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Example
Synthesis of Sulfoxide and Sulfone Mycothiol Bioisosteres and Novel Carbohydrate-based Thiochromans

By

PASEKA THENDO MOSHAPO

A dissertation submitted in partial fulfilment for the Degree

of

Masters in Chemistry

in

The Department of Chemistry

Faculty of Science

UNIVERSITY OF JOHANNESBURG

Supervisor: Dr Henok H. Kinfe

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Abstract

Inhibition of mycothiol biosynthesis pathway has attracted attention from chemists and biochemists who aim to develop novel anti-TB drugs. A possible route to inhibit the production of mycothiol in cells may be via the inhibition of enzymes involved in the biosynthetic pathways. Molecular analogues that mimic mycothiol and containing tetrahedral-forming functional groups have been reported to show activity against mycothiol biosynthesis by inhibiting the enzymes in the mycothiol biosynthetic pathway.

In this research we report the synthesis of simplified sulfoxide and sulfone-based mycothiol molecular analogues that are targeted against the inhibition of mycothiol biosynthesis. To achieve our goals, appropriately protected glucal 113 was transformed into α-1,2 cyclopropanated sugar 115 which was easily opened to afford C-2 branched iodomethyl O-glycosides in α- and β-anomeric mixtures. Cyclohexanol was employed as the glycosyl acceptor and, thus, replacing the more hydrophilic myo-inositol moiety found in mycothiol with a hydrophobic cyclohexyl group. S_N2 substitution of iodide group by alkyl and aryl thiols afforded the different alkyl and aryl thio-methyl O-glycosides 117 and 123-131 upon which oxidation of the sulfides afforded their tetrahedral sulfoxide and sulfone derivatives which were then deprotected to yield the target mycothiol analogues 120 and 144-154. Also reported is a possible poisoning of palladium metal by sulfur which lead to the use of methoxybenzyl ethers as ideal protecting groups in place of benzyl ethers. The synthesized compounds have been sent for anti-TB activity testing.
Coupled to the mycothiol derivatives we also report on the diastereoselective synthesis of novel carbohydrate-based thiochromans 170 and 177-181 as thiochromans are reported to contain interesting pharmaceutical properties.

To achieve our aims, appropriately protected glucal was transformed into α- and β-anomeric mixtures of iodomethyl acetates 168. $S_N2$ substitution of iodine afforded the pyranosyl glycosides 169 and 172-176 which were cyclized under acidic conditions to afford the target thiochromans as single isomers. The mechanism of cyclization is also proposed. Oxidation of the thiochromans into their sulfoxide and sulfone derivatives afforded compounds containing tetrahedral moieties and the α-C-glycosylated aryl group presented a “hydrophobic core” which resembled the cyclohexyl ring in the simplified mycothiol analogues, thus, making these compounds suitable candidates for the inhibition of mycothiol biosynthesis.

The thiochroman derivatives were investigated for their anticancer and antimalarial activity and were found to possess unprecedented antimalarial activity, especially compound C027_1/184 which demonstrated high activity against the parasite plasmodium falciparum (IC$_{50}$ = 0.07846 µM). No anticancer activity was observed for the compounds tested against human breast cancer, human colon cancer and human prostate cancer cell lines.
Abbreviations

Ac Acetate
Bn Benzyl
c.a. Approximately
Calcd. Calculated
CAN Ammonium Cerium (IV) Nitrate
COSY Correlation Spectroscopy
DCM Dichloromethane
DEPT Distortionless Enhancement by Polarisation Transfer
DMAP N,N-Dimethylaminopyridine
Eq. Equivalents
EtOAc Ethyl Acetate
HMBC Heteronuclear Multiple Bond Coherence
HRMS High Resolution Mass Spectrometry
HSQC Heteronuclear Single Quantum Coherence
Hz Hertz
IC$_{50}$ Concentration of compound needed to inhibit cell growth by 50%
ID$_{50}$ Concentration of a drug which induces a response halfway between the baseline and maximum after a specified exposure time
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>LAH</td>
<td>Lithium aluminium hydride</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>Multi-drug Resistant Tuberculosis</td>
</tr>
<tr>
<td>MHz</td>
<td>Mega Hertz</td>
</tr>
<tr>
<td>Min</td>
<td>Minute(s)</td>
</tr>
<tr>
<td>Mp.</td>
<td>Melting point</td>
</tr>
<tr>
<td>MSH</td>
<td>Mycothiol</td>
</tr>
<tr>
<td>NaH</td>
<td>Sodium Hydride</td>
</tr>
<tr>
<td>NIS</td>
<td>N-Iodosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>Nuclear Overhauser Effect</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>RT</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TBAI</td>
<td>Tetrabutyl Ammonium Iodide</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>Extensively Drug Resistant Tuberculosis</td>
</tr>
<tr>
<td>XRD</td>
<td>X-ray diffraction</td>
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Chapter 1: Literature

1.1 Tuberculosis

1.1.1 Introduction

Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium tuberculosis* and enters the human host mainly through the respiratory system, infecting primarily the lungs (pulmonary TB) before spreading to other parts of the body (extrapulmonary TB) in extreme cases of the disease. The bacillus is Gram positive with high lipid content in the cell wall, which contributes to its robust nature and ability to survive harsh conditions. TB is characterized by forming of tubercles in the infected parts of the body and patients often suffer from excessive coughs and excretion of sputum, fever and weight loss.\(^1,2\) More drug resistance and fatal TB strains such as multi-drug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB)\(^*\) can develop if the disease is not well managed and these are more expensive and difficult to treat, thus, presenting a greater challenge in TB management.\(^3-5\)

TB remains one of the most ancient and toughest diseases to eradicate; as a result the Stop TB partnership had to implement a strategic plan in 2006, The Global Plan to Stop TB, to control the damage caused by the disease.\(^6,7\)

\(^*\)According WHO MDR-TB is defined as a specific form of drug-resistant TB due to a bacillus resistant to at least isoniazid and rifampicin, the two most powerful anti-TB drugs and XDR-TB is defined as a form of TB which is resistant to at least four of the core anti-TB drugs. XDR-TB involves resistance to the two most powerful anti-TB drugs, isoniazid and rifampicin in addition to resistance to any of the fluoroquinolones (such as ofloxacin or moxifloxacin) and to at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin)
The reduction of TB prevalence and death rates by 50% relative to death rates in 1990 by 2015 is the intermediate goal before a complete eradication by 2050 (7.5 million cases reported in 1990). The partnership aims to reach these objectives through the research and development of new anti-TB drugs that are safe, affordable, effective and easily accessible to the needy, the development of new technologies that offer accurate and early detection of TB in infected patients and provision of educational programs and guidance to limit the spread of TB in health institutions and public areas. With over 8.8 million new TB incident cases reported for 2010 clearly TB still remains a major global health threat.

1.1.2 A brief history of TB

The history of TB, previously known as “phthisis”, “consumption” or “the white plague”, has been well documented and modern research and carbon-dating techniques have shown that the plague has pestered mankind for centuries. The earliest indication of human TB can be dated back more than 5000 years. Archaeological evidence of early TB is found in the well-preserved Egyptian mummies, Egyptian art, ancient literature as well as human archaeological species from Europe. The characteristic formation of plural adhesions, rib and vertebral lesions in TB infected specimen has enabled morphological analysis and physical identification of individuals that had succumbed to the disease (Figure 1.1). Paleomicrobiology and the development of ancient DNA analysis using PCR techniques have verified the ancient origin of the TB microbe.
Figure 1.1. a) An ancient Egyptian painting showing deformity of the cervical-thoracic spine due to TB infection.\textsuperscript{17} b) An image showing a compressed spinal vertebrae characteristic of TB in infection.\textsuperscript{19}

The etiology of TB was not understood until early 1882, when Robert Koch (the father of TB) made his Nobel Prize winning discovery, that ‘tubercle bacillus’, as he named it, was the causative agent of TB.\textsuperscript{11,22} Koch further demonstrated that \textit{Mycobacterium tuberculosis} was responsible for the fatal TB in human beings and that although \textit{Mycobacterium bovis}, which is found mainly in cattle, did infect humans, it was rarely fatal. Koch continued working on the prevention and treatment of tuberculosis. In 1890 he isolated tuberculin from tubercle bacilli as a treatment for TB. However, tests resulted in adverse reactions and a variety of symptoms in individuals who were infected with TB and no effect in healthy individuals.\textsuperscript{23} Clemens Von Piquet worked on Koch’s discoveries and proposed that a tuberculin test could be developed from Koch’s discoveries. Eventually a tuberculin TB diagnostic tool was developed in 1907 by Charles Mantoux.\textsuperscript{24,25}

Amidst the lack of a TB treatment drug and high mortality rates, physicians and nurses returned to sanitaria for treatment of the sick (Figure 1.2).\textsuperscript{26,27} These were first established in 1857 mainly to isolate infected individuals and treat them with rest, fresh air and improved nutrition and it was previously reported that these comforts contributed to the wellness of TB patients.\textsuperscript{28}
The first TB vaccine, BCG (Bacille Calmette-Guérin) was developed in 1921 by Albert Calmette and his associate Camille Guérin. Although there are varying reports on the efficacy of the vaccine, BCG is the only licenced vaccine to date and is currently administered to infants and young children for the immunisation against childhood TB. The modern era of TB treatment is rooted in the 1944 discovery of streptomycin (SM) by Albert Schatz, Elizabeth Bugie, and Selman Waksman and the subsequent discovery of para-aminosalicylic acid (PAS) by Jorgen Lehmann. The individual drugs were effective against *Mycobacterium tuberculosis* but the bacilli acquired resistance over time. However, a combined administration of the drugs showed greater activity and potency by delaying the emergence of drug resistant tubercle strains. As a result TB treatment using a combination of drugs was initiated. Continued research for anti-TB drugs lead to the discovery of isoniazid (INH), ethambutol (EMB), rifamycin (RIF) and pyrazinamide (PZA) between 1950 and 1960 (see Figure 1.2 for structures). The combination of INH, SM and PAS was found to achieve treatment in 24 months. More trials and drug combinations reduced the treatment period to 9 months using a combination of INH, SM, EMB and RIF. The treatment period was further reduced to 6 months with >95% cure using a combination of PZA, INH, and RIF. The discovery of these effective drugs revolutionised TB treatment.
as chemotherapy replaced sanatoria and the focus shifted from controlling the spread of the disease to cure.\textsuperscript{35}

\textbf{Streptomycin (SM)}

\textbf{Para-aminosalicyclic acid (PAS)}

\textbf{Isoniazid (INH)}

\textbf{Ethambutol (EMB)}

\textbf{Rifamycin (RIF)}

\textbf{Pyrazinamide (PZA)}

\textbf{Figure 1.3.} Commercial anti-TB drugs

\textbf{1.1.3 Current TB therapy and challenges}

\textbf{1.1.3.1 Drug resistance}

According to WHO the standard treatment of TB can take up to 6 months using a combination of 4 drugs which include INH, EMB, RIF and PAZ. EMB and PAZ are administered for the first 2 months whilst RIF and INH are administered for the full 6 month period.\textsuperscript{36} Non-compliance by the patient or failure of the health professional to follow proper guidelines when treating the patient may result in the development of drug resistant TB strains such as MDR-TB and XDR-TB.\textsuperscript{37} Resistance can occur through the mutations of target genes and thus, rendering the drugs ineffective.\textsuperscript{38,39} An example is the mutation of the
katG gene in the case of resistance to INH.\textsuperscript{40} This gene encodes the synthesis of a peroxidase enzyme which is required for the activation of INH. In the case of rifamycin resistance can be due to point mutations in the \textit{rpoB} gene in the beta subunit of DNA-dependent RNA polymerase.\textsuperscript{41}

Thus, second-line TB drugs are required for the treatment of drug resistant TB strains. Some of these drugs are listed in Table 1.2.\textsuperscript{36} Treatment can take up to 20 months and the treatment regimen can differ from patient to patient\textsuperscript{42} but should consist of a minimum of 5 different second-line drugs. One drug from each group depending on the potency and safety of the drug, except group 4 where two drugs can be administered at the same time. All the 5 drugs are administered for the first 8 months followed by 12 months without the injectable agents (Group 2).\textsuperscript{36} The drugs are highly effective but are limited by their toxicity and side effects such as ototoxicity resulting in hearing loss, psychiatric complications such as depression and anxiety as well as gastrointestinal disturbances resulting in diarrhoea.\textsuperscript{43,44} These complications may also lead to the premature termination of therapy.

### Table 1.1 First-line drugs for TB treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Administration in Standard TB treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>6 months</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>6 months</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>First 2 months</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>First 2 months</td>
</tr>
</tbody>
</table>
Table 1.2 Second-line drug for MDR-TB treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Classification</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>First-line oral agents</td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ethambutol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rifabutin</td>
</tr>
<tr>
<td>2</td>
<td>Injectable agents</td>
<td>Kanamycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amikacin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Capreomycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Streptomycin</td>
</tr>
<tr>
<td>3</td>
<td>Fluoroquinolones</td>
<td>Levofloxacin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moxifloxacin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ofloxacin</td>
</tr>
<tr>
<td>4</td>
<td>Oral bacteriostatic second-line agents</td>
<td>Para-aminosalicylic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cycloserine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Terizidone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ethionamide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protionamide</td>
</tr>
</tbody>
</table>

1.1.3.2 HIV and TB co-infection

The epidemic of HIV has added more burden to the efforts of controlling and eliminating TB.45 HIV weakens the immune system, thus, making the host vulnerable to infection by opportunistic diseases such as TB which is the leading cause of death in HIV infected patients.46 The incompatibility of TB and HIV drugs due to drug-drug interactions and associated side effects makes co-treatment of the two diseases unsafe. Rifamycins are known to have pharmacokinetic interactions with protease inhibitors and non-nucleotide reverse transcriptase inhibitors and thus, activating Cytochrome P450 enzymes which increase the rate of the metabolism and excretion of the antiretrovirals.47,48 This results in a low plasma concentration of the antiretroviral drugs and thus, reduces their efficacy. Adverse effects such as hepatitis, development of rash, gastrointestinal disturbances and neurological disorders are more likely to occur in co-infected patients than in patients receiving treatment for TB only.49
1.1.3.3 Development of new anti-TB drugs

Modern era of TB infection which is coupled to MDR-TB, XDR-TB and HIV co-infection requires the development of novel anti-TB drugs that are safer, effective against drug resistant TB-strains, can achieve treatment in a reduced period and are compatible with drugs used in HIV treatment. The fluoroquinolones gatifloxacin and moxifloxacin are currently the drugs in the 3rd phase of anti-TB clinical trials and these have shown efficacy as potential anti-TB agents in humans and animals.\textsuperscript{50,51}

The reduction of treatment periods may be achieved through the weakening of the bacterium’s defensive mechanisms.\textsuperscript{76} Alternative anti-TB drugs may be developed by inhibiting the biosynthesis of molecules involved in the defensive mechanisms of Mycobacteria and exposing the defenceless bacterium to toxic agents. One of the compounds involved in Mycobacterium defensive mechanisms is a low-molecular weight thiol known as mycothiol and serves as a scavenger of reactive oxygen species, alkylating agents and xenobiotics. Essentially these low-molecular weight thiols maintain a constant intracellular redox homeostasis required for normal cellular functioning and metabolism.\textsuperscript{74} The inhibition of biosynthesis of this molecule may lead to increased sensitivity of Mycobactrium tuberculosis to drug treatment resulting in shorter treatment periods.
1.2 Mycothiol

1.2.1 Introduction

Actinomycetes are a large variety of Gram-positive bacteria which are widely distributed in nature. These bacteria possess a wide range of biochemical properties that are both beneficial and detrimental to human life. A few examples of the former are the bio-production of agroactive compounds that benefit the agricultural industries and the production of antibiotics such as streptomycin as secondary metabolites. In the later, some actinomycetes can be pathogenic to humans and animals, causing diseases such as tuberculosis and necrosis. These bacteria are known to produce mycothiol (MSH) (Fig 1.3) as their low molecular weight thiol instead of glutathione which is found mainly in eukaryotes and Gram-negative bacteria.

Glutathione (GSH) (Fig 1.3) has been well-studied and is known to protect organisms from reactive oxygen species (ROS), alkylating agents and xenobiotics, thus, maintaining a redox homeostasis within the cellular environment. The absence of GSH in actinomycetes and the high levels of MSH serve as an indication that the two thiols could play similar biological roles. In addition to their functional similarities mycothiol and glutathione contain a cysteine amino acid in their structure. Mycothiol further contains an inositol and a glucosamine moiety whilst glutathione consists of glycine and glutamic acid in addition to cysteine (Figure 1.3). Essentially these low molecular weight thiols are anti-oxidising agents, maintaining a constant intracellular redox homeostasis required for normal cellular functioning and metabolism.
Mycothiol was first identified in 1993 by Fahey and co-workers as a major thiol in *Streptomyces.* The thiol was isolated as a bimane derivative and named U17 (Figure 1.3) as it eluted at 17 minutes during HPLC analysis. Steenkamp and co-workers later isolated U17 in *Mycobacterium bovis* and successfully purified it for characterization using $^1$H and $^{13}$C NMR techniques combined with mass spectrometry. Analysis results afforded the name 1D-myoinositol-2-(N-acetyl-L-cysteinyl) amine-2-deoxy-$\alpha$-D-glucopyranoside, which was simplified to mycothiol.

The distribution of mycothiol in a variety of actinomycetes has been characterized and *Mycobacterium tuberculosis* as well as *Mycobacterium smegmatis* were found to have the highest content of MSH, producing 9 -12 µmol/g and 19 µmol/g of residual dry weight respectively. To investigate the role of mycothiol, mutants of *Mycobacterium smegmatis* lacking mycothiol were found to be susceptible to oxidative species, alkylating agents and antibiotics such as streptomycin, vancomycin, penicillin G, rifamycin and rifampin. The results indicate that MSH could be involved in the anti-oxidant pathways protecting cells.
against oxidative stress and xenobiotics targeted against the bacteria. As a result of these findings, mycothiol biochemistry has since attracted great interest as a target for the design and development of new anti-TB drug candidates.

1.2.2 Mycothiol Biochemistry

1.2.2.1 Mycothiol Biosynthesis

The metabolism and biological activities of mycothiol enables researchers to gain knowledge and understanding of the functioning of mycothiol. Its biosynthetic routes together with the associated enzymes and co-factors have been well established.\textsuperscript{75,76} Scheme 1.1 shows the mycothiol biosynthetic pathway which has six steps starting with the biosynthesis of 1\textit{L}-\textit{myo}-inositol-1-phosphate 2 (1L-Ins-1-P) from glucose-6-phosphate (G-6-P) 1 catalysed by inositol phosphate synthase.\textsuperscript{77} A glycosyl transferase, MshA1 then forms a glycosidic bond between substrates 1-L-Ins-1-P 2 and UDP GlcNAc 3 to form the precursor pseudo-disaccharide 1-O-(2-acetamido-2-deoxy-\textalpha-D-glucopyranosyl)-D-\textit{myo}-inositol-3-phosphate 4 (GlcNAc-Ins-P).

The phosphate group is then removed by a phosphatase, MshA2 to form 1-O-(2-acetamido-2-deoxy-\textalpha-D-glucopyranosyl)-D-\textit{myo}-inositol 5 (GlcNAc-Ins). The metalloprotein MshB catalyses the hydrolysis of \textit{N}-acetyl sugar to form the aminosugar 1-O-(2-amido-2-deoxy-\textalpha-D-glucopyranosyl)-D-\textit{myo}-inositol 6 (GlcN-Ins).\textsuperscript{78} MshC, an ATP-independant ligase then couples a cysteine peptide to the free amine to form 1-O-[2-\{(2\textit{R})-2-amino-3-mercapto-1-oxopropyl\}amino]-2-deoxy-\textalpha-D-glucopyranosyl]-D\textit{myo}-inositol 7 (Cys-GlcN-Ins)\textsuperscript{79} which is then \textit{N}-acetylated by acetyl coenzyme A catalysed by an acetyl transferase MshD to form 1-O-[2-\{(2\textit{R})-2-(acetylamino)-3-mercapto-1-oxopropyl\}amino]-2-deoxy-\textalpha-D-glucopyranosyl]-D-\textit{myo}-inositol 8 (MSH).\textsuperscript{80}
1.2.2.2 Mycothiol-dependent detoxification

Mycothiol-dependent detoxification pathways (Scheme 1.2) illustrate the protective role of this low molecular weight thiol. More importantly the pathways show how the thiol conjugates to foreign substances or toxic bio-waste within the cellular environment and the different enzymes that are involved in these metabolic processes. Reactive oxygen species (ROS) such as alkyl and lipid hydroperoxides are some of the harmful species that can be generated as by-products of metabolic processes and can cause a homeostasis imbalance in the cellular environment. To combat this potential threat, two molecules of mycothiol
(MSH) assisted by a thiol peroxidase enzyme reduce the oxidative species to their alcohol derivatives \( I \) and the two MSH molecules form the more oxidised disulfide MSSM \( 9 \). Mycothiol disulfide reductase (Mtr) or mycothione reductase cleaves the disulfide linkage in MSSM \( 9 \) and regenerates two reduced MSH molecules ready to maintain the bacteria’s homeostasis \( II \).\(^{84-87}\)

Mycothiol is also implicated in the detoxification of electrophilic harmful substance by forming MS-toxin \( S \)-conjugates \( 10 \) catalysed by MSH \( S \)-transferase \( III \).\(^{88}\) The \( S \)-conjugate can be excreted or cleaved by mycothiol-\( S \)-conjugate amidase (Mca) which hydrolyses the glucosamine amide bond to form GlcN-Ins \( 6 \) and a mercapturic acid \( 11 \) derivative of the toxin \( IV \). The later activity by Mca could be more useful in the maintaining cellular levels of MSH as the formed GlcN-Ins is retained within the cell and recycled back into the MSH biosynthesis pathway \( V \) whilst the mercapturic acid toxin derivative is excreted \( VI \). The excreted mercapturic acid derivatives can be detected in urine samples. Steffek and co-workers have shown Mca to be active to a wide range of compounds conjugated to the sulfur atom of mycothiol.\(^{89}\) Mca enzyme has, however, shown more specificity for the MSH with complete inositol and glucosamine moieties. The active site of Mca has been proposed based on its sequence similarity to MshB deacetylase.\(^{90}\) Both enzymes deacetylate their respective substrates, contain a metal binding site and identical amino acids except for the presence of Ser20 in MshB which is replaced by Lys19 in Mca.\(^{89,90}\)

Mycothiol and other low molecular weight thiols such as glutathione conjugate to reactive nitrogen species (RNS) such as \( \text{NO}^- \) to form S-nitroso-mycothiol (MSNO) or S-nitroso-glutathione (GSNO) conjugates respectively \( VII \).\(^{91}\) High levels of these conjugates can be a threat to regular cellular functioning due to their binding to protein thiols by transnitration.\(^{92}\) To prevent any cellular damage in \textit{Mycobacteria}, enzyme S-nitroso-mycothione reductase
(MscR) readily converts the nitrosothiol to mycothiol-\(N\)-hydroxy-sulfenamide 13 which is further converted to less toxic \(\text{NO}_3^–\) and MSH by pathways yet to be established IX. *Mycobacterium smegmatis* has shown resistance to nitric oxide toxicity and was found to be sensitive in MSH deficient mutants.\(^{93}\)

**Scheme 1.2.** Mycothiol-dependent detoxification pathways.
1.2.2.3 Mycothiol as co-factor and cysteine reservoir

Aromatic compounds can be used as a source of carbon in biological metabolism. Glutathione-producing organisms convert a large number of aromatic compounds to pyruvate and fumarate which are intermediates of the Krebs cycle via the gentisate pathway catalysed by a GSH-dependent enzyme maleylpyruvate isomerase. Mycothiol has also been reported to function as a co-factor of maleylpyruvate isomerase in the gentisate pathway of MSH-producing organisms such as Corynebacterium glutamicum. Mutants of C. glutamicum deficient in MSH were unable to grow when aromatics were used as the only carbon source which suggests that MSH may be a co-factor and plays a major role in the generation of energy required for bacterial growth.

Cysteine is extensively used in antioxidant biological activities by both eukaryotes and prokaryotes. However, cysteine auto-oxidises rapidly and can compromise the cell’s intracellular reducing environment whilst MSH oxidises slowly and thus, serves as an enhanced cysteine carrier and as an antioxidant.

1.2.2.4 Enzyme and substrate specificity studies in MSH biosynthesis

The identification of MshB as a critical enzyme in the biosynthesis pathway of MSH by Newton and co-workers has drawn much interest in the enzyme’s structure, functions and substrate specificity. Nicholas and co-workers have synthesised 1-D- and 1-L-myoinositol GlcNAc-Ins diastereomers and observed that MshB activity was specific for the 1-D-myoinositol isomer and no deacetylation was observed when the L-isomer was used.
X-ray crystallographic analysis by Maynes and colleagues has revealed the structure of MshB deacetylase protein. The protein was found to contain amino acids that make the active site hydrophilic and highly electronegative. Also identified was a zinc metal coordinated to two water molecules and a few amino acids that function to stabilize the substrate during catalysis (see Figure 1.4).

The proposed mechanism of catalysis involves the disposition of one water molecule from the active site by the incoming substrate (GlcNAc-Ins 5) a zinc ion then co-ordinates to the carbonyl oxygen of the acetyl group. The remaining water molecule acts as a nucleophile and attacks the electrophilic carbonyl carbon of the acetyl group. Asp15 contributes to the nucleophilicity of the water molecule by deprotonating it. As the substrate is deacetylated the formed negatively charged tetrahedral intermediate of the carbonyl oxygen is stabilized by the positively charged His144 imidazole side chain. The leaving product is then protonated by Asp15 to form GlcN-Ins 6.

Figure 1.4. Proposed mechanism of catalysis in MshB deacetylase active site.
1.2.3 Mycothiol Chemical Synthesis

The chemical synthesis of mycothiol is of importance in understanding of the biosynthesis and function of mycothiol. Jardine and co-workers semi-synthesised MSH and illustrated that D-\textit{myo}-inositol was utilised by MshC in the biosynthetic pathway and not the L-isomer. Thus, confirming the absolute stereochemistry of the inositol sugar moiety. Working separately Nicholas and co-workers synthesized MSH bimane (MSmB) and also confirmed the absolute stereochemistry of MSH by comparing analytical data of the synthesised molecule with the natural molecule. The activity of Mca was found to be the same for both the natural and synthesized MSH bimane.

The first complete chemical synthesis of mycothiol was reported by Lee and Rosazza in 2004. The multi-step synthesis (Scheme 1.3) entails the use of a strategically protected \textit{myo}-inositol that has a free OH group at C-1 which was then glycosylated with trichloroacetimidate using trimethylsilyl trifluoromethane sulfonate (TMSOTf) to form the glycoside. The formed product was then reduced to an amine and subsequently isolated as the hydrochloride. \textit{N,S}-diacetyl-L-cysteine was conjugated to the amine using HATU*, 1-hydroxy-7-azabenzotriazole (HOAt) and collidine to form the per-acetylated MSH. Selective S- and O-deacetylation in the presence of \textit{N}-acetyl group was achieved by using Mg(OMe)$_2$ in methanol to afford MSH and MSSM which was reduced to MSH by treatment with bis(2-mercaptoethyl)sulfone (BMS).

* HATU - \textit{O}-(7-azabenzotriazol-1-yl)-\textit{N,N,N',N'}-tetramethyluroniumhexafluorophosphate
Scheme 1.3. MSH chemical synthesis.  

1) TMSOTf, molecular sieves, CH$_2$Cl$_2$, 0 °C, 1 h, 56%;  
2) H$_2$, Pd/C, EtOAc, HCl, rt, 6 h, 81%;  
3) HATU, HOAt, collidine, DMF, 0 °C to rt, 22 h 25%;  
4) Mg(OMe)$_2$, MeOH, rt, 2 h, 69%;  
5) BMS, H$_2$O, rt, 5 days, 100%.

The overall chemical synthesis of mycothiol was low yielding (~ 11% overall) and challenges were encountered during the regio-selective protection and resolution of myo-inositol, formation of α and β glycosidic bonds during glycosylation and the low yielding coupling of the cysteine residue. In an attempt to solve some of these synthetic hurdles, Gammon and co-workers synthesized bicyclic a thioglycoside of N-acetylated glucoseamine 25 according to Scheme 1.4.106
Scheme 1.4. N-acetylated glucoseamine synthesis by Gammon and co-workers. i) BF$_3$Et$_2$O, CH$_2$Cl$_2$, reflux, overnight, 68%; ii) NH$_2$(CH$_2$)$_2$NH$_2$, MeOH, 60 °C, overnight, 86%; iii) a) EDCl, HOBr, DMF-H$_2$O (9:3), 1 h, rt; b) Pyridine, Ac$_2$O, 50%; iv) NaOMe, MeOH, 82%.

The product 25 already contained a cysteine side chain that was β-linked at the anomeric position. It was expected that glycosylation with an appropriate acceptor would form the desired 1,2-cis-linked glycosides, with the cysteine residue at C-2. However, no suitable promoter or reaction conditions were found as the compounds were too stable to undergo any type of glycosylation. Thus, efficient total synthesis of mycothiol still remained a challenge.

1.2.4 Mycothiol Molecular Analogues and Enzyme Inhibitors

1.2.4.1 Natural product enzyme inhibitors of mycothiol biosynthesis

The biosynthesis of mycothiol has been exploited with the aim of developing novel potential anti-TB drugs. Two enzymes involved in MSH biosynthesis and function, MshB and Mca
respectively have been identified as potential targets in achieving such aims. *Mycobacterium tuberculosis* mutants lacking MshB were found to produce a substantial amount of MSH over time and this was attributed to the activity of the amidase Mca which cleaves the amide bond of mycothiol-S-conjugates in a similar fashion as MshB deacetylates GlcNAc-Ins.\(^8\) Thus, it would be essential to inhibit the activities of both MshB and Mca in order to hinder the biosynthesis of mycothiol and then expose the bacterium to xenobiotics.

MshB enzyme has shown a 4700-fold higher activity than Mca for 0.1 mM GlcNAc-Ins (its natural substrate) whilst Mca showed a 170-fold higher activity than MshB for 0.1 mM MSmB.\(^1\) Mycothiol-acetophenone 26 indicated 66% and 87% activities as substrate for both MshB and Mca respectively.

![Image of MS-acetophenone](image)

*Figure 1.5. Mycothiol derivate MS-acetophenone showed activity against both MshB and Mca enzymes.*

Nicholas *et al.* have reported active bromotyrosine-based alkaloids extracted from marine sponges and terrestrial fungus.\(^108\)-\(^110\) These compounds were found to be active against Mca in both *Mycobacterium tuberculosis* and *Mycobacterium smegmatis* (Figure 1.6). Common amongst these compounds was the presence of a central amide group coupled to an oxyimine and a heterocyclic-containing group. Inhibition studies showed that the spiroisoxaline 28a and oximinoamide 29 exhibited competitive inhibition. The glycosylated sphingolipid 30 and tricyclic piperazine 31 showed non-competitive inhibition properties. The removal of the sugar moiety on the sphingolipid 30 resulted in a 50 – 100 fold reduction in...
activity of the compound indicating that the sugar moiety could be important for enzyme recognition and binding. These natural products may serve as lead compounds providing researchers with a reference for the design and modelling of active compounds based on the active functional groups present in these natural products.

![Chemical structures of natural product inhibitors](image)

**Figure 1.6.** Natural product inhibitors.

### 1.2.4.2 Synthesized enzyme inhibitors of mycothiol biosynthesis

The biosynthesis of mycothiol offers a variety of potential targets for drug development. The exclusive presence of mycothiol in Gram positive bacteria such as *Mycobacteria* makes the molecule and its biosynthesis an ideal target for TB-drug development. There are a few reports on the synthesis of mycothiol derivatives as potential inhibitors of MSH biosynthesis pathway.\textsuperscript{111-113} One such report was by Knapp and co-workers who synthesized a simplified cyclohexyl thioglycoside analogue of mycothiol 32 (Figure 1.7) which was deacetylated by Mca indicating that the myo-inositol pseudosaccharide and oxygen atom forming the glycosidic bond were not important for Mca enzyme recognition and deacetylation.\textsuperscript{114} These
findings resulted in the synthesis of a variety of mycothiol analogues (Figure 1.9) from a simplified thioglycoside scaffold 33. These analogues 33a-d showed potential activity exhibiting inhibitions between 4 and 51%.

Patel and Blanchard also showed that the disulfide substrate 34 lacking the inositol group and in α,β-anomeric mixtures could undergo successful reduction by mycothiol disulfide reductase (Mtr) hinting that the inositol moiety and O-glycoside atom were of no major importance for the enzyme’s recognition and binding. As a result mycothiol analogues with a potential to inhibit the enzymes involved in the biosynthesis of mycothiol could be synthesized without the tedious preparation and resolution of partially protected myo-inositol moiety and its troublesome stereospecific glycosylation, instead the myo-inositol moiety may be replaced by a more hydrophobic cyclohexyl group.

Gammon and co-workers reported the synthesis and activity of mycothiol molecular analogues containing cyclohexyl and phenyl S- and O-glycosides in substitute for the inositol moiety present in GlcNac-Ins. The type of aglycon used was an important determinant for substrate recognition by MshB enzyme. The planar thiophenyl ring was found to be better

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**Figure 1.7.** Thioglycoside MSH analogues and MSH disulfide lacking inositol moiety and their % inhibition of MSH synthesis in *Mycobacterium tuberculosis*. 

<table>
<thead>
<tr>
<th>% inhibition in <em>M.tuberculosis</em></th>
<th>33a</th>
<th>33b</th>
<th>33c</th>
<th>33d</th>
</tr>
</thead>
<tbody>
<tr>
<td>R = Cl</td>
<td>51</td>
<td>27</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>
recognized than the thiocylohexyl group. Amongst the molecular analogues, the 2-C-alkylglucoside 35 lacking a cleavable group in the side chain showed 74% inhibitory activity against enzyme Mca but was not active against MshB indicating a difference in the active sites and binding affinity between MshB and Mca. However, plumbagin-linked thiophenylglucosides 36a-d showed activities against both Mca (45%) and MshB (95%) with the potency increasing with the increase of the methylene chain linking the plumbagin moiety to the acetamido group. Plumbagin is known to possess a variety of pharmacological properties\(^ {117} \) and its presence could be responsible for the increased activity of the analogues.

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>n</th>
<th>MshB</th>
<th>Mca</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td></td>
<td>0</td>
<td>74</td>
</tr>
<tr>
<td>36a</td>
<td>2</td>
<td>57</td>
<td>29</td>
</tr>
<tr>
<td>36b</td>
<td>3</td>
<td>82</td>
<td>38</td>
</tr>
<tr>
<td>36c</td>
<td>4</td>
<td>81</td>
<td>23</td>
</tr>
<tr>
<td>36d</td>
<td>5</td>
<td>95</td>
<td>45</td>
</tr>
<tr>
<td>37</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Figure 1.8.** % Inhibition of MshB and Mca enzymes by cyclohexyl-2-deoxy-2-C-alkylglucoside 35 and substituted naphthoquinones 36a–d and the β-linked 20-amino thioglycoside 37. % Inhibition was determined at substrate and inhibitor concentrations of 500 µM each for MshB and 250 µM each for Mca.

Metaferia and co-workers synthesised a library of different mycothiol analogues 18 of which were based on the cyclohexyl thioglycoside analogue 33.\(^ {118} \) Sulfoneamides and their
heterocycle derivatives replaced the cysteine moiety and were found to be potent inhibitors against both the Mca and MshB enzymes in *Mycobacterium tuberculosis* (see Figure 1.9).

![Figure 1.9. MshB and Mca inhibitors and their corresponding half maximal inhibitory concentrations (IC\textsubscript{50}).](image)

The proposed mechanism of MshB-mediated enzyme catalysis indicates formation of an intermediate tetrahedral co-ordination in the active site is critical for the substrate binding and subsequent deacetylation. The activity of compounds such as sulfones 38 and 39 (Figure 1.9) which contain a functional groups with a tetrahedral geometry in their side chain serves as an indication of the importance of the tetrahedral intermediate in MshB and Mca inhibition. To support this observation Tokutake and co-workers have reported the inhibition of Escherichia coli γ-glutamylcysteine synthase using transition-state molecular analogues that contained sulfone 44, sulfoximine 46 and phosphonic functional groups (Figure 1.10\textsuperscript{119}).
Other compounds that have shown potential antimicrobial, antiviral and anticancer activities but have not been reported for anti-TB activity are thiochromans.\textsuperscript{122-126} These compounds contain a sulfur heterocyclic moiety which could be oxidized to sulfoxides and sulfone resulting in compounds with an appropriate tetrahedral-forming intermediate which has been reported to be an essential feature for the inhibition of mycothiol biosynthesis enzymes as stated above. Coupled to this, the pharmacological properties contained within the thiochroman moiety may enhance the activity of the compounds towards mycothiol inhibition.
1.3 Thiochromans

1.3.1 Introduction

Thiochroman is a general name given to molecules which contain a benzene ring fused with a thio-pyran ring. As shown in Figure 1.11 thiochromans 47 or 3,4-Dihydro-2H-1-benzothiopyrans, are sulfur analogues of the chroman 49 family. Unlike thiochromans, chromans have been more extensively studied and this is mainly due to their abundance in nature and their biological properties. Sulfur-containing heterocyclic compounds however, have also shown beneficial pharmaceutical properties and as a result several of these compounds form part of the top 200 most selling drugs in 2010. Thiochromans have shown interesting medicinal and pharmaceutical properties such as anticancer, anti-HIV, antifungal, antidepressant and analgesic activities.

![Figure 1.11. Substituted chroman and thiochroman derivatives.](image)

Chuangxinmycin 49 is one of the reported natural compounds that contains a thiochroman moiety within its structure and was isolated from *Actinoplanes tsinanensis* obtained from a soil sample in China. This compound and its synthetic derivatives have been reported by Brown and co-workers to possess antimicrobial activities by selectively inhibiting the aminoacylation of tRNA in *Staphylococcus aureus*. The compound has a similar structure as the amino acid tryptophan 50 and was found to impose a competitive inhibition of the tRNA synthetase enzyme with respect to tryptophan. Chuangxinmycin is also structurally similar to the antibiotic indomycin 51 which was isolated from *Streptomyces griseus* and has shown inhibitory activity against tryptophanyl tRNA synthetase. The synthetic derivative 52
also showed antibacterial activity against bacterial pathogens such as *Staphylococcus aureus*, *Haemophilus influenza* Q1, and *Moraxella catarrhalis* 1502, at 4 mg/mL, 16 mg/mL, and 16 mg/mL minimum inhibitory concentrations (MIC) respectively.\(^{129}\)

![Figure 1.12. Antimicrobial natural product Chuangxinmycin 49 amino acid tryptophan 50 and their biologically active synthetic derivatives 51 and 52.](image)

Other thiochroman-containing compounds that have shown interesting biological properties are heteroaretinoids. These are molecular analogues of retinoids which are structurally similar to vitamin A \(^{53}\).\(^{131}\) Aretinoids similar to 54 have shown potential anticancer properties. However, the application of these compounds as therapeutic agents has been limited by their toxicity.\(^{132-136}\) Retinoic acid 55 (or Tretinoin) is an example of one of the naturally occurring retinoids and is used to promote anti-aging, treat acne vulgaris and other severe skin conditions.\(^{137-139}\)

![Figure 1.13. Anticancer agents, Retinoids and their thiochroman derivatives which have shown less toxicity and increased potency.](image)
Retinoids’ anticancer mode of action is reported to be via the inhibition of ornithine decarboxylase (ODC) induction which catalyses the synthesis of polyamines that are required for the stabilization of DNA during its synthesis. A high presence of ODC as in tumour cells promotes more cellular production and proliferation.\textsuperscript{140}

Due to their pharmaceutical potential, retinoids have received great attention and have been transformed into different analogues with the aim of producing safer compounds that can be used clinically without severe side effects. The replacement of a carbon atom in the cyclic ring of retinoids with a sulfur atom, to generate thiochroman-containing heteroaretinoids has rendered these compounds less toxic and transformed them into more potent agents. For example heteroaretinoid 56 was found to be 3000-fold less toxic than heteroaretinoid 54 and 3-fold less toxic than the natural retinoid 55.\textsuperscript{141} Compounds 57 and 58 have shown good anticancer activity with a 0.30 nmol IC\textsubscript{50} for ODC compared to 0.12 nmol obtained for Tretinoin 55. However, the later was found to be toxic at 50 nM in human leukaemia cell line (HL-60) whilst the thiochroman derivative 57 showed toxicity at concentrations above 1000 nM.\textsuperscript{131} Compound 59 which is a heteroaretinoid derivative containing a thio-urea group has been reported by Liu and co-workers to have shown significant activity against ovarian cancer cell line which has been reported to be resistant to standard cis-platin therapy and is currently under clinical development for cancer prevention and treatment, under the name ShetA\textsubscript{2}.\textsuperscript{142,143}

Song and co-workers reported the synthesis and biological activity of thiosemicarbazones analogues 60 and 61 (Figure 1.14) which were found to inhibit the synthesis of cathepsin L, a cancer-associated cysteine protease found in humans and animals.\textsuperscript{144} Cathepsin L is over-produced by tumour-forming cell lines and catalyses the degradation of interstitial matrix and basement membranes enabling tumour cell invasion and promoting the spread of cancerous
cells. The inhibition of cathepsin L expression was found to reduce the development of tumours in malignant cells.\textsuperscript{145} Thiochroman thiosemicarbazone 60 was found to be the most potent inhibitor of cathepsin L at IC\textsubscript{50} of 46 nM whilst sulfone derivative 61 showed activity at 112 nM.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{thiochroman_compounds}
\caption{Synthetic thiochroman-containing multi-cyclic compounds with ant-cancer and anti-HIV activities.}
\end{figure}

Sharon and co-workers reported the biosynthesis of biaryls and heterobiaryls 62-65 and their inhibitory activities against α-glycosidase, an enzyme that catalyses the breakdown of starch and disaccharides into glucose.\textsuperscript{146} Thus, the inhibition of α-glycosidase prevents the processing of these complex dietary carbohydrates and reduces the absorption of glucose in type 2 diabetic patients. Compound 62 showed a 72% inhibition of α-glycosidase at 100 µM whilst the thiochroman derivative 63 had a 96% inhibition at the same concentration which is indicative of the pharmaceutical beneficiation of a thiochroman ring. The benzothiopyran 65 showed almost complete inhibition (98%) of the α-glycosidase compared to the biaryl 64 which had a 94% inhibition.
Another example of the importance of sulfur-containing heterocyclic compounds was demonstrated by the increased inhibitory activity of the khellactone’s 66 (DCK) derivative thia-khellactone 67 (thia-DCK).\textsuperscript{125} Thia-DCK was found to have extremely potent inhibitory activity against HIV-1 replication in H9 lymphocyte cells, showing EC\textsubscript{50} (half maximal effective concentration) of 2.56 x 10\textsuperscript{-4} µM.\textsuperscript{147} Thus, thiochromans as shown above have shown a wide range of pharmaceutical properties that warrants for their synthesis.

1.3.2 Synthesis of thiochromans

1.3.2.1 Thio-Claisen rearrangement

The medicinal properties and the potential of chemical and functional diversity contained within thiochromans have resulted in the development of a number of synthetic methodologies for the synthesis of such compounds. In the classical procedure, thiochromans are accessed via the thio-Claisen rearrangement of allyl phenyl sulfides. Meyers and co-workers reported the formation of thiocoumaran 72 and thiochroman 73 as mixtures via Claisen rearrangement mechanisms after boiling allyl phenyl sulfide in an amine solvent (Scheme 1.5).\textsuperscript{148} This observation was disputed by Kwart and Evans who proposed that the rearrangement did not follow traditional Claisen rearrangement as observed for oxy- and amino-Claisen rearrangements.\textsuperscript{149} The electronegativity of the heteroatom contributes to the energy required to break the carbon-heteroatom bond during Claisen rearrangements. Oxygen (3.44) and nitrogen (3.04) are highly electronegative compared to carbon (2.55) and this significant electronegativity difference creates a polarity in the bond and thus, lowering the energy required for bond-breaking. On the contrary sulfur (2.58) and carbon (2.55) have comparable electronegativities. Thus, the bond between the two atoms does not have a sufficient amount of polarity to facilitate a similar type of Claisen rearrangement mechanisms as in the oxy- and amino-Claisen rearrangement.
Scheme 1.5. Thio-Claisen rearrangement of allylic aryl thiols to form 5 and 6-membered sulfur-containing heterocyclic products.

Kwart and Evans then proposed the formation of 72 and 73 by the thio-Claisen rearrangement shown in Scheme 1.5. The hypervalent nature of the sulfur atom allows for the atom’s multiple bond formation as depicted in the transition state. Deprotonation by a base forms the thiirane anion intermediate 71 which can be protonated at position 2 or 3 to form the cyclised products 72 and 73 in yields of 20% and 73% respectively. Kinetic studies reported by Danilova and co-workers have confirmed the formation of cyclized thiochromans and thiocoumarans via the thio-Claisen rearrangement.\textsuperscript{150}

Waugh and co-workers synthesized the fused aryl and thiochroman rings which are required for the synthesis of heteroarotinoids via thio-Claisen rearrangement mechanisms (Scheme 1.6).\textsuperscript{151} The allyl phenyl sulfide 75 was cyclised under acidic conditions using benzene as solvent, to generate thiochroman 76 in 76% yield. The thiochroman was further functionalised to obtain the desired heteroarotinoids synthetic building block 77.
Scheme 1.6. Synthesis of thiochroman building blocks required for heteroarotinoid synthesis. i) 1) NaOH, acetone, heat, 1 h; 2) Br\textsuperscript{−}; ii) P\textsubscript{2}O\textsubscript{5}, H\textsubscript{3}PO\textsubscript{4}, benzene, heat, 24 h; iii) acetyl chloride, SnCl\textsubscript{4}, benzene, rt., 5 h.

1.3.2.2 Intramolecular electrophilic aromatic substitution

Thiochromans have been synthesised via intramolecular cyclisation mechanisms which involve the displacement of a good leaving group by the phenyl ring to form Friedel-Crafts-type electrophilic ring substitutions.\textsuperscript{152,153} Jenson and co-workers prepared substituted thiochromans 81 in 100% yield by intramolecular cyclisation mechanisms using the benzyl phenyl sulfide 78 as starting material (Scheme 1.7).\textsuperscript{154} Treating the phenyl sulfide 78 with epoxide 79 under basic conditions afforded the corresponding hydroxy sulfides 80 which could be cyclised under acidic conditions into the thiochroman 81 with water acting as the leaving group. Heteroarotinoid cyclic fused rings can also be generated by such reaction procedures as observed in the synthesis strategy used by Waugh and co-workers.\textsuperscript{151}

Scheme 1.7. Synthesis of substituted thiochromans via acid-promoted intramolecular electrophilic cyclisation. i) BuLi, -78 °C, THF, 12.5 h 100%; ii) TsOH, Toluene, reflux, 12 h, 100%.
1.3.2.3 Asymmetric synthesis mediated by organocatalysts

Asymmetric synthesis of substituted thiochromans has been achieved using organocatalysts to stereoselectively conjugate arylthiols to α,β-unsaturated electrophiles via Michael addition-type reactions with subsequent cyclization to generate chiral thiochromans.\textsuperscript{155,156} Michael acceptors include α,β-unsaturated aldehydes,\textsuperscript{157} enones,\textsuperscript{158} nitro olefins,\textsuperscript{159} imines\textsuperscript{160} and benzylidenemalonates\textsuperscript{161} which have been reported to undergo tandem Michael-Michael, Michael-Henry and Michael-Knoevenagel condensations with aryl thiols to yield the desired multisubstituted thiochromans. Zu and co-workers reported the enantioselective synthesis of optically active thiochromans\textsuperscript{156} \textsuperscript{85a-d} from α,β-unsaturated oxazolidinones \textsuperscript{82} and 2-mercaptobenzaldehydes \textsuperscript{83a-d} catalysed by 1 mol% chiral organocatalyst \textsuperscript{84} (Scheme 1.8). The proposed hydrogen-bonding interactions between the thiourea catalyst, oxazolidinone and the thiol group aligns the molecules such that conjugation occurs from one direction generating products that are obtained in high enantiomeric excess (97 – 99\% ee). The substitution of the β-phenyl group with different aryl groups also results in different aryl substituents at position 2 of the thiochromans thus, generating highly substituted thiochromans that can be used as synthesis scaffolds.

\[ \text{O} \quad \text{N} \quad \text{O} \quad \text{Ph} \quad \text{O} \quad \text{N} \quad \text{S} \quad \text{N} \quad \text{H} \quad \text{H} \]

\[ \text{Chiral scaffold} \]

\[ \text{R} \quad \text{S} \quad \text{H} \]

\[ \text{Ph} \quad \text{N} \quad \text{O} \quad \text{O} \]

\[ \text{catalyst} = \text{Ar} \quad \text{N} \quad \text{H} \quad \text{H} \]

\[ \text{OMe} \]

\[ \text{R} \quad \text{S} \quad \text{H} \quad \text{S} \quad \text{OH} \quad \text{Ph} \quad \text{N} \quad \text{O} \quad \text{O} \]

Scheme 1.8. Catalyst-promoted synthesis of enantiopure thiochromans.
1.3.3 Versatility of thiochromans

The sulfur atom and its versatility make thiochromans and other sulfur containing heterocyclic compounds more attractive precursors during chemical synthesis. The sulfur atom can be oxidized to form sulfoxides and sulfones which can also be used as reaction intermediates that can be alkylated under basic conditions\textsuperscript{162} or can undergo bond rearrangements such as Pummerer rearrangements\textsuperscript{163} to form highly functionalized products as demonstrated in Scheme 1.9.

\begin{center}
\includegraphics[width=\textwidth]{Scheme_19.png}
\end{center}

\textbf{Scheme 1.9} Derivatization of the thiochroman ring. a, b) Oxidation c) Alkylation d) Pummerer rearrangement.

Thiochromans have also been employed as synthons in the synthesis of natural product (±) cuparane and its derivatives (Scheme 1.10).\textsuperscript{164} These compounds form part of a group of secondary metabolic products produced in plants and insects known as sesquiterpenoids.\textsuperscript{165} Due to their reported antimicrobial and antibiotic properties, the synthesis of these compounds and their derivatives has attracted an interest from synthetic chemists.\textsuperscript{166-168} However, the presence of a quaternary carbon in their structure had presented a challenge in obtaining such compounds. Work published by Nakatani and co-workers shows the versatility of the thiochroman ring. The thiochromans were synthesised by electrophilic intramolecular cyclization-type reactions between \textit{m}-tolylthiomethyl chloride \textbf{86} and 1-methylcyclopentene \textbf{87} in the presence of the strong Lewis acid, TiCl\textsubscript{4}. The thiochroman \textbf{89} was then desulfurised to form the cuparane derivative \textbf{90}.
Furthermore, Foubelo and Yus have published a review on the extensive use of sulfur containing compounds as organolithium intermediates, to access multifunctional organic compounds (Scheme 1.11).\textsuperscript{169} These synthesis protocols can be used to expand sulfur-containing rings and simultaneously add side chains of different functional groups to the heterocyclic ring. Thiochromans 91 can be reductively cleaved between alkyl carbon and the sulfur atom, by

\begin{align*}
\text{Scheme 1.11. Thiochromans as organolithium precursors.} & \quad \text{\textit{i) LDTB, THF, 0}^\circ\text{C; } \text{ii) } a) 93a-d, b) H_2O, \text{ iii) } H^+.}
\end{align*}

thiourea 4,4'-di-tert-butylbiphenylide to form the synthetically useful organolithium compounds 92 which can be reacted with electrophilic carbonyl compounds 93a-d and undergo subsequent hydrolysis to form the hydroxyl thiophenols 94a-d. Acid-promoted intramolecular cyclisation forms ring expanded thiochromans 95a-d in 45 – 87% yields. Thus, although
thiochromans have not received extensive research, these compounds can be useful organic synthons and they have shown potential as pharmaceutical agents.
1.4 Objectives of study

Mycothiol has been identified as the major low-molecular weight thiol in Actinomycetes and plays a critical role in the defensive mechanisms in these bacteria including *Mycobacterium tuberculosis*.\textsuperscript{73,74} As a result chemists and biochemists aiming to develop novel anti-TB drugs have targeted the inhibition of the mycothiol biosynthesis and detoxification pathways. The presence of mycothiol exclusively in Actinomycetes has made this pathway an ideal target for drug development. Deacetylase enzymes MshB and Mca are involved in the biosynthesis and detoxification pathways, respectively, and their catalytic activities has shown a formation of a tetrahedral intermediate which is formed by the co-ordination between the substrate to the metal in the active site of the enzymes.\textsuperscript{89,113} Compounds containing an appropriate tetrahedral-forming functional groups in their side chain have shown activity against MshB and Mca.\textsuperscript{118}

In addition to the mycothiol derivatives are thiochromans that have shown interesting pharmaceutical properties ranging from anticancer to antifugal activities.\textsuperscript{121-127} However, these have not yet been reported for their anti-TB activity. Oxidation of the thiochromans to their sulfoxide and sulfone derivatives results in compounds that contain tetrahedral-forming moieties which can be evaluated for their anti-TB activities by inhibiting MSH biochemical pathways.

Thus, guided by the information in the literature review we aim:

- To synthesize sulfoxide and sulfone-based mycothiol molecular bioisosteres that would be investigated for their ability to inhibit enzymes involved in the mycothiol biosynthesis pathway.
- To synthesize carbohydrate-based thiochromans and their oxidized derivatives containing sulfoxides and sulfones as the tetrahedral-forming intermediates.
- To evaluate the biological activity of the thiochroman derivatives against a variety of infectious and chronic diseases such as TB, malaria and cancer.
Chapter 2: Synthesis and Characterization of mycothiol molecular analogues

2.1 Retrosynthetic analysis and proposed route for mycothiol analogues synthesis

As reported in the literature review, chemical preparation of mycothiol has presented several challenges ranging from stereo as well as regioselective glycosylation of the myo-inositol moiety to the possible epimerization of the cysteine side-chain during its coupling to the glucosamine moiety resulting in the reported low overall yields (~11%).\textsuperscript{84} As a result, simplified mycothiol analogues with cyclohexyl, phenyl glycosyl acceptors and containing tetrahedral-forming functional groups that mimic the transition state geometry in the enzyme-catalysed hydrolysis of the amide bond in mycothiol analogues as shown in the literature review have been investigated for their inhibition of mycothiol biosynthesis and these have shown promising results.

To contribute to the library of mycothiol analogues that have been reported we designed compounds that are similar to the mycothiol derivative \textbf{38} (which showed 74\% inhibition of Mca) in that they do not contain a cleavable amide bond and we aimed to incorporate sulfoxides and sulfones as the tetrahedral-forming functional groups which may increase the affinity and binding to the mycothiol biosynthetic enzymes. As shown in Scheme 2.1, the myo-inositol moiety is replaced by an aglycone with R” being the different aryl and alkyl substituents.
The sulfoxides I and sulfones II can be obtained through the oxidation of sulfides III which in turn can be synthesized through the S\textsubscript{N}2 substitution of good leaving groups such as halides present on the terminal of C-2 branched glycosides IV. Cyclopropanes V have been widely used as glycosyl donors for the synthesis of C-2 branched glycosides under electrophilic conditions with nucleophiles VI acting as the glycosyl acceptors. Cyclopropanes can in turn be obtained by cyclopropanation of alkenes in carbohydrate derivatives such as glycals VII which are readily available starting materials.

Scheme 2.1. Retrosynthetic analysis of target compounds.

2.2 Glycals as suitable starting materials in carbohydrate synthesis

Carbohydrates are the most abundant compounds found in nature and play various essential biological roles such as serving as a source of energy as well as forming part of structural components such as cellulose (in plants), chitin (in insects) and structural proteins such as keratin.\textsuperscript{170} Due to their varied biological functions carbohydrate-based molecules have been utilised to develop and synthesize novel therapeutic agents in the field of medicinal chemistry, biochemistry, and biology.\textsuperscript{171-173} One family of carbohydrates that has been widely utilised as a starting material for the synthesis of these complex but yet beneficial structures are glycals.\textsuperscript{174-178}
Glycals are unsaturated carbohydrates containing a double bond between C-1 and C-2 vicinal to the ring oxygen atom. The first glycal was synthesized by Emil Fischer and Karl Zach (see Scheme 2.2) who treated peracetylated glycosyl bromide with zinc powder in acetic acid to afford the sugar which they mistakenly named ‘glucal’ as they thought they had synthesized an aldehyde. This observation ‘aldehyde observation’ could be due to the possible hydrolysis of glycals under acidic conditions and their equilibration to aldehydes.

![Scheme 2.2. Fischer-Zach synthesis of tri-O-acetyl D-glucal. i) Excess Ac₂O; ii) HBr in AcOH; iii) Zn dust AcOH](image)

The reactive nature of double bonds makes glycals useful starting materials for the synthesis of substituted carbohydrate derivatives. The double bond can undergo regiospecific as well as stereoselective additions to form cyclopropanated, hydrated and halohydrogenated derivatives, 2-amino-2-deoxy glycosides as well as double bond rearrangement reactions that can be used to obtain 2,3-unsaturated glycosidic products. Thus, with the possibility to undergo such a wide range of reactions, D-glucal which has the same stereochemistry at positions 3, 4 and 5 as the mycothiol glucosamine moiety was selected as the suitable starting material for the synthesis of the target mycothiol bioisosteres.

### 2.3 Synthesis of α-1,2-cyclopropanated glucal derivatives as glycosyl donors

The synthesis of α-cyclopropanes from alkenes can be done under basic reaction conditions and acetylated glucal was used as starting material as it is commercially available, relatively cheaper and more stable than unprotected glucal. However, acetyl protecting groups are incompatible for such conditions due to the susceptibility of the
electrophilic carbonyl carbon to nucleophilic attack.\textsuperscript{182} To avoid these side reactions, the acetyl protecting groups were replaced by benzyl protecting groups using a convenient one-pot procedure reported by Madhusudan and co-workers.\textsuperscript{183} To achieve this protecting group transformation, glucal 99 dissolved in THF was treated with finely crushed NaOH, TBAI as a phase-transfer catalyst and benzyl chloride. The reaction was stirred at room temperature for 48 h to form a clear syrup upon work-up and purification by column chromatography. The product was crystallized from hexane to yield 56\% of tri-O-benzyl-D-glucal 100. The formed product was confirmed by NMR analysis and the data was found to be in agreement with the reported data.\textsuperscript{183} With the suitable protecting groups in place the pure product was then ready to be utilised in basic reaction conditions used to synthesize \(\alpha\)-cyclopropane derivatives.

\textbf{Scheme 2.3.} Synthesis of 3,4,6-tri-O-benzyl-D-glucal. NaOH, TBAI, BnCl, THF, 48 h, 56\%.

Cyclopropanes have been found to be essential synthetic intermediates for generating highly functionalized products in organic synthesis.\textsuperscript{184} Due to their chemical similarity to alkenes and the strain contained within the rings, these functional groups can undergo ring rearrangements to form ring-expanded adducts or undergo electrophilic additions to form 2-C-branched glycosides that are useful intermediates in carbohydrate synthesis.\textsuperscript{181} As a result of their ease of transformation, procedures to stereoselectively synthesize cyclopropanated sugars have been established.\textsuperscript{185,186}

The Simmons-Smith cyclopropanation is the traditional procedure used to stereoselectively cyclopropanate allylic alcohols on the \textit{syn}-face of an oxygen atom proximal to the double
bond using methylene iodide, zinc and copper chloride.\textsuperscript{187} The oxygen atom of the substrate co-ordinates to the zinc metal and assists in delivering the methylene nucleophile to the alkene and thus, stereoselectively forming the cyclopropane on the \textit{syn} face of oxygen atom. Nagarajan and co-workers first reported the use of this procedure to cyclopropanate glycals and observed that the oxygen on C-3 directed the face on which the cyclopropane was formed (Scheme 2.4).\textsuperscript{188}

![Scheme 2.4. Simmons-Smith diastereoselective cyclopropanation. CH$_2$I$_2$, Zn, CuCl, AcCl, Et$_2$O, reflux, 89%.](image)

Nagarajan and co-workers further reported the synthesis of cyclopropanes \textit{anti} to the C-3 ring substituent by using dihalocarbenes.\textsuperscript{181} A bulky substituent at C-3 hinders the approach of a nucleophile from the \textit{syn} face, thus, the incoming nucleophile preferably reacts with the alkene from the face opposite to the C-3 substituent resulting in the diastereoselective formation of \textit{anti} dihalocyclopropanes which can further be dehalogenated to form cyclopropanes. Therefore, this procedure was employed to synthesize the target \(\alpha\)-1,2-cyclopropanated glucal 102 according to Scheme 2.5 so that an equatorial orientation at C-2 would be obtained.

Benzylated glucal 100 in chloroform was treated with 50% aqueous NaOH and benzyltriethylammonium chloride (TEBAC) was used as the phase transfer catalyst at 35 °C for 6 h to afford the dichlorocyclopropane 101 in 60% yield.
Scheme 2.5. Cyclopropanation of tri-O-Bn-glucal.  

Proton NMR analysis of 101 confirmed the formation of the cyclopropane ring on the α-face of the sugar ring. H-2 resonated at δ\textsubscript{H} 1.44 ppm as a doublet of doublets and J values of 2.0 Hz and 7.6 Hz with the greater value being the proton’s coupling to H-1 which had a coupling constant of 8.0 Hz. The lower coupling constant was between H-2 and H-3. This data was found to be in agreement with the report that for cyclopropanated sugars the cis \textit{J}_{1,2} coupling constant is larger than the trans \textit{J}_{2,3} coupling constant\textsuperscript{181,189,190} indicating that H-1 and H-2 are on the same face of the sugar ring and that cyclopropanation occurred \textit{syn} to H-3 and \textit{anti} to the C-3 benzylolx substituent, thus, confirming the preferred formation of the α-1,2-cyclopropane over the β-1,2-cyclopropane.

The dechlorination of 101 to form cyclopropanated sugar 102 was achieved in 84% yield using LAH and THF as solvent under anhydrous reaction conditions (Scheme 2.5). Protons H-7\textsubscript{a} and H-7\textsubscript{b} appeared as a multiplet around δ\textsubscript{H} 0.70 ppm whilst H-2 shifted upfield from 1.44 ppm to 0.93 ppm and resonated as a multiplet due to couplings to H-7\textsubscript{a} and H-7\textsubscript{b} in addition to H-1 and H-3 coupling. The obtained cyclopropanes were ready to be utilized as glycosyl donors for the synthesis of 2-C-branched glycosides.
2.4 Synthesis of 2-C-branched thiomethyl analogues

1,2-Cyclopropanated sugar derivatives have been used as a gateway to accessing C-2 branched glycosides through the regioselective cleavage of the C-1 and C-7 bond with the cyclopropane stereochemistry forming the inherent stereochemistry of the resultant C-2 extension. In general, opening of the cyclopropanes has been achieved under electrophilic reaction conditions by using halonium ions\textsuperscript{181}, strong mineral acids\textsuperscript{191,192} and via metal promoted fragmentations by mercury catalyst\textsuperscript{193,194} as well as platinum catalysts.\textsuperscript{195}

Thus, 2-C-branched glycosides were obtained by treating the cyclopropane 102 with N-iodosuccinimide (NIS) as the source of electrophilic iodonium ions and cyclohexanol as the glycosyl acceptor to furnish the glycosides 103\textsubscript{a} and 103\textsubscript{b} in α,β-anomeric mixtures (1:2) which were separated by column chromatography (Scheme 2.6).

![Scheme 2.6. Glycosylation of cyclopropanated sugar 102. NIS, cyclohexanol, CH\textsubscript{3}Cl, 3 h, 24% 103\textsubscript{a} and 48% 103\textsubscript{b}.](image)

The formation of the products has been proposed by Nagarajan and co-workers to proceed via two mechanisms. The first being the S\textsubscript{N}2 mechanism (see Scheme 2.7) which favours formation of the β-anomer because the nucleophile can easily attack C-1 at a 180° angle to the breaking C-1 and C-7 bond. The nucleophile’s angle of approach is essential for electron transfer from the nucleophile to C-1’s anti-bonding orbital.\textsuperscript{196} Thus, the mechanism may not
be favourable for formation of the $\alpha$-anomer as the nucleophile would have to approach C-1 at a reduced angle.

Scheme 2.7. Proposed $S_N2$ mechanism for the formation of the $\beta$-glycosides (green arrows).

Another possible mechanism could involve the formation of an oxocarbenium ion intermediate via an $S_N1$ mechanism which favours the formation of the $\alpha$-anomer due to the anomeric effect. However, this mechanism may have been slower than the $S_N2$ mechanism resulting in the lower selectivity for the $\alpha$-anomer compared to the $\beta$-anomer.

Nagarajan and co-workers also observed similar selectivity for the $\beta$-anomer when opening 1,2-cyclopropanated sugars using NIS and suggested the poor formation of levomannosan II to be via an $S_N1$ mechanism as opposed to the $S_N2$ mechanism which rapidly formed its diastereoisomer IV in substantial yields. In this case the sluggishness of the $S_N1$ mechanism was attributed to the steric hindrance of the C-3 substituent, which restricted the incoming electrophile on the $\beta$-face. The approach of the iodonium electrophile to the $\alpha$-cyclopropane was, however, not hindered in the case of 103a and 103b synthesis thus, suggesting that the $S_N1$ mechanism may generally be slower than the $S_N2$ mechanism which resulted in the formation of the $\beta$-anomer as our major product.
Scheme 2.8. Nagarajan and co-workers observed different rates in formation of the levomannosan derivatives II (36h, 35%) and IV (5h, 71%) with IV being formed faster and in higher yields. NBS, CH$_3$CN, 4Å molecular sieves, 5 or 36 h.

The oxocarbenium ion 104 (Scheme 2.9) formed by $S_{N}1$ mechanism may also be stabilized by the neighbouring group participation effect from the iodine group forming the cyclic four-membered ring intermediate 105.$^{199,200}$ Similar to the cyclopropane, the cyclic butane intermediate could also hinder the approach of the glycosyl acceptor from the $\alpha$-face and thus, directing the incoming glycosyl acceptor to the top face of the sugar ring and favouring the formation of $\beta$-glycosides as the major product through $S_{N}2$ mechanisms.$^{201-203}$
Scheme 2.9. Proposed S_N_1 mechanism for the formation of α- and β-glycosides.

Formation of the α- and β-anomers 103a and 103b, respectively, was confirmed by proton NMR analysis. The α-glycoside’s anomeric proton resonated at δ_H 5.22 ppm as a doublet due to coupling to H-2 with J = 3.3 Hz whilst the β anomeric proton resonated upfield at δ_H 4.45 ppm with a higher coupling constant J = 8.0 Hz which is in agreement with the literature finding that the trans-diaxial couplings are higher than the axial-equatorial couplings. The presence of an iodine substituent was demonstrated by the downfield shift of H-7_a and H-7_b signals for both anomers from around 0.73 ppm to around 3.0 ppm. The multiplicity of the protons changed from multiplets to doublet of doublets as the protons only experienced vicinal coupling to H-2 and geminal coupling to the other proton on C-7 resulting in the doublet of doublets H-7 peaks observed for the α-anomer. H-7 protons for the β-anomer overlapped with H-1’, H-3, H-4, H-5, H-6_a and H-6_b. The cyclohexyl CH_2 peaks were observed as multiplets around δ_H 1.20 ppm with H-1’ resonating downfield around δ_H 3.68 ppm.
The iodomethyl glycoside \textbf{103b} was used as a model to establish the route and pathway of synthesis as the $\beta$-anomer was formed in a better yield during glycosylation. This was transformed into its sulfide derivative \textbf{106} by $S_N2$ substitution of the iodide group using thiophenol as the nucleophile under similar reaction conditions as those reported by Chaveriat and co-workers.\textsuperscript{182} The sulfide \textbf{106} was formed in 15 min in excellent yield (96%).

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme2.10.png}
\end{center}

\textbf{Scheme 2.10.} Sulfide synthesis via $S_N2$ substitution. Thiophenol, NaH, THF:DMSO (4:1), 15 min, 96%.

\subsection*{2.5 Possible poisoning of Palladium metal by the sulfide functional group}

Thus, with the aim of synthesizing our desired mycothiol analogues, the sulfide \textbf{106} was subjected to debenzylation by treating with 10\% palladium on carbon under hydrogen atmosphere and using MeOH:EtOAc (8:2) as solvent. The reaction was left to stir overnight and no product formation was observed by TLC analysis and the starting material was recovered. The reaction was then done in different solvents such as THF, EtOAc and AcOH and varying hydrogen pressure ranging from 1 – 8 bar without success. The \textit{in situ} generation of hydrogen by using ammonium formate as the source of hydrogen did not yield the desired results either.
Scheme 2.11. Attempted debenzylation using conventional Pd/C. 10% Pd/C, 1 - 8 Bar, solvent.

Palladium metal is known to be susceptible to poisoning by certain functional groups such as amino alcohols and thus, decreasing its activity towards hydrogenolysis of benzyl groups.\textsuperscript{206} Albers and co-authors also published a summary on the poisoning and deactivation of palladium catalysts and highlighted sulfur-containing gases such as hydrogen sulfide and sulfones to be contaminants during palladium catalysed hydrogenolysis.\textsuperscript{207} The possibility of metal poisoning was verified by treating the dichloro 101 with Pd/C under similar reaction conditions as those used for the sulfide 106 to achieve complete debenzylation and formation of the triol 108 which was acetylated (Scheme 2.12). Crude NMR analysis of 109 displayed the three acetate peaks and the disappearance of the aromatic as well as the CH$_2$ benzyl peaks. Thus, confirming a complete debenzylation of the dichloro adduct 109 using palladium catalysed hydrogenolysis which was not possible in the presence of a sulfide (see Figure 2.1 for NMR).

Scheme 2.12. Pd/C catalysed debenzylation.  i) 10% Pd/C, THF, 16 h yield calculated after acetylation; ii) Ac$_2$O, DMAP, Pyridine, 16 h, 64% overall yield.
As a result we concluded that the sulfide functional group in 106 could be poisoning the palladium metal resulting in its deactivation. In desperation to remove the benzyl groups we resorted to alternative reported debenzylation procedures such as the use of strong Lewis acids to cleave benzyl protecting groups.

Park and co-workers reported the cleavage of monosaccharide benzyl ethers using ferric chloride, a strong Lewis acid, under anhydrous reaction conditions to form the hydroxyl derivatives in >70% yield. The utility of ferric chloride as a debenzylation reagent was

\[^{1}H\text{NMR}: (\text{CDCl}_3, 400\text{ MHz}): \delta_{\text{H}} 5.00 - 4.85 (\text{m}, 2\text{H}, \text{H}-6_\text{a} \text{ and H}-6_\text{b}), 4.31 (\text{dd}, 1\text{H}, J = 6.4\text{ Hz and 12.4 Hz}, \text{H}-4), 4.07 (\text{dd}, 1\text{H}, J = 2.8\text{ Hz and 12.4 Hz}, \text{H}-3), 4.05 - 3.98 (\text{m}, \text{H}-5), 3.89 (\text{d}, 1\text{H}, J = 7.8\text{ Hz}, \text{H}-1), 2.15 - 1.90 (\text{m}, 9\text{H}, 3 x -\text{OAc}), 1.82 (\text{dd}, 1\text{H}, J = 3.0\text{ Hz and 7.8 Hz}, \text{H}-2).\]
further demonstrated by Radebaugh and co-workers who cleaved benzyl ethers of complex oligosaccharides.\textsuperscript{209}

As a result ferric chloride was perceived as a viable option for the debenzylation of the sulfide \textit{106} to form the triol \textit{107}. Working under anhydrous conditions \textit{106} was dissolved in dry DCM and treated with 3 – 6 equivalents of ferric chloride at room temperature. The reaction was monitored by TLC and indicated the disappearance of starting material and the formation of products. To our disappointment these could not be isolated or characterized as the reaction mixture was messy on TLC plate. Acetylation of the recovered crude material did not show any desired product formation on TLC. The procedure was abandoned after several unsuccessful trial reactions.

Acetolysis using different lewis acids such as \textit{AlCl}_{3} and \textit{Al(OTf)}_{3} proved to be futile cleaving only the primary benzyl group which is known to be labile under acidic conditions.\textsuperscript{210} These unsuccessful debenzylation reactions prompted the use of a different protecting group that would be stable under basic conditions and at the same time present a lesser challenge during cleavage.

\textbf{2.6 Substitution of the benzyl ethers by \textit{para}-methoxybenzyl ethers for the preparation of mycothiol bioisosteres}

\textit{Para}-methoxybenzyl or PMB protecting groups have also been used to protect hydroxyl groups during organic synthesis of carbohydrate-based compounds. The ease of introducing (which is similar as benzyl group) and their stability under basic reaction conditions as well as removal under oxidative conditions made these groups a viable option for the synthesis of our target compounds.\textsuperscript{211}
Due to the higher cost of para-methoxybenzyl chloride (PMBCl) compared to para-methoxybenzyl alcohol (PMBOH), fresh PMBCl 111 was prepared from PMBOH 110 by treating the latter with a drop wise addition of thionyl chloride under anhydrous conditions. The formed PMBCl was found to be sensitive to aqueous work-up especially when using saturated sodium bicarbonate. Thus, the reaction mixture was washed twice with ice-cold water and once with brine to minimize the formation of alcohol starting material.

\[
\begin{array}{c}
\text{OMe} \\
\text{MeO} \\
\text{Cl}
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{OMe} \\
\text{MeO} \\
\text{Cl}
\end{array}
\]

**Scheme 2.13.** Synthesis of PMBCl. SOCl₂, DMF, 0 °C, 1.5 h.

PMBCl 111 was dried under reduced pressure and used without further purification to prepare PMB protected glucal derivative 113. However, one-pot synthesis reaction conditions used to prepare benzylated glucal 102 as reported in Section 2.3 were found to be incompatible with the PMBCl group which formed alcohol starting material 110. As a result per-O-acetylated glucal 99 was first deacetylated using a saturated solution of KOH in methanol to form triol 112 which was dried under reduced pressure and protected without further purification to form PMB protected glucal 113 according to Scheme 2.14. Spectroscopic data of 113 was found to be in agreement with literature reported data²¹² with the characteristic aromatic signals resonating between δ_H 7.30 and 6.45 ppm complemented by a three-proton singlet for the methoxy groups at δ_H 3.79 ppm. The alkene protons were also observed as a doublet for H-1 at 6.41 ppm with a J value of 6.0 Hz due to coupling to H-2 which resonated at δ_H 4.85 ppm as an apparent broad doublet and J value of 6.0 Hz.
Synthesis of 2-C-branched glycosides has been established and outlined in Section 2.4. Similar reaction conditions were, thus, used for the synthesis of PMB protected adducts according to Scheme 2.15 with NMR techniques used as the principal tool for analysis and confirmation of each product. The dichloro adduct 114 was obtained in 69% yield and an X-ray diffraction (XRD) (Figure 2.2) was used to confirm formation of the α-1,2-cyclopropanated dichloro sugar derivative. As observed for benzylated dichloro adduct 101 H-2 also resonated around $\delta_H$ 1.73 ppm as a doublet of doublets with $J$ values of 4.2 and 7.8 Hz. The larger coupling constant was due to coupling between H-2 and H-1 which had a $J$ value of 8.0 Hz. The smaller coupling of 4.2 Hz resulted from coupling between H-2 and H-3 which were on opposite faces of the sugar ring. This data further confirms that the cis $J_{1,2}$ coupling is larger than the trans $J_{2,3}$ coupling. These observations from NMR data can be used to establish the formation of cyclopropanes on the α- or β-face of the sugar ring.\(^{181}\)

The dichloro adduct was then dehalogenated using LAH to form cyclopropane 115 in 65% yield under anhydrous conditions. Cleavage of the C-1 and C-7 bond under electrophilic conditions afforded the iodomethly glycosides in α- and β-anomeric mixtures (1:2) of 116a and 116b which were separated by column chromatography.
Scheme 2.15. Preparation of α/β-2-iodomethyl glycosides. i) NaOH 50% (aq), TEBAC, CH₂Cl₂, 35 °C, 6 h, 69%; ii) LAH, THF, 48 h, 65%; iii) NIS, cyclohexanol, CH₂Cl₂, 3 h, 69%.

Figure 2.2. XRD diagram of dichlorocyclopropanated sugar 114.

Similar to compounds 103a and 103b these glycosides had the α-anomeric proton resonating downfield around δ_H 5.14 ppm as an apparent broad singlet (see Figure 2.3). The β-anomeric proton resonated upfield around δ_H 4.40 ppm as a doublet with J = 8.0 Hz which is in the region of 1,2-trans coupling constants for H-1 and H-2 coupling for glycosides (see Figure 2.4). H-7_a and H-7_b appeared downfield at δ_H 3.40 and 3.50 ppm compared to the H-7_a and H-7_b protons of the cyclopropane starting material 115 (protons resonated at δ_H 0.70 ppm as multiplets) due to the electron withdrawing effect of the iodine atom attached to C-7. H-1’ from the cyclohexyl ring resonated around δ_H 3.55 ppm overlapping with H-3, H-4 and
H-6 for the α-anomer and H-3, H-4, H-6\textsubscript{a} and H-6\textsubscript{b} for the β-anomer. The rest of the CH\textsubscript{2}'s of the cyclohexyl were observed as multiplets in the region of δ\textsubscript{H} 2.00 – 1.10 ppm.

Figure 2.3. \textsuperscript{1}H NMR spectra of the α-iodomethyl glycoside 116\textsubscript{a}.

Figure 2.4. \textsuperscript{1}H NMR spectra of the β-iodomethyl glycoside 116\textsubscript{b}.
The β-iodomethyl glycoside 116b which was formed as the major product during glycosylation was again used to model and optimize our reactions. This was then transformed into its sulfide derivative 117 according to Scheme 2.15 by $S_N2$ substitution of the iodide group. To achieve substitution 116b was treated with sodium thiophenolate under anhydrous conditions as reported by Chaveriat and co-workers. The solvent was removed under reduced pressure and the crude product was purified by column chromatography to afford the sulfide 117 as a white solid in 95% yield.

Scheme 2.15. Thiolation of the O-glycosides. Thiophenol, NaH, THF:DMSO (4:1), 15 min, 95%.

2.7 Oxidative transformation of sulfides to sulfoxides and sulfones and subsequent deprotection of PMB ethers to achieve target mycothiol bioisosteres

Sulfides can easily be transformed into their sulfoxides and sulfones derivatives using different oxidizing agents such as meta-chloroperoxybenzoic acid (m-CPBA), hydrogen peroxide, urea hydrogen peroxide, tert-butylhydroperoxide (Bu'OOH) and OXONE® (potassium peroxymonosulfate). These oxidations can be achieved using the oxidant alone or using a combination of the oxidant carried on a solid support system such as silica gel or aluminium oxide which serves as an adsorbent onto which the oxidizing agent is dispersed, thus, facilitating maximum contact between the oxidizing agent and substrate.
Kropp and co-workers reported the use of OXONE® supported on aluminium oxide (Al₂O₃) to efficiently oxidize sulfides to their sulfone derivatives. The procedure was found to be attractive for the oxidation of our sulfides to sulfones due to the ease of reagent-handling as well as the separation of products from the heterogeneous mixture by vacuum filtration without the need for aqueous work-up.

Thus, in order to synthesize sulfone molecular analogues, sulfide 117 was dissolved in DCM in the presence of wet Al₂O₃ and was treated with excess OXONE® for over 12 h according to Scheme 2.16 to provide the sulfone 118 in 65% yield. The formed product was characterized by NMR and absorption infrared (IR) spectrometries. Sulfone oxygen-sulfur bond absorptions were observed around 1300 cm⁻¹ which was in agreement with literature.

Before attempting the deprotection of the sulfones, our attention was turned to the selective oxidation of sulfides to sulfoxides which have been utilised as useful intermediates during the synthesis of biologically important compounds as well as in stereoselective glycosylation reactions. To prevent overoxidation, selective oxidation procedures have been reported and these include the use of OXONE® or Bu'OOH supported on silica gel to mention a few. Zolfigol and co-workers also reported the selective oxidation of simple sulfides using...
ammonium cerium (IV) nitrate (CAN) and catalytic KBr. CAN is also used to deprotect PMB groups. Thus, we envisaged a one-pot deprotection and selective oxidation of sulfides to sulfoxides using CAN as the deprotection and oxidizing agent.

Thus, to achieve the one-pot deprotection and simultaneous oxidation, sulfide 117 was dissolved in acetonitrile before 50% wet silica, KBr and CAN were successively added. Reactions showed disappearance of starting material and formation of product which was very difficult to purify and often low yielding. With the aim of synthesizing highly pure target compounds for biological assay, we opted for a step wise synthesis of the target sulfoxide analogues using 1.2 equivalents of OXONE® according to Scheme 2.17 with minimal over-oxidation. The products were obtained as an inseparable diastereomeric mixture of sulfoxides 119a,b in 64% yield. $^{13}$C NMR spectra also indicated the presence of a diastereomeric mixture of the products. C-1 for one isomer appeared around $\delta_H$ 100.4 and at 100.3 ppm for the other isomer. 2D NMR techniques were also used to establish that the H-7a protons for both isomers were overlapping around $\delta_H$ 3.10 ppm whilst the H-7b protons resonated around $\delta_H$ 2.95 (for one isomer) and 2.82 ppm (for the other isomer) as broad doublets. Infrared absorptions around 1030 cm$^{-1}$ also confirmed the presence of sulfoxides.

![Scheme 2.17](image)

**Scheme 2.17.** Stoichiometric oxidation of sulfides to sulfoxides. $\text{Al}_2\text{O}_3$, Sulfide, OXONE® (1.2 eq), DCM, 4 h, 64%.
PMB protecting groups can be effectively cleaved under oxidizing conditions using dichlorodicyanobenzoquinone (DDQ) or CAN as the oxidizing agents.\textsuperscript{225,226} The latter has been found to be more favourable due to its better efficacy and shorter reaction times.\textsuperscript{227} DDQ is pricier and slightly more toxic liberating cyanide gases when in contact with water.\textsuperscript{228}

Thus, CAN was used to treat PMB protected sulfoxides and sulfones in acetonitrile:water (9:1) at room temperature according to Scheme 2.18. The products were purified by aqueous work-up and recrystallized from a mixture of DCM and hexane (0.5:9.5) to afford the target sulfoxides 121\textsubscript{a,b} and sulfone-based 120 mycothiol analogues as white solids. The products were insoluble in both polar and non-polar deuterated solvents such as MeOD, D\textsubscript{2}O, DMSO-d\textsubscript{6} and CD\textsubscript{3}Cl. DMSO-d\textsubscript{6} was found to dissolve the compounds, however, the solvent and compounds complexed and made NMR analysis difficult. Presence of the hydroxyl groups was established by IR spectroscopy with the O-H bond stretches appearing as humps around 3400 cm\textsuperscript{-1} which was found to be in agreement with the reported literature.\textsuperscript{219}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme_2.18.png}
\caption{PMB group deprotection. CAN, CH\textsubscript{3}CN:H\textsubscript{2}O (9:1), 2 h, 75\% (sulfone) and 64\% (sulfoxides).}
\end{figure}
To further confirm full deprotection of the PMB groups, a few milligrams of each triol was acetylated by treating the sample dissolved in pyridine with acetic anhydride and DMAP according to Scheme 2.19.229 The acetylated and purified products were characterized by NMR spectrometry. Three acetate peaks were observed for each of the compounds with the disappearance of the $CH_2$ benzyl and methoxy peaks. The aromatic peaks present were those of the different aryl thiols used (see Figure 2.5) confirming global deprotection of the PMB groups.

Sulfoxide diastereomeric mixtures could be separated by column chromatography in their acetylated form. This also served to confirm that the PMB groups were cleanly removed without oxidizing the sulfoxides into sulfones.

Scheme 2.19. Acetylation of the triols for NMR characterization. Ac$_2$O, DMAP, Et$_3$N, pyridine, 12 h, 88%.
Having developed a general procedure for the synthesis of our target mycothiol bioisosteres, we then substituted the thiophenol with different alkyl and aryl thiols to generate more sulfides as presented below in Table 2.1. These were transformed into their target mycothiol bioisosteres as reported above for the thiophenol. The results are summarized in the Tables 2.2 and 2.3.
Table 2.1. Summary of the sulfide mycothiol derivatives synthesized

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>R'''</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>106</td>
<td>Ph</td>
<td>Bn</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>96%</td>
</tr>
<tr>
<td>117</td>
<td>Ph</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>87%</td>
</tr>
<tr>
<td>123</td>
<td>Ph</td>
<td>PMB</td>
<td>O-cyclohexyl</td>
<td>H</td>
<td>95%</td>
</tr>
<tr>
<td>124</td>
<td>p-C₆H₄Cl</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>95%</td>
</tr>
<tr>
<td>125</td>
<td>p-C₆H₄Br</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>94%</td>
</tr>
<tr>
<td>126</td>
<td>p-C₆H₄CH₃</td>
<td>PMB</td>
<td>O-cyclohexyl</td>
<td>H</td>
<td>71%</td>
</tr>
<tr>
<td>127</td>
<td>p-C₆H₄CH₃</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>90%</td>
</tr>
<tr>
<td>128</td>
<td>p-C₆H₄C(CH₃)₃</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>86%</td>
</tr>
<tr>
<td>129</td>
<td>2-Naphthyl</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>53%</td>
</tr>
<tr>
<td>130</td>
<td>Propyl</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>82%</td>
</tr>
<tr>
<td>131</td>
<td>i-Propyl</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>90%</td>
</tr>
</tbody>
</table>
Table 2.2. Summary of the sulfone mycothiol derivatives synthesized

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>118</td>
<td>Ph</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>65%</td>
</tr>
<tr>
<td>132</td>
<td>Ph</td>
<td>PMB</td>
<td>O-cyclohexyl</td>
<td>H</td>
<td>72%</td>
</tr>
<tr>
<td>133</td>
<td>p-C₆H₄Cl</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>65%</td>
</tr>
<tr>
<td>134</td>
<td>p-C₆H₄Br</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>55%</td>
</tr>
<tr>
<td>135</td>
<td>p-C₆H₄CH₃</td>
<td>PMB</td>
<td>O-cyclohexyl</td>
<td>H</td>
<td>69%</td>
</tr>
<tr>
<td>136</td>
<td>p-C₆H₄CH₃</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>74%</td>
</tr>
<tr>
<td>137</td>
<td>p-C₆H₄C(CH₃)₃</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>68%</td>
</tr>
<tr>
<td>138</td>
<td>2-Naphthyl</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>62%</td>
</tr>
<tr>
<td>139</td>
<td>Propyl</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>73%</td>
</tr>
<tr>
<td>140</td>
<td>i-Propyl</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>73%</td>
</tr>
<tr>
<td>120</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>75%</td>
</tr>
<tr>
<td>144</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>70%</td>
</tr>
<tr>
<td>145</td>
<td>p-C₆H₄Cl</td>
<td>H</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>69%</td>
</tr>
<tr>
<td>146</td>
<td>p-C₆H₄Br</td>
<td>H</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>68%</td>
</tr>
<tr>
<td>147</td>
<td>p-C₆H₄CH₃</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>H</td>
<td>77%</td>
</tr>
<tr>
<td>148</td>
<td>p-C₆H₄C(CH₃)₃</td>
<td>H</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>63%</td>
</tr>
<tr>
<td>149</td>
<td>2-Naphthyl</td>
<td>H</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>62%</td>
</tr>
<tr>
<td>150</td>
<td>Propyl</td>
<td>H</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>67%</td>
</tr>
<tr>
<td>151</td>
<td>i-Propyl</td>
<td>H</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>73%</td>
</tr>
<tr>
<td>122</td>
<td>Ph</td>
<td>Ac</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>88%</td>
</tr>
<tr>
<td>155</td>
<td>Ph</td>
<td>Ac</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>85%</td>
</tr>
<tr>
<td>156</td>
<td>p-C₆H₄Cl</td>
<td>Ac</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>74%</td>
</tr>
<tr>
<td>157</td>
<td>p-C₆H₄Br</td>
<td>Ac</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>94%</td>
</tr>
<tr>
<td>158</td>
<td>p-C₆H₄CH₃</td>
<td>Ac</td>
<td>O-cyclohexyl</td>
<td>H</td>
<td>84%</td>
</tr>
<tr>
<td>159</td>
<td>p-C₆H₄C(CH₃)₃</td>
<td>Ac</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>80%</td>
</tr>
<tr>
<td>160</td>
<td>2-Naphthyl</td>
<td>Ac</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>84%</td>
</tr>
<tr>
<td>161</td>
<td>Propyl</td>
<td>Ac</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>78%</td>
</tr>
<tr>
<td>162</td>
<td>i-Propyl</td>
<td>Ac</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>81%</td>
</tr>
</tbody>
</table>
Table 2.3. Summary of the sulfoxide mycothiol derivatives synthesized

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>R'1</th>
<th>R'2</th>
<th>R'3</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>119a,b</td>
<td>Ph</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>64%</td>
</tr>
<tr>
<td>141a,b</td>
<td>p-C₆H₄Cl</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>63%</td>
</tr>
<tr>
<td>142a,b</td>
<td>p-C₆H₄Br</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>57%</td>
</tr>
<tr>
<td>143a,b</td>
<td>2-Naphthyl</td>
<td>PMB</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>58%</td>
</tr>
<tr>
<td>121a,b</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>64%</td>
</tr>
<tr>
<td>152a,b</td>
<td>p-C₆H₄Cl</td>
<td>H</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>63%</td>
</tr>
<tr>
<td>153a,b</td>
<td>p-C₆H₄Br</td>
<td>H</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>57%</td>
</tr>
<tr>
<td>154a,b</td>
<td>2-Naphthyl</td>
<td>H</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>60%</td>
</tr>
<tr>
<td>163a,b</td>
<td>Ph</td>
<td>Ac</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>64%</td>
</tr>
<tr>
<td>164a,b</td>
<td>p-C₆H₄Cl</td>
<td>Ac</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>63%</td>
</tr>
<tr>
<td>165a,b</td>
<td>p-C₆H₄Br</td>
<td>Ac</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>57%</td>
</tr>
<tr>
<td>166a,b</td>
<td>2-Naphthyl</td>
<td>Ac</td>
<td>H</td>
<td>O-cyclohexyl</td>
<td>60%</td>
</tr>
</tbody>
</table>

2.9 Conclusion

We have reported a route to the synthesis of simplified mycothiol analogues using glucal 99 as suitable starting material. Due to its stability under various reaction conditions, the benzyl protecting groups was initially utilized to protect the hydroxyl groups, however, removal of the protecting groups using conventional heterogeneous catalysis procedures could not be achieved due to a possible poisoning of the palladium metal. As a result, the benzyl (Bn) protecting group was replaced by it close relative, para-methoxybenzyl (PMB) ether which was found to be stable through all the reaction conditions employed.
Cyclopropanated glucal derivatives 102 and 113 obtained via the dihalo cyclopropanation of glucal 100 and 115 respectively were used as a gateway to access C-2-branched iodo glycosides 103a and 103b as well as 116a and 116b in α-, β-anomeric mixtures. Cyclohexanol was used as the glycosyl acceptor and replaced the myo-inositol moiety of mycothiol. In both Bn protected as well as PMB protected sugars, glycosylation afforded the β-glycoside as the major product which was formed twice more favourably than its α-isomer.

The S_N2 substitution of the iodo group by aryl and alkyl thiols afforded sulfides 106, 117 and 123-131 which were subsequently oxidized to their sulfoxide and sulfone derivatives 118, 119 and 132-143. The target compounds were obtained through the oxidative cleavage of the PMB ethers to afford the triols 120 and 144-154 which were characterized by NMR in their acetylated form due to their insolubility in both polar and non-polar deuterated solvents. Three acetate peaks observed on the NMR spectra indicated complete cleavage of the PMB ethers. NMR analysis, HRMS (High Resolution Mass Spectrometry) and IR were used to further characterize the obtained products.

Due to a higher selectivity for formation of β-glycosides and time limit, we were able to report fewer α-anomers compared to their β counterparts. The target compounds that have been reported have been sent for their anti-TB biological activity evaluation.
Chapter 3: Diastereoselective synthesis and characterization of novel carbohydrate-based thiochroman derivatives

3.1 Retrosynthetic analysis and proposed route for thiochroman synthesis

As highlighted in the introduction, thiochromans are reported to possess various medicinal properties that warrant for their synthesis. Also highlighted in the introduction was the stereoselective synthesis of thiochromans using organocatalysts. We ventured into the diastereoselective synthesis of thiochromans using carbohydrates as building blocks and investigated their ability to inhibit mycothiol biosynthesis. To the best of our knowledge the use of carbohydrates to synthesize thiochromans has not been explored.

We envisioned the synthesis of tricyclic unit of carbohydrate-based thiochromans I and II (Scheme 3.1) which contain an α-C-glycosylated hydrophobic core which is similar to the cyclohexyl moiety in the mycothiol bioisosteres reported in Chapter 2. The tricyclic units also contain tetrahedral-forming functional groups in the form of sulfoxides and sulfones. To achieve this thiochroman derivative III can be oxidized using procedures reported in Chapter 2. In turn thiochroman III can be obtained through Friedel-Crafts type intramolecular alkylation of the aryl thiol IV. The sulfides can be synthesized in a similar fashion as discussed in Section 2.4 by S_N2 substitution of the iodide group in the iodomethyl acetate VI which can be obtained by opening of cyclopropanes VII under electrophilic conditions. The synthesis of cyclopropanes from glycals VIII has also been reported in Section 2.4.
Scheme 3.1. Retrosynthetic analysis of carbohydrate-based thiochromans.  a) α-C-glycosylated hydrophobic core; b) tetrahedral-forming intermediate.

3.2 Towards the synthesis of carbohydrate-based thiochromans

3.2.1 Preparation of 2-C-aryliothiomethyl acetates

To achieve our aims, glycosyl iodomethyl acetate 168 was prepared from benzylated α-1,2-cyclopropanated sugar 102 using procedures reported by Gammon and co-workers (Scheme 3.2)\textsuperscript{230} to afford the iodomethyl acetate anomeric mixtures 168 in 67% yield. Benzyl protecting groups were used as model protecting groups due to their stability under both basic and acidic reaction conditions. Confirmation of the products formed was achieved by NMR analysis which was in agreement with data reported in the literature.\textsuperscript{230} The anomeric acetate peaks resonated at $\delta_H$ 2.10 and 2.14 ppm for α and β anomers, respectively. Integration of the NMR peaks showed that the anomers were formed in a 1:2 α:β anomeric ratio.
Scheme 3.2. Synthesis of iodoacetate glycosides. NaI, Ac₂O, H₂O₂, CH₂CN:AcOH (1:1), 0 °C to Room temp, 1 h, 67%.

The iodomethyl acetates were then transformed into their aryl sulfide derivatives 169 by Sₙ₂ substitution of the iodide group. Utilising procedures reported by Chaveriat and co-workers, the iodomethyl acetates were treated with freshly prepared sodium thiophenolate in dry THF:DMSO (1:1) according to Scheme 3.3. The reaction was quenched upon completion (15 min) by drop wise addition of methanol. The solvent was removed under reduced pressure and the crude products were purified by column chromatography to yield the anomeric mixture of sulfides 169 in 83% yield.

Scheme 3.3. Preparation of 2-C-arylthiomethyl glycosides. NaH, thiophenol, THF:DMSO (4:1), 15 min, 83%.

3.2.2 Lewis acid promoted diastereoselective intramolecular cyclization

Cyclization was achieved under Lewis acid conditions. BF₃·Et₂O was used by Hainke and co-workers to prepare aryl C-glycosides and was thus selected as the Lewis acid of choice to achieve our aims according to Scheme 3.4. The sulfide 169 was dissolved in DCM and treated with BF₃·Et₂O (6 equivalents) at 0 °C under anhydrous conditions for 5 min and then
stirred to completion at room temperature for 15 min to afford pure product 170 in 69% yield upon purification. The structure of thiochroman 5a was established by $^1$H, $^{13}$C and 2D NMR techniques (Figure 3.1 and 3.2). The decrease in the integration of the aromatic protons from 20 in the aryl sulfide 169 to 19 in thiochroman 170 coupled with the upfield shift of the anomeric proton from $\delta_H$ 6.42 and 5.67 ppm for the $\alpha$- and $\beta$-anomers, respectively, to $\delta_H$ 5.13 ppm. The disappearance of the acetate group signal in the absence of any external nucleophile during the cyclization reaction reasonably indicates intramolecular alkylation at C-1. This was supported by $^{13}$C NMR spectroscopy which displayed an upfield shift of C-1.

**Scheme 3.4.** Intramolecular cyclization to afford carbohydrate-based thiochromans. BF$_3$Et$_2$O, DCM, 0 $^\circ$C, 20 min, 69%.
Figure 3.1. $^1$H NMR spectra of the aryl thiomethyl acetate anomeric mixtures 169

Figure 3.2. $^1$H NMR of the thiochroman 170
Nuclear Overhauser Effect (NOE) experiments were employed as one of the tools to assign overall conformation of the cyclic rings.\textsuperscript{232} For a sugar ring with a \textsuperscript{4}C\textsubscript{1} chair conformation as in I and II (Scheme 3.5) the β-anomer I can be identified by correlation between H-1 and H-5 or H-3 which are all axial and thus making their nuclei spatially close for coupling (Scheme 3.5). However, no correlation would be observed for the α-anomer II in which case H-1 is equatorial whilst H-3 and H-5 of the sugar moiety are axial resulting in a greater average distance between the protons. Thus, Nuclear Overhauser Effect Spectroscopy (NOESY) was used to determine the anomeric configuration of \textbf{170} and H-1 coupled to H-2 and H-7\textsubscript{a} (Figure 3.3). However, no correlation was observed between H-1, H-3 and H-5 indicating the formation of an α-C-glycoside during cyclization.

\textbf{Scheme 3.5.} Differentiation of β I and α II C-glycosides using NOE experiments
Figure 3.3 NOESY spectrum showing H-1 coupling to H-2 and H-7a.

Attempts to grow crystals of thiochroman 170 for absolute structure determination using X-ray crystallography were unsuccessful. However, oxidation of thiochroman 170 using excess OXONE® in the presence of wet alumina as reported in Section 2.7 resulted in formation of sulfone 171 in 78% yield as colourless crystals. XRD diagram (Scheme 3.6) confirmed Friedel-Crafts alkylation and formation of the α-C-glycoside through the thio aryl ring. Thus, although a mixture of anomeric isomers were used as starting material only one isomer was formed as product. Ring puckering analysis showed the pyranosyl ring in a chair conformation, whereas the formed six membered thiochroman moiety had an envelope conformation.233
Scheme 3.6. Oxidation of thiochromans and the XRD image of the sulfone 171. Wet Al₂O₃, OXONE®, DCM, 12 h, 78%.

The proposed mechanism of cyclization may be through the activation of -OAc by its co-ordination to BF₃ and the resultant formation of an oxocarbenium ion II. The formed ion could have a ⁴H₃ conformation III which is the most stable conformation as all the bulky substituents are in the equatorial positions, thus, reducing ring strain caused by steric interactions. This conformation results in the aryl sulfide aromatic ring being below the sugar ring. Thus, electron delocalization and nucleophilic attack of electrophilic C-1 position by the aromatic ring can only occur from the bottom face of the ring resulting in the diastereoselective formation of the α-C-glycoside and the resultant thiochroman VI.

Scheme 3.7. Proposed mechanism of the diastereoselective formation of the carbohydrate-based thiochromans.
To investigate the generality and scope of the synthetic methodology, several *ortho* and *para* substituted aryl thiols were employed and provided their corresponding thiochromans in good yields. However, cyclization reactions with *meta* alkyl and halide substituted aryl thiols afforded a mixture of products and this could be due to competitive directing effect from the sulfur and aryl substituents. The electron-withdrawing effect of halides may also deactivate electron delocalization and cyclization.\textsuperscript{234} Table 3.1 summarizes the different aryl thiols utilized to synthesize sulfides and their corresponding thiochromans.

**Table 3.1.** Summary of the pyranosyl acetates and their thiochroman derivatives

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Yield</th>
<th>Product</th>
<th>R</th>
<th>R'</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>169</td>
<td>Ph</td>
<td>83%</td>
<td>170</td>
<td>H</td>
<td>H</td>
<td>69%</td>
</tr>
<tr>
<td>172</td>
<td>(p)-C(_6)H(_4)CH(_3)</td>
<td>87%</td>
<td>177</td>
<td>H</td>
<td>CH(_3)</td>
<td>71%</td>
</tr>
<tr>
<td>173</td>
<td>(o)-C(_6)H(_4)CH(_3)</td>
<td>87%</td>
<td>178</td>
<td>CH(_3)</td>
<td>H</td>
<td>73%</td>
</tr>
<tr>
<td>174</td>
<td>(p)-C(_6)H(_4)C(CH(_3))_3</td>
<td>93%</td>
<td>179</td>
<td>H</td>
<td>C(CH(_3))_3</td>
<td>69%</td>
</tr>
<tr>
<td>175</td>
<td>(p)-C(_6)H(_4)OCH(_3)</td>
<td>*</td>
<td>180</td>
<td>H</td>
<td>OCH(_3)</td>
<td>70%</td>
</tr>
<tr>
<td>176</td>
<td>2-Naphthyl</td>
<td>86%</td>
<td>181</td>
<td>See structure below</td>
<td>68%</td>
<td></td>
</tr>
</tbody>
</table>

*Product was used without further purification and due to its instability*
To generate thiochromans that contain sulfoxide and sulfone tetrahedral centres, and in the hope that change in conformation of the sugar derivatives would enable deprotection of benzyl groups, the thiochromans were then oxidized to their sulfone derivatives (Table 3.2) using the same protocol used to synthesize sulfone mycothiol derivatives in Section 2.7 and according to Scheme 3.6. To a suspension of thiochroman in DCM was added wet Al₂O₃, excess OXONE® and the reaction was stirred overnight at room temperature. Work-up and purification afforded sulfone products as white crystals in good yields. IR spectrometry displayed O=S=O stretches around 1300 cm⁻¹ to confirm formation of the sulfones which was in agreement with the literature.²¹⁹ Formed products were also confirmed by HRMS data which was found to be in agreement with the calculated molecular weights. A series of sulfone derivatives were synthesized and the results are summarized in Table 3.2.

Having synthesized the sulfone derivatives attention was then focused on the selective oxidation of the thiochromans to their sulfoxide derivatives (Table 3.2) which were obtained by treating the thiochromans with CAN and catalytic amounts of KBr as reported by Zolfigol and co-workers who selectively synthesized sulfoxides from simple sulfides.²²³ The general procedure for the synthesis of sulfoxides entails dissolving the sulfides in DCM at room temperature followed by the addition of 50% wet silica gel, KBr and CAN and the reaction was stirred for approximately 30 min to afford the diastereomeric sulfoxide products in appreciable yields. Formation of sulfoxides was confirmed by IR spectroscopy with the S-O vibrations observed between 1020 and 1049 cm⁻¹.²¹⁸ Molecular weights of the products were also confirmed by HRMS analysis. Calculated molecular weights were found to be in agreement with the analysed results.
Scheme 3.8 CAN oxidation of sulfides to sulfoxides. 50% Wet silica, KBr, CAN, DCM, 1 h, 40% (186a) and 27% (186b).

Table 3.2. Summary of the sulfone and sulfoxide thiochroman derivatives

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>R'</th>
<th>Yield</th>
<th>Product</th>
<th>R</th>
<th>R'</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>171</td>
<td>H</td>
<td>H</td>
<td>73%</td>
<td>186a,b</td>
<td>H</td>
<td>H</td>
<td>40 &amp; 27%</td>
</tr>
<tr>
<td>182</td>
<td>H</td>
<td>CH₃</td>
<td>72%</td>
<td>187a,b</td>
<td>H</td>
<td>CH₃</td>
<td>44 &amp; 24%</td>
</tr>
<tr>
<td>183</td>
<td>CH₃</td>
<td>H</td>
<td>72%</td>
<td>188a,b</td>
<td>CH₃</td>
<td>H</td>
<td>43 &amp; 28%</td>
</tr>
<tr>
<td>184</td>
<td>H</td>
<td>C(CH₃)₃</td>
<td>67%</td>
<td>189a,b</td>
<td>H</td>
<td>OCH₃</td>
<td>49 &amp; 23%</td>
</tr>
<tr>
<td>185</td>
<td>H</td>
<td>OCH₃</td>
<td>57%</td>
<td>190</td>
<td>H</td>
<td>C(CH₃)₃</td>
<td>61%</td>
</tr>
</tbody>
</table>

tert-Butyl thiochroman derivative 179 was oxidized using 1.2 eq of OXONE® to afford a single isomer of the sulfoxides as the major product. This may suggest that one of the two enantiotopic lone pairs is more reactive than the other and thus favourably forming a sulfoxide on one face of the substrate depending on the method of oxidation used. To further determine the scope of this selectivity, thiochroman 169 was also subjected to sulfoxidation using OXONE® and also afforded a single isomer as a major product. TLC and NMR analysis of the formed product showed that the formed sulfoxide was the same compound as the minor product obtained by CAN sulfoxidation. The difference in reactivity
of the lone pairs can also be explained by the mechanisms of the two oxidative protocols (Scheme 3.9 and 3.10). Thus, according to mechanisms reported by Kropp and co-workers and assuming that the bottom lone pair electrons (in the Schemes) are the most reactive or most accessible of the two lone pairs, abstraction of an oxygen atom from OXONE® dispersed on the surface of Al₂O₃ occurs via these ‘reactive’ lone pair electrons to afford a single product (Scheme 3.9).

![Diagram](image)

**Scheme 3.9** Proposed mechanism of OXONE® suloxidation.

According to the mechanism proposed by Zolfigol and co-workers, the same exo (upper face as drawn) lone pair electrons abstract an oxidized bromide ion Br⁺ to form the intermediate I (Scheme 3.10). The electrophilic sulfur atom is then attacked by a water molecule from the opposite face of the bromide atom and subsequent loss of a proton to afford the intermediate II. HBr is then eliminated to afford the sulfoxide product as a major product and Br⁻ is reoxidized to Br⁺ which is used to generate more sulfoxides in the reaction. Nucleophilic attack of the Br⁺ ion by the endo (lower face as drawn) lone pair electrons would afford the other isomer.

* Absolute stereochemistry of sulfur in the formed sulfoxides was not determined and is used here for demonstration purposes only.
Scheme 3.10 Proposed mechanism of CAN promoted sulfoxidation.

The naphthalene derivative 181 was found to be unstable in the oxidative conditions and formed by-products. This may be due to decreased nucleophilicity of the sulfur atom by the electron withdrawing effect of the naphthyl group. The yields of the sulfoxide thiochroman derivatives are summarized in Table 3.2.

Efforts to cleave the benzyl groups were yet again unsuccessful. Similar protocols using Pd/C as reported in Section 2.5 were unable to fully deprotect the sulfide, sulfoxide and sulfone derivatives. However, acetalolysis reactions using Al(OTf)$_3$ at 45 °C according to Scheme 3.9 afforded the monodebenzylated product 191. The results were anticipated as primary benzyl groups are known to be labile under acetalolysis conditions and Lewis acids.$^{210,236}$ The reaction was left to stir for over 2 days without further debenzylation. Vigorous acetalolysis reaction conditions using sulfuric acid as reported by Cao and co-workers formed too many by-products which were observed on TLC and no desired fully debenzylated products could be isolated.$^{237}$ FeCl$_3$ was found to cleave the benzyl groups but the reactions were low yielding and due to time constraints this method could not be further optimized.
Scheme 3.9. Acid-promoted acetolysis of the primary benzyl group. i) Al(OTf)$_3$ (10 mol%), Ac$_2$O:AcOH (1:1), 45 °C, 90 min, 72%.

The PMB protecting group employed during the synthesis of mycothiol analogues could not be employed for thiochroman synthesis due to its susceptibility under acidic conditions such as those employed during the cyclization step (Scheme 3.4). Studies to cleave the benzyl protecting groups are currently underway.

The thiochromans and their sulfoxide and sulfone derivatives have been evaluated for their anticancer and antimalarial activities and the results are discussed in Chapter 4. Mycothiol inhibition is currently under investigation along with the analogues synthesized in Chapter 2.

3.3 Conclusion

In conclusion, we have demonstrated an efficient synthetic protocol for diastereoselective preparation of novel carbohydrate-based thiochromans in which the orientation of the substituent at C-2 of the starting pyranosyl acetate induces the stereochemistry of the thiochroman products. 1α-,2α-aryl-C-glycoside thiochromans 170, 177-181 were successfully synthesized as pure isomers from an anomeric mixture of thio aryl acetate substrates 169, 172-176. 2D NMR techniques such as NOE as well as crystal structures were used to establish the formation of α-C-glycosides.
In a similar fashion to the mycothiol analogues, the thiochromans were oxidized to their sulfoxide 186a,b,189a,b; 190 and sulfone 171, 182-185 derivatives that contain a tetrahedral centre which may be essential for the inhibition of enzymes implicated in mycothiol biosynthesis. The α-C-glycosylated aryl ring could serve as a “hydrophobic core” that replaces the myo-inositol moiety in mycothiol, thus, making these compounds suitable candidates for the inhibition of MshB and Mca enzymes involved in mycothiol biosynthesis pathways.

Selective oxidation with CAN afforded both sulfoxide diastereomers albeit in unequal yields. Sulfoxidation with OXONE® afforded a single isomer which was found to be the minor product obtained during CAN oxidation. Procedures to cleave the benzyl ethers are still under development and will be reported in future.
Chapter 4: Thiochroman biological activity assay

4.1 Introduction

Having synthesized the thiochromans and their oxidized derivatives attention was shifted to their biological activity. The compounds were randomly selected and accessed for their anticancer, antimalarial as well as anti-TB activities. The preliminary in vitro anticancer and antimalarial tests are presented in this chapter. Anti-TB activity tests took longer than expected and are thus, not present in this chapter.

4.2 In vitro anticancer screening report

Cancer screening was done by the CSIR’s Biosciences Pharmacology Group. A total of 5 thiochroman derivatives were sent for anticancer screening and these were screened against a 3 cell line panel consisting of human breast cancer (MCF7), human colon cancer (HCT116) and human prostate cancer (PC3) using Sulforhodamine B (SRB) assay. SRB assay was developed by Skehan and co-workers and measures drug-induced cytotoxicity and cell proliferation based on the ability of the protein dye (SRB) to bind electrostatically and in a pH dependant manner to protein basic amino acid residues of cells fixed to microtiter plates by trichloroacetic acid. The protein dye binds to the amino acids of cells fixed to the plates under mild acidic conditions and can be extracted from the cells and solubilized for measurement under basic conditions.
For the screening experiment, the cells were inoculated in 96-well microtiter plates at plating densities of 7-10 000 cells/well and were incubated for 24 h. After 24 h one plate was fixed with trichloroacetic acid (TCA) to represent a measurement of the cell population for each cell line at the time of drug addition. The other plates with cells were treated with the experimental drugs which were previously dissolved in DMSO and diluted in medium to produce 5 concentrations (6.25-100 µg/mL or 0.01-100µM). Cells without drug addition served as control. The blank contained the complete medium without cells. Parthenolide, a sesquiterpene lactone found in the plant Feverfew and known to possess anti-inflammatory and anticancer properties was used as a reference standard.

The plates were incubated for 48 h after addition of the drugs and then viable cells were fixed to the bottom of each well with cold 50% TCA, washed, dried and dyed by SRB. Unbound dye was removed and protein-bound dye was extracted with 10mM Tris base for optical density determination at the wavelength 540 nm using a multi-well spectrophotometer. Optical density measurements were used to calculate the net percentage cell growth.

For each tested compound, four response parameters, GI50 (50% growth inhibition and signifies the growth inhibitory power of the test agent), TGI (which is the drug concentration resulting in total growth inhibition and signifies the cytostatic effect of the test agent), LC50 (50% lethal concentration and signifies the cytotoxic effect of the test agent), LC100 (100% lethal concentration and signifies the cytotoxic effect of the test agent), were calculated for each cell line. The biological activities were separated into 4 categories according to their TGI concentrations and these are: I) Inactive (TGI >100µM); II) Weak activity (30 µM < TGI <100 µM); III) Moderate activity (10 µM < TGI <30 µM) and IV) Potent activity (TGI <10 µM). The anticancer results are presented in the graphs and tables below.
4.2.1 Anticancer screening results

Sample: Parthenolide/ 192 (Standard)

![Parthenolide Graph]

<table>
<thead>
<tr>
<th>Activities</th>
<th>MCF7</th>
<th>HCT116</th>
<th>PC3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI50 [µM]</td>
<td>5.89</td>
<td>19.77</td>
<td>13.19</td>
</tr>
<tr>
<td>TGI [µM]</td>
<td>26.71</td>
<td>49.34</td>
<td>46.73</td>
</tr>
<tr>
<td>LC50 [µM]</td>
<td>96.49</td>
<td>78.91</td>
<td>80.26</td>
</tr>
<tr>
<td>LC100 [µM]</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

Sample: B085/ 179

![B085 Graph]

<table>
<thead>
<tr>
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<th>MCF7</th>
<th>HCT116</th>
<th>PC3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI50 [µM]</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>TGI [µM]</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>LC50 [µM]</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>LC100 [µM]</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>
Sample: C027-1/184

![Graph showing net growth percentage against extract concentration for different cell lines.]

<table>
<thead>
<tr>
<th>Activities</th>
<th>MCF7</th>
<th>HCT116</th>
<th>PC3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI50 [uM]</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>TGI [uM]</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>LC50 [uM]</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>LC100 [uM]</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

Sample: C027-2/190

![Graph showing net growth percentage against extract concentration for different cell lines.]

<table>
<thead>
<tr>
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<th>HCT116</th>
<th>PC3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI50 [uM]</td>
<td>6.69</td>
<td>8.65</td>
<td>5.97</td>
</tr>
<tr>
<td>TGI [uM]</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>91.34</td>
</tr>
<tr>
<td>LC50 [uM]</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
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<tr>
<td>LC100 [uM]</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>
Sample: C028-1A/ 187a

<table>
<thead>
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<th>PC3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI50 [uM]</td>
<td>21.19</td>
<td>&gt;100</td>
<td>7.03</td>
</tr>
<tr>
<td>TGI [uM]</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>LC50 [uM]</td>
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<td>&gt;100</td>
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<tr>
<td>LC100 [uM]</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
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</tbody>
</table>

Sample: C028-2/ 182

<table>
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<th>HCT116</th>
<th>PC3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI50 [uM]</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>TGI [uM]</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>LC50 [uM]</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>LC100 [uM]</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>
4.2.2 Summery of cancer screening results

According to the CSIR criteria which are indicated in Table 4.2, a compound is considered to be inactive if its TGI parameter for two cell lines is higher than 100 µM and to our disappointment all of the submitted samples had a TGI value above 100 µM for all 3 cell lines and were thus, classified as inactive. Sample C027-2/190 showed slight activity against the PC3 cell line with a TGI value of 91.34 µM. However, the sample had TGI values above 100 µM for the other 2 cell lines. Therefore the compound can also be estimated as inactive.

Table 4.1 Summery of anticancer screening results showing sample TGI concentrations for the different cell lines

<table>
<thead>
<tr>
<th>Sample</th>
<th>MCF7</th>
<th>HCT116</th>
<th>PC3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parthenolide/192</td>
<td>26.71</td>
<td>49.34</td>
<td>46.73</td>
</tr>
<tr>
<td>B085/179</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>C027-1/184</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>C027-2/190</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>91.34</td>
</tr>
<tr>
<td>C028-1A/187a</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>C028-2/182</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

Table 4.2 Biological activity criteria based on TGI values

<table>
<thead>
<tr>
<th>TGI</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 100 µM</td>
<td>Inactive</td>
</tr>
<tr>
<td>30 - 100 µM</td>
<td>Weak Activity</td>
</tr>
<tr>
<td>10 - 30 µM</td>
<td>Moderate Activity</td>
</tr>
<tr>
<td>&lt; 10 µM</td>
<td>Potent Activity</td>
</tr>
</tbody>
</table>
4.3 \textit{In vitro} antimalarial screening

The \textit{in vitro} antimalarial screening of our compounds was done by the CSIR Biosciences Biomedical Technologies Group. A total of 5 thiochroman-based compounds were sent for antimalarial screening. The compounds were tested against the 3D7 strain of the malaria parasite \textit{Plasmodium falciparum} and their activity was measured by assessing parasite survival after drug exposure using a parasite lactate dehydrogenase (pLDH) colorimetric enzyme assay.\textsuperscript{240} Lactate dehydrogenase (LDH) is an enzyme found in a wide range of living organisms and catalyses the conversion of lactate to pyruvate and in the process reducing the co-enzyme NAD\textsuperscript{+} (nicotinamide adenine dinucleotide) to NADH.\textsuperscript{241} In the pLDH assay, the NAD analogue APAD (3-acetylpyridine adenine nucleotide) is reduced to APADH which then reacts with a yellow reagent consisting of nitro blue tetrazolium and phenazine ethosulfate (NBT + PES) resulting in the formation of purple formazan crystals. Thus, formation of formazan is directly proportional to pLDH activity which is in turn indicative of the number of parasites in the cultures following drug exposure. Formation of formazan can be measured by spectrophotometric methods. The inability of human LDH found in the host blood cells to utilise APAD as co-factor ensures the specificity of the assay for pLDH activity.

Compound inhibitory activity was determined by preparing serial dilutions of test compounds in transparent 96-well flat bottom plates. Parasitized red blood cells were added to a final concentration of 1\% haematocrit, 2\% parasitaemia and the plates incubated for 48 h before proceeding with the pLDH assay. Percentage parasite survival in each well was calculated relative to control wells that received no drug. Results are presented below as percentage parasite viability at the various compound concentrations and 50\% inhibitory concentration (IC\textsubscript{50}) of individual compounds calculated from fitted sigmoidal dose-response curves. Chloroquine 193 which is currently used to prevent and treat malaria was used as the
standard reference drug. IC \textsubscript{50} values obtained from the graphs are in µg/mL see summary Table 4.4 for IC \textsubscript{50} values calculated in µM.

### 4.3.1. Antimalarial screening results

**Sample: Chloroquine/ 193**

<table>
<thead>
<tr>
<th>Drug [ ] (µg/mL)</th>
<th>Log [ ] (µg/mL)</th>
<th>%Parasite Viability</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00 e+00</td>
<td>0.00</td>
<td>-8.47</td>
<td>1.52</td>
</tr>
<tr>
<td>3.33 e-01</td>
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<td>-10.36</td>
<td>7.01</td>
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<td>1.11 e-01</td>
<td>-0.95</td>
<td>-7.65</td>
<td>6.25</td>
</tr>
<tr>
<td>3.70 e-02</td>
<td>-1.43</td>
<td>1.17</td>
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<td>16.10</td>
<td>3.46</td>
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<td>71.27</td>
<td>2.30</td>
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<td>1.69 e-05</td>
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<td>79.34</td>
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</table>

**Sample: B085/ 179**

<table>
<thead>
<tr>
<th>Drug [ ] (µg/mL)</th>
<th>Log [ ] (µg/mL)</th>
<th>%Parasite Viability</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>2.000</td>
<td>6.01</td>
<td>4.69</td>
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<tr>
<td>33.33</td>
<td>1.523</td>
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<td>3.14</td>
</tr>
<tr>
<td>11.11</td>
<td>1.046</td>
<td>16.41</td>
<td>0.46</td>
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<td>3.70</td>
<td>0.569</td>
<td>44.00</td>
<td>4.64</td>
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<td>1.23</td>
<td>0.092</td>
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<td>4.51</td>
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<td>4.12E-01</td>
<td>-0.386</td>
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<td>15.57</td>
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<td>1.37E-01</td>
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<td>100.00</td>
<td>9.92</td>
</tr>
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<td>4.57E-02</td>
<td>-1.34</td>
<td>99.87</td>
<td>0.23</td>
</tr>
<tr>
<td>1.52E-02</td>
<td>-1.818</td>
<td>95.22</td>
<td>1.78</td>
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**Sample: C026_1/ 171**

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**Sample: C026_2/ 186b**

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<td>0.77</td>
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<th>SD</th>
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Sample: C027_2/ 190

<table>
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<th>Log [µg/mL]</th>
<th>% Parasite Viability</th>
<th>SD</th>
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<tr>
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<td>2.000†</td>
<td>0.00</td>
<td>0.77</td>
</tr>
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<td>33.33</td>
<td>1.523</td>
<td>4.28</td>
<td>7.56</td>
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<td>1.046</td>
<td>17.84</td>
<td>1.64</td>
</tr>
<tr>
<td>3.70</td>
<td>0.569</td>
<td>86.50</td>
<td>6.10</td>
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<tr>
<td>1.23</td>
<td>0.092</td>
<td>95.81</td>
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<td>93.50</td>
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<td>84.27</td>
<td>5.83</td>
</tr>
</tbody>
</table>

* Depicts outlier value detected in each respective graph
4.3.2 Summery of the anti-malarial screening results

As a general rule, compounds can be classified as marginally active or inactive for IC\textsubscript{50} > 10\mu M; moderately active for IC\textsubscript{50} = 1 - 10\mu M; active for IC\textsubscript{50} = 0.1-1\mu M and highly active for IC\textsubscript{50} < 0.1\mu M. To our excitement and based on their IC\textsubscript{50} values four of the five randomly selected compounds demonstrated inhibitory activity against \textit{P. falciparum} 3D7 (see Table 4.4). Samples B185/179, C026_1/171 and C027_2/190 displayed moderate activity whilst sample C027_1/184 was found to be highly active with an IC\textsubscript{50} value = 0.07846 \mu M compared to the standard drug chloroquine/193 which had an IC\textsubscript{50} value of 0.02882 \mu M. Precipitation was observed during the performance of assays for compounds C026_1/171 and C026_2/186b when these were added to the media. Significantly more precipitation was also observed for C027_1/184 and C027_2/190 which is likely to have contributed to the observed level of variance of the data between replicates.

Table 4.3. General biological activity criteria based on their IC\textsubscript{50} values

<table>
<thead>
<tr>
<th>IC\textsubscript{50}</th>
<th>Status</th>
</tr>
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<td>&gt; 10 \mu M</td>
<td>Marginally active</td>
</tr>
<tr>
<td>1 - 10 \mu M</td>
<td>Moderately active</td>
</tr>
<tr>
<td>0.1 - 1 \mu M</td>
<td>Active</td>
</tr>
<tr>
<td>&lt; 0.1 \mu M</td>
<td>Highly active</td>
</tr>
</tbody>
</table>

Table 4.4. Summary of the antimalarial screening results

<table>
<thead>
<tr>
<th>Sample</th>
<th>IC\textsubscript{50} (\mu g/mL)</th>
<th>IC\textsubscript{50} (\mu M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine/193</td>
<td>0.009219</td>
<td>0.02882</td>
</tr>
<tr>
<td>B085/179</td>
<td>3.143</td>
<td>5.284</td>
</tr>
<tr>
<td>C026_1/171</td>
<td>2.344</td>
<td>4.107</td>
</tr>
<tr>
<td>C026_2/186b</td>
<td>6.871</td>
<td>12.32</td>
</tr>
<tr>
<td>C027_1/184</td>
<td>0.04918</td>
<td>0.07846</td>
</tr>
<tr>
<td>C027_2/190</td>
<td>1.202</td>
<td>1.968</td>
</tr>
</tbody>
</table>
A general activity trend observed for the tested compounds showed that compounds containing sulfones, which are less polar, were found to be more active than their more polar sulfoxide derivatives. The presence of the tert-butyl group may have increased the hydrophobicity or steric bulk of \textbf{C027\_1/184} and \textbf{C027\_2/190}, thus, enhancing their activity. However, more thiochromans and their oxidized derivatives need to be analysed and compared in order to determine the activity trend with certainty. Studies to determine the mechanism of action of these compounds are also underway and will be reported at a later stage.
Chapter 5: Overall Conclusion

This work demonstrated the successful synthesis of mycothiol molecular bioisosteres containing sulfoxide and sulfone functional groups as the tetrahedral-forming moieties. Although more β-anomers were obtained compared to α-anomers, these obtained analogues will serve as model compounds for testing their ability to inhibit mycothiol biosynthesis. Efforts to deprotect the benzyl ethers at the final stages of synthesis were fruitless. The use of para-methoxybenzyl ethers which were easier to cleave under oxidative conditions afforded the synthesis of our target mycothiol molecular analogues. In all instances the acetylation of the final product confirmed full deprotection and formation of target compounds. IR and HRMS techniques also confirmed the formation of sulfoxide and sulfone functional groups.

Synthesized analogues have been sent for biological activity evaluation and their inhibition of mycothiol biosynthesis will contribute to the efforts directed at developing novel anti-TB drugs.

An efficient route for the diastereoselective synthesis of novel carbohydrate-based thiochromans was also established. α-, β-Anomeric mixtures of C-2-aryl thiomethyl acetates were cyclized under acidic conditions forming α-C-glycosides through the aromatic ring to afford the desired thiochromans. Aryl thiols containing electron-withdrawing substituents could not be cyclized as these were deactivated by their substituents. Oxidation of the thiochromans to sulfoxides and sulfones afforded thiochroman derivatives that contained tetrahedral-forming intermediates, thus, making the compounds suitable candidates for inhibition of mycothiol biosynthesis. The reported potency of thiochroman moieties may
increase the activity of these compounds. However, efforts to fully debenzylate the benzyl groups using Pd/C were yet unsuccessful. Further studies to cleave the benzyl groups are being conducted and will be reported in due course.

Randomly selected thiochromans were tested against 3 cancer cell lines namely MCF7, HCT116 and PC3 and no activity was observed against any of the cell lines. However, the compounds demonstrated good activity against the malarial parasite *Plasmodium falciparum*. As a result more thiochroman derivatives are being assessed for their antimalarial activities and their potency and mode of activity will be reported in the near future.
Chapter 6: Experimental Section

6.1 Materials

All reagents used were purchased from Sigma-Aldrich and were used without further purification. All the solvents were dried using conventional methods and inert reactions were done under Nitrogen atmosphere. Glassware was oven dried before use and reactions were constantly stirred using a magnetic bar and a stirrer plate. “Room temperature” refers to ca. 20 – 25 °C.

6.2 Melting Points

Melting points were determined using a Reichert-Jung Thermovar hot-stage microscope and are uncorrected.

6.3 Chromatography methods

Reactions were monitored by thin layer chromatography (TLC) on aluminium-backed Merck silica gel 60 F_{254} plates. Chromatograms were eluted using an appropriate solvent system as indicated for column chromatography. Compounds were visualized under UV light (254 nm) as well as by spraying the plate with a 1:1 solution of 5% p-anisaldehyde in ethanol and 10% sulphuric acid in ethanol baking at 150 °C until dark spots were observed. Gravity column chromatography was done on Merck silica gel 60 (70 – 230 mesh) with eluents mixed in volume per volume ratios.
6.4 Spectroscopic and XRD techniques

$^1$H NMR and $^{13}$C NMR were recorded on a Bruker Ultrashield (400 MHz) spectrometer using deuterated chloroform as solvent, unless otherwise stated. $^1$H NMR data were reported in the following order: I) Chemical shift (δ) in ppm and referred to the residual solvent peak of CDCl$_3$ [δ = 7.24 ppm] or an internal standard such as TMS [δ = 0.00 ppm]. II) Multiplicity (s = singlet, bs = broad singlet d = doublet, bd = broad doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, dt = doublet of triplets, q = quartets). III) Number of protons. IV) Coupling constant (J in Hertz) and V) Assignment of protons. $^{13}$C NMR data were recorded at 100 MHz on the same instrument and are reported in the order: I) Chemical shift (δ) in ppm and referred to the residual solvent peak of CDCl$_3$ [δ = 77.00 ppm] and II) Specific carbon allocation. 2 Dimensional (2D) NMR techniques such as Correlation Spectroscopy (COSY), Heteronuclear Single Quantum Coherence (HSQC), Heteronuclear Multiple Bond Coherence (HMBC), Distortionless Enhancement by Polarisation Transfer (DEPT) and Nuclear Overhauser Effect (NOE) experiments were used to assist in assigning the spectra.

Mass spectrometers were recorded on a Walters API Quattro Micro spectrometer at the University of Stellenbosch, South Africa. Infrared spectra were recorded using Tensor 27 Bruker and Perkin Elmer FT-IR spectrum BX with characteristic peaks reported in wavenumber (cm$^{-1}$).

Crystal evaluation and data collection were performed on a Bruker APEX Duo 4 K KappaCCD diffractometer.

6.5 Optical Rotations

Optical rotations were determined on a Perkin-Elmer 141 polarimeter in chloroform solutions at 25 °C. The concentration c refers to g/100 mL.
6.6 Synthesis of mycothiol molecular analogues

3,4,6-Tri-O-benzyl-D-glucal (100)

3,4,6-Tri-O-acetyl-D-glucal (0.50 g, 1.84 mmol) was weighed into a round-bottom flask and
diluted with THF (10 mL). TBAI (0.14 g, 0.37 mmol) was then added to the reaction flask
followed by a finely crushed NaOH (0.44 g, 11.04 mmol). Benzyl chloride (0.95 mL, 8.82
mmol) was then added in a dropwise manner to the reaction mixture which was left to stir at
room temperature for 48 h. Upon completion, the reaction was diluted by adding water (15
mL) and the aqueous phase was extracted thrice with DCM (10 mL portions). The combined
organic extracts were dried over anhydrous MgSO₄ and filtered before solvent removal by
rotary evaporation. The residue was purified by column chromatography on silica gel using
hexane and ethyl acetate (9:1) as eluent to yield a colourless syrup which was recrystallized
from hexane as white crystals.

Yield: 0.43 g, 56% white solid.

Mp: 54 – 56 °C.

¹H NMR: (CDCl₃, 400 MHz): δH 7.32 – 7.23 (m, 15H, Ar), 6.42 (d, 1H, J = 6.0 Hz, H-1),
4.87 (dd, 1H, J = 2.6 Hz and 6.2 Hz, H-2), 4.83 (d, 1H, J = 11.2 Hz, –CH₂Ph),
4.65 – 4.50 (m, 5H, –CH₂Ph), 4.20 (bd, 1H, J = 6.0 Hz, H-3), 4.10 – 4.00 (m,
1H, H-5), 3.90 – 3.80 (m, 3H, H-4, H-6a, H-6b).

¹³C NMR: (CDCl₃, 100 MHz): δC 144.7 (C-1), 138.3, 138.1, 137.9, 128.4, 128.3, 127.9,
127.8, 127.7, 127.6 (Ar), 99.9 (C-2), 77.4 (C-3), 75.7 (C-5), 74.3 (C-4), 73.7,
73.5, 70.4 (–CH₂Ph), 68.5 (C-6) (Spectroscopic data were in agreement with the reported data).\(^\text{183}\)

3,4,6-Tri-O-benzyl-1,5-anhydro-2-deoxy-1,2-C-dichloromethylene-D-glycero-D-gulohexitol (101)

Benzyltriethylammonium chloride (BTEAC) (0.03 g, 0.12 mmol) was added to a stirring solution of tri-o-benzyl glucal 100 (0.25 g, 0.60 mmol) dissolved in chloroform (15 mL). 50% aqueous NaOH (0.96 g, 24.01 mmol) was then added and the reaction was stirred at 35 °C for 6 h to completion. The reaction mixture was then quenched by adding water (25 mL) and the aqueous layer was extracted thrice with DCM (15 mL portions). The combined organic extracts were dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue product was purified by column chromatography on silica gel using hexane and ethyl acetate (9:1) as eluent. Pure compound was obtained by recrystallization from hexane.

Yield: 0.04 g, 60% white solid.

Mp: 62 – 64 °C.

\(^1\)H NMR: (CDCl₃, 400 MHz): δ\(_H\) 7.40 – 7.20 (m, 15H, Ar), 4.93 – 4.41 (m, 6H, –CH₂Ph), 3.92 (d, \(J = 8.0\) Hz, 1H, H-1), 3.86 – 3.80 (m, 1H, H-3), 3.79 – 3.75 (m, 2H, H-4, H-5), 3.60 – 3.48 (m, 2H, H-6\(_a\), H-6\(_b\)), 1.44 (dd, \(J = 2.0\) Hz and 7.6 Hz, H-2).

\(^{13}\)C NMR: (CDCl₃, 100 MHz): δ\(_C\) 138.2, 137.9, 137.7, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, (Ar), 79.9 (C-3), 77.4 (C-4), 75.1 (C-5), 74.6, 73.3, 71.8
(–CH₂Ph), 70.1 (C-6), 61.5 (C-7), 58.9 (C-1), 34.3 (C-2) (Spectroscopic data found to be in agreement with the reported data).¹⁸¹

3,4,6-tri-O-benzyl-1,5-anhydro-2-deoxy-1,2-C-methylene-D-glycero-D-gulo-hexitol (102)

Lithium aluminium hydride (0.34 g, 9.00 mmol) was added to a two-neck flask containing THF (15 mL) under nitrogen atmosphere. The mixture was stirred vigorously and the dichlorocyclopropane 101 (0.30 g, 0.60 mmol) was added and the reaction was stirred for 48 h at room temperature under nitrogen atmosphere. The reaction was then cooled on ice and quenched by slow addition of 10% aqueous Na₂SO₄·10H₂O. The formed solids were washed with hot ethyl acetate and the solvent was dried over anhydrous MgSO₄ and concentrated under reduced pressure. The compound was purified by column chromatography on silica gel using hexane and ethyl acetate (8:2) eluent.

Yield: 0.217 g, 84% colourless syrup.

¹H NMR: (CDCl₃, 400 MHz): δH 7.40 – 7.20 (m, 15H, Ar), 4.80 – 4.45 (m, 6H, –CH₂Ph), 3.79 – 3.49 (m, 6H, H-1, H-3, H-4, H-5, H-6a, H-6b), 0.95 – 0.91 (m, 1H, H-2), 0.80 – 0.65 (m, 2H, H-7a, H-7b).

¹³C NMR: (CDCl₃, 100 MHz): δC 138.7, 138.6, 138.4, 128.4, 128.0, 127.8, 127.7, (Ar) 80.2 (C-3), 77.2 (C-4), 76.9 (C-5), 73.5, 73.4, 71.2 (–CH₂Ph), 70.2 (C-6), 49.7 (C-1), 14.9 (C-2), 11.6 (C-7) (Spectroscopic data found to be in agreement with the reported data).¹⁸¹
Cyclohexyl-3,4,6-tri-O-benzyl-2-deoxy-2-C-iodomethyl-α- and -β-D-glucopyranoside (103a) and (103b)

Cyclopropanated sugar 102 (0.15 g, 0.35 mmol) was dissolved in chloroform under anhydrous conditions and cyclohexanol (0.48 ml) was added followed by NIS (0.12 g, 0.52 mmol) and stirred at room temperature. The reaction showed completion after 3 h and was quenched by adding a 10 mL solution of 10% Na$_2$S$_2$O$_3$. The aqueous layer was extracted thrice with DCM (10 mL portions). The organic fractions were dried over anhydrous MgSO$_4$ and concentrated under reduced pressure. The products were separated and purified by column chromatography on silica gel using hexane and ethyl acetate as solvent (5:1).

**α-Anomer (103a)**

Yield: 0.06 g, 24% clear oil.

$^1$H NMR: (CDCl$_3$ 400 MHz): $\delta$H 7.40 – 7.17 (m, 15H, Ar), 5.22 (d, 1H, $J = 3.3$ Hz, H-1), 4.94 (d, 1H, $J = 11.4$ Hz, –CH$_2$Ph), 4.81 (d, 1H, $J = 10.8$ Hz, –CH$_2$Ph), 4.63 (d, 1H, $J = 11.1$ Hz, –CH$_2$Ph), 4.56 (d, 1H, $J = 10.8$ Hz, –CH$_2$Ph), 4.54 (d, 1H, $J = 12.2$ Hz, –CH$_2$Ph), 4.52 (d, 1H, $J = 12.2$ Hz, –CH$_2$Ph), 3.93 (ddd, 1H, $J = 1.8$ Hz, 3.3 Hz and 9.3 Hz, H-5), 3.83 (dd, 1H, $J = 3.6$ Hz and 10.2 Hz, H-6$_a$), 3.74 – 3.63 (m, H-1’, 4H, H-3, H-4, H-6$_b$), 3.52 (dd, 1H, $J = 3.3$ Hz and 9.3 Hz, H-7$_a$), 3.06 (dd, 1H, $J = 9.3$ Hz and 11.4 Hz, H-7$_b$), 2.19 (tt, 1H, $J = 3.3$ Hz and 11.1 Hz, H-2), 1.97 – 1.25 (m, 10H, cyclohexyl).
$^{13}$C NMR: (100 MHz): $\delta_c$ 138.1, 138.0, 128.4, 128.3, 127.8, 127.7, 127.6 (Ar), 97.9 (C-1), 81.3 (C-3), 79.2 (C-4), 75.3 (C-1'), 75.2 (C-5), 74.8, 73.5, 71.1 (–CH$_2$Ph), 68.7 (C-6), 48.6 (C-2), 33.4, 31.7, 25.6, 24.0, 23.8, (cyclohexyl), 3.3 (C-7).

IR: 1454.5, 1095.3, 1039.5, 730.6, 695.6 cm$^{-1}$ (neat).

$[\alpha]_D$: +84.9 (c 1.0, CHCl$_3$).

β-Anomer (103b)

Yield: 0.11 g, 48% white solid.

Mp: 96 – 98 °C.

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta_h$ 7.40 – 7.20 (m, 15H, Ar), 4.96 (d, 1H, $J = 10.8$ Hz, CH$_2$Ph), 4.83 (d, 1H, $J = 10.8$ Hz, 10.9 Hz, –CH$_2$Ph), 4.78 (d, 1H, $J = 10.8$ Hz, –CH$_2$Ph), 4.68 – 4.51 (m, 3H, –CH$_2$Ph), 4.43 (d, 1H, $J = 8.0$ Hz, H-1), 3.80 – 3.42 (m, 8H, H-1’, H-3, H-4, H-5, H-6a, H-6b, H-7a, H-7b), 2.10 – 1.78 (m, 2H, H-2, cyclohexyl), 1.80 – 1.66 (m, 2H, cyclohexyl), 1.58 – 1.12 (cyclohexyl).

$^{13}$C NMR: (100 MHz): $\delta_c$ 138.5, 138.4, 138.1, 128.5, 128.3, 127.9, 127.8, 127.7, 115.3 (Ar), 101.4 (C-1), 81.9 (C-3), 78.9 (C-4), 77.2 (C-1’), 75.4 (C-5), 75.0, 74.8, 73.4 (–CH$_2$Ph), 69.1 (C-6), 46.3 (C-2), 33.7, 33.2, 25.6, 24.1, 24.0, (cyclohexyl), 7.5 (C-7).

IR: 1620.6, 1249.7, 1030.3, 809.8 cm$^{-1}$ (neat).

$[\alpha]_D$: +15.7 (c 0.1, CHCl$_3$).
**Cyclohexyl-3,4,6-tri-O-benzyl-2-deoxy-2-C-phenylthiomethyl-β-D-glucopyranoside**

(106)

Thiophenol (0.13 g, 1.14 mmol) was added to a solution of THF:DMSO (4:1) (5 mL) under anhydrous conditions followed by NaH (60% dispersion, 0.05 g, 1.14 mmol) and the reaction left to stir until cessation of bubble formation (~ 5 min). Iodomethyl glycoside 103b (0.65 g, 1.02 mmol) was added and the reaction was left to continue stirring under anhydrous conditions for a further 15 min upon which the reaction showed completion on TLC. Methanol (~2 mL) was added until the solution became clear and the solvents were removed under reduced pressure. The residue product was then purified by column chromatography on silica gel using hexane and ethyl acetate (5:1) as eluent.

Yield: 0.63 g, 96% white solid.

Mp: 61 – 63 °C.

**¹H NMR:** (CDCl₃ 400 MHz): δₜ 7.40 – 7.10 (m, 20H, Ar), 4.89 (d, 1H, J = 11.2 Hz, −CH₂Ph), 4.80 (d, 1H, J = 10.8 Hz, −CH₂Ph), 4.65 – 4.51 (m, 5H, H-1, −CH₂Ph), 3.88 (dd, J = 8.6 Hz and 10.6 Hz, 1H, H-3), 3.77 (dd, J = 2.0 Hz and 10.8 Hz, 1H, H-6ₐ), 3.71 (dd, J = 4.8 Hz and 10.8 Hz, 1H, H-6ₐ), 3.65 – 3.43 (m, 3H, H-1',H-4, H-5), 3.36 (d, J = 3.6 Hz, 2H, H-7ₐ, H-7ₐ), 2.20 – 2.08 (m, 1H, H-2), 2.00 – 1.90 (m, 1H, cyclohexyl), 1.84 – 1.08 (m, 9H, cyclohexyl).

**¹³C NMR:** (100 MHz): δₜ 138.5, 138.4, 138.1, 137.5, 129.5, 128.9, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 127.5, 126.0 (Ar), 99.6 (C-1), 80.6 (C-3), 80.1 (C-4), 77.5
(C-1’), 75.1 (C-5), 74.9, 74.7, 73.4 (–CH$_2$Ph), 69.2 (C-6), 47.6 (C-2), 33.7 (cyclohexyl), 31.8 (C-7, cyclohexyl), 25.6, 24.2, 24.0 (cyclohexyl).

**Para-methoxybenzyl chloride (111)**

![Para-methoxybenzyl chloride](image)

Thionyl chloride (0.56 g, 4.71 mmol) was added in a dropwise manner over a period of 10 min to a solution of para-methoxybenzyl alcohol (0.50 g, 3.62 mmol), in dry DMF (15 mL) cooled on ice. The reaction was stirred on ice under nitrogen atmosphere for 1 h and removed from the ice bath. The reaction was further stirred for 0.5 h at room temperature. TLC plate indicated reaction completion and the reaction was transferred to a separating funnel and extracted thrice with diethyl ether (10 mL portions). The combined diethyl ether extracts were then washed twice with ice-cold water (10 mL portions) and once with brine (10 mL). The organic layer was dried over anhydrous MgSO$_4$ and the filtrate was removed under reduced pressure to yield the residue product as a pale yellow oil that was used without further purification.

**D-Glucal (1.5-anhydro-2-deoxy-D-arabino-hex-enitol) (112)**

3,4,6-Tri-O-acetylated glucal (0.90 g, 3.31 mmol) was weighed into a 100 mL round-bottom flask and 10 mL methanol was added. A saturated solution of KOH in methanol (~0.5 mL) was slowly added until the glucal was completely dissolved. The reaction was stirred for 10 min at room temperature for complete glucal deacetylation. The solvent was removed under reduced pressure and the golden product was used without further purification.
D-glucal 112 (0.84 g, 5.75 mmol) was dissolved in dry DMF (15 mL) under nitrogen atmosphere. The reaction was then cooled to 0 °C and NaH (60% dispersion, 0.26 g, 6.44 mmol) was added to the reaction in small portions. The mixture was allowed to stir for 20 min before TBAI (0.21 g, 0.57 mmol) and PMBCl (3.15 g, 20.12 mmol) were successfully added. The reaction was stirred for 30 min on ice and allowed to stir at room temperature for 12 h. The reaction was diluted by adding water (25 mL) and the aqueous layer was extracted with ether (4 x 20 mL portions). The organic solvent was washed with water (3 x 15 mL portions) and once with brine (15 mL). The organic layer was then dried over anhydrous MgSO₄ and the solvent removed under reduced pressure. The residue product was purified by column chromatography on silica gel using hexane and ethyl acetate (8:2) as solvent.

**Yield:** 2.45 g, 84% colourless oil.

**¹H NMR:** (CDCl₃ 400 MHz): δ_H 7.24 (d, 4H, J = 8.0 Hz, Ar), 7.12 (d, 2H, J = 8.4 Hz, Ar), 6.91 – 6.78 (m, 6H, Ar), 6.41 (d, 1H, J = 6.0 Hz, H-1), 4.85 (bd, 1H, J = 6.0 Hz, H-2), 4.74 (d, 1H, J = 10.8 Hz, –CH₂Ph), 4.65 – 4.40 (m, 5H, –CH₂Ph), 4.14 (bd, 1H, J = 5.6 Hz, H-3), 4.04 – 3.95 (m, 1H, H-5), 3.82 – 3.65 (m, 12H, H-6a, H-6b, H-4, 3 x –OCH₃).

**¹³C NMR:** (100 MHz): δ_C 159.2, 159.1 (x2) (–COCH₃), 144.48 (C-1), 130.4, 130.2, 130.0, 129.4, 129.2, 128.5, 113.8, 113.7, 113.6 (Ar), 100.0 (C-2), 76.7 (C-5), 75.4 (C-3), 74.0 (C-4), 73.2, 73.0, 70.1 (–CH₂Ph), 68.1 (C-6), 55.1 (x3) (–OCH₃). (Spectroscopic data found to be in agreement with the reported data).²¹²
Para-methoxybenzyl-D-glucal 113 (0.55 g, 0.93 mmol) was dissolved in chloroform (15 mL) and BTEAC (0.04 g, 0.19 mmol) was added to the reaction flask and the mixture was stirred before 50% aqueous NaOH (1.12 g, 28.00 mmol) was added. The reaction was stirred at 35 °C for 6 h and showed completion on TLC. The reaction was diluted by adding water (15 mL) and extracted thrice with DCM (15 mL portions). The combined organic extracts were dried over anhydrous MgSO₄ and filtered. The organic solvent was removed under reduced pressure and residue product was purified by column chromatography on silica gel using hexane and ethyl acetate (8:2) as solvent.

Yield: 0.38 g, 69% white solid.

Mp: 51 – 53 °C.

¹H NMR: (CDCl₃ 400 MHz): δH 7.32 (d, 2H, J = 8.0 Hz, Ar), 7.21 (d, 2H, J = 8.4 Hz, Ar), 7.11 (d, 2H, J = 8.0 Hz, Ar), 6.92 – 6.74 (m, 6H, Ar), 4.77 (d, 1H, J = 10.8 Hz, –CH₂Ph), 4.70 (d, 1H, J = 11.2 Hz, –CH₂Ph), 4.60 (d, 1H, J = 11.2 Hz, –CH₂Ph), 4.40 (m, 2H, –CH₂Ph), 4.35 (d, 1H, J = 11.6 Hz, –CH₂Ph), 3.84 (d, 1H, J = 8.0 Hz, H-1), 3.75 – 3.60 (m, 12H, H-3, H-4, H-5, 3 x –OCH₃), 3.52 – 3.42 (m, 2H, H-6a, H-6b), 1.73 (dd, 1H, J = 4.2 Hz and 7.8 Hz, H-2).

¹³C NMR: (CDCl₃ 100 MHz): δC 159.3, 159.2, (–COCH₃), 130.3 130.0, 129.8, 129.7, 129.5, 129.2, 113.8, 113.7, 113.6 (3 x Ar), 79.8 (C-3), 77.2 (C-4), 74.7 (C-5), 74.0, 72.8, 71.4, (–CH₂Ph), 69.7 (C-6), 61.5 (C-1), 58.8 (C-7), 55.2 (x3) (–OCH₃), 34.2 (C-2).
IR: 1613.8, 1513.6, 1245.0, 1081.1, 814.6 cm\(^{-1}\) (neat).

\([\alpha]_D\): +24.5 (c 0.1, CHCl\(_3\)).

HRMS (ESI): \(m/z\) [M+Na\(^+\)] Calcd: 611.1574; Found: 611.1579.

3,4,6-tri-O-para-methoxybenzyl-1,5-anhydro-2-deoxy-1,2-C-methylene-D-glycero-D-
gulo-hexitol (115)

Lithium aluminium hydride (0.12 g, 3.17 mmol) was added to dry THF under anhydrous conditions and vigorously stirred before dichloro 114 (0.15 g, 0.29 mmol) was added. Stirring was continued under anhydrous conditions for two days upon which the reaction showed completion on TLC. The reaction mixture was then cooled on ice and quenched by slow addition of 10% aqueous Na\(_2\)SO\(_4\) \(\cdot\) 10H\(_2\)O. The formed precipitates were washed several times with boiling EtOAc and the organic fractions were dried over MgSO\(_4\). The organic solvent was removed under reduced pressure and pure product obtained by column chromatography on silica gel using hexane and ethyl acetate (5:1).

Yield: 0.10 g, 65% colourless syrup.

\(^1\)H NMR: (CDCl\(_3\) 400 MHz): \(\delta\) \(H\) 7.30 (d, 2H, \(J = 8.4\) Hz, \(Ar\)), 7.25 (d, 2H, \(J = 8.0\) Hz, \(Ar\)), 7.15 (d, 2H, \(J = 8.4\) Hz, \(Ar\)), 6.92 – 6.88 (m, 6H, \(Ar\)), 4.73 – 4.65 (m, 2H, –CH\(_2\)Ph), 4.65 – 3.90 (m, 4H, –CH\(_2\)Ph), 3.82 – 3.77 (m, 9H, 3 x –OCH\(_3\)), 3.75 – 3.68 (m, 1H, H-3), 3.66 – 3.42 (m, 5H, H-1, H-4, H-5, H-6\(_a\), H-6\(_b\)), 0.98 – 0.88 (m, 1H, H-2), 0.77 – 0.65 (m, 2H, H-7\(_a\), H-7\(_b\)).
\(^{13}\)C NMR: (CDCl\(_3\) 100 MHz): \(\delta_{C} 159.1\) (x3) (–COCH\(_3\)), 130.6, 130.5, 130.3, 129.4, 129.2, 129.1, 113.7, 113.7, 113.6 (Ar), 79.7 (C-3), 76.5 (C-4), 73.0 (C-5), 72.8, 70.7 (–CH\(_2\)Ph), 69.6 (C-6), 55.2 (x3) (–OCH\(_3\)), 49.6 (C-1), 14.7 (C-2), 11.2 (C-7).

IR: 1611.4, 1511.5, 1244.9, 1023.3, 816.6 cm\(^{-1}\) (neat).

\([\alpha]_D\): +21.5 (c 0.1, CHCl\(_3\)).

HRMS (ESI): \(m/z [M+Na]^+\) Calcd: 543.2353; Found: 543.2351.

\textit{Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-iodomethyl-\(\alpha\)- and -\(\beta\)-D-glucopyranoside (116a and 116b)}

Cyclopropanated sugar 115 (0.80 g, 1.54 mmol) was dissolved in chloroform (10 mL) under anhydrous conditions and cyclohexanol (1.25 mL) was added followed by NIS (0.52 g, 2.30 mmol) and stirred at room temperature. The reaction showed completion after 3 h and was quenched by adding 10 mL solution of 10% Na\(_2\)S\(_2\)O\(_3\), the aqueous layer was extracted with DCM (3 x 10 mL portions). The organic fractions were dried over anhydrous MgSO\(_4\) and concentrated under reduced pressure. The products were purified and separated by column chromatography on silica gel using hexane and ethyl acetate as solvent (5:1).

\(\alpha\)-Anomer (116a)

Yield: 0.24 g, 21% colourless syrup.
$^1$H NMR: (CDCl$_3$ 400 MHz): δ$_H$ 7.30 – 7.18 (m, 4H, Ar), 7.02 (d, 2H, J = 8.4 Hz, Ar), 6.90 – 6.70 (m, 6H, Ar), 5.14 (bs, 1H, H-1), 4.82 (d, 1H, J = 10.4 Hz, –CH$_2$Ph), 4.74 – 4.59 (m, 2H, –CH$_2$Ph), 4.50 (d, 1H, J = 10.8 Hz, –CH$_2$Ph), 4.48 – 4.35 (m, 2H, –CH$_2$Ph), 3.90 – 3.68 (m, 11H, H- 5, H-6, 3 x –OCH$_3$), 3.65 – 3.50 (m, 4H, H-1', H-3, H-4, H6b), 3.43 (bd, 1H, J = 7.2 Hz, H-7a), 3.10 – 2.92 (m, 1H, H-7b), 2.15 – 2.06 (m, 1H, H-2), 1.95 – 1.15 (m, 10H, cyclohexyl).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): δ$_C$ 159.3 (x2), 159.2 (–COCH$_3$), 130.4, 130.3, 130.1, 129.6, 129.5, 129.4, 113.9, 113.8 (Ar), 98.0 (C-1), 81.0 (C-3), 78.9 (C-4), 75.1 (C-1'), 75.0 (C-5), 74.5, 73.1 (–CH$_2$Ph) 71.0 (C-5), 68.1 (C-6), 55.3 (x2), 55.2 (–OCH$_3$), 48.6 (C-2), 33.4, 31.7, 25.6, 24.0, 23.8 (cyclohexyl).

IR: 1613.7, 1514.0, 1245.4, 1028.9, 810.4 cm$^{-1}$ (neat).

[α]$_D$: +38.0 (c 0.1, CHCl$_3$).

β-Anomer (116b)

Yield: 0.55 g, 48% white solid.

Mp: 90 – 92 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): δ$_H$ 7.32 – 7.18 (m, 4H, Ar), 7.10 (d, 2H, J = 8.4 Hz, Ar), 6.92 – 6.85 (m, 6H), 4.89 (d, 1H, J = 10.4 Hz, –CH$_2$Ph), 4.78 – 4.66 (m, 2H, –CH$_2$Ph), 4.56 (d, 1H, J = 11.6 Hz, –CH$_2$Ph), 4.48 (d, 2H, J = 11.2 Hz, –CH$_2$Ph), 4.40 (d, 1H, J = 8.0 Hz, H-1), 3.82 – 3.70 (m, 9H, 3 x –OCH$_3$), 3.68 – 3.59 (m, 5H, H-1', H-3, H-4, H-6a, H-6b), 3.54 (dd, 1H, J = 2.6 Hz and 9.8 Hz, H-7a), 3.48 (dd, 1H, J = 2.6 Hz and 9.8 Hz, H-7b), 2.00 – 1.88 (m, 2H, cyclohexyl), 1.80 – 1.68 (m, 2H, cyclohexyl), 1.58 – 1.10 (m, 7H, H-2, cyclohexyl).
$^{13}$C NMR: (CDCl$_3$ 100 MHz): δ C 159.3 (x3) (–COCH$_3$), 130.7, 130.4, 130.2, 129.5, 129.4, 113.9, 113.8, 113.7 (Ar), 101.3 (C-1), 81.6 (C-3), 79.5 (C-4), 77.3 (C-1’), 75.2 (C-5), 74.9, 74.4, 73.0 (–CH$_2$Ph), 68.6 (C-6), 55.3, 55.2 (–OCH$_3$), 46.3 (C-2), 33.7, 32.2, 25.6, 24.1, 24.0 (cyclohexyl), 7.7 (C-7).

IR: 1611.6, 1514.3, 1245.8, 1030.3, 809.5 cm$^{-1}$ (neat).

[α]$_D$: +2.5 (c 0.1, CHCl$_3$).

**General procedure for the thiolation of the iodomethyl glycosides**

Thiophenol (53.56 µL, 0.52 mmol) was added to a solution of THF:DMSO (4:1) (5 mL) under anhydrous conditions and NaH (60% dispersion, 0.02 g, 0.52 mmol) was added and the reaction left to stir until cessation of bubble formation (~ 5 min). Iodomethyl glycoside 116b (0.35 g, 0.47 mmol) was then added and the reaction was left to continue stirring under anhydrous conditions for a further 15 min upon which the reaction showed completion. Methanol (~2 mL) was added in a dropwise fashion until the solution became clear and the solvents were removed under reduced pressure. The residue was purified by column chromatography using hexane and ethyl acetate (5:1) as eluent.

*Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-phenylthiomethyl-α-D-glucopyranoside (123)*
Yield: 0.33 g, 95% white solid.
Mp: 63 – 65 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): $\delta_H$ 7.32 – 7.09 (m, 9H, Ar), 7.12 (d, 2H, $J = 6.8$ Hz, Ar), 6.90 – 6.71 (m, 6H, Ar), 5.21 (d, 1H, $J = 3.2$ Hz, H-1), 4.86 (d, 1H, $J = 10.8$ Hz, $-CH_2$Ph), 4.68 (d, 1H, $J = 10.4$ Hz, $-CH_2$Ph), 4.62 – 4.54 (m, 2H, $-CH_2$Ph), 4.93 – 4.84 (m, 2H, $-CH_2$Ph), 3.89 – 3.50 (m, 15H, $\text{H-1}''$, H-3, H-4, H-5, H-6a, H-6b, 3 x $-OCH_2$), 3.38 (bd, 1H, $J = 7.2$ Hz, H-7a), 2.82 – 2.79 (m, 1H, H-7b), 2.10 – 2.00 (m, 1H, H-2), 1.79 – 1.60 (m, 4H, cyclohexyl), 1.52 – 1.11 (m, 6H cyclohexyl).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): $\delta_C$ 159.2 (x3) ($-OCH_3$), 136.5, 130.7, 130.4, 130.0, 129.6, 129.4, 129.3, 128.8, 128.2, 125.4, 113.8, 113.7 (Ar), 96.2 (C-1), 80.6 (C-3), 79.5 (C-4), 75.0 (C-1''), 74.9, 74.4, 73.0 ($-CH_2$Ph), 70.8 (C-5), 68.2 (C-6), 55.2 (x2), 55.1 ($-OCH_3$), 45.4 (C-2), 33.3 (cyclohexyl), 31.4 (C-7), 30.6, 25.6, 23.9, 23.7 (cyclohexyl).

IR: 1514.0, 1246.0, 1032.6, 813.8, 690.8 cm$^{-1}$ (neat).

$\lbrack\alpha\rbrack_D$: -13.5 (c 0.1, CHCl$_3$).

Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-phenylthiomethyl-β-D-glucopyranoside (117)
Yield: 0.34 g, 87% white solid.

Mp: 53 – 55 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): $\delta_H$ 7.34 (d, 2H, $J = 8.0$ Hz, Ar), 7.30 – 7.20 (m, 4H, Ar), 7.18 – 7.10 (m, 5H, Ar), 6.90 – 6.72 (m, 6H, Ar), 4.83 (d, 1H, $J = 10.4$ Hz, $-$CH$_2$Ph), 4.72 (d, 1H, $J = 10.4$ Hz, $-$CH$_2$Ph), 4.60 – 4.45 (m, 5H, H-1, $-$CH$_2$Ph), 3.88 – 3.69 (m, 12H, H-3, H-6$_a$, H-6$_b$, 3 x $-$OCH$_3$), 3.58 – 3.49 (m, 3H, H-1', H-4, H-5), 3.32 (d, 2H, $J = 3.2$ Hz, H-7$_a$, H-7$_b$), 2.11 – 2.04 (m, 1H, H-2), 2.00 – 1.90 (m, 1H, cyclohexyl), 1.84 – 1.60 (m, 3H, cyclohexyl), 1.52 – 1.10 (m, 6H, cyclohexyl).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): $\delta_C$ 159.2, 159.1 (x2) ($-$COCH$_3$), 137.6, 130.7, 130.4, 130.3, 129.5, 129.4, 128.9, 125.8, 113.8, 113.8, 113.7 (Ar), 99.6 (C-1), 80.4 (C-3), 79.8 (C-4), 77.3 (C-1'), 74.9 (C-5), 74.8, 74.3, 73.0 ($-$CH$_2$Ph), 68.8 (C-6), 55.2 (x3) ($-$OCH$_3$), 47.5 (C-2), 33.7, 31.8 (cyclohexyl), 31.7 (C-7), 25.6, 24.1, 24.0 (cyclohexyl).

IR: 1614.0, 1514.0, 1246.6, 1034.7, 816.2, 744.1 cm$^{-1}$ (neat).

$[\alpha]_D$: +1.5 (c 0.1, CHCl$_3$).

*Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-para-chlorophenylthiomethyl-β-D-glucopyranoside (124)*
Yield: 0.34 g, 95% white solid.

Mp: 78 – 80 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): δ$_H$ 7.30 – 7.15 (m, 6H, Ar), 7.12 (t, 4H, J = 8.4 Hz, Ar), 6.88 – 6.72 (m, 6H, Ar), 4.84 (d, 1H, J = 10.4 Hz, –CH$_2$Ph), 4.70 (d, 1H, J = 10.4 Hz, –CH$_2$Ph), 4.60 – 4.48 (m, 5H, H-1, –CH$_2$Ph), 3.82 – 3.60 (m, 12H, H-3, H-6$_a$, H-6$_b$, 3 x –OCH$_3$), 3.58 – 3.32 (m, 3H, H-1', H-4, H-5), 3.24 (d, 2H, J = 2.8 Hz, H-7$_a$, H-7$_b$), 2.10 – 2.01 (m, 1H, H-2), 1.97 – 1.86 (m, 1H, cyclohexyl), 1.79 – 1.60 (m, 3H, cyclohexyl), 1.52 – 1.08 (m, 6H, cyclohexyl).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): δ$_C$ 159.3, 159.2 (x2) (–COCH$_3$), 136.3, 131.7, 130.6, 130.4, 130.3, 129.5, 129.4, 129.3, 128.9, 113.9, 113.8, 113.7 (Ar), 99.6 (C-1), 80.5 (C-3), 79.8 (C-4), 77.3 (C-1') 75.0 (C-5), 74.8, 74.3, 73.1 (–CH$_2$Ph), 68.8 (C-6), 55.2 (x3) (–OCH$_3$), 47.5 (C-2), 33.7, 31.9 (cyclohexyl), 31.8 (C-7), 25.6, 24.1, 24.0 (cyclohexyl).

IR: 1610.4, 1511.0, 1248.4, 1034.8, 814.7 cm$^{-1}$ (neat).

$[\alpha]_D$: +4.5 (c 0.1, CHCl$_3$).

_Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-para-bromophenylthiomethyl-β-D-glucopyranoside (125)_

Yield: 0.28 g, 74% white solid.
Mp: 70 – 72 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): $\delta_H$ 7.34 (d, 2H, $J = 7.6$ Hz, Ar), 7.27 (d, 2H, $J = 9.2$ Hz, Ar), 7.19 – 7.05 (m, 6H, Ar), 6.90 – 6.70 (m, 6H, Ar), 4.84 (d, 1H, $J = 10.4$ Hz, –CH$_2$Ph), 4.71 (d, 1H, $J = 10.4$ Hz, –CH$_2$Ph), 4.62 – 4.45 (m, 5H, H-1, –CH$_2$Ph), 3.83 – 3.60 (m, 12H, H-3, H-6$_a$, H-6$_b$, 3 x –OCH$_3$), 3.58 – 3.34 (m, 3H, H-1’, H-4, H-5), 3.24 (bs, 2H, H-7$_a$, H-7$_b$), 2.22 – 2.00 (m, 1H, H-2), 1.98 – 1.87 (m, 1H, cyclohexyl), 1.82 – 1.60 (m, 4H, cyclohexyl), 1.55 – 1.10 (m, 5H, cyclohexyl).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): $\delta_C$ 159.3, 159.2, 159.1 (–OCCH$_3$), 137.0, 131.8, 130.6, 130.4, 130.2, 129.5, 129.4, 119.5, 113.8, 113.7 (Ar), 99.5 (C-1), 80.5 (C-3), 79.8 (C-4), 77.3 (C-1’), 74.9 (C-5), 74.8, 74.3, 73.0 (–CH$_2$Ph), 68.7 (C-6), 55.2 (x3) (–OCH$_3$), 47.4 (C-2), 33.6, 31.8 (cyclohexyl), 31.7 (C-7), 25.6, 24.1, 24.0 (cyclohexyl).

IR: 1612.0, 1513.7, 1245.8, 1034.8, 810.2 cm$^{-1}$ (neat).

$\alpha$D: -3.0 (c 0.1, CHCl$_3$).

*Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-para-methylphenylthiomethyl-α-D-glucopyranoside (126)*

Yield: 0.25 g, 71% white solid.
Mp: 109 – 111 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): $\delta_H$ 7.26 (dd, 4H, $J = 2.8$ Hz and $8.6$ Hz, Ar), 7.19 (d, 2H, $J = 8.0$ Hz, Ar), 7.10 – 7.00 (m, 4H, Ar), 6.91 – 6.73 (m, 6H, Ar), 5.23 (d, 1H, $J = 3.2$ Hz, H-1), 4.84 (d, 1H, $J = 10.8$ Hz, $-\text{CH}_2\text{Ph}$), 4.68 (d, 1H, $J = 10.4$ Hz, $-\text{CH}_2\text{Ph}$), 4.63 – 4.54 (m, 2H, $-\text{CH}_2\text{Ph}$), 3.92 – 3.84 (m, 2H, $-\text{CH}_2\text{Ph}$), 3.88 – 3.50 (m, 15H, H-1', H-3, H-4, H-5, H-6$_a$, H-6$_b$, 3 x $-\text{OCH}_3$), 3.33 (dd, 1H, $J = 2.8$ Hz and 13.2 Hz, H-7$_a$), 2.80 – 2.68 (m, 1H, H-7$_b$), 2.30 (s, 3H, $-\text{CH}_3$), 2.08 – 2.00 (m, 1H, H-2), 1.88 – 1.78 (m, 2H, cyclohexyl), 1.74 – 1.63 (m, 2H, cyclohexyl), 1.53 – 1.18 (m, 6H, cyclohexyl).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): $\delta_C$ 159.2 (x3) ($-\text{COCH}_3$), 135.6, 132.7, 130.8, 130.4, 130.1, 129.6, 129.4, 129.3, 129.2, 113.8, 113.7 (Ar), 96.3 (C-1), 80.6 (C-3), 79.5 (C-4), 75.1 (C-1'), 74.8, 74.4, 73.0 ($-\text{CH}_2\text{Ph}$), 70.8 (C-5), 68.3 (C-6), 55.2 (x2), 55.1 ($-\text{OCH}_3$), 45.5 (C-2), 33.4, 31.5 (cyclohexyl), 31.4 (C-7), 25.7, 24.0, 23.7 (cyclohexyl), 20.9 ($-\text{CH}_3$).

IR: 1614.6, 1514.7, 1247.0, 1120.1, 1034.7, 812.4, 773.3 cm$^{-1}$ (neat).

$[\alpha]_D$: +9.5 (c 0.1, CHCl$_3$).

**Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-para-methylphenylthiomethyl-\(\beta\)-D-glucopyranoside (127)**
Yield: 0.31 g, 90% white solid.

Mp: 87 – 89 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): $\delta_h$ 7.30 – 7.20 (m, 4H, Ar), 7.15 – 7.02 (m, 6H, Ar), 6.88 – 6.75 (m, 6H, Ar), 4.82 (d, 1H, $J = 10.4$ Hz, $-CH_2$Ph), 4.71 (d, 1H, $J = 10.4$ Hz, $-CH_2$Ph), 4.62 – 4.48 (m, 5H, H-1, $-CH_2$Ph), 3.90 – 3.62 (m, 10H, H-3, 3 x $OCH_3$), 3.70 (dd, 1H, $J = 1.6$ Hz and 10.4 Hz, H-6a), 3.63 (dd, 1H, $J = 4.8$ Hz and 10.4 Hz, H-6b), 3.56 – 3.38 (m, 3H, H-1', H-4, H-5), 3.29 (d, 2H, $J = 3.2$ Hz, H-7a, H-7b), 2.29 (s, 3H, $-CCH_3$), 2.10 – 1.90 (m, 2H, H-2, cyclohexyl), 1.80 – 1.60 (m, 3H, cyclohexyl), 1.52 – 1.10 (m, 6H, cyclohexyl).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): $\delta_c$ 159.3, 159.2 ($-COCH_3$), 136.0, 134.0, 130.8, 130.5, 130.4, 130.2, 129.7, 129.5, 129.4, 113.8, 113.7 (Ar), 99.7 (C-1), 80.4 (C-3), 79.9 (C-4), 77.5 (C-1'), 74.9 (C-5), 74.8, 74.3, 73.0 ($-CH_2$Ph), 68.9 (C-6), 55.2 (x2) ($-OCH_3$), 47.7 (C-2), 33.7, 32.5 (cyclohexyl), 31.9 (C-7), 25.6, 24.2, 24.1 (cyclohexyl), 21.0 ($-CCH_3$).

IR: 1614.3, 1512.6, 1246.0, 1034.9, 813.8, 755.5 cm$^{-1}$ (neat).

$[\alpha]_D$: +0.5 (c 0.1, CHCl$_3$).

*Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-para-tert-butylphenylthiomethyl-β-D-glucopyranoside (128)*
Yield: 0.32 g, 86% white solid.

Mp: 59 – 61 °C.

\(^1\)H NMR: (CDCl\(_3\) 400 MHz): \(\delta\) \(H\) 7.34 – 7.16 (m, 6H, Ar), 7.13 – 7.08 (m, 4H, Ar), 6.90 – 6.72 (m, 6H), 4.81 (d, 1H, \(J = 10.4\) Hz –CH\(_2\)Ph), 4.71 (d, 1H, \(J = 10.4\) Hz, –CH\(_2\)Ph), 4.62 – 4.42 (m, 5H, H-1, –CH\(_2\)Ph), 3.90 – 3.25 (m, 15H, H-1', H-3, H-4, H-5, H-6\(_a\), H-6\(_b\), 3 x –OCH\(_3\)), 3.40 – 3.25 (m, 2H, H-7\(_a\), H-7\(_b\)), 2.10 – 2.00 (m, 1H, H-2), 1.98 – 1.88 (m, 1H, cyclohexyl), 1.80 – 1.58 (m, 3H, cyclohexyl), 1.50 – 1.60 (m, 15H, –C(CH\(_3\))\(_3\), cyclohexyl).

\(^{13}\)C NMR: (CDCl\(_3\) 100 MHz): \(\delta\) \(C\) 159.3, 159.1 (–COCH\(_3\)), 149.3, 134.0, 130.8, 130.5, 130.4, 130.2, 129.8, 129.6, 129.5, 129.4, 129.3, 125.9, 113.9, 113.8, 113.7 (Ar), 99.6 (C-1), 80.3 (C-3), 79.9 (C-4), 77.3 (C-1'), 74.9 (C-5), 74.7, 74.3, 73.0 (–CH\(_2\)Ph), 68.9 (C-6), 55.3, 55.2 (–OCH\(_3\)), 47.7 (C-2), 34.4 (–O(CH\(_3\))\(_3\)), 33.7, 32.2 (cyclohexyl), 31.8 (C-7), 31.3 (–C(CH\(_3\))\(_3\)), 25.6, 24.2, 24.1 (cyclohexyl).

IR: 1612.7, 1513.6, 1245.8, 1034.4, 819.7, 755.2 cm\(^{-1}\) (neat).

\([\alpha]_D\): -5.0 (c 0.1, CHCl\(_3\)).

_Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-2-napthalenethiomethyl-β-D-glucopyranoside (129)_
Yield: 0.19 g, 53% white solid.

Mp: 85 – 87 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): $\delta_{H}$ 7.83 – 7.15 (m, 4H, Ar), 7.50 – 7.38 (m, 3H, Ar), 7.30 – 7.22 (m, 2H, Ar), 7.16 – 7.07 (m, 4H, Ar), 6.88 – 6.80 (m, 4H, Ar), 6.70 (d, 2H, $J = 8.4$ Hz, Ar), 4.85 (d, 1H, $J = 10.8$ Hz, $-\text{CH}_2\text{Ph}$), 4.73 (d, 1H, $J = 10.4$ Hz, $-\text{CH}_2\text{Ph}$), 4.63 – 4.47 (m, 5H, H-1, $-\text{CH}_2\text{Ph}$), 3.90 – 3.82 (m, 1H, H-3), 3.78 (s, 6H, 2 x $-\text{OCH}_3$), 3.64 – 3.12 (m, 5H, H-6$_a$, H-6$_b$, $-\text{OCH}_3$), 3.50 – 3.38 (m, 4H, H-1', H-5, H-7$_a$, H-7$_b$), 2.20 – 2.10 (m, 1H, H-2), 1.98 – 1.89 (m, 1H, cyclohexyl), 1.78 – 1.62 (m, 2H, cyclohexyl), 1.60 – 1.50 (m, 1H, cyclohexyl), 1.46 – 1.30 (m, 2H, cyclohexyl), 1.25 – 1.00 (m, 4H, cyclohexyl).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): $\delta_{C}$ 159.3, 159.1 (x2) ($-\text{OCH}_3$), 135.2, 133.8, 131.7, 130.6, 130.4, 130.3, 129.5, 129.4, 128.3, 127.6, 127.0, 126.7, 126.5, 125.5, 113.8, 113.7 (Ar), 99.6 (C-1), 80.5 (C-3), 79.8 (C-4), 77.3 (C-1'), 74.9 (C-5), 74.8, 74.3, 73.0 ($-\text{CH}_2\text{Ph}$), 68.8 (C-6), 55.2 (x2), 55.1 ($-\text{OCH}_3$), 47.5 (C-2), 33.6, 31.8 (cyclohexyl), 31.5 (C-7), 25.5, 24.1, 23.9 (cyclohexyl).

IR: 1612.2, 1513.7, 1245.4, 1025.3, 813.1, 751.6 cm$^{-1}$ (neat).

$[\alpha]_D$: -15.0 (c 0.1, CHCl$_3$).

*Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-n-propylthiomethyl-β-D-glucopyranoside* (130)
Yield: 0.27 g, 82% white solid.

Mp: 56 – 58 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): $\delta_H$ 7.32 – 7.20 (m, 4H, Ar), 7.11 (d, 2H, J = 8.0 Hz, Ar), 6.90 – 6.75 (m, 6H, Ar), 4.86 (d, 1H, J = 10.8 Hz, –CH$_2$Ph), 4.71 (d, 2H, J = 10.4 Hz, –CH$_2$Ph), 4.60 – 4.45 (m, 4H, H-1, –CH$_2$Ph), 3.82 – 3.58 (m, 13H, H-1', H-3, H-6$_a$, H-6$_b$, 3 x –OCH$_3$), 3.55 – 3.47 (m, 1H, H-4), 3.42 – 3.35 (m, 1H, H-5), 2.94 (bd, 1H, J = 9.6 Hz, H-7$_a$), 2.82 (bd, 1H, J = 9.6 Hz, H-7$_b$), 2.45 (t, 2H, J = 7.2 Hz, H-8$_a$, H-8$_b$), 2.20 – 1.98 (m, 3H, H-2, cyclohexyl), 1.80 – 1.68 (m, 2H, cyclohexyl), 1.64 – 1.13 (m, 8H, H-9$_a$, H-9$_b$, cyclohexyl), 0.96 (t, 3H, J = 7.4 Hz, –CH$_2$CH$_3$).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): $\delta_C$ 159.2, 159.1 (x2) (–OCH$_3$), 131.0, 130.4, 130.4, 129.5, 129.3, 113.8, 113.7 (Ar), 99.7 (C-1), 80.6 (C-3), 79.6 (C-4), 77.3 (C-1'), 74.8 (C-5), 74.7, 74.2, 73.0 (–CH$_2$Ph), 68.8 (C-6), 55.2 (x2) (–OCH$_3$), 47.4 (C-2), 35.8 (C-8), 33.7, 31.9 (cyclohexyl), 29.6 (C-7), 25.6, 24.2, 24.1 (cyclohexyl), 23.0 (C-9), 13.4 (C-10).

IR: 1614.5, 1513.3, 1246.6, 1035.0, 815.5 cm$^{-1}$ (neat).

[\alpha]_D: -7.5 (c 0.1, CHCl$_3$).
Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-isopropylthiomethyl-β-D-glucopyranoside (131)

Yield: 0.31 g, 91% white solid.

Mp: 58 – 60 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): $\delta_H$ 7.34 – 7.20 (m, 4H, Ar), 7.11 (d, 2H, $J = 8.0$ Hz, Ar), 6.90 – 6.76 (m, 6H, Ar), 4.85 (d, 1H, $J = 10.4$ Hz, $-CH_2$Ph), 4.79 – 4.68 (m, 2H, $-CH_2$Ph), 4.61 – 4.45 (m, 4H, H-1, $-CH_2$Ph), 3.85 – 3.58 (m, 13H, H-1’, H-3, H-6a, H-6b, 3 x $-OC_3H_3$), 3.50 (t, 1H, $J = 9.2$ Hz, H-4), 3.43 – 3.32 (m, 11H, H-5), 2.97 (bd, 1H, $J = 11.6$ Hz, H-7a), 2.89 – 2.71 (m, 2H, H-7b, H-8), 2.03 – 1.85 (m, 2H, H-2, cyclohexyl), 1.80 – 1.65 (m, 2H, cyclohexyl), 1.55 – 1.11 (m, 11H, $-CH(CH_3)_2$, cyclohexyl).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): $\delta_C$ 159.2, 159.1 (x2) ($-OC_3H_3$), 131.0, 130.4, 129.6, 129.4, 113.8, 113.7, 113.6 (Ar), 99.6 (C-1), 80.6 (C-3), 79.6 (C-4), 77.2 (C-1’), 74.8 (C-5), 74.7, 74.2, 73.0 ($-CH_2$Ph), 68.8 (C-6), 55.2 (x2) ($-OCH_3$), 47.2 (C-2), 36.5 (C-8), 33.7, 31.9 (cyclohexyl), 27.7 (C-7), 25.6, 24.2, 24.1 (cyclohexyl), 23.6, 23.5 ($-CH(CH_3)_2$).

IR: 1613.9, 1545.1, 1246.9, 1032.7, 819.3 cm$^{-1}$ (neat).

$[\alpha]_D$: -3.0 (c 0.1, CHCl$_3$).
General procedure for the oxidation of sulfides to their sulfone derivatives

Aluminium oxide (0.87 g, 8.53 mmol) was weighed into a round-bottom reaction flask and was wetted with H₂O (0.15 mL). The mixture was rotated on a rotary evaporator until it was free-flowing. Sulfide 117 (0.25 g, 0.34 mmol) dissolved in DCM was added to the reaction flask and the mixture was stirred vigorously. OXONE® (1.70 g, 2.77 mmol) was then added and the reaction was left to stir for 12 h upon which it showed completion on TLC. The solids were filtered over a pad of celite® and solvent removed under reduced pressure. The residue product was purified by column chromatography on silica gel using hexane and ethyl acetate (7:3) as eluent.

Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-phenylsulfonylmethyl-β-D-glucopyranoside (118)

Yield: 0.17 g, 65% white solid.

Melting point: 92 – 94 °C.

¹H NMR: (CDCl₃ 400 MHz): δₜ 7.83 (d, 2H, J = 7.6 Hz, Ar), 7.64 – 7.58 (m, 1H, Ar), 7.54 – 7.48 (m, 2H, Ar), 7.33 – 7.23 (m, 4H, Ar), 7.12 (d, 2H, J = 8.4 Hz, Ar), 6.90 – 6.77 (m, 6H, Ar), 4.96 – 4.90 (m, 2H, H-1, –CH₂Ph), 4.83 (d, 1H, J = 10.8 Hz, –CH₂Ph), 4.71 (d, 1H, J = 10.8 Hz, –CH₂Ph), 4.60 – 4.44 (m, 3H, –CH₂Ph), 4.08 (dd, 1H, J = 7.6 Hz and 11.2 Hz, H-3), 3.83 – 3.72 (m, 9H, 3 x –OCH₃), 3.71 – 3.59 (m, 3H, H-1’, H-6a, H-6b), 3.58 – 3.36 (m, 2H, H-4, H-5),
3.41 (dd, 1H, \( J = 4.0 \) Hz, and 14.0 Hz, H-7\(_a\)), 3.30 (dd, 1H, 4.0 Hz and 14.0 Hz, H-7\(_b\)), 2.20 – 2.10 (m, 1H, H-2), 1.99 – 1.83 (m, 2H, cyclohexyl), 1.75 – 1.63 (m, 2H, cyclohexyl), 1.60 – 1.45 (m, 2H, cyclohexyl), 1.40 – 1.10 (m, 4H, cyclohexyl).

\(^{13}\text{C} \text{NMR:}\) (CDCl\(_3\) 100 MHz): \(\delta\)\(_C\) 159.3, 159.2 (–OCC\(_3\)), 141.4, 133.4, 131.1, 130.4, 130.4, 130.3, 129.5, 129.2, 127.6, 113.8, 113.7 (Ar), 99.4 (C-1), 80.5 (C-4), 79.7 (C-3), 78.0 (C-1’), 74.8 (C-5), 74.1, 74.1, 73.0 (–CH\(_2\)Ph), 68.7 (C-6), 55.3, 55.2 (–OCH\(_3\)), 53.0 (C-7), 45.7 (C-2), 33.8, 32.0, 25.6, 24.3 (cyclohexyl).

\text{IR:} 1613.9, 1514.0, 1302.8, 1246.5, 1034.5, 819.3 cm\(^{-1}\) (neat).

\([\alpha]_D\): -11.0 (c 0.1, CHCl\(_3\)).

\textit{Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-phenylsulfonylmethyl-\(\alpha\)-D-glucopyranoside (132)}

\[
\begin{align*}
\text{PMBO} & \quad \text{OPMB} \\
\text{OMBO} & \quad \text{OPMB}
\end{align*}
\]

\text{Yield:} 0.19 g, 72% white solid.

\text{Mp:} 83 – 85 °C.

\(^1\text{H} \text{NMR:}\) (CDCl\(_3\) 400 MHz): \(\delta\)\(_H\) 7.80 (d, 2H, \( J = 8.0 \) Hz, Ar), 7.65 - 7.57 (m, 1H, Ar), 7.54 - 7.47 (m, 2H, Ar), 7.28 (d, 2H, \( J = 8.0 \) Hz, Ar), 7.11 (d, 2H, \( J = 8.0 \) Hz, Ar), 7.02 (d, 2H, \( J = 8.0 \) Hz, Ar), 6.92 – 6.71 (m, 6H, Ar), 5.37 (d, 1H, \( J = 2.8 \) Hz, H-1), 4.81 (d, 1H, \( J = 11.2 \) Hz, –CH\(_2\)Ph), 4.68 – 4.57 (m, 2H, –CH\(_2\)Ph), 4.46 –
4.34 (m, 3H, –CH₂Ph), 3.90 – 3.67 (m, 11H, H-3, H-6ₐ, 3 x –OCH₃), 3.65 – 3.46 (m, 4H, H-1', H-4, H-5, H-6ₜ), 3.22 (d, 2H, J = 6.0 Hz, H-7ₐ, H-7ₜ), 2.32 – 2.18 (m, 1H, H-2), 1.97 – 1.10 (m, 4H, cyclohexyl), 1.54 – 1.13 (m, 6H, cyclohexyl).

¹³C NMR: (CDCl₃ 100 MHz): δC 159.1 (x3) (–COCH₃), 139.4, 133.3, 130.1, 130.0, 129.8, 129.5, 129.3, 129.2, 129.0, 128.9, 127.6, 113.7, 113.6 (Ar), 95.8 (C-1), 79.2 (C-4), 78.4 (C-3), 75.6 (C-1'), 74.2 (C-5), 73.0, 70.5 (–CH₂Ph), 67.9 (C-6), 55.0 (x3) (–OCH₃), 53.1 (C-7), 41.3 (C-2), 33.2, 31.2, 25.5, 23.9, 23.7 (cyclohexyl).

IR: 1613.9, 1514.3, 1302.1, 1247.3, 1034.0, 815.1 cm⁻¹ (neat).

[α]D: +12.0 (c 0.1, CHCl₃).

Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-para-chlorophenylsulfonfylmethyl-β-D-glucopyranoside (133)

Yield: 0.18 g, 65% colourless solid.

Mp: 80 – 82 °C.

¹H NMR: (CDCl₃ 400 MHz): δH 7.74 (d, 2H, J = 8.4 Hz, Ar), 7.46 (d, 2H, J = 8.4 Hz, Ar), 7.32 – 7.22 (m, 4H, Ar), 7.13 (d, 2H, J = 8.4 Hz, Ar), 6.91 – 6.78 (m, 6H, Ar), 4.95 (d, 1H, J = 11.2 Hz, –CH₂Ph), 4.86 – 4.75 (m, 2H, H-1, –CH₂Ph), 4.72 (d,
$1H, J = 10.4 \text{ Hz}, \text{–}CH_2\text{Ph}$), $4.62 - 4.47 \text{ (m, 3H, –}CH_2\text{Ph)}$, $3.96 \text{ (dd, 1H, } J = 8.2 \text{ Hz and 11.0 Hz, H-3)}$, $3.83 - 3.74 \text{ (m, 9H, 3 x –OCH}_3\text{)}$, $3.72 - 3.42 \text{ (m, 5H, H-1'), H-4, H-5, H-6a, H-6b}$), $3.36 \text{ (dd, 1H, } J = 4.0 \text{ Hz and 14.0 Hz, H-7a)}$, $3.26 \text{ (dd, 1H, } J = 4.0 \text{ Hz and 14.0 Hz, H-7b)}$, $2.22 - 2.14 \text{ (m, 1H, H-2)}$, $2.00 - 1.82 \text{ (m, 2H, cyclohexyl), 1.78 - 1.64 (m, 2H, cyclohexyl), 1.58 - 1.45 (m, 1H, cyclohexyl), 1.45 - 1.08 (m, 5H, cyclohexyl)}$.

$^{13}C$ NMR: $\delta_c$ 159.2, 159.1 (x2) (–COCH$_3$), 140.0, 139.5, 130.8, 130.2, 130.1, 129.4, 129.3, 129.1, 113.7 (Ar), 99.3 (C-1), 80.2 (C-4), 79.8 (C-3), 77.6 (C-1’), 74.7 (C-5), 74.0, 72.9 (–CH$_3$Ph), 68.4 (C-6), 55.1 (x3) (–OCH$_3$), 53.2 (C-7), 45.2 (C-2), 33.6, 31.8, 25.5, 24.1 (x2) (cyclohexyl).

IR: 1614.1, 1514.3, 1309.7, 1247.2, 817.4, 764.2 cm$^{-1}$ (neat).

$[\alpha]_b$: -7.0 (c 0.1, CHCl$_3$).

*Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-para-bromophenylsulfonylmethyl-β-D-glucopyranoside (134)*

Yield: 0.16 g, 55% colourless solid.

Mp: 107 – 109 °C.

$^1H$ NMR: $\delta_H$ 7.70 – 7.58 (m, 4H, Ar), 7.25 (d, 4H, $J = 8.4$ Hz, Ar), 7.11 (d, 2H, $J = 8.0$ Hz, Ar), 6.91 – 6.74 (m, 6H, Ar), 4.93 (d, 1H, $J = 10.8$ Hz,
-CH₂Ph), 4.82 – 4.74 (m, 2H, H-1, -CH₂Ph), 4.70 (d, 1H, J = 10.4 Hz, -CH₂Ph), 4.60 – 4.45 (m, 3H, -CH₂Ph), 3.97 – 3.88 (m, 1H, H-3), 3.84 – 3.72 (m, 9H, 3 x -OCH₃), 3.70 – 3.40 (m, 5H, H-1', H-4, H-5, H-6a, H-6b), 3.33 (dd, 1H, J = 3.8 Hz and 14.0 Hz, H-7a), 3.22 (dd, 1H, J = 3.2 Hz and 14.0 Hz, H-7b), 2.18 – 2.10 (m, 1H, H-2), 1.96 – 1.78 (m, 2H, cyclohexyl), 1.74 – 1.46 (m, 4H, cyclohexyl), 1.32 – 1.08 (m, 4H, cyclohexyl).

¹³C NMR: (CDCl₃ 100 MHz): δC 159.3, 159.2 (x2) (C=OCH₃), 140.1, 132.4, 130.8, 130.3, 130.2, 129.5, 129.4, 129.3, 128.7, 113.9, 113.7 (Ar), 99.4 (C-1), 80.3 (C-4), 79.9 (C-3), 77.8 (C-1'), 74.8 (C-5), 74.1, 73.0 (C=CH₂Ph), 68.5 (C-6), 55.3 (x2), 55.2 (C=OCH₃), 53.3 (C-7), 45.3 (C-2), 33.8, 32.0, 25.6, 24.2 (x2) (cyclohexyl).

IR: 1614.2, 1512.8, 1304.8, 1246.1, 1035.1, 819.8, 754.1 cm⁻¹ (neat).

[α]D: -9.0 (c 0.1, CHCl₃).

Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-para-methylphenylsulfonylmethyl-α-D-glucopyranoside (135)

Yield: 0.18 g, 69% white solid.

Mp: 69 – 71 °C.

¹H NMR: (CDCl₃ 400 MHz): δH 7.71 (d, 2H, J = 8.0 Hz, Ar), 7.40 – 7.25 (m, 5H, Ar), 7.13 (d, 2H, J = 8.4 Hz, Ar), 7.03 (d, 1H, J = 8.4 Hz, Ar), 6.95 – 6.72 (m, 6H,
$^1$H NMR: (CDCl$_3$ 400 MHz): $\delta_H$ 7.71 (d, 2H, $J = 8.4$ Hz, Ar), 7.34 – 7.20 (m, 6H, Ar), 7.13 (d, 2H, $J = 8.8$ Hz, Ar), 6.90 – 6.78 (m, 6H, Ar), 4.98 – 4.88 (m, 2H, H-1, Ar), 4.82 (d, 1H, $J = 11.2$ Hz, -CH$_2$Ph), 4.66 – 4.58 (m, 2H, -CH$_2$Ph), 4.50 – 4.35 (m, 3H, -CH$_2$Ph), 3.90 – 3.70 (m, 10H, -CH$_2$), 3.68 – 3.42 (m, 5H, -CH$_2$), 3.23 (d, 2H, $J = 6.0$ Hz, H-7$_a$, H-7$_b$), 2.47 (s, 3H, -CH$_3$), 2.26 – 2.10 (m, 1H, H-2), 1.94 – 1.10 (m, 10H, cyclohexyl).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): $\delta_C$ 159.3, 159.2 (-COCH$_3$), 144.4, 136.5, 130.4, 130.2, 130.0, 129.9, 129.8, 129.7, 129.5, 129.4, 129.0, 127.9, 113.8, 113 (Ar), 96.0 (C-1), 79.4 (C-4), 78.7 (C-3), 77.4 (C-1'), 75.9 (C-5), 74.4, 73.2, 70.6 (-CH$_2$Ph), 68.1 (C-6), 55.3, 55.2 (-OCH$_3$), 53.4 (C-7), 41.6 (C-2), 33.4, 31.4, 25.6, 24.1, 23.9 (cyclohexyl), 21.6 (-CH$_3$).

IR: 1614.3, 1514.4, 1300.1, 1248.9, 1034.5, 814.9 cm$^{-1}$ (neat).

$[\alpha]_D$: +5.0 (c 0.1, CHCl$_3$).

**Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-para-methylphenylsulfonylmethyl-β-D-glucopyranoside (136)**

Yield: 0.19 g, 74% white solid.

Mp: 106 – 108 °C.
–CH₂Ph), 4.84 (d, 1H, J = 10.8 Hz, –CH₂Ph), 4.71 (d, 1H, J = 10.8 Hz, –CH₂Ph), 4.61 – 4.46 (m, 3H, –CH₂Ph), 4.15 – 4.05 (m, 1H, H-3), 3.82 – 3.78 (m, 9H, 3 x –OCH₃), 3.72 – 3.58 (m, 3H, H-1’, H-6ₐ, H-6ₐ), 3.56 – 3.48 (m, 2H, H-4, H-5), 3.41 (dd, 1H, J = 4.2 Hz and 14.0 Hz, H-7ₐ), 3.30 (dd, 1H, J = 4.0 Hz and 14.0 Hz, H-7ₐ), 2.42 (s, 3H, –CCH₃), 2.18 – 2.08 (m, 1H, H-2), 2.00 – 1.84 (m, 2H, cyclohexyl), 1.75 – 1.60 (m, 2H, cyclohexyl), 1.57 – 1.46 (m, 1H, cyclohexyl), 1.40 – 1.08 (m, 5H, cyclohexyl).

¹³C NMR: (CDCl₃ 100 MHz): δC 159.3, 159.2 (–OCH₃), 144.3, 138.6, 131.1, 130.4, 130.3, 129.8, 129.5, 129.4, 127.7, 113.8, 113.7 (Ar), 99.5 (C-1), 80.5 (C-4), 79.7 (C-3), 78.0 (C-1’), 74.8 (C-5), 74.0, 73.0 (–CH₂Ph), 68.7 (C-6), 55.2 (x2) (–OCH₃), 53.1 (C-7), 45.8 (C-2), 33.8, 32.0, 25.6, 24.3 (cyclohexyl), 21.6 (–CCH₃).

IR: 1614.3, 1514.4, 1300.1, 1248.9, 1034.5, 814.9 cm⁻¹ (neat).

[α]₀: -14.0 (c 0.1, CHCl₃).

**Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-para-tert-butylphenylsulfonylmethyl-β-D-glucopyranoside (137)**

![Chemical structure of 137](image)

Yield: 0.19 g, 68% white solid.

Mp: 84 – 86 °C.
**1H NMR:** $(\text{CDCl}_3$ 400 MHz): $\delta_H$ 7.78 (d, 2H, $J = 8.4$ Hz, Ar), 7.53 (d, 2H, $J = 8.4$ Hz, Ar), 7.31 (d, 2H, $J = 8.4$ Hz, Ar), 7.27 (d, 2H, $J = 8.4$ Hz, Ar), 7.14 (d, 2H, $J = 8.4$ Hz, Ar), 6.92 – 6.87 (m, 6H, Ar), 5.00 – 4.92 (m, 2H, H-1, –CH$_2$Ph), 4.86 (d, 1H, $J = 10.4$ Hz, –CH$_2$Ph), 4.73 (d, 1H, $J = 10.4$ Hz, –CH$_2$Ph), 4.61 – 4.46 (m, 3H, –CH$_2$Ph), 4.09 (dd, 1H, $J = 8.0$ Hz and 11.2 Hz, H-3), 3.84 – 3.40 (m, 16H, H-1’, H-3, H-4, H-5, H$_6a$, H-6$_b$, H-7$_a$, 3 x –OCH$_3$), 3.32 (dd, 1H, $J = 3.8$ Hz and 14.2 Hz, H-7$_b$), 2.20 – 2.14 (m, 1H, H-2), 2.00 – 1.86 (m, 2H, cyclohexyl), 1.76 – 1.63 (m, 2H, cyclohexyl), 1.59 – 1.46 (m, 1H, cyclohexyl), 1.41 – 1.05 (m, 14H, (–C(CH$_3$)$_3$, cyclohexyl).

**13C NMR:** $(\text{CDCl}_3$ 100 MHz): $\delta_C$ 159.2, 159.1, 157.2 (–COCH$_3$), 138.3, 131.0, 130.3, 130.2, 129.5, 129.4, 129.3, 127.4, 126.1, 113.7, 113.6 (Ar), 99.4 (C-1), 80.3 (C-4), 79.6 (C-3), 77.8 (C-1’), 74.7 (C-5), 74.0, 72.9 (–CH$_2$Ph), 68.5 (C-6), 55.1 (x2) (–OCH$_3$), 53.0 (C-7), 45.6 (C-2), 35.1, 33.7, 31.9 (cyclohexyl), 31.0 (–C(CH$_3$)$_3$), 25.5, 24.2 (cyclohexyl).

**IR:** 1614.4, 1513.7, 1304.9, 1053.2, 819.6 cm$^{-1}$ (neat).

$[\alpha]_D$: -13.0 (c 0.1, CHCl$_3$).

**Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-2-napthalenesulfonylmethyl-\(\beta\)-D-glucopyranoside (138)**

Yield: 0.17 g, 62% white solid.
Mp: 98 – 100 °C.

\(^1\)H NMR: (CDCl\(_3\) 400 MHz): \(\delta\) \(H\) 8.41 (s, 1H, Ar), 8.00 – 7.88 (m, 3H, Ar), 7.79 (d, 1H, \(J = 8.4\) Hz, Ar), 7.70 – 7.57 (m, 2H, Ar), 7.35 – 7.18 (m, 4H, Ar), 7.12 (d, 2H, \(J = 8.4\) Hz, Ar), 6.90 – 6.75 (m, 6H, Ar), 4.96 – 4.80 (m, 3H, H-1, –CH\(_2\)Ph), 4.71 (d, 1H, \(J = 10.8\) Hz, –CH\(_2\)Ph), 4.60 – 4.43 (m, 3H, –CH\(_2\)Ph), 4.10 (dd, 1H, \(J = 8.0\) Hz and 10.8 Hz, H-3), 3.84 – 3.41 (m, 15H, H-1", H-4, H-5, H-6\(_a\), H-6\(_b\), H-7\(_a\) 3 x –OCH\(_3\)), 3.38 (dd, 1H, \(J = 3.8\) Hz and 14.2 Hz, H-7\(_b\)), 2.24 – 2.12 (m, 1H, H-2), 1.98 – 1.80 (m, 2H, cyclohexyl), 1.73 – 1.40 (m, 5H, cyclohexyl), 1.30 – 1.00 (m, 5H, cyclohexyl).

\(^{13}\)C NMR: (CDCl\(_3\) 100 MHz): \(\delta\) \(C\) 159.2, 159.1 (–COCH\(_3\)), 138.2, 135.2, 132.2, 131.0, 130.4, 130.2, 129.5, 129.4, 129.2, 129.2, 129.1, 127.9, 127.6, 122.6, 113.8, 113.7 (Ar), 99.4 (C-1), 80.4 (C-4), 79.8 (C-3), 77.3 (C-1’), 74.8 (C-5), 74.1 (x2), 73.0 (–CH\(_2\)Ph), 68.6 (C-6), 55.2 (x2) (–OCH\(_3\)), 53.1 (C-7), 45.7 (C-2), 33.7, 32.0, 25.6, 24.2 (cyclohexyl).

IR: 1612.5, 1512.0, 1363.5, 1305.1, 1035.1, 815.3 cm\(^{-1}\) (neat).

[\(\alpha\)]\(_D\): -27.5 (c 0.1, CHCl\(_3\)).

**Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-n-propylsulfonylmethyl-ß-D-glucopyranoside (139)**

Yield: 0.18 g, 73% white solid.
Mp: 96 – 98 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): $\delta_H$ 7.33 – 7.21 (m, 4H, Ar), 7.10 (d, 2H, J = 8.0 Hz, Ar), 6.90 – 6.77 (m, 6H, Ar), 4.91 (d, 1H, J = 10.8 Hz, –CH$_2$Ph), 4.75 – 4.63 (m, 3H, H-1, –CH$_2$Ph), 4.56 (d, 1H, J = 12.0 Hz, –CH$_2$Ph), 4.53 – 4.45 (m, 2H, –CH$_2$Ph), 3.80 – 3.60 (m, 13H, H-1’, H-3, H-6$_a$, H-6$_b$, 3 x –OCH$_3$), 3.58 – 3.52 (m, 1H, H-4), 3.48 – 3.38 (m, 1H, H-5), 3.13 (dd, 1H, J = 3.6 Hz and 14.4 Hz, H-7$_a$), 3.01 (dd, 1H, J = 3.6 Hz and 14.4 Hz, H-7$_b$), 2.96 – 2.80 (m, 2H, H-8$_a$, H-8$_b$), 2.20 – 2.10 (m, 1H, H-2), 2.03 – 1.62 (m, 6H, H-9$_a$, H-9$_b$, cyclohexyl), 1.56 – 1.48 (m, 1H, cyclohexyl), 1.44 – 1.18 (m, 5H, cyclohexyl) 1.00 (t, 3H, J = 7.4 Hz, –CH$_2$CH$_3$).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): $\delta_C$ 159.3, 159.2 (x2) (–COCH$_3$), 130.5, 130.3, 130.1, 129.7, 129.4, 113.8, 113.7 (Ar), 99.5 (C-1), 80.1 (C-4), 80.0 (C-3), 77.5 (C-1’), 74.9 (C-5), 74.1, 74.0, 73.0 (–CH$_2$Ph), 68.5 (C-6), 56.1 (C-8), 55.2 (x2) (–OCH$_3$), 49.9 (C-7), 44.5 (C-2), 33.8, 31.9, 25.6, 24.3, 24.2 (cyclohexyl), 15.5 (C-9), 13.1 (C-10).

IR: 1614.8, 1515.7, 1302.5, 1247.8, 1030.4, 811.0 cm$^{-1}$ (neat).

$[\alpha]_D$: -13.5 (c 0.1, CHCl$_3$).

*Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-iso-propylsulfonylmethyl-β-D-glucopyranoside* (140)
Yield: 0.18 g, 73% white solid.

Mp: 82 – 84 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): $\delta_H$ 7.33 – 7.20 (m, 4H, Ar), 7.11 (d, 2H, $J = 8.0$ Hz, Ar), 6.90 – 6.73 (m, 6H, Ar), 4.94 – 4.86 (m, 2H, H-1, $-CH_2$Ph), 4.79 (d, 1H, $J = 10.8$ Hz, $-CH_2$Ph), 4.70 (m, 1H, $J = 10.4$ Hz, $-CH_2$Ph), 4.56 (d, 1H, $J = 11.6$ Hz, $-CH_2$Ph), 4.54 – 4.44 (m, 2H, $-CH_2$Ph), 4.01 – 3.93 (m, 1H, H-3), 3.77 (s, 9H, 3 x $-OCH_3$), 3.72 – 3.61 (m, 3H, H-1', H-6a, H-6b), 3.58 – 3.42 (m, 2H, H-4, H-5), 3.24 (dd, 1H, $J = 3.8$ Hz and 13.8 Hz, H-7a), 3.10 (dd, 1H, $J = 3.8$ Hz and 13.8 Hz, H-7b), 3.08 – 2.96 (m, 1H, H-8), 2.24 – 2.12 (m, 1H, H-2), 2.18 – 1.90 (m, 2H, cyclohexyl), 1.78 – 1.65 (m, 2H, cyclohexyl), 1.58 – 1.46 (m, 1H, cyclohexyl), 1.43 – 1.06 (m, 11H, cyclohexyl, $-CH(CH_3)_2$).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): $\delta_C$ 159.2, 159.1 (x2) ($-COCH_3$), 130.9, 130.4, 130.2, 129.6, 129.4, 129.3, 113.8, 113.7 (Ar), 99.2 (C-1), 80.4 (C-4), 79.7 (C-3), 77.8 (C-1'), 74.8 (C-5), 74.0, 73.9, 73.0 ($-CH_2$Ph), 68.6 (C-6), 55.2 (3 x $-OCH_3$), 54.6 (C-7), 45.1 (C-8), 45.0 (C-2), 33.9, 32.0, 25.6, 24.4, 24.3 (cyclohexyl), 15.8, 15.2 ($-CH(CH_3)_2$).

IR: 1613.8, 1514.0, 1299.9, 1246.4, 1034.5, 819.2 cm$^{-1}$ (neat).

$[\alpha]_D$: -7.0 (c 0.1, CHCl$_3$).

General procedure for the synthesis of sulfoxide derivatives

Aluminium oxide (0.87 g) was weighed into a round-bottom reaction flask and was wetted with H$_2$O (0.15 mL). The mixture was rotated on a rotary evaporator until it was free-flowing. Sulfide 117 (0.25 g, 0.34 mmol) dissolved in DCM was added to the reaction flask and the mixture was vigorously stirred before OXONE® (0.25 g, 0.40 mmol) was added. The
reaction was left to stir for 4 h upon which it showed completion on TLC. The solids were filtered over a pad of celite® and solvent removed under reduced pressure. The residue product was purified by column chromatography on silica gel using hexane and ethyl acetate (6:4) as eluent.

Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-phenylsulfinylmethyl-β-D-glucopyranoside (119a and 119b)

\[
\text{Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-phenylsulfinylmethyl-β-D-glucopyranoside (119a and 119b)}
\]

\[
\text{119a}
\]

\[
\text{119b}
\]

Yield: 0.16 g, 64% white solid.

Mp: 99 – 101 °C.

**Major diastereoisomer**

\[\text{H NMR: (CDCl}_3\text{ 400 MHz): } \delta_H \text{ 7.72 – 7.60 (m, 1H, Ar), 7.53 – 7.40 (m, 4H, Ar), 7.32 – 7.21 (m, 3H, Ar), 7.17 (d, 1H, } J = 8.0 \text{ Hz, Ar), 7.09 (d, 1H, } J = 8.4 \text{ Hz, Ar), 7.04 (d, 1H, } J = 8.4 \text{ Hz, Ar), 6.90 – 6.72 (m, 6H, Ar), 4.97 (d, 1H, } J = 10.4 \text{ Hz, } \text{–CH}_2\text{Ph), 4.80 – 4.35 (m, 6H, H-1, –CH}_2\text{Ph), 3.83 – 3.48 (m, 15H, H-1, H-3, H-4, H-6a, H-6b, 3 x –OCH}_3\text{), 3.44 – 3.33 (m, 1H, H-1, H-5), 3.15 – 3.02 (m, 1H, H-7a), 2.95 (bd, 1H, } J = 12.4 \text{ Hz, H-7b), 2.08 – 1.10 (m, 11H, H-2, cyclohexyl).}
\]

\[\text{C NMR: (CDCl}_3\text{ 100 MHz): } \delta_C \text{ 159.2 (x2) (–COCH}_3\text{), 131.1, 130.5, 130.3, 130.2, 130.2, 129.6, 129.4, 129.3, 129.2, 124.6, 124.4, 113.8, 113.7 (Ar), 100.4 (C-1a, C-1b), 81.4 (C-4), 79.8 (C-3a), 77.6 (C-1’), 75.1 (C-5), 74.4, 74.2 (x3), 73.0 (–}
\]
Minor diastereoisomer

$^1$H NMR:  
(CDCl$_3$ 400 MHz): $\delta_H 2.82$ (bd, 1H, $J = 8.4$ Hz, H-7$_b$).

$^{13}$C NMR:  
(CDCl$_3$ 100 MHz): $\delta_C 130.9$, 130.3, 130.2, 129.3, 129.1, 124.4 (Ar), 81.3 (C-4), 79.4 (C-3), 75.0 (C-5), 68.5 (C-6), 56.5 (C-7), 44.6 (C-2), 33.6, 31.7, 25.6, 24.2 (cyclohexyl).

IR:  
1511.6, 1245.4, 1086.0, 1032.4, 811.0 cm$^{-1}$ (neat).

Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-para-chlorophenylsulfinylmethyl-$\beta$-D-glucopyranoside (141a and 141b)

Yield: 0.17 g, 63% white solid.

Mp: 122 – 124 °C.

Major diastereoisomer

$^1$H NMR:  
(CDCl$_3$ 400 MHz): $\delta_H 7.58$ (d, 1H, $J = 8.0$ Hz, Ar), 7.48 – 7.35 (m, 3H, Ar), 7.31 – 7.18 (m, 4H, Ar), 7.15 – 7.00 (m, 2H, Ar), 6.88 – 6.72 (m, 6H, Ar) 4.96 (d, 1H, $J = 10.8$ Hz, –CH$_2$Ph), 4.80 – 4.35 (m, 6H, H-1, –CH$_2$Ph), 3.85 – 3.30 (m, 15H, H-1’, H-3, H-4, H-5, H-6a, H-6b, 3 x –OCH$_3$), 3.10 – 2.93 (m, 1H, H-
7\(a\), 2.73 (dd, 1H, \(J = 4.8\) Hz and \(12.8\) Hz, H-7\(b\)), 2.19 – 1.11 (m, 11H, H-2, cyclohexyl).

\(^{13}\)C NMR: (CDCl\(_3\) 100 MHz): \(\delta\)C 159.3 (x3), 159.2 (–COCH\(_3\)), 130.3, 130.0, 129.7, 129.5, 129.3, 126.0, 113.9, 113.8, 113.7 (Ar), 100.2 (C-1), 81.5 (C-4), 79.8 (C-3), 77.6 (C-1\(^\prime\)), 75.1 (C-5), 74.5, 74.3, 74.2 (–CH\(_2\)Ph), 68.5 (C-6), 55.2 (x2) (–OCH\(_3\)), 57.3 (C-7), 44.4 (C-2), 33.5, 31.7, 25.6, 23.9 (cyclohexyl).

**Minor diastereoisomer**

\(^1\)H NMR: (CDCl\(_3\) 400 MHz): \(\delta\)H 2.89 (bd, 1H, \(J = 10.4\) Hz, H-7\(ab\)).

\(^{13}\)C NMR: (CDCl\(_3\) 100 MHz): \(\delta\)C 130.2, 129.4, 126.2, 100.4 (C-1), 81.4 (C-4), 79.4 (C-4), 75.0 (C-5), 73.1 (–CH\(_2\)Ph), 68.4 (C-6), 57.1 (C-7), 33.7, 32.0, 24.1 (cyclohexyl).

IR: 1514.0, 1245.3, 1033.5, 817.3 cm\(^{-1}\) (neat).

**Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-para-bromophenylsulfinylmethyl-\(\beta\)-D-glucopyranoside (142a and 142b)**

Yield: 0.16 g, 57% white solid.

Mp: 103 – 105 °C.
Major diastereoisomer

$^1$H NMR: (CDCl$_3$ 400 MHz): δ$_H$ 7.65 – 7.47 (m, 3H, Ar), 7.40 – 7.19 (m, 4H, Ar), 7.16 – 7.00 (m, 3H, Ar), 6.90 – 6.72 (m, 6H, Ar), 4.96 (d, 1H, $J$ = 10.8 Hz, –CH$_2$Ph), 4.80 – 4.46 (m, 6H, H-1, –CH$_2$Ph), 3.90 – 3.33 (m, 15H, H-1”, H-3, H-4, H-5, H-6$_a$, H-6$_b$, 3 x –OCH$_3$), 3.10 – 2.92 (m, 1H, H-7$_a$), 2.85 (dd, 1H, $J$ = 3.2 Hz and 12.8 Hz, H-7$_b$), 2.05 – 1.14 (m, 11H, H-2, cyclohexyl).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): δ$_C$ 159.3 (x2), 159.2 (–COCH$_3$), 132.4, 132.3, 130.2, 130.1, 129.7, 129.4, 129.2, 126.4, 126.2, 125.5, 113.8, 113.7 (Ar), 100.4 (C-1), 81.5 (C-4), 79.8 (C-3), 77.6 (C-1’), 75.1 (C-5), 74.5, 74.2, 73.1 (–CH$_2$Ph), 68.5 (C-6), 57.1 (C-7), 55.3, 55.2 (–OCH$_3$), 44.6 (C-2), 33.8, 32.0, 25.6, 24.1, 23.9 (cyclohexyl).

Minor diastereoisomer

$^1$H NMR: (CDCl$_3$ 400 MHz): δ$_H$ 2.70 (dd, 1H, $J$ = 5.2 Hz and 12.8 Hz, H-7$_b$).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): δ$_C$ 159.3 (x2), (–COCH$_3$), 132.3, 130.2, 130.1, 129.4, 125.5, 113.8, 100.2 (C-1), 81.3 (C-4), 79.4 (C-3), 75.0 (C-5), 74.3 (–CH$_2$Ph), 68.4 (C-6), 56.8 (C-7), 44.4 (C-2), 33.5, 31.7, 24.2 (cyclohexyl).

IR: 1613.5, 1513.1, 1245.4, 1031.0, 818.2 cm$^{-1}$ (neat).
Cyclohexyl-3,4,6-tri-O-para-methoxybenzyl-2-deoxy-2-C-2-naphthalenephenylsulfinylmethyl-β-D-glucopyranoside (143a and 143b)

Yield: 0.16 g, 58% white solid.

Mp: 105 – 107 °C.

Major diastereoisomer

\(^1\)H NMR: (CDCl\(_3\) 400 MHz): δ\(_H\) 8.21 (s, 1H, Ar), 7.96 – 7.80 (m, 3H, Ar), 7.60 – 7.48 (m, 3H, Ar), 7.37 – 7.20 (m, 3H, Ar), 7.18 – 7.02 (m, 3H, Ar), 6.90 – 6.71 (m, 6H, Ar), 5.02 (d, 1H, \(J = 11.2\) Hz, –CH\(_2\)Ph), 4.79 – 4.38 (m, 6H, H-1, –CH\(_2\)Ph), 3.86 – 3.55 (m, 14H, H-1", H-3, H-4, H-6\(_a\), H-6\(_b\), 3 x –OCH\(_3\)), 3.50 – 3.35 (m, 1H, H-5), 3.20 – 3.08 (m, 1H, H-7\(_a\)), 3.04 (dd, 1H, \(J = 3.8\) Hz and 13.2 Hz, H-7\(_b\)), 2.10 – 1.12 (m, 11H, H-2, cyclohexyl).

\(^13\)C NMR: (CDCl\(_3\) 100 MHz): δ\(_C\) 159.2 (x2), 159.1 (–COCH\(_3\)), 141.6, 134.5, 132.8, 130.4, 130.2, 130.1, 129.6, 129.4, 129.3, 129.2, 128.6, 128.5, 128.0, 127.9, 127.6, 127.0, 125.3, 120.5, 120.2, 113.8, 113.7 (Ar), 100.4 (C-1), 81.4 (C-4), 79.8 (C-3), 77.5 (C-1"), 75.0 (C-5), 74.4, 73.0 (CH\(_2\)Ph), 68.5 (C-6), 56.4 (C-7), 55.2 (x2) (OCH\(_3\)), 44.7 (C-2), 33.7, 32.0, 25.6, 24.2, 23.9 (cyclohexyl).

Minor diastereoisomer

\(^1\)H NMR: (CDCl\(_3\) 400 MHz): δ\(_H\) 7.98 (s, 1H, Ar), 7.65 (dd, 1H, \(J = 1.4\) Hz and 8.6 Hz, Ar), 2.88 (dd, 1H, \(J = 5.2\) Hz and 13.2 Hz, H-7\(_b\)).
\(^{13}\)C NMR:  (CDCl\(_3\) 100 MHz): \(\delta_C\) 159.2, 159.1 (–COCH\(_3\)), 134.5, 132.8, 130.4, 130.2, 130.1, 129.4, 127.6, 127.0, 113.7 (Ar), 100.3 (C-1), 81.3 (C-4), 79.4 (C-3), 77.1 (C-1'), 74.9 (C-5), 68.4 (C-6), 56.3 (C-7), 44.6 (C-2), 33.5, 31.7, 24.1 (cyclohexyl).

IR:  1614.1, 1513.1, 1245.6, 1030.9, 817.1 cm\(^{-1}\) (neat).

**General procedure for the deprotection of para-methoxybenzyl protecting groups**

PMB protected sulfone 118 (0.15 g, 0.20 mmol) sugar derivative was dissolved in a 9:1 solution of CH\(_3\)CN:H\(_2\)O (5 mL) and CAN (0.43 g, 0.79 mmol) was added. The mixture was stirred at room temperature for 2 h upon which the reaction showed completion on TLC. The reaction mixture was then diluted with EtOAc and washed once with saturated NaHCO\(_3\), twice with 10 mL portions of H\(_2\)O and once with brine. The organic layer was dried over anhydrous MgSO\(_4\), filtered and solvent removed under reduced pressure. The residue was recrystallized from DCM and hexane (0.5:9.5) without further purification to yield white crystals as product. (The products were characterized by NMR after acetylation).

*Cyclohexyl-3,4,6-tri-hydroxyl-2-deoxy-2-C-phenylsulfonylmethyl-\(\beta\)-D-glucopyranoside*  
(120)

Yield:  0.06 g, 75% white solid.

Mp:  185 – 187 °C.
IR: 3468.2, 1304.1, 1137.4, 1095.3, 793.9 cm$^{-1}$ (neat).

Cyclohexyl-3,4,6-tri-hydroxyl-2-deoxy-2-C-phenylsulfonylmethyl-$\alpha$-D-glucopyranoside (144)

Yield: 0.06 g, 70% white solid.

Mp: 178 – 180 °C.

IR: 3385.4, 1301.8, 1165.5, 1018.7, 745.4 cm$^{-1}$ (neat).

HRMS (ESI): $m/\text{z}$ [M+H]$^+$ Calcd: 401.1629; Found: 401.1635.

Cyclohexyl-3,4,6-tri-hydroxyl-2-deoxy-2-C-para-chlorophenylsulfonylmethyl-$\beta$-D-glucopyranoside (145)

Yield: 0.06 g, 69% white solid.

Mp: 159 – 161 °C.

IR: 3477.3, 1305.1, 1080.9, 770.0 cm$^{-1}$ (neat).
Cyclohexyl-3,4,6-tri-hydroxyl-2-deoxy-2-C-para-bromophenylsulfonylmethyl-β-D-glucopyranoside (146)

Yield: 0.07 g, 68% white solid.
Mp: 177 – 179 °C.
IR: 3482.1, 1390.1, 1306.6, 1081.0, 769.5 cm⁻¹ (neat).

Cyclohexyl-3,4,6-tri-hydroxyl-2-deoxy-2-C-para-methylphenylsulfonylmethyl-α-D-glucopyranoside (147)

Yield: 0.06 g, 77% white solid.
Mp: 158 – 160 °C.
IR: 3493.8, 1299.5, 1140.3, 1027.1 cm⁻¹ (neat).
Cyclohexyl-3,4,6-tri-hydroxyl-2-deoxy-2-C-para-tert-butylphenylsulfonylmethyl-β-D-glucopyranoside (148)

Yield: 0.06 g, 63% white solid.

Mp: 79 – 82 °C.

IR: 3494.8, 1190.3, 1145.8, 1015.4, 835.8 cm\(^{-1}\) (neat).

Cyclohexyl-3,4,6-tri-hydroxyl-2-deoxy-2-C-naphthalene phenylsulfonylmethyl-β-D-glucopyranoside (149)

Yield: 0.06 g, 62% white solid.

Mp: 158 – 160 °C.

IR: 3364.8, 1075.3, 1022.6, 809.9 cm\(^{-1}\) (neat).
Cyclohexyl-3,4,6-tri-hydroxyl-2-deoxy-2-C-n-propylsulfonylmethyl-β-D-glucopyranoside (150)

Yield: 0.05 g, 67% white solid.

Mp: 181 – 183 °C.

IR: 3487.6, 1299.3, 1249.6, 1029.3, 989.4 cm\(^{-1}\) (neat).

Cyclohexyl-3,4,6-tri-hydroxyl-2-deoxy-2-C-iso-propylsulfonylmethyl-β-D-glucopyranoside (151)

Yield: 0.05 g, 73% white solid.

Mp: 163 – 165 °C.

IR: 3490.2, 1299.0, 1080.3, 1029.7, 989.9 cm\(^{-1}\) (neat).
Cyclohexyl-3,4,6-tri-hydroxyl-2-deoxy-2-C-phenylsulfinylmethyl-β-D-glucopyranoside (121a and 121b)

Yield: 0.05 g, 77% white solid.

Mp: 174 – 176 °C.

IR: 3295.6, 1366.1, 1080.4, 1029.0, 986.0 cm\(^{-1}\) (neat).

Cyclohexyl-3,4,6-tri-hydroxyl-2-deoxy-2-C-para-chlorophenylsulfinylmethyl-β-D-glucopyranoside (152a and 152b)

Yield: 0.06 g, 74% white solid.

Mp: 195 – 197 °C.

IR: 3369.3, 1365.3, 1098.7, 1029.1, 814.3 cm\(^{-1}\) (neat).
Cyclohexyl-3,4,6-tri-hydroxyl-2-deoxy-2-C-para-bromophenylsulfinylmethyl-β-D-glucopyranoside (153a and 153b)

Yield: 0.07 g, 73% white solid.

Mp: 147 – 149 °C.

IR: 3295.0, 1365.2, 1099.0, 1029.5, 809.8 cm⁻¹ (neat).

Cyclohexyl-3,4,6-tri-hydroxyl-2-deoxy-2-C-naphthalenephenylsulfinylmethyl-β-D-glucopyranoside (154a and 154b)

Yield: 0.05 g, 60% white solid.

Mp: 158 – 160 °C.

IR: 3343.0, 1099.2, 1021.3, 986.0, 810.1 cm⁻¹ (neat).
Cyclohexyl-3,4,6-tri-hydroxyl-2-deoxy-2-C-para-methylphenylsulfinylmethyl-β-D-glucopyranoside (154a and 154b)

\[
\begin{align*}
&\text{154a} & & + & & \text{154b}
\end{align*}
\]

Yield: 0.06 g, 72% white solid.

Mp: 165 – 167 °C.

IR: 3275.3, 1099.1, 1029.7, 987.0, 800.8 cm\(^{-1}\) (neat).

General procedure for the tri-O-acetylation of mycothiol molecular analogues

Catalytic amount of DMAP (3.00 mg, 0.02 mmol) was added to a solution of triol 120 (50.00 mg, 0.12 mmol) dissolved in pyridine (3 mL). Acetic anhydride (2 mL) was then added to the stirring solution and the reaction was left to stir overnight (~16 h). The reaction was diluted by ether (~15.0 mL) and washed twice with 10.0 mL portions of saturated copper(II) sulfate and once with 10.0 mL brine. The ethereal layer was dried over anhydrous MgSO\(_4\) and solvent removed under reduced pressure. The sulfonyl residues were recrystallized from hexane and DCM, whilst the sulfinyl diastereoisomers were separated by column chromatography using hexane and ethyl acetate (1:1) as eluent.
Cyclohexyl-3,4,6-tri-O-acetyl-2-deoxy-2-C-phenylsulfonylmethyl-β-D-glucopyranoside (122)

Yield: 0.06 g, 88 % white solid.

\(^1\)H NMR: (CDCl\(_3\) 400 MHz): δ\(_H\) 7.85 (d, 2H, J = 7.6 Hz, Ar), 7.69 – 7.30 (m, 3H, Ar), 5.24 (t, 1H, J = 10.2 Hz, H-3), 4.91 (t, 1H, J = 9.6 Hz, H-4), 4.56 (d, 1H, J = 8.4 Hz, H-1), 4.24 (dd, 1H, J = 5.2 Hz and 12.0 Hz, H-6), 4.04 (bd, 1H, J = 12.0 Hz, H-6), 3.68 – 3.48 (m, 2H, H-1' and H-5), 3.28 (d, 2H, J = 4.0 Hz, H-7, H-7), 2.42 – 2.33 (m, 1H, H-2), 2.06 – 1.95 (m, 9H, 3 x –OC\(_3\)H\(_3\)), 1.85 – 1.57 (m, 4H, cyclohexyl), 1.53 – 1.44 (m, 1H, cyclohexyl), 1.30 – 1.08 (m, 5H, cyclohexyl).

\(^13\)C NMR: (CDCl\(_3\) 100 MHz): δ\(_C\) 170.8, 170.6, 169.7 (–OC\(_3\)H\(_3\)), 140.1, 133.7, 129.2, 128.0 (Ar), 99.4 (C-1), 77.8 (C-1'), 72.8 (C-3), 71.6 (C-5), 69.6 (C-4), 62.4 (C-6), 54.2 (C-7), 42.7 (C-2), 33.3, 31.5, 25.4, 23.8 (cyclohexyl), 20.8, 20.7, 20.6 (–OC\(_3\)H\(_3\)).
**Cyclohexyl-3,4,6-tri-O-acetyl-2-deoxy-2-C-phenylsulfonylmethyl-α-D-glucopyranoside (155)**

![Chemical Structure](image)

**Yield:** 0.05 g, 85% white solid.

**Mp:** 98 – 100 °C.

**¹H NMR:** (CDCl₃ 400 MHz): δH 7.85 (d, 2H, J = 7.6 Hz, Ar), 7.72 – 7.62 (m, 1H, Ar), 7.60 – 7.51 (m, 2H, Ar), 5.34 (d, 1H, J = 3.2 Hz, H-1), 5.08 (t, 1H, J = 10.0 Hz, H-3), 4.89 (t, 1H, J = 9.4 Hz, H-4), 4.21 (dd, 1H, J = 4.6 Hz and 12.2 Hz, H-6a), 4.08 – 3.95 (m, 2H, H-5, H-6b), 3.57 – 3.45 (m, 1H, H-1’), 3.36 (dd, 1H, J = 4.4 Hz and 14.4 Hz, H-7a), 2.90 (d, 1H, J = 14.4 Hz, H-7b), 2.50 – 2.88 (m, 1H, H-2), 2.05 (s, 3H, –COC₃H₃), 1.96 (s, 3H, –COCH₃), 1.92 – 1.80 (m, 5H, –COCH₃, cyclohexyl), 1.78 – 1.62 (m, 2H, cyclohexyl) 1.53 – 1.47 (m, 1H, cyclohexyl), 1.40 – 1.10 (m, 5H, cyclohexyl).

**¹³C NMR:** (CDCl₃ 100 MHz): δC 170.6 (x2), 169.7 (–OCCH₃), 139.2, 134.0, 129.5, 127.8 (Ar), 96.0 (C-1), 77.1 (C-1’), 70.7 (C-3), 69.5 (C-4), 67.3 (C-5), 62.2 (C-6), 53.7 (C-7), 40.2 (C-2), 33.3, 31.5, 25.4, 24.1, 23.9 (cyclohexyl), 20.7, 20.6 (x2) (–OCCH₃).

**IR:** 1742.3, 1366.0, 1307.5, 1224.9, 1020.8 cm⁻¹ (neat).

**[α]₀:** +42.5 (c 0.1, CHCl₃).
**Cyclohexyl-3,4,6-tri-O-acetyl-2-deoxy-2-C-para-chlorophenylsulfonylmethyl-β-D-glucopyranoside (156)**

![Chemical structure](image)

**Yield:** 0.05 g, 74% white solid.

**Mp:** 151 – 153 °C.

**$^1$H NMR:** (CDCl$_3$ 400 MHz): $\delta_h$ 7.80 (d, 2H, $J$ = 8.0 Hz, Ar), 7.51 (d, 2H, $J$ = 8.4 Hz, Ar), 5.22 (t, 1H, $J$ = 10.2 Hz, H-3), 4.96 (t, 1H, 9.4 Hz, H-4), 4.52 (d, 1H, $J$ = 8.8 Hz, H-1), 4.25 (dd, 1H, $J$ = 5.0 Hz and 12.2 Hz, H-6$_a$), 4.06 (d, 1H, $J$ = 10.8 Hz, H-6$_b$), 3.67 – 3.45 (m, 2H, H-1', H-5), 3.35 – 3.20 (m, 2H, H-7$_a$, H-7$_b$), 2.40 – 2.27 (m, 1H, H-2), 2.09 – 1.98 (m, 9H, 3 x –OCCH$_3$), 1.89 – 1.41 (m, 5H, cyclohexyl), 1.27 – 1.03 (m, 5H, cyclohexyl).

**$^{13}$C NMR:** (CDCl$_3$ 100 MHz): $\delta_c$ 171.0, 170.6, 169.7 (–OCCH$_3$), 140.5, 138.3, 129.6 (Ar), 99.3 (C-1), 77.7 (C-1'), 72.9 (C-3), 71.7 (C-5), 69.5 (C-4), 62.3 (C-6), 54.4 (C-7), 42.6 (C-2), 33.3, 31.6, 25.4, 23.9 (cyclohexyl), 20.9, 20.7, 20.6 (–OCCH$_3$).

**IR:** 1740.7, 1225.3, 1145.0, 1029.4, 764.9 cm$^{-1}$ (neat).

**[α]$_D$:** -11.5 (c 0.1, CHCl$_3$).
Cyclohexyl-3,4,6-tri-O-acetyl-2-deoxy-2-C-para-bromophenylsulfonylmethyl-β-D-glucopyranoside (157)

Yield: 0.07 g, 94% white solid.

Mp: 172 – 174 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): δ$_H$ 7.78 – 7.63 (m, 4H, Ar), 5.21 (t, 1H, $J = 10.2$ Hz, H-3), 4.96 (t, 1H, $J = 9.4$ Hz, H-4), 4.51 (d, 1H, $J = 8.8$ Hz, H-1), 4.25 (dd, 1H, $J = 5.0$ Hz and 12.2 Hz, H-6$_a$), 4.04 (d, 1H, $J = 12.0$ Hz, H-6$_b$), 3.64 – 3.48 (m, 2H, H-1”, H-5), 3.33 – 3.20 (m, 2H, H-7$_a$, H-7$_b$), 2.40 – 2.29 (m, 1H, H-2), 2.10 – 1.96 (m, 9H 3 x –OCCH$_3$), 1.85 – 1.44 (m, 5H, cyclohexyl), 1.40 – 1.04 (m, 5H, cyclohexyl).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): δ$_C$ 171.0, 170.6, 169.7 (–OCCH$_3$), 138.9, 132.6, 129.7, 129.1 (Ar), 99.3 (C-1), 77.7 (C-1’), 72.9 (C-3), 71.7 (C-5), 69.5 (C-4), 62.3 (C-6), 54.4 (C-7), 42.6 (C-2), 33.3, 31.6, 25.4, 23.9 (cyclohexyl), 20.9, 20.7, 20.6 (–OCCH$_3$).

IR: 1737.6, 1315.1, 1229.2, 1050.5, 754.9 cm$^{-1}$ (neat).

$[\alpha]_D$: -18.0 (c 0.1, CHCl$_3$).
Cyclohexyl-3,4,6-tri-O-acetyl-2-deoxy-2-C-para-methylphenylsulfonylmethyl-α-D-glucopyranoside (158)

Yield: 0.05 g, 84% white solid.

Mp: 95 – 97 °C.

$^{1}$H NMR: (CDCl$_3$ 400 MHz) $\delta$H 7.73 (d, 2H, $J = 8.0$ Hz, Ar), 7.35 (d, 2H, $J = 8.0$ Hz, Ar), 5.33 (d, 1H, $J = 3.2$ Hz, H-1), 5.08 (t, 1H, $J = 10.2$ Hz, H-3), 4.88 (t, 1H, $J = 9.4$ Hz, H-4), 4.21 (dd, 1H, $J = 4.8$ Hz and 12.4 Hz, H-6$_a$), 4.30 – 3.98 (m, 2H, H-5, H-6$_b$), 3.55 – 3.44 (m, 1H, H-1’), 3.34 (dd, 1H, $J = 9.8$ Hz and 14.6 Hz, H-7$_a$), 2.88 (d, 1H, $J = 14.8$ Hz, H-7$_b$), 2.48 – 2.37 (m, 4H, H-2, –CCH$_3$), 2.05 (s, 3H, –OCC$_3$H$_3$), 1.96 (s, 3H –OCC$_3$H$_3$), 1.93 – 1.80 (m, 5H, –OCC$_3$H$_3$, cyclohexyl), 1.76 – 1.62 (m, 2H, cyclohexyl), 1.55 – 1.48 (m, 1H, cyclohexyl), 1.42 – 1.13 (m, 5H, cyclohexyl).

$^{13}$C NMR: (CDCl$_3$ 100 MHz) $\delta$C 170.6 (x2), 169.7 (–OCC$_3$H$_3$), 145.1, 136.2, 130.1, 127.9 (Ar), 96.0 (C-1), 77.3 (C-1’), 70.7 (C-3), 69.6 (C-5), 67.3 (C-4), 62.2 (C-6), 53.7 (C-7), 40.3 (C-2), 33.3, 31.5, 25.4, 24.1, 24.0 (cyclohexyl), 21.6 (–CCH$_3$), 20.7, 20.6 (x2) (–OCC$_3$H$_3$).

IR: 1743.9, 1225.1, 1020.9 cm$^{-1}$ (neat).

$[\alpha]_D$: +37.5 (c 0.1, CHCl$_3$).
Cyclohexyl-3,4,6-tri-O-acetyl-2-deoxy-2-C-para-tert-butylphenylsulfonylmethyl-β-D-glucopyranoside (159)

Yield: 0.06 g, 80% white solid.

Mp: 157 – 159 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): $\delta_H$ 7.76 (d, 2H, $J = 8.4$ Hz, Ar), 7.53 (d, 2H, $J = 8.0$ Hz, Ar), 5.25 (t, 1H, $J = 10.2$ Hz, H-3), 4.95 (t, 1H, $J = 9.6$ Hz, H-4), 4.57 (d, 1H, $J = 8.8$ Hz, H-1), 4.25 (dd, 1H, $J = 5.0$ Hz and 12.2 Hz, H-6$\alpha$), 4.04 (d, 1H, $J = 12.0$ Hz, H-6$\beta$), 3.65 – 3.46 (m, 2H, H-5), 3.27 (d, 2H, $J = 3.6$ Hz, H-7$\alpha$, H-7$\beta$), 2.43 – 2.30 (m, 1H, H-2), 2.06 – 1.97 (m, 9H, 3 x –OCC$_3$H$_3$), 1.80 – 1.53 (m, 4H, cyclohexyl), 1.52 – 1.42 (m, 1H, cyclohexyl), 1.46 – 1.03 (m, 13H, –C(CH$_3$)$_3$, cyclohexyl).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): $\delta_C$ 170.9, 170.6, 169.7 (–OCC$_3$H$_3$), 157.5, 137.1, 127.9, 126.3 (Ar), 99.4 (C-1), 77.7 (C-1'), 72.8 (C-3), 71.6 (C-5), 69.7 (C-4), 62.4 (C-6), 54.2 (C-7), 42.8 (C-2), 35.2 (–CCH$_3$), 33.3, 31.5 (cyclohexyl), 31.0 (–C(CH$_3$)$_3$), 25.4, 23.9 (cyclohexyl), 20.9, 20.7 (x2) (–OCC$_3$H$_3$).

IR: 1740.2, 1364.9, 1044.7, 1023.6 cm$^{-1}$ (neat).

$[\alpha]_D$: -17.0 (c 0.1, CHCl$_3$).
**Cyclohexyl-3,4,6-tri-O-acetyl-2-deoxy-2-C-2-naphthalenesulfonylmethyl-β-D-glucopyranoside (160)**

Yield: 0.06 g, 84% white solid.

Mp: 175 – 177 °C.

**¹H NMR:** (CDCl₃ 400 MHz): δ H 8.14 (s, 1H, Ar), 8.00 – 7.82 (m, 3H, Ar), 7.62 – 7.53 (m, 3H, Ar), 5.28 (t, 1H, J = 10.2 Hz, H-3), 4.96 (t, 1H, J = 9.4 Hz, H-4), 4.64 (d, 1H, J = 8.8 Hz, H-1), 4.25 (dd, 1H, J = 4.8 Hz and 12.0 Hz, H-6a), 4.05 (dd, 1H, J = 1.8 Hz and 12.2 Hz, H-6b), 3.72 – 3.58 (m, 2H, H-1', H-5), 2.99 (dd, 1H, J = 5.6 Hz and 13.6 Hz, H-7a), 2.89 (dd, 1H, J = 4.4 Hz and 13.6 Hz, H-7b), 2.30 – 2.15 (m, 1H, H-2), 2.23 (s, 3H, –OCC₃H₃), 2.09 – 1.94 (m, 6H, 2 x –OCC₃H₃), 1.91 – 1.76 (m, 2H, cyclohexyl), 1.74 – 1.58 (m, 2H, cyclohexyl), 1.56 – 1.45 (m, 1H, cyclohexyl), 1.40 – 1.10 (m, 5H, cyclohexyl).

**¹³C NMR:** (CDCl₃ 100 MHz): δ C 170.6, 170.5, 169.7 (–OCC₃), 134.6, 132.8, 129.7, 128.6, 128.0, 127.9, 127.3, 125.0, 119.9 (Ar), 100.2 (C-1), 77.9 (C-1'), 73.1 (C-3), 71.5 (C-5), 69.7 (C-4), 62.3 (C-6), 56.9 (C-7) 43.3 (C-2), 33.3, 31.6, 25.4, 23.8, 23.8 (cyclohexyl), 21.0, 20.7, 20.6 (–OCC₃).

**IR:** 1742.3, 1221.7, 1024.8, 814.8 cm⁻¹ (neat).

**[α]₀:** +22.5 (c 0.1, CHCl₃).
Cyclohexyl-3,4,6-tri-O-acetyl-2-deoxy-2-C-n-propylsulfonylmethyl-β-D-glucopyranoside (161)

Yield: 0.05 g, 78% white solid.

Mp: 142 – 144 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): $\delta$H 5.16 (t, 1H, $J = 10.0$ Hz, H-3), 4.97 (t, 1H, $J = 9.4$ Hz, H-4), 4.58 (d, 1H, $J = 8.8$ Hz, H-1), 4.25 (dd, 1H, $J = 5.0$ Hz and 12.2 Hz, H-6a), 4.06 (d, 1H, $J = 12.0$ Hz, H-6b), 3.70 – 3.59 (m, 2H, H-1", H-5), 3.14 (dd, 1H, $J = 2.4$ Hz and 14.8 Hz, H-7a), 3.07 – 2.86 (m, 3H, H-7b, H-8a, H-8b), 2.43 – 2.82 (m, 1H, H-2), 2.10 – 1.67 (m, 11H, H-9a, H-9b, 3 x –OCCH$_3$), 1.58 – 1.47 (m, 1H, cyclohexyl), 1.40 – 1.09 (m, 5H, cyclohexyl), 1.03 (t, 3H, $J = 7.4$ Hz, –CH$_2$CH$_2$CH$_3$).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): $\delta$C 171.0, 170.6, 169.6 (–OCCH$_3$), 99.4 (C-1), 77.9 (C-1’), 72.9 (C-3), 71.7 (C-5) 69.4 (C-4), 62.2 (C-6), 55.3 (C-7), 50.8 (C-8), 42.4 (C-2), 33.5, 31.7, 25.4, 24.1, 24.0 (cyclohexyl), 20.9, 20.7, 20.6 (3 x –OCCH$_3$), 15.5 (C-9), 13.1 (C-10).

IR: 1740.2, 1365.3, 1224.8, 1027.0, 1738.2 cm$^{-1}$ (neat).

$[\alpha]_D$: -7.0 (c 0.1, CHCl$_3$).
Cyclohexyl-3,4,6-tri-O-acetyl-2-deoxy-2-C-iso-propylsulfonylmethyl-\(\beta\)-D-glucopyranoside (162)

Yield: 0.05 g, 81% white solid.

Mp: 143 – 145 °C.

\(^1\)H NMR: (CDCl\(_3\) 400 MHz): \(\delta_H\) 5.25 (t, 1H, \(J = 11.0\) Hz, H-3), 4.97 (t, 1H, \(J = 9.6\) Hz, H-4), 4.67 (d, 1H, \(J = 8.8\) Hz, H-1), 4.26 (dd, 1H, \(J = 4.8\) Hz and 12.0 Hz, H-6\(_a\)), 4.15 – 4.03 (m, 1H, H-6\(_b\)), 4.70 – 3.60 (m, 2H, H-1', H-5), 3.22 (d, 1H, \(J = 2.4\) Hz, H-7\(_a\)), 3.15 – 3.06 (m, 1H, H-8), 3.01 (dd, 1H, \(J = 5.6\) Hz and 14.4 Hz, H-7\(_b\)), 2.50 – 2.41 (m, 1H, H-2), 2.10 – 1.83 (m, 11H, 3 x –CCH\(_3\), cyclohexyl), 1.77 – 1.48 (m, 4H, cyclohexyl), 1.40 – 1.10 (m, 10H, –CH(CH\(_3\))\(_2\), cyclohexyl).

\(^13\)C NMR: (CDCl\(_3\) 100 MHz): \(\delta_C\) 170.9, 170.7, 169.7 (–OCH\(_3\)), 99.2 (C-1), 77.9 (C-1'), 72.8 (C-3), 71.7 (C-5), 69.6 (C-4), 62.3 (C-6), 53.9 (C-7), 46.7 (C-8), 42.3 (C-2), 33.5, 31.8, 25.4, 24.1 (cyclohexyl), 20.9, 20.7, 20.6 (–OCCH\(_3\)), 16.0, 14.7 (–CH(CH\(_3\))\(_2\)).

IR: 1740.2, 1365.6, 1245.1, 1156.5, 1028.8 cm\(^{-1}\) (neat).

\([\alpha]_D\): -3.0 (c 0.1, CHCl\(_3\)).
**Cyclohexyl-3,4,6-tri-O-acetyl-2-deoxy-2-C-phenylsulfinymethyl-\(\beta\)-D-glucopyranoside**

(163a and 163b)

![Chemical Structures](attachment:image.png)

**First diastereoisomer**

Yield: 0.03 g, 43% white solid.

Mp: 177 – 179 °C.

\(^1\)H NMR: (CDCl\(_3\) 400 MHz): \(\delta_H \) 7.65 – 7.42 (m, 5H, Ar), 5.25 (t, 1H, \(J = 10.0\) Hz, H-3), 4.95 (t, 1H, \(J = 9.4\) Hz, H-4), 4.62 (d, 1H, \(J = 8.4\) Hz, H-1), 4.25 (dd, 1H, \(J = 3.6\) Hz and 12.0 Hz, H-6\(_a\)), 4.04 (d, 1H, \(J = 12.0\) Hz, H-6\(_b\)), 3.69 – 3.57 (m, 2H, H-1\(_a\), H-5), 2.93 (dd, 1H, \(J = 5.2\) Hz and 13.2 Hz, H-7\(_a\)), 2.76 (d, 1H, \(J = 9.6\) Hz, H-7\(_b\)), 2.25 – 2.12 (m, 1H, H-2), 2.00 – 1.91 (m, 9H, 3 x –CH\(_3\)), 1.88 – 1.77 (m, 2H, cyclohexyl), 1.75 – 1.60 (m, 2H, cyclohexyl), 1.52 – 1.41 (m, 1H, cyclohexyl), 1.40 – 1.12 (m, 5H, cyclohexyl).

\(^13\)C NMR: (CDCl\(_3\) 100 MHz): \(\delta_C \) 170.6, 170.5, 169.7 (–OC\(_3\)), 144.2, 131.4, 129.4, 124.2 (Ar), 100.1 (C-1), 77.9 (C-1\(_a\)), 73.1 (C-3), 69.7 (C-5), 62.3 (C-4), 57.0 (C-6), 43.2 (C-2), 33.3, 31.6, 25.4, 23.8 (cyclohexyl), 21.0, 20.7, 20.6 (–OC\(_3\)).

IR: 1736.6, 1370.4, 1054.1, 1025.9 cm\(^{-1}\) (neat).

\([\alpha]_D\): -39.5 (c 0.1, CHCl\(_3\)).

**Second diastereoisomer**
Yield: 0.02 g, 32% white solid.

Mp: 157 – 152 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): $\delta$H 7.64 (bs, 2H), 7.51 (bs, 3H), 5.05 (t, 1H, $J = 10.0$ Hz, H-3), 4.84 (t, 1H, $J = 9.2$ Hz, H-4), 4.54 (d, 1H, $J = 8.0$ Hz, H-1), 4.25 (dd, 1H, $J = 3.6$ Hz and 12.0 Hz, H-6$_a$), 4.65 (d, 1H, $J = 10.8$ Hz, H-6$_b$), 3.72 – 3.58 (m, 2H, H-1', H-5), 3.05 – 2.95 (m, 1H, H-7$_a$), 2.63 (bd, 1H, $J = 8.8$ Hz, H-7$_b$), 2.10 – 1.82 (m, 12H, H-2, cyclohexyl, 3 x –OCC$_3$H$_3$), 1.80 – 1.16 (m, 2H, cyclohexyl), 1.57 – 1.21 (m, 6H, cyclohexyl).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): $\delta$C 170.6, 170.5, 169.6 (–OCCH$_3$), 131.4, 129.3, 124.5 (Ar), 100.3 (C-1), 78.1 (C-1'), 73.2 (C-3), 71.7 (C-5), 69.4 (C-4), 62.3 (C-6), 57.1 (C-7) 42.2 (C-2), 33.4, 31.7, 25.4, 24.0 (x2) (cyclohexyl), 20.8, 20.7, 20.6 (–OCCH$_3$).

IR: 1735.8, 1367.1, 1225.4, 1020.8 cm$^{-1}$ (neat).

$[\alpha]_D$: +17.5 (c 0.1, CHCl$_3$).

**Cyclohexyl-3,4,6-tri-O-acetyl-2-deoxy-2-C-para-chlorophenylsulfinylmethyl-β-D-glucopyranoside (164a and 164b)**

![Chemical structures of 164a and 164b](image)

**First diastereoisomer**
Yield: 0.02 g, 38% white solid.

Mp: 169 – 171 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): δ$_H$ 7.54 (d, 2H, $J = 8.4$ Hz, Ar), 7.47 (d, 2H, $J = 8.4$ Hz, Ar), 5.22 (d, 1H, $J = 10.0$ Hz, H-3), 4.94 (d, 1H, $J = 9.4$ Hz, H-4), 4.59 (d, 1H, $J = 8.4$ Hz, H-1), 4.25 (dd, 1H, $J = 4.6$ Hz and 12.2 Hz, H-6$_a$), 4.04 (d, 1H, $J = 12.2$ Hz, H-6$_b$), 3.68 – 3.53 (m, 2H, H-1”, H-5), 2.90 (dd, 1H, $J = 5.4$ Hz and 13.0 Hz, H-7$_a$), 2.73 (bd, 1H, $J = 9.2$ Hz, H-7$_b$), 2.21 – 1.91 (m, 10H, H-2, 3 x –OCCH$_3$), 1.89 – 1.76 (m, 2H, cyclohexyl), 1.72 – 1.58 (m, 2H, cyclohexyl), 1.55 – 1.11 (m, 6H, cyclohexyl).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): δ$_C$ 170.6, 170.5, 169.6 (–OCCH$_3$), 142.8, 137.6, 129.7, 129.3, 125.8, 125.7 (Ar), 100.0 (C-1), 77.9 (C-1’), 73.1 (C-3), 71.5 (C-5), 69.6 (C-4), 62.3 (C-6), 57.2 (C-7), 43.2 (C-2), 33.3, 31.6, 25.4, 23.8 (cyclohexyl), 21.0, 20.7, 20.6 (–OCCH$_3$).

IR: 1741.6, 1366.1, 1221.8, 1029.6 cm$^{-1}$ (neat).

$[\alpha]_D$: +20.0 (c 0.1, CHCl$_3$).

**Second diastereoisomer**

Yield: 0.03 g, 41% white solid.

Mp: 146 – 148 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): δ$_H$ 7.68 – 7.45 (m, 4H, Ar), 5.12 – 4.98 (m, 1H, H-3), 4.91 – 4.83 (m, 1H, H-4), 4.25 (bd, 1H, $J = 10.8$ Hz, H-6$_a$), 4.04 (d, 1H, $J = 12.0$ Hz, H-6$_b$), 3.73 – 3.55 (m, 2H, H-1’, H-5), 3.06 – 2.90 (m, 1H, H-7$_a$), 2.70 – 2.51 (m, 1H, H-7$_b$), 2.12 – 1.82 (m, 11H, H-2, cyclohexyl, 3 x –OCCH$_3$), 1.81 – 1.64 (m, 3H, cyclohexyl), 1.60 – 1.21 (m, 6H, cyclohexyl).
\(^{13}\)C NMR: (CDCl\(_3\) 100 MHz): \(\delta_c\) 170.6, 170.5, 169.6 (–OC\(_3\)), 137.7, 129.7, 126.1 (Ar), 100.2 (C-1), 78.2 (C-1'), 73.3 (C-3), 71.7 (C-5), 69.3 (C-4), 62.3 (C-6), 42.2 (C-2), 33.4, 31.7, 25.4, 24.1, 24.0 (cyclohexyl), 20.8, 20.7, 20.6 (–OC\(_3\)).

IR: 1740.2, 1247.6, 1227.2, 1023.1, 820.0 cm\(^{-1}\) (neat).

\([\alpha]_D\): -31.5 (c 0.1, CHCl\(_3\)).

\textit{Cyclohexyl-3,4,6-tri-O-acetyl-2-deoxy-2-C-para-bromophenylsulfinylmethyl-\(\beta\)-D-glucopyranoside (165a and 165b)}

![Diagram of 165a and 165b]

\textbf{First diastereoisomer}

Yield: 0.03 g, 47\% white solid.

Mp: 171 - 173 \(^\circ\)C.

\(^1\)H NMR: (CDCl\(_3\) 400 MHz): \(\delta_h\) 7.64 (d, 2H, \(J = 8.0\) Hz, Ar), 7.48 (d, 2H, \(J = 8.0\) Hz, Ar), 5.23 (t, 1H, \(J = 10.0\) Hz, H-3), 4.95 (t, 1H, \(J = 9.2\) Hz, H-4), 4.60 (d, 1H, \(J = 8.8\) Hz, H-2), 4.25 (dd, 1H, \(J = 4.4\) Hz and 12.0 Hz, H-6\(_a\)), 4.05 (d, 1H, \(J = 12.0\) Hz, H-6\(_b\)), 3.69 – 3.56 (m, 2H, H-1', H-5), 2.91 (dd, 1H, \(J = 5.6\) Hz and 13.2 Hz, H-7\(_a\)), 2.73 (dd, 1H, \(J = 3.8\) Hz and 13.0 Hz, H-7\(_b\)), 2.22 – 1.95 (m, 10H, H-2, 3 x –OC\(_3\)), 1.90 – 1.78 (m, 2H, cyclohexyl), 1.72 – 1.58 (m, 2H, cyclohexyl), 1.52 – 1.11 (m, 6H, cyclohexyl).
$^{13}$C NMR: (CDCl$_3$ 100 MHz): $\delta_C$ 170.6, 170.5, 169.7 (–OCCH$_3$), 143.4, 132.6, 125.9, 125.8 (Ar), 100.0 (C-1), 78.0 (C-1'), 73.1 (C-3), 71.5 (C-5), 69.5 (C-4), 62.2 (C-6), 57.2 (C-7), 43.2 (C-2), 33.3, 31.6, 25.4, 23.8 (cyclohexyl), 21.0, 20.7, 20.6 (–OCCH$_3$).

IR: 1754.0, 1367.7, 1223.2, 1030.6, 818.1 cm$^{-1}$ (neat).

$[\alpha]_D$: +25.0 (c 0.1, CHCl$_3$).

**Second diastereoisomer**

Yield: 0.03 g, 36% white solid.

Mp: 150 – 152 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): $\delta_H$ 7.64 (d, 2H, $J = 8.0$ Hz, Ar), 7.52 (d, 2H, $J = 8.0$ Hz, Ar), 5.04 (t, 1H, $J = 10.0$ Hz, H-3), 4.86 (t, 1H, $J = 9.2$ Hz, H-4), 4.52 (t, 1H, $J = 8.0$ Hz, H-1), 4.24 (dd, 1H, $J = 4.4$ Hz and 12.0 Hz, H-6a), 4.03 (d, 1H, $J = 9.2$ Hz, H-6b), 3.72 – 3.59 (m, 2H, H-1' and H-5), 3.04 – 2.98 (m, 1H, H-7a), 2.64 – 2.50 (m, 1H, H-7b), 2.10 – 1.83 (m, 12H, H-2, 3 x –OCCH$_3$, cyclohexyl), 1.80 – 1.64 (m, 2H, cyclohexyl), 1.55 – 1.12 (m, 6H, cyclohexyl).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): $\delta_C$ 170.7, 170.6, 169.7 (–OCCH$_3$), 132.6, 126.3, 126.0 (Ar), 100.2 (C-1), 78.2 (C-1'), 73.3 (C-3), 71.8 (C-5), 69.4 (C-4), 62.3 (C-6), 57.3 (C-7), 42.2 (C-2), 33.5, 31.8, 25.5, 24.2, 24.1 (cyclohexyl), 20.9, 20.8, 20.7 (–OCCH$_3$).

IR: 1740.7, 1364.7, 1225.8, 1031.6, 819.9 cm$^{-1}$ (neat).

$[\alpha]_D$: -36.0 (c 0.1, CHCl$_3$).
**Cyclohexyl-3,4,6-tri-O-acetyl-2-deoxy-2-C-2-naphthalenesulfinylmethyl-\(\beta\)-D-glucopyranoside (166a and 166b)**

First diastereoisomer

**Yield:** 0.02 g, 35% white solid.

**Mp:** 173 – 175 °C.

**\(^1\)H NMR:** (CDCl\(_3\) 400 MHz): \(\delta_h\): 8.14 (s, 1H, Ar), 8.00 – 7.85 (m, 3H, Ar), 7.63 – 7.50 (m, 3H, Ar), 5.28 (t, 1H, \(J = 10.0\) Hz, H-3), 4.97 (t, 1H, \(J = 9.4\) Hz, H-4), 4.64 (d, 1H, \(J = 8.8\) Hz, H-1), 4.25 (dd, 1H, \(J = 4.4\) Hz and 12.0 Hz, H-6\(_a\)), 4.05 (d, 1H, \(J = 12.0\) Hz, H-6\(_b\)) 3.71 – 3.57 (m, 2H, H-1", H-5), 2.99 (dd, 1H, \(J = 5.2\) Hz and 13.2 Hz, H-7\(_a\)), 2.89 (dd, 1H, \(J = 3.8\) Hz and 13.4 Hz, H-7\(_b\)), 2.31 – 2.15 (m, 1H, H-2), 2.12 (s, 3H, –OCC\(_3\)H), 2.00 – 1.95 (m, 6H, 2 x –OCC\(_3\)H), 1.92 – 1.77 (m, 2H, cyclohexyl), 1.75 – 1.57 (m, 2H, cyclohexyl), 1.54 – 1.42 (m, 1H, cyclohexyl), 1.40 – 1.10 (m, 5H, cyclohexyl).

**\(^{13}\)C NMR:** (CDCl\(_3\) 100 MHz): \(\delta_c\): 170.6, 170.5, 169.7 (–OCC\(_3\)H), 141.2, 134.6, 132.8, 129.7, 128.6, 128.0, 127.9, 127.3, 125.1, 119.9 (Ar), 100.1 (C-1), 77.9 (C-1'), 73.1 (C-3), 71.5 (C-5), 69.7 (C-4), 62.3 (C-6), 56.8 (C-7), 43.3 (C-2), 33.3, 31.6, 25.4, 23.8 (x2) (cyclohexyl), 21.0, 20.7, 20.6 (–OCC\(_3\)H).

**IR:** 1745.6, 1217.9, 1029.4, 822.2 cm\(^{-1}\) (neat).

**[\(\alpha\)]\(_D\):** -37.5 (c 0.1, CHCl\(_3\)).
Second diastereoisomer

Yield: 0.02 g, 37% white solid.

Mp: 187 – 189 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): $\delta$H 8.19 (s, 1H, Ar), 8.02 – 7.88 (m, 3H, Ar), 7.69 – 7.53 (m, 3H, Ar), 5.08 (t, 1H, $J = 10.0$ Hz, H-3), 4.84 (t, 1H, $J = 9.2$ Hz, H-4), 4.55 (d, 1H, $J = 8.0$ Hz, H-1), 4.24 (dd, 1H, $J = 4.0$ Hz and $12.0$ Hz, H-6a), 4.04 (d, 1H, $J = 12.0$ Hz, H-6b), 3.75 – 3.56 (m, 2H, H-1’, H-5), 3.07 (dd, 1H, $J = 6.0$ Hz and $12.8$ Hz, H-7a), 2.75 (dd, 1H, $J = 4.8$ Hz and $12.8$ Hz, H-7b), 2.20 – 1.63 (m, 14H, H-2, cyclohexyl, 3 x –OCCH$_3$), 1.60 – 1.22 (m, 6H, cyclohexyl).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): $\delta$C 170.6 (x2), 169.6 (–OCCH$_3$), 141.0, 134.6, 132.8, 129.6, 128.6, 128.1, 127.9, 127.3, 125.4, 120.1 (Ar), 100.3 (C-1), 78.1 (C-1’), 73.3 (C-3), 71.7 (C-5), 69.4 (C-4), 62.3 (C-6), 56.9 (C-7), 42.1 (C-2), 33.4, 31.7, 25.4, 24.1, 24.0 (cyclohexyl), 20.8, 20.7, 20.6 (–OCCH$_3$).

IR: 1745.3, 1368.0, 1219.4, 1069.6, 1029.8 cm$^{-1}$ (neat).

$[\alpha]_D$: -27.5 (c 0.1, CHCl$_3$).

Cyclohexyl-3,4,6-tri-O-acetyl-2-deoxy-2-C-para-methylphenylsulfinylmethyl-β-D-glucopyranoside (167a and 167b)
First diastereoisomer

Yield: 0.03 g, 45% white solid.

Mp: 169 – 171 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): $\delta$H 7.49 (d, 2H, $J$ = 7.6 Hz, Ar), 7.30 (d, 2H, $J$ = 7.2 Hz, Ar), 5.24 (t, 1H, $J$ = 10.0 Hz, H-3), 4.93 (t, 1H, $J$ = 9.4 Hz, H-4), 4.60 (d, 1H, $J$ = 8.4 Hz, H-1), 4.25 (dd, 1H, $J$ = 4.6 Hz and 12.2 Hz, H-6$_a$), 4.04 (d, 1H, $J$ = 12.0, H-6$_b$), 3.70 – 3.58 (m, 2H, H-1", H-5), 2.94 (dd, 1H, $J$ = 5.8 Hz and 13.0 Hz, H-7$_a$), 2.77 (bd, 1H, $J$ = 9.6 Hz, H-7$_b$), 2.39 (s, 3H, –CCH$_3$), 2.18 – 1.92 (m, 10H, H-2, 3 x –OCCH$_3$), 1.90 – 1.78 (m, 2H, cyclohexyl), 1.74 – 1.62 (m, 2H, cyclohexyl).

$^{13}$C NMR: (CDCl$_3$ 100 MHz): δC 170.7, 170.5, 169.7 (–OCCH$_3$), 142.0, 140.9, 130.1, 124.4 (Ar), 100.2 (C-1), 78.0 (C-1’), 73.2 (C-3), 71.5 (C-5), 70.0 (C-4), 62.4 (C-6), 57.0 (C-7), 43.3 (C-2), 33.3, 31.6, 25.5, 23.8 (cyclohexyl), 21.4 (–CCH$_3$), 21.0, 20.7 (–OCCH$_3$).

IR: 1748.6, 1365.8, 1220.9, 1032.9 cm$^{-1}$ (neat).

$[\alpha]_D$: +18.0 (c 0.1, CHCl$_3$).

Second diastereoisomer

Yield: 0.02 g, 33% white solid.

Mp: 158 – 160 °C.

$^1$H NMR: (CDCl$_3$ 400 MHz): $\delta$H 7.53 (d, 1H, $J$ = 7.6 Hz, Ar), 7.30 (d, 1H, $J$ = 7.6 Hz, Ar), 5.04 (t, 1H, $J$ = 9.8 Hz, H-3), 4.84 (t, 1H, $J$ = 9.0 Hz, H-4), 4.53 (d, 1H, $J$ = 5.6 Hz, H-1), 4.24 (dd, 1H, $J$ = 3.8 Hz and 11.8 Hz, H-6$_a$), 4.03 (d, 1H, $J$ = 12.0 Hz, H-6$_b$), 3.70 – 3.56 (m, 2H, H-1’, H-5), 3.08 – 2.84 (m, 1H, H-7$_a$), 2.65 – 2.57 (m, 1H, H-7$_b$), 2.41 (s, 3H, –CCH$_3$), 2.10 – 1.85 (m, 12H, H-2, H-3, H-5).
cyclohexyl, 3 x –OCCH₃), 1.80 – 1.65 (m, 2H, cyclohexyl), 1.56 – 1.12 (m, 6H, cyclohexyl).

^{13}C NMR: (CDCl₃ 100 MHz): δC 170.6, 170.4, 169.7 (–OCCH₃), 142.0, 130.1, 124.7 (Ar), 100.4 (C-1), 78.1 (C-1'), 73.2 (C-3), 71.7 (C-5), 69.4 (C-4), 62.4 (C-6), 57.0 (C-7), 42.2 (C-2), 33.4, 31.7, 25.4, 24.1, 24.0 (cyclohexyl), 21.5 (–CCH₃), 20.8, 20.7, 20.6 (–OCCH₃).

IR: 1741.4, 1366.5, 1229.3, 1088.5, 1030.7 cm⁻¹ (neat).

[α]₀⁻: -30.5 (c 0.1, CHCl₃).
6.7 Synthesis of carbohydrate-based thiochromans

1-O-Acetyl-3,4,6-tri-O-benzyl-2-deoxy-2-C-iodomethyl-α- and -β-D-glucopyranoses

![Diagram](168)

Cyclopropanated sugar 103 (0.32 g, 0.74 mmol) was dissolved in a solution of CH$_3$CN (5.0 mL) and acetic acid (3.0 mL) and cooled on ice. Acetic anhydride (0.60 mL, 5.95 mmol), NH$_3$I (0.12 g, 0.83 mmol), and 30% H$_2$O$_2$ (0.33 mL, 3.33 mmol) were successfully added and the reaction was stirred on ice for 10 min and then a further 1 h at room temperature. The mixture was diluted with DCM (10 mL) and washed with a 10% solution of Na$_2$S$_2$O$_3$ (10 mL). The aqueous layer was extracted twice with DCM (10 mL portions). The combined organic fractions were washed twice with saturated NaHCO$_3$ (10.0 mL portions) and once with brine (10 mL). The organic layer was then dried over anhydrous Mg$_2$SO$_4$ and removed under reduced pressure. The residue was purified by column chromatography on silica gel using hexane and ethyl acetate (9:1) as eluent.

Yield: 0.31 g, 67% clear oil 1:2 α:β anomeric ratio

β-anomer

$^{1}$H NMR: (CDCl$_3$, 400 MHz): δ$_H$ 7.48 – 7.03 (m, 15H, Ar), 5.57 (d, 1H, $J = 8.4$ Hz, H-1), 5.05 – 4.42 (m, 6H, –CH$_2$Ph), 3.94 – 3.40 (m, 6H, H-3, H-4, H-5, H-6$_a$, H-6$_b$, H-7$_a$), 3.26 (d, 1H, $J = 10.0$ Hz, H-7$_b$), 2.35 – 2.05 (s, 3H, –OCH$_3$), 1.60 – 1.44 (m, 1H, H-2).
\[ ^{13}C \text{NMR: } (\text{CDCl}_3, 100 \text{ MHz}): \delta_C \ 169.0, 168.9 (-\text{OCCH}_3), 137.8, 128.6, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7 (Ar), 94.9 (C-1), 81.3 (C-3), 78.8 (C-4), 75.5 (C-5), 75.0, 73.6, 73.5, (-\text{CH}_2\text{Ph}), 68.0 (C-6), 44.9 (C-2), 21.0 (-\text{OCH}_3), 4.3 (C-7). \]

\( \alpha \)-Anomer

\[ ^1H \text{NMR: } (\text{CDCl}_3, 400 \text{ MHz}): \delta_H \ 6.35 \text{ (s, 1H, H-1), 2.90 – 2.75 (m, 1H, H-7\text{b}), 2.30 – 2.19 (m, 1H, H-2), 2.08 \text{ (s, 3H, –OCCH}_3). \]

\[ ^{13}C \text{NMR: } (\text{CDCl}_3, 100 \text{ MHz}): \delta_C \ 93.7 \text{ (C-1), 80.8 (C-3), 78.4 (C-4), 76.0 (C-5), 75.4, 74.8, 73.3 (-\text{CH}_2\text{Ph}), 46.7 (C-2), 0.9 (C-7).} \]

\text{IR: } 1752, 1496, 1453, 1226, 1096, 1026, 954, 735, 695.3 \text{ cm}^{-1} \text{ (neat).}

**General procedure for the thiolation of iodomethyl glycosides**

Thiophenol (65.13 \mu L, 0.64 mmol) was added to a 9:1 solution of THF:DMSO (5 mL) under anhydrous conditions and NaH (60\% dispersion, 0.03 g, 0.64 mmol) was added. The reaction left to stir until cessation of bubble formation (~ 5 min). Iodomethyl glycoside 124 (0.35 g, 0.57 mmol) was then added and the reaction was left to continue stirring under anhydrous conditions for a further 15 min upon which the reaction showed completion on TLC. Methanol (~2 mL) was added in a dropwise fashion until the solution became clear and the solvents were removed under reduced pressure. The residue product was purified by column chromatography on silica gel using hexane and ethyl acetate (5:1) as eluent.
1-O-Acetyl-3,4,6-tri-O-benzyl-2-deoxy-2-C-phenylthiomethyl-D-glucopyranoside (169)

Yield: 0.28 g, 83% white solid of α:β anomeric mixtures.

Mp: 74 – 76 °C.

$^1$H NMR: (CDCl$_3$, 400 MHz): δ$^\beta$ 7.46 – 7.03 (m, 20H, Ar), 5.66 (d, $J = 9.2$ Hz, 1H, H-1), 4.93 (d, $J = 10.8$ Hz, 1H, –CH$_2$Ph), 4.79 (d, $J = 10.4$ Hz, 1H, –CH$_2$Ph), 4.75 – 4.40 (m, 4H, –CH$_2$Ph), 3.90 – 3.70 (m, 5H, H-3, H-4, H-5, H-6$_a$, H-6$_b$), 3.27 (dd, $J = 3.6$ Hz and 13.2 Hz, 1H, H-7$_a$), 3.18 (d, $J = 13.2$ Hz, 1H, H-7$_b$), 2.32 – 2.18 (m, 1H, H-2), 1.98 (s, 3H, –OCOC$_H_3$).

$^{13}$C NMR: (CDCl$_3$, 100 MHz): δ$^\beta$ 168.9 (–OCOC$_H_3$), 138.1, 137.9, 137.8, 136.7, 129.8, 129.0, 128.4, 128.3, 127.9, 127.8, 127.7, 126.4 (Ar), 93.1 (C-1), 80.3 (C-4), 79.0 (C-3), 75.4 (C-5), 74.9 (–CH$_2$Ph), 73.6 (–CH$_2$Ph), 73.5 (–CH$_2$Ph), 73.0 (C-6), 46.1 (C-2), 31.4 (C-7), 20.9 (–OCOC$_H_3$).

$^1$H NMR: (CDCl$_3$, 400 MHz): δ$^\alpha$ 6.42 (s, 1H, H-1), 4.98 (d, $J = 11.2$ Hz, 1H, CH$_2$Ph), 3.44 (d, $J = 13.2$ Hz, 1H, H-7$_a$), 2.57 (t, $J = 12.4$ Hz, 1H, H-7$_b$), 2.05 (s, 3H, OCOCH$_3$).

$^{13}$C NMR: (CDCl$_3$, 100 MHz): δ$^\alpha$ 168.9 (–OCOC$_H_3$), 137.7, 135.6, 128.9, 128.5, 128.3, 128.0, 127.7, 127.6, 126.0 (Ar), 92.0 (C-1), 80.2 (C-4), 78.8 (C-3), 75.3 (C-5), 74.9 (–CH$_2$Ph), 73.7 (–CH$_2$Ph), 73.5 (–CH$_2$Ph), 68.1 (C-6), 44.4 (C-2), 30.6 (C-7), 20.9 (–OCOC$_H_3$).
IR: 1752, 1483, 1452, 1137, 699 cm\(^{-1}\) (CHCl\(_3\)).

HRMS (ESI): \(m/z\) [M+Na]\(^+\) Calcd: 621.2287; Found: 621.2289.

\(1\)-O-Acetyl-3,4,6-tri-O-benzyl-2-deoxy-2-C-(4-methylphenyl)thiomethyl-D-glucopyranoside (172)

Yield: 0.30 g, 87% colourless oil of \(\alpha:\beta\) anomeric mixtures.

\(^1\)H NMR: (CDCl\(_3\), 400 MHz): \(\delta\) 5.68 (d, \(J = 8.8\) Hz, 1H, H-1), 3.27 (d, \(J = 11.6\) Hz, 1H, H-7\(_a\)), 3.15 (d, \(J = 12.8\) Hz, H-7\(_b\)), 2.0 (s, 3H, –OCOC\(_3\)H\(_3\)).

\(^13\)C NMR: (CDCl\(_3\), 100 MHz): \(\delta\) 169.0 (–OCOC\(_3\)H\(_3\)), 137.8, 136.5, 132.9, 129.7, 128.4, 128.5, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6 (Ar), 93.1 (C-1), 80.3 (C-4), 79.8 (C-3), 75.4 (C-5), 75.2 (–CH\(_2\)Ph), 74.6 (–CH\(_2\)Ph), 73.4 (–CH\(_2\)Ph), 46.1 (C-2), 32.1 (C-7), 20.9 (–OCOC\(_3\)H\(_3\)) 20.8 (–CCH\(_3\)).

\(^1\)H NMR: (CDCl\(_3\), 400 MHz): \(\delta\) 7.51 – 7.05 (m, 19H, Ar), 6.43 (bs, 1H, H-1), 4.96 (d, \(J = 11.2\) Hz, 1H, –CH\(_2\)Ph), 4.79(d, \(J = 10.4\) Hz, 1H –CH\(_2\)Ph), 4.75 – 4.42 (m, 4H, –CH\(_2\)Ph), 3.95 – 3.62 (m, 5H, H-3, H-4, H-5, H-6\(_a\), H-6\(_b\)), 3.40 (d, \(J = 13.2\) Hz, 1H, H-7\(_a\)), 2.58 (t, \(J = 12.4\) Hz, 1H, H-7\(_b\)), 2.32 (s, 3H, –CCH\(_3\)), 2.95 – 2.18 (m, 1H, H-2), 2.05 (s, 3H, –OCOC\(_3\)H\(_3\)).

\(^13\)C NMR: (CDCl\(_3\), 100 MHz): \(\delta\) 169.0 (–OCOC\(_3\)H\(_3\)), 138.1, 137.9, 137.7, 136.2, 131.8, 130.6, 129.7, 128.4, 128.3, 127.9, 127.8, 127.7 (Ar), 92.0 (C-1), 78.9 (C-4), 78.7 (C-2), 47.9 (C-3), 47.5 (C-4), 46.8 (C-5), 46.5 (C-6), 32.5 (C-7), 32.3 (C-8), 20.9 (–OCOC\(_3\)H\(_3\)) 20.8 (–CCH\(_3\)).
78.8 (C-3), 75.3 (C-5), 74.9 (–CH₂Ph), 75.0 (–CH₂Ph), 68.1 (C-6), 44.3 (C-2), 31.4 (C-7), 20.9 (–OCOCH₃), 20.8 (–C(CH₃)₂).

IR: 1749, 1494, 1454, 1091, 699 cm⁻¹ (CHCl₃).

HRMS (ESI): m/z [M+Na]⁺ Calcd: 635.2444; Found: 635.2444.

1-O-Acetyl-3,4,6-tri-O-benzyl-2-deoxy-2-C-(2-methylphenyl)thiomethyl-D-glucopyranoside (173)

Yield: 0.30 g, 87% colourless oil of α:β anomeric mixtures.

¹H NMR: (CDCl₃, 400 MHz): δβ 7.45 – 7.05 (m, 19H, Ar), 5.70 (d, J = 8.8 Hz, 1H, H-1), 4.94 (d, J = 10.8 Hz, 1H, –CH₂Ph), 4.80 (d, J = 10.4 Hz, 1H, –CH₂Ph), 4.75 – 4.40 (m, 4H, –CH₂Ph), 3.95 – 3.55 (m, 5H, H-3, H-4, H-5, H-6a, H-6b), 3.24 (d, J = 10.8 Hz, 1H, H-7a), 3.17 (d, J = 12.8Hz, 1H, H-7b), 2.40 (s, 3H, –C(CH₃)₂), 2.30 – 2.21 (m, 1H, H-2), 2.00 (s, 3H, –OCOCH₃).

¹³C NMR: (CDCl₃, 100 MHz): δβ 169.0, (–OCOCH₃), 138.0, 137.9, 137.8, 135.8, 130.2, 128.4, 128.3, 128.0, 127.9, 127.8, 126.5, 126.1 (Ar), 93.2 (C-1), 80.5 (C-4), 79.0 (C-3), 75.4 (C-5), 75.4 (–CH₂Ph), 74.7 (–CH₂Ph), 73.5 (–CH₂Ph), 68.1 (C-6), 45.9 (C-2), 30.6 (C-7), 20.9 (–OCOCH₃), 20.5 (–C(CH₃)₂).
$^{1}$H NMR: (CDCl$_3$, 400 MHz): $\delta$ 6.4 (bs, 1H, H-1), 4.98 (d, $J$ = 10.8 Hz, 1H, CH$_2$Ph), 3.41 (d, $J$ = 13.2 Hz, 1H, H-7$_a$), 2.56 (t, $J$ = 12.2 Hz, 1H, H-7$_b$) 2.32 (s, 3H, CCH$_3$), 2.06 (s, 3H, -OCOC$\text{H}_3$).

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta$ 169.0 (–OCOCH$_3$), 137.9, 137.8, 137.4, 134.9, 129.0, 128.5, 127.7, 127.6, 127.4, 126.5, 126.4, 125.6 (Ar), 92.0 (C-1), 80.3 (C-4), 78.9 (C-3), 75.4 (C-5), 74.9 (–CH$_2$Ph), 73.6 (–CH$_2$Ph), 73.0 (–CH$_2$Ph), 68.1 (C-6), 44.2 (C-2), 29.7 (C-7), 20.9 (–OCOCH$_3$), 20.3 (–CCH$_3$).

IR: 1752, 1496, 1455, 1130, 698 cm$^{-1}$ (CHCl$_3$).

HRMS (ESI): $m/z$ [M+Na]$^+$ Calcd: 635.2444; Found: 635.2444.

1-O-Acetyl-3,4,6-tri-O-benzyl-2-deoxy-2-C-(4-tert-butylphenyl)thiomethyl-D-glucopyranoside (174)

Yield: 0.35 g, 93% colourless oil of $\alpha$: $\beta$ anomeric mixtures.

$^{1}$H NMR: (CDCl$_3$, 400 MHz): $\delta$ 7.45 – 7.21 (m, 19H, Ar), 5.67 (d, $J$ = 8.8 Hz, 1H, H-1), 4.92 (d, $J$ = 10.8 Hz, 1H, –CH$_2$Ph), 4.80 (d, $J$ = 10.4 Hz, 1H, –CH$_2$Ph), 4.75 – 4.38 (m, 4H, –CH$_2$Ph), 3.92 – 3.55 (m, 5H, H-3, H-4, H-5, H-6$_a$, H-6$_b$), 3.29 (d, $J$ = 12.0 Hz, 1H, H-7$_a$), 3.20 – 3.11 (m, 1H, H-7$_b$), 2.37 – 2.18 (m, 1H, H-2), 1.96 (s, 3H, –OCOCH$_3$), 1.28 (s, 9H, –C(CH$_3$)$_3$).
13C NMR: (CDCl3, 100 MHz): δβ 169.0 (–OCOCH3), 149.3, 142.2, 138.1, 137.9, 137.7, 130.2, 129.4, 128.5, 128.4, 128.3, 128.0, 127.8, 126.0 (Ar), 93.2 (C-1), 80.6 (C-4), 80.4 (C-3), 75.9 (C-5), 75.3 (–CH2Ph), 74.9 (–CH2Ph), 74.2 (–CH2Ph), 70.6 (C-6), 44.6 (C-2), 34.4 (–CCH3), 32.0 (C-7), 31.2 (–C(CH3)3), 20.9 (–OCOCH3).

1H NMR: (CDCl3, 400 MHz): δα 6.42 (bs, 1H, H-1), 4.97 (d, J = 11.2Hz, 1H, CH2Ph), 3.45 (d, J = 13.2Hz, 1H, H-7a), 2.57 (t, J = 12.2Hz, 1H, H-7b), 2.04 (s, 3H, OCOCH3), 1.30 (s, 9H, C(CH3)3).

13C NMR: (CDCl3, 100 MHz): δβ 168.8 (–OCOCH3), 149.7, 138.2, 138.1, 137.9, 133.1, 132.0, 131.2, 128.8, 128.3, 128.0, 127.7, 127.6, 126.0, 125.8 (Ar), 92.1 (C-1), 80.4 (C-4), 79.0 (C-3), 75.5 (C-5), 75.2 (–CH2Ph), 74.6 (–CH2Ph), 73.6 (–CH2Ph), 68.3 (C-6), 44.6 (C-2), 36.6 (–CCH3), 32.0 (C-7), 31.3 (–C(CH3)3), 20.9 (–OCOCH3).

IR: 1750, 1498, 1454, 1130, 698 cm⁻¹ (CHCl3).


1-O-Acetyl-3,4,6-tri-O-benzyl-2-deoxy-2-C-(2-naphthalene)thiomethyl-D-glucopyranoside (176)

Yield: 0.32 g, 86% yellow oil of α:β anomeric mixtures.
$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta$ 7.85 – 7.56 (m, 4H, Ar), 7.48 – 7.12 (m, 18H, Ar), 5.72 (d, $J = 8.8$ Hz, 1H, H-1), 4.94 (d, $J = 10.8$ Hz, 1H, –CH$_2$Ph), 4.79 (d, $J = 10.4$ Hz, 1H, –CH$_2$Ph), 4.74 – 4.42 (m, 4H, –CH$_2$Ph), 3.95 – 3.51 (m, 5H, H-3, H-4, H-5, H-6$_{a}$, H-6$_{b}$), 3.34 (d, $J = 13.2$ Hz, 1H, H-7$_{a}$), 3.26 (d, $J = 12.8$ Hz, 1H, H-7$_{b}$), 2.39 – 2.24 (m, 1H, H-2), 1.90 (s, 3H, –OCOC$_2$H$_3$).

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta$ 169.1 (–OCOC$_3$H$_3$), 138.0, 137.9, 134.1, 133.7, 133.1, 131.8, 128.4, 128.3, 127.8, 127.7, 127.1, 126.6, 125.8 (Ar), 93.2 (C-1), 80.4 (C-4), 79.0 (C-3), 75.4 (C-5), 74.9 (–CH$_2$Ph), 73.6 (–CH$_2$Ph), 73.1 (C-6), 46.0 (C-2), 31.2 (C-7), 20.9 (–OCOC$_3$H$_3$).

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta$ 5.01 (d, $J = 11.2$ Hz, 1H, –CH$_2$Ph), 2.70 – 2.59 (m, 1H, H-7$_{b}$), 2.05 (s, 3H, –OCOC$_2$H$_3$).

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta$ 169.1 (–OCOC$_3$H$_3$), 138.0, 137.9, 134.1, 133.7, 133.1, 131.8, 128.4, 128.3, 127.8, 127.7, 127.1, 126.6, 125.8 (Ar), 92.0 (C-1), 80.2 (C-4), 79.0 (C-3), 75.3 (C-5), 74.7 (–CH$_2$Ph), 73.5 (–CH$_2$Ph), 73.1 (C-6), 44.4 (C-2), 30.4 (C-7), 20.9 (OCOC$_3$H$_3$).

IR: 1723, 1497, 1453, 1130, 695 cm$^{-1}$ (CHCl$_3$).


**General procedure for the synthesis of the thiochromans**

An anomeric mixture of sulfides 169 (0.30 g, 0.50 mmol) was dissolved in dry DCM (3.0 mL) under a nitrogen atmosphere and cooled to 0 °C. The solution was then treated with a dropwise addition of BF$_3$·Et$_2$O (48% BF$_3$ in dietherate) (0.79 mL, 3.00 mmol). After stirring at this temperature for 5 min, the reaction was left to stir to completion at room temperature for 15 min before Et$_3$N (0.70 mL) was added. The solution was then diluted with water (10 mL).
and the aqueous phase was extracted with DCM. The combined organic phases were successively washed with saturated aqueous NaHCO$_3$ (10 mL) solution and brine (10 mL). The organic layer was then dried over anhydrous MgSO$_4$, filtered and solvents removed under reduced pressure. The residue product was purified by column chromatography on silica gel using hexane and ethyl acetate as eluent to yield the corresponding thiochromans.

(2R,3S,4R,4aS,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-b]pyran (170)

Yield: 0.19 g, 69% white solid.

Mp: 91 – 95 °C.

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta_H$ 7.53 (d, $J = 7.2$ Hz, 1H, Ar), 7.42 – 7.30 (m, 13H, Ar), 7.13 – 7.03 (m, 5H, Ar), 5.13 (d, $J = 5.6$ Hz, 1H, H-1), 4.96 (d, $J = 11.2$ Hz, 1H, $-CH_2$Ph), 4.85 (d, $J = 10.8$ Hz, 1H, $-CH_2$Ph), 4.78 (d, $J = 10.8$ Hz, 1H, $-CH_2$Ph), 4.70 (d, $J = 12.0$ Hz, 1H, $-CH_2$Ph), 4.60 – 4.58 (m, 2H, $-CH_2$Ph), 4.03 (t, $J = 13.2$ Hz, 1H, H-3), 3.88 – 3.69 (m, 3H, H-4, H-6$_a$, H-6$_b$), 3.47 (d, $J = 9.2$ Hz, 1H, H-5), 3.35 (d, $J = 13.2$ Hz, 1H, H-7$_a$), 3.19 (dd, $J = 3.6$ Hz and 13.6 Hz, 1H, H-7$_b$), 2.62 – 2.50 (m, 1H, H-2).

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta_C$ 138.7, 138.0, 134.4, 131.4, 128.5, 127.9, 127.8, 127.7, 127.6, 126.3, 124.8 (Ar), 80.0 (C-4), 78.7 (C-3), 75.9 ($-CH_2$Ph), 74.8 ($-CH_2$Ph), 73.5 ($-CH_2$Ph), 72.8 (C-5), 72.4 (C-1), 68.9 (C-6), 38.4 (C-2), 26.4 (C-7).
IR: 1452, 1082, 694 cm\(^{-1}\) (neat).

\([\alpha]_D\): -125.0 (c 0.1, CHCl\(_3\)).

HRMS (ESI): \(m/z [M+H]^+\) Calcd: 539.2251; Found: 539.2259.

\((2R,3S,4R,4aS,10bS)-3,4\text{-bis(benzyloxy)}\)-2-(benzyloxymethyl)-9-methyl-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-b]pyran (177)

Yield: 0.20 g, 71% white solid.

Mp: 105 – 107 °C.

\(^1\)H NMR: (CDCl\(_3\), 400 MHz): \(\delta_H\) 7.45 – 7.20 (m, 14H, Ar), 7.18 – 7.06 (m, 2H, Ar), 7.0 – 6.88 (m, 2H, Ar), 5.09 (d, \(J = 5.6\) Hz, 1H, H-1), 4.95 (d, \(J = 10.8\) Hz, 1H, –CH\(_2\)Ph), 4.85 (d, \(J = 11.2\) Hz, 1H, –CH\(_2\)Ph), 4.78 (d, \(J = 10.8\) Hz, 1H, –CH\(_2\)Ph), 4.71 (d, \(J = 9.2\) Hz, 1H, –CH\(_2\)Ph), 4.60 – 4.48 (m, 2H, –CH\(_2\)Ph), 4.03 (t, \(J = 9.8\) Hz, 1H, H-3), 3.80 – 3.68 (m, 3H, H-4, H-6\(_a\), H-6\(_b\)), 3.59 - 3.49 (m, 1H, H-5), 3.33 (d, \(J = 11.2\) Hz, 1H, H-7\(_a\)), 3.18 (dd, \(J = 3.8\) Hz and 13.6 Hz, 1H, H-7\(_b\)), 2.60 – 2.49 (m, 1H, H-2), 2.23 (s, 3H, –CH\(_3\)).

\(^{13}\)C NMR: (CDCl\(_3\), 100 MHz): \(\delta_C\) 138.1, 134.5, 131.2, 130.6, 128.6, 128.5, 128.4, 128.0, 127.8, 127.7, 127.6, 126.2 (Ar), 80.1 (C-4), 78.8 (C-3), 75.9 (–CH\(_2\)Ph), 74.8 (–CH\(_3\)Ph), 73.4 (–CH\(_2\)Ph), 72.8 (C-5), 72.5, (C-1) 69.1 (C-6), 38.6 (C-2), 26.5 (C-7), 21.0. (–CCH\(_3\)).

IR: 1453, 1108, 695 cm\(^{-1}\) (neat).
[α]D: +91.0 (c 0.1, CHCl₃).

HRMS (ESI): m/z [M+H]+ Calcd: 553.2407; Found: 553.2410.

(2R,3S,4R,4aS,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-7-methyl-2,3,4,4a,5,10b-
hexahydrothiochromeno[4,3-b]pyran (178)

Yield: 0.20 g, 73% white solid.

Mp: 119 – 121 °C.

¹H NMR: (CDCl₃, 400 MHz): δH 7.50 – 7.20 (m, 14H, Ar), 7.18 – 7.19 (m, 2H, Ar), 7.05
– 6.95 (m, 2H, Ar), 5.17 (d, J = 5.2 Hz, 1H, H-1), 4.97 (d, J = 10.8 Hz, 1H, –CH₂Ph),
4.88 (d, J = 11.2 Hz, 1H, –CH₂Ph), 4.79 (d, J = 10.4 Hz, 1H, –CH₂Ph),
4.71 (d, J = 12.0 Hz, 1H, –CH₂Ph), 4.62 – 4.48 (m, 2H, –CH₂Ph), 4.04 (t, J = 9.8 Hz, 1H, H-3),
3.80 – 3.60 (m, 3H, H-4, H-6a, H-6b), 3.47 (d, J = 9.2 Hz, 1H, H-5),
3.38 – 3.20 (m, 2H, H-7a, H-7b), 2.60 – 2.52 (m, 1H, H-2),
2.23 (s, 3H –CCH₃).

¹³C NMR: (CDCl₃, 100 MHz): δC 138.7, 138.0, 137.9, 134.3, 133.9, 131.4, 128.7, 128.5,
128.4, 127.9, 127.8, 127.7, 125.0, 124.0 (Ar), 79.9 (C-4), 78.6 (C-3), 75.8 (–CH₂Ph),
74.7 (–CH₂Ph), 73.4 (–CH₂Ph), 72.7 (C-5), 72.6 (C-1), 68.8 (C-6),
37.9 (C-7), 26.0 (C-2), 20.1 (–CCH₃).

IR: 1496, 1406, 1140, 694 cm⁻¹ (neat).
([α]D) +127.0 (c 0.1, CHCl₃).

HRMS (ESI): m/z [M+H]+ Calcd: 553.2407; Found: 553.2415.

(2R,3S,4R,4aS,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-tert-butyl-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-b]pyran (179)

Yield: 0.21 g, 69% white solid.

Mp: 157 – 159 ºC.

H NMR: (CDCl₃, 400 MHz): δH 7.61 (s, 1H Ar), 7.42 – 7.21 (m, 14H Ar), 7.18 – 7.07 (m, 3H Ar), 6.97 (d, J = 8Hz, 1H Ar), 5.13 (d, J = 5.6 Hz, 1H, H-1), 4.96 (d, J = 11.2 Hz, 1H, –CH₂Ph), 4.87 (d, J = 11.2 Hz, 1H, –CH₂Ph), 4.77 (d, J = 10.4 Hz, 1H, –CH₂Ph), 4.68 (d, J = 12.0 Hz, 1H, –CH₂Ph), 4.56 (d, J = 12.0 Hz, 1H, –CH₂Ph), 4.48 (d, J = 10.8 Hz, 1H, –CH₂Ph), 4.04 (t, J = 9.8 Hz, 1H, H-3), 3.79 – 3.18 (m, 3H, H-4, H-6a, H-6b), 3.55 – 3.48 (m, 1H, H-5), 3.34 (d, J = 13.6 Hz, 1H, H-7a), 3.18 (dd, J = 3.6 and 13.2Hz, 1H, H-7b), 2.10 – 2.08 (m, 1H, H-2), 1.24 (s, 9H, –C(CH₃)₃).

C NMR: (CDCl₃, 100 MHz): δC 148.0, 138.8, 138.0, 137.9, 130.7, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 125.9, 124.8, 124.6 (Ar), 80.3 (C-4), 78.8 (C-3), 75.9 (–CH₂Ph), 74.9 (–CH₂Ph), 73.6 (–CH₂Ph), 73.0 (C-5), 72.7 (C-1), 69.1 (C-6), 38.7 (C-7), 34.4 (–C(CH₃)₃), 31.2 (–C(CH₃)₃), 26.3 (C-2).

IR: 1478, 1134, 1103, 697 cm⁻¹ (neat).
$[\alpha]_D^0$: +92.0 (c 0.1, CHCl$_3$).

HRMS (ESI): $m/z$ [M+H]$^+$ Calcd: 595.2877; Found: 595.2880.

(2R,3S,4R,4aS,10bS)-3,4-bis(benzyl oxy)-2-(benzyl oxymethyl)-9-methoxy-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-b]pyran (180)

![Chemical Structure](image)

Yield: 0.20 g, 70% white solid.

Melting point: 130 – 132 °C.

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta_H$ 7.42 – 7.20 (m, 14H Ar), 7.17 – 7.11 (m, 3H Ar), 6.96 (d, $J = 8.4$ Hz, 1H Ar), 6.71 (bd, $J = 8.4$ Hz, 1H Ar), 5.09 (d, $J = 5.6$ Hz, 1H, H-1), 4.96 (d, $J = 10.8$ Hz, 1H, $-\text{CH}_2\text{Ph}$), 4.87 (d, $J = 11.2$ Hz, 1H, $-\text{CH}_2\text{Ph}$), 4.79 (d, $J = 10.4$ Hz, 1H, $-\text{CH}_2\text{Ph}$), 4.66 (d, $J = 12.0$ Hz, 1H, $-\text{CH}_2\text{Ph}$), 4.52 (t, $J = 11.0$ Hz, 2H, $-\text{CH}_2\text{Ph}$), 4.05 (t, $J = 9.8$ Hz, 1H, H-3), 3.80 – 3.72 (m, 3H, H-4, H-6$_a$, H-6$_b$), 3.66 (s, 3H, $-\text{OCH}_3$), 3.53 (bd, $J = 9.6$ Hz, 1H, H-5), 3.33 (d, $J = 13.2$ Hz, 1H, H-7$_a$), 3.18 (dd, $J = 3.6$ Hz and 13.6 Hz, 1H, H-7$_b$), 2.62 – 2.51 (m, 1H, H-2).

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta_C$ 157.5, 138.7, 138.0, 132.5, 128.4, 128.3, 128.0, 127.7, 127.3, 124.8, 115.2, 112.0 (Ar), 80.2 (C-4), 78.8 (C-3), 75.9 ($-\text{CH}_2\text{Ph}$), 74.8 ($-\text{CH}_2\text{Ph}$), 73.6 ($-\text{CH}_2\text{Ph}$), 73.0 (C-5), 72.6 (C-1), 69.2 (C-6), 55.3 ($-\text{OCH}_3$), 38.6 (C-7), 26.5 (C-2).

IR: 1472, 1134, 1103, 698 cm$^{-1}$ (neat).
[α]D: +111.0 (c 0.1, CHCl₃).

HRMS (ESI): m/z [M+H]+ Calcd: 569.2356; Found: 569.2354.

(2R,3S,4R,4aS,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,5,12c-hexahydro-1H-dibenzo[c,f]thiochromeno[4,3-b]pyran (181)

Yield: 0.20 g, 68% yellow solid.

Melting point: 154 – 156 °C.

¹H NMR: (CDCl₃, 400 MHz): δH 8.00 (d, J = 8.4 Hz, 1H, Ar), 7.69 (d, J = 7.6 Hz, 1H, Ar), 7.57 (d, J = 8.8 Hz, 1H, Ar), 7.49 – 7.18 (m, 17H, Ar), 7.10 (d, J = 8.4 Hz, 1H, Ar), 4.98 (d, J = 10.8 Hz, 1H, H-1), 4.96 - 4.72 (m, 2H, −CH₂Ph), 4.69 (d, J = 11.2 Hz, 1H, −CH₂Ph), 4.61 (d, J = 10.8 Hz, 1H, −CH₂Ph), 4.58 – 4.47 (m, 3H, −CH₂Ph), 4.00 – 3.91 (m, 1H, H-3), 3.85 (d, J = 10.4 Hz, 1H, H-6a), 3.80 – 3.63 (m, 2H, H-4, H-6b), 3.60 – 3.52 (m, 1H, H-5), 3.12 (d, J = 12.4 Hz, 1H, H-7a), 2.73 (t, J = 12.4 Hz, 1H, H-7b), 2.65 – 2.50 (m, 1H, H-2).

¹³C NMR: (CDCl₃, 100 MHz): δC 138.0, 128.7, 128.6, 128.5, 128.5, 128.2, 128.0, 127.8, 127.5, 126.2, 125.6, 125.2, 124.5 (Ar), 85.0 (C-4), 80.4 (C-3), 80.3 (C-1), 76.2 (−CH₂Ph), 75.3 (−CH₂Ph), 75.0 (−CH₂Ph), 73.4 (C-5), 69.6 (C-6), 46.3 (C-7), 25.3 (C-2).

IR: 1496, 1363, 1124, 1071, 697 cm⁻¹ (neat).
[α]_D: +91.0 (c 0.1, CHCl₃).


**General procedure of the OXONE®-promoted oxidation of thiochromans to sulfones**

Aluminium oxide (0.85 g, 8.36 mmol) was weighed into a round-bottom reaction flask and was wetted with H₂O (90.00 µL, 4.99 mmol). The mixture was rotated on a rotary evaporator until it was free-flowing. Thiochroman 170 (0.15 g, 0.28 mmol) dissolved in DCM was added to the reaction flask and the mixture was vigorously stirred before OXONE® (1.40 g, 2.28 mmol) was added. The reaction was left to stir for 12 h upon which it showed completion on TLC. The solids were filtered over a pad of celite® and solvent removed under reduced pressure. The residue product was purified by column chromatography on silica gel using hexane and ethyl acetate (7:3) as eluent.

**(2R,3S,4R,4aS,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,5,10b-hexahydro-S-S-dioxothiochromeno[4,3-b]pyran (171)**

![Diagram of compound 171](image)

**Yield:** 0.12 g, 73% white solid.

**Mp:** 116 – 118 °C.

**¹H NMR:** (CDCl₃, 400 MHz): δ 7.92 (d, 1H, J = 7.6 Hz, Ar), 7.63 – 7.47 (m, 3H, Ar), 7.42 – 7.21 (m, 13H, Ar), 7.29 – 7.10 (m, 2H, Ar), 5.19 (d, 1H, J = 4.0 Hz, H-1), 4.90 – 4.78 (m, 2H, –CH₂Ph), 4.74 – 4.62 (m, 2H, –CH₂Ph), 4.59 – 4.48
\[(\text{2R,3S,4R,4aS,10bS)}\)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-methyl-2,3,4,4a,5,10b-hexahydro-S-S-dioxothiochromeno[4,3-b]pyran (182)\]

Yield: 0.12 g, 72% white solid.

Mp: 115 – 117 °C.

\(^1\)H NMR: (CDCl\(_3\), 400 MHz): \(\delta_H\) 7.79 (d, 1H, \(J = 8.0\) Hz, Ar), 7.44 – 7.08 (m, 18H, Ar), 5.13 (d, 1H, \(J = 4.4\) Hz, H-1), 4.89 – 4.50 (m, 6H, \(-\text{CH}_2\text{Ph}\)), 4.10 – 3.98 (m, 2H, H-3, H-7\(_a\)), 3.89 – 3.60 (m, 4H, H-4, H-5, H-6\(_a\), H-6\(_b\)), 3.37 (bd, 1H, \(J = 3.0\) Hz, H-7\(_b\)), 2.93 – 2.80 (m, 1H, H-2), 2.36 (s, 3H, \(-\text{CH}_3\)).

\(^{13}\)C NMR: (CDCl\(_3\), 100 MHz): \(\delta_C\) 143.7, 138.1, 137.9, 137.6, 136.5, 133.9, 130.3, 128.6, 128.5, 128.4, 127.9, 127.8, 127.6, 123.7 (Ar), 78.0 (C-4), 77.3 (C-3), 74.3 (C-
5), 74.1, 73.9, 73.4 (CH2Ph), 69.3 (C-1), 68.4 (C-6), 49.4 (C-7), 39.5 (C-2), 21.6 (CCH3).

IR: 1454.6, 1300.3, 1105.4, 754.1, 695.6 cm⁻¹ (neat).

[α]D: +6.5 (c 0.1, CHCl3).


(2R,3S,4R,4aS,10bS)-3,4-bis(benzylxy)-2-(benzyloxymethyl)-7-methyl-2,3,4,4a,5,10b-hexahydro-S,S-dioxothiochromeno[4,3-b]pyran (183)

Yield: 0.12 g, 72% white solid.

Mp: 94 – 96 °C.

¹H NMR: (CDCl3, 400 MHz): δH 7.56 – 7.08 (m, 17H, Ar), 5.15 (d, 1H, J = 4.8 Hz, H-1), 4.90 (d, 1H, J = 10.4 Hz, CH2Ph), 4.83 (d, 1H, J = 10.8 Hz, CH2Ph), 4.74 (d, 1H, J = 11.2 Hz, CH2Ph), 4.66 (d, 1H, J = 12.0 Hz, CH2Ph), 4.62 – 4.48 (m, 2H, CH2Ph), 4.14 – 3.99 (m, 2H, H-3, H-7a), 3.79 – 3.65 (m, 4H, H-4, H-5, H-6a, H-6b), 3.42 (dd, 1H, J = 3.2 Hz and 14.4 Hz, H-7b), 2.85 – 2.70 (m, 4H, H-2, CH3).

¹³C NMR: (CDCl3, 100 MHz): δC 138.3, 137.8, 137.6, 137.4, 137.2, 134.4, 132.6, 132.3, 128.5, 128.4, 128.0, 127.8, 127.6, 125.9 (Ar), 78.9 (C-4), 74.6 (C-3), 74.2 (C-5, CH2Ph), 73.8, 73.5 (CH2Ph), 70.5 (C-1), 68.4 (C-6), 51.3 (C-7), 39.7 (C-2), 19.6 (CH3).
IR: 1454.3, 1300.1, 1149.9, 734.6, 695.3 cm\(^{-1}\) (neat).

\([\alpha]_D\): +21.5 (c 0.1, CHCl\(_3\)).

HRMS (ESI): \(m/z \ [M+NH_4]^+\) Calcd: 602.2571; Found: 602.2577.

\((2R,3S,4R,4aS,10bS)-3,4\text{-bis}(\text{benzyloxy})\text{-2-(benzyloxymethyl)}\text{-9-}\text{tert-butyl}\
\text{-2,3,4a,5,10b-hexahydro-S-S-dioxothiochromeno[4,3-b]pyran} (184)\)

Yield: 0.12 g, 67% white solid.

Mp: 114 – 116 °C.

\(^1\)H NMR: (CDCl\(_3\), 400 MHz): \(\delta\)H 7.83 (d, 1H, \(J = 8.4 \text{ Hz, } \text{Ar}\)), 7.65 (s, 1H, \(\text{Ar}\)), 7.52 (d, 1H, \(J = 8.0 \text{ Hz, } \text{Ar}\)), 7.40 – 7.08 (m, 15H, \(\text{Ar}\)), 5.18 (d, 1H, \(J = 4.8 \text{ Hz, } \text{H-1}\)), 4.88 (d, 1H, \(J = 10.8 \text{ Hz, } \text{–CH}_2\text{Ph}\)), 4.81 (d, 1H, \(J = 10.8 \text{ Hz, } \text{–CH}_2\text{Ph}\)), 4.72 (d, 1H, \(J = 10.8 \text{ Hz, } \text{–CH}_2\text{Ph}\)), 4.64 (d, 1H, \(J = 12.0 \text{ Hz, } \text{–CH}_2\text{Ph}\)), 4.57 (d, 1H, \(J = 11.6 \text{ Hz, } \text{–CH}_2\text{Ph}\)), 4.51 (d, 1H, \(J = 11.2 \text{ Hz, } \text{–CH}_2\text{Ph}\)), 4.05 (dd, 1H, \(J = 7.8 \text{ Hz and 9.4 Hz, H-3}\)), 3.98 (dd, 1H, \(J = 5.8 \text{ Hz and 14.2 Hz, H-7a}\)), 3.83 – 3.56 (m, 4H, H-4, H-5, H-6a, H-6b), 3.41 (dd, 1H, \(J = 3.8 \text{ Hz and 14.2 Hz, H-7b}\)), 2.88 – 2.69 (m, 1H, H-2), 1.28 (s, 9H, \(–\text{C(CH}_3)_3\)).

\(^{13}\)C NMR: (CDCl\(_3\), 100 MHz): \(\delta\)C 156.8, 138.2, 137.8, 137.5, 136.5, 133.4, 128.5, 128.4, 128.0, 127.9, 127.7, 126.7, 125.0, 123.6 (\(\text{Ar}\)), 78.9 (C-4), 77.4 (C-3), 74.5 (C-5), 74.3, 74.1, 73.6 (–CH\(_2\)Ph), 70.1 (C-1), 68.6 (C-6), 49.6 (C-7), 40.1 (C-2), 35.2 (–C(CH\(_3\))\(_3\)), 30.9 (–C(CH\(_3\))\(_3\)).
IR: 1455.0, 1299.2, 1105.2, 749.9, 695.7 cm$^{-1}$ (neat).

$[\alpha]_D$: +44.0 (c 0.1, CHCl$_3$).


(2R,3S,4R,4aS,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-methoxy-2,3,4,4a,5,10b-hexahydro-S-S-dioxothiochromeno[4,3-b]pyran (185)

Yield: 0.10 g, 57% white solid.

M.p: 99 – 101 °C.

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta_H$ 7.82 (d, 1H, $J = 8.8$ Hz, Ar), 7.50 – 7.04 (m, 16H, Ar), 7.00 (d, 1H, $J = 9.2$ Hz, Ar), 5.15 (d, 1H, $J = 5.2$ Hz, H-1), 4.91 – 4.70 (m, 3H, –CH$_2$Ph), 4.66 – 4.49 (m, 3H, –CH$_2$Ph), 4.07 (t, 1H, $J = 8.8$ Hz, H-3), 3.95 (dd, 1H, $J = 5.2$ Hz and 14.4 Hz, H-7a), 3.88 – 3.57 (m, 7H, H-4, H-5, H-6a, H-6b, –OCH$_3$), 3.42 (dd, 1H, $J = 3.2$ Hz and 14.4 Hz, H-7b), 2.91 – 2.78 (m, 1H, H-2).

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta_C$ 163.0, 138.2, 137.8, 137.6, 136.2, 131.3, 128.5, 128.4, 128.0, 127.8, 127.6, 125.8, 116.3, 111.6 (Ar), 79.1 (C-4), 77.4 (C-3), 74.6 (C-5), 74.3, 74.1, 73.6 (–CH$_2$Ph), 70.2 (C-1), 68.7 (C-6), 55.5 (–OCH$_3$), 49.6 (C-7), 40.2 (C-2).

IR: 1600.5, 1299.5, 1290.4, 1089.5, 744.8, 696.1 cm$^{-1}$ (neat).
[α]D: +39.5 (c 0.1, CHCl₃).


General procedure for the CAN-promoted oxidation of thiochromans to their sulfoxides derivatives

KBr (10.00 mg, 0.08 mmol), 0.10 g wet silica (50 % w/w) and (CAN 0.61 g, 1.12 mmol) were consecutively added to the stirring solution of sulfide 170 (0.15 g, 0.28 mmol) dissolved in DCM (10 mL). The reaction was stirred for 30 min and the solids were filtered through a pad of celite®. The solvents were removed under reduced pressure and residue product was purified by column chromatography on silica gel using hexane and ethyl acetate as solvent (1:1) to yield the respective sulfoxides.

(2R,3S,4R,4aS,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (186a and 186b)

Major diastereoisomer

Yield: 0.06 g, 40% white solid.

Mp: 103 – 105 °C.

¹H NMR: (CDCl₃, 400 MHz): δH 7.84 (d, 1H, J = 7.2 Hz, Ar), 7.71 (d, 1H, J = 7.6 Hz, Ar), 7.60 – 7.44 (m, 2H, Ar), 7.42 – 7.07 (15H, Ar), 5.04 (d, 1H, J = 5.6 Hz, H-
1), 4.96 (d, 1H,  J = 10.4 Hz, –CH₂Ph), 4.85 – 4.72 (m, 2H, –CH₂Ph), 4.65 (d, 1H,  J = 12.0 Hz, –CH₂Ph), 4.61 – 4.48 (m, 3H, –CH₂Ph), 4.21 (dd, 1H,  J = 7.6 Hz and 10.0 Hz, H-3), 3.82 – 3.60 (m, 5H, H-4, H-5, H-6a, H-6b, H-7a), 3.09 (dd, 1H,  J = 3.8 Hz and 14.6 Hz, H-7b), 2.72 – 2.60 (m, 1H, H-2).

\(^{13}\text{C}\) NMR: (CDCl₃, 100 MHz): \(\delta\)C 139.5, 138.8, 138.0, 133.5, 132.0, 129.1, 128.4, 128.0, 127.7, 127.6, 127.5 (Ar), 79.4 (C-4), 78.9 (C-3), 74.2 (C-5, –CH₂Ph), 73.9, 73.5 (–CH₂Ph), 71.2 (C-1), 68.8 (C-6), 44.8 (C-7), 35.8 (C-2).

IR: 1454.7, 1090.2, 1025.1, 734.6, 695.4 cm⁻¹ (neat).

\([\alpha]_D\): +84.0 (c 0.1, CHCl₃).

HRMS (ESI): \(m/z\) [M+H]⁺ Calcd: 555.2200; Found: 555.2207.

Minor diastereoisomer

Yield: 0.04 g, 27% white solid.

Mp: 68 – 70 °C.

\(^1\text{H}\) NMR: (CDCl₃, 400 MHz): \(\delta\)H 7.76 (d, 1H,  J = 7.2 Hz, Ar), 7.58 – 7.43 (m, 3H, Ar), 7.40 – 7.12 (m, 15H, Ar), 5.17 (d, 1H,  J = 4.4 Hz, H-1), 4.79 – 4.50 (m, 6H, –CH₂Ph), 3.94 – 3.84 (m, 2H, H-6a, H-7a), 3.82 – 3.71 (m, 2H, H-6b, H-5), 3.70 – 3.58 (m, 2H, H-3, H-4), 3.06 – 2.96 (m, 2H, H-2, H-7b).

\(^{13}\text{C}\) NMR: (CDCl₃, 100 MHz): \(\delta\)C 137.8, 137.7, 137.6, 134.2, 131.9, 130.0, 129.7, 129.3, 128.5, 128.4, 128.0, 127.8, 127.7, 127.6 (Ar), 78.2 (C-4), 76.6 (C-3), 74.1 (C-5), 74.0, 73.5, 73.4 (–CH₂Ph), 68.8 (C-1), 68.0 (C-6), 46.7 (C-7), 34.9 (C-2).

IR: 1454.4, 1049.8, 1024.8, 730.8, 696.1 cm⁻¹ (neat).

\([\alpha]_D\): -4.0 (c 0.1, CHCl₃).

HRMS (ESI): \(m/z\) [M+H]⁺ Calcd: 555.2200; Found: 555.2207.
(2R,3S,4R,4aS,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-methyl-2,3,4,4a,5,10b-
hexahydro-S-oxothiochromeno[4,3-b]pyran (187a and 187b)

Major diastereoisomer

Yield: 0.07 g, 44% white solid.

Mp: 103 – 105 °C.

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta_{H}$ 7.72 (d, 1H, $J = 8.0$ Hz, Ar), 7.53 (s, 1H, Ar), 7.41 – 7.10 (m, 16H, Ar), 5.04 – 4.97 (m, 2H, H-1, $\text{--CH}_2\text{Ph}$), 4.78 (d, 1H, $J = 10.8$ Hz, $\text{--CH}_2\text{Ph}$), 4.66 (d, 1H, $J = 12.0$ Hz, $\text{--CH}_2\text{Ph}$), 4.61 – 4.50 (m, 2H, $\text{--CH}_2\text{Ph}$), 4.26 (t, 1H, $J = 9.2$ Hz, H-3), 3.81 – 3.59 (m, 5H, H-4, H-5, H-6$_a$, H-6$_b$, H-7$_a$), 3.04 (dd, 1H, $J = 3.6$ Hz and 14.8 Hz, H-7$_b$), 2.70 – 2.59 (m, 1H, H-2), 2.37 (s, 3H, $\text{--CH}_3$).

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta_{C}$ 142.7, 138.8, 138.0, 136.3, 133.2, 131.2, 129.9, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4 (Ar), 79.6 (C-4), 78.8 (C-3), 74.2 (C-5, $\text{--CH}_2\text{Ph}$), 73.8, 73.4 ($\text{--CH}_2\text{Ph}$), 71.4 (C-1), 67.0 (C-6), 44.6 (C-7), 35.9 (C-2), 21.6 ($\text{--CH}_3$).

IR: 1077.6, 1049.5, 740.2, 695.9 cm$^{-1}$ (neat).

$[\alpha]_D$: -9.0 (c 0.1, CHCl$_3$).

HRMS (ESI): $m/z$ [M+H]$^+$ Calcd: 569.2356; Found: 569.2354.
Minor diastereoisomer

Yield: 0.04 g, 24% white solid.

Mp: 104 – 106 °C.

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta$ 7.63 (d, 1H, $J = 8.0$ Hz), 7.42 – 7.13 (m, 15H, Ar), 5.11 (bs, 1H, H-1), 4.78 – 4.50 (m, 6H, –CH$_2$Ph), 4.00 – 3.73 (m, 4H, H-5, H-6a, H-6b, H-7a), 3.69 – 3.59 (m, 2H, H-4, H-5), 3.10 – 2.95 (m, 2H, H-2, H-7a), 2.36 (s, 3H, –CCH$_3$).

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta$C 142.6, 137.9, 137.7, 137.6, 134.0, 130.4, 130.2, 130.1, 128.5, 128.4, 127.9, 127.8, 127.7, 127.6 (Ar), 78.2 (C-4), 76.2 (C-3), 74.1 (x2) (C-5, –CH$_2$Ph), 73.8, 73.3 (–CH$_2$Ph), 68.2 (C-1), 68.0 (C-6), 46.4 (C-7), 33.9 (C-2), 21.4 (–CCH$_3$)

IR: 1454.6, 1049.5, 1026.0, 731.3, 696.5 cm$^{-1}$ (neat).

$[\alpha]_D$: -11.5 (c 0.1, CHCl$_3$).

HRMS (ESI): $\text{m/z [M+H]}^+$ Calcd: 569.2356; Found: 569.2363.

$(2R,3S,4R,4aS,10bS)$-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-7-methyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (188a and 188b)

Major diastereoisomer

Yield: 0.07 g, 43% white solid.
Mp: 99 – 101 °C.

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta_H$ 7.66 (d, 1H, $J = 7.6$ Hz, Ar), 7.48 – 7.09 (17H, Ar), 5.11 (d, 1H, $J = 10.8$ Hz, –CH$_2$Ph), 5.05 (d, 1H, $J = 5.6$ Hz, H-1), 4.83 (d, 1H, $J = 11.2$ Hz, –CH$_2$Ph), 4.67 (d, 2H, $J = 12.0$ Hz, –CH$_2$Ph), 4.60 – 4.47 (m, 3H, H-3, –CH$_2$Ph), 3.84 (dd, 1H, $J = 3.2$ Hz and 15.2 Hz, H-7$_b$), 3.80 – 3.50 (m, 4H, H-4, H-5, H-6$_a$, H-6$_b$), 2.94 (dd, 1H, $J = 3.0$ Hz and 15.0 Hz, H-7$_b$), 2.80 – 2.14 (m, 4H, H-2, –CH$_3$).

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta_C$ 141.4, 139.1, 138.1, 137.9, 136.5, 133.8, 132.1, 131.2, 128.4, 128.3, 128.1, 127.8, 127.7, 127.5, 127.4, 127.3, 124.9 (Ar), 80.6 (C-4), 78.3 (C-3), 74.4, 74.3, 73.5 (–CH$_2$Ph), 73.4 (C-5), 72.9 (C-1), 68.8 (C-6), 43.0 (C-7), 35.3 (C-2), 19.4 (–CH$_3$).

IR: 1594.5, 1070.4, 736.7, 697.3 cm$^{-1}$ (neat).

$[\alpha]_D$: +38.5 (c 0.1, CHCl$_3$).

HRMS (ESI): $m/z$ [M+H]$^+$ Calcd: 569.2356; Found: 569.2362.

Minor diastereoisomer

Yield: 0.04 g, 28% clear syrup.

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta_H$ 7.41 – 7.19 (m, 18H, Ar), 5.05 (d, 1H, $J = 2.8$ Hz, H-1), 4.70 – 4.50 (m, 6H, –CH$_2$Ph), 4.08 – 3.97 (m, 2H, H-6$_a$, H-7$_b$), 3.84 – 3.59 (m, H-3, H-4, H-5, H-6$_b$), 3.16 – 3.00 (m, 2H, H-2, H-7$_b$), 2.67 (s, 3H, –CH$_3$).

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta_C$ 138.0, 137.7, 137.6, 136.1, 134.7, 132.0, 131.5, 129.2, 128.5, 128.4, 127.9, 127.8, 127.7, 127.6 (Ar), 77.8 (C-4), 74.5 (C-3), 74.3 (C-5), 73.2, 72.9, 72.6 (–CH$_2$Ph), 67.8 (C-1), 66.4 (C-6), 44.6 (C-7), 30.0 (C-2), 19.2 (–CH$_3$).

IR: 1453.1, 1089.2, 1028.5, 730.6, 695.1 cm$^{-1}$ (neat).
([α]D):  -24.0 (c 0.1, CHCl₃).

HRMS (ESI):  m/z [M+H]+ Calcd: 569.2356; Found: 569.2364.

(2R,3S,4R,4aS,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-methoxy-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (189a and 189b)

Major diastereoisomer

Yield: 0.08 g, 49% white solid.

Mp: 106 – 108 °C.

1H NMR: (CDCl₃, 400 MHz): δH 7.73 (d, 1H, J = 8.4 Hz, Ar), 7.48 – 7.10 (m, 16H, Ar), 7.00 (d, 1H, J = 8.4 Hz, Ar), 5.11 – 4.99 (m, 2H, H-1, –CH₂Ph), 4.80 (d, 1H, J = 10.4 Hz, –CH₂Ph), 4.67 – 4.50 (m, 3H, –CH₂Ph), 4.37 (t, 1H, J = 9.8 Hz, H-3), 3.85 – 3.62 (m, 7H, H-4, H-6a, H-6b, H-7a, –OCH₃), 3.61 – 3.50 (m, 1H, H-5), 2.99 (dd, 1H, J = 3.2 Hz and 14.8 Hz, H-7b), 2.73 – 2.61 (m, 1H, H-2).

13C NMR: (CDCl₃, 100 MHz): δC 162.8, 139.0, 138.0, 137.9, 134.5, 133.6, 130.6, 128.4, 128.3, 128.0, 128.0, 127.7, 127.6, 127.5, 127.4, 115.8, 111.4 (Ar), 80.3 (C-4), 78.6 (C-3), 74.4 (C-5), 74.3, 73.8, 73.6 (–CH₂Ph), 72.1 (C-1), 69.3 (C-6), 55.4 (–OCH₃), 44.1 (C-7), 36.1 (C-2).

IR: 1596.5, 1071.3, 1022.5, 735.7, 697.5 cm⁻¹ (neat).

([α]D): -1.0 (c 0.1, CHCl₃).
Minor diastereoisomer

Yield: 0.04 g, 23% white syrup.

\(^1\)H NMR: (CDCl\textsubscript{3}, 400 MHz): \(\delta_H\) 7.66 (d, 1H, \(J = 8.4\) Hz, Ar), 7.50 – 7.12 (m, 15H, Ar), 7.05 (d, 1H, \(J = 2.0\) Hz, Ar), 6.97 (dd, 1H, \(J = 2.4\) Hz and 8.8 Hz, Ar), 5.14 (d, 1H, \(J = 4.0\) Hz, H-1), 4.80 – 4.50 (m, 6H, –CH\textsubscript{2}Ph), 3.93 – 3.70 (m, 7H, H-5, H-6\textsubscript{a}, H-6\textsubscript{b}, H-7\textsubscript{a}, –OCH\textsubscript{3}), 3.65 – 3.52 (m, 2H, H-3, H-4), 3.06 – 2.92 (m, 2H, H-2, H-7\textsubscript{b}).

\(^{13}\)C NMR: (CDCl\textsubscript{3}, 100 MHz): \(\delta_C\) 162.4, 137.9, 137.7, 137.6, 136.3, 132.0, 128.6, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 115.8, 114.0 (Ar), 78.5 (C-4), 77.0 (C-3), 74.2 (C-5), 74.0, 73.5, 73.4 (–CH\textsubscript{2}Ph), 68.8 (C-1), 68.3 (C-6), 55.5 (–OCH\textsubscript{3}), 46.8 (C-7), 34.7 (C-2).

IR: 1594.8, 1083.7, 1018.4, 738.4, 697.3 cm\textsuperscript{-1} (neat).

\([\alpha]_D\): +91.5 (c 0.1, CHCl\textsubscript{3}).

HRMS (ESI): \(m/z\) [M+H]\textsuperscript{+} Calcd: 585.2306; Found: 585.2308.

\((2R,3S,4R,4aS,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-tert-butyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (190)\)
Aluminium oxide (0.67 g, 6.55 mmol) was weighed into a round-bottom reaction flask and was wetted with H₂O (71.00 µL, 3.94 mmol). The mixture was rotated on a rotary evaporator until it was free-flowing. A solution of sulfide 179 (0.13 g, 0.22 mmol) dissolved in DCM (10 mL) was added to the reaction flask and the mixture was vigorously stirred before OXONE® (0.54 g, 0.88 mmol) was added. The reaction was left to stir for 4 h upon which it showed completion on TLC. The reaction was filtered and solvent removed under reduced pressure. The residue product was purified by column chromatography on silica gel using hexane and ethyl acetate (4:6) as eluent to yield a single product 190.

Yield: 0.08 g, 61% white solid.

Mp: 115 – 117 °C.

¹H NMR: (CDCl₃, 400 MHz): δ H 7.68 (d, 1H, J = 8.0 Hz, Ar), 7.59 (s, 1H, Ar), 7.48 (dd, 1H, J = 1.6 Hz and 8.0 Hz, Ar), 7.41 – 7.10 (m, 15H, Ar), 5.19 (d, 1H, J = 4.4 Hz, H-1), 4.80 – 4.49 (m, 6H, –CH₂Ph), 3.95 – 3.85 (m, 2H, H-6ₐ, H-7ₐ), 3.80 – 3.70 (m, 2H, H-5, H-6ₐ), 3.65 – 3.57 (m, 2H, H-3, H-4), 3.04 – 2.94 (m, 2H, H-2, H-7ₐ), 1.28 (s, 9H, –C(CH₃)₃).

¹³C NMR: (CDCl₃, 100 MHz): δ C 155.6, 138.0, 137.8, 137.6, 136.4, 133.7, 129.9, 128.6, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 126.6, 126.5 (Ar), 126.5 (Ar), 78.5 (C-4), 77.0 (C-3), 74.1 (x2) (C-5, –CH₂Ph), 73.7, 73.5 (CH₂Ph), 69.2 (C-1), 68.4 (C-6), 46.9 (C-7), 35.4 (–C(CH₃)₃), 35.0 (C-2), 31.0 (–C(CH₃)₃).

IR: 1455.4, 1085.5, 1039.7, 749.2, 695.5 cm⁻¹ (neat).

[α]₀: +72.5 (c 0.1, CHCl₃).

HRMS (ESI): m/z [M+H]⁺ Calcd: 611.2826; Found: 611.2835.
(3,4-bis(benzyloxy)-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-b]pyran-2-yl)methyl acetate (191)

Tri-O-benzylated thiochroman 170 (0.10 g, 0.19 mmol) was dissolved in a 5 mL of Ac₂O:AcOH (1:1) and the solution was heated to 45 °C. 10 mol% of Al(OTf)₃ (9.00 mg, 0.02 mmol) was then added to the solution and the reaction left to stir for 90 min upon which TLC analysis showed completion. The reaction was diluted by adding DCM (10 mL) and washed twice with H₂O (10 mL) and once with brine (10mL). The organic solvent was dried over anhydrous MgSO₄ and filtered. The organic solvent was removed under reduced pressure and the residue product was purified by column chromatography on silica gel using hexane and ethyl acetate (9:1).

Yield: 0.07 g, 72% white solid.

Mp: 93 – 95 °C.

¹H NMR: (CDCl₃, 400 MHz): δH 7.48 (d, 1H, J = 7.2 Hz, Ar), 7.40 – 7.15 (m, 11H, Ar), 7.18 – 7.00 (m, 3H, Ar), 5.10 (d, 1H, J = 5.6 Hz, H-1), 4.97 (d, 1H, J = 10.8 Hz, –CH₂Ph), 4.95 – 4.79 (m, 2H, –CH₂Ph), 4.56 (d, 1H, J = 10.8 Hz, –CH₂Ph), 4.38 – 4.23 (m, 2H, H-6ₐ, H-6ₐ), 4.06 (t, 1H, J = 9.6 Hz, H-3), 3.64 (t, 1H, J = 9.2 Hz, H-4), 3.58 – 3.46 (m, 1H, H-5), 3.35 (dd, 1H, J = 2.0 Hz and 13.4 Hz, H-7ₐ), 3.19 (dd, 1H, J = 3.8 Hz and 13.4 Hz, H-7ₐ), 2.60 – 2.48 (m, 1H, H-2), 2.11 (s, 3H, –OCOC₆H₃).
$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta$C 170.8 –OCOCH$_3$, 138.5, 137.6, 134.3, 131.0, 128.5, 128.0, 127.9, 127.8, 127.7, 127.5, 126.4, 124.9 (Ar), 79.9 (C-4), 78.8 (C-3), 75.9, 75.0 (–CH$_2$Ph), 72.4 (C-1), 71.5 (C-5), 63.5 (C-6), 38.6 (C-2), 26.3 (C-7), 20.9 (–OCOCH$_3$).

IR: 1734.1, 1249.3, 1114.2, 730.7, 695.3 cm$^{-1}$ (neat).

$[\alpha]_D$: +67.5 (c 0.1, CHCl$_3$).

Chapter 7: References


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