at room temperature. The reaction was monitored periodically using thin layer chromatography but only starting material was observed. The same reaction was repeated but, this time, under reflux and this successfully yielded the target free thiol group-containing compound 134. This compound was then used in a thiol-ene click radical reaction with the C-allyl sugar 135.
Scheme 2.6: Thiol-ene click chemistry. Reagents and reaction conditions: i) Potassium thioacetate, methanol, 65 °C, 5 h, 79% ii) HATU or HBTU, 1-hydroxybenzotriazole hydrate, benzylamine, overnight, rt, 72% iii) K$_2$CO$_3$, methanol, 65 °C, 50 min, 72% iv) 1,1′-Azobis(cyclohexanecarbonitrile), 1,4-dioxane, 80 °C, 10 h, 25%, α:β 3:1.

The $^1$H NMR spectrum recorded for compound 149 matched the literature data. The corresponding $^{13}$C NMR spectrum for 149 showed two carbon signals for the C=O groups at 179.6 and 196.1 ppm, respectively and mass spectrometry also confirmed the formation of compound 149. The $^1$H NMR spectrum obtained for compound 150 showed a broad signal for the amide proton at 8.41 ppm, a singlet at 4.31 ppm for the CH$_2$ benzyl protons and a multiplet peak for the aromatic protons between 7.04 and 8.53 ppm. The $^{13}$C NMR spectrum recorded for this compound showed a signal for the benzylic carbon at 44.2 ppm, while the signals for the C=O group attached to the thioacetate and the C=O group attached to NH were found at 197.6 and 176.1 ppm, respectively. The structure of the synthesised compound 150 was also confirmed using MS ($m/z$ 302 [M + Na$^+$, 100%]) and HRMS. The IR spectrum recorded for 150 showed peak at 3296 cm$^{-1}$ for the N-H bond. The IR spectrum also showed peaks at 1686 cm$^{-1}$ for the C=O group (thioacetate) and at 1638 cm$^{-1}$ for the C=O group.
attached to amide bond. The $^1$H NMR spectrum recorded for compound 134 showed the appearance of the proton signal for the SH group as a triplet at 1.27 ppm and disappearance of the proton signal for the thioacetate group at 2.29 ppm, which had been present in the spectrum of the starting material 150. The $^{13}$C spectrum for this compound showed the disappearance of the C=O signal at 197.6 ppm, which had been observed in the spectrum recorded for 150 and the carbon signal for the CH$_2$-SH showed at 25.0 ppm, while it appeared at 29.2 ppm in the spectrum of starting material. The structure of compound 134 was also confirmed with the help of MS (m/z 260 [M + Na$^+$, 100%]) and HRMS. The IR spectrum was also recorded for 134 showing disappearance of the peak at 1686 cm$^{-1}$ for the thioacetate C=O group, which had been observed in the IR spectrum recorded for 150 and the emergence of a weak band at 2550 cm$^{-1}$ due to the stretching of the S-H bond in 134.

Subsequently, the free thiol group-containing compound 134 was reacted with allyl glycoside 135 in the presence of a radical initiator to give the target novel compound 136 in 25% yield. The preliminary structure of novel compound 136 was confirmed using $^1$H NMR, $^{13}$C NMR, COSY, HMQC, DEPT-135 spectroscopy, mass spectrometry and IR spectroscopy. The four thioether protons (i.e. -CH$_2$-S-CH$_2$-) appeared as a multiplet peak between 2.34 and 2.59 ppm in the $^1$H NMR spectrum (Figure 2.8). The triplet peak at 2.15 ppm corresponded to the two protons of the methylene group joined to the C=O group and the broad singlet peak at 5.90 ppm was assigned to the amide NH proton. The doublet peak at 4.36 ppm evidenced the presence of the two benzylic protons. The peaks attributed to the eight methylene protons at positions 7, 8, 11 and 13 were found between 1.45 and 1.68 ppm and the protons of the CH$_2$ group at position 12 gave signals between 1.30 and 1.40 ppm. The signals between 7.19 and 7.26 ppm represented the five protons of the benzene ring (Figure 2.8).
Figure 2.8: $^1$H NMR spectrum of 136.

Figure 2.9: Partial $^1$H NMR spectrum of 136.
The signals associated with the acetate protons of the α-diastereomer of 136 were observed at 1.94, 1.98, 2.02 and 2.05 ppm whereas for the β-diastereomer, these protons appeared at 1.89, 1.97, 2.01 and 2.09 ppm, respectively (Figure 2.9). These signals confirmed the diastereomeric ratio of 136 to be α:β 3:1.

The $^{13}$C NMR spectrum for 136 showed the five carbon signals for the five C=O groups at 169.9, 170.3, 170.6, 171.0 and 173.0 ppm (C=O amide) (Figure 2.11). Carbon C-10 and C-9 (i.e. -CH$_2$-S-CH$_2$) were observed at 31.4 and 31.9 ppm, respectively. The carbon signal for the C-14 CH$_2$ group, which was directly attached to the C=O group, was observed at 36.5 ppm, whilst the carbon signal for the C-16 CH$_2$ group was observed at 43.6 ppm. All carbon signals of the benzene ring were observed between 127.5 and 138.4 ppm and signals for C-7, C-8, C-11, C-12 and C-13 were observed at 28.4, 25.3, 29.3, 25.2 and 27.3 ppm, respectively (Figure 2.10).

![Figure 2.10: $^{13}$C NMR spectrum of 136.](image-url)
The structure of novel compound 136 was further established from the MS (m/z 632 [M + Na⁺, 100%]) and HRMS data (Figure 2.12). In addition, an IR spectrum recorded for 136 showed peaks at 1647 cm⁻¹ for the C=O group and at 3292 cm⁻¹ for the N-H bond. The IR spectrum also showed peaks at 646 cm⁻¹ for the C-S bond and at 1220 cm⁻¹ for the C-O bond (Figure 2.13).
Figure 2.12: Accurate mass spectrum of 136.
2.2.3. Synthesis of Free Thiol-containing Sugars

The synthesis of the free thiol group-containing sugar 138 proceeded with reaction of a solution of 3-(2,3,4,6-tetra-<i>O</i>-acetyl-α,β-<i>D</i>-mannopyranosyl) propene 135 in 1,4-dioxane with thioacetic acid in the presence of the radical initiator 1,1′-azobis(cyclohexanecarbonitrile) to give the target compound 137 in 89% yield (Scheme 2.7). Deprotection of the thioacetate function in the presence of the acetate groups was successfully achieved using hydrazine hydrate and this gave the required target novel compound 138. The dimerised product 151 was also observed in low yield together with 138. The title compounds 138 and 151 were characterised by <sup>1</sup>H NMR, COSY, <sup>13</sup>C NMR, HMQC, DEPT-135, MS and IR techniques.
**Scheme 2.7:** Synthesis of thiosugars. Reagents and reaction conditions: *i*) Thioacetic acid, 1,1′-azobis(cyclohexanecarbonitrile), 1, 4-dioxane, 80 °C, 10 h, 89%, α:β 3:1  *ii*) N₂H₄, H₂O, acetic acid, overnight, rt, 73% for 138, α:β 2.5:1 and 23% for 151, α:β 2.5:1.

The ¹H NMR spectrum of compound 137 showed the disappearance of the CH and CH₂ allyl signals, which had been present in the ¹H NMR spectrum recorded for 135, along with the emergence of a triplet peak corresponding to a CH₂ group at 2.92 ppm. This was accompanied by the thioacetate CH₃ signal at 2.35 ppm as a singlet.

**Figure 2.14:** Partial ¹H NMR spectrum of 137.
The $^1$H NMR spectrum clearly showed the acetate and thioacetate peaks between 1.99 and 2.35 ppm (Figure 2.14). The peaks attributed to the acetate protons of the $\alpha$-diastereomer of 137 were observed at 2.04, 2.08, 2.10 and 2.14 ppm whereas for the $\beta$-diastereomer, these protons appeared at 1.99, 2.05, 2.10 and 2.19 ppm. The thioacetate protons of the $\alpha$-diastereomer 137 gave rise to a signal at 2.35 ppm while for the $\beta$-diastereomer, this peak appeared at 2.33 ppm. These signals confirmed the diastereomeric mixture of 137 to be $\alpha$:$\beta$ 3:1. In the $^{13}$C spectrum, recorded for 137, the carbon signals for the CH$_2$ attached to the thioacetate group and the CH$_3$ signal of the thioacetate moiety were observed at 28.3 and 30.6 ppm, respectively. The $^{13}$C NMR spectrum recorded for 137 also showed four carbon signals for the C=O groups of the $\alpha$-diastereomer of 137 at 169.9, 170.2, 170.5 and 170.9 ppm whereas for the $\beta$-diastereomer, these signals appeared at 170, 170.5, 170.8 and 171 ppm. Furthermore, the carbon signal for the C=O of the thioacetate group of the $\alpha$-diastereomer of 137 was observed at 195.8 ppm while for the $\beta$-diastereomer, it was observed at 195.9 ppm (Figure 2.15).

![Figure 2.15](image-url): Partial $^{13}$C NMR spectrum of 137.
The structure of the novel compound 137 was also confirmed with the help of mass spectrometry MS ($m/z$ 472 [M + Na⁺, 100%]) and HRMS. Finally, an IR spectrum recorded for 137 showed peaks at 1668 cm⁻¹ for the C=O group, and at 1044 cm⁻¹ for the C-S bond.

The $^1$H NMR studies of 138 showed the disappearance of the CH₃ signal of the thioacetate group at 2.35 ppm, which had been present in the spectrum recorded for 137 and the emergence of a proton signal for the free SH group at 1.4 ppm. The COSY spectrum recorded for compound 138 was important for assigning the SH proton and the neighbouring CH₂ protons. The proton signal for the methylene group at C-9 appeared as a multiplet between 3.45 - 2.63 ppm. The proton signals for the methylene groups at C-7 and C-8 were observed between 1.49 - 1.94 ppm as a series of multiplet peaks (Figure 2.16).

![1H NMR spectrum of 138.](image)

**Figure 2.16:** $^1$H NMR spectrum of 138.

In the $^1$H NMR spectrum recorded for compound 138, the acetate protons in the α-diastereomer 138 were observed at 2.01, 2.05, 2.09 and 2.12 ppm whereas in the β-
diastereomer, these were observed at 1.97, 2.03, 2.08 and 2.17 ppm. These signals confirmed the diastereomeric ratio of 136 to be α:β 2.5:1 (Figure 2.17).

![Partial 1H NMR spectrum of 138.](image)

**Figure 2.17:** Partial $^1$H NMR spectrum of 138.

The $^{13}$C NMR spectrum recorded for 138 showed the disappearance of the carbon signals at 195.0 ppm for the C=O group and at 30.6 ppm for the CH$_3$ group, which had been present in the $^{13}$C NMR spectrum recorded for the starting material 137. The appearance of the carbon signal at 24.1 ppm for the methylene group at C-9, which had been observed at 28.4 ppm in the $^{13}$C NMR spectrum of the starting material, confirmed its formation (Figure 2.18).
The $^{13}$C NMR spectrum recorded for 138 showed four carbon signals for the C=O groups of the $\alpha$-diastereomer of 138 at 169.9, 170.3, 170.5 and 170.8 ppm whereas for the $\beta$-diastereomer these signals appeared at 170.0, 170.5, 170.8 and 171.0 ppm, conforming the diastereomeric ratio of 138 (Figure 2.19).

**Figure 2.18:** $^{13}$C NMR spectrum of 138.

**Figure 2.19:** Partial $^{13}$C NMR spectrum of 138.
The IR spectrum recorded for 138 (2942 cm\(^{-1}\) weak stretch for S-H) confirmed the preparation of compound 138 (Figure 2.20). Both low- and high-resolution mass spectrometry also supported the structural assignments for compounds 138 and 151.

![IR spectrum of 138](image)

**Figure 2.20:** IR spectrum of 138.

We also aimed to investigate the synthesis of the free thiol group-containing sugar 140 via a two-step pathway starting from allyl mannopyranoside 65 (Scheme 2.9). In this case, the robust benzyl group was chosen for hydroxyl protection. The title compound 64 was synthesised in good yield (85%) by treating methyl-\(\alpha\)-D-mannopyranoside 49 with benzyl bromide in the presence of sodium hydride. Characterisation of 64 matched the spectral data reported in literature for this compound. The C-1-allylation reaction was effected using TMSOTf and allyltrimethylsilane (Scheme 2.8).
Scheme 2.8: Synthesis of protected C-allyl mannopyranoside. Reagents and reaction conditions: i) Sodium hydride (60% mineral oil dispersion), DMF, 25 ºC, 1 h, benzyl bromide in DMF then 70 ºC, 15 h, 85% ii) Allyltrimethylsilane, TMSOTf, 50 ºC, acetonitrile, 16 h, 54%.

The synthesis of 65 was verified by $^1$H NMR, $^{13}$C NMR, MS, IR and optical rotation techniques. The data collected for 65 matched those reported in the literature. The $^1$H NMR spectrum recorded for 65 showed the disappearance of the proton signal for the methoxy group at 3.34 ppm, which had been present in the spectrum recorded for 64, along with the emergence of signals for the allyl CH proton between 5.66 and 5.81 ppm and for the allyl CH$_2$ protons between 4.97 and 5.05 ppm (Figure 2.21).

Figure 2.21: Partial $^1$H NMR spectrum of 65.

The synthesis of compound 139 proceeded with reaction of a solution of 3-(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl) propene 65 in 1,4-dioxane with thioacetic acid in the presence of the radical initiator 1,1'-azobis(cyclohexanecarbonitrile) to give the target compound 139.
in 60% yield. Finally, thioacetate group of compound 139 was deprotected using hydrazine hydrate, to give the required target novel compound 140 in 60% yield. In this case, the dimerised side product was not observed (Scheme 2.9).

**Scheme 2.9:** Synthesis of free thiol group-containing sugar. Reagents and reaction conditions: i) Thioacetic acid, 1,1'-azobis(cyclohexanecarbonitrile), 1,4-dioxane, 80 ºC, 10 h, 89% ii) N₂H₄·H₂O, acetic acid, overnight, rt, 60%.

¹H NMR data of the novel compound 139 showed the disappearance of the signals for the allyl CH proton between 5.66 and 5.81 ppm and for the allyl CH₂ protons between 4.97 and 5.05 ppm at 5.7 and 5.0 ppm, which had been present in the ¹H NMR spectrum of starting material 65. The ¹H NMR spectrum recorded for 139 also showed the appearance of signal for the thioacetate group at 2.3 ppm. Furthermore, the signals for the methylene protons at C-9 next to the thioacetate group were observed between 2.77 and 2.87 ppm (Figure 2.22).

**Figure 2.22:** Partial ¹H NMR spectrum of 139.
The $^{13}$C NMR spectrum recorded for 139 showed the following carbon signals for the carbon at 195.8 ppm (C=O), for the CH$_3$ carbon at 30.9 ppm and for the CH$_2$ carbon next to the thioacetate group at 29.5 ppm (Figure 2.23).

![Figure 2.23: Partial $^{13}$C NMR spectrum of 139.](image)

The structure of the novel compound 139 was also established through MS ($m/z$ 663 [M + Na$^+$, 100%]) and HRMS (Figure 2.24). Finally, an IR spectrum recorded for 139 showed peaks at 1686.6 cm$^{-1}$ for the C=O group, and at 1025.0 cm$^{-1}$ for the C-S bond.

The $^1$H NMR spectrum recorded for 140 showed the disappearance of the signal at 2.3 ppm for the thioacetate group, which had been present in the $^1$H NMR spectrum recorded for the starting material 139. It also showed the emergence of the signal between 2.38 and 2.52 ppm for the methylene group at C-9, which had been observed between 2.75 and 2.87 ppm in the $^1$H NMR spectrum of the starting material 139 (Figure 2.24).
The $^{13}$C NMR spectrum recorded for 140 showed the disappearance of the thioacetate CH$_3$ carbon signal at 30.9 ppm and the C=O carbon signal at 196.1 ppm, which had been present in the $^{13}$C NMR spectrum of the starting material 139. The disappearance of both these peaks showed that successful deprotection of the thioacetate group had occurred. Both low- and high-resolution mass spectrometry also supported the structural assignment for compound 140.

### 2.3. Conclusions

3-(2,3,4,6-tetra-O-acetyl-$\alpha$,$\beta$-D-mannopyranosyl) propene 135 was successfully synthesised. However, methods were evaluated for the synthesis of 3-(2,3,4,6-tetra-O-acetyl-$\alpha$,$\beta$-D-mannopyranosyl) propene under optimised reaction conditions. Several attempts were made to separate the mixture of anomers of compound 135 by flash chromatography, but this was found to be unsuccessful.
Novel organosulfur compounds, $\alpha$/$\beta$-(2R,3S,4R,5R,6R)-2-(acetoxymethyl)-6-((6-(benzylamino)-6-oxohexyl)thio)propyl)tetrahydro-2H-pyran-3,5,4,5-triyl triacetate 136, $\alpha$/$\beta$-(2R,3S,4R,5R,6R)-2-(acetoxymethyl)-6-((2-hydroxyethyl)thio)propyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate 147, $\alpha$/$\beta$-(2R,3S,4R,5R,6R)-2-(acetoxymethyl)-6-((acetylthio)propyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate 137 and $\alpha$/$\beta$-(2R,3S,4R,5R,6R)-2-(acetoxymethyl)-6-((benzyloxy)methyl) tetrahydro-2H-pyran-2-yl)propyl)ethanethioate 139 were successfully synthesised from 3-(2,3,4,6-tetra-0-acetyl-$\alpha$,\$\beta$-D-mannopyranosyl) propene 135 [in the presence of 1, 1'-azobis(cyclohexane carbonitrile) as radical initiator]. The free thiol group-containing novel sugars, $\alpha$/$\beta$-(2R,3S,4R,5R,6R)-2-(acetoxymethyl)-6-(3-mercaptopropyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate 138 and 3-((2R,3R,4R,5S,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)propane-1-thiol 140 were also synthesised in 73% and 60% respectively, bearing either acetyl or benzyl protecting groups. It is important to mention here that an efficient two-step methodology had been developed for the synthesis of free thiol group-containing sugars 138 and 140. Optimisation of these reactions is now underway, with a view to attaching a free thiol group-containing sugar to the alkene scaffold to obtain multivalent carbohydrates specifically directed toward applications in the treatment of different pathological conditions including cancer and infectious diseases.

2.4. FUTURE WORK

The work embodied within this thesis could be extended in the future as follows:

1) Based on the findings of the model study (Scheme 2.6), we expect that it should be possible to extend this idea to the preparation of glycodendrimers of the type shown in Figure 2.25. Thus, a similar strategy could be employed to prepare these free thiol-containing dendrimers involving the thiol-ene click reaction as a key step.
**Figure 2.25:** Graphical representation of the key step of the synthesis of glycodendrimers involving thio-ene reaction using free thiol-containing dendrimers.

2) It is envisaged that the route that has been developed for the synthesis of the free thiol-containing carbohydrates will enable the synthesis of multivalent carbohydrates (Figure 2.26) via a thio-ene click reaction.

**Figure 2.26:** Graphical representation of the key step of the synthesis of glycodendrimers involving thio-ene reaction using alkene cores.
CHAPTER 3

EXPERIMENTAL
3.1. General Experimental

Reagents and solvents were purchased from Sigma-Aldrich. All reactions were carried out in dry glassware under an atmosphere of dry nitrogen, unless mentioned otherwise. Deuterated chloroform was used as the solvent, unless otherwise stated, to record the nuclear magnetic resonance (NMR) spectra. $^1$H NMR spectra were recorded on a Bruker Advance Ultrashield DPX 400 (400 MHz) or Bruker Advance Ultrashield 500 (500 MHz) and $^{13}$C NMR spectra were recorded at 75 or 100 MHz on Bruker 300 and 400 DPX spectrometer. Signal splitting patterns are described as singlet (s), doublet (d), triplet (t) and multiplet (m). Coupling constants ($J$) are designated in Hz and assignments were made with the help of DEPT-135, COSY, HMBC and HMQC experiments. A Stuart Scientific SMP1 melting point apparatus was used for melting point determinations. Low-resolution mass spectra were recorded on a Micro Mass Trio 200 spectrometer while high-resolution mass spectra were measured on a Kratos Concept IS spectrometer. The IR was measured using a Bruker Alpha FT-IR machine and absorption peaks (υ<sub>max</sub>) are quoted in wave numbers (cm<sup>−1</sup>). Flash chromatography was conducted using Merck silica gel 60 (particle size 40-60 µm). Plastic plates pre-coated with Merck silica gel 60 F<sub>254</sub> used to conduct thin layer chromatography (TLC). Optical rotations were measured at 589 nm in a 1 dm cell using an Optical Activity AA1000 polarimeter.
3.2. Experimental Procedures and Data

3.2.1. 1-(α,β-D-Mannopyranosyl)-2-propene 141

To a solution of methyl-α-D-mannopyranoside (1.01 g; 5.01 mmol) in dry acetonitrile (5 mL), was added bis(trimethylsilyl)trifluoroacetamide (BSTFA) (5.30 mL; 20.04 mmol) and the mixture was heated under N₂ atmosphere at 80 °C for 4 h. After this time, the reaction mixture was cooled first to rt and then 0 °C, in an ice-water bath and allyltrimethylsilane (1.50 mL; 9.01 mmol) and trimethylsilyltrifluoromethanesulfonate (TMSOTf) (0.55 mL; 3.01 mmol) were added. The mixture was allowed to warm to rt before being left to stir for 20 h. The reaction mixture was poured into the ice-cold water (20 mL) and the resulting mixture was stirred for 3 h. Concentrated ammonia solution was then added dropwise to the reaction mixture until neutralisation (pH = 7) had been achieved. The mixture was then filtered through Celite® and the solvents were removed in vacuo. Purification of the crude product by flash chromatography (ethyl acetate:methanol, 15:1) afforded the title compound as a yellow oil (0.75 g, 74%, Rₙ = 0.40), in the ratio α:β 9:1.

¹H NMR (400 MHz, CD₃OD) δ ppm 2.26 - 2.53 (2H, m, CH, H-7 & H-7'), 3.94 (1H, ddd, J = 9.0, 6.0, 2.0 Hz, CH, H-5'), 3.39 - 3.49 (1H, m, H-5), 3.55 - 3.85 (5H, m, H-2,3,4,6 & H-2',3',4',6'), 3.94 (1H, ddd, J = 9.0, 7.0, 2.0 Hz, CH, H-1), 4.99 - 5.18 (2H, m, CH₂, H-9 & H-9'), 5.72 - 5.91 (1H, m, CH, H-8 & H-8'); ¹³C NMR (100 MHz, CDCl₃) δ ppm 34.6 (CH₂, C-7), 36.3 (CH₂, C-7'), 62.8 (CH₂, C-6), 62.9 (CH, C-6'), 78.4 (CH, C-4'), 69.0 (CH, C-4), 72.1 (CH, C-3'), 72.4 (CH, C-3), 72.8 (CH, C-2), 75.8 (CH, C-5), 76.5 (CH, C-2'), 78.4 (CH, C-
1), 79.2 (CH, C-5'), 117.4 (CH₂, C-9), 135.7 (CH, C-8), 135.8 (CH, C-8); **MS (ES)**⁺: m/z [M + Na]⁺ 227.0; **Accurate Mass**: C₉H₁₆O₅Na requires 227.0890 found 227.0880.

**3.2.2. Methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside 142**

To a stirred solution of methyl-α-D-mannopyranoside (1.25 g; 6.44 mmol) in dry pyridine (9 mL) at 0 ºC, was added acetic anhydride (4.50 mL; 47.64 mmol). The mixture was stirred for 4 h at rt and then extracted with ethyl acetate (30 mL). The organic solution was washed with water (3 x 15 mL), 10% aqueous solution of copper sulfate (3 x 15 mL), water (3 x 15 mL), 5% aqueous solution of HCl (3 x 10 mL) and finally brine (3 x 10 mL). The organic layer was dried (MgSO₄) and the solvents were removed in vacuo. Purification of the crude product by flash chromatography (ethyl acetate:hexane, 1:2), afforded the title compound as a white solid (1.90 g, 86%, Rf = 0.37). Melting point 68-69 ºC [lit.¹⁰⁹h 67-69 ºC].

**¹H NMR** (400 MHz, CDCl₃) δ ppm 1.98 (3H, s, CH₃Ac), 2.03 (3H, s, CH₃Ac), 2.10 (3H, s, CH₃Ac), 2.15 (3H, s, CH₃Ac), 3.40 (3H, s, CH₃ OMe), 3.96 (1H, ddd, J = 9, 5, 2.5 Hz, CH, H-5), 4.11 (1H, dd, J = 12, 2.5 Hz, CH₂, H-6a), 4.28 (1H, dd, J = 12, 5 Hz, CH₂, H-6b Ac), 4.71 (1H, d, J = 2.0 Hz, CH, H-1), 5.23 (1H, d, J = 3.0, 2.0 Hz, CH, H-2), 5.24 - 5.29 (1H, m, CH, H-4), 5.31 - 5.34 (1H, m, CH, H-3); **¹³C NMR** (100 MHz, CDCl₃) δ ppm 20.7 (CH₃, Ac), 20.7 (CH₃, Ac), 20.8 (CH₃, Ac), 20.9 (CH₃, Ac), 55.3 (CH₃, OMe), 62.5 (CH₂, C-6), 66.1 (CH, C-4), 68.3 (CH, C-3), 69.1 (CH, C-2), 69.5 (CH, C-5), 98.6 (CH, C-1), 169.7 (C=O), 169.9 (C=O), 170.1 (C=O), 170.7 (C=O); **IR** (neat) vmax 2906, 2360, 1742, 1364, 1225, 1214, 1133, 1037 cm⁻¹; **MS (ES)**⁺: m/z [M + Na]⁺ 385.0; **Accurate Mass**: 
C_{13}H_{22}O_{10}Na requires 385.1105 found 385.1110; \textbf{Specific Rotation} [\alpha]^{24} = + 11.4^\circ \text{ (c 1.0, CH}_2\text{Cl}_2).

3.2.3. 3-(2,3,4,6-Tetra-O-acetyl-\alpha,\beta-D-mannopyanosyl) propene 135^{109}

To a stirred solution of methyl 2,3,4,6-tetra-O-acetyl-\alpha-D-mannopyanoside (1.03 g; 2.76 mmol) in dry acetonitrile (20 mL), was added allyltrimethylsilane (4.80 mL; 30.01 mmol) and trimethylsilyltrifluoromethanesulfonate (TMSOTf) (4.01 mL; 15.01 mmol). The mixture was heated at 80 °C for 48 h. After this time, the reaction mixture was allowed to cool to rt and then extracted with DCM (30 mL). The organic solution was washed with water (3 x 15 mL), 5% aqueous solution of NaHCO_3 (3 x 15 mL) and water (15 mL). The organic layer was dried (MgSO_4) and the solvents were removed in vacuo. Purification of the crude product by flash chromatography (ethyl acetate:hexane, 1:2) afforded the title compound as a white solid (0.56 g, 54%, R_f = 0.44), in the ratio \alpha:\beta 4:1. Melting point 62-63 °C [lit.\^107-108 °C for \alpha-diastereomer and 75-76 °C for \beta-diastereomer of 3-(2,3,4,6-tetra-O-acetyl-D-glucopyranosyl) propene]).

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl_3) \delta ppm 1.98 (s, CH_3Ac'), 2.03 (3H, s, CH_3Ac), 2.04 (s, CH_3Ac'), 2.07 (3H, s, CH_3Ac), 2.09 (3H, s, CH_3Ac), 2.09 (s, CH_3Ac'), 2.13 (3H, s, CH_3Ac), 2.18 (s, CH_3Ac'), 2.35 - 2.56 (2H, m, CH_2, H-7& H-7'), 3.59 - 3.64 (m, H-5'), 3.88 (1H, ddd, J = 8, 6, 3 Hz, CH, H-5), 4.03 (1H, ddd, J = 9, 6, 3 Hz, CH, H-1 & H-1'), 4.09 (1H, dd, J = 12, 3 Hz, CH_2, H-6b Ac, & H-6b Ac'), 4.26 (dd, J = 12, 6 Hz, CH_2, & H-6a'), 4.30 (1H, dd, J = 12, 6 Hz, CH_2, H-6a), 5.02 - 5.16 (2H, m, CH, H-3,4 & H-3',4'), 5.17 - 5.23 (2H, m, CH_2, H-
9), 5.24 - 5.28 (1H, m, CH, H-2), 5.34 (dd, J = 3, 1 Hz, H-2'), 5.69 - 5.82 (1H, m, CH, H-8 & H-8'); \[^{13}\text{C}\text{ NMR}\] (100 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 20.9 (CH\textsubscript{3}, Ac'), 20.9 (CH\textsubscript{3}, Ac), 21.0 ([2CH\textsubscript{3}] Ac'), 21.0 ([2CH\textsubscript{3}] Ac'), 21.1 (CH\textsubscript{3}, Ac'), 21.2 (CH\textsubscript{3}, Ac), 33.8 (CH\textsubscript{2}, C-7), 35.2 (CH\textsubscript{2}, C-7'), 62.6 (CH, C-6), 63.1 (CH\textsubscript{2}, C-6'), 66.4 (CH, C-4'), 67.2 (CH, C-4), 69.0 (CH, C-2), 69.3 (CH\textsubscript{2}, C-2'), 70.2 (CH, C-3), 70.8 (CH, C-5), 72.4 (CH, C-3'), 74.4 (CH, C-1), 76.2 (CH, C-5'), 118.6 (CH\textsubscript{2}, C-9), 132.8 (CH, C-8), 133.0 (CH, C-8'), 169.9 (C=O), 170.0 (C=O'), 170.2 (C=O), 170.3 (C=O'), 170.5 (C=O), 170.7 (C=O'), 171.0 (C=O), 171.1 (C=O'); \text{IR} (\text{neat}) \(\nu_{\text{max}}\) 2983, 2901, 2360, 2341, 1747, 1734, 1366, 1231, 1044, 916 cm\textsuperscript{-1}; \text{MS} (\text{ES})^+: m/z [M + Na]^+ 395.0; \text{Accurate Mass}: C\textsubscript{17}H\textsubscript{12}O\textsubscript{9}Na requires 395.1313 found 395.1320; \textbf{Specific Rotation} \(\left[\alpha\right]_D^{21} = + 4.3^\circ\) (c 1.0, CH\textsubscript{2}Cl\textsubscript{2}).

### 3.2.4. 6-(Acetylthio) hexanoic acid 149\textsuperscript{108}

![Chemical Structure](image)

To a stirred solution of potassium thioacetate (4.39 g; 38.43 mmol) in dry methanol (15 mL), was added a solution of 6-bromohexanoic acid (3.01 g; 15.43 mmol) in methanol (5 mL) dropwise. The reaction mixture was heated at reflux for 5 h. The reaction mixture was allowed to cool to rt and then diluted with water (100 mL). The reaction mixture was acidified with 1 N HCl solution (pH = 3.0) and extracted with DCM (40 mL). The organic layer was washed with water (3 x 15 mL) and brine (3 x 15mL). The organic layer was dried (MgSO\textsubscript{4}) and the solvents were removed in vacuo. Purification of the crude product by flash chromatography (methanol:DCM, 1:10), afforded the title compound as a yellow oil (2.30 g, 79%, \(R_f = 0.60\)).
$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 1.38 - 1.46 (2H, m, CH$_2$, H-5), 1.55 - 1.69 (4H, m, CH$_2$, H-4,6), 2.33 (3H, s, SOCH$_3$), 2.33 - 2.41 (2H, t, $J = 7.5$ Hz, CH$_2$, H-7), 2.82 - 2.90 (2H, t, $J = 7$, Hz , CH$_2$, H-3); $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 24.1 (CH$_2$, C-5), 28.1 (CH$_2$, C-6), 28.8 (CH$_2$, C-3), 29.2 (CH$_2$, C-4), 30.7 (CH$_3$, C-1), 33.8 (CH$_2$, C-7), 179.6 (C=O, C-8), 196.1 (C=O, C-2); IR (neat) $\nu_{\text{max}}$ 2933, 2859, 1687, 1411, 1131, 954, 731, 624 cm$^{-1}$; MS (ES)$^+$: m/z [M + Na]$^+$ 213.0; Accurate Mass: C$_8$H$_{14}$O$_3$SNa requires 213.1313 found 213.1320.

3.2.5. S-(6-(Benzy lamino)-6-oxohexyl) ethanethioate 150

![Chemical structure](image)

To a stirred solution of 6-(acetylthio) hexanoic acid (0.22 g; 1.16 mmol) in dry DMF (10 mL), were added O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (0.39 g; 1.01 mmol) or N,N,N',N'-tetramethyl-O-(1H-benzotriazol-1-yl)uranium hexafluorophosphate (HBTU) (0.39 g; 1.01 mmol) and 1-hydroxybenzotriazole hydrate (0.12 g; 0.90 mmol). The reaction mixture was cooled to 0 °C for 0.5 h before benzylamine (0.08 mL; 0.70 mmol) was added dropwise. The reaction mixture was allowed to warm to rt before being left to stir overnight. The reaction was quenched with water (15 mL) and extracted with ethyl acetate (30 mL). The organic layer was washed with water (3 x 15 mL), 5% aqueous solution of HCl (2 x 15 mL), 5% aqueous solution of NaHCO$_3$ (2 x 15 mL), water (3 x 15 mL) and finally brine (2 x 15 mL). The organic layer was dried (MgSO$_4$) and the solvents were removed in vacuo. Purification of the crude product by flash chromatography (ethyl acetate:hexane, 2:1), afforded the title compound as a yellow solid (0.24 g, 72%, $R_f = 0.60$. Melting point 104-105 °C.
**1H NMR** (400 MHz, CD$_3$OD) δ ppm 1.34 - 1.43 (2H, m, CH$_2$, H-5), 1.52 - 1.68 (4H, m, CH$_2$, H-4,6), 2.23 (2H, t, J = 7 Hz, CH$_2$, H-7), 2.29 (3H, s, SOCH$_3$), 2.85 (2H, t, J = 7 Hz, CH$_2$, H-3), 4.37 (2H, d, J = 6 Hz, CH$_2$, H-7), 8.41 (1H, br, s, NH), 1.04 - 8.53 (5H, m, Ar); **13C NMR** (100 MHz, CDCl$_3$) δ ppm 26.6 (CH$_2$, C-5), 29.4 (CH$_2$, C-6), 29.8 (CH$_2$, C-4), 29.2 (CH$_2$, C-3), 30.7 (CH$_3$, C-1), 37.0 (CH$_2$, C-7), 44.2 (CH$_2$, C-9), 128.3 (CH, C-15), 128.7 (CH, C-11,12), 129.7 (CH, C-13,14), 140.2 (CH, C-10), 176.1 (C=O, C-8), 197.6 (C=O, C-2); **IR** (neat) ν$_{max}$ 3296, 2929, 1686, 1638, 1544, 1454, 1269, 1136, 737, 628 cm$^{-1}$; **MS (ES)$^+$**: m/z [M + Na]$^+$ 302.0; **Accurate Mass**: C$_{15}$H$_{21}$O$_2$NSNa requires 302.1185 found 302.1187.

### 3.2.6. N-Benzyl-6-mercaptohexanamide 134

To a solution of S-6-(benzylamino)-6-oxohexyl ethanethioate (0.10 g; 0.36 mmol) in methanol (4 mL), was added a solution of K$_2$CO$_3$ (0.16 g; 1.02 mmol) in distilled water (2 mL) under an inert N$_2$ atmosphere. The reaction mixture was heated to reflux for 50 min and then allowed to cool to rt. The reaction mixture was quenched with 2 N HCl solution (15 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were washed with water (3 x 10 mL) followed by brine (2 x 10 mL). The organic layer was dried (MgSO$_4$) and the solvents were removed in vacuo. Purification of the crude product by flash chromatography (ethyl acetate:hexane, 2:1), afforded the title compound as a yellow solid (0.20 g, 82%, R$_f$ = 0.61). Melting point 101-103 °C.

**1H NMR** (400 MHz, CDCl$_3$) δ ppm 1.27 (1H, t, J = 8 Hz, SH), 1.33 - 1.41 (2H, m, CH$_2$, H-3), 1.51 - 1.61 (4H, m, CH$_2$, H-2,4), 2.15 (2H, t, J = 7 Hz, CH$_2$, H-5), 2.45 (2H, q, J = 7 Hz, CH$_2$, H-1), 4.36 (2H, d, J = 6 Hz, CH$_2$, H-7), 5.86 (1H, br, s, NH), 7.18 - 7.28 (5H, m, Ar);
$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 24.4 (CH$_2$, C-3), 25.0 (CH$_2$, C-1), 27.8 (CH$_2$, C-4), 33.6 (CH$_3$, C-2), 36.4 (CH$_2$, C-5), 43.5 (CH$_2$, C-7), 127.4 (CH, C-13), 127.7 (CH, C-9,10), 128.6 (CH, C-11,12), 138.3 (CH, C-8), 172.6 (C=O, C-6); IR (neat) $\nu_{\text{max}}$ 3298, 2926, 2854, 1637, 1544, 1453, 1267, 1233, 737, 718 cm$^{-1}$; MS (ES)$^+$/m/z [M + Na]$^+$ 260.0; Accurate Mass: C$_{13}$H$_{19}$ONSNa requires 260.1080 found 260.1083.

3.2.7. $\alpha/\beta$-(2R,3S,4R,5R,6R)-2-(Acetoxymethyl)-6-(3-((6-(benzylamino)-6-oxohexyl)thio)propyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate 136

To a stirred solution of 3-(2,3,4,6-tetra-$O$-acetyl-$\alpha$,\$\beta$-$D$-mannopyranosyl) propene (0.19 g; 0.53 mmol) in 1,4-dioxane (4 mL), added N-benzyl-6-mercaptohexanamide (0.24 g; 1.01 mmol) and 1,1′-azobis(cyclohexanecarbonitrile) (0.15 g; 0.60 mmol) at rt under an inert N$_2$ atmosphere. The mixture was heated for 10 h at 80 ºC. The reaction mixture was allowed to cool to rt and then the reaction was quenched with cyclohexane (1 mL). The reaction mixture was concentrated with toluene (3 x 10 mL) and the residue was co-evaporated. Purification of the crude product by flash chromatography (ethyl acetate:hexane, 2:1) afforded the title compound as a white oil (0.15 g, 25%, $R_f = 0.40$), in the ratio $\alpha$:$\beta$ 3:1.
\[ \text{H NMR (400 MHz, CDCl}_3) \delta \text{ ppm 1.15 - 1.40 (2H, m, CH}_2, \text{ H-12 & H-12')}, 1.45 - 1.87 (8H, m, CH}_2, \text{ H-7.8,11,13 & H-7',8',11',13')}, 1.89 (s, CH}_3\text{Ac'}), 1.94 (3H, s, CH}_3\text{Ac}), 1.97 (3H, s, CH}_3\text{Ac'}), 1.98 (3H, s, CH}_3\text{Ac}), 2.01 (3H, s, CH}_3\text{Ac'}), 2.02 (3H, s, CH}_3\text{Ac}), 2.05 (3H, s, CH}_3\text{Ac}), 2.09 (3H, s, CH}_3\text{Ac'}), 2.15 (2H, t, J = 8 Hz, CH}_2, \text{ H-14}), 2.34 - 2.63 (4H, m, CH}_2, \text{ H-9,10 & H-9',10')}, 3.50-3.67 (m, CH, \text{ H-5'}), 3.77-3.80 (1H, m, CH, \text{ H-5}), 3.88 (1H, dt, J = 10, 3 Hz, CH, \text{ H-1}), 4.01 (1H, dd, J = 12, 3 Hz, CH}_2, \text{ H-6a Ac}), 4.19 (dd, J = 12, 6 Hz, CH}_2, \text{ H-6b Ac}), 4.25 (1H, dd, J = 12, 6 Hz, CH}_2, \text{ H-6b Ac}), 4.32 (2H, d, J = 6 Hz, CH}_2, \text{ H-16}), 4.36 (2H, d, J = 6 Hz, CH}_2, \text{ H-16}), 4.94 - 5.25 (3H, m, CH, \text{ H-2,3,4 & H-2',3',4'}), 5.90 (1H, br, s, NH), 7.19 - 7.33 (5H, m, Ar & Ar'); \text{C NMR (100 MHz, CDCl}_3) \delta \text{ ppm 20.7 (CH}_3, \text{ Ac}), 20.8 (CH}_3, \text{ Ac}), 20.9 (CH}_3, \text{ Ac}), 21.1 (CH}_3, \text{ Ac}), 25.3 (CH}_2, \text{ C-13}), 25.3 (CH}_2, \text{ C-11}), 27.3 (CH}_2, \text{ C-8}), 28.4 (CH}_2, \text{ C-12}), 29.3 (CH}_2, \text{ C-7}), 31.4 (CH}_2, \text{ C-10}), 31.9 (CH}_2, \text{ C-9}), 36.5 (CH}_2, \text{ C-14}), 43.6 (CH}_2, \text{ C-16}), 62.5 (CH}_2, \text{ C-6}), 66.2 (CH, \text{ C-4'}), 66.8 (CH, \text{ C-4}), 69.0 (CH, \text{ C-2}), 69.6 (CH, \text{ C-2'}), 70.2 (CH, \text{ C-3}), 70.8 (CH, \text{ C-5}), 71.7 (CH, \text{ C-3'}), 74.8 (CH, \text{ C-1}), 76.1 (CH, \text{ C-5'}), 127.5 (CH, \text{ C-22}), 127.8 (CH, \text{ C-18,19}), 128.7 (CH, \text{ C-20,21}), 138.4 (CH, \text{ C-17}), 169.9 (\text{C=O}), 170.3 (\text{C=O}), 170.6 (\text{C=O}), 171.0 (\text{C=O}), 173.0 (\text{C=O}, \text{ C-15}); \text{IR (neat) } \nu_{\text{max}} 3292, 3031, 2930, 2857, 1740, 1647, 1534, 1496, 1432, 1367, 1220, 1045, 913, 730, 699, 646 \text{ cm}^{-1}; \text{MS (ES)}^+: \text{m/z} [\text{M + Na}]^+ 632.0; \text{Specific Rotation } [\alpha]_D^{21} = + 8.9^o (c 1.0, \text{ CH}_2\text{Cl}_2).]

3.2.8. a/β-(2R,3S,4R,5R,6R)-2-(Acetoxymethyl)-6-(3-((2-hydroxyethyl(thio)propyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate 147
To a stirred solution of 3-(2,3,4,6-tetra-O-acetyl-α,β-D-mannopyranosyl) propene (0.29 g; 0.81 mmol) in 1,4-dioxane (4 mL), added 2-mercaptoethanol (0.88 mL; 12.54 mmol) and 1,1’-azobis(cyclohexanecarbonitrile) (0.15 g; 0.60 mmol) at rt under an inert N$_2$ atmosphere. The mixture was heated at 80 °C for 10 h. The reaction mixture was allowed to cool to rt and then the reaction was quenched with cyclohexane (1 mL). The reaction mixture was concentrated with toluene (3 x 10 mL) and the residue was co-evaporated. Purification of the crude product by flash chromatography (ethyl acetate:hexane, 3:1) afforded the title compound as a white oil (0.13 g, 57%, Rf = 0.37), in the ratio α:β 5:1.

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 1.49 - 1.95 (4H, m, CH$_2$, H-7,8 & H-7′,8′), 1.97 (s, CH$_3$Ac′), 2.02 (3H, s, CH$_3$Ac), 2.04 (3H, s, CH$_3$Ac′), 2.06 (3H, s, CH$_3$Ac), 2.09 (3H, s, CH$_3$Ac′), 2.10 (3H, s, CH$_3$Ac), 2.13 (3H, s, CH$_3$Ac), 2.17 (3H, s, CH$_3$Ac′), 2.50 - 2.63 (2H, m, CH$_2$, H-9 & H-9′), 2.70 - 2.75 (2H, m, CH$_2$, H-10), 2.88 (t, H-10′), 3.58-3.64 (m, H-5′), 3.70 (1H, s, OH & OH′), 3.69 - 3.76 (2H, t, J = 6.0 Hz, CH$_2$, H-11), 3.84 - 3.92 (1H, m, CH, H-5 & H-11′), 3.94 - 3.99 (1H, m, CH, H-1), 4.08 (1H, dd, J = 12, 3 Hz, CH$_2$, H-6a Ac), 4.25 (1H, dd, J = 12, 6 Hz, CH$_2$, H-6b Ac′), 4.34 (1H, dd, J = 12, 6 Hz, CH$_2$, H-6b Ac), 5.02 (1H, dd, J = 10, 3.5 Hz, CH, H-3′), 5.14 - 5.25 (3H, m, CH, H-2,3,4 & H-4′), 5.32 (dd, J = 3.5, 1 Hz, CH, H-2′); $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 20.4 (CH$_3$, Ac), 20.4 (CH$_3$, Ac), 20.62 (CH$_3$, Ac), 25.1 (CH$_2$, C-8), 25.3 (CH$_2$, C-8′), 27.1 (CH$_2$, C-7), 29.1 (CH$_2$, C-7′), 30.6 (CH$_2$, C-9), 30.9 (CH$_2$, C-9′), 34.7 (CH$_2$, C-10), 40.1 (CH$_2$, C-10′), 60.0 (CH$_2$, C-11′), 60.1 (CH$_2$, C-11), 62.1 (CH$_2$, C-6), 62.5 (CH, C-6′), 66.5 (CH, C-4), 67.0 (CH, C-4′), 68.5 (CH, C-2), 69.2 (CH, C-2′), 70.0 (CH, C-3), 70.3 (CH, C-5), 72.1 (CH, C-3′), 74.1 (CH, C-1), 75.9 (CH, C-5′), 169.3 (C=O), 169.4 (C=O′), 169.7 (C=O), 169.9 (C=O′), 170.1 (C=O), 170.6 (C=O′), 170.7 (C=O), 170.8 (C=O′); IR (neat) $\nu_{max}$ 3472, 2945, 2872, 1737, 1432, 1368, 1217, 1042 cm$^{-1}$; MS (ES)⁺: m/z [M + Na]$^+$ 473.0; Accurate Mass: C$_{19}$H$_{30}$O$_{10}$SNa requires 473.1452 found 473.1463.
3.2.9. 1-C-(2,3,4,6-Tetra-O-acetyl-(α,β-D-mannopyanosyl)-3-iodopropan-2-ol 143

To a stirred solution of 3-(2,3,4,6-tetra-O-acetyl-α,β-D-mannopyranosyl) propene (0.36 g; 1.02 mmol) in DMSO (3 mL), were added water (1 mL) and N-iodosuccinimide (NIS) (0.24 g; 1.01 mmol) at rt under an inert N₂ atmosphere. The reaction mixture was left to stir overnight at rt. After this time, an aqueous solution of 1 N Na₂S₂O₃ was added dropwise until the reaction mixture appeared clear. The residue was taken up in diethylether (15 mL) and the organic extract was washed with water (3 x 50 mL). The organic layer was dried (MgSO₄) and the solvents were removed in vacuo. The crude product was purified by flash chromatography (ethyl acetate:hexane, 1:1) afforded the title compound as a white oil (0.16 g, 65%, Rf = 0.34).

¹H NMR (400 MHz, CDCl₃) δ ppm 1.65 - 1.91 (2H, m, CH₂, H-7 & H-7'), 1.99 - 2.12 (12H, m, CH₃Ac & CH₃Ac'), 3.17 - 3.29 (2H, m, CH, H-9 & H-9'), 3.50 (br. s, OH'), 3.64 - 3.71 (m, CH, H-5'), 3.92 - 3.98 (1H, br. s, OH), 3.95 (1H, m, CH, H-8 & H-8'), 4.03-4.05 (1H, m, CH, H-5), 4.19 - 4.25 (1H, m, CH, H-1), 4.48 (1H, dd, J = 12, 8 Hz, CH₂, H-6a Ac), 4.63 (1H, dd, J = 12, 8 Hz, CH₂, H-6b Ac), 5.06 - 5.26 (3H, m, CH, H-2,3,4 & H-2',3',4'); ¹³C NMR (100 MHz, CDCl₃) δ ppm 13.0, 13.6 (CH₂, C-9), 20.7 – 20.8 ([4CH₃], Ac) 35.5, 36.1 (CH, C-7), 61.6 (CH, C-6), 67.2, 67.4, 67.6 (CH, C-4), 68.0, 68.1, 68.1 (CH, C-2), 69.9, 69.9 (CH, C-3), 71.8 (CH, C-5), 72.1 (CH₂, C-8), 72.2, 72.3 (CH₂, C-1); IR (neat) νmax 3483, 2956, 2361, 2111, 1737, 1367, 1219, 1044, 913, 731 cm⁻¹; MS (ES⁺): m/z [M + Na]⁺ 539.0; Accurate Mass: C₁₇H₂₅O₁₀Na requires 539.0385 found 539.0384.
3.2.10. α/β-(2R,3S,4R,5R,6R)-2-(Acetoxymethyl)-6-(3-(acetylthio)propyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate 137

To a stirred solution of 3-(2,3,4,6-tetra-O-acetyl-α,β-D-mannopyranosyl) propene (0.38 g; 1.05 mmol) in 1,4-dioxane (4 mL), was added 1,1’-azobis(cyclohexanecarbonitrile) (0.24 g; 1.0 mmol) at rt under an inert N₂ atmosphere. The reaction mixture was heated at 80 °C for 10 min. After this time, the reaction mixture was treated with thioacetic acid (0.90 mL; 12.01 mmol) dropwise at 80 °C. The reaction mixture was kept at 80 °C for a further 10 h. The reaction mixture was allowed to cool to rt, quenched with 1 N NaHCO₃ solution (10 mL) and then extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (3 x 10mL) followed by brine (2 x 10 mL). The organic layer was dried (MgSO₄) and the solvents were removed in vacuo. The crude product was purified by flash chromatography (ethyl acetate:hexane, 1:2) afforded the title compound as a light yellow oil (0.40 g, 89%, Rf = 0.33), in the ratio α:β 3:1.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.60 - 1.94 (4H, m, CH₂, H-7,8 & H-7',8'), 1.99 (3H, s, CH₃Ac'), 2.04 (3H, s, CH₃Ac), 2.05 (s, CH₃Ac'), 2.08 (3H, s, CH₃Ac), 2.10 (3H, s, CH₃Ac'), 2.10 (3H, s, CH₃Ac), 2.14 (3H, s, CH₃Ac), 2.19 (3H, s, CH₃Ac'), 2.33 (3H, s, CH₃Ac'), 2.35 (3H, s, SOCH₃), 3.80 - 3.89 ( m, CH, H-9'), 2.87 - 2.96 (2H, t, J = 7 Hz, CH₂, H-9), 3.58 - 3.65 (m, CH, H-5'), 3.82 - 3.88 (1H, m, CH, H-5), 3.96 (1H, dt, J = 10, 4 Hz, CH, H-1), 4.10 (1H, dd, J = 12, 3 Hz, CH₂, H-6a Ac), 4.26 (dd, J = 12, 7 Hz, CH₂, H-6b Ac'), 4.34 (1H, dd, J = 12, 7 Hz, CH₂, H-6b Ac), 5.04 (dd, J = 10, 3.5 Hz, CH₂, H-3'), 5.12 - 5.33 (3H, m, CH,
H-2,3,4 & H-4',2'); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 20.3 (CH$_3$, Ac'), 20.4 (CH$_3$, Ac), 20.4 (CH$_3$, Ac), 20.4 (CH$_3$, Ac'), 20.5 (CH$_3$, Ac'), 20.6 (CH$_3$, Ac) 20.7 (CH$_3$, Ac'), 25.1 (CH$_2$, C-8), 25.2 (CH$_2$, C-8'), 27.1 (CH$_2$, C-7), 27.4 (CH$_2$, C-7'), 28.4 (CH$_2$, C-9), 28.5 (CH$_2$, C-9'), 30.5 (CH$_3$, SOCH$_3$), 30.6 (CH$_3$, SOCH$_3$), 62.1 (CH$_2$, C-6), 62.5 (CH$_2$, C-6'), 65.8 (CH$_2$, C-4'), 66.5 (CH, C-4), 68.5 (CH, C-2), 69.3 (CH$_2$, C-2'), 70.0 (CH, C-3), 70.3 (CH, C-5), 72.1 (CH$_2$, C-3'), 74.1 (CH, C-1), 76.1 (CH$_2$, C-5'), 169.9 (C=O), 170.0 (C=O'), 170.2 (C=O), 170.5 (C=O'), 170.8 (C=O), 170.9 (C=O), 171.0 (C=O'), 195.8 (C=O) 195.9 (C=O'); IR (neat) $\nu_{\text{max}}$ 3475, 2944, 2256, 1738, 1668, 1367, 1217, 1044, 952, 914, 730, 625 cm$^{-1}$; MS (ES)$^+$: m/z [M + Na]$^+$ 471.0; Specific Rotation $[\alpha]_D^{21} = +8.2^\circ$ (c 1.0, CH$_2$Cl$_2$).

3.2.11. $\alpha/\beta$-(2R,3S,4R,5R,6R)-2-(Acetoxymethyl)-6-(3-mercaptopropyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate 138

To a stirred solution of (2R,3S,4R,5R,6R)-2-(acetoxymethyl)-6-(3-(acetylthio)propyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (0.14 g; 0.33 mmol) in DMF (4 mL), hydrazine hydrate (23.50 µL; 0.50 mmol) was added dropwise at rt under an inert N$_2$ atmosphere. After 20 min, acetic acid (117.50 µL; 2.01 mmol) was added slowly to the reaction mixture. The reaction mixture was left to stir for 12 h at rt. After this time, ethyl acetate (10 mL) was added and the resulting mixture was washed with water (5 mL). The water phase was re-extracted with ethyl acetate (2 x 10 mL) and the combined organic layers were washed with water (3 x 5 mL) followed by brine (2 x 5 mL). The organic layer was
dried (MgSO₄) and the solvents were removed in vacuo. The crude product was purified by flash chromatography (ethyl acetate:hexane, 1:1) afforded the title compound as a light yellow oil (0.10 g, 73%, Rf = 0.55), in the ratio α:β 2.5:1.

\(^1\)H NMR (400 MHz, CDCl₃) δ ppm 1.30 - 1.37 (1H, m, SH), 1.49 - 1.94 (4H, m, CH₂, H-7,8 & H-7',8'), 1.97 (s, CH₃Ac'), 2.01 (3H, s, CH₃Ac), 2.03 (3H, s, CH₃Ac'), 2.05 (3H, s, CH₃Ac), 2.08 (s, CH₃Ac'), 2.09 (3H, s, CH₃, Ac), 2.12 (3H, s, CH₃Ac), 2.17 (s, CH₃Ac'), 2.45 - 2.63 (2H, m, CH₂, H-9 & H-9'), 3.54 - 3.64 (m, H-5'), 3.83 - 3.89 (1H, m, CH, H-5), 3.94 (1H, dt, J = 11, 3 Hz, CH, H-1), 4.05 - 4.11 (1H, m, CH, H-6a Ac & H-6a Ac'), 4.24 (dd, J = 12, 6 Hz, CH, H-6b Ac'), 4.33 (1H, dd, J = 12, 6 Hz, CH, H-6b Ac), 5.02 (dd, J = 10, 3 Hz, H-3'), 5.13 - 5.25 (3H, m, CH, H-2,3,4 & H-4'), 4.33- 4.36 (dd, J = 3, 1 Hz, CH, H-2'); \(^13\)C NMR (100MHz, CDCl₃) δ ppm 20.6 (CH₃, Ac'), 20.7 (CH₃, Ac), 20.7 ([2CH₃], Ac'), 20.7 (CH₃, Ac), 20.7 (CH₃, Ac), 20.8 (CH₃, Ac'), 20.9 (CH₃, Ac), 24.1 (CH₂, C-9), 24.3 (CH₂, C-9'), 27.1 (CH₂, C-8), 29.1 (CH₂, C-8'), 29.7 (CH₂, C-7), 29.8 (CH₂, C-7'), 62.3 (CH₂, C-6), 62.8 (CH₂, C-6'), 66.2 (CH₂, C-4'), 66.5 (CH, C-4), 66.8 (CH, C-2), 67.6 (CH₂, C-2'), 68.8 (CH, C-3), 70.3 (CH, C-5), 72.0 (CH, C-3'), 74.4 (CH, C-1), 76.2 (CH₂, C-5'), 169.9 (C=O'), 170.0 (C=O), 170.3 (C=O), 170.5 (C=O'), 170.5 (C=O), 170.9 (C=O'), 170.9 (C=O') 171.0 (C=O). IR (neat) νmax 3472, 2942, 2572, 1737, 1433, 1367, 1043, 1044, 910, 731 cm⁻¹; MS (ES)⁺: m/z [M + Na]⁺ 429.0.

3.2.12. 1,2-Bis(3-(2,3,4,6-tetra-O-acetyl-α,β-D-mannopyranosyl) propyldisulfane 151
The title compound was synthesised using the above procedure. After flash chromatography (ethyl acetate:hexane, 1:1), it was obtained as a light yellow oil (0.06 g, 23%, $R_f = 0.33$), in the ratio $\alpha:\beta 2.5:1$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.57 - 1.94 (8H, m, CH$_2$, H-7,8,11,12), 2.02 (6H, s, [2CH$_3$], Ac), 2.06 (6H, s, [2CH$_3$], Ac), 2.09 (6H, s, CH$_3$ ([2CH$_3$], Ac), 2.13 (6H, s, [2CH$_3$], Ac), 2.63 - 2.75 (4H, m, CH$_2$, H-9,10), 3.58 - 3.67 (1H, m, H-5'), 3.78-3.82 (2H, m, CH, H-5,17), 3.97 (2H, d, $J = 10$ Hz, CH, H-1,13), 4.09 (2H, dd, $J = 12$, 3 Hz,CH$_2$, H-6a, 18a ), 4.34 (2H, dd, $J = 12$, 6 Hz, CH$_2$, H-6b,18b Ac), 5.14 - 5.24 (6H, m, CH, H-2,3,4,14,15,16); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 20.7 ([2CH$_3$], Ac), 20.7 ([2CH$_3$], Ac), 20.7 ([2CH$_3$], Ac), 20.94 ([2CH$_3$], Ac), 24.7 (CH$_2$, C-8,11), 26.9 (CH$_2$, C-7,12), 37.5 (CH$_2$, C-9,10), 62.4 (CH$_2$, C-6,18), 66.8 (CH, C-4,16), 68.9 (CH, C-5,17), 70.3 (CH, C-2,15), 70.7 (CH, C-3,14), 74.6 (CH, C-1,13), 169.6 (2[C=O]), 170.1 (2[C=O]), 170.3 (2[C=O]), 170.7 (2[C=O]); IR (neat) $\nu_{\text{max}}$ 2942, 1735, 1423, 1366, 1213, 1035, 951, 910, 767, 626 cm$^{-1}$ MS (ES)$^+$: m/z [M + Na]$^+$ 833.0; Specific Rotation $\lbrack \alpha \rbrack_d^{21} = + 16.5^\circ$ (c 1.0, CH$_2$Cl$_2$).

3.2.13. Methyl 2,3,4,6-tetra-O-benzyl-$\alpha$-$d$-mannopyranoside 64$^{67}$

![Chemical Structure](image)

To a stirred solution of methyl-$\alpha$-$d$-mannopyranoside (1.01 g; 5.21 mmol) in DMF (20 mL) at 0 °C, was added sodium hydride (1.70 g; 42.01 mmol, 60% mineral oil dispersion). The mixture was stirred at rt for 1 h. The reaction mixture was heated to 70 °C and then a solution of benzyl bromide (5.70 mL; 48.01 mmol) in DMF (5 mL) was added slowly via a syringe. The mixture was stirred at 70 °C for 15 h and then allowed to cool to rt. Water (30 mL) was added to the mixture and the resulting aqueous solution was extracted with hexane (3 x 50
The combined organic layers were washed with brine (2 x 30 mL), which was then back-extracted with hexane (3 x 25 mL). The organic layer was dried (MgSO₄) and the solvents were removed in vacuo. The resulting oil was re-dissolved in ethyl acetate (5 mL) and then 5% aqueous ammonia (15 mL) was added to the solution. The solution was stirred for 2 h at rt and then extracted with DCM (3 x 25 mL). The combined organic layers were washed with water (3 x 15 mL) followed by brine (2 x 15 mL). The organic layer was dried (MgSO₄) and the solvents were removed in vacuo. The crude product was purified by flash chromatography (ethyl acetate:hexane, 1:9) afforded the title compound as a yellow oil (2.40 g, 85%, Rf = 0.15).

¹H NMR (400 MHz, CDCl₃) δ ppm 3.34 (3H, s, OCH₃), 3.72 - 3.82 (4H, m, CH,-2,5,6), 3.87 - 3.93 (1H, m, CH, H-4), 3.95 - 4.04 (1H, m, CH, H-3), 4.49 - 4.60 (2H, m, CH₂, H-OCH₂Ph), 4.62 (2H, s, CH₂, H-OCH₂Ph), 4.69 (1H, d, J = 12 Hz, CH₂, H-OCH₂Ph), 4.75 (2H, s, CH₂, H-OCH₂Ph), 4.80 (1H, d, J = 2 Hz, CH, H-1), 4.90 (1H, d, J = 11 Hz, H-OCH₂Ph), 7.21 - 7.46 (20H, m, CH, C-Ar); ¹³C NMR (100 MHz, CDCl₃) δ ppm 55.0 (CH₃, OCH₃), 69.5 (CH₂, C-6), 71.9 (CH, C-5), 72.6 (CH₂, C-OCH₂Ph), 72.8 (CH₂, C-OCH₂Ph), 73.6 (CH₂, C-OCH₂Ph), 74.7 (CH, C-2), 75.2 (CH, C-3), 75.4 (CH₂, C-OCH₂Ph), 80.5 (CH, C-4), 99.2 (CH, C-1), [(127.7, 127.8, 127.8, 127.9, 128.0, 128.1, 128.2, 128.6, 128.6, 128.6, 138.6, 138.7, 138.8, 138.8), CH, C-Ar]; IR (neat) νmax 3449, 3029, 2904, 2360, 1496, 1453, 1361, 1100, 1058, 1026, 967, 733, 695 cm⁻¹; MS (ES)⁺: m/z [M + Na]⁺ 577.0; Accurate Mass: C₃₅H₃₉O₆ requires 555.2742 found 555.2744. Specific Rotation [α]D²¹ = + 22.4° (c 0.5, CH₂Cl₂). [Lit⁵¹b [α]D²₅ = +24.7 (c 0.55, CHCl₃)].
3.2.14. 3-(2,3,4,6-Tetra-O-benzyl-α-D-mannopyranosyl) propene 65

To a stirred solution of methyl 2,3,4,6-tetra-O-benzyl mannopyranoside (0.56 g; 1.01 mmol) in acetonitrile (20 mL), was added allyltrimethylsilane (0.50 mL; 3.02 mmol) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.25 mL; 1.40 mmol). The mixture was heated at 50 °C overnight with stirring. After this time, the reaction mixture was allowed to cool to rt and then it was diluted with diethyl ether (20 mL). The organic layer was washed with an aqueous solution of 1 N NaHCO₃ (2 x 10 mL) and aqueous solution of 1 N NH₄Cl (2 x 10 mL). The organic layer was dried (MgSO₄) and the solvents were removed in vacuo.

The crude product was purified by flash chromatography (ethyl acetate:hexane, 1:5) afforded the title compound as a yellow oil (0.34 g , 60%, Rf = 0.50).

¹H NMR (400 MHz, CDCl₃) δ ppm 2.24 - 2.41 (2H, m, CH₂-7), 3.62 (1H, dd, J = 5, 3 Hz, CH, H-2), 3.67 - 3.74 (1H, m, CH, H-5), 3.74 - 3.80 (2H, m, CH₂, H-6), 3.80 - 3.89 (2H, m, CH, H-3,4), 4.01 - 4.08 (1H, m, CH, H-1), 4.49 - 4.62 (7H, m, CH₂, H-OCH₂Ph), 4.70 (1H, d, J = 11 Hz, CH₂, H-OCH₂Ph), 4.97 - 5.05 (2H, m, CH₂, H-9), 5.66 - 5.81 (1H, m, CH, H-8), 7.17 - 7.36 (20H, m, Ar); ¹³C NMR (100 MHz, CDCl₃) δ ppm 34.8 (CH, C-7), 31.4 (CH₂, C-6), 71.7 (CH₂, C-OCH₂Ph), 72.2 (CH₂, C-OCH₂Ph), 72.5 (CH, C-1), 73.5 (CH₂, C-OCH₂Ph), 73.8 (CH, C-4), 74.1 (CH₂, C-OCH₂Ph), 75.1 (CH, C-5), 75.2 (CH, C-3), 77.1, (CH, C-2), 117.5 (CH₂, C-9), [(127.7, 127.8, 127.8, 127.9, 127.9, 128.1, 128.2, 128.3, 128.5, 128.6, 128.7), CH, C-Ar], 134.5 (CH, C-8), [(138.3, 138.4, 138.5, 138.6), CH, C-Ar]. IR (neat) νmax 3675, 3063, 3029, 2864, 2360, 1495, 1453, 1361, 1206, 1090, 1063, 1026, 909, 730, 695
cm$^{-1}$; MS (ES)$^+$: m/z [M + Na]$^+$ 587.0; Accurate Mass: C$_{37}$H$_{40}$O$_5$Na requires 587.2763 found 587.2768; Specific Rotation $[\alpha]_D^{21} = +3.9^\circ$ (c 1.0, CH$_2$Cl$_2$) [Lit $^{85}$ $[\alpha]_D^{25} = +3.3$ (c 1.0, CHCl$_3$)].

3.2.15. S-(3-((2R,3R,4R,5R,5S,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)propyl)ethanethioate 139

![Chemical Structure](image)

To a stirred solution of 3-(2,3,4,6-tetra-O-benzyl-\(\alpha\)-D-mannopyranosyl) propene (0.19 g; 0.34 mmol) in 1,4-dioxane (4 mL), was added 1,1′-azobis(cyclohexanecarbonitrile) (0.06 g; 0.25 mmol). The reaction mixture was heated to 80 °C and then thioacetic acid (0.30 mL; 4.19 mmol) was added dropwise at this temperature. The reaction mixture was left to stir at 80 °C for 10 h. The reaction mixture was allowed to cool to rt and then the mixture was quenched with aqueous 1 N NaHCO$_3$ (5 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with water (3 x 5 mL) followed by brine (2 x 5 mL). The organic layer was dried (MgSO$_4$) and the solvents were removed in vacuo. The crude product was purified by flash chromatography (ethyl acetate:hexane, 1:4) afforded the title compound as a light yellow oil. This was re-purified by column chromatography (ethyl acetate:hexane, 1:9) (0.11 g, 50%, Rf $= 0.5$).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.41 - 1.97 (4H, m, CH$_2$, H-7,8), 2.21 - 2.26 (3H, m, CH$_3$, SO$_2$CH$_3$), 2.75 - 2.87 (2H, m, CH$_2$, H-9), 3.47 (1H, dd, $J = 5$, 3 Hz, CH, H-2), 3.53 - 3.91 (5H, m, CH, H-3,4,5,6), 3.92 - 4.04 (1H, m, H-1), 4.30 - 4.79 (8H, m, H-OCH$_2$Ph), 7.03 - 7.59 (20H, m, CH, H-Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 26.1 (CH, C-8), 29.1 (CH$_2$, ...
C-7), 29.5 (CH₂, C-9), 30.9 (CH₃ SOCH₃), 69.3 (CH, C-6), 71.7 (CH₂, C-OCH₂Ph), 72.4 (CH₂, C-OCH₂Ph), 73.5 (CH, C-1), 73.6 (CH₂, C-OCH₂Ph), 73.7 (CH, C-4), 74.0 (CH₂, C-OCH₂Ph), 75.0 (CH, C-5), 76.2 (CH, C-3), 78.1, (CH, C-2), [(127.8, 127.9, 128.1, 127.9, 128.1, 128.3, 128.6, 128.6, 128.7), CH, C-Ar], [(138.4, 138.4, 138.6), CH, C-Ar]; 195.47 (C=O); IR (neat) νmax 3028, 2864, 1722, 1686, 1495, 1452, 1366, 1314, 1206, 1093, 1068, 1026, 734, 696, 624 cm⁻¹; MS (ES): m/z [M + Na]⁺ 663.0; Accurate Mass: C₃₉H₄₅O₅S - e requires 641.2932 found 641.2937; Specific Rotation [α]D²¹ = + 5.3° (50 mg/5 mL, CH₂Cl₂).

3.2.16. 3-((2R,3R,4R,5S,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)propane-1-thiol 140

To a stirred solution of S-(3-((2R,3R,4R,5R,5S,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)propyl)ethanethioate (0.05 g; 0.08 mmol) in DMF (2 mL), was added hydrazine hydrate (8.0 µL; 0.16 mmol) dropwise to rt. After 20 min, acetic acid (45.0 µL; 0.80 mmol) was added slowly. The reaction mixture was left to stir for 12 h at rt. After this time, ethyl acetate (10 mL) was added and the resulting mixture was washed with water (5 mL). The water phase was re-extracted with ethyl acetate (2 x 10 mL) and then the combined organic phases were washed with water (3 x 5 mL) followed by brine (2 x 5 mL). The organic layer was dried (MgSO₄) and the solvents were removed in vacuo. The crude product was purified by flash chromatography (ethyl acetate:hexane, 1:4, 1:7) affording the title compound as a yellow oil (0.03 g, 60%, R₄ = 0.33).
\( ^1H \text{ NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) ppm 1.15 - 1.30 (2H, m, H-7), 1.53 - 1.68 (2H, m, CH\(_2\), H-8), 2.38 - 2.52 (2H, m, CH\(_2\), H-9), 3.48 (1H, dd, \( J = 5, 3 \) Hz, CH, H-2), 3.60 - 3.82 (4H, m, CH, H-4,5,6), 3.83 - 3.92 (1H, m, CH, H-3), 3.93 - 4.05 (1H, m, H-1), 4.36 - 4.84 (8H, m, CH\(_2\), H-OCH\(_2\)Ph), 5.33 - 5.57 (1H, m, H-OCH\(_2\)Ph), 7.00 - 7.55 (19H, m, CH, Ar); \( ^{13}C \text{ NMR} \) (100 MHz, CDCl\(_3\)) \( \delta \) ppm 24.5 (CH, C-8), 28.3 (CH\(_2\), C-7), 30.2 (CH\(_2\), C-9), 69.0 (CH, C-6), 71.5 (CH\(_2\), C-OCH\(_2\)Ph), 72.1 (CH\(_2\), C-OCH\(_2\)Ph), 72.2 (CH, C-1), 73.3 (CH\(_2\), C-OCH\(_2\)Ph), 73.4 (CH, C-4), 73.8 (CH\(_2\), C-OCH\(_2\)Ph), 74.8 (CH, C-5), 75.9 (CH, C-3), 77.2 (CH, C-2), [(127.7, 127.8, 128.1, 128.3, 128.3, 128.4, 128.4), CH, C-Ar], [(138.1, 138.2, 138.3), CH, C-Ar]); MS (ES): m/z [M + Na]\(^+\) 621.0; IR (neat) \( \nu_{\text{max}} \) 3028, 2864, 1720, 1495, 1452, 1313, 1270, 1206, 1089, 1068, 1025, 804, 734, 712, 696 cm\(^{-1}\); Accurate Mass: C\(_{37}\)H\(_{43}\)O\(_5\)S - e requires 599.2826 found 599.2837; Specific Rotation [\( \alpha \)]\(_D\)\(^{21}\) = + 4.7\(^o\) (50 mg/5 mL, CH\(_2\)Cl\(_2\)).
CHAPTER 4

BIBLIOGRAPHY AND APPENDIX
4.1. References


52. (a) P. H. Seeberger and D. B. Werz, *Nature*, 2007, **446**, 1046-1051. (b) Y. C. Lee and R.
   2700-2704.

53. (a) M. Reynolds and S. Perez, *Comptes Rendus Chimie*, 2011, **14**, 74-95. (b) J. H. Gabius,
   543-551.


   **93**, 9827-9832.


1999, 1, 1759-1762. (d) P. Arya, A. Barkley and K. D. Randell, J. Am. Chem. Soc.,

4.2. Appendix

**Compound: 85**

Table 1: Crystal data and structure refinement for s3435m.

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<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0596, wR2 = 0.1079</td>
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</table>
R indices (all data)  \[ R1 = 0.0755, \ wR2 = 0.1141 \]
Largest diff. peak and hole  \[ 0.282 \text{ and } -0.210 \text{ e.A}^{-3} \]

**Table 2:** Atomic coordinates ( \( x \times 10^4 \)) and equivalent isotropic displacement parameters (\( A^2 \times 10^3 \)) for s3435m. \( U_{eq} \) is defined as one third of the trace of the orthogonalized \( U_{ij} \) tensor.

<table>
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<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>( U_{eq} )</th>
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**Table 3:** Bond lengths [Å] and angles [deg] for s3435m

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C(16)-C(17)  1.328(8)
C(16)-H(16)  0.9500
C(17)-H(17A)  0.9500
C(17)-H(17B)  0.9500

C(1)-O(1)-C(5)  114.4(4)
C(7)-O(2)-C(6)  116.4(4)
C(9)-O(4)-C(2)  118.5(3)
C(11)-O(6)-C(3)  116.9(3)
C(13)-O(8)-C(4)  116.7(4)
O(1)-C(1)-C(2)  107.5(4)
O(1)-C(1)-C(2)  108.1(4)
C(6)-C(1)-C(2)  116.7(4)
O(1)-C(1)-H(1)  108.1
C(6)-C(1)-H(1)  108.1
C(2)-C(1)-H(1)  108.1
O(4)-C(2)-C(1)  109.6(4)
O(4)-C(2)-C(3)  107.7(4)
C(1)-C(2)-C(3)  108.2(3)
O(4)-C(2)-H(2)  110.4
C(1)-C(2)-H(2)  110.4
C(3)-C(2)-H(2)  110.4
O(6)-C(3)-C(2)  108.0(3)
O(6)-C(3)-C(4)  111.4(4)
C(2)-C(3)-C(4)  111.4(4)
O(6)-C(3)-H(3)  108.7
C(2)-C(3)-H(3)  108.7
C(4)-C(3)-H(3)  108.7
O(8)-C(4)-C(5)  106.5(4)
O(8)-C(4)-C(3)  108.9(3)
C(5)-C(4)-C(3)  113.0(4)
O(8)-C(4)-H(4)  109.4
C(5)-C(4)-H(4)  109.4
C(3)-C(4)-H(4)  109.4
O(1)-C(5)-C(4)  111.5(4)
O(1)-C(5)-C(15)  112.1(4)
C(4)-C(5)-C(15)  113.4(4)
O(1)-C(5)-H(5)  106.4
C(4)-C(5)-H(5)  106.4
C(15)-C(5)-H(5)  106.4
O(2)-C(6)-C(1)  108.3(4)
O(2)-C(6)-H(6A)  110.0
C(1)-C(6)-H(6A)  110.0
O(2)-C(6)-H(6B)  110.0
C(1)-C(6)-H(6B)  110.0
H(6A)-C(6)-H(6B)  108.4
O(3)-C(7)-O(2)  122.1(5)
O(3)-C(7)-C(8)  125.6(5)
O(2)-C(7)-C(8)  112.2(4)
C(7)-C(8)-H(8A)  109.5
C(7)-C(8)-H(8B)  109.5
H(8A)-C(8)-H(8B)  109.5
C(7)-C(8)-H(8C)  109.5
H(8A)-C(8)-H(8C)  109.5
H(8B)-C(8)-H(8C)  109.5
O(5)-C(9)-O(4)  122.4(4)
O(5)-C(9)-C(10)  125.3(5)
O(4)-C(9)-C(10)  112.3(4)
C(9)-C(10)-H(10A)  109.5
C(9)-C(10)-H(10B)  109.5
H(10A)-C(10)-H(10B)  109.5
C(9)-C(10)-H(10C)  109.5
H(10A)-C(10)-H(10C)  109.5
H(10B)-C(10)-H(10C)  109.5
O(7)-C(11)-O(6)  122.8(4)
O(7)-C(11)-C(12)  126.2(4)
O(6)-C(11)-C(12)  111.0(4)
C(11)-C(12)-H(12A)  109.5
C(11)-C(12)-H(12B)  109.5
H(12A)-C(12)-H(12B)  109.5
C(11)-C(12)-H(12C)  109.5
H(12A)-C(12)-H(12C)  109.5
H(12B)-C(12)-H(12C)  109.5
O(9)-C(13)-O(8)  124.8(5)
O(9)-C(13)-C(14)  124.9(5)
O(8)-C(13)-C(14)  110.3(5)
C(13)-C(14)-H(14A)  109.5
C(13)-C(14)-H(14B)  109.5
H(14A)-C(14)-H(14B)  109.5
C(13)-C(14)-H(14C)  109.5
H(14A)-C(14)-H(14C)  109.5
C(16)-C(15)-C(5)  110.3(4)
C(16)-C(15)-H(15A)  109.6
C(5)-C(15)-H(15A)  109.6
C(16)-C(15)-H(15B)  109.6
C(5)-C(15)-H(15B)  109.6
H(15A)-C(15)-H(15B)  108.1
C(17)-C(16)-C(15)  124.3(6)
C(17)-C(16)-H(16)  117.9
C(15)-C(16)-H(16)  117.9
C(16)-C(17)-H(17A)  120.0
C(16)-C(17)-H(17B)  120.0
H(17A)-C(17)-H(17B)  120.0

Symmetry transformations used to generate equivalent atoms: