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How to cite this thesis
Diastereoselective Synthesis of Thiochromenes and 1,2-cis-2-Deoxy-α-Aryl-Glycosides from Thiochroman Precursors

by

F.M. Mebrahtu

Thesis submitted in fulfilment of the requirements for the degree

Philosophiae Doctor

in

Chemistry

in

Faculty of Science

of the

University of Johannesburg

Promoter: Prof. H. H. Kinfe

Co-Promoter: Prof. C. W. Holzapfel
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Abstract

The work in this thesis is divided into two parts. The first part describes the stereoselective synthesis of carbohydrate-based thiochromenes from pyranothiochroman precursors. The substrate pyranothiochromans were prepared stereoselectively in good to excellent yields in gram quantities starting from iodomethyl glycosyl acetates.

Treatment of the iodomethyl glycosyl acetate with arylthiolates at 0 °C produces aryl thiomethyl glycosides via S_N2 mechanism. The resulting aryl thiomethyl glycosides were treated with BF3.Et2O in dry CH2Cl2 at 0 °C to afford the corresponding pyranothiochromans. The iodomethyl glucosyl acetate affords α-1,2-aryl-C-glucoside pyranothiochromans while the mannosyl analogue prepared by opening of a β-1,2-cyclopropanated sugar (mannose) with N-Iodosuccinimide (NIS) in the presence of water as a nucleophile generated a β-1,2-aryl-C-mannoside pyranothiochroman with opposite stereochemistry at positions C1 and C2 relative to the former analogue.

These pyranothiochromans were treated with oxidizing agents to afford the corresponding sulfoxides. The sulfoxide derivatives were then transformed into thiochromenes via Pummerer rearrangement followed by hydrolysis. The reaction pathways followed by the glucosyl (α-1,2-aryl-C-glucoside) and mannosyl (β-1,2-aryl-C-mannoside) sulfoxides under these conditions are different and led to two different sets of thiochromene derivatives. The mechanisms and plausible reasons that lead to these differences are discussed.

The second part of the thesis describes the synthesis of O-, S- and C-glycosides. There have been several methods reported on the synthesis of these types of glycosides. 2,3-Unsaturated glycosides have been prepared by Ferrier rearrangement using various promoters. The search to find a better promoter has been an on-going endeavor. In this aspect this thesis evaluated the use of NaHSO4 supported on silica gel as an alternative catalyst for the formation of 2,3-unsaturated O- and S- glycosides. The catalyst was found to be as good as and in some cases superior to the existing Ferrier rearrangement reaction promoters. The catalyst is a new entrant to the already reported acids that catalyze the Ferrier rearrangement with the added advantage of being easy to handle and environmental benigness.

On the other hand 2-C-branched-α-aryl-C-glycosides were synthesized by careful desulfurization of pyranothiochroman precursors. In this aspect two desulfurizing agents were
employed: nickel boride which generates selectively the 1,2-cis-2-hydroxymethyl-α-aryl-C-glucoside and Raney nickel (W-1) which produces inseparable mixtures of 1,2-cis-2-formyl-α-aryl-C-glucoside and 1,2-cis-2-formyl-α-aryl-C-mannoside.

The 1,2-cis-2-hydroxymethyl-α-aryl-C-glucosides having the proper orientation and stereochemistry were converted, as a proof of concept, into precursors of potential inhibitors of the enzymes involved in Mycothiol biosynthesis, thereby disrupting the biosynthesis of Mycothiol. Finally to expand the synthetic utility of the 1,2-cis-2-formyl-α-aryl-C-glucoside and mannose mixtures, they were transformed to 2,3-unsaturated-2-formyl-α-aryl-C-glucosides under a base-catalyzed reaction.
### Abbreviations

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<tr>
<th>Abbreviation</th>
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<tr>
<td>Å</td>
<td>Angstrom</td>
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<tr>
<td>Ac</td>
<td>acetate</td>
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<tr>
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<td>c</td>
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</tr>
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</tr>
<tr>
<td>dd</td>
<td>doublet of doublet</td>
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<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5,4,0]undec-7-ene</td>
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<tr>
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<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
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<td>DEAD</td>
<td>diethyl Azodicarboxylate</td>
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<tr>
<td>DHEA</td>
<td>didehydroepiandrosterone</td>
</tr>
<tr>
<td>DIEA</td>
<td>N,N-Diisopropylethylamine</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
</tr>
<tr>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethyl formamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
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<tr>
<td>DMAP</td>
<td>4-(N,N-dimethylamino) pyridine</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
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<tr>
<td>E</td>
<td>electrophile</td>
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<td>electrospray-ionization time of flight mass spectrometry</td>
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<td>electron withdrawing group</td>
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<td>g</td>
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<td>HMBC</td>
<td>heteronuclear multiple bond coherence</td>
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<tr>
<td>IC₅₀</td>
<td>half maximal inhibitory concentration</td>
</tr>
<tr>
<td>IDCP</td>
<td>iodine dicollidine perchlorate</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
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<tr>
<td>J</td>
<td>coupling constant</td>
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<tr>
<td>LAH</td>
<td>lithium aluminium hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropyl amide</td>
</tr>
<tr>
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<td>------------</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
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<tr>
<td>MAD</td>
<td>bis(2,6-di-tert-butyl-4-methyl phenoxide) methyl aluminium</td>
</tr>
<tr>
<td>MCR</td>
<td>multi component reaction</td>
</tr>
<tr>
<td>Me</td>
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</tr>
<tr>
<td>MHz</td>
<td>mega hertz</td>
</tr>
<tr>
<td>Min</td>
<td>minute (s)</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>Mp</td>
<td>melting point</td>
</tr>
<tr>
<td>MVK</td>
<td>methyl vinyl ketone</td>
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<tr>
<td>MW</td>
<td>microwave</td>
</tr>
<tr>
<td>m/z</td>
<td>mass to charge ratio</td>
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<td>NaOAc</td>
<td>sodium acetate</td>
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<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NIS</td>
<td>N-iodosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PPA</td>
<td>polyphosphoric acid</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>PPr₃</td>
<td>tripropylphosphine</td>
</tr>
<tr>
<td>PTSA</td>
<td>p-toluenesulfonic acid</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>--------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>RCM</td>
<td>ring closing metathesis</td>
</tr>
<tr>
<td>Rf</td>
<td>retention factor</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>TBAI</td>
<td>tetrabutyl ammonium iodide</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethane sulfonyl</td>
</tr>
<tr>
<td>TFAA = TFO⁻</td>
<td>trifluoroacetic anhydride</td>
</tr>
<tr>
<td>TF₂O</td>
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</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
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<td>UV</td>
<td>ultra-violet</td>
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**Contributions**

Parts of the work covered in this thesis have been published in international journals and presented in a conference.

**Research papers**


**Oral presentation:**

12th Frank Warren conference of the South African Chemical Institute (SACI), 15-18 April, Bloemfontein, South Africa, **2012**
CHAPTER 1: LITERATURE SURVEY

1.1. Thiochromenes

1.1.1. Introduction

Heterocyclic compounds are broadly classified by the size of the heterocyclic ring and the number and type of the hetero atoms. Common heteroatoms in heterocyclic compounds are: nitrogen, oxygen and sulfur. Unlike nitrogen- and oxygen- containing heterocycles, which are widely available in natural products, sulfur heterocycles are less abundant and relatively less explored.\textsuperscript{1,2,3,4} The commonly known S-heterocycles besides thiophene are benzo-fused compounds, namely: thiochromans, thiochromenes, and benzothiophenes.\textsuperscript{5} In line with the theme of this thesis, the chemistry of thiochromenes is discussed below in detail.

Thiochromenes are benzothiopyran derivatives possessing a double bond between C3 and C4 or between C2 and C3 (A and B, respectively, in Figure 1.1). Depending on the position of the $sp^3$ hybridized carbon relative to the ring sulfur, they are named as 2$H$ (A)- and 4$H$ (B)-thiochromenes. Similarly, when a carbonyl is attached to what was an $sp^3$ carbon, the same terminology applies as 2$H$-chromen-2-one (C) and 4$H$-chromen-4-one (D), respectively (Figure 1.1).\textsuperscript{6}

\begin{center}
\includegraphics[width=\textwidth]{fig1.png}
\end{center}

\textbf{Figure 1.1:} Thiochromene derivatives and their corresponding numbering system.

Thiochromenes are the main sub-structural features of a number of compounds which possess anti-cancer,\textsuperscript{7} anti-HIV,\textsuperscript{8} anti-viral,\textsuperscript{9} anti-tumor,\textsuperscript{10} antibacterial/antimicrobial,\textsuperscript{11} fungicidal,\textsuperscript{12} and anti-malaria activities.\textsuperscript{13}
Razdan and co-workers evaluated 2,4-substituted thiochromenes with an amine group at C4 and an aryl group at C2 as shown in 1 against *Plasmodium berghei*.\textsuperscript{13}

\begin{center}
\includegraphics[width=0.5\textwidth]{figure1.png}
\end{center}

**Figure 1.2**: 2,4-substituted anti-malarial thiochromene.\textsuperscript{13}

The structural activity relationship (SAR) studies suggested that a strongly basic nitrogen atom separated by three to four carbon atoms from the imino nitrogen at C4 position is required. Additionally, an aryl group at C2 seems crucial for activity, as its replacement with an adamantyl group resulted in loss of activity. The presence of chlorine at both C4’ and C6 or at either position was also found to be necessary for activity.\textsuperscript{13}

With the emergence of drug resistant and new viral infections, the need for new anti-viral agents with a broad-spectrum of activity and new modes of action becomes imperative. Towards this goal, Zhang and co-workers screened several thiochromenes out of which thiochromenes 2a-e exhibited anti-viral activities.

\begin{center}
\begin{tabular}{ll}
2a : & \(R_1 = \text{fluorophenyl} ; R_2 = \text{H}\) \\
2b : & \(R_1 = 4\text{-methoxyphenyl} ; R_2 = \text{H}\) \\
2c : & \(R_1 = \text{methyl} ; R_2 = \text{H}\) \\
2d : & \(R_1 = \text{methyl} ; R_2 = \text{phenyl}\) \\
2e : & \(R_1 = 4\text{-nitrophenyl} ; R_2 = \text{H}\)
\end{tabular}
\end{center}

\begin{center}
\includegraphics[width=0.5\textwidth]{figure2.png}
\end{center}

**Figure 1.3**: Thioflavone derivatives evaluated for anti-viral activities.

The thioflavone 2b showed the highest inhibitory activity of all the compounds tested against EV71, with an IC\textsubscript{50} value of 5.48 \(\mu\text{M}\). However, it was not as potent as the reference standard
drug Pirodavir, which is reported to have an IC₅₀ value of 0.32 μM. Furthermore, it was noted that, compounds with an electron donating methoxy group at C4’ on the phenyl ring (thioflavone 2b) showed enhanced inhibitory activity against CVB3 with an IC₅₀ value of 6.44 μM and a selectivity index (SI) of 11.60. On the contrary, electron withdrawing groups like fluorine in thioflavone 2a and nitro group in thioflavone 2e showed no activity against CVB3. On the other hand, Compounds 2a, 2c and 2d all showed strong inhibitory activity against CVB6 at very low concentrations (IC₅₀ 2.91–3.77 μM). The SI values in these compounds (>15) were much higher than that of the reference drug.⁹

While Zhang and co-workers focused on substitution effects at positions C2 and C3 of thioflavones as anti-viral agents, Nakazumi and co-workers evaluated C3 hydroxymethyl and acetoxyethyl substituted thioflavones 3a-b as potential anti-microbial agents (Figure. 1.4).¹¹

While the un-substituted thioflavone 4 didn’t show any activity for all the microorganisms tested, the 3-hydroxymethyl and 3-acetoxyethyl substituted thioflavones 3a-b exhibited activity against Trichophyton rubrum and Trichophyton mentagrophytes; but their activity was not better than the reference compound Tolnaftate, the antifungal agent, used without medical prescription. Further evaluation on sulfone analogues were done on thioflavones 5a-b and 6 prepared by the oxidation of 3a-b and 4 respectively. The sulfone analogues of the un-substituted thioflavone 4 exhibited anti-microbial activities against fungi, while sulfone

![Figure 1.4: Thioflavone derivatives evaluated as antimicrobial agents.](image-url)
thioflavones 6a-b on the contrary resulted in a 500 to 600 fold decrease in activity against trichophytons.\textsuperscript{11} This is indicative of a synergistic interaction between the C3 substituent and the oxidation state are important for the activity.\textsuperscript{11}

The efforts of the last two research groups were focused on the substituents on the thiopyran ring and the oxidation state of the heteroatom to evaluate activities. On the other hand, Hui-Kang Wang and co-workers evaluated the structure activity relationship of thioflavones with emphasis on substituents on the benzo-ring of the thiochromone moiety (\textbf{Figure. 1.5}) as potential cytotoxic, topoisomerase I and II inhibitors, and anti-HIV agents. Towards this end, the group prepared a series of 5,6,7,8-substituted-2-phenylthiochromen-4-ones.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Substituted thioflavones (7a-e) and sulfoxide derivative (8a) evaluated for cytotoxicity, topoisomerase inhibition and HIV-1 protease inhibition.}
\end{figure}

Whereas the un-substituted thioflavones 7a (R\textsuperscript{5} = R\textsuperscript{6} = R\textsuperscript{7} = R\textsuperscript{8} = R\textsuperscript{3} = H) did not display any activity, the substituted compounds 7b, 7c, 7d and the sulfoxide 8a (R\textsuperscript{5} = R\textsuperscript{6} = R\textsuperscript{7} = R\textsuperscript{8} = R\textsuperscript{3} = H) showed good cytotoxicity at dose levels of (ED\textsubscript{50} < 4.0 \mu l) against several tumor human cell lines including ileoocoecal carcinoma (HCT-8), murine leukaemia (P-388), human melanoma (RPMI), and a central nervous system (CNS) tumor (TE671). \textit{In vitro} studies indicated that compounds 7c, and 8 are potential inhibitors of the DNA topoisomerase I. HIV inhibition tests on the other hand revealed that compounds 7b, 7c, 7d and 7h displayed selective anti-viral
activity at levels of ED$_{50}$ 0.65-9.5 μg/ml. Similar to the results reported by Zhang and co-workers above (Figure 1.4) the oxidation state of sulfur has imparted activity relative to the corresponding sulfide.$^{10}$

Thiochromone 1,1-dioxide, the sulfone derivative of thiochromone, is a bioisoster of 1,4-naphtoquinone in which one of the carbonyl groups in 1,4-naphthoquinone is replaced by a sulfone group. Quinones are reported to have anti-tumor activities. The widely used chemotherapeutic agent Mitomycin C $^{9}$ (Figure 1.6) which contains a benzoquinone core is an active alkylating agent crosslinking DNA and thereby blocking DNA replication. The drug contains a benzoquinone, a carbamyl and aziridine moieties.$^{14}$

![Figure 1.6: The chemotherapeutic agent Mitomycin C.](image)

Kinoshita and co-workers showed that the carbamyl group and the aziridine ring of the Mitomycins were not essential for biological activity; it is the benzoquinone scaffold that induces the activity.$^{15,16}$ Holshouser and co-workers encouraged by bioisosterism principle and the activity of quinones as anti-tumor agents, prepared a series of 2,3-unsaturated, 2,3 substituted thiochromone oxides $^{10}$ and 2,3 substituted thiochroman-4-one oxide $^{11}$ as bioisosters of 1,4-naphtoquinone (Figure 1.7) and tested them for antitumor activity.
Figure 1.7: Thiochromone 1,1-dioxide analogues of 1,4-naphtoquinone.

The authors reported that the compounds were not active against P-388 lymphocytic leukaemia. However, all of them exhibited good activity against Ehrlich ascites tumor growth in CFI mice with compounds 10a and 10b showing significant activity against the Ehrlich ascites tumor screen with 99.9 and 99.3% inhibition, respectively. Interestingly while 10c showed some activity compound 11 did not exhibit any activity, which implies the double bond between C2 and C3 had a role in activity. The investigators have also made an observation that the compounds show higher lipid solubility which would render them useful candidate drugs against brain tumors.17

Thiochromones have also showed activity against Cytomegalovirus (CMV), a member of the β-herpes virus family that is responsible for a diverse set of diseases in humans in general and particularly in the immuno-compromised, such as AIDS patients and organ transplant recipients.18,19 The available treatments are largely ineffective, with the exception of a few drugs for the treatment of herpes simplex virus (HSV) infections.20 Molecular studies indicated that viral proteases play a critical role in the life cycle of many viruses by affecting the cleavage of high-molecular-weight viral polyprotein precursors to yield functional products or by catalyzing the processing of the structural proteins necessary for assembly and morphogenesis of virus particles.21,22 It is anticipated that potent inhibitors of this protease will ultimately prove to be effective antiviral agents. Dhanak and co-workers prepared a series of benzothiopyran-4-one derivatives (Figure 1.8) as human CMV inhibitors. The authors found that the oxidation state of sulfur has a role in inhibition activities, with sulfones being the most potent inhibitors. Sulfides showed no activity and racemic sulfoxides were weak inhibitors.23 This complements
the results found by Nakazumi and co-workers in which case the sulfone derivative thioflavone 5 (Figure 1.4) had enhanced activity against fungi than its corresponding sulfide derivative.\textsuperscript{11}

![Figure 1.4: Thioflavone sulfone derivative](image)

**Figure 1.8:** Thiochromone 1,1-dioxide substituted at C1 Cytomegalovirus (CMV) inhibitors.\textsuperscript{20}

The replacement of 3-methylpyridine $N$-oxide 12a by pyridine 12b showed a moderate increase in potency. However, replacing the heterocycle by a phenyl group 12d reduced the activity; on the other hand the activity was enhanced 20 fold with a phenyl containing electron withdrawing groups like sulfones 12e and nitro groups 12f. However, substituents on the benzo ring showed no significant change in activity on the basis of which the authors suggested that this part of the molecule doesn’t make many interactions with the enzyme.\textsuperscript{23}

The protease enzyme similarly plays a critical role in the replication of the HIV virus which has been targeted for chemotherapeutic intervention by targeting the HIV-1 protease enzyme. Ritonavir 13 (Figure 1.9) with a trade name Norvir, is a protease inhibitor to treat HIV-1/AIDS.\textsuperscript{23, 24}
Kaye and co-workers synthesized analogues of Ritonavir 13 by replacing the terminal moieties of ritonavir with a heterocyclic system of thiochromene 14. They reported negative van der Waals protein-ligand interaction energies (-46.1 to 68.1 kcal/mol) which is less than the value obtained for ritonavir (-98.2 kcal/mole). This was an encouraging result and it indicated that further studies on enzyme binding and inhibition activities had to be done.8,25

The development of new strains of fungi which are resistant to azole therapies, the high toxicity of polyenes and the decreased susceptibility of newly emerging fungi in a growing setting of immune-compromised patients, such as HIV positive and neutropenic patients9 prompted the need to develop new anti-fungal agents with novel modes of action.26,27 Quinoline-fused heterocycles known for several activities against pathogens have been the subject of enormous research interest in medicinal chemistry and chemical biology. Against this background, Zhengyue and co-workers synthesized quinoline-fused thiochromenes (6H-thiochromeno[4,3-b]quinolones) as anti-fungal agents (Figure 1.10).28

Figure 1.9: The protease inhibitor Ritonavir 13 and its thiochromene analogue 14.8

Figure: 1.10: The most active thiochromeno quinoline antifungal compounds.28
Substrates with different substituents attached to the aminophenol and the thiochromene moieties were tested for their in vitro antifungal activities, with fluconazole, a known antifungal agent as a standard. The results showed that compounds 15 and 16 showed highest in vitro anti-fungal activity.28

The thiochromene scaffold is also found in various enzyme inhibitors. The enzyme steroid sulfatase is a 65 kDa membrane-bound protein, mainly associated with the endoplasmatic reticulum found in most mammalian tissues. The enzyme catalyzes the hydrolysis of the sulfate esters of 3-hydroxy-steroids, which are inactive transport forms of the 3-hydroxy steroids.29,30 This enzyme is involved in the pathogenesis of a number of diseases such as: breast cancer, androgen-dependent skin diseases, cognitive dysfunction, and immune functions. Hence, steroid sulfatase inhibitors are potential therapeutic agents for the treatment of these diseases.31-36

Figure 1.11: Steroid sulfatase (STS) inhibitor Sulfamate 17 and thiochromone sulfamate 18.

The most active STS inhibitors known so far are sulfamic acid esters, such as estrone sulfamate 17 (Figure 1.11) which inactivates its target enzyme irreversibly33. However, these agents could not be developed further into effective therapies due to their estrogenic activity,37 hence, there has been continuous effort to find non-estrogenic sulfamate type STS inhibitors. Tricyclic coumarin sulfamate inhibitors showed good inhibitory activity without showing any estrogenic activity. One such example is, Coumate-667 18 (Figure 1.11).38, 39 Interestingly, cholesterol and DHEA sulfatase were not able to inhibit the enzyme even at higher concentrations of 30 µM. This suggests that the phenyl ring attached to the cyclohexane in 17 is crucial for the inhibition activity.40 Inspired by these results, Nussbaumer and co-workers have synthesized a series of non-steroidal chromenes 18 and thiocromenes 19 with the bicyclic core group
mimicking estrone’s A, B rings and the side chains filling the space of C and D rings of estrone (Figure 1.12). The STS inhibition results showed that the sulfur analogues 18 were 4-17 fold more potent than the corresponding Oxo analogues 19 (For instance 18c exhibited an IC₅₀ value of 0.34 nM and 19c 5.6 nM). Compound 18c was the most potent STS inhibitor discovered and it is about 170-fold more potent than the steroidal lead compound 17 (Figure 1.11).⁴⁰

![Thiochromone and chromone derivatives evaluated for STS inhibition and estrone structure.](image)

Similar to the observation made by Holshouser and co-workers on the importance of the double bond in thiochromone for anti-tumor activity,¹⁷ reduction of the double bond in thiochromone 18 caused slight loss in inhibition activity.⁴⁰

1.1.2. Synthesis of Thiochromenes

There are various methods for the synthesis of thiochromene derivatives in the laboratory. Most reported synthetic methodologies are, however, not stereoselective and produce mixtures of enantiomers and diastereomers. Thioflavones, which are derivatives of thiochromenes, are bioisosters of the extensively studied biologically and medicinally useful flavones, hence of all the benzothiopyran family, this group is privileged with relatively better literature reported
synthetic methodologies. The well-established synthetic protocols thus led to the use of the easily accessible thiochromones as substrates for the synthesis of thiochromenes via simple transformations (which includes simple 1,2-addition reactions of the carbonyl functional group).

The most common and widely known synthesis methodology of thiochromones is the cyclic condensation of benzenethiols 20 with ethyl benzoylacettes 21 using polyphosphoric acid as dehydrating agent at 90 °C (Scheme 1.1a). This method mostly affords the thioflavone 22. However in the reaction of arylthiols with dimethoxy-substituted ethyl benzoylacettes, the benzocyclopentenones 27 is mainly formed instead of the thioflavone 22. The competitive cyclization into the cinnamyl aromatic ring, rather than the sulfur-bearing ring, became important when the cinnamyl ring was strongly activated by methoxy substituents 28 (Scheme 1.1b).
Scheme 1.1: a) (a) PPA, 90-100 °C, 2 h, 95%; (b) The methoxy activated cinnamyl ring out competes the sulfur bearing phenyl ring.

Lee and co-workers on the other hand prepared 2-phenyl-4H-1-benzothiopyran-4-ones 31 from thiosalicylic acid 29 in the presence of methyl lithium and LDA (Scheme 1.2). The condensation of the resulting adduct 30 with N-methoxy-N-methyl benzamide in the presence of an acid produced the thioflavone 31 in an overall yield of 94% at room temperature in one hour.45
Zhengyue and co-workers synthesized 3,4-di-functionalized thiochromene 35 (4-chloro-2H-thiochromene-3-carbaldehydes) by coupling 3-chloropropanoic acid 33 and methyl thienophenol 32 under microwave irradiation, followed by subsequent cyclization in concentrated sulfuric acid to yield thiochroman-4-one 34. The thiochromanone 34 was then transformed into 4-chloro-2H-thiochromene-3-carbaldehydes 35 via the Vilsmeier-Haack-Arnold reaction, in which a chloroiminium ion formed in situ from the reaction of an N,N-di-substituted formamide, such as dimethylformamide (DMF), with phosphorus oxychloride reacting with the ketone enolate of the thiochromone (Scheme 1.3).
This synthetic strategy inserted aldehyde and chloro functionalities at positions 3 and 4, which are amenable for further transformations. The carbaldehydes were further transformed into quinoline fused thiochromenes 37 when treated with amino phenol 36 at high temperature. (Scheme 1.4).48b

![Scheme 1.4](image)

**Scheme 1.4:** (i) DMF, 25 °C, 1 h; (ii) 120 °C, 2-4 h, 67%.

Thiochromones are employed as synthetic precursors of thiochromenes via different reaction mechanisms. Un-substituted 2H thiochromene 40 was prepared by reduction of the carbonyl group of thiochromone 38 with sodium amalgam, lithium aluminum hydride, or sodium borohydride followed by dehydration of the resulting 3-hydroxyl thiochromene 40 with phosphorous pentoxide (Scheme 1.5).49,50 While the use of these reducing agents on the reduction of thioflavone 41 provided thiochromene 42 in low yield, employing a mixture of LiAlH4/AlCl3 (1:1) afforded a better yield (95%) (Scheme 1.6).51

![Scheme 1.5](image)

**Scheme 1.5:** (i) LiAlH4, THF; (ii) Piperidine, P2O5, benzene, reflux, 5 h, 54%.
Scheme 1.6: LiAlH₄/AlCl₃ (1:1), THF, 25 °C, 24 h, 95%.

The reduction of thiochromones afforded un-substituted thiochromenes, however, alkyl and aryl substituted thiochromones were also possible by treating the thiochromone 38 with Grignard reagents. 4-Aryl or alkyl substituted 2H-thiochromenes 43 were prepared by the reaction of aryl or alkyl magnesium halide with thiochromone 38 (Scheme 1.7).⁴⁶,⁵²,⁵³,⁵⁴

Scheme 1.7: (i) CH₃MgI, ether, reflux, 1 h, 75%; (ii) KHSO₄, 120-150 °C

Tilak and Vaida synthesized 2,2-di-methylthiochromene 46 starting from 4-Methyl-3-pentene-2-one (methyl oxide) 44 and thiophenol 20 via the PPA mediated cyclocondensation of 44 (Scheme 1.8).

Scheme 1.8: (i) Piperidine, benzene, reflux, 5 h, 88% (ii) PPA, 90 °C, 60%.
However, when the un-substituted alkene, methyl vinyl ketone (MVK) instead of 4-Methyl-3-pentene-2-one (methyl oxide) 44 to generate the 3-oxoalkyl aryl sulfide 47 the thiochromene formed undergoes disproportionation to provide benzothiopyrylium 48 and thiochroman 49 in 25% and 45% yields respectively. This disproportionation occurs due to abstraction of the labile hydrogen’s at C2 **Scheme 1.9**.

![Scheme 1.9: Piperidine, PPA, benzene, reflux, 5 h, 25% (48) and 45% (49).](image)

The mechanism of benzothiopyrylium salt 48 formation is assumed to proceed through the carbenium ion intermediate 54, generated by protonation of 54 at C3 and subsequent hydride transfer from un-protonated 55 to the carbenium ion that accounts the formation of the products 48 and 49 (**Scheme 1.10**). 52

![Scheme 1.10: Possible mechanism of the PPA mediated 3-oxo-butyl sulfide phenyl condensation and subsequent disproportionation.](image)
The use of hydride-ion acceptor like triphenylmethyl perchlorate increased the chemoselectivity of benzothiopyrylium salt to 60-90% yield.\textsuperscript{50,53} While the method failed to generate the expected thiochromenes, the benzothiopyrylium salt thus prepared becomes useful substrate for the synthesis of several thiochromene derivatives.

Reduction of benzothiopyrylium perchlorates with lithium aluminum hydride is another useful synthetic tool for the preparation of 2\textit{H}- and 4\textit{H}-thiochromenes. 4-Aryl- and 2-aryl-1-benzothiopyrylium perchlorate \textbf{56} reacts with LiAlH\textsubscript{4} in diethyl ether to generate thiochromenes \textbf{57} or \textbf{58} in up to 90% yield. The hydride ion adds to the un-substituted carbon atom (\textbf{Scheme 1.11}).\textsuperscript{53}

\textbf{Scheme 1.11}: LiAlH\textsubscript{4}, diethyl ether, rt, 90%.

Hydrolysis of 4-substituted benzothiopyrylium salt \textbf{59} can react with nucleophiles such as H\textsubscript{2}O to provide mixtures of thiocoumarin \textbf{61} and thiochromene \textbf{62} in a 1:1 ratio \textit{via} the intermediate \textbf{60} (\textbf{Scheme 1.12}).\textsuperscript{54}

\textbf{Scheme 1.12}: NaHCO\textsubscript{3}, rt, 43%.
On the other hand, its reaction with thiophenol at room temperature gives 2\(H\)-thiochromene series in 83% yield (Scheme 1.13).\(^{54}\)

![Scheme 1.13: Thiophenol, THF, rt, 83%](image)

There are few reported methods on transition metal catalyzed synthesis of thiochromene derivatives. Intra-molecular ring closing metathesis (RCM) is one of the examples.\(^{55,56}\) Whitehead et al. employed this method to prepare phosphate substituted thiochromene 66 (2\(H\) thiochromenyl enol phosphates). The reaction started with nucleophilic aromatic substitution of sodium allylmercaptide with 2-fluoroacetophenone 64 to provide the metathesis precursor 65. Treating this intermediate with ring closing metathesis reagents afforded 2\(H\)-thiochromen-4-yl enol phosphates 66 in 48% yield (Scheme 1.14).\(^{57}\)

![Scheme 1.14: (i) CH=CH=CHSH, NaH, THF, 90%; (ii) LDA, THF, Cl(O)(POEt)2, 80%; (iii) 10 mol% (ImesH2)(PCy3)(Cl)2Ru=CHPh, CH2Cl2, 45 °C, 48%](image)

Seijiro and co-workers prepared substituted thiochromones 69 and isothiochromones 70 from thiophthalic anhydrides 67 with 4-octyne 68 using a nickel catalyst via oxidative addition of phthalic anhydride to Ni (0), decarbonylation, and insertion of alkyne followed by reductive elimination. The group noted that Ni(0)/PPr\(_3\) used as a catalyst produced 6% of isothiochroman
and 6% of thiochromene 69. Interestingly, addition of a 10 mol% of methylaluminium bis(2,6-di-tert-butyl-4-methylphenoxide) as a Lewis acid enhanced the yield to furnish 69 in 99%. The chemoselectivity of the reaction was changed by changing the solvent from toluene to benzene to furnish thiochromone 70 in 89% yield (Scheme 1.15).58

![Scheme 1.15](image)

**Scheme 1.15:** (i) Ni(cod)2 10 mol%, PPr3 40 mol%, MAD 10 mol%, toluene, 130 °C, 5 h, 99%; (ii) Ni(cod)2 10 mol%, tripropylphosphine (PPr3) 40 mol%, MAD 10 mol%, benzene, 130 °C, 3 h, 89%.

Vijay and co-workers reported a transition metal-free synthesis of thioflavones 73 and 74 via a coupling of dithioester 71 and acetophenone 72 followed by an intramolecular S-arylation in the presence of sodium hydride.59 (Scheme 1.16). Despite the relatively lower yield, this method avoids the use of a transition metal catalyst and high temperatures.

![Scheme 1.16](image)

**Scheme 1.16:** (i) NaH, DMF, rt, 3-4 h, 38% (73), 33% (74).
NaH deprotonation of an α-hydrogen from the 2,4-dichloroacetophenone 72 initiates the reaction by generating a carbanion intermediate 75, which reacts with dithioester 71 to produce the 1,3-thioketone adduct 76. The 1,3-thioketone adduct 76 undergoes keto-enol tautomerization to produce 77. Finally, an intra-molecular nucleophilic Sarians substitution occurs at the o-halo position 78 by the attack of the mercapto group leading to the formation of 4H-thiochromene-4-one 73 in 38% yield. Further, the chloro derivative 73 undergoes direct nucleophilic substitution with the sodium thiomethoxide to generate the methylthio thiochromene 74 in 33% (Scheme 1.17).59

The Baylis-Hillman C-C bond forming organic reaction, 60-62 which involves the reaction of an activated alkene with an aldehyde in the presence of a tertiary amine catalyst was also used for the synthesis of thiochromenes by Kaye and co-workers. 25
The synthesis of thiochromene started by reduction of thiosalicylic acid 29 to mercapto alcohol 79. During oxidation of the hydroxyl group in 79 to an aldehyde, a spontaneous dimerization to a disulfide dicarbaldehyde 80 occurred, which is facilitated by self-protection of the nucleophilic thiol group. Baylis-Hillman reaction of the disulfide dicarbaldehyde 80 with methyl vinyl ketone (MVK) 81 using 1,6-diazabicyclo[4.4.0]undecane (DBU) as the tertiary amine catalyst, afforded the required thiochromene 82 in good yield with in situ reduction of the disulfide (Scheme 1.18).25

Scheme 1.18: (i) LiAlH4, THF; (ii) 1,6-diazabicyclo[4.4.0]undecane (DBU), 59%.

Regiospecific synthesis of tetrahydrothiochromen-5-ones 86 was reported by Singh and co-workers in a multi component reaction (MCR) by coupling β-oxodithioester 83, an aldehyde 84 and cyclic 1,3 diketone 85 in a one pot synthesis using phosphorous pentoxide as a catalyst under solvent free conditions at 100 °C (Scheme 1.19). The reaction is a one-pot Knoevenagel condensation-Michael addition-cyclization cascade reaction. The good reaction yield (72-90%) and the regiospecific nature of the reaction were the advantages of this method. However, the generation of inseparable mixtures when aliphatic aldehydes are used is its drawback.63
Scheme 1.19: (i) P₂O₅ 20 mol%, 100 °C, 2 h, 82%.

Scheme 1.20: Possible mechanism for the regiospecific synthesis of thiochromen-5-one-4.

The reaction starts by the Knoevenagel condensation between the aldehyde 84 and cyclic 1,3-di-ketone 85 to generate the intermediate 87, which was used as the Michael acceptor. The enol tautomer of β-oxodithioester 83 undergoes intra-molecular cyclization via its two possible rotamers 88a and 88b, through pathways I and II to generate thiochromone 86 and chromone.
89, 88b undergoes regiospecific S-alkylation followed by dehydration to give the thiochromone 86. However, the chromone through path II was not formed which supports the idea that S-alkylation is favoured over O-alkylation (Scheme 1.20).63

The synthesis of fused thiochromenes can be done either by the synthesis of functionalized thiochromenes which can be transformed further by manipulating the functional groups, or by starting from fused substrates and adding the thiochromene scaffold. Mashelkar and co-workers have synthesized fused benzothiophene thiochromenes via intra-molecular electrophilic hydroarylation through Claisen rearrangement. The dibenzothiophene 90 was treated with n-butyl lithium and propargyl bromide 91 at -40 °C to provide the thioether 92 which was heated at 220 °C with N,N-diethylaniline in DMF for 8 hours to generate the cyclized thiochromene fused di-benzofuran 93 in 55% yield (Scheme 1.21).64

\[
\begin{align*}
\text{Scheme 1.21:} & \quad (i) \quad \text{K}_2\text{CO}_3, \text{n}-\text{BuLi}, \text{S}, \text{DMF}, -40 \, ^\circ\text{C}-\text{rt}, 2 \, \text{h}; \ 30\% \quad (ii) \quad \text{N,N-diethylaniline, 220 } ^\circ\text{C,} \ 8 \, \text{h}, \ 70\%.
\end{align*}
\]

Although the above mentioned protocols on thiochromene synthesis are reported, very few protocols exist on the stereoselective synthesis of thiochromenes. Stereoselective synthesis of thiochromenes becomes important in developing them as potential therapeutic agents. The very few existing stereoselective synthetic strategies of thiochromenes are dominated by asymmetric organocatalysis. Organocatalysis in turn is mostly dominated by Lewis base catalysts such as amines and carbenes.65

Wang and co-workers employed bifunctional amine thiourea catalyst 94, which participates in multiple hydrogen bonding, in the stereoselective synthesis of thiochromans. The hydrogen bonding activates the substrates by making the mercapto benzaldehyde 95 more nucleophilic and the oxazolidone 96 counterpart more electrophilic (Scheme 1.22). It was reported that a catalyst loading as low as 1 mol% catalyzed the reaction in 1 hour at room temperature to provide the corresponding thiochroman 97 in 90% yield and 99% ee and > 20:1 dr.67
**Scheme 1.22:** Organocatalyzed Enantioselective tandem thio-Michael-Aldol reaction.

Although the enantioselectivity was not as good as the method by Wang and co-workers, Rajasekhar and co-workers have evaluated a series of alkaloid organocatalysts for the synthesis of *tri*-substituted thiochroman 100 by tandem Henry-Michael reaction using mercapto benzaldehyde 95 and nitrostyrene 99 (Scheme 1.23).\(^6^8\) The results revealed that the alkaloid cupreine 98 was the most efficient catalyst giving only two diastereomers with best conversion (100%), ee (86%) for the major diastereomer.\(^6^8\)
Scheme 1.23: Diethyl ether, catalyst (10 mol%), -10 °C, 100%.

In a different report, Wang and co-workers showed organo-catalyzed thiochromene synthesis via imine 103 generated by covalent interactions between chiral (S)-pyrrolidine silyl ether 101 and cinnamaldehyde 102 to provide thiochromene 104 enantioselectively by a domino Michael addition/intra-molecular aldol condensation (Scheme 1.24).70

Scheme 1.24: Organocatalytic asymmetric Michael-aldol-dehydration cascade reaction of trans-3-phenylpropenal with 2-mercaptobenzaldehyde.
The iminium ion 104 generated by the reaction of \(\alpha,\beta\)-unsaturated aldehyde 102 with the (S)-pyrrolidine silyl ether 101 undergoes an intra-molecular sulfa-Michael addition reaction to produce thiochroman 104 which upon dehydration affords thiochromene 105 in 85% yield and 94% ee.69-71

Co’rdoval and co-workers similarly prepared tetrahydrothioxanthenones 108 with subsequent dehydration providing 109 in 74% yield and 62% ee by reacting 2-mercaptobenzaldehyde 95 and \(\alpha,\beta\)-unsaturated cyclic ketone 107 in the presence of chiral (S)-prolinol 106 (20 mol%) as the asymmetric organocatalyst (Scheme 1.25).72

\[
\begin{align*}
\text{Scheme 1.25: DMF, catalyst (20 mol%), -20 °C, 24 h, 74%}.
\end{align*}
\]

Although a number of organo-catalytic enantioselective hetero-Michael cascade reactions involving \(\alpha,\beta\)-unsaturated aldehydes and ketones have been reported, there hasn’t been much work done on olefins with an ester group activating the Michael acceptor. One type of domino reaction of substrates activated by ester groups is the Horner-Wadsworth-Emmons reaction.73

This reaction is a sub-class of the well-known Wittig reaction. The Horner-Wadsworth-Emmons (HWE) reaction modifies the Wittig reaction using phosphonate esters as Wittig reagents instead of the classical phosphonium yildes. It was reported that these Wittig reagents give better results on their reaction with sterically hindered ketones to produce alkenes.74,75

This reaction, which has broadened the scope of the Wittig reaction, was employed by Mukherjee and co-workers in a domino sulfa Michael/ Horner-Wadsworth-Emmons reaction to organo-catalytically activate alkene attached to an ester group 111. These alkenes usually require an additional binding site for activation by the organo-catalyst. The bi-functional urea
derived catalyst, 110 was used to promote the reaction between 2-mercaptobenzaldehyde and a tri-substituted vinyl phosphonate 111. This domino reaction provides a better way of organo-catalytic activation of ester containing substrates for asymmetric transformations which has been one drawback in organo-catalysis. The bi-functional catalyst activates the thiol and phosphonate groups making them more nucleophilic and electrophilic respectively by hydrogen bonding, thereby enhancing the enantiofacial discrimination of one enantiomer over the other 113 (Scheme 1.27).

The sulfa-Michael addition triggers the reaction in stereo-controlled fashion and the HWE reaction in which the phosphonate reacts with the aldehyde, eliminating the phosphonate group to give the 2,3- substituted thiochromene 112 (Scheme 1.26).  

![Scheme 1.26: Catalyst 10 mol%, PhCl, 25 °C, 6 h 96% (er 94.5:5.5).](image)

Scheme 1.26: Proposed stereochemical model for the sulfa-Michael/ HWE cascade reaction.
Although the organo-catalytic tandem Michael reaction is efficient, lack of a general principle to govern catalyst choice and the tedious nature of the design and synthesis of these chiral catalysts is a serious limitation. Another method of stereoselective synthesis of thiochromenes that doesn’t use organocatalysts was reported by Kobayashi and co-workers. They reported synthesis of an intermediate thiochroman 116 via the condensation of 2-mercaptobenzophenone 114 and α,β-unsaturated carboxylates 115 in the presence of bis(diisopropylamino)magnesium. Dehydration of 116 with methylsulfonyl chloride in the presence of triethylamine afforded 117 in 93% ee in good yields (Scheme 1.28). 77

Scheme 1.28:  

(i) magnesium-bis(diisopropyl)amide (MBDA), 0 °C, 3 h, 78%; (ii) methylsulfonyl chloride (MsCl), Et3N, 0 °C, 4 h, 92%.

Pummerer rearrangement reaction, an extensively used reaction of activated sulfoxides to furnish α-substituted sulfides, is also used in the synthesis of thiochromenes. 84 The reaction utilizes sulfur stabilized carbanions generated through electrophilic activation of sulfoxides via elimination/addition mechanisms (Scheme 1.29). 78

Scheme 1.29: The Pummerer rearrangement reaction.

The reaction is commonly carried out in the presence of sulfoxide activating agents such as acetic anhydride, trifluoroacetic anhydride (TFAA), trifluoromethanesulfonic anhydride (Tf2O) or silyl chloride in non-participating solvent. 79 Common nucleophiles used for the
reaction are arenes, alkenes, acetates, amides and phenols, which are less active towards the electrophile used to activate the sulfoxide. Hence, the nucleophiles used are those which are not reactive towards acids and acylating agents.\textsuperscript{78,79,80,81-83}

Parhaman and co-workers\textsuperscript{84} have synthesized 4\textit{H}-thiochromenes from thiochromanone \textit{38} via reduction with zinc amalgam to generate the thiochroman \textit{118}, oxidation with hydrogen peroxide to generate the sulfoxide \textit{119} and Pummerer rearrangement to produce the thiochromene \textit{120} (Scheme 1.30). The acetate counter anion abstracts the $\alpha$-proton as shown in \textit{121} generates the sulfonium ion \textit{122}, which is intra-molecularly attacked by the acetate group to provide \textit{123}. The thiochromene \textit{120} was then generated upon heating $\alpha$-acyloxy thiochroman \textit{123} (Scheme 1.31).

![Scheme 1.30](image)

Scheme 1.30: (i) Zn/Hg, HCl, rt, 65%; (ii) H$_2$O$_2$, AcOH, rt, 93%; (iii) Ac$_2$O, NaOAc, 140 $^\circ$C, 74%.

![Scheme 1.31](image)

Scheme 1.31: Possible mechanism of Pummerer rearrangement to generate 4\textit{H} thiochromene.

### 1.2 Glycosides

The reaction that condenses carbohydrates with aliphatic, aromatic or another sugar moiety is referred to as a glycosylation reaction. The bond that connects them together is called a glycosidic bond.\textsuperscript{85-87} Glycosides can be $O$, $C$, $N$, $S$ glycosides depending on the bond connecting the glycosyl donor and glycosyl acceptor. When the sugar residue establishes an $O$-
glycosyl linkage with an aglycon, the glycoside is known as \( O \)-glycoside. Monosaccharaides linked together by an \( O \)-glycosidic linkage constitute di-, oligo-, or poly-saccharides depending on the number of saccharide base units in the linkage. \(^{88-92}\) The chemistry of glycosides is mostly focused on creating and controlling the electrophilicity of C1 in the carbohydrate.\(^ {93,94}\)

There are several methods for the synthesis of glycosides based on various reactions of the anomic carbon. The most common one involves the activation of a leaving group on the glycosyl donor 124 by an electrophilic promoter generating the activated complex 125. Nucleophilic attack by a glycosyl acceptor of the activated complex 125 at the anomic carbon provides the glycoside 126 (Scheme 1.32).\(^ {93}\) The most commonly used electrophilic glycosyl donors are glycosyl halides, sugar lactones, glycals and 1,2-anhydro sugars and the acceptors can be alcohols, thiols or carbanions.\(^ {93}\)

Another common method for the synthesis of glycosides employs 1,2-unsaturated sugars, (glycals) as glycosyl donors generating 2-deoxy glycosides. The glycal donor 127 (Scheme 1.33) is activated by an electrophile (\( E^+ \)) providing the activated complex 128 which is then attacked by the glycosyl acceptor nucleophile to generate glycoside 129. This glycosylation type was first reported on the reaction of glycal with various alcohols using \( I_2 \) and silver salts as promoters. Ever since, several other promoters have been reported, of which, IDCP (Iodine dicollidine perchlorate), NBS, and NIS are common.\(^ {94-96}\)
Glycals are also used for the synthesis of 2,3-unsaturated glycosides through rearrangement of the double bond with concomitant formation of the glycoside via the Ferrier rearrangement reaction discussed below.

1.2.1. Ferrier Rearrangement Reaction and 2,3- Unsaturated Glycosides

Ferrier rearrangement is a Lewis acid-catalyzed allylic rearrangement of glycals in the presence of alcohols to yield 2,3-unsaturated glycosides. Thus, Ferrier rearrangement is a versatile tool to obtain various 2,3-unsaturated glycosides which can be transformed into several important molecules such as: antibiotics, oligosaccharides, and glycopeptides.

The proposed reaction mechanism for the transformation is an S_N1 substitution followed by allylic rearrangement. Since, Ferrier first reported the allylic rearrangement of tri-O-acetyl-D-glucal to anomeric mixtures of 2,3-unsaturated O-glycosides with alcohols in the presence of BF3.OEt as a Lewis acid, several promoters of the reaction have been reported which include various Lewis acids, ionic liquids and other reagents.

As shown in Scheme 1.34, the reaction proceeds via a cyclic oxocarbenium intermediate which can be intercepted by nucleophiles, including halides and carbanions to give the corresponding glycosides.

Scheme 1.34: The Ferrier rearrangement.
The selectivity of the reaction is explained on the basis of anomic effect. The stability of a certain conformer from all other possible conformers is generally explained on steric grounds. Studies of conformational analysis on cyclohexane ring revealed that the equatorial position is the preferred conformation for large substituents. However, contrary to this fact, an electronegative element adopts an axial orientation at the anomeric center in the pyran ring.\textsuperscript{104} This unusual effect was first described by Edward\textsuperscript{105} and later named as the anomic effect by Lemieux and Chu.\textsuperscript{106} There have been several models to explain this effect which have been subjects of considerable controversy.\textsuperscript{107} One model that explains this effect is the dipole-dipole or electron pair-electron pair repulsion (\textbf{Figure 1.13}). These interactions are pronounced in the $\beta$-anomer hence it is a disfavoured configuration.\textsuperscript{105}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{dipole_dipole_interactions.png}
\caption{Dipole-dipole interactions in $\alpha$ and $\beta$ alkoxy group-substituted pyran.}
\end{figure}

The observation made on detailed conformational studies revealed that in the $\alpha$-anomeric configuration the C-X ($X =$ halogen) bond length is increased while the adjacent C-O bond is shortened. This effect was not observed in the $\beta$-anomer. The dipole-dipole interaction model failed to account for these observations. Hence, an alternative explanation was proposed.\textsuperscript{119} The axial conformer is stabilized by delocalization of the lone pair of electrons on the oxygen atom to the periplanar C-X bond antibonding orbital (\textbf{Figure 1.14}) resulting in the shortening of the C-O bond and giving it a double bond character. It was shown that the anomic effect
out-competes the steric factor to produce a preferred α-configuration at the anomeric carbon.\textsuperscript{108}-\textsuperscript{110}

\[ \text{Figure 1.14: The anomeric effect: interaction of the endocyclic oxygen electron lone pair with the nonbonding orbital in an axially substituted pyran.} \]

Additionally, it was observed that the electronegativity of the substituent has a marked effect on the axial preference, and in general, more electronegative anomeric substituents exhibit a strong preference for axial orientation. The anomeric effect explains the stereochemical outcome of glycosidic reactions and the favoured α-configuration at the anomeric center. A similar effect when the stabilizing lone pair of electrons comes from the exocyclic oxygen of an aglycon to the antibonding orbital of endocyclic C-O bond is called the exoanomeric effect. Essentially, this effect is maximized when the \( p \) orbital of the unshared electrons is periplanar to the C1 ring oxygen bond.\textsuperscript{111,112}

\subsection*{1.2.2. Aryl-C-Glycosides}

Glycosides in which the linker atom at the anomeric center is carbon are called C-glycosides. The aglycan can be either an alkyl or an aryl group. These glycosides are recent entrants to glyco-chemistry relative to the \( O \), \( N \), and \( S \)-glycosides.\textsuperscript{113,114} Naturally occurring biologically active molecules that contain this linkage have pharmacological properties.\textsuperscript{114,116} Furthermore, C-glycosides are also used as the chiral pool for the synthesis of macromolecules such as palytoxin, spongistatin and halichondrin B.\textsuperscript{115} Additionally, owing to their inherent stability
toward enzymatic and chemical hydrolysis, they are potential inhibitors of carbohydrate processing enzymes.114-116

Aryl-C-glycosides are a subclass of these important C-glycosides, in which the substituent at the anomeric position is an aromatic group and are present in many biologically active natural products such as pluramycins (antibacterial and antitumor activities), angucyclines (antibacterial, antitumor activities, and inhibitors of oxidative enzymes), and benzoisochromanequinones (antibacterial, antitumor and antiplatelet aggregation activities).117 Several aryl glycosides are undergoing clinical trials as sodium-glucose linked transporter 2 (SGLT2) inhibitors for the treatment of diabetes and related complications.118,119

Although there are several routes reported on their preparation,94-96,120 the most common has been a Friedel-Crafts reaction between a glycosyl donor and an aryl compound which most of the time is activated by electron donating group.121,122 Most aryl-C-glycoside synthesis reactions are known to produce the thermodynamically favored β configuration and procedures yielding the α-anomer are rare.122,123 The very few reported methods on synthesis of the α-anomer and their stereoselectivity strongly depends on the nature of the aglycone and the nature of the reaction. The selectivity is not easily rationalized, making these methods unpredictable.123 One exception to this is the intra-molecular 1,2-cis-C-glycosylation via Friedel Crafts arylation of 2-O-benzylated glycosides (Scheme 1.35).122 Pyranoses, which are mostly known to generate the thermodynamically stable 1,2-trans anomer, afford the 1,2-cis anomer by intra-molecular 1,2-cis-C-glycosylation via Friedel Crafts arylation.122,123 6-O-acetyl-2,3,4-tri-O-benzyl-α-D-glucopyranosyl chloride 132 treated with silver tetrafluoroborate to generate 133, oxidation of 133 provides lactone 134 which upon hydrolysis provides the C-glycoside 135 in complete α-anomer selectivity.
Scheme 1.35: (i) AgBF₄; (CH₂Cl)₂, 0 °C, 74% (ii) RuCl₃, KIO₄, (CH₂Cl)₂, reflux, 17 h, 25%; (iii) NaOMe, MeOH, rt, 24 h, 87%.

Another interesting method for C-glycoside synthesis was nature inspired. Suzuki and co-workers noticed that the natural product benzanthrin B 136 (Figure 1.15) has an O- and C-glycoside bonds installed in two adjacent positions. The authors believed that the biosynthesis of this compound was by initial formation of the O-glycoside with subsequent migration of the glycoside residue to form the C-glycoside.¹²⁴a

Figure 1.15: Benzanthrin B.
To verify this claim they prepared $O$-glycoside using fluoro sugar 137 with phenol 138 at -78 °C and found out that the $O$-glycoside rearranges itself to $C$-glycoside when it is warmed up to 0 °C from -78 °C in the presence of a Lewis acid (Scheme 1.36).

![Scheme 1.36: Rearrangement of $O\rightarrow C$-glycoside.](image)

The glycosyl acceptor, phenol 138, is so reactive that the reaction took place with mild Lewis acids and weak leaving groups on the glycosyl donor such as acetate. The $O\rightarrow C$ rearrangement is initiated through initial activation of the exo oxygen by the Lewis acid to provide 141, which generates the oxonium phenolate ion pair 142 (Scheme 1.36). However, the trapping of the oxocarbenium ion by the aromatic $\pi$ electrons in Friedel-Crafts like reaction pushes the reaction forward forming the $\beta$-$C$-glycoside 140. The selectivity for the $\beta$ anomer was explained to be due to in situ anomerization induced by the Lewis acid activation 143 of the endocyclic oxygen which produces the ortho-quinone methide 144 that goes via 145 to provide the $\beta$-$C$-aryl-glycoside 140 (Scheme 1.37).
Scheme 1.37: In situ-anomerization of the C-glycoside.

1.2.3. 2-C-Branched-C-Glycosides
C-Branched sugars have attracted the attention of organic chemists in recent times as potential antibiotic agents. C2 Branched sugars in particular enjoyed much attention as they can be used as mimetics of the 2-N-acetylsugars which are used in cell surface engineering\(^\text{126}\) and as inhibitors in the biosynthesis of lipids.\(^\text{125,126}\) Gammon et al prepared a series of 2-C-branched carbohydrates as potential inhibitors of enzymes implicated in the biosynthesis of mycothiol, *Mycobacterium tuberculosis*’s defensive low molecular weight thiol.\(^\text{127}\)

As discussed in the preceding section above, there are several facile methods for the synthesis of C-glycosides through C-functionalization at the anomeric carbon; however, C-functionalization at other carbon positions of the sugar requires many steps of synthesis.\(^\text{128-130}\) The commonly reported synthetic methods for 2-C branched sugars are radical additions to various glycals\(^\text{128}\) and electrophilic ring opening of 1,2-cyclopropanated monosaccharides.\(^\text{131}\) The ring opening of 1,2-cyclopropanated monosaccharides has come out as the most useful, facile and reliable method for the stereoselective synthesis of 2-C branched sugars. Owing to this synthetic privilege brought about by the reactive cyclopropane ring, they have been incorporated into carbohydrates for various carbohydrate based transformations.\(^\text{131-136}\) Solvolysis of the cyclopropanated sugar 146 cleaves the ring along the C1-C7 bond *via* the intermediate 147 to provide the 2-C branched glycoside 148.
Scheme 1.38: Electrophilic ring opening of cyclopropane generating 2-C branched glycoside.

1.3. Conclusions
Thiochromans and thiochromenes are found as substructures of many interesting biologically active compounds. They are reported to have many biological activities, such as: anti-bacterial, anti-fungal, anti-cancer, anti-malarial, anti-HIV, anti-viral, and anti-tumor activities. They are bioisosters of chromans and chromenes which are reported to have a wide range of medicinal and pharmaceutical applications, in most cases showing comparable or superior biological activities. This might possibly be due to sulfur’s higher binding tendency towards proteins and higher lipophilicity of sulfur containing compounds over their oxygen counterparts, which might enable them to cross much more easily through the blood-barrier. With all these applications found in the literature, there was not any report on carbohydrate-based thiochromans and thiochromenes and their subsequent transformation into various synthetically useful substrates. Hence, the present study aims at the synthesis of carbohydrate based thiochromenes from pyranothiochroman precursors.

The second section of the survey is focused on the formation $O$, $S$ and $C$ glycosides and 2- $C$ branched sugars. The 2,3-unsaturated $O$- and $S$-glycosides are formed by the allylic rearrangement of glycals in the presence of good leaving groups at C-3 via the Ferrier rearrangement reaction, which is mediated by various promoters. There have been several Lewis acids and other promoters reported in the literature. The use of Lewis acids as a catalyst causes restriction to the glycals and glycosyl acceptors to be used and its wider synthetic applications. Another important class of glycosides which have wide medicinal applications is the class of $C$-glycosides. This class of glycosides can be broadly divided into alkyl or aryl glycosides depending on the group attached at the anomeric center. Aryl-$C$-glycosides are a subclass of the $C$-glycosides in which the substituent at the anomeric position is an aromatic group. They are present in many biologically important natural products. Branched chain aryld-
C-glycosides are reported for various pharmacological activities; and 2-C branched aryl-C-glycosides elicit interest in their potential to be used as mimetics of the 2-N-acetylsugars which are used in cell surface engineering and as inhibitors in the biosynthesis of lipids. However, the synthesis of these glycosides suffers poor selectivity for the useful isomer 1,2-cis-2-C branched aryl glycosides, mainly producing the thermodynamically favourable 1,2-trans-2-C branched aryl glycosides product.
1.4. Present Study

Thiochromans and thiochromenes are an important class of compounds which have not been widely studied compared to their chroman and chromene analogues. Pyranothiochromans have been synthesized in our research group. And given the synthetic potential this important class of heterocycles can offer, it was the aim of this thesis to exploit the synthetic potential of these pyranothiochromans in the stereoselective synthesis of carbohydrate based thiochromenes and 1,2-\textit{cis}-\textalpha-aryl-C-glucoside derivatives.

The very few current methods of diastereoselective synthesis of thiochromenes mainly use organocatalysts which pose a challenge with the design and synthesis of a particular chiral organocatalyst for each specific reaction. Furthermore, these methods can only introduce alkyl and aryl groups at the stereogenetic center. Against this background we aimed at the diastereoselective synthesis of thiochromenes with groups that are amenable to further transformation at the stereogenetic center from pyranothiochroman substrates.

The second aim of this project was the synthesis of several 2,3-unsaturated \textit{O}- and \textit{S}-glycosides and 1,2-\textit{cis}-2-C-branched-\textalpha-aryl-C-glycosides. To achieve this aim we proposed that the 2,3-unsaturated glucosides could be made \textit{via} the Lewis acid catalyzed Ferrier rearrangement of glycals. Noting the restriction of glycals and glycosyl acceptors that can be used due to the requirement of Lewis acids for catalysis, it was our aim to develop a catalyst that is efficient and a milder promoter of this reaction.

Thirdly, taking note of the 1,2-\textit{cis} locked rigid tricyclic configuration of pyranothiochromans, we intended to subject these pyranothiochromans and their carefully prepared derivatives to desulfurization reagents (Nickel boride and Raney nickel) to produce 1,2-\textit{cis}-2-C-branched aryl-C-glucosides and transform them further into phosphonate and thiophosphonate derivatives to serve as potential substrates for the enzymes of \textit{Mycobacterium tuberculosis}. 
1.5. References


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CHAPTER 2: SYNTHESIS OF PYRANOTHIOCHROMANS

2.1. Introduction
Thiochromans are important structural units found in a number of biologically important natural products. Besides their biological importance, they are also employed as suitable precursors for the synthesis of biologically active sesquiterpenoids, which are reported to be
difficult to synthesize by other methods due to the congested quaternary carbon structures present in their molecular frameworks. Owing to their importance, there are several methods reported for the synthesis of thiochromans. However, these methods suffer inefficiencies. Lack of readily and commercially available starting materials, long reaction times, and the need for reagents which are not environmentally benign are some of the limitations of the reported protocols. Hence, there is still a room for improvement towards simple, mild and environmentally friendly protocols which would alleviate these inefficiencies. Moreover, the enantio- and diastereoselective synthesis of thiochromans is still a challenge with only few methods reported in the literature. Thus, there is a need for the development of stereoselective synthetic methodologies. It becomes even more appealing to stereoselectively synthesize pyranothiochromans which might enhance the bioavailability and delivery of the potentially active thiochroman agents in physiological systems to serve as therapeutic agents.

D-Glucose is the most abundant monosaccharide found in nature and its epimer mannose differs in the configuration of the hydroxyl group at C2. The ready availability and renewability of these carbohydrates encouraged our research group to use them for the stereoselective synthesis of thiochromans (benzothiopyrans) using appropriately protected glucose and its epimer mannose as chiral pool substrates.

In this work we proposed that pyranothiochoroman \( I \) (Scheme 2.1) could be employed as a key substrate for the stereoselective synthesis of pyranothiochromenes and 1,2-\textit{cis}-2-deoxy-\textit{α}-aryl-C-glycosides as well as 1,2-\textit{cis}-2,3-unsaturated-\textit{α}-aryl-C-glycosides (II-VIII) as depicted in Scheme 2.1.
Scheme 2.1: Transformation of carbohydrate based thiochromans into various important molecules.

The sulfide of pyranothiochroman I can be oxidized to a sulfoxide analogue that can be transformed into $\alpha$-substituted sulfide II via a Pummerer rearrangement reaction. This $\alpha$-substituted sulfide can then be transformed into highly functionalized pyranothiochromenes III and IV using a glucosyl and a mannosyl based pyranothiochromans, respectively. Different desulfurizing agents can also be employed to effect the C-S bond cleavage in the thiochroman moiety of II to provide, for example, 1,2-cis-2-C-branched-$\alpha$-aryl-C-glycoside V.

These important transformations of the pyranothiochroman I are elaborated in the next two chapters. Moreover, since the thiochroman I is the key starting material in all of the proposed transformations depicted in Scheme 2.1, its synthesis and characterization will be discussed below in detail.

2.2 Diastereoselective Synthesis of Pyranothiochromans
The relative ease of preparing arylsulfides via $S_N2$ substitution of alkylhalides and the activation of aromatic O-acetates by Lewis acids prompted our research group to propose a
method of preparing pyranothiochromans 158 from readily available iodomethyl glucosyl acetate 154 as shown in the retrosynthetic analysis in Scheme 2.2. These intermediates could be synthesized by opening of a 1,2-cyclopropanated sugar derivative 152 that was obtained by cyclopropanation of a glycal 150.

Scheme 2.2: Retrosynthetic analysis of pyranothiochromans.

Thiochroman 158 (Scheme 2.8) was identified as our key starting material for the proposed transformations due to the readily availability of the key starting material, acetylated glucal 149 (Scheme 2.3). The synthesis commenced with the exchange of protecting groups from acetyl of the acetylated glucal 149 to benzyl protecting groups, since acetyl protecting groups are not compatible with the subsequent reaction conditions. Thus, the acetylated glucal 149 was transformed into benzyl protected glucal 150. Finely crushed sodium hydroxide was added to a solution of glucal 149 and tetrabutylammonium iodide (TBAI) in THF was added to provide the benzyl protected glucal 150 in 80% yield after stirring for 24 hours at room temperature. The product was characterized by NMR spectroscopy and found to be in agreement with the reported literature data (Scheme 2.3).\textsuperscript{10}
2.2.1. 2-C Arylthiomethyl Glucosyl Acetate and Intramolecular Cyclization to α-1,2-aryl-C-Glucoside.

The synthesis of pyranothiochromans begins with the readily available appropriately protected glycal 150 as depicted in Scheme 2.3 above. The double bond in glycals undergoes similar reactions to simple alkenes but with interesting stereo-and regioselectivity due to the presence of the ring oxygen. Glycals, like alkenes, undergo cyclopropanation reactions and depending on the reaction conditions the cyclopropanation can either take place from the top (β) or bottom (α) face of the glucal. The 1,2-cyclopropanated product so obtained can be further transformed.\textsuperscript{11,12}

Following Nagaragan and co-workers\textsuperscript{11} reported protocol benzyl protected glucal 150 was treated with 50% sodium hydroxide (aq) in the presence of benzyltriethylammonium chloride as a phase transfer catalyst at 35 °C (Scheme 2.4) for 18 hours to afford cyclopropaned sugar derivative 151 exclusively as white crystals in 79% yield after precipitating of ethanol (instead of purification by column chromatography). The spectra data were in agreement to the literature reported data \textsuperscript{11,12}

\begin{equation}
\begin{array}{c}
\text{Scheme 2.4: } (i) \text{ NaOH, BTEAC, CHCl}_3, 35 ^\circ\text{C, 6 h, 79 \%}; (ii) \text{ LiAlH}_4, \text{ THF, rt, 48 h, 84 \%.}
\end{array}
\end{equation}
The NMR showed H-2 as doublet of a doublet with \( J \) values of 1.6 Hz and 7.7 Hz. The larger \( J \) value is attributed to the coupling between H-1 and H-2 which was also confirmed by the coupling of H-1.\(^{10}\) This result is in agreement with the literature reported values of cyclopropanated sugars with \textit{cis} \( J_{1,2} \) value being greater than the \textit{trans} \( J_{2,3} \) value. This indicates that H-1 and H-2 are on the same side of the sugar ring and opposite to H-3 which is indicative that the cyclopropanation occurs \textit{syn} to H-3 and \textit{anti} to the substituent at C-3 confirming the formation of \( \alpha \)-1,2-dichloro cyclopropane.

The \( \alpha \)-1,2-di-chlorocyclopropane 151 was then subjected to reduction under LiAlH\(_4\) to generate the corresponding \( \alpha \)-1,2-cyclopropane 152 (Scheme 2.4), which are known to undergo an electrophilic ring opening in the presence of protic solvent to afford a 2-deoxy-2-C-branched chain glycoside with defined C2 stereochemistry, inherent to the cyclopropane.\(^{10,11}\)

The complete dechlorination of 151 was confirmed by the up field shift of the H-2 signal from 1.40 to 0.90 ppm and its appearance as multiplet as opposed to a doublet of doublet in the case of cyclopropane 152, which could be due to couplings to H-7\(_a\) and H-7\(_b\) in addition to H-1 and H-3.\(^{11}\)

After successful synthesis of the \( \alpha \)-1,2-cyclopropanated sugar the next step was to open the cyclopropane ring under electrophilic conditions. The ring opening of \( \alpha \)-1,2-cyclopropanated sugar 152 was achieved employing the methodology reported by Gammon and co-workers using \textit{in situ} generated electrophilic iodonium ion from the reaction of ammonium iodide and hydrogen peroxide in acetic acid and acetonitrile mixture (1:1).\(^{13}\)

Although this methodology was reported to constitute a high yielding protocol for the opening of the cyclopropane 152, in our hands, the yields obtained were inferior with reactions carried out on a larger scale (greater than 1 gram) under otherwise identical reaction conditions. It was later determined that the cause of the poor yield obtained in a larger scale was due to competitive formation of the iodohydrine intermediate 153 in the presence of a large volume of nucleophilic water in the hydrogen peroxide solution. The yield of the product was, thus, improved by subjecting the crude product from the ring opening reaction directly to acetylation conditions using acetic anhydride in the presence of a catalytic amount of DMAP (Scheme 2.5) this furnished iodomethyl glycosyl acetate 154 in 1:2 \( \alpha:\beta \) anomic ratio in 73% yield (over
two steps). Taking into consideration the readily availability of the reagents and better atom economy, this synthetic route was adopted in our synthesis in preference to the NIS-H$_2$O mediated opening of the cyclopropane ring$^{12}$ followed by acetylation.

![Scheme 2.5](image)

**Scheme 2.5:** (a) NH$_4$I, H$_2$O$_2$, Ac$_2$O, CH$_3$CN:AcOH (1:1), rt; (b) AC$_2$O, DMAP, DCM, rt, 30 min, 73% (over the two steps).

The selectivity for the $\beta$-anomer could be due to the orientation of the $\alpha$-1,2-cyclopropane ring which is suitably oriented for an $S_N$2 type of reaction as shown in **Scheme 2.6** in a similar fashion to the NIS-mediated ring opening of cyclopropanes.$^{12}$

![Scheme 2.6](image)

**Scheme 2.6:** Selectivity for the $\beta$-anomer iodomethyl glucosyl acetate.

However, the poor 1:2 selectivity does not rule out the possibility that the reaction may have proceeded *via* a competitive mechanism involving an oxocarbenium intermediate $^{155}$ in an $S_N$1 fashion to form an $\alpha$-anomer and anchimeric assistance induced steric hindrance by the iodine might then have favored the approach of the acetate from the $\beta$-face of the molecule (**Scheme 2.7**).
Scheme 2.7: Anchimeric assistance induced steric hindrance of oxocarbenium intermediate preventing an α attack.

The iodomethyl glucosyl acetate 154 synthesized above was then added to a freshly prepared thiophenolate nucleophile which was generated in situ by the reaction of sodium hydride and thiophenol in DMF to provide 2-C-arylthiomethyl glucosyl acetate 157a in 79% yield (Scheme 2.8).\textsuperscript{14,15} The presence of an additional aromatic group in 2-C-arylthiomethyl glucosyl acetate 157a was confirmed by \textsuperscript{1}H NMR spectroscopy in which the integration of the aromatic signals corresponded to 20 protons. The spectroscopic data were in agreement with the reported literature values.\textsuperscript{15} Following the same protocol, a series of 2-C-arylthiomethyl glucosyl acetates 157b-e were prepared and the yields were comparable to the literature reported values.\textsuperscript{15} The results are summarized in Table 2.1 with the products identified by \textsuperscript{1}H and \textsuperscript{13}C NMR spectroscopy.
Scheme 2.8: (i) NaH (60% dispersion on oil), thiophenol, DMF, rt, 5 min; (ii) BF₃·Et₂O, CH₂Cl₂, 0 °C, 5 m (see Table 2.1 for yields).

The final step in the synthesis of thiochromans was the Lewis acid (BF₃·Et₂O) promoted diastereoselective intramolecular Friedel-Crafts alkylation of the intermediate arylthiomethyl glucosyl acetate intermediate 157a to furnish the corresponding pyranothiochroman 158a (Scheme 2.8) which was obtained in 65% yield. Thiochromans 158b-e were prepared in a similar fashion and provided comparable yields to the literature report (Table 2.1). The structures of the pyranothiochromans and their corresponding stereochemistries were established using NMR spectroscopy and were in agreement with published data.

Table 2.1. Yields of glucosyl arylthiomethyl acetate and pyranothiochroman products.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Sulfides Product</th>
<th>% yield</th>
<th>Thiochromans Product</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R¹ = R² = H</td>
<td>157a</td>
<td>79</td>
<td>158a</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>R¹ = H, R² = CH₃</td>
<td>157b</td>
<td>83</td>
<td>158b</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>R¹ = CH₃, R² = H</td>
<td>157c</td>
<td>82</td>
<td>158c</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>R¹ = H, R² = Buᵗ</td>
<td>157d</td>
<td>90</td>
<td>158d</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>R¹ = H, R² = OCH₃</td>
<td>157e*</td>
<td>-</td>
<td>158e</td>
<td>68</td>
</tr>
</tbody>
</table>
*sulfide 169e was decomposing with time and was cyclized without purification.

The proposed mechanism involves the Lewis acid activation of the anomeric acetate leaving group to provide the oxocarbenium intermediate XI. In the absence of an external nucleophile, the \( \pi \) electrons of the phenyl ring attack the electrophilic oxocarbenium intermediate at the anomeric position resulting in intramolecular cyclization. Proton abstraction from intermediate XII regenerates aromaticity and provides pyranothiochroman XIII.\(^\text{15}\)

![Scheme 2.9: Possible mechanism for the synthesis of thiochromans.](image)

2.2.2. 2-C-Arylthiomethyl Mannosyl Acetate and Intramolecular Cyclization to \( \beta \)-1,2-aryl-C- Mannoside

To generate pyranothiochromans with opposite stereochemistries (pyranothiochromans 164a-e in Scheme 2.12) at the C1 and C2 positions to the pyranothiochromans 158a-e, a \( \beta \)-1,2 cyclopropanated sugar 159 was employed as a starting material. The Simons-Smith cyclopropanation of glycals introduces the cyclopropyl ring from the \( \beta \)-side \( \text{syn} \) to the alkoxy group at C3.\(^\text{11,12,17}\) The selectivity for cyclopropanation from the \( \beta \)-side of the glucal is due to the chelation of the oxygen atom at C3 to the zinc atom 160 (Figure 2.1) which directs the delivery of the methylene group from the \( \text{syn} \) side providing the 1,2-\( \beta \)-cyclopropanated sugar 159 stereoselectively.\(^\text{17}\)
Scheme 2.10: Zn dust, cuprous chloride, rt, acetyl chloride, diiodiomethane, diethyl ether, 90 min, 85%.

Figure 2.1: The zinc chelated/coordinated intermediate in Simmons-Smith cyclopropanation of glucal.

Attempts to open the cyclopropane ring of 1,2-β-cyclopropanated sugar 159 using the method employed for opening cyclopropyl 152 was unsuccessful and the starting material was recovered intact. This was in agreement with a literature report.15 Thus, we turned our attention to the NIS-mediated methodology reported by Nagarajan.12 Treatment of 1,2-β-cyclopropanated sugar 159 with NIS in a mixture of water and dioxane followed by acetylation using acetic anhydride in the presence of DMAP provided the iodomethyl mannosyl acetate 162 exclusively as the α-anomer in 93% yield (Scheme 2.11).12
Scheme 2.11: (a) NIS, Dioxane: H₂O (2:1), 50 °C, 12 h; (b) AC₂O, DMAP, DCM, rt, 30 min, 93%.

S₂N₂ substitution of the iodine in the iodomethyl mannosyl acetate 162 with a series of thiolates followed by Lewis acid catalyzed intramolecular Friedel-Crafts cyclization provided pyranothiochromans 164a-e as outlined in Scheme 2.12. The results are summarized in Table 2.2 with the products identified by ¹H and ¹³C NMR spectroscopy and the spectroscopic data were in agreement with the literature reported values.¹⁵

Scheme 2.12: (i) NaH (60% dispersion on oil), thiophenol, DMF, 0 °C (see table 2.1 for the yields); (ii) Synthesis of 1β,2β thiochroman: BF₃·Et₂O, CH₂Cl₂, 0 °C, 5 m (see Table 2.2 for yields).
Table 2.2. Yields of mannosyl arylthiomethyl acetate and pyranothiochroman products.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Sulfides</th>
<th>Thiochromans</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Product % yield</td>
<td></td>
<td>Product % yield</td>
</tr>
<tr>
<td>1</td>
<td>R¹ = R² = H</td>
<td>163a</td>
<td>164a</td>
</tr>
<tr>
<td>2</td>
<td>R¹ = H, R² = CH₃</td>
<td>163b</td>
<td>164b</td>
</tr>
<tr>
<td>3</td>
<td>R¹ = CH₃, R² = H</td>
<td>163c</td>
<td>164c</td>
</tr>
<tr>
<td>4</td>
<td>R¹ = H, R² = Bu'</td>
<td>163d</td>
<td>164d</td>
</tr>
<tr>
<td>5</td>
<td>R¹ = H, R² = OCH₃</td>
<td>163e</td>
<td>164e</td>
</tr>
</tbody>
</table>

2.3 Stereoselectivity in the Intramolecular Friedel-Crafts Alkylation Reaction

The α-anomeric selectivity during the cyclization in the formation of pyranothiochroman 158 can be rationalized in terms of the oxocarbenium ion XIV (Scheme 2.13) in the 4H₃ conformation. In this conformation, the pendant arylthiol is suitably positioned to attack the anomeric center from the bottom face to generate an intermediate in a chair conformation XVI, while attack from the top face of the oxocarbenium ion VI will lead to the less stable twist boat conformation XV, which is disfavored.
Scheme 2.13: The preferred conformation for the glucosyl pyranose.

On the other hand, with regards to pyranothiochromans 164, two conformations of the oxocarbenium ion are possible (Scheme 2.14, $^4H_3$ and $^3H_4$). Oxocarbenium ion (XVIIa) in a $^4H_3$ conformation with C3, C4, and C5 substituents adopting an equatorial position thus avoiding a 1,3-diaxial interaction, is usually considered to be more stable than the corresponding $^3H_4$ (XVIIb) conformer.

However, computational and spectroscopic studies$^{18-20}$ have demonstrated that the benzyloxy substituents at positions C3, C4, and C5 stabilize the positive charge of the oxocarbenium intermediate better in pseudoaxial orientations as in the $^3H_4$ conformer (XVIIb) compared to equatorial position. This suggests that the electronic stabilization overrides the steric effects (1,3-diaxial interaction) on the respective conformers. However, the C2 substituent adopts a pseudoequatorial position so that the C-H sigma bond aligns parallel to the empty $p$-orbital of the anomeric center for hyperconjugative stabilization (Figure 2.2).
Figure 2.2: Hyperconjugative stabilization of the carbocation from C2-H bond.

Furthermore, had the \(^4\text{H}_3\) conformer been the preferred intermediate, the cyclization would have proceeded \textit{via} the high energy twisted \((1\text{S}_3)\) transition state (XIX) upon nucleophilic attack from the \(\beta\) face (Scheme 2.14).\(^{18-21}\)

Scheme 2.14: Possible conformations of the oxocarbenium intermediate for mannosyl pyranose.
Having a series of pyranothiochromans 158a-e and 164a-e in gram quantities, our focus turned into applying these thiochromans for the synthesis of novel and interesting derivatives as outlined in the next chapters.
2.4 References


CHAPTER 3: SYNTHESIS OF PYRANOTHIOCHROMENES

3.1 Introduction
Thiochromenes are privileged analogs of the extensively studied, naturally occurring, chromenes, and chromene derivatives. Chromenes and chromene derivatives are reported as therapeutic and medicinal agents against various pathogens. The scarcity of thiochromenes in nature, the isosterism of Sulfur with Oxygen and the ease of functionalizing sulfur to various functional groups makes synthesizing thiochromenes an important endeavor. Biological activity evaluations so far undertaken to date of thiochromene derivatives showed that the double bond of the thiopyran moiety imparts medicinal and biological activities.\(^1,2,3\) Several synthetic protocols and strategies have been reported for thiochromene synthesis. However, the stereoselective synthesis of thiochromenes is less explored. The recent stereoselective synthesis of thiochromenes has only managed to introduce simple aryl or \(n\)-alkyl groups at the \(\alpha\)-carbon (relative to sulfur) stereoselectively.\(^4\)

Pyranothiochromenes offer an inherently defined stereochemistry in addition to being highly bioavailable in physiological systems when employed as medicinal agents.\(^5-7\)

Intra-molecular reactions are known to be mostly region- and stereo-selective and are important in the synthesis of complex molecules. The selectivity and success of these reactions are generally demonstrated in molecules containing ring systems.\(^8\) Noting the cyclic nature of the pyranothiochromans \(158a-e\) and \(164a-e\) discussed in Chapter 2, we aimed to develop a synthetic strategy for the diastereoselective transformation of these pyranothiochromans into novel pyranothiochromenes via intramolecular reactions.

3.2. Oxidation of Thiochroman to Sulfoxide Derivative
Sulfoxides are important synthetic intermediates in the preparation of biologically and medicinally important compounds. Sulfoxides have also been used extensively in C–C bond-forming, molecular rearrangements, and functional group transformations.\(^9\) One of these reactions is the transformation of sulfoxides to \(\alpha\)-acetoxy sulfides, which can be further manipulated to generate aldehydes.

Iriuchijima and co-workers reported the basic hydrolysis of \(\alpha\)-acetoxy sulfides to produce an aldehyde and a thiol.\(^10\) Accordingly, it was suggested that the pyranothiochromans \(158a-e\)
could be transformed into \(\alpha\)-acet oxy sulfides 165a-e, which upon hydrolysis provide \(\alpha,\beta\)-unsaturated aldehydes 166 that are prone to a thio-Michael addition.

![Scheme 3.1: Basic hydrolysis of acetoxy sulfide produce thiophenolate tethered at C1.](image)

With this intention, the first step required the oxidation of the sulfide moiety of the thiochromans to sulfoxide. Reactions with the following oxidants: peroxide in acetic acid,\(^{11}\) ceric ammonium nitrate (CAN) with catalytic KBr.\(^{11}\) The use of Oxone\(^{\circledR}\) supported on wet aluminum oxide (alumina)\(^{11}\) are reported for the chemoselective oxidation of sulfides to sulfoxides preventing over-oxidation to sulfone. We opted to use the latter (Oxone\(^{\circledR}\) supported on wet aluminum oxide) for our synthesis. The ease of handling of the reagent, environmental benignness, and easy workup which only requires filtration after completion of the reaction prompted us to employ Oxone\(^{\circledR}\) as our choice of oxidizing agent.

To optimize the oxidation method using Oxone\(^{\circledR}\), pyranothiochroman 158a (Scheme 3.2a) was used as model substrate. Treatment of a solution of 158a in DCM with 1.2 equivalents of Oxone\(^{\circledR}\) and alumina afforded a diastereoisomeric mixture of sulfoxide 167 in 69% yield after 3 hours of stirring at room temperature. Although the diastereoisomers were separable by column chromatography, efforts to identify the stereochemistry of each sulfoxide by growing crystals of the respective compounds with a view to obtain single crystal X-ray diffraction patterns were unsuccessful. However, for the purpose of our current synthesis sequence, the identification of the absolute stereochemistry of the sulfoxide was immaterial since the stereochemistry is destroyed in the subsequent reactions.
Scheme 3.2: (i) OXONE®, wet alumina, DCM, rt, 3 h, 65-90%.

The formation of the corresponding sulfoxides was confirmed by IR spectroscopy which showed the S-O vibration at around 1030-1055 cm⁻¹. Although the signals in the NMR spectra of the sulfoxide did not exhibit significant shift in comparison to the substrate thiochroman 158a, the HRMS showed molecular ions of 167a and 168a (555.2207 and 555.2205 respectively) which corresponds to the calculated molar mass of the sulfoxides. Following the same procedure, sulfoxides 167b-e and 168b-e were prepared in good to very good yields as diastereoisomeric mixtures, respectively (Scheme 3.2). The results are summarized in Table 3.1 with the products identified by IR, NMR and HRMS.
Table 3.1. Reaction yields and diastereomeric ratios (dr) of sulfoxides.

<table>
<thead>
<tr>
<th>Thiochroman</th>
<th>R</th>
<th>Sulfoxide</th>
<th>Product</th>
<th>d.r</th>
<th>Combined yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Thiochroman Structure" /></td>
<td>R₁ = R₂ = H</td>
<td>167a</td>
<td>1:2</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R₁ = H, R₂ = CH₃</td>
<td>167b</td>
<td>1:2.1</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R₁ = CH₃, R₂ = H</td>
<td>167c</td>
<td>1:1.4</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R₁ = H, R₂ = Buⁿ</td>
<td>167d</td>
<td>1:3</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R₁ = H, R₂ = OCH₃</td>
<td>167e</td>
<td>1:1.7</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Thiochroman Structure" /></td>
<td>R₁ = R₂ = H</td>
<td>168a</td>
<td>1:2.3</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R₁ = H, R₂ = CH₃</td>
<td>168b</td>
<td>1:2.3</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R₁ = CH₃, R₂ = H</td>
<td>168c</td>
<td>1:2</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R₁ = H, R₂ = Buⁿ</td>
<td>168d</td>
<td>1:2.6</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R₁ = H, R₂ = OCH₃</td>
<td>168e</td>
<td>1:2</td>
<td>72</td>
<td></td>
</tr>
</tbody>
</table>

3.3 Pummerer Reaction and Hydrolysis under Basic Condition

After successfully synthesizing the desired sulfoxides, the stage was set for introducing an acyloxy substituent at the α-position relative to the sulfur atom of the pyranothiochroman framework. This was achieved via a Pummerer rearrangement reaction by treating the diastereoisomeric mixture of the sulfoxides 167a-e with acetic anhydride and NaOAc ¹⁴,¹⁰ at 140 °C. After completion of the reaction (TLC analysis), the crude product was hydrolyzed with NaOH (aq.) in methanol at 120 °C following the protocol reported by Iriuchijima and co-workers¹⁰ to generate thiochromene 169a in 71% yield (Scheme 3.4) as a result of a cascade of transformations. We then decided to investigate the reaction at lower temperatures in order to optimize the yield and also make the method environmentally benign. Thus, a suspension of the crude product 165 from the Pummerer reaction in methanol was treated with NaOH (aq.). However, instead of the expected thiochromene 169 (Scheme 3.4), hemithioacetal 170 precipitated from the solution and was obtained in 60% yield after simple filtration (the
characterization and further transformation of the hemithioacetal is discussed in the next chapter). It is important to mention that the starting substrate obtained from the Pummerer reaction was sparingly soluble in methanol but the precipitation of the hemithioacetal product drove the equilibrium towards the dissolved substrate according to Le Châtelier's principle (Scheme 3.3) to enable 100% conversion.

**Scheme 3.3:** NaOH, CH₃OH, rt, 30 min, 60%.

It was later found out that if solvents like DCM and ethyl acetate (in which the 165 is soluble) are not strictly avoided, the reaction proceeds further to provide the expected thiochromene. We assume this could be due to the low solubility of substrate 165 in methanol that makes the base exert its effect only on the surface of the molecule, deacetyllating the easily accessible acyloxy group. On the other hand in solution the hydrolysis goes further to generate the thiochromene 169 as shown in Scheme 3.5. After this serendipitous result we investigated the hydrolysis in a mixture of solvents such as DCM-methanol. Gratifyingly, treatment of a solution of the product from the Pummerer reaction in DCM-MeOH (1:1) with different bases (NaOH, K₂CO₃, NaHCO₃ and NaOMe) provided the desired thiochromene product as tabulated in Table 3.2. While stoichiometric amounts of the NaOH, K₂CO₃, and NaHCO₃ were required to effect the cascade of transformation to provide thiochromene 169, only a catalytic amount of the NaOMe was required to give a superior yield.
Table 3.2. Bases used for hydrolysis (Scheme 3.4).

<table>
<thead>
<tr>
<th>substrate</th>
<th>Base</th>
<th>Reaction time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Image]</td>
<td>NaOH</td>
<td>30 min</td>
<td>68</td>
</tr>
<tr>
<td>[Image]</td>
<td>K₂CO₃</td>
<td>37 min</td>
<td>62</td>
</tr>
<tr>
<td>[Image]</td>
<td>NaHCO₃</td>
<td>40 min</td>
<td>59</td>
</tr>
<tr>
<td>[Image]</td>
<td>NaOMe</td>
<td>10 min</td>
<td>80</td>
</tr>
</tbody>
</table>

Scheme 3.4: (i) Oxone®, wet silica, DCM, rt, 30 min, 69%; (ii) a. NaOAc, Ac₂O, 140 °C, 3 h; b. NaOMe, CH₂Cl₂:CH₃OH (1:1), rt, 10 min, 80%; (iii) Ac₂O, Et₃N, DMAP, rt, 30 min, 79%.

The structure of thiochromene 169a was established on the basis of NMR spectroscopy and HRMS. The appearance of the aldehyde proton signal at δH 9.51 and carbon signal at δC 193.6 confirmed the presence of an aldehyde functional group. The appearance of H-2 as a doublet at δH 4.39 due to coupling to H-1’ only and the C-4 and H-4 signals downfield in the aromatic region (as evidenced from HMBCAD spectrum due to coupling to the aldehydic proton) suggested the presence of a double bond between C-3 and C-4. To confirm the presence and
position of the \( \text{OH} \) group, thiochromene \( \text{169a} \) was transformed into the acetylated product \( \text{171a} \) in quantitative yield (Scheme 3.4). The downfield shift of \( \text{H-2}' \) from around \( \delta_\text{H} \) 3.50 in thiochromene \( \text{169a} \) to the region of \( \delta_\text{H} \) 5.20–5.03 in thiochromene \( \text{171a} \) coupled with the appearance of the \( \text{OAc} \) signals at \( \delta_\text{H} \) 2.06, \( \delta_\text{C} \) 169.9 and 21.1 confirmed acetylation of the \( \text{OH} \) group at \( \text{C-2}' \) (\( \text{C-2}' \) in \( \text{171a} \) corresponds to \( \text{C-2} \) in \( \text{167a} \)), which indirectly indicated an opening of the sugar ring moreover, the integration of the methylene signals of the benzyl protecting groups was found to be four, confirming the cleavage of one benzyl group from the starting thiochroman. \(^1\text{H} \) NMR comparisons of \( \text{169a} \) and \( \text{171a} \) as depicted below shows the down field shift of \( \text{H-5} \) and the presence of the acetate peak after acetylation of \( \text{169a} \).

**Figure 3.1:** \(^1\text{H} \) NMR spectra of the hydroxyl \( \text{169a} \) and acetylated \( \text{171a} \) thiochromenes.
Once the method was developed using thiochroman 167a the generality and scope of the method was evaluated with various thiochromans which generated the respective thiochromenes in quantitative yields. The results are summarized in Table 3.2 (171a-e).

Table 3.3. Reaction yields of thiochromenes 171a-e.

<table>
<thead>
<tr>
<th>Sulfoxide substrate</th>
<th>Thiochromene product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>167a R₁ = R₂ = H</td>
<td>171a R₁ = R₂ = H, R₃ = Ac</td>
<td>79</td>
</tr>
<tr>
<td>167b R₁ = H, R₂ = CH₃</td>
<td>171b R₁ = H, R₂ = CH₃, R₃ = Ac</td>
<td>69</td>
</tr>
<tr>
<td>167c R₁ = H, R₂ = OCH₃</td>
<td>171c R₁ = H, R₂ = OCH₃, R₃ = Ac</td>
<td>69</td>
</tr>
<tr>
<td>167d R₁ = H, R₂ = C(CH₃)₃</td>
<td>171d R₁ = H, R₂ = C(CH₃)₃, R₃ = Ac</td>
<td>75</td>
</tr>
<tr>
<td>167e R₁ = CH₃, R₂ = H</td>
<td>171e R₁ = CH₃, R₂ = H, R₃ = Ac</td>
<td>72</td>
</tr>
</tbody>
</table>

The proposed mechanism is illustrated in Scheme 3.5. The sulfoxide is transformed into α-acyloxy sulfide 165 via Pummerer rearrangement. Hydrolysis of the acetate results in formation of the hemimercaptal derivative 172 which equilibrates with the mercapto-aldehyde 173.\(^{15}\) Deprotonation of the acidic α-hydrogen gives enolate 174 which then undergoes cleavage of the benzyloxy under the alkaline medium to provide α,β-unsaturated aldehyde 166 in accordance to the literature report by Yamakawa \textit{et al.}\(^{16}\) Attack by the thiolate at the β-position of the double bond provides the desired thiochromene 169 via a tandem Michael addition type reaction.
Scheme 3.5: Proposed mechanism of the one pot tandem Michael addition type reaction for the stereoselective synthesis of thiochromene 169.

3.4 Stereoselectivity of the Thiochromenes 169a and 171a-e

The absolute configuration of the new stereogenetic center was established from the coupling constant between H-2 and H-1'. It is well established that for two protons which are in a gauche relationship, the coupling constant is between 2-5 Hz. The coupling constant in compound 169a between H-2 and H-1' \( \text{J}_{H-2, H-1'} \) was found to be 3.4 Hz which is indicative of the gauche relationship between H-2 and H-1'. This relationship is possible if the stereogenetic center has an S absolute configuration. In the S conformation at C2 thiochromene 169a can adopt three possible staggered conformations (XX, XXI, XXII) as shown in Scheme 3.6a. Conformations XX and XXI having \( \text{H}_a \) and \( \text{H}_b \) a gauche relationship would be the favored due to the hydrogen-bonding stabilization made possible by spatial proximity of the carbonyl oxygen and the
hydroxyl proton contributing more to the population of conformers. However, conformation XXII with H\textsubscript{a} and H\textsubscript{b} positioned \textit{trans} to each other would be less favored due to the absence of stabilization by hydrogen bond between the distant carbonyl oxygen and the OH group and contributes less to the equilibrium.

In thiochromene 171\textsubscript{a}, the absence of the hydrogen-bonding stabilization in the staggered conformations was confirmed from the relatively higher $^3J_{H_2, H_1'}$ coupling constant (5.7 Hz inferred from the signal of H-1') which resulted from the average of all the possible conformers (Scheme 3.6b).

![Scheme 3.6](image)

\textbf{Scheme 3.6:} Possible staggered conformations of thiochromene 169\textsubscript{a} and 171\textsubscript{a}: a. hydrogen bond stabilization; b. absence of hydrogen bond stabilization.

Selectivity in favor of the $S$-configuration at the C2 position of thiochromenes 169 could be explained in terms of the preference in the $\alpha,\beta$-unsaturated aldehyde intermediate 166 for the
OH$_5$ conformation (Figure 3.2). In this conformation the thiolate moiety is prepositioned for intramolecular delivery from the α-face of the sugar to give the stereochemistry depicted in thiochromene 169a. On the other hand the ring flip conformation $^5$Ho will place the aryl-thiolate nucleophile and the benzyloxy group at C5 in pseudoaxial positions with larger spatial distance for the aryl-thiolate to attack the carbocation thus accounting for the predominantly S-configuration observed.

Figure 3.2: Preferred OH$_5$ conformation of α, β-unsaturated aldehyde intermediate and its ring flipped conformer $^5$Ho.

In an attempt to prepare thiochromenes with opposite stereochemistry at C2, we employed pyranothiochroman 164a with opposite stereochemistry at C1 and C2 relative to the pyranothiochroman 158a as a starting material under the same reaction conditions in the same sequences as depicted in Scheme 3.7. However, contrary to our expectation, subjecting the sulfoxide 168a to Pummerer reaction conditions produced what was thought to be pyranothiochromene 175a on the basis of $^1$H and $^{13}$C NMR and HRMS analysis. This was due to the disappearance of H-4a and appearance of H-5 downfield at $\delta$H 6.72 as a singlet which suggested the formation of a double bond between C4a and C5. This was further supported by the appearance of C4a and C5 down field in the aromatic region and also appearance of H-10a as a singlet. However, single crystal X-ray analysis (Figure 3.3) proved the structure of the product to be different from what was proposed and unambiguously confirmed that the product obtained is pyranothiochromene 176a. Although, the standard protocol did not provide the
expected pyranothiochromene diastereoisomer 177 (Scheme 3.8), the protocol provided a new variant of pyranothiochromene derivatives which could not have been prepared by any methodology we could think of at the moment. To evaluate the generality of this unprecedented protocol, sulfoxides 168b-e were transformed into their corresponding pyranothiochromenes 176b-e in quantitative yields under the same reaction conditions (Scheme 3.7). The results are summarized in Table 3.4.

Scheme 3.7: (i) OXONE® wet alumina, CH₂Cl₂, rt, 3 h, 67-90%; (ii) NaOAc, Ac₂O, 140 °C, overnight, 60-86%.
Figure 3.3: Single X-ray crystal structure of pyranothiochromene 176a.

Table 3.4 Reaction yields of pyranothiochromenes 176a-e.

<table>
<thead>
<tr>
<th>Sulfoxide substrate</th>
<th>Thiochromene product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td>168a $R^1 = R^2 = H$</td>
<td>176a $R^1 = R^2 = H$</td>
</tr>
<tr>
<td><img src="image2.png" alt="Image" /></td>
<td>168b $R^1 = H, R^2 = CH_3$</td>
<td>176b $R^1 = H, R^2 = CH_3$</td>
</tr>
<tr>
<td><img src="image3.png" alt="Image" /></td>
<td>168c $R^1 = H, R^2 = OCH_3$</td>
<td>176c $R^1 = H, R^2 = OCH_3$</td>
</tr>
<tr>
<td><img src="image4.png" alt="Image" /></td>
<td>168d $R^1 = H, R^2 = C(CH_3)_3$</td>
<td>176d $R^1 = H, R^2 = C(CH_3)_3$</td>
</tr>
<tr>
<td><img src="image5.png" alt="Image" /></td>
<td>168e $R^1 = CH_3, R^2 = H$</td>
<td>176e $R^1 = CH_3, R^2 = H$</td>
</tr>
</tbody>
</table>

This unexpected transformation may have resulted from the abstraction of the $\beta$-hydrogen instead of the $\alpha$-proton from the sulfonium intermediate 179 to give intermediate 175 (Scheme 3.8). This intermediate undergoes rearrangement from the aryl-C-glycoside to the corresponding aryl S-glycoside 176 via the ring opened intermediate 178. The possibility of this rearrangement occurring during workup and isolation cannot be excluded. The abstraction of the $\beta$-hydrogen may have been favored by the possible coplanar arrangement of the H–C and C=O bonds in a similar fashion to an E2 reaction.
Scheme 3.8: Possible mechanism of reaction for thiochromene synthesis.

3.5 Conclusion
In conclusion, we have shown an efficient and highly stereoselective strategy to the synthesis of 2,3-substituted thiochromenes via a tandem thio-Michael addition reaction. The current protocol is superior to reported protocols in that the carbohydrate derived substituent at the stereogenic center of the thiochromene is versatile and is amenable for further transformation. The stereochemistry of the starting pyranothiochroman has an influence on the type of thiochromene that can be provided giving rise to synthetic varieties of thiochromenes.
3.6 References

CHAPTER 4: SYNTHESIS OF 1,2-CIS-2-C-BRANCHED-α-ARYL-C-GLYCOSIDES VIA DESULFURIZATION OF PYRANOHEMITHIOACETALS AND PYRANOTHIOCHROMANS

4.1 Introduction

C-glycosides are analogs of O-glycosides in which the glycosyl donor and glycosyl acceptor are linked together by a carbon atom. Their relative resistance to chemical and enzymatic hydrolysis increased the interest of evaluating them as therapeutic agents. C-glycosides are relatively easily available via C-functionalization at C1. However, C-functionalization at C2 and other positions require many reaction steps. 2-C branched sugars, in which the sugar is functionalized at C2 become important mimetics of the 2-N-acetylsugars which are used in cell surface engineering and as inhibitors in the biosynthesis of lipids. 2-C branched glycosides which combine the functionalization at positions C-1 and C-2 are commonly referred to as 2-C branched glycosides. Although the synthetic methodologies developed for the synthesis of C-glycosides and 2-C-branched sugars are extensively studied, the synthesis of 1,2-cis-2-C-branched C-, S-, and N-glycosides is less explored. With this background we embarked on the development of novel methods for the synthesis of 1,2-cis-aryl-glycosides from pyranothiochroman and hemithioacetal precursors.

The C1 and C2 substituents of the sugar moiety in the pyranothiochroman derivatives that have been synthesized so far are locked in a 1,2-cis configuration (both the gluco and manno analogs). The locked structure of these pyranothiochromans inspired us to utilize them in the stereospecific synthesis of 1,2-cis-2-C-deoxy-α-aryl-C-glycosides alleviating some of the limitations in the reported methodologies. Of the different pyranothiochroman derivatives we synthesized, the one that caught our attention most was the hemithioacetal product 205 (Scheme 3.3 on page 86). It was envisioned that a careful desulfurization of the C-S bonds in α-acyloxy pyranothiochroman 165 could provide the aryl-C-glucoside with inherent 1,2-cis relationship between the easily transformable 2-C-branch and the aryl group at the C2 and C1 positions, respectively. However, instead of investigating desulfurization conditions in this α-acyloxy pyranothiochroman we employed pyranothiochroman 158 as a model and used Raney nickel as a desulfurization agent.
4.2 Raney Nickel a Versatile Desulfurization Reagent

Raney nickel was first discovered by Murray Raney in 1927. The catalyst is prepared by leaching of aluminum in a powdered aluminum nickel alloy with sodium hydroxide producing a high surface area nickel having a porous, spongy like microstructure. The activity of the Raney nickel mainly depends on the concentration of the base and the temperature of the reaction between the alloy and the base. Commercial Raney nickel is 50% nickel and 50% aluminum. These alloys are made of different phases, NiAl3, and an Al-NiAl3 eutectic. The eutectic and NiAl3 are reactive to hydroxide and readily lose the Al to give skeletal nickel. Ni2Al3 needs temperatures of around 50 °C to remove the aluminum. The catalyst prepared from the commercial alloy of pure NiAl3 or Ni2Al3 have almost the same activity when the aluminum is completely removed in preparation of the catalyst.

The general method of synthesis of Raney nickel is by the addition of the alloy to a solution of sodium hydroxide at a specific temperature. This removes the aluminum and generates hydrogen gas that activates the nickel catalyst. Different types of Raney nickel catalysts of differing activities have been generated by the addition of the commercially available alloy to sodium hydroxide solution which are designated as W1, W2, W3, W4, W5, W6, W7 and W8 depending on: the amount of sodium hydroxide used, the temperatures at which the alloy is added, the temperature and duration of the alloy digestion and the way the catalyst is washed to remove the sodium aluminate and the excess sodium hydroxide as shown in Table 4.1.
Table 4.1. Preparation of different types of Raney Nickel

<table>
<thead>
<tr>
<th>Type</th>
<th>Add. T°</th>
<th>NaOH:alloy Ratio (w/w)</th>
<th>Digestion T° and time</th>
<th>Washing process</th>
<th>Relative activity</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>W1</td>
<td>0 °C</td>
<td>1:1</td>
<td>115-120 °C 4 h</td>
<td>Filter; wash with H₂O to neutral, EtOH wash by decantation.</td>
<td>Least active</td>
<td>11</td>
</tr>
<tr>
<td>W2</td>
<td>25 °C</td>
<td>4:3</td>
<td>Steam bath 8-12 h</td>
<td>H₂O wash by decantation, EtOH wash by decantation.</td>
<td>&lt; W4: &gt;W3 most common type</td>
<td>12</td>
</tr>
<tr>
<td>W3</td>
<td>-20 °C</td>
<td>4:3</td>
<td>50 °C 50 min</td>
<td>H₂O wash by decantation several times.</td>
<td>Quite active</td>
<td>&gt;W2: &lt;W7</td>
</tr>
<tr>
<td>W4</td>
<td>50 °C</td>
<td></td>
<td>continuous wash with large volume of H₂O</td>
<td></td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>W5</td>
<td>50 °C</td>
<td></td>
<td>EtOH wash without contact with air</td>
<td></td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>W6</td>
<td>50 °C</td>
<td>4:3</td>
<td>50 °C 50 min</td>
<td>Continuous H₂O wash under H₂ atmosphere EtOH wash without contact of catalyst with air.</td>
<td>Most active</td>
<td>15, 16</td>
</tr>
<tr>
<td>W7</td>
<td>50 °C</td>
<td>4:3</td>
<td>50 °C 50 min</td>
<td>Three decantation with H₂O EtOH wash without contact of catalyst with air.</td>
<td>Very active</td>
<td>&lt;W6 : &gt;W4</td>
</tr>
<tr>
<td>W8</td>
<td>0 °C</td>
<td>1:1</td>
<td>100-105 °C 4 h</td>
<td>Continuous H₂O wash to remove lighter Ni particles. Dioxane wash by decantation. Distil portion of the dioxane from the catalyst.</td>
<td>Least active</td>
<td>17</td>
</tr>
</tbody>
</table>
It is widely believed that the mechanism of the Raney nickel reaction proceeds by initial chemisorption of the sulfur atom on the catalyst followed by the fission of the sulfur-carbon bonds to generate free radicals. What happens to the free radical depends on the amount of hydrogen still present on the metal surface. If the concentration is high enough as, in the hydrogen poor nickel, hydrogenolytic desulfurization takes place and the radicals are either hydrogenated to the corresponding hydrocarbons as in Scheme 4.1 (II) or, if there is insufficient hydrogen, recombine forming another product (III). If the concentration is too low, as in the hydrogen free nickel, sulfides are formed Scheme 4.1 (I)\(^{18,19}\)

\[
\begin{align*}
\text{II} & \quad \text{R-S-R} + \text{Ni} \rightarrow \text{R}^\cdot + \text{Ni-S-R} \\
\text{III} & \quad 2\text{R}^\cdot \rightarrow \text{R}-\text{R}
\end{align*}
\]

**Scheme 4.1:** Possible products of Raney nickel desulfurization

### 4.3 Synthesis of 1,2-cis-2-C-Branched-α-Aryl-C-Glucosides

In our first attempt on desulfurization, pyranothiochroman 158a was treated with Raney nickel (W-2) in ethanol at reflux to provide 1,2-cis-2-C-methyl-α-aryl glycoside. Pyranothiochroman 158a provided the expected 2-C glycoside product 180a after stirring for 30 minutes with half a spatula of Raney nickel. The structure of glycoside 180a was established using NMR spectroscopy and HRMS. The appearance of a doublet signal at \(\delta_H 0.90\) ppm which corresponds to three protons and resonance of the corresponding carbon upfield at \(\delta_C 12.3\) ppm while the methylene proton signals of the benzyl protecting groups remain intact suggests the presence of a CH\(_3\) at the C2 position. The cleavage of the S-Ar bond was also confirmed by the presence of an additional proton in the aromatic region of the \(^1\)H-NMR spectrum and this was further confirmed by HRMS which displayed a molecular ion of 509.2692 that corresponds to the calculated molar mass of glycoside 180a. H-1 appeared as a doublet with a \(J\) value of 3.2 Hz which corresponds to an axial-equatorial relationship between H-1 and H-2 suggesting α-configuration of the glycosidic bond.\(^{20,21}\)
Scheme 4.2: Raney nickel, ethanol reflux, 30 min, 82-85%.

In order to investigate the generality of the protocol, pyranothiochromans (158b-d) were subjected to the desulfurization reaction. The pyranothiochromans were transformed into their corresponding 1,2-\textit{cis}-2-methyl-\textit{\alpha}-aryl-C-glucosides in moderate to excellent yields. The results are summarized in Table 4.2.

Table 4.2: Formation of 1,2-\textit{cis}-2-methyl-aryl-C-glycosides via desulfurization of pyranothiochroman derivatives 180a-d and 181a-b

<table>
<thead>
<tr>
<th>Thiochroman substrate</th>
<th>R</th>
<th>2-deoxy-aryl-C-glycosides</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>158a R = H</td>
<td>180a R = H</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>158b R = CH$_3$</td>
<td>180a R = CH$_3$</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>158c R = OCH$_3$</td>
<td>180c R = OCH$_3$</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>158d R = C(CH$_3$)$_3$</td>
<td>180d R = C(CH$_3$)$_3$</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>164a R = H</td>
<td>181a R = H</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>164b R = C(CH$_3$)$_3$</td>
<td>181b R = C(CH$_3$)$_3$</td>
<td>85</td>
<td></td>
</tr>
</tbody>
</table>
In a similar fashion, 1,2-cis-2-methyl-β-aryl-C-mannosides 181a-b (Table 4.2) were synthesized from pyranothiochromans 164a and 164b under the optimized desulfurization conditions (Scheme 4.3). The structures of mannosides 181a-b were established using NMR spectroscopy and HRMS.

![Scheme 4.3](image)

**Scheme 4.3:** Raney nickel, EtOH, reflux, 30 min, 82-85%.

After synthesizing 1,2-cis-2-methyl-aryl-C-glucosides and mannosides successfully, our attention turned to the synthesis of the corresponding such compounds containing an easily transformable 2-C-branch using α-acyloxy pyranothiochroman 182.

![Scheme 4.4](image)

**Scheme 4.4:** Raney nickel (W-2), ethanol reflux, 30 min.

In our first attempt the desulfurization was carried out with the α-acyloxy pyranothiochroman 165a with the aim of generating 1,2-cis-2-acetoxy-α-aryl-C-glucoside 182a using Raney nickel (W-2). However, this resulted in the cleavage of the acetate group to generate 1,2-cis-2-
methyl-α-aryl-C-glucoside 180 (Scheme 4.4). Gowoda and Chane 22 effected desulfurization of acyloxy bearing substrates using Raney nickel in the presence of formic acid, under the conditions the the acyloxy group survived. However, in our case the same conditions failed to provide the required 2-C branched glucoside 182. After all efforts to generate the 2-acyloxy-C-glucoside from α-acetoxy pyranothiochroman failed, our attention was shifted to a similar compound; hemithioacetal 170a (Scheme 4.5) obtained by the deacetylation the α-acyloxy pyranothiochroman 165a.

Although most hemithioacetals (RCH(OH)SR) are unstable and difficult to isolate as they readily dissociate to their corresponding aldehydes and thiols, 23 cyclic hemithioacetals like hemithioacetal 170a (Scheme 4.5) are stable.24 Thus the acyloxy pyranothiochroman 165a was employed as a model substrate to optimize the method for preparing pyranohemithioacetal 170a. The pyranohemithioacetal 170a was fully characterized using IR, NMR, HRMS and single crystal X-ray diffraction. The appearance of a broad peak centered at 3320cm\(^{-1}\) in the IR spectra represents the OH stretching. The disappearance of the OAc peak in \(^1\)H and \(^{13}\)C NMR and the appearance of C-OH signal at 2.28 ppm and 73.2 ppm confirm the formation of the pyranohemithioacetal. Finally, single crystal X-ray diffraction unequivocally confirmed the structure 170a (Figure 4.1).24 The generality of the method was established using different acyloxy pyranothiochroman substrates, the yields of which are reported in Table 4.3.

\[
\text{Scheme 4.5: NaOMe, MeOH, rt, 76%}
\]
Figure 4.1: Single X-Ray crystal structure of pyranohemithioacetal (2R,3S,4R,4aS,5S,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-b]pyran-5-ol (170a).

Table 4.3. Reaction yields of pyranohemithioacetals 170a-d.

<table>
<thead>
<tr>
<th>Sulfoxide</th>
<th>R</th>
<th>Hemithioacetal Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Sulfoxide" /></td>
<td><img src="image" alt="R" /></td>
<td><img src="image" alt="Product" /></td>
<td>76</td>
</tr>
<tr>
<td>167a</td>
<td>R = H</td>
<td>170a</td>
<td>76</td>
</tr>
<tr>
<td>167b</td>
<td>R = CH₃</td>
<td>170b</td>
<td>71</td>
</tr>
<tr>
<td>167c</td>
<td>R = OCH₃</td>
<td>170c</td>
<td>73</td>
</tr>
<tr>
<td>167d</td>
<td>R = C(CH₃)₃</td>
<td>170d</td>
<td>80</td>
</tr>
</tbody>
</table>
Although detailed studies on the desulfurization of hemithioketals are well documented, the desulfurization of the related hemithioacetals (RCH(OH)SR) are less explored.25,26 With the generality and scope of the pyranohemithioacetal synthesis established, our focus shifted to the desulfurization of the pyranohemithioacetals. To a solution of pyranohemithioacetal 170a in ethanol was added half a spatula freshly prepared Raney nickel (W-2). This reaction resulted in the formation of the desired product in un-usable quantities along with randomly de-benzylated and other by-products. Attempts for the exclusive synthesis of glucoside 183a using different strengths of Raney nickel and reaction conditions (solvent, temperature and reaction time) were all unsuccessful.

Interestingly, during the course of the investigation it was noted that the reaction proceeded via formation of a less polar intermediate (TLC analysis). This intermediate was properly isolated and detailed NMR and HRMS studies indicated that the intermediate was an inseparable mixture of carbaldehydes 184a and 184a’. Evidence for carbaldehyde 184a include the appearance of the aldehydic proton at δ 9.58 as a doublet (J = 2.4 Hz) due to coupling to H-2. The anomeric proton appeared as a doublet with a J value of 2.8 Hz which corresponds to an axial-equatorial relationship between H-1 and H-2 suggesting an α-configuration of the glycosidic bond.20,21 Similarly, the aldehydic and anomeric protons of carbaldehyde 184a’ appeared as doublets at 9.79 and 5.21 ppm with 2.0 and 5.2 Hz J values, respectively. The assignment of the glucoside 184a and mannoside 184a’ was based on a prolonged treatment of the aldehydic mixture with trifluoroacetic acid which effected no change in the ratio of the two epimers suggesting that it represents an equilibrium mixture. This led us to the conclusion that the major isomer was more stable carbaldehyde 184a which contains the minimum number of axial substituents. Upon further investigation we found out that carbaldehydes 184a and 184a’ (10:1.3 ratio) could be exclusively prepared (as mixtures) by treatment of hemithioacetal 170a with W-1 Raney nickel in acetone at ambient temperature with no evidence on formation of the glucoside 183a and ring contraction by sulfur extrusion (Scheme 4.6).
Scheme 4.6: (i) W-1 Raney nickel, acetone, rt, 10 min; (ii) NiCl₂·6H₂O, NaBH₄, MeOH:THF (11:4), 0 °C, 10 min.

Consideration of the conditions required for the formation of the mixture of carbaldehydes 184a and 184a’ suggests that hydrogenolytic desulfurization of the C(sp²)-S bond of hemithioacetal 185a was followed by dissociation/decomposition of the resulting thioaldehyde hydrate 185a to yield carbaldehyde 184a. Keto-enol tautomerization (equilibration) of the carbaldehyde 184a via enol 186a might have then resulted in the formation of carbaldehyde 184a’ as shown in Scheme 4.7.
Scheme 4.7: Proposed reaction sequence for the synthesis of a mixture of carbaldehydes 184\(\text{a}\) and 184\(\text{a}'\) using Raney nickel, Ni\textit{H}, as a desulfurizing agent.

In order to investigate the generality of the protocol pyranohemithioacetals 170\textit{b-d} were synthesized and subjected to the desulfurization reaction (Scheme 4.6). The pyranohemithioacetals were transformed into their corresponding carbaldehydes 184 in excellent yields shown in Table 4.4.

Table 4.4. Reaction yields of gluco and manno carbaldehydes.

<table>
<thead>
<tr>
<th>Hemithioacetal</th>
<th>2-carbaldehyde and manno</th>
<th>Gluco:manno</th>
<th>Combined yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>184(\text{a, a}') R = H</td>
<td>67:33</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>184(\text{b, b}') R = CH(_3)</td>
<td>96:4</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>184(\text{c, c}') R = OCH(_3)</td>
<td>96:4</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>184(\text{d, d}') R = C(CH(_3))(_3)</td>
<td>89:11</td>
<td>86</td>
<td></td>
</tr>
</tbody>
</table>
After the serendipitous and successful exclusive synthesis of carbaldehydes 184 using W-1 Raney nickel, we considered whether it would be possible to furnishing the glucoside 183 stereospecifically by using other desulfurizing agents but starting with the same pyranohemithioacetal 170 substrate. Treatment of a solution of pyranohemithioacetal 170a and nickel chloride hexahydrate in a mixture of methanol and tetrahydrofuran with sodium borohydride at 0 °C following the protocol reported by Back et. al.27,28 provided the desired glucoside 183a in 80% yield (Scheme 4.6). The pyranohemithioacetals 170a-d were transformed into 1,2-cis-2-hydroxymethyl-α-aryl-C-glucosides 183a-d with inherent 1,2-cis relationship between the easily transformable 2-C-branch and the aryl group at the C2 and C1 positions respectively, by a careful desulfurization in moderate to excellent yields (Table 4.5).

In all cases, no other significant product was identified upon TLC analysis and in the NMR spectra of the crude products. However, no plausible mechanism as in the case of the synthesis of carbaldehydes 184 could be postulated since the reaction proceeded too fast to allow for the identification and isolation of possible intermediates to give insight into a possible mechanism.

<table>
<thead>
<tr>
<th>Hemithioacetal</th>
<th>2-C-hydroxyl-α-aryl-C-glucoside</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>183a R = H</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>183b R = CH₃</td>
<td></td>
<td>84</td>
</tr>
<tr>
<td>183c R = OCH₃</td>
<td></td>
<td>87</td>
</tr>
<tr>
<td>183d R = C(CH₃)₃</td>
<td></td>
<td>83</td>
</tr>
</tbody>
</table>

4.4. Base Catalyzed Synthesis of 1,2-cis-2,3- Unsaturated-2-C-Branched-α-Aryl-C-Glucosides.

Most 2,3-unsaturated glycosides are usually prepared by Ferrier rearrangement reaction. This reaction often uses glycal precursors in acidic media. The requirement for acid catalyst in the Ferrier rearrangement reaction restrict the number and structures of glycals and glycosyl acceptors to be used and limits its wider synthetic applications.29 Hence, it will be desirable to find alternative methods for the synthesis of 2,3-unsaturated glycosides that avoid the use of
acids. Taking note of the α proton in carbaldehydes 184a and 184a’ we explored the possibility of base catalyzed 2,3-unsaturated-2-C branched-α-aryl-C-glycosides.

Towards this end, the mixture of carbaldehydes 184a and 184a’ was treated with a catalytic amount of K2CO3 according to Scheme 4.8 to afford 2,3-unsaturated-2-C branched-α-aryl-C-glycoside 187a. This represents a completely different reaction protocol to the commonly employed Ferrier rearrangement synthesis of 2,3-unsaturated glycosides.30. The aldehydic carbon appeared 191 ppm in 13C NMR and aldehydic proton at 9.8 ppm, H-1 resonated at 5.55 ppm as a singlet. The appearance of the aldehydic proton and the H-1 as singlets, H-3 downfield in the aromatic region as well as the integration of the aromatic protons and benzylic protons to 15 and 4, respectively, indicated the abstraction of H-2 and elimination of the benzyloxy group at C3. The absence of coupling between H-1 and H-5 in the NOE NMR spectrum confirmed the α-configuration of the glycosidic bond at C1. The formation of a single product from a mixture of starting materials indirectly confirmed that carbaldehydes 184a and 184a’ were indeed epimers at C2.

In order to evaluate the generality and scope of the proposed synthesis of the 2,3-unsaturated-α-aryl-C-glycosides, the reaction was monitored with carbaldehydes 184a, 184b and 184d (Scheme 4.8). The reaction provided the corresponding 2,3-unsaturated-2-C-branched-α-aryl-C-glycosides 187a-c in excellent yields. The high stereospecificity for α-anomer, mild, non-acidic (alkaline) reaction conditions as well as absence of the need for transition-metal reagents makes the current protocol a viable alternative to the literature reported methodologies.

![Scheme 4.8](image)

Scheme 4.8: K2CO3 (catalytic amount), MeOH, rt, 30 min, 92-94%.

Table 4.3. Reaction yields of 1,2-cis-2-C-branched 2,3-unsaturated-α-aryl-C-glucosides.
<table>
<thead>
<tr>
<th>Carbaldehydes</th>
<th>R</th>
<th>2,3-unsaturated glucoside product</th>
<th>Combined yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>184a, 184a’ R = H</td>
<td>187a</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>184b, 184b’ R = CH₃</td>
<td>187b</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>184d, 184d’ R = C(CH₃)₃</td>
<td>187c</td>
<td>94</td>
<td></td>
</tr>
</tbody>
</table>

4.5 Conclusion

In conclusion, we have demonstrated that desulfurization of pyranohemithioacetals allows for the stereoselective synthesis of 1,2-cis-2-C-branched-α-aryl-C-glucosides. The method has been applied to the synthesis of either 1,2-cis-2-hydroxymethyl-α-C-glucosides or 1,2-cis-2-formyl-α-aryl-C-glucoside from a common starting material.

Compared to the previously reported protocols, especially via opening of 1,2-cyclopropanated sugars, the current strategy is superior in stereoselectivity and amenability of the 2-C-branch for further manipulation. The unexpected exclusive formation of carbaldehydes 184 is expected to shed light into the understanding of the mechanism of desulfurization using Raney nickel.
4.6 References

7. Murray Raney, Chattanooga, Tennessee, U. S. Patent 1,628,190, May 19, 1927
24. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as deposition number CCDC-988973.


CHAPTER 5: SYNTHESIS OF 2,3-UNSATURATED GLYCOSIDES VIA FERRIER REARRANGEMENT

5.1 Introduction
For 2,3-unsaturated glycosides, Ferrier rearrangement, a Lewis acid catalyzed allylic rearrangement of glycalcs in the presence of nucleophiles, is the mainstay for their preparation. As shown in Scheme 5.1 the reaction proceeds via a cyclic oxocarbenium intermediate and can be intercepted by nucleophiles such as alcohols, halides and carbanions to give the corresponding products. Even though the reaction is efficient, the requirement for an acid as a catalyst (Examples include: BF$_3$·OEt$_2$, Bi(OTf)$_3$ with and without SiO$_2$, FeCl$_3$, acidic Montmorillonite K-10, I$_2$, InCl$_3$, CeCl$_3$·7H$_2$O, Sc(OTf)$_3$, Al(OTf)$_3$, Al$_2$O$_3$, TMSOTf, Pd(OAc)$_2$, K$_5$CoW$_{12}$O$_{44}$·3H$_2$O, Fe$_2$(SO$_4$)$_3$·xH$_2$O, zeolites and SiO$_2$ by microwave irradiation at 650W, H$_2$SO$_4$-SiO$_2$, HClO$_4$-SiO$_2$, H$_3$PO$_4$) causes restriction to the glycals and glycosyl acceptors to be used and its wider synthetic applications. This called for the development of non-acidic catalyzed allylic rearrangement as an alternative to the original Ferrier rearrangement reaction (Examples include: NIS, DDQ, CAN, iodonium dicollidinium perchlorate) providing different degrees of selectivities and efficiencies.

Schem 5.1: Ferrier rearrangement reaction.

Besides the nature of the catalysts/promoters, the conformation of the glycal plays an important role with regard to the reactivity of the Ferrier rearrangement. The endocyclic double bond between C1 and C2 atoms of the pyranoid ring forces, atoms O5, C1, C2 and C3 to lie in one plane, with C4 and C5 atoms being able to move below and above the plane. In this configuration the glycal adopts two different half chair conformations ($^4$H$_5$ and $^3$H$_4$) (Figure 5.1). As unsaturated pyranose rings are known to be conformationally more flexible than their
saturated counterparts, a small change in configuration results in a change in $^4\text{H}_5$ and $^5\text{H}_4$ conformational equilibrium. The main factor that affects the conformational equilibria of peractylated glycals, for instance, is the vinylogous anomic effect (VAE) which dictates the pseudoaxial orientation of the allylic acyloxy group at C3 in a glycal. This effect induces bond lengthening of C3-O bond and enhances reactivity.$^{25, 26}$

![Figure 5.1](image.png)

**Figure 5.1:** Conformational equilibrium and conformer percentages of in 3,4-di-$\text{O}$-acetyl-d-xyal (vinylogous anomic effect).

The other factor that affects the conformational equilibrium of acetylated glycals is the 1,3 diaxial interactions. This effect competes with VAE and destabilizes the $^5\text{H}_4$ conformer when there is a substituent at C5 (Figure 5.2a). Thus, the glycal shows no preference for the $^5\text{H}_4$ due to the repulsion between these two groups. Additionally, these 1,3 interactions are affected by the orientation of the C4-OAc group and it is reported that 1,3 diaxial interactions are stronger when C4-OAc and C3-OAc are located on the same side of the pyranoid ring (i.e C4-OAc equatorially oriented, C3-OAc axially oriented as depicted in Figure 5.2b).$^{27}$

![Figure 5.2](image.png)

**Figure 5.2:** Pseudo 1,3-diaxial repulsion for $^5\text{H}_4$ form with axial-axial-axial substituent orientation (a) and (b) axial-equatorial-axial substituent orientation.

Thus, on the bases of VAE, molecules with pseudo axial leaving groups at C3 undergo substitution/or rearrangement readily than their corresponding epimers which provides. The
importance of this stereochemical factor was shown in the reaction of 3-pentenoyl \(\alpha\)-gulal 188 and \(\alpha\)-galactal 190 (Scheme 5.2) with iodonium dicollidinium perchlorate (IDCP).

![Scheme 5.2: Effect of the configuration of the allylic center in the iodonium catalyzed Ferrier rearrangement reaction.](image)

While compound 188 produced 2,3 unsaturated glycoside 189 exclusively, galactal 190 produced the 2,3-unsaturated glycoside 191 along with the addition product 2-deoxy-2-iodogalactoside 192.\(^{28}\)

The regioselectivity of the oxocarbenium cation is rationalized on the basis of hard/soft acid/base principle, proposed by Zamojski and co-workers\(^ {29}\) for reactivities of glycals. The oxocarbenium intermediate behaves as a hard acid at the C1 site. Thus, an alcohol being a hard base will attack the oxocarbenium at C1 (anomeric carbon) affording 2,3 unsaturated glycoside.\(^ {29}\)

With \(S\)- and \(N\)-glycosides, the regioselectivity is dependent on the reaction conditions and on whether the products are formed under kinetic or thermodynamic control. As shown in Scheme 5.3, under acidic conditions the Ferrier rearrangement of glycals in the presence of thiols generates 2,3-unsaturated-\(\alpha\)-glycoside 194, but under forcing conditions the initial thioglycosides rearranges to the thermodynamically favoured C3-pseudoaxial 3-thioaryl- or thioaryl-glycals 195. Complete equilibration of the kinetic to thermodynamic product could be
achieved in the presence of a Lewis acid, using longer reaction times or even during chromatographic purification on silica gel.\textsuperscript{30-32}

![Scheme 5.3: Thermodynamic and kinetic control in Ferrier rearrangement reaction with thiol nucleophiles.](image)

However, the common use of strong acids as catalysts in Ferrier transformations which are incompatible with acid sensitive substrates, prompted us to explore alternatives. Towards this end, in addition to the base catalyzed synthetic strategy for the synthesis of 2,3-unsaturated glycosides discussed in Chapter 4, we have investigated the use of NaHSO\textsubscript{4} supported on SiO\textsubscript{2} as an alternative environmentally benign and recyclable catalyst to effect the Ferrier rearrangement of glycals.

### 5.2 NaHSO\textsubscript{4} supported on silica gel effective catalyst for Ferrier rearrangement

Although a number of catalysts for the Ferrier reaction have been reported in the literature as discussed above, none of the methods reported is superior in terms of yield, anomeric selectivity, reaction time, temperature, amount of catalyst, catalyst reusability, environmental benignness, and cost of catalyst. NaHSO\textsubscript{4} supported on silica gel has attracted considerable attention due to its low cost, ease of preparation, mildness, recoverability, reusability and insensitivity to moisture. It has been applied as a catalyst in the opening of epoxides into β-
hydroperoxy alcohols, synthesis of tri-substituted quinolines, β-enaminones, N-acylsulfonamides, aryl-14-H-dibenzo[a,j]xanthenes, amidoalkyl naphthols, coumarins, and selective mono-acetylation of unsymmetrical diols. Against this background we decided to explore NaHSO₄ supported on silica gel as an alternative catalyst for a Ferrier reaction.

In our first attempts a solution of acetylated glucal and benzyl alcohol in acetonitrile was treated with catalytic amounts of NaHSO₄-SiO₂ at room temperature. However, TLC analysis showed no formation of a product. Addition of stoichiometric amount of the catalyst also failed. Reactions at different temperatures were then carried out using benzyl alcohol as a model nucleophile to investigate the optimum conditions to effect Ferrier rearrangement and it was found that the minimum temperature required to favor formation of the product was at 80 °C. This was in accordance with the literature report where H₂SO₄-SiO₂ was employed as a promoter. Temperatures lower than 80 °C resulted in no effect while temperatures higher than 80 °C resulted in the formation of many by-products as shown by TLC analysis. After establishing the right temperature, investigation was carried out to determine the minimum amount of catalyst required to effect complete conversion of the starting glucal into a product. Thus, catalyst loadings of 1 and 2 mol % were investigated to provide a guide. Reactions that were carried out at 80 °C using 1 mol % catalyst loadings went to completion in 60 min providing low yield of the product while reactions carried out at the same temperature but with 2 mol % were completed in less than 5 min and provided excellent yields. The low yields with longer reaction time could be attributed to the decomposition of the starting/product material at high temperature in acidic medium.

Since SiO₂ alone has been reported to catalyze Ferrier rearrangement reaction under 650 W microwave irradiation, it was imperative to investigate whether the activity of the NaHSO₄-SiO₂ was as a result of the SiO₂ alone or a combination of the two. Thus, a reaction was set up at 80 °C using SiO₂ as a catalyst to provide a Ferrier product to no avail. The importance of the SiO₂ was then tested by attempting to effect Ferrier rearrangement of acetylated glucal with benzyl alcohol in the presence of unsupported NaHSO₄ (10 mol %). To our surprise the reaction gave the desired Ferrier product but the reaction was very sluggish (45 min vs 5 min). This result indicated that the combination of the NaHSO₄ and SiO₂ was required for an efficient catalyst. Under the optimum conditions 1.2 equivalents of several alcohols, including primary, secondary, allylic and propargyl alcohols, and thiols reacted with acetylated glucal according
to Scheme 5.4 using 2 mol % NaHSO₄-SiO₂ (3.0 mmol NaHSO₄/g) at 80 °C to give the corresponding 2,3-unsaturated-\(O\) and \(S\)-glycosides in good to excellent yields and in very short reaction time with \(\alpha\)-anomer as a major product. The results are shown in Table 5.1 and the selectivities and yields compare favorably with reported methods (Table 5.2). Products were identified by \(^1\)H and \(^{13}\)C NMR spectroscopy.

Scheme 5.4: Ferrier rearrangement of acetylated glucal 202 with different nucleophiles.

Table 5.1. NaHSO₄-SiO₂ catalyzed synthesis of 2,3-unsaturated glycosides 3,4,6-\(\text{tri-}O\)-acetyl-\(D\)-glucal and 3,4,6-\(\text{tri-}O\)-benzyl-\(D\)-glucal.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product</th>
<th>Rt*</th>
<th>Yield, %</th>
<th>(\alpha:\beta) ratio</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{Ph}OH)</td>
<td>(196a)</td>
<td>5</td>
<td>91</td>
<td>4:1</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>(\text{prop-2-yn-1-ol})</td>
<td>(196b)</td>
<td>5</td>
<td>72</td>
<td>9:1</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>(\text{prop-2-yn-1-ol})</td>
<td>(196c)</td>
<td>5</td>
<td>90</td>
<td>6:1</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Compound</td>
<td>Structure</td>
<td>% Yield</td>
<td>% Conversion</td>
<td>Molar Ratio</td>
<td>Time (h)</td>
</tr>
<tr>
<td>---</td>
<td>----------</td>
<td>-----------</td>
<td>---------</td>
<td>--------------</td>
<td>------------</td>
<td>----------</td>
</tr>
<tr>
<td>4</td>
<td>HO-(\text{C}_4)-OH</td>
<td><img src="image" alt="Structure 196d" /></td>
<td>40</td>
<td>85</td>
<td>8:1</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>OH-(\text{C}_7)-OH</td>
<td><img src="image" alt="Structure 196e" /></td>
<td>60</td>
<td>80</td>
<td>7:1</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>OH-(\text{C}_6)-SH</td>
<td><img src="image" alt="Structure 196f" /></td>
<td>5</td>
<td>96</td>
<td>4:1</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>OH-(\text{C}_6)-SH</td>
<td><img src="image" alt="Structure 196g" /></td>
<td>8</td>
<td>55</td>
<td>5:1</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>OH-(\text{C}_{10})-SH</td>
<td><img src="image" alt="Structure 196h" /></td>
<td>5</td>
<td>60</td>
<td>&gt;99:1</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>OH-(\text{C}_6)-SH</td>
<td><img src="image" alt="Structure 196i" /></td>
<td>8</td>
<td>50</td>
<td>&gt;99</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>MeOH</td>
<td><img src="image" alt="Structure 196a" /></td>
<td>180(^d)</td>
<td>20</td>
<td>5:1</td>
<td>22(a)</td>
</tr>
<tr>
<td>11</td>
<td>OH-(\text{C}_6)-O(\text{C}_6)-O(\text{C}_6)-OBn</td>
<td><img src="image" alt="Structure 196b" /></td>
<td>180(^d)</td>
<td>90</td>
<td>4:1</td>
<td>44</td>
</tr>
</tbody>
</table>
Table 5.2: Comparison of NaHSO₄-SiO₂ with literature reported catalysts for the Ferrier rearrangement of 3,4,6-tri-O-acetyl-D-glucal with different alcohols.⁴,¹¹,¹⁷

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>Catalyst</th>
<th>Time</th>
<th>Yield %</th>
<th>α:β ratio</th>
<th>Cat*</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>CAN</td>
<td>3 h</td>
<td>90</td>
<td>7:1</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sc(OTf)₃</td>
<td>3.5 h</td>
<td>85</td>
<td>5:1</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yb(OTf)₃</td>
<td>3 h</td>
<td>94</td>
<td>9:1</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BiCl₃</td>
<td>1 h</td>
<td>94</td>
<td>10:1</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>InCl₃</td>
<td>10 min</td>
<td>86</td>
<td>6.3:1</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bi(OTf)₃-SiO₂</td>
<td>15 min</td>
<td>90</td>
<td>2.2:1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bi(OTf)₃</td>
<td>3 min</td>
<td>69</td>
<td>4:1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SiO₂ MW</td>
<td>10 min</td>
<td>92</td>
<td>5:1</td>
<td>100</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NaHSO₄-SiO₂</td>
<td>5 min</td>
<td>91</td>
<td>4:1</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>CAN</td>
<td>6 h</td>
<td>80</td>
<td>4:1</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sc(OTf)₃</td>
<td>1.5 h</td>
<td>93</td>
<td>10:1</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yb(OTf)₃</td>
<td>4 h</td>
<td>91</td>
<td>10:1</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BiCl₃</td>
<td>1.5 h</td>
<td>95</td>
<td>10:1</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bi(OTf)₃-SiO₂</td>
<td>2.5 h</td>
<td>76</td>
<td>7.8:1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bi(OTf)₃</td>
<td>5 min</td>
<td>73</td>
<td>α</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

* Substrate (1.8 mmol), 1.2 equiv alcohol/thiol, 1 mL CH₃CN, 2 mol % NaHSO₄-SiO₂, 80 °C. † Isolated yields. The anomeric ratios were based on the integration of the corresponding anomeric protons in the ¹H NMR spectrum. ‡ Performed at room temperature.

* Rt (reaction time)
<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Reaction Time</th>
<th>Yield</th>
<th>α</th>
<th>Conversion</th>
<th>Product Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZnCl₂/Al₂O₃</td>
<td>10 min</td>
<td>88</td>
<td>α</td>
<td>250</td>
<td>11</td>
</tr>
<tr>
<td>NaHSO₄·SiO₂</td>
<td>5 min</td>
<td>90</td>
<td>6:1</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

3. **HO**
- CAN | 3 h | 90 | 4:1 | 10 | 4 |
- Sc(OTf)₃ | 1.5 h | 95 | 7:1 | 5 | 4 |
- BiCl₃ | 1.5 h | 95 | 11:1 | 5 | 4 |
- Bi(OTf)₃·SiO₂ | 2 h | 51 | α | 2 | 4 |
- Bi(OTf)₃ | 3 min | 75 | α | 2 | 4 |
- I₂ | 1 h | 88 | 7:1 | 20 | 4 |
- ZnCl₂/Al₂O₃ | 20 min | 83 | α | 11 | |
- NaHSO₄·SiO₂ | 5 min | 72 | 9:1 | 2 | - |

4. **HO**
- CAN | 4.5 h | 80 | 14:1 | 10 | 4 |
- Sc(OTf)₃ | 3 h | 83 | 7:1 | 5 | 4 |
- Yb(OTf)₃ | 18 h | 89 | 11:1 | 10 | 4 |
- InCl₃ | 30 min | 90 | 9:1 | 20 | 4 |
- Bi(OTf)₃·SiO₂ | 2 h | 80 | 3:1 | 2 | 4 |
- Bi(OTf)₃ | 30 min | 82 | α | 2 | 4 |
- ZnCl₂/Al₂O₃ | 10 min | 85 | α | 11 | |
- NaHSO₄·SiO₂ | 5 min | 85 | 8:1 | 2 | - |

* catalyst in mol %

The notion that the group at position C-3 of the glucal has to be a good leaving group (3-OAc or 3-SR) has been over ruled since 3-O-unprotected⁸c and 3-O-benzyl protected¹⁰,¹⁵,¹⁶ glucals have resulted to formation of 2,3-unsaturated glycosides on treatment with different Lewis acids. In agreement with recent report using Al(OTf)₃,¹⁰ NaHSO₄·SiO₂ catalyzed the Ferrier rearrangement reaction of perbenzylated glucal with alcohols and resulted in a mixture of the desired 2,3-unsaturated product and a significant amount of the competitive product, benzyl glycoside 197k, due to the strong nucleophilicity of the benzyloxy group eliminated from position C-3 of the starting glucal (Scheme 5.5). However, when stronger nucleophiles such as thiols were employed, the formation the competitive product, glycoside 197k, was suppressed resulting in 2,3-unsaturated thioglycosides (entry 12 and 13 in Table 1) as major products.
Scheme 5.5: Ferrier rearrangement of benzylated glucal 203 with methanol and thiols.

5.3 Conclusion
In conclusion, we have demonstrated that NaHSO₄ supported on silica gel can catalyse the Ferrier rearrangement of 3,4-6-tri-O-acetyl-D-glucal and 3,4-6-tri-O-benzyl-D-glucal with alcohols and thiols. The short reaction time, high anomeric selectivity, low catalyst loading, low cost and stability of the catalyst make the method attractive in organic synthesis. To the best of our knowledge, this is the second report where a weak protic acid (the first being H₃PO₄) has been used as a catalyst for the Ferrier rearrangement reaction of glycals.
5.4 References


CHAPTER 6: FUTURE WORK AND OVERALL CONCLUSION

6.1 Future Work

6.1.2. 1,2-cis-2-Diphenyl Phosphonate-α-Aryl-C-Glucoside and 1,2-cis Diphenyl Thiophosphonate-α-Aryl-C-Glucoside, Potential Substrates of MshB Enzyme in mycothiol Biosynthesis.

One of the defense mechanisms of the *Mycobacterium tuberculosis* that causes tuberculosis is the low molecular weight thiol known as Mycothiol (MSH). Mycothiol, 1-D-myo-inositol-2-(N-acetyl-L-cysteinyl)amino-2-deoxy-α-D-glucopyranoside (Figure 6.1), is a low molecular weight thiol which is present exclusively in Gram-positive bacteria such as *Mycobacterium tuberculosis*.

![Figure 6.1: Structure of mycothiol (MSH)](image)

Studies have shown that mycothiol-deficient *Mycobacterium smegmatis* mutants are hypersensitive to alkylating agents, free radicals and antibiotics. Hence, disruption of the enzymatic pathways of mycothiol biosynthesis and/or mycothiol-dependent detoxification by enzyme inhibitors may lower the level of mycothiol and leave the *Mycobacterium tuberculosis* vulnerable to antibiotics and other stress factors allowing the development of new anti-tuberculars. Based on these reports, a couple of research groups have shown that mycothiol analogs and also C2 modified glucosamine isosteres, can indeed effect the biosynthesis of mycothiol paving a new road for the design of new TB drugs. The biosynthetic pathway of mycothiol in *Mycobacterium tuberculosis* involves four enzymatic reactions and the enzymes...
are designated as: MshA, MshB, MshC and MshD, encoded by the genes: mshA, mshB, mshC and mshD, respectively.\textsuperscript{4}

Owing to the difficulties in the synthesis, resolution and stereoselective incorporation of the myo-inositol moiety of the natural substrate, analogs having simple six-membered rings such as cyclohexyl and phenyl have been synthesized and evaluated for their enzyme inhibition potential. The analogues so synthesized exhibited significant inhibition demonstrating that the myo-inositol moiety is not a necessity and cyclohexyl and phenyl analogues could be used as alternatives.\textsuperscript{1,5-9} It was, thus, envisioned that the 1,2-\textit{cis}-2-C-hydroxymethyl-\textit{α}-aryl-C-glucoside 183 having the phenyl ring in the \textit{α} position at the anomeric center and the equatorial substituent at the C2 position which is amenable for further transformation, could be an ideal starting material for the synthesis of mimics of the natural substrate. Furthermore, having the C-glycoside instead of an O-glycoside offers an added advantage of stability in the physiological medium since C-glycosides are reported to be resistant to acid and enzymatic hydrolysis.

The deacetylase enzyme (MshB) is identified as a key in the biosynthesis of mycothiol.\textsuperscript{8} Hence, its inhibition could disrupt the biosynthesis of the defensive agent, mycothiol, making the \textit{mycobacterium tuberculosis} vulnerable to drugs and other stress factors. The deacetylation is proposed to proceed \textit{via} tetrahedral transition state (\textit{II}) after enzyme assisted nucleophilic attack at the carbonyl carbon (Scheme 6.1).
Scheme 6.1: Proposed mechanism of N-deactylation.

It is also reported that Phosphinic acid-, sulfoximine- and sulfone-based transition-state analogues display inhibition of *Escherichia coli* γ-glutamylcysteine synthetase. Thus, we assume phosphonates 198 and thiophosphonates 199 depicted in Figure 6.2 with tetracoordinated side-chain might be potential inhibitors of the MshB enzyme.

Figure 6.2: Phosphonate 198 and thiophosphonate 199 potential MshB enzyme inhibitors.
To provide a proof of concept for this potential MshB inhibitors we employed benzyl protected glycosides 183a and 183b as starting substrates to generate the phosphonate 200 and thiophosphonate 201 (Scheme 6.2).

The synthesis of the glucoside was achieved by treating the glucoside 183a in toluene with triethyl amine and chlorodiphenylphosphine, according to the protocol of preparing P-O bonds, 10-12 Once the P (III)-O bond is formed (monitored by TLC), hydrogen peroxide was added to oxidize the P (III) to P (V), however the addition of the peroxide rather hydrolyzed the P(III)-O bond to give back the glucoside 183a (judged by TLC). Upon further investigation it was found that the same reaction performed at reflux generates the expected product 200. It was assumed that the HCl generated in the reaction oxidizes the phosphine sugar adduct from P (III) to P (V) affording phosphonate 200.

The formation of the product was confirmed by the disappearance of the OH signal in proton NMR and IR spectra, the increase in number aromatic protons from 15 to 29, shift in 31P at 31.1 ppm and the agreement between the calculated and found in HRMS.

Glucoside 183b was also subjected to the same reaction conditions, but was oxidized to P (V) by elemental sulfur at reflux according to the protocol reported by Williams and co-workers to afford the thiophosphonate 201.12 The formation of this product was similarly characterized by the disappearance OH signal in NMR and IR spectra, the increased aromatic protons to 29 in 1H NMR, the chemical shift 31P NMR at 81.5 and HRMS calculated and found fall within the acceptable range.
Scheme 6.2: (a) Et₃N, P(Ph)₂Cl, Toluene, reflux, 88%; (b) Et₃N, P(Ph)₂Cl, S₈, Toluene, reflux, 87%.
6.2 References


6.3 Overall Conclusion

This study has shown an efficient synthetic protocol for diastereoselective preparation of novel pyranothiochromenes from pyranothiochromans which are locked in 1,2-cis-configurition. Owing to the amenability of the sulfur hetero-atom in the pyranothiochromans, they were further transformed to the corresponding sulfoxide derivatives which in turn were transformed via the Pummerer rearrangement reaction to alpha acyloxy sulfides. The acyloxy sulfides were hydrolyzed to the corresponding thiochromenes in an efficient and highly stereoselective method for the synthesis of 2,3-substituted thiochromenes via a tandem thio-Michael addition reaction. This protocol is superior to existing protocols in that the carbohydrate derived substituent at the stereogenic center of the thiochromene is versatile and is amenable to further manipulation.

Finally the synthesis of unsaturated O and S glycosides via Ferrier rearrangement reaction and C aryl glycosides were successfully undertaken in this project. The Ferrier rearrangement reaction was done with environmentally benign NaHSO₄ supported on silica gel. We were able to demonstrate that NaHSO₄ supported on silica gel can catalyze the Ferrier rearrangement of 3, 4-6-tri-O-acetyl-D-glucal with alcohols and thiols as nucleophiles. The short reaction time, high anomeric selectivity, low catalyst loading, low cost, and stability of the catalyst make the method attractive in organic synthesis. This method has been the second reported of a weak protic acid besides H₃PO₄ used as a catalyst for the Ferrier rearrangement reaction of glycals.

Finally it was demonstrated that desulfurization of pyranohemithioacetals allows for the stereoselective synthesis of 1,2-cis-2-C-branched-α-aryl-C-glucosides. The method has been applied to the synthesis of either 1,2-cis-2-hydroxymethyl-α-aryl-C-glucosides or 1,2-cis-2-formyl-α-aryl-C-glucosides from a common starting material. Compared to the previously reported protocols, especially via opening of 1,2-cyclopropanated sugars, the current strategy is superior in stereoselectivity and amenability of the 2-C-branch for further manipulation. The synthetic application of the 2-formyl-α-aryl-C-glucosides was demonstrated by their ease of stereospecific transformation into the 2,3-unsaturated-2-formyl -α-aryl-C-glucosides without the need for acid catalysts or transition metal-based reagents as normally required.

Finally, having the required orientation at the anomeric and C2 positions, the 1,2-cis-2-C-branched-α-aryl-glucosides can be used as potential substrates for the enzymes involved in the
synthesis of *Mycobacterium tuberculosis*. Besides the required α hydrophobic core at the anomeric position, a phosphonate group was introduced at the C2 branch to give it a tetrahedral like structure that would enhance its chances as substrate for the *Mycobacterium tuberculosis* enzymes.
CHAPTER 7: EXPERIMENTAL DATA

7.1 Standard Experimental Procedures

7.1.1 Materials
All reagents were purchased from Sigma Aldrich and were used without further purification. All solvents were dried by appropriate techniques and inert reaction conditions were maintained using a nitrogen atmosphere. Reactions were done in oven or flame dried glass-ware with constant stirring with a magnetic stirrer. Room temperature refers to ca 20-25 °C.

7.1.2 Chromatography
Qualitative thin layer chromatography (TLC) was done on Merck GF254 pre-coated silica gel aluminum backed plates (0.25 mm). The chromatograms were eluted using various mixtures of hexane and ethyl acetate. Compounds were visualized either by their fluorescence under UV light (254 nm), or by spraying the TLC with anisaldehyde spray with subsequent heating with a heat gun.

Flash chromatography refers to column chromatography under the pressure of nitrogen using Merck Kieselgel 60 (230-400 mesh) with appropriate solvent mixture mixed in a volume per volume ratio.

7.1.3 Spectroscopic Methods

7.1.3.1 Nuclear Magnetic Resonance Spectroscopy (NMR)
1H and 13C NMR spectra were recorded using a Bruker ultrashield 400 MHZ spectrometer using CDCl3 as a solvent, unless otherwise indicated. 1H are reported in the order: chemical shift (δ, reported in ppm referenced to the residual solvent peak of CDCl3 [δ = 7.24 ppm] or TMS as an internal standard [0.00 ppm], multiplicity (s = singlet, d = doublet, q = quartet, br s = broad singlet, dd = doublet of doublets, dt = doublet of a triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, dtd = doublet of triplet of doublets, p = pentet, sx = sextet, sp = septet.), number of protons, coupling constants (J, in Hertz) and assignment of protons.

13C data are listed in the order: chemical shift (δ, reported in ppm referenced to the residual solvent peak of CDCl3 [δ = 77.0 ppm] and the specific carbon atom allocation. 2 dimensional
(2D) NMR techniques like: correlation spectroscopy (COSY), heteronuclear single quantum coherence (HMBC), distortionless enhancement by polarization transfer (DEPT) and Nuclear Overhauser effect (NOE) spectroscopy were used to assign individual atoms.

7.1.3.2 Mass Spectroscopy \((m/z)\)
Mass spectrometry were recorded on a Walters API Quattro Micro spectrometer at the University of Stellenbosch, South Africa.

7.1.3.3 Infrared Spectroscopy (IR)
Infrared spectra were recorded in a Tensor 27 spectrometer with ATR fitting. The data are reported with the characteristic peaks indicated in \((\text{cm}^{-1})\).

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

7.1.5 Optical Rotations
Optical rotations were determined on Perkin-Elmer 141 polarimeter in chloroform solutions at 25 °C. The concentration \(c\) refers to g/100 mL.

7.2 Experimental Methods

3,4,6 Tri-O-benzyl-D-glucal (150)

3, 4, 6 Tri-acetyl-\(\alpha\)-glucal (10 g, 36.75 mmol) was weighed into a round bottomed flask and diluted with THF (50 mL). TBAI (0.36 g, 0.97 mmol) was then added with subsequent addition of finely ground NaOH (8.92 g, 223 mmol). Benzyl bromide (19.64ml, 114.84 mmol) was then added to the reaction mixture after which it was left to stir for 48 hours at room temperature. After completion of the reaction, the reaction mixture was poured into 100 mL water and was extracted with DCM (100 mL) three times. The combined organic extracts were dried over
anhydrous magnesium sulfate, filtered and solvent removed under reduced pressure. The residue was crystallized from ethanol.

Yield: 12.2 g, 80%, white solid

MP 55-56°C

¹H NMR: (CDCl₃, 400 MHz): δH 7.40 – 7.10 (m, 15H, Ar), 6.43 (d, 1H, J = 6.08Hz, H-1), 4.85 (dd, 1H, J =2.27Hz and 6.19Hz, H-2), 4.82 (d, 1H, J =11.1Hz, -CH₂Ph), 4.65-4.49 (m, 5H, -CH₂Ph), 4.21 (bd, 1H, J = 6.1 Hz, H-3), 4.12-4.10 (m, 1H, H-5), 3.90-3.80 (m, 3H, H-4, H-6a, H-6b)

¹³C NMR: (CDCl₃, 100 MHz): δ 144.6 (C-1), 138.3, 138.1, 137.8, 128.4, 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 is in agreement with reported values).¹

3,4,6-tri-O-benzyl-1,5-anhydro-2-deoxy-1,2-C-dichloromethylene-α-glycerol-α-gulohexitol (151)

Benzyl triethyl ammonium chloride (BTEAC) (0.72 g, 3.16 mmol) was added to a stirring solution of tri-O-benzyl glucal 150 (6 g, 14.42 mmol) dissolved in chloroform (30 ml). 50% of aqueous NaOH (23.04 g, 576 mmol) was then added and the reaction was stirred at 35 °C for 18 h. The reaction mixture was then quenched with water (50 ml) and extracted with DCM 50 (mL) three times. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and solvent removed under reduced pressure. The residue was crystallized from ethanol.

Yield: 5.7 g, 79%, white solid

Mp: 62-64 °C
$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta$H 7.40 – 7.10 (m, 15H, Ar), 4.93-4.41 (m, 6H, -CH$_2$Ph), 3.93 (d, J =8.1Hz, 1H, H-1), 3.86-3.80 (m, 1H, H-3), 3.60-3.48 (m, 2H, H-6$_a$, H-6$_b$), 1.44 (dd, J = 2.0Hz and J = 7.2 Hz, H-2)

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta$C 138.2, 137.9, 137.7, 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, (-CH$_2$Ph), 70.1 (C-6), 61.5 (C-7), 58.9 (C-1), 34.2 (C-2). (Spectroscopic data is in agreement with reported values).$^2$

3,4,6-tri-O-benzyl-1,5-anhydro-2-deoxy-1,2-C-methylene-α-glycero-β-gulo hexitol (152)

![Image](152)

Lithium aluminum hydride (4.53 g, 119.46 mmol) was added into a flask containing (15 mL) THF under nitrogen atmosphere. While stirring vigorously the dichlorocyclopropane 151 (4 g, 8 mmol) was added. The reaction was stirred for 72 hours at room temperature. The reaction was then cooled in ice and quenched by drop-wise addition of 10% aqueous NaSO$_4$.10H$_2$O. The white paste formed was then washed with hot ethyl acetate several times and the solvent was dried over MgSO$_4$ and concentrated under vacuum. The mixture was then purified by column chromatography using hexane ethyl acetate mixture (8:2) as eluent.

Yield: 3 g, 84%, colorless syrup

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta$H 7.40 – 7.10 (m, 15H, Ar), 4.80-4.45 (m, 6H, -CH$_2$Ph), 3.79-3.49 (m, 6H, H-1, H-3, H-4, H-5, H-6$_a$, H-6$_b$), 0.95-0.91 (m, 1H, H-2), 0.85-0.65 (m, 2H, H-7$_a$, H-7$_b$)

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta$C 138.7, 138.6, 138.4, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, (Ar), 80.2 (C-3), 77.4 (C-4), 76.9 (C-5), 73.6, 73.3, 71.2, (-CH$_2$Ph), 70.1 (C-6), 49.7 (C-1), 14.9 (C-2), 11.6 (C-7) (spectroscopic data is in agreement with reported values).$^2$
1,3,4,6-Tetra-O-acetyl-2-deoxy-2-C-iodomethyl-α-and-β-D-glucopyranoses (154)

Cyclopropanated sugar 152 (3 g, 6.97 mmol), was dissolved in a solution acetonitrile (10 ml) and acetic acid (10 mL) cooled in ice. Acetic anhydride (5.63 mL, 55.83 mmol), NH₃I (1.13 g, 7.82 mmol), and 30% of H₂O₂ (3.10 mL, 31.28 mmol) was added and the reaction was left to stir in ice for 10 minutes and further 2 hours at room temperature. Once the reaction was completed it was diluted with 15 mL of DCM and washed with 10% Na₂S₂O₃ (15 ml). The organic layer was then washed three times with 15 mL portions of saturated NaHCO₃ and once with brine (10 mL). The combined extracts were then dried over MgSO₄, filtered and solvent was removed under reduced pressure and the residue was purified by column chromatography using hexane ethyl acetate mixture (9:1) as eluent.

Yield: 3.1 g, 73%, colorless oil

β anomer

¹H NMR: (CDCl₃, 400 MHz): δH 7.45 – 7.02 (m, 15H, Ar), 5.49 (d, 1H, J = 8.2Hz, H-1), 5.03-4.42 (m, 6H, -CH₂Ph), 3.90-3.98 (m, 6H, H-3, H-4, H-5, H-6a, H-6b, H-7a ), 3.28 (d, 1H, J = 9.98Hz, H-7b ), 2.31-2.10 (s, 3H, -OC₃H₃), 1.58-1.39 (m, 1H, H-2)

¹³C NMR: (CDCl₃, 100 MHz): δC 168.9, 168.8, (-OCCH₃), 137.7, 128.8, 128.4, 128.3, 128, 127.8, 127.9, 127.8, 127.7 (Ar) 94.9, (C-1), 81.2, (C-3), 78.7, (C-4), 75.4, (C-5), 75.1, 73.6, 73.4, (-CH₂Ph) 68.1 (C-6), 44.9 (C-2), 21.1 (-OCH₃), 4.3 (C-7).
α anomer

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta$H 6.65 (s, 1H, H-1), 2.89-2.73 (m, 1H, H-7b), 2.30-2.18 (m, 1H, H-2), 2.07 (s, 3H, -OCH$_3$).

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta$c 93.8, (C-1), 80.6 (C-3), 78.2 (C-4), 75.9 (C-5), 75.2, 74.6, 73.1 (-CH$_2$Ph), 46.6 (C-2), 1.0 (C-7) (spectroscopic data is in agreement with reported values).³

7.2.1 General procedure for the synthesis of arylthiomethyl glucosyl acetate (157a-d)
To a solution of arylthiol (3.60 mmol) in DMF (20 mL), sodium hydride (60% dispersion in oil, 87.03 mg, 3 mmol) was added and the mixture was vigorously stirred at room temperature for 5-10 min under nitrogen. A solution of iodoacetate 154 (2 g, 3 mmol) in DMF (4 mL) was then added and after 5 min of stirring of the reaction mixture, methanol (3 mL) was added dropwise and the resulting clear solution was concentrated under reduced pressure. The solution was directly submitted to silica gel chromatography (ethyl acetate/petroleum ether, 2:8) to give the corresponding sulfides:

1-$O$-Acetyl-3,4,6-tri-$O$-benzyl-2-deoxy-2-$C$-phenylthiomethyl-$D$-glucopyranosyl (157a)

Yield 1.4 g, 79%, white solid $\alpha$-$\beta$ anomeric mixtures (1:3)

Mp 74 °C-76 °C

β anomer

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta$H 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$_a$ and H-6$_b$), 3.27 (dd, $J$= 3.6 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, OCOCH$_3$);

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta$C 168.9 (OCOCH$_3$), 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 (OCOCH$_3$);

$^\alpha$ anomeric

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta$H 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): $\delta$C 168.9 (OCOCH$_3$), 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 (OCOCH$_3$) (spectroscopic data is in agreement with reported values).

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-$\beta$-glucopyranosyl (157b):

Yield: 1.5 g, 83%; colorless oil; $\alpha$:$\beta$ anomeric mixtures (1:3)

$\beta$-anomer:

$^1$H NMR: (CDCl$_3$, 400 MHz) $\delta$H 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, 123
-CH₂Ph), 3.95 – 3.62 (m, 5H, H-3, H-4, H-5, H-6ₐ and H-6ₐ), 3.40 (d, J = 13.2 Hz, 1H, H-7ₐ), 2.58 (t, J = 12.4 Hz, 1H, H-7ₐ), 2.32 (s, 3H, -CC₃H₃), 2.95 – 2.18 (m, 1H, H-2), 2.05 (s, 3H, OCOCH₃);

**¹³C NMR:** (CDCl₃, 100 MHz) δC 169.0 (OOCCH₃), 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), 78.8 (C-3), 75.3 (C-5), 74.9 (CH₂Ph), 73.5 (CH₂Ph), 73.0 (CH₂Ph), 68.1 (C-6), 44.3 (C-2), 31.4 (C-7), 20.9 (OCOCH₃), 20.8 (-CCH₃); for

**α-anomer:**

**¹H NMR:** (CDCl₃, 400 MHz): δH 5.68 (d, J = 8.8 Hz, 1H, H-1), 3.27 (d, J = 11.6 Hz, 1H, H-7ₐ), 3.15 (d, J = 12.8 Hz, H-7ₐ), 1.98 (s, 3H, OCOCH₃);

**¹³C NMR:** (CDCl₃, 100 MHz) : δC 169.0 (-OOCCH₃), 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 (-CH₂Ph), 74.6 (-CH₂Ph), 73.4 (-CH₂Ph), 46.1 (C-2), 32.1 (C-7), 20.9 (OCOCH₃) 20.8 (-CCH₃) (spectroscopic data is in agreement with reported values).

**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-glucopyranosyl (157c):**

![157c](image)

Yield: 1.5 g, 82%, colorless oil α:β anomeric mixtures (1:3)

**β-anomer:**

**¹H NMR:** (CDCl₃, 400 MHz) δH 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, -CH$_2$Ph), 3.95 – 3.55 (m, 5H, H-3, H-4, H-5, H-6$_a$ and H-6$_b$), 3.24 (d, $J = 10.8$ Hz, 1H, H-7$_a$), 3.17 (d, $J = 12.8$ Hz, 1H, H-7$_b$), 2.40 (s, 3H, -CCH$_3$), 2.30 – 2.21 (m, 1H, H-2), 2.00 (s, 3H, -OCOCH$_3$);

$^{13}$C NMR: (CDCl$_3$, 100 MHz) : $\delta$C 169.0 (-OCOCH$_3$), 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 (-CH$_2$Ph), 74.7 (-CH$_2$Ph), 73.5 (-CH$_2$PH), 68.1 (C-6), 45.9 (C-2), 30.6 (C-7), 20.9 (-OCOCH$_3$), 20.5 (-CCH$_3$); for $\alpha$ anomer:

$^1$H NMR: (CDCl$_3$, 400 MHz) $\delta$H 6.40 (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, -OCOCH$_3$);

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta$C 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$_3$); (spectroscopic data is in agreement with reported values).$^4$

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-($\text{4-tert-butylphenyl}$)thiomethyl-$\alpha$-glucopyranosyl (157d):

Yield: 1.8 g, 90%; colorless oil; 1:3 $\alpha$ $\beta$ anomeric mixture

$\beta$-anomer
1H NMR: (CDCl₃, 400 MHz): δH 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, -CH₂Ph), 4.80 (d, J = 10.4 Hz, 1H, -CH₂Ph), 4.75 – 4.38 (m, 4H, -CH₂Ph), 3.92 – 3.55 (m, 5H, H-3, H-4, H-5, H-6a and H-6b), 3.29 (d, J = 5.0 Hz, 1H, H-7a), 3.20 – 3.11 (m, 1H, H-7b), 2.37 – 2.18 (m, 1H, H-2), 1.96 (s, 3H, -OCOC₃H₃), 1.28 (s, 9H, -CC(C₃H₃)₃);

13C NMR: (CDCl₃, 100 MHz): δC 169.0 (-OCC₃H₃), 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 (-C(CH₃)₃), 32.0 (C-7), 31.2 (-C(CH₃)₃), 20.9 (-OCOC₃H₃);

α anomer

1H NMR: (CDCl₃, 400 MHz): δH 6.42 (bs, 1H, H-1), 4.97 (d, J = 11.2 Hz, 1H, -CH₂Ph), 3.45 (d, J = 13.2 Hz, 1H, H-7a), 2.57 (t, J = 12.2 Hz, 1H, H-7b), 2.04 (s, 3H, -OCOC₃H₃), 1.30 (s, 9H, -CC(CH₃)₃);

13C NMR: (CDCl₃, 100 MHz): δC 168.8 (-OCOC₃H₃), 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-4), 75.5 (C-5), 75.2 (-CH₂Ph), 74.6 (-CH₂Ph), 73.6 (-CH₂Ph), 68.3 (C-6), 44.6 (C-2), 36.6 (ArCCH₃), 32.0 (C-7), 31.3 (-CC(CH₃)₃), 20.9 (-OCOC₃H₃); (spectroscopic data is in agreement with reported values).

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

HRMS (ESI): m/z [M+Na]^+ Calcd 677.2913; found: 677.2899.

7.2.2 General procedure for the synthesis of α-1,2-aryl-C-glucoside-thiochroman (158a-e)

Sulfide 157 (2 mmol) was dissolved in dry dichloromethane (5 mL) under an atmosphere of nitrogen and stirred together with 4Å molecular sieves at room temperature for 1 h. The mixture was cooled down to 0 °C and BF₃·Et₂O (2.90 mL of 48% BF₃ solution in diethyl ether, 23.29 mmol) was added drop-wise. After stirring at this temperature for 5 min, Et₃N (2 mL) was added and the solids removed by filtration through a celite® bed. The solution was then diluted
with water (15 mL) and the aqueous phase was extracted with dichloromethane. The combined organic phases were successively washed with saturated aqueous NaHCO₃ solution and brine, dried over MgSO₄, filtered and evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 1:9) 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 (158a):**

![Structure of 158a](image)

Yield: 0.7 g, 65%; white solid

Mp 91 – 95 ºC

**¹H NMR:** (CDCl₃, 400 MHz): δH 7.53 (d, J = 7.2 Hz, 1H, Aromatic), 7.42 – 7.30 (m, 13H, Aromatic), 7.13 – 7.03 (m, 5H, Aromatic), 5.13 (d, J = 5.6 Hz, 1H, H-10b), 4.96 (d, J = 11.0 Hz, 1H, CHA HBPh), 4.85 (d, J = 11.0 Hz, 1H, CHA HBPh), 4.78 (d, J = 10.8 Hz, 1H, CHA HBPh), 4.70 (d, J = 12.0 Hz, 1H, CHA HBPh), 4.60 – 4.58 (m, 2H, the rest of the CH A HB Ph), 4.03 (t, J = 13.2 Hz, 1H, H-4), 3.88 – 3.69 (m, 3H, H-4, H-1’a and H-1’b), 3.47 (d, J = 9.2 Hz, 1H, H-2), 3.35 (bd, J = 13.2 Hz, 1H, H-5a), 3.19 (dd, J = 3.6 and 13.6 Hz, 1H, H-5b), 2.62 – 2.50 (m, 1H, H-4a);

**¹³C NMR:** (CDCl₃, 100 MHz): δC 138.7, 138.0, 134.4, 131.4, 128.5, 127.9, 127.8, 127.7, 127.6, 126.3, 124.8 (Aromatic), 80.0 (C-3), 78.7 (C-4), 75.9 (CH₂Ph), 74.8 (CH₂Ph), 73.5 (CH₂Ph), 72.8 (C-5), 72.4 (C-10b), 68.9 (C-1’), 38.4 (C-4a), 26.4 (C-5) (spectroscopic data is in agreement with reported values).³

[α]D: -125.0 (c 0.1, CHCl₃)

IR: 1452, 1082, 694 cm⁻¹ (neat)
HRMS (ESI): \( m/z [M+H]^+ \) Calcd 539.2256; found: 539.2259.

\((2R,3S,4R,4aS,10bS)-3,4\text{-bis(benzyloxy)-2-(benzyloxy)methyl}-9\text{-methyl-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-b]}\)pyran (158b):

Yield: 0.76 g, 69%; white solid

Mp 105 – 107 °C

\(^1\text{H NMR:}\) (CDCl\(_3\), 400 MHz): \( \delta \)H 7.45 – 7.20 (m, 14H, Aromatic), 7.18 – 7.06 (m, 2H, Aromatic), 7.02 – 6.88 (m, 2H, Aromatic), 5.09 (d, \( J = 5.6 \) Hz, 1H, H-10b), 4.95 (d, \( J = 11.0 \) Hz, 1H, CH\(_3\)H\(_3\)Ph), 4.85 (d, \( J = 11.0 \) Hz, 1H, CH\(_3\)H\(_3\)Ph), 4.78 (d, \( J = 10.8 \) Hz, 1H, CH\(_3\)H\(_3\)Ph), 4.71 (d, \( J = 9.2 \) Hz, 1H, CH\(_3\)H\(_3\)Ph), 4.60 – 4.48 (m, 2H, the rest of the CH\(_3\)H\(_3\)Ph), 4.03 (t, \( J = 9.8 \) Hz, 1H, H-4), 3.80 – 3.68 (m, 3H, H-4, H-1’ and H-1”b), 3.59 - 3.49 (m, 1H, H-2), 3.33 (bd, \( J = 11.2 \) Hz, 1H, H-5a), 3.18 (dd, \( J = 3.8 \) Hz and 13.6 Hz, 1H, H-5b), 2.60 – 2.49 (m, 1H, H-4a), 2.23 (s, 3H, ArCH\(_3\));

\(^{13}\text{C NMR:}\) (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 (Aromatic), 80.1 (C-3), 78.8 (C-3), 75.9 (CH\(_2\)Ph), 74.8 (CH\(_2\)Ph), 73.4 (CH\(_2\)Ph), 72.8 (C-2), 72.5, (C-10b) 69.1 (C-1”), 38.6 (C-4a), 26.5 (C-5), 21.0 (ArCH\(_3\)) (spectroscopic data is in agreement with reported values).\(^4\)

\([\alpha]_D\): +91.0 (c 0.1, CHCl\(_3\))

IR: 1453, 1108, 695 cm\(^{-1}\) (neat)

HRMS (ESI): \( m/z [M+H]^+ \) Calcd 553.2412; 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 (158c):

Yield: 0.77 g, 70%; white solid

Mp 119 – 121 °C

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta$H 7.50 – 7.20 (m, 14H, Aromatic), 7.18 – 7.19 (m, 2H, Aromatic), 7.05 – 6.95 (m, 2H, Aromatic), 5.17 (d, $J = 5.2$ Hz, 1H, H-10b), 4.97 (d, $J = 11.0$ Hz, 1H, CH$_{\alpha}$H$_{\beta}$Ph), 4.88 (d, $J = 11.0$ Hz, 1H, CH$_{\alpha}$H$_{\beta}$Ph), 4.79 (d, $J = 10.8$ Hz, 1H, CH$_{\alpha}$H$_{\beta}$Ph), 4.71 (d, $J = 12.0$ Hz, 1H, CH$_{\alpha}$H$_{\beta}$Ph), 4.62 – 4.48 (m, 2H, the rest of the CH$_{\alpha}$H$_{\beta}$Ph), 4.04 (t, $J = 9.8$ Hz, 1H, H-4), 3.80 – 3.60 (m, 3H, H-4, H-1’a and H-1’b), 3.47 (d, $J = 9.2$ Hz, 1H, H-5), 3.38 – 3.20 (m, 2H, H-5a and H-5b), 2.60 – 2.52 (m, 1H, H-4a), 2.23 (s, 3H ArCH$_3$); (spectroscopic data is in agreement with reported values).

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta$C 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 (Aromatic), 79.9 (C-4), 78.6 (C-4), 75.8 (CH$_2$Ph), 74.7 (CH$_2$Ph), 73.4 (CH$_2$Ph), 72.7 (C-2), 72.6 (C-10b), 68.8 (C-1’), 37.9 (C-5), 26.0 (C-4a), 20.1 (ArCH$_3$); (spectroscopic data is in agreement with reported values).

[$\alpha$]$_D$: +127.0 (c 0.1, CHCl$_3$)

IR: 1496, 1406, 1140, 694 cm$^{-1}$ (neat)

HRMS (ESI): $m/z$ [M+H]$^+$ Calcd 553.2412; 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 (158d):

Yield: 0.77 g, 65%; white solid

Mp 157 – 159 °C

$^1$H NMR: (CDCl$_3$, 400 MHz): δ$_H$ 7.61 (s, 1H, Aromatic), 7.42 – 7.21 (m, 13H, Aromatic), 7.18 – 7.07 (m, 3H, Aromatic), 6.97 (d, $J = 8$ Hz, 1H, Aromatic), 5.13 (d, $J = 5.6$ Hz, 1H, H-10b), 4.96 (d, $J = 11.2$ Hz, 1H, CH$_2$H$_2$Ph), 4.87 (d, $J = 11.2$ Hz, 1H, CH$_2$H$_2$Ph), 4.77 (d, $J = 10.8$ Hz, 1H, CH$_2$H$_2$Ph), 4.68 (d, $J = 12.0$ Hz, 1H, CH$_2$H$_2$Ph), 4.56 (d, $J = 12.0$ Hz, 1H, CH$_2$H$_2$Ph), 4.04 (t, $J = 9.8$ Hz, 1H, H-4), 3.79 – 3.18 (m, 3H, H-4, H-1’a and H-1’b), 3.55 – 3.48 (m, 1H, H-2), 3.34 (bd, $J = 13.6$ Hz, 1H, H-5a), 3.18 (dd, $J = 3.6$ and 13.2 Hz, 1H, H-5b), 2.10 – 2.08 (m, 1H, H-4a), 1.24 (s, 9H, ArC(CH$_3$)$_3$);

$^{13}$C NMR: (CDCl$_3$, 100 MHz): δ$_C$ 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 (Aromatic), 80.3 (C-4), 78.8 (C-4), 75.9 (CH$_2$Ph), 74.9 (CH$_2$Ph), 73.6 (CH$_2$Ph), 73.0 (C-2), 72.7 (C-10b), 69.1 (C-1’), 38.7 (C-5), 34.4 (ArC(CH$_3$)$_3$), 31.2 (ArC(CH$_3$)$_3$), 26.3 (C-2); (spectroscopic data is in agreement with reported values).

$[\alpha]_D$: +92.0 (c 0.1, CHCl$_3$)

IR: 1478, 1134, 1103, 697 cm$^{-1}$ (neat)
HRMS (ESI): $m/z$ [M+H]$^+$ Calcd 595.2882; found: 595.2880.

$\text{(2R,3S,4R,4aS,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-methoxy-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-b]pyran (158e):}$

Yield: 0.77 g, 68%; white solid

Mp 130 – 132 °C

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta$H 7.42 – 7.20 (m, 13H, Aromatic), 7.17 – 7.11 (m, 3H, Aromatic), 6.96 (d, $J = 8.4$ Hz, 1H, Aromatic), 6.71 (d, $J = 8.4$ Hz, 1H, Aromatic), 5.09 (d, $J = 5.6$ Hz, 1H, H-1), 4.96 (d, $J = 11.0$ Hz, 1H, CH$_2$H$_6$Ph), 4.87 (d, $J = 11.0$ Hz, 1H, CH$_2$H$_6$Ph), 4.79 (d, $J = 10.8$ Hz, 1H, CH$_2$H$_6$Ph), 4.66 (d, $J = 12.0$ Hz, 1H, CH$_2$H$_6$Ph), 4.52 (m, 2H, the rest of the CH$_2$H$_6$Ph), 4.05 (t, $J = 9.8$ Hz, 1H, H-4), 3.80 – 3.72 (m, 3H, H-4, H-1’a and H-1’b), 3.66 (s, 3H, ArOC$_2$H$_5$), 3.53 (m, 1H, H-2), 3.33 (bd, $J = 13.2$ Hz, 1H, H-5a), 3.18 (dd, $J = 3.6$ and 13.6 Hz, 1H, H-5b), 2.62 – 2.51 (m, 1H, H-4a);

$^{13}$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 (Aromatic), 80.2 (C-4), 78.8 (C-3), 75.9 (CH$_2$Ph), 74.8 (CH$_2$Ph), 73.6 (CH$_2$Ph), 73.0 (C-2), 72.6 (C-10b), 69.2 (C-1’), 55.3 (ArOCH$_3$), 38.6 (C-5), 26.5 (C-4a); (spectroscopic data is in agreement with reported values).$^4$

$[\alpha]_D$: +111.0 (c 0.1, CHCl$_3$)

IR: 1472, 1134, 1103, 698 cm$^{-1}$ (neat)

HRMS (ESI): $m/z$ [M+H]$^+$ Calcd 569.2361; found: 569.2354.
3,4,6-Tri-\textit{O}-benzyl-1,5-anhydro-2-deoxy-1,2-\textit{C}-methylene-\textit{D}-\textit{glycero}-\textit{D}-\textit{talo}-hexitol (159)

![Chemical Structure](image)

To a suspension of zinc dust (765 mg, 11.7 mmol) and cuprous chloride (250 mg, 2.5 mmol) in dry ether (1 mL) at room temperature, diiodomethane was added under an atmosphere of nitrogen. Acetyl chloride (20 µL) was added to the mixture after 5 minutes and was heated at 40 °C for 5 minutes. A solution of benzylated glucal 150 (1.10 g, 2.65 mmol) dissolved in 4 mL in diethyl ether was then added to the mixture. After 5 minutes, additional 2 equivalents of diiodomethane were added and heating continued for 90 minutes. After the reaction was completed the reaction mixture was diluted with ether and washed with 5% NaOH solution (3 mL) three times and brine (3 mL) three times and dried over anhydrous MgSO$_4$. After filtration, the solvent was removed under reduced pressure and the resulting residue purified by column chromatography using hexane ethyl acetate mixture (8:2) as eluent.

Yield: 885.1 mg, 85%, colorless syrup, low melting solid

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta$ H 7.40-7.10 (m, 15H, Ar), 4.99-4.41 (m, 6H), 4.07-4.01 (t, $J$ 5.5 Hz, 1H), 3.90-3.82 (m, 2H), 3.51-3.45 (m, 3H), 1.60-1.40 (m, 1H), 1.30-1.20 (m, 1H), 0.80-0.60 (m, 1H)

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta$ C 138.8, 138.7, 137.9, 128.3, 128, 127.9, 127.8, 127.6, 127.3, 76.0, 74.6, 74.2, 73.8, 73.3, 69.5, 69.3, 53.9, 14.1, 12.1. (spectroscopic data is in agreement with reported values).

1, 3, 4, 6-\textit{Tetra-\textit{O}-acetyl-2-deoxy-2-\textit{C}-iodomethyl-\textit{D}-\textit{mannopyranose} (162)

![Chemical Structure](image)
To a solution of the β-1,2-cyclopropanated sugar 159 (2.55 mg, 5.92 mmol) in 30 mL of THF-H2O (2:1) NIS (1.91 mg, 7.89 mmol) was added. The resulting mixture was stirred at 50 °C for 12 h. The residue was then taken up in ethyl acetate, washed successively with 10% Na2S2O3, water and brine, dried over MgSO4 filtered and dried in vacuo. The crude product was re-dissolved in DCM (20 mL) and treated with Et3N (3 mL), a catalytic amount of DMAP and Ac2O (3 mL) and the resulting solution was then stirred at room temperature. After 30 min, the reaction mixture was diluted with DCM, washed successively with water and brine and then dried over MgSO4. The crude product was purified by column chromatography (ethyl acetate/petroleum ether, 5:95) to give the title compound.

Yield 3.4 mg, 93%, colorless oil

1H NMR: (CDCl3, 400 MHz): δH 7.40 – 7.10 (m, 15H, Ar), 6.32 (s, 1H, H-1), 4.78 (d, J = 10.8 Hz, 1H, -CH2Ph), 4.70 – 4.56 (m, 3H, -CH2Ph), 4.53 – 4.40 (m, 2H, -CH2Ph), 4.00 – 3.88 (m, 1H, H-3), 3.83 – 3.55 (m, 5H, H-5, H-4, H-6a, H-6b and H-7a), 3.11 (t, J = 10.8 Hz, 1H, H-7b), 2.60 – 2.45 (m, 1H, H-2), 2.05 (s, 3H, -OCOC2H5);

13C NMR: (CDCl3, 100 MHz): δC 168.9 (OCOCH3), 138.1, 137.9, 128.5, 128.4, 128.0, 127.8, 127.7 (Ar), 93.9 (C-1), 79.1 (C-3), 74.9 (CH2Ph), 73.8 (C-4), 73.5 (CH2Ph), 73.4 (C-5), 72.0 (CH2Ph), 68.5 (C-6), 45.8 (C-2), 21.0 (-OCOCH3), 0.2 (C-7);

[α]D: +13.7°(c 0.5, CHCl3):

IR: 1752, 1496, 1453, 1226, 1096, 1026, 954, 735, 695.3 cm⁻¹ (neat):


(Spectroscopic data is in agreement with reported values).5

7.2.3 General procedure for the synthesis of arylthiomethyl mannosyl acetate
163a-e

To a solution of arylthiol (3.60 mmol) in DMF (20 mL), sodium hydride (60% dispersion in oil, 87.03 mg, 3 mmol) was added and the mixture was vigorously stirred at room temperature for 5-10 minutes under nitrogen. A solution of iodoacetate 162 (2 g, 3 mmol) in DMF (4 mL) was then added and after 5 minutes of stirring of the reaction mixture, methanol (3 mL) was
added drop wise and the resulting clear solution was concentrated under reduced pressure. The
solution was subjected to silica gel chromatography (ethyl acetate/petroleum ether, 2:8) to give
the corresponding sulfides:

1-O-Acetyl-3,4,6-tri-O-benzyl-2-deoxy-2-C-phenylthiomethyl-α-D-mannopyranosyl
(163a):

![163a](image)

Yield: 1.7 g, 94%, colorless oil

1H NMR: (CDCl₃, 400 MHz): δH 7.50 – 7.10 (m, 20H, Ar), 6.44 (s, 1H, H-1), 4.83 (d, J
= 10.4 Hz, 1H, -CH₂Ph), 4.64 (d, J = 12.0 Hz, 1H, -CH₂Ph), 4.55 – 4.35 (m, 4H,
-CH₂Ph), 4.10 – 3.96 (m, 1H, H-3), 3.88 – 3.72 (m, 3H, H-5, H-4 and H-6a),
3.65 (d, J = 10.4 Hz, 1H, H-6a), 3.52 (d, J = 14.0 Hz, 1H, H-7a), 2.90 – 2.78 (m,
1H, H-7b), 2.45 – 2.30 (m, 1H, H-2), 2.04 (s, 3H, -OCOCH₃);

13C NMR: (CDCl₃, 100 MHz): δC 169.0 (-OCOCH₃), 138.1, 138.0 , 137.9, 135.5, 130.2,
128.9, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.5, 126.4 (Ar), 93.3 (C-1),
78.3 (C-3), 75.0 (-CH₂Ph), 73.9 (C-4), 73.6 (-CH₂Ph), 73.5 (-CH₂Ph), 71.8 (C-
5), 68.5 (C-6), 41.7 (C-2), 29.7 (C-7), 21.0 (-OCOCH₃); (spectroscopic data is
in agreement with reported values).⁴

[α]D: +49.6 (c 0.5, CHCl₃)

IR: 1749, 1496, 1454, 1363, 1096, 1025, 695 cm⁻¹; (neat)

HRMS (ESI): m/z [M+Na]⁺ Calcd 621.2287; found 621.2287.
1-O-Acetyl-3,4,6-tri-O-benzyl-2-deoxy-2-C-(4-methylphenyl)thiomethyl-α-D-mannopyranosyl (163b):

Yield: 1.4 g, 78%; colorless oil

\(^1\)H NMR: (CDCl\textsubscript{3}, 400 MHz): \(\delta_H\) 7.45 – 6.95 (m, 19H, Ar), 6.43 (s, 1H, H-1), 4.81 (d, \(J = 10.8\) Hz, 1H, -CH\textsubscript{2}Ph), 4.62 (d, \(J = 12.4\) Hz, 1H, -CH\textsubscript{2}Ph), 4.60 – 4.30 (m, 4H, -CH\textsubscript{2}Ph), 4.01 – 3.90 (m, 1H, H-3), 3.85 – 3.55 (m, 4H, H-5, H-4, H-6\textsubscript{a} and H-6\textsubscript{b}), 2.80 – 2.72 (m, 1H, H-7\textsubscript{a}), 2.40 – 2.23 (m, 4H, H-2 and -CC\textsubscript{6}H\textsubscript{3}), 2.02 (s, 3H, -OCOC\textsubscript{6}H\textsubscript{3});

\(^13\)C NMR: (CDCl\textsubscript{3}, 100 MHz): \(\delta_C\) 169.0 (-OCOCH\textsubscript{3}), 138.2, 138.1, 137.9, 136.7, 131.7, 131.2, 129.8, 128.4, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.5 (Ar), 93.4 (C-1), 78.3 (C-3), 75.0 (-CH\textsubscript{2}Ph), 73.9 (C-4), 73.6 (-CH\textsubscript{2}Ph), 73.5 (-CH\textsubscript{2}Ph), 71.5 (C-5), 68.6 (C-6), 41.6 (C-2), 30.5 (C-7), 21.1 (-CCH\textsubscript{3}), 21.0 (-OCOCH\textsubscript{3}); (spectroscopic data is in agreement with reported values).\(^4\)

\([\alpha]_D\): +19.9 \((c 0.5, \text{CHCl}_3)\)

IR: 1749, 1494, 1454, 1367, 1094, 1026, 697 cm\textsuperscript{-1} (neat)

HRMS (ESI): \(m/z\) [M+Na\textsuperscript{+}] Calcd 635.2443; found 635.2446.

1-O-Acetyl-3,4,6-tri-O-benzyl-2-deoxy-2-C-(2-methylphenyl)thiomethyl-α-D-mannopyranosyl (163c):
Yield: 1.7 g, 90%; colorless oil

1H NMR: (CDCl₃, 400 MHz): δH 7.50 – 6.90 (m, 19H, Ar), 6.45 (s, 1H, H-1), 4.83 (d, J = 10.4 Hz, 1H, -CH₂Ph), 4.63 (d, J = 12.0 Hz, 1H, -CH₂Ph), 4.60 – 4.35 (m, 4H, -CH₂Ph), 4.10 – 3.94 (m, 1H, H-3), 3.90 – 3.70 (m, 3H, H-4, H-5 and H-6a), 3.64 (d, J = 10.0 Hz, 1H, H-6b), 3.48 (d, J = 13.2 Hz, 1H, H-7a), 2.88 – 2.76 (m, 1H, H-7b), 2.45 – 2.20 (m, 4H, H-2 and -CH₃), 2.03 (s, 3H, -COCH₃);

13C NMR: (CDCl₃, 100 MHz): δC 169.0 (-OCOCH₃), 138.6, 138.1, 138.0, 137.9, 134.7, 130.3, 129.2, 128.4, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 126.4, 126.2 (Ar), 93.3 (C-1), 78.4 (C-3), 75.1 (-CH₂Ph), 74.0 (C-4), 73.6 (-CH₂Ph), 73.5 (-CH₂Ph), 71.8 (C-5), 68.5 (C-6), 41.6 (C-2), 28.7 (C-7), 21.1 (-CH₃), 20.4 (-OCOCH₃); (spectroscopic data is in agreement with reported values).  

[α]D: +23.0 (c 0.5, CHCl₃)

IR: 1749, 1496, 1454, 1366, 1098, 1026, 697 cm⁻¹ (neat)

HRMS (ESI): m/z [M+Na]⁺ Calcd 635.2443; found 635.2438.

1-O-Acetyl-3,4,6-tri-O-benzyl-2-deoxy-2-C-(4-tert-butylphenyl)thiomethyl-α-D-mannopyranosyl (163d):

Yield: 1.7 g, 89%; colorless oil

1H NMR: (CDCl₃, 400 MHz): δH 7.45 – 7.05 (m, 19H, Ar), 6.42 (s, 1H, H-1), 4.82 (d, J = 10.4 Hz, 1H, -CH₂Ph), 4.62 (d, J = 12.0 Hz, 1H, -CH₂Ph), 4.55 – 4.30 (m, 4H, -CH₂Ph), 4.04 – 3.91 (m, 1H, H-3), 3.85 – 3.72 (m, 3H, H-4 and H-6a), 3.64 (d, J = 10.4 Hz, 1H, H-6b), 3.46 (d, J = 14.0 Hz, 1H, H-7a), 2.81 – 2.75 (m, 1H, H-7b), 2.45 – 2.25 (m, 1H, H-2), 2.03 (s, 3H, -COCH₃), 1.27 (s, 9H, -CC(CH₃)₃);
**13C NMR:** (CDCl₃, 100 MHz): δC 169.0 (-OCOCH₃), 149.8, 138.2, 138.1, 137.9, 132.0, 130.5, 128.4, 128.4, 128.0, 127.8, 127.7, 127.7, 127.6, 127.6, 126.0 (Ar), 93.4 (C-1), 78.3 (C-3), 75.0 (-CH₂Ph), 73.9 (C-4), 73.6 (-CH₂Ph), 73.5 (-CH₂Ph), 71.5 (C-5), 68.6 (C-6), 41.7 (C-2), 34.4 (-CC(CH₃)₃), 31.2 (-CC(CH₃)₃), 30.2 (C-7), 21.1 (-OCOCH₃); (spectroscopic data is in agreement with reported values).⁴

[α]D: +25.8 (c 0.5, CHCl₃)

IR: 1750, 1496, 1454, 1364, 1099, 1025, 697, cm⁻¹ (neat)

HRMS (ESI): m/z [M+Na]⁺ Calcd 677.2913; found 677.2910.

1-O-Acetyl-3,4,6-tri-O-benzyl-2-deoxy-2-C-(4-methoxyphenyl)thiomethyl-α-D-mannopyranosyl (163e):

![Structure of 163e](image)

Yield 1.4 g, 76%; colorless oil

**1H NMR:** (CDCl₃, 400 MHz); δH 7.50 – 7.05 (m, 17H, Ar), 6.79 (d, J = 8.4 Hz, 2H, Ar), 6.45 (s, 1H, H-1), 4.80 (d, J = 10.8 Hz, 1H, -CH₂Ph), 4.61 (d, J = 12.0 Hz, 1H, -CH₂Ph), 4.60 – 4.47 (m, 2H, -CH₂Ph), 4.35 (d, J = 11.4 Hz, 1H, -CH₂Ph), 4.26 (d, J = 11.4 Hz, 1H, -CH₂Ph), 4.05 – 3.90 (m, 1H, H-3), 3.85 – 3.70 (m, 6H, H-5, H-4, -COCH₃ and H-6a), 3.63 (d, J = 10.4 Hz, 1H, H-6b), 3.34 (d, J = 14.0 Hz, 1H, H-7a), 2.84 – 2.62 (m, 1H, H-7b), 2.36 – 2.24 (m, 1H, H-2), 2.03 (s, 3H, -OCOCH₃);

**13C NMR:** (CDCl₃, 100 MHz); δC 169.0 (-OCOCH₃), 159.2, 138.1, 138.1, 137.9, 134.2, 128.4, 128.4, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 127.6, 127.5, 125.6, 114.6 (Ar), 93.4 (C-1), 78.3 (C-3), 75.1 (-CH₂Ph), 73.9 (C-4), 73.6 (-CH₂Ph), 73.5 (-CH₂Ph), 71.2 (C-5), 68.6 (C-6), 55.3 (-COCH₃), 41.3 (C-2), 31.7
(C-7), 21.0 (-OCOCH3); (spectroscopic data is in agreement with reported values).4

[α]D: +12.0 (c 0.5, CHCl3)

IR: 1746, 1591, 1493, 1454, 1366, 1096, 1026, 697 cm⁻¹ (neat)

HRMS (ESI): m/z [M+Na]+ Calcd 651.2392; found 651.2394.

7.2.4 General procedure for the synthesis of the β-1,2-aryl-C-mannoside-thiochroman (164a-e)

Sulfide 163 (2 mmol) was dissolved in dry dichloromethane (3 mL) under an atmosphere of nitrogen and stirred together with 4Å molecular sieves at room temperature for 1 h. The mixture was cooled down to 0 °C and BF3·Et2O (2.90 mL of 48% BF3 solution in diethyl ether, 23.29 mmol) was added drop-wise. After stirring at this temperature for 5 min, Et3N (2 mL) was added and the solids removed by filtration through a celite® bed. The solution was then diluted with water (15 mL) and the aqueous phase was extracted with dichloromethane. The combined organic phases were successively washed with saturated aqueous NaHCO3 solution and brine, dried over MgSO4, filtered and evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 1:9) to yield the corresponding thiochromans:

(2R,3S,4R,4aR,10bR)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-b]pyran (164a):

![164a]

Yield: 753 mg, 70%; white solid

Mp: 87 – 89 °C

1H NMR: (CDCl3, 400 MHz): δH 7.45 – 6.95 (m, 19H, Aromatic), 4.88 (d, J = 10.8 Hz, 1H, CH3H8Ph), 4.75 (d, J = 11.6 Hz, 1H, CH3H8Ph), 4.68 – 4.40 (m, 4H, the
rest of the CH$_2$Ph), 4.35 (s, 1H, H-10b), 4.00 – 3.85 (m, 1H, H-4), 3.80 – 3.55 (m, 4H, H-1’a, H-1’b, H-2 and H-3), 3.26 (t, $J = 12.6$ Hz, 1H, H-7a), 2.96 (bd, $J = 12.4$ Hz, 1H, H-5b), 2.70 – 2.50 (m, 1H, H-4a);

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta$C 138.4, 138.3, 138.0, 134.1, 133.3, 131.2, 128.7, 128.5, 128.3, 127.9, 127.8, 127.7, 127.6, 127.5, 126.4, 124.1 (Aromatic), 82.9 (C-4), 79.9 (C-3), 75.1 (CH$_2$Ph), 74.6 (C-10b), 74.3 (C-5), 73.4 (CH$_2$Ph), 71.3 (CH$_2$Ph), 69.4 (C-1’), 39.0 (C-4a), 21.3 (C-5); (spectroscopic data is in agreement with reported values).$^4$

$[\alpha]_D$: +35.2 (c 0.5, CHCl$_3$)

IR: 1454, 1361, 1075, 1010, 694 cm$^{-1}$(neat)

HRMS (ESI): m/z [M+Na]$^+$ Calcd 539.2256; found 539.2260.

(2$R$,3$S$,4$R$,4a$R$,10b$R$)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-methyl-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-b]pyran (164b):

Yield: 884 mg, 80%; white solid

Mp 101 – 103 °C

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta$H 7.45 – 6.90 (m, 18H, Aromatic), 4.87 (d, $J = 10.8$ Hz, 1H, CH$_3$HbPh), 4.74 (d, $J = 11.6$ Hz, 1H, CH$_3$HsPh), 4.68 – 4.40 (m, 4H, the rest of the CH$_2$Ph), 4.31 (s, 1H, H-10b), 4.00 – 3.85 (m, 1H, H-4), 3.82 – 3.55 (m, 4H, H-1’a, H-1’b, H-2 and H-3), 3.25 (t, $J = 12.6$ Hz, 1H, H-5a), 2.94 (bd, $J = 12.4$ Hz, 1H, H-5b), 2.70 – 2.50 (m, 1H, H-4a), 2.27 (s, 3H, ArCH$_3$);

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta$C 138.3, 138.2, 138.0, 133.8, 130.9, 130.4, 129.8, 128.5, 128.4, 128.3, 128.0, 127.8, 127.7, 127.5, 126.2 (Aromatic), 83.0 (C-4), 79.8 (C-
3), 75.1 (CH₂Ph), 74.5 (C-10b), 74.4 (C-2), 73.4 (CH₂Ph), 71.2 (CH₂Ph), 69.4 (C-1’), 39.1 (C-4a), 21.2 (C-5), 20.7 (ArCH₃); (spectroscopic data is in agreement with reported values).⁴

IR: 1485, 1455, 1369, 1072, 1027, 698 cm⁻¹(neat)

[α]D: +29.9 (c 0.5, CHCl₃)

HRMS (ESI): m/z [M+Na]⁺ Calcd 553.2413; found 553.2422.

(2R,3S,4R,4aR,10bR)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-7-methyl-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-b]pyran (164c):

Yield: 995 mg, 90%; white solid

Mp 82 – 84 °C

¹H NMR: (CDCl₃, 400 MHz); δH 7.50 – 6.90 (m, 18H, Aromatic), 4.88 (d, J = 10.8 Hz, 1H, CH₃HaPh), 4.75 (d, J = 11.6 Hz, 1H, CH₃HaPh), 4.68 – 4.42 (m, 4H, the rest of the CH₂Ph), 4.37 (s, 1H, H-10b), 4.40 – 3.85 (m, 1H, H-4), 3.81 – 3.55 (m, 4H, H-1’a, H-1’n, H-2 and H-3), 3.24 (t, J = 12.8 Hz, 1H, H-5a), 3.03 (bd, J = 12.4 Hz, 1H, H-5b), 2.70 – 2.50 (m, 1H, H-4a), 2.25 (s, 3H, ArCH₃);

¹³C NMR: (CDCl₃, 100 MHz); δC 138.3, 138.2, 138.0, 134.3, 133.4, 131.0, 130.8, 130.0, 128.5, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 123.5 (Aromatic), 82.8 (C-3), 79.8 (C-3), 75.1 (CH₂Ph), 74.7 (C-10b), 74.5 (C-2), 73.4 (CH₂Ph), 71.2 (CH₂Ph), 69.4 (C-1’), 38.5 (C-4a), 21.2 (C-5), 19.3 (ArCH₃); (spectroscopic data is in agreement with reported values).⁴

[α]D: +25.2 (c 0.5, CHCl₃);

IR: 1455, 1361, 1072, 1029, 696; cm⁻¹(neat,)
HRMS (ESI): $m/z$ [M+Na]$^+$ Calcd 553.2413; found 553.2411.

$\left(2R,3S,4R,4aR,10bR\right)$-$3,4$-bis(benzyloxy)-2-(benzyloxymethyl)$-9$-$tert$-butyl-$2,3,4,4a,5,10b$-hexahydrothiochromeno$[4,3-b]$pyran (164d):

Yield: 808 mg, 68%; white solid

Mp 83 – 84 °C

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta$H 7.50 – 7.00 (m, 18H, Aromatic), 4.91 (d, $J = 10.4$ Hz, 1H, CH$_2$H$_3$Ph), 4.77 (d, $J = 11.6$ Hz, 1H, CH$_2$H$_3$Ph), 4.70 – 4.45 (m, 4H, the rest of the CH$_2$Ph), 4.37 (s, 1H, H-10b), 4.00 – 3.60 (m, 5H, H-3, H-1’a, H-1’b, H-5 and H-3), 3.29 (t, $J = 12.6$ Hz, 1H, H-5a), 2.98 (bd, $J = 12.4$ Hz, 1H, H-5b), 2.70 – 2.50 (m, 1H, H-4a), 1.31 (s, 9H, (ArC(CH$_3$)$_3$);

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta$C 147.1, 138.3, 138.3, 138.0, 130.6, 130.6, 130.0, 128.4, 128.3, 128.2, 128.0, 127.7, 127.7, 127.7, 127.6, 127.4, 126.3, 126.0 (Aromatic), 83.0 (C-4), 79.9 (C-3), 75.1 (CH$_2$Ph), 74.6 (C-10b), 74.6 (C-2), 73.4 (CH$_2$Ph), 71.2 (CH$_2$Ph), 69.4 (C-1’), 39.2 (C-4a), 34.2 (ArC(CH$_3$)$_3$), 31.2 (ArC(CH$_3$)$_3$), 21.2 (C-5); (spectroscopic data is in agreement with reported values).

$\left[\alpha\right]_D$: $+32.4$ (c 0.5, CHCl$_3$)

IR: 1454, 1361, 1072 1030, 696 cm$^{-1}$(neat)

HRMS (ESI): $m/z$ [M+Na]$^+$ Calcd 595.2882; found 595.2888.

$\left(2R,3S,4R,4aR,10bR\right)$-$3,4$-bis(benzyloxy)-2-(benzyloxymethyl)$-9$-methoxy-$2,3,4,4a,5,10b$-hexahydrothiochromeno$[4,3-b]$pyran (164e):
Yield: 1 g, 90%; yellow solid

Mp 106 – 108 °C

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta$H 7.50 – 7.10 (m, 15H, Aromatic), 7.03 (d, $J = 8.8$ Hz, 1H, Aromatic), 6.86 (s, 1H, Aromatic) 6.78 (d, $J = 8.4$ Hz, 1H, Aromatic), 4.87 (d, $J = 10.4$ Hz, 1H, CH$_3$H$_2$Ph), 4.75 (d, $J = 11.6$ Hz, 1H, CH$_3$H$_2$Ph), 4.68 – 4.40 (m, 4H, the rest of the CH$_2$Ph), 4.32 (s, 1H, H-10b), 4.00 – 3.55 (m, 8H, H-4, ArOCH$_3$, H-1’a, H-1’b, H-2 and H-3), 3.24 (t, $J = 12.6$ Hz, 1H, H-5a), 2.94 (bd, $J = 12.4$ Hz, 1H, H-5b), 2.70 – 2.50 (m, 1H, H-4a);

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta$C 156.7, 138.3, 138.2, 138.0, 132.0, 128.5, 128.3, 128.3, 128.0, 127.8, 127.7, 127.5, 127.3, 124.8, 117.6, 116.2 (Aromatic), 82.9 (C-4), 79.9 (C-3), 75.1 (CH$_2$Ph), 74.5 (C-10b and C-2), 73.4 (CH$_2$Ph), 71.2 (CH$_2$Ph), 69.4 (C-1’), 55.4 (ArOCH$_3$), 39.3 (C-4a), 21.3 (C-5); (spectroscopic data is in agreement with reported values).4

$\alpha$D: $+30.5$ (c 0.5, CHCl$_3$)

IR: 1483, 1454, 1369, 1062, 1028, 698 cm$^{-1}$ (neat)

HRMS (ESI): $m/z$ [M+Na]$^+$ Calcd 569.2362; found 569.2357

7.2.5 General procedure for the synthesis of thiochroman sulfoxide derivatives 167a-e and 168a-e

To a vigorously stirring suspension of wet alumina (1.11 g wetted with 117 µL of water) and OXONE® (332 mg, 0.54 mmol) in DCM (5 mL) was added thiochroman 158 or thiochroman 164 (0.54 mmol). After 3 h of stirring at room temperature, the adsorbent was filtered over a
celite bed and washed several times with DCM. The filtrate was evaporated in under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane, 4:6) to give the corresponding diastereomeric sulfoxides:

\[
(2R,3S,4R,4aS,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (167a first diastereomer):
\]

Yield: 110.9 mg, 40%; white solid

Mp 103 – 105°C

\(^1\)H NMR: (400 MHz, CDCl\(_3\)): \(\delta_{H}:\) 7.84 (d, \(J = 7.2\) Hz, 1H, \(Ar\)), 7.71 (d, \(J = 7.6\) Hz, 1H, \(Ar\)), 7.60 – 7.44 (m, 2H, \(Ar\)), 7.42 – 7.07 (15H, \(Ar\)), 5.04 (d, \(J = 5.6\) Hz, 1H, H-10b), 4.96 (d, \(J = 10.4\) Hz, 1H, -CH\(_2\)Ph), 4.85 – 4.72 (m, 2H, -CH\(_2\)Ph), 4.65 (d, 
\(J = 12.0\) Hz, 1H, -CH\(_3\)Ph), 4.61 – 4.48 (m, 2H, -CH\(_3\)Ph), 4.21 (dd, \(J = 7.6\) and 10.0 Hz, 1H, H-4), 3.82 – 3.60 (m, 5H, H-4, H-2, H-1’a, H-1’b, H-5a), 3.09 (dd, 
\(J = 3.8\) and 14.6 Hz, 1H, H-5b), 2.72 – 2.60 (m, 1H, H-4a);

\(^{13}\)C NMR: (100 MHz, CDCl\(_3\)): \(\delta_{C}:\) 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-3), 78.9 (C-4), 74.2 (C-2, -CH\(_3\)Ph), 73.9, 73.5 (-CH\(_3\)Ph), 71.2 (C-10b), 68.8 (C-1’), 44.8 (C-5), 35.8 (C-4a).

\([\alpha]_D:\) +84.0 (c 0.1, CHCl\(_3\))

IR: 1454, 1090, 1025, 734, 695 cm\(^{-1}\) (neat)

HRMS (ESI-TOF) \(m/z:\) [M + H]\(^+\) Calcd for C\(_{34}\)H\(_{35}\)O\(_5\)S 555.2205; Found: 555.2207.

\[
(2R,3S,4R,4aS,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (167a second diastereomer):
\]
Yield: 74.9 mg, 27%; white solid

Mp 68 – 70 ºC

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta$: 7.76 (d, $J = 7.2$ Hz, 1H, Ar), 7.58 – 7.43 (m, 3H, Ar), 7.40 – 7.12 (m, 15H, Ar), 5.17 (d, $J = 4.4$ Hz, 1H, H-10b), 4.79 – 4.50 (m, 6H, CH$_2$Ph), 3.94 – 3.84 (m, 2H, H-1’a and H-5a), 3.82 – 3.71 (m, 2H, H-1’b and H-2), 3.70 – 3.58 (m, 2H, H-4 and H-3), 3.06 – 2.96 (m, 2H, H-4a and H-5b);

$^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$: 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-3), 76.6 (C-4), 74.1 (C-2), 74.0, 73.5, 73.4 (CH$_2$Ph), 68.8 (C-10b), 68.0 (C-1’), 46.7 (C-5), 34.9 (C-4a).

$[\alpha]_{D}$: -4.0 (c 0.1, CHCl$_3$)

IR: 1454, 1049, 1024, 730, 696 cm$^{-1}$(neat)

HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{34}$H$_{35}$O$_5$S 555.2205; 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 (167b first diastereomer):

\[ \text{Yield: 135.1 mg, 44%; white solid} \]

Mp 103 – 105 ºC

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta$: 7.72 (d, $J = 8.0$ Hz, 1H, Ar), 7.53 (s, 1H, Ar), 7.41 – 7.10 (m, 16H, Ar), 5.04 – 4.97 (m, 2H, H-1 and -CH$_2$Ph), 4.78 (d, $J = 10.8$ Hz, 1H, -CH$_2$Ph), 4.66 (d, $J = 12.0$ Hz, 1H, -CH$_2$Ph), 4.61 – 4.50 (m, 2H, -CH$_2$Ph), 4.26 (t, $J = 9.2$ Hz, 1H, H-4), 3.81 – 3.59 (m, 5H, H-3, H-2, H-1’a, H-1’b, H-5a),
3.04 (dd, $J = 3.6$ Hz and 14.8 Hz, 1H, H-5b), 2.70 – 2.59 (m, 1H, H-2), 2.37 (s, 3H, -CCH3);

$^{13}$C NMR: (100 MHz, CDCl3) δC: 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-3), 78.8 (C-4), 74.2 (C-2, -CH2Ph), 73.8, 73.4 (-CH2Ph), 71.4 (C-10b), 67.0 (C-1’), 44.6 (C-5), 35.9 (C-4a), 21.6 (CCH3).

[α]D: -9.0 (c 0.1, CHCl3)

IR: 1077, 1049, 740, 695 cm$^{-1}$ (neat)

HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{35}$H$_{37}$O$_5$S 569.2362; Found: 569.2354.

(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 (167b second diastereomer):

Yield: 73.7 mg, 24%; white solid

Mp 104 – 106 ℃

$^1$H NMR: (400 MHz, CDCl3) δH: 7.63 (d, $J = 8.0$ Hz, 1H, Ar), 7.42 – 7.13 (m, 15H, Ar), 5.11 (bs, 1H, H-10b), 4.78 – 4.50 (m, 6H, -CH2Ph), 4.00 – 3.73 (m, 4H, H-2, H-1’a, H-1’B, H-5a), 3.69 – 3.59 (m, 2H, H-4 and H-2), 3.10 – 2.95 (m, 2H, H-4a, H-5b), 2.36 (s, 3H, -CCH3);

$^{13}$C NMR: (100 MHz, CDCl3) δC: 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, -CH2Ph), 73.8, 73.3 (-CH2Ph), 68.2 (C-10b), 68.0 (C-1’), 46.4 (C-5), 33.9 (C-2), 21.4 (-CCH3).

[α]D: -11.5 (c 0.1, CHCl3)

IR: 1454, 1049, 1026, 731, 696 cm$^{-1}$ (neat)

HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{35}$H$_{37}$O$_5$S 569.2362; Found: 569.2363.

(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 (167c first diastereomer):
Yield: 154.7 mg, 49%; white solid

Mp 106 – 108 °C

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta$: 7.73 (d, $J = 8.4$ Hz, 1H, Ar), 7.48 – 7.10 (m, 16H, Ar), 7.00 (d, $J = 8.4$ Hz, 1H, Ar), 5.11 – 4.99 (m, 2H, H-10b, -CH$_2$Ph), 4.80 (d, $J = 10.4$ Hz, 1H, -CH$_2$Ph), 4.67 – 4.50 (m, 3H, -CH$_2$Ph), 4.37 (t, $J = 9.8$ Hz, 1H, H-4), 3.85 – 3.62 (m, 7H, H-1’a, H-1’b, H-5a, H-4’, -OCH$_3$), 3.61 – 3.50 (m, 1H, H-2), 2.99 (dd, 1H, $J = 3.2$ Hz and 14.8 Hz, H-5b), 2.73 – 2.61 (m, 1H, H-4a);

$^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$: 162.8, 139.0, 138.0, 137.9, 134.5, 133.6, 130.6, 128.4, 128.3, 128.0, 127.0, 127.5, 127.4, 115.8, 111.4 (Ar), 80.3 (C-3), 78.6 (C-4), 74.4 (C-5), 74.3, 73.8, 73.6 (-CH$_2$Ph), 72.1 (C-10b), 69.3 (C-1’), 55.4 (-OCH$_3$), 44.1 (C-5), 36.1 (C-4a).

[$\alpha$]$_D$: -1.0 (c 0.1, CHCl$_3$)

IR: 1596, 1071, 1022, 735, 697 cm$^{-1}$ (neat)

HRMS (ESI-TOF) $m/z$: [M + H]$^+$ Calcd for C$_{35}$H$_{37}$O$_6$S 585.2311; Found: 585.2302.

$(2R,3S,4R,4aS,10bS)-3,4$-bis(benzyloxy)-2-(benzyloxymethyl)-9-methoxy-2,3,4,4a,5,10b-hexahydro-$S$-oxothiochromeno[4,3-b]pyran (167c second diastereomer):

Yield: 79.8 mg, 23%; colorless oil

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta$: 7.66 (d, $J = 8.4$ Hz, 1H, Ar), 7.50 – 7.12 (m, 15H, Ar), 7.05 (d, $J = 2.0$ Hz, 1H, Ar), 6.97 (dd, $J = 2.4$ Hz and 8.8 Hz, 1H, Ar), 5.14 (d, $J = 4.0$ Hz, 1H, H-10b), 4.80 – 4.50 (m, 6H, -CH$_2$Ph), 3.93 – 3.70 (m, 7H, H-2,
H-1’, H-1'b, H-5a, OCH₃), 3.65 – 3.52 (m, 2H, H-3 and H-4), 3.06 – 2.92 (m, 2H, H-2 and H-5b);

¹³C NMR: (100 MHz, CDCl₃) δC: 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-4), 74.2 (C-2), 74.0, 73.5, 73.4 (-CH₂Ph), 68.8 (C-10b), 68.3 (C-1’), 55.5 (-OCH₃), 46.8 (C-5), 34.7 (C-4a).

IR: 1594, 1083, 1018, 738, 697 cm⁻¹ (neat)

[α]D: +91.5 (c 0.1, CHCl₃)

HRMS (ESI-TOF) m/z: [M + H]^+ Calcd for C₃₅H₃₇O₆S 585.2311; 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 (167d first diastereomer):

Yield: 128.6 mg, 39%; white solid

Mp 113 – 115 °C

¹¹H NMR: (400 MHz, CDCl₃) δH: 7.70 (s, 1H, Ar), 7.65 (d, J = 8.4 Hz, 1H, Ar), 7.40 (dd, J = 1.6 Hz and 8.4 Hz, 1H, Ar), 7.35 – 7.08 (m, 13H, Ar), 7.05 – 6.95 (m, 2H, Ar), 5.00 – 4.88 (m, 2H, H-10b, -CH₂Ph), 4.78 – 4.63 (m, 2H, -CH₂Ph), 4.54 (d, J = 12.0 Hz, 1H, -CH₂Ph), 4.46 (d, J = 12.0 Hz, 1H, -CH₂Ph), 4.38 (d, J = 11.2 Hz, 1H, -CH₂Ph), 4.20 (dd, J = 8.4 Hz and 10.8 Hz, 1H, H-4), 3.70 – 3.40 (m, 5H, H-5a, H-1’a, H-1’b, H-2, H-3), 2.92 (dd, J = 3.8 Hz and 15.0 Hz, 1H, H-5b), 2.65 – 2.50 (m, 1H, H-4a); 1.19 (s, 9H, C(CH₃)₃);
$^{13}$C NMR: (100 MHz, CDCl₃) δC: 156.0, 138.9, 137.8, 135.8, 132.2, 131.4, 128.0, 127.7, 127.6, 127.5, 126.3, 124.3 (Ar), 80.2 (C-4), 78.6 (C-3), 74.5, 74.3, 73.7 (-CH₂Ph), 73.6 (C-2), (C-5, -CH₂Ph) 72.0 (-CH₂Ph), 69.0 (C-1'), 44.2 (C-5), 36.1 (C-4a), 35.1 (C(CH₃)₃), 31.0 (C(CH₃)₃).

IR: 1453, 1064, 735, 696 cm⁻¹ (neat)

[$\alpha$]D: -0.5 (c 0.1, CHCl₃)

HRMS (ESI-TOF) m/z: [M + H]⁺ Calcd for C₃₈H₄₃O₅S 611.2831; Found: 611.2821.

(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 (167d second diastereomer):

Yield: 108.8 mg, 33%; white solid

Mp: 115 – 117 °C

$^1$H NMR: (400 MHz, CDCl₃) δH: 7.68 (d, J = 8.0 Hz, 1H, Ar), 7.59 (s, 1H, Ar), 7.48 (dd, J = 1.6 Hz and 8.0 Hz, 1H, Ar), 7.41 – 7.10 (m, 15H, Ar), 5.19 (d, J = 4.4 Hz, 1H, H-10b), 4.80 – 4.49 (m, 6H, CH₂Ph), 3.85 – 3.85 (m, 2H, H-5a and H-1′a), 3.70 (m, 2H, H-5b and H-4a), 1.28 (s, 9H, C(CH₃)₃);

$^{13}$C NMR: (100 MHz, CDCl₃) δC: 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), 78.5 (C-3), 77.0 (C-4), 74.1 (C-2, CH₂Ph), 73.7, 73.5 (2x CH₂Ph), 69.2 (C-10b), 68.4 (C-1′c), 46.9 (C-5), 35.4 (C(CH₃)₃), 35.0 (C-4a), 31.0 (C(CH₃)₃).

IR: 1455, 1085, 1039, 749, 695 cm⁻¹ (neat)

[$\alpha$]D: +72.5 (c 0.1, CHCl₃)

HRMS (ESI-TOF) m/z: [M + H]⁺ Calcd for C₃₈H₄₃O₅S 611.2831; Found: 611.2835.

(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 (167e first diastereomer):

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Yield: 132.1 mg, 43%; white solid;

Mp 99 – 101 °C

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

$^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$: 141.4, 139.1, 138.1, 137.9, 136.5, 135.5, 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-3), 78.3 (C-4), 74.4, 74.3, 73.5 (-CH$_2$Ph), 73.4 (C-2), 72.9 (C-10b), 68.8 (C-1’), 43.0 (C-5), 35.3 (C-4a), 19.4 (-CCH$_3$).

IR: 1594, 1070, 736, 697 cm$^{-1}$ (neat)

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

HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{35}$H$_{37}$O$_5$S 569.2362; Found: 569.2362.

(2$R$3$S$,4$R$,4a$S$,10b$S$)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-7-methyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (167e second diastereomer):

Yield: 86 mg, 28%; colorless oil

$^1$H NMR: 7.65 (d, $J = 7.6$ Hz, 1H, Ar), 7.50 – 7.06 (17H, Ar), 5.10 (d, $J = 10.4$ Hz, 1H, CH$_2$Ph), 5.04 (d, $J = 6.0$ Hz, 1H, H-10b), 4.87 – 4.76 (m, 2H, CH$_2$Ph), 4.66 (d, $J = 12.0$ Hz, 1H, CH$_2$Ph), 4.58 – 4.45 (m, 3H, CH$_2$Ph and H-4), 3.84 (dd, $J = 15.2$ Hz and 3.6 Hz, 1H, H-5a), 3.75 – 3.68 (m, 2H, H-1’a and H-1’b), 3.72 (t, $J$
= 2.0 Hz, 1H, H-3), 3.58 – 3.50 (m, 1H, H-2), 2.94 (dd, \( J = 15.0 \) Hz and 3.8 Hz, 1H, H-5b), 2.85 – 2.60 (m, 4H, CHCH₂, H-4a)

\( ^{13}C \) NMR: (100 MHz, CDCl₃) \( \delta \)c 141.4, 139.2, 138.2, 138.0, 133.9, 132.2, 131.2, 128.4, 128.3, 128.1, 127.8, 127.7, 127.5, 127.4, 127.3, 124.9 (Ar), 80.7 (C-3), 78.3 (C-4), 74.4 (C-2), 74.3, 73.5 (3x CH₂Ph), 72.9 (C-10b), 68.9 (C-1’), 43.1 (C-5), 35.3 (C-4a), 19.4 (CCH₃).

IR: 1453, 1089, 1028, 730, 695 cm⁻¹ (neat)
[\( \alpha \)]D: -24.0 (c 0.1, CHCl₃)

HRMS (ES+ - TOF) m/z: [M + H]+ Calcd for C₃₅H₃₇O₅S 569.2362; Found: 569.2364.

(2R, 3S, 4R, 4aR, 10bR)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (168a first diastereomer):

Yield: 134.8 mg, 45%; colorless oil

\( ^{1}H \) NMR: (CDCl₃, 400 MHz): \( \delta \)H 7.75 (d, \( J = 7.2 \) Hz, 1H, Ar), 7.65 – 7.00 (m, 18H, Ar), 4.91 (d, \( J = 10.8 \) Hz, 1H, CH₂Ph), 4.80 (d, \( J = 11.6 \) Hz, 1H, CH₂Ph), 4.65 – 4.30 (m, 5H, 4x CH₂Ph and H-10b), 4.10 – 3.90 (m, 1H, H-4), 3.80 – 3.50 (m, 5H, H-1’a, H-1’b, H-2, H-3, and H-4a), 3.36 (d, \( J = 13.2 \) Hz, 1H, H-5a), 3.15 (t, \( J = 13.0 \) Hz, 1H, H-5b);

\( ^{13}C \) NMR: (CDCl₃, 100 MHz): \( \delta \)c 137.6, 133.4, 132.7, 132.3, 131.6, 130.0, 128.5, 128.4, 128.3, 128.0, 128.0, 127.8, 127.7, 127.6 (Ar), 81.0 (C-4), 79.8 (C-2), 75.2 (CH₂Ph), 74.5 (C-3), 73.5 (C-10b), 73.4 (CH₂Ph), 70.8 (CH₂Ph), 69.2 (C-1’), 40.2 (C-5), 28.3 (C-4a).

IR: 1028, 696 cm⁻¹ (neat)
[α]D: -33.5 (c 0.1, CHCl3)

HRMS (ESI-TOF) m/z: [M + H]+ Calcd for C34H35O5S 555.2205; Found 555.2200.

(2R,3S,4R,4aR,10bR)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (168a second diastereomer):

Yield: 59.9 mg, 20%; white solid
Mp 115 – 117 °C

1H NMR: (CDCl3, 400 MHz): δH 7.85 (d, J = 7.6 Hz, 1H, Ar), 7.70 – 7.00 (m, 18H, Ar), 4.86 (d, J = 10.8 Hz, 1H, CH2Ph), 4.70 (s, 2H, CH2Ph), 4.60 – 4.30 (m, 4H, 3x CH2Ph and H-10b), 4.00 – 3.50 (m, 6H, H-3, H-1’a, H-1’b, H-5a, H-3 and H-2), 3.40 – 3.20 (m, 1H, H-5b), 2.60 – 2.40 (m, 1H, H-4a);

13C NMR: (CDCl3, 100 MHz): δC 142.5, 138.1, 138.1, 137.7, 133.6, 131.8, 130.6, 130.0, 128.6, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6, 127.0 (Ar), 81.5 (C-4), 80.4 (C-3), 75.2 (CH2Ph), 74.6 (C-2), 73.6 (C-10b), 73.5 (CH2Ph), 72.1 (CH2Ph), 69.2 (C-1’), 42.3 (C-5), 34.4 (C-4a).

IR: 1026, 695 cm⁻¹ (neat)
[α]D: +24.5 (c 0.1, CHCl3)

HRMS (ESI-TOF) m/z: [M + H]+ Calcd for C34H35O5S 555.2205; Found 555.2205.

(2R,3S,4R,4aR,10bR)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-methyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (168b first diastereomer):

Yield: 153.6 mg, 50%, colorless oil
$^1$H NMR: (CDCl$_3$, 400 MHz) $\delta$H: 7.62 (d, $J = 8.4$ Hz, 1H, Ar), 7.50 – 7.00 (m, 17H, Ar), 4.91 (d, $J = 10.8$ Hz, 1H, CH$_2$Ph), 4.81 (d, $J = 11.2$ Hz, 1H, CH$_2$Ph), 4.65 – 4.35 (m, 5H, 4x CH$_2$Ph and H-10b), 4.10 – 3.90 (m, 1H, H-4), 3.80 – 3.50 (m, 5H, H-1’, H-1’b, H-2, H-3, and H-4a), 3.36 (d, $J = 13.6$ Hz, 1H, H-5a), 3.11 (t, $J = 13.0$ Hz, 1H, H-5b), 2.39 (s, 3H, CCH$_3$);

$^{13}$C NMR: (CDCl$_3$, 100 MHz) $\delta$C: 143.0, 138.3, 138.1, 137.6, 134.7, 133.3, 133.2, 131.6, 130.7, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6 (Ar), 81.1 (C-4), 79.8 (C-2), 75.2 (CH$_2$Ph), 74.6 (C-3), 73.5 (C-10b), 73.4 (CH$_2$Ph), 70.7 (CH$_2$Ph), 69.3 (C-1’), 40.1 (C-5), 28.2 (C-4a), 21.4 (CCH$_3$).

IR: 1027, 695 cm$^{-1}$(neat)

[$\alpha$]D: -20 (c 0.1, CHCl$_3$)

HRMS (ESI-TOF) $m/z$: [M + H]$^+$ Calcd for C$_{35}$H$_{37}$O$_5$S 569.2362; Found 569.2365.

(2R,3S,4R,4aR,10bR)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-methyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (168b second diastereomer):

Yield: 67.6 mg, 22%; white solid

Mp 99 – 101 °C

$^1$H NMR: (CDCl$_3$, 400 MHz) $\delta$H: 7.75 (d, $J = 8.0$ Hz, 1H, Ar), 7.50 – 7.10 (m, 17H, Ar), 4.88 (d, $J = 10.8$ Hz, 1H, CH$_2$Ph), 4.73 (s, 2H, CH$_2$Ph), 4.65 – 4.42 (m, 3H, CH$_2$Ph), 4.37 (s, 1H, H-10b), 3.90 – 3.50 (m, 6H, H-4, H-1’a, H-1’b, H-5a, H-3 and H-2), 3.40 – 3.20 (m, 1H, H-5b), 2.60 – 2.43 (m, 1H, H-4a); 2.40 (s, 3H, CCH$_3$);

$^{13}$C NMR: (CDCl$_3$, 100 MHz) $\delta$C: 141.0, 138.5, 138.1, 138.0, 137.7, 133.4, 132.3, 130.9, 128.6, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.0 (Ar), 81.6 (C-4), 80.3 (C-3), 75.2 (CH$_2$Ph), 74.6 (C-5), 73.7 (C-10b), 73.4 (CH$_2$Ph), 72.1 (CH$_2$Ph), 69.2 (C-1’), 42.4 (C-5), 34.5 (C-4a), 21.2 (CCH$_3$).

IR: 1026, 696 cm$^{-1}$(neat)

[$\alpha$]D: +7.5 (c 0.1, CHCl$_3$)
HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{35}$H$_{37}$O$_5$S 569.2362; Found 569.2365

$^{(2R,3S,4R,4aR,10bR)}$-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-methoxy-2,3,4,4a,5,10b-hexahydro-$S$-oxothiochromeno[4,3-b]pyran (168c):

**Yield:** 94.7 mg, 30%; colorless oil

**$^1$H NMR:** (CDCl$_3$, 400 MHz) $\delta$H: 7.59 (d, $J = 8.4$ Hz, 1H, Ar), 7.40 – 7.05 (m, 15H, Ar), 7.00 – 6.80 (m, 2H, Ar), 4.85 (d, $J = 10.8$ Hz, 1H, CH$_2$Ph), 4.74 (d, $J = 11.6$ Hz, 1H, CH$_2$Ph), 4.60 – 4.30 (m, 5H, 4x CH$_2$Ph and H-10b), 4.10 – 3.90 (m, 1H, H-3), 3.85 – 3.45 (m, 8H, OCH$_3$, H-1$'$a, H-1$'$b, H-2, H-3, and H-4a), 3.30 (d, $J = 13.6$ Hz, 1H, H-5a), 3.00 (t, $J = 13.2$ Hz, 1H, H-5b);

**$^{13}$C NMR:** (CDCl$_3$, 100 MHz) $\delta$C: 126.5, 138.2, 138.1, 137.6, 135.3, 133.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 117.6, 115.8, (Ar), 81.0 (C-4), 79.8 (C-2), 75.1 (CH$_2$Ph), 74.5 (C-3), 73.6 (C-10b), 73.4 (CH$_2$Ph), 70.7 (CH$_2$Ph), 69.3 (C-1$'$), 55.6 (OCH$_3$), 40.0 (C-5), 27.9 (C-4a).

**IR:** 1028, 697 cm$^{-1}$(neat)

[α]$_D$: -15.5 (c 0.1, CHCl$_3$)

HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{35}$H$_{37}$O$_6$S 585.2311; Found 585.2313.

$^{(2R,3S,4R,4aR,10bR)}$-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-$t$-butyl-2,3,4,4a,5,10b-hexahydro-$S$-oxothiochromeno[4,3-b]pyran (168d first diastereomer):
Yield: 214.4 mg, 65%; colorless oil

$^1$H NMR: (CDCl$_3$, 400 MHz) δ$_H$: 7.66 (d, $J = 8.0$ Hz, 1H, Ar), 7.60 – 7.10 (m, 17H, Ar), 4.91 (d, $J = 10.8$ Hz, 1H, CH$_2$Ph), 4.80 (d, $J = 11.6$ Hz, 1H, CH$_2$Ph), 4.65 – 4.35 (m, 5H, 4x CH$_2$Ph and H-10b), 4.10 – 3.90 (m, 1H, H-4), 3.80 – 3.50 (m, 5H, H-1’a, H-1’b, H-2, H-3, and H-4a), 3.36 (d, $J = 12.4$ Hz, 1H, H-5a), 3.13 (t, $J = 13.0$ Hz, 1H, H-5b), 1.31 (s, 9H, (C(CH$_3$)$_3$));

$^{13}$C NMR: (CDCl$_3$, 100 MHz) δ$_C$: 156.0, 138.3, 138.1, 137.6, 134.7, 132.9, 131.4, 129.7, 128.5, 128.4, 128.3, 128.0, 128.0, 127.8, 127.7, 127.7, 127.6, 127.3 (Ar), 81.1 (C-4), 79.8 (C-2), 75.2 (CH$_2$Ph), 74.6 (C-3), 73.8 (C-10b), 73.4 (CH$_2$Ph), 70.7 (CH$_3$Ph), 69.2 (C-1’), 40.2 (C-5), 35.1 (C(CH$_3$)$_3$), 31.1 (C(CH$_3$)$_3$), 28.4 (C-4a).

IR: 1051, 683 cm$^{-1}$(neat)

$[\alpha]_D$: -28.5 (c 0.1, CHCl$_3$)

HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{38}$H$_{43}$O$_5$S 611.2831; Found 611.2828.

(2R,3S,4R,4aR,10bR)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-tert-butyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (168d second diastereomer): Yield 82.4 mg, 25%; white solid

Mp 136 – 138 °C

$^1$H NMR: (CDCl$_3$, 400 MHz) δ$_H$: 7.76 (d, $J = 8.4$ Hz, 1H, Ar), 7.60 – 7.10 (m, 17H, Ar), 4.86 (d, $J = 10.8$ Hz, 1H, CH$_2$Ph), 4.70 (s, 2H, CH$_2$Ph), 4.60 – 4.40 (m, 3H, CH$_2$Ph), 4.37 (s, 1H, H-10b), 3.90 – 3.50 (m, 6H, H-4, H-1’a, H-1’b, H-5a, H-3
and H-2), 3.40 – 3.20 (m, 1H, H-5b), 2.60 – 2.40 (m, 1H, H-4a), 1.31 (s, 9H, (C(CH₃)₃);

**¹³C NMR:** (CDCl₃, 100 MHz): δc: 154.1, 139.4, 138.2, 138.1, 137.7, 133.3, 128.7, 128.6, 128.4, 128.3, 128.0, 127.8, 127.8, 127.6, 127.5, 127.3, 126.9 (Ar), 81.6 (C-4), 80.4 (C-3), 75.2 (CH₂Ph), 74.7 (C-2), 73.9 (C-10b), 73.4 (CH₂Ph), 72.1 (CH₂Ph), 69.2 (C-1’), 42.4 (C-5), 34.8 (C-4a), 34.6 (C(CH₃)₃), 31.1 (C(CH₃)₃).

[α]D: +10.0 (c 0.1, CHCl₃)

IR: 1051, 683 cm⁻¹ (neat)

HRMS (ESI-TOF) m/z: [M + H]⁺ Calcd for C₃₈H₄₃O₅S 611.2831; Found 611.2828.

(2R,3S,4R,4aR,10bR)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-7-methyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (168e first diastereomer):

Yield: 153.6 mg, 50%; colorless oil

**¹H NMR:** (CDCl₃, 400 MHz) δH: 7.50 – 7.00 (m, 18H, Ar), 4.92 (d, J = 10.4 Hz, 1H, CH₂Ph), 4.81 (d, J = 11.2 Hz, 1H, CH₂Ph), 4.65 – 4.35 (m, 5H, 4 x CH₂Ph and H-10b), 4.10 – 3.90 (m, 1H, H-4), 3.80 – 3.50 (m, 5H, H-1’a, H-1’b, H-2, H-3, and H-4a), 3.43 (d, J = 14.0 Hz, 1H, H-5a), 3.06 (t, J = 13.4 Hz, 1H, H-5b), 2.72 (s, 3H, CCH₃);

**¹³C NMR:** (CDCl₃, 100 MHz): δc: 140.3, 138.3, 138.1, 137.6, 135.6, 133.6, 132.0, 130.9, 128.5, 128.3, 128.3, 128.1, 127.9, 127.8, 127.8, 127.7, 127.6, (Ar), 81.0 (C-4), 79.7 (C-2), 75.2 (CH₂Ph), 74.5 (C-3), 73.8 (C-10b), 73.4 (CH₂Ph), 70.7 (CH₂Ph), 69.2 (C-1’), 39.3 (C-5), 27.5 (C-4a), 18.8 (CCH₃).

IR: 1027, 695 cm⁻¹ (neat)
[α]D:  -24.6 (c 0.1, CHCl₃)

HRMS (ESI-TOF) m/z: [M + H]+ Calcd for C₃₅H₃₇O₅S 569.2362; Found 569.2366.

(2R,3S,4R,4aR,10bR)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-7-methyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (168e second diastereomer):

Yield:  76.8 mg, 22%; colorless oil

1H NMR:  (CDCl₃, 400 MHz) δH:  7.50 – 7.00 (m, 18H, Ar), 4.85 (d, J = 10.4 Hz, 1H, CH₂Ph), 4.69 (s, 2H, CH₂Ph), 4.60 – 4.40 (m, 3H, CH₂Ph), 4.31 (s, 1H, H-10b), 3.95 – 3.30 (m, 6H, H-4, H-1’a, H-1’b, H-5a, H-3, H-2 and H-5b), (m, 1H, H-5b), 2.67 (s, 3H, ArCH₃), 2.55 – 2.40 (m, 1H, H-4a);

13C NMR:  (CDCl₃, 100 MHz): δC: 140.4, 139.1, 138.2, 138.1, 137.8, 134.5, 132.6, 130.3, 128.6, 128.4, 128.3, 128.0, 128.0, 127.8, 127.6, 127.5 (Ar), 81.6 (C-4), 80.4 (C-3), 75.2 (CH₂Ph), 74.5 (C-2), 74.4 (C-10b), 73.5 (CH₂Ph), 71.9 (CH₂Ph), 69.2 (C-1’), 42.6 (C-5), 34.4 (C-4a), 21.0 (ArCH₃).

IR:  1026, 696 cm⁻¹(neat)

[α]D:  +11.6 (c 0.1, CHCl₃)

HRMS (ESI-TOF) m/z: [M + H]+ Calcd for C₃₅H₃₇O₅S 569.2362; Found 569.2366.

7.2.6 General procedure for the synthesis of thiochromene 169a and thiochromenes 171a-e

A stirred mixture of sulfoxide 167a (160 mg, 0.29 mmol) and sodium acetate ( 4.1 mg, 0. 05 mmol) in acetic anhydride (1 mL) was refluxed at 140 °C for 3 h. The reaction was allowed to cool to room temperature. Diethyl ether (5 mL) and methanol (1 mL) were added to the reaction mixture and stirred for 1 h. The solution was then concentrated under reduced pressure. And the residue was diluted with DCM (5 mL) and washed several times with saturated aqueous sodium bicarbonate solution. The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure to give an orange oil. To a solution of this oil in CH₂Cl₂ and CH₃OH (5 mL, 1:1) was added a catalytic amount of sodium methoxide and the mixture was stirred at room temperature for 10 min. Water was added and the mixture was extracted with CH₂Cl₂ (10 mL) three times. The combined organic layer was dried, concentrated under
reduced pressure and purified by flash column chromatography on silica gel (ethyl acetate/hexane, 1:9) to obtain thiochromene 169a.

Thiochromenes 171a-e were synthesized using the same conditions described for the synthesis of 169a. However, prior to purification by column chromatography, the thiochromenes so obtained were dispersed in CH₂Cl₂ (5 mL) and treated with acetic anhydride (1 mL), triethylamine (0.5 mL) and a catalytic amount of DMAP. The solution was stirred at room temperature until completion of the reaction (monitored by TLC). The solution was diluted with CH₂Cl₂, washed with water and dried over MgSO₄. The residue was then purified by flash column chromatography on silica gel (ethyl acetate/hexane, 1:9) to afford thiochromene 171a-e:

(S)-2-((1R,2R)-1,3-bis(benzyloxy)-2-hydroxypropyl)-2H-thiochromene-3-carbaldehyde (169a):

Yield: 119.7 mg, 80%, yellow syrup

¹H NMR: (400 MHz, CDCl₃) δ: 9.51 (s, 1H, CHO), 7.38 – 6.90 (m, 13H, Ar and H-4), 6.44 – 6.56 (m, 2H, 2H, Ar), 4.34 (d, J = 10.6 Hz, 1H, CH₆CH₃Ph), 4.28 (d, J = 10.6 Hz, 1H, CH₆CH₃Ph), 4.39 (d, J = 3.6 Hz, 1H, H-2), 4.50 (d, J = 12.0 Hz, 1H, CH₆CH₃Ph), 4.44 (d, J = 12.0 Hz, 1H, CH₆CH₃Ph), 3.73 (dd, J = 3.2 and 8.4 Hz, 1H, H-1’), 3.61 (bd, J = 4.4 Hz, 1 H, OH), 3.62 – 3.37 (m, 3H, H-2’, H-3a, H-3’b);

¹³C NMR: (100 MHz, CDCl₃) δ: 193.6 (CHO), 149.7, 138.0, 137.4, 135.7, 131.7, 131.3, 131.0, 130.7, 128.4, 128.0, 127.9, 127.6, 127.5, 126.7, 125.5 (Ar, C-3 and C-4), 85.6 (C-1’), 75.5 (CH₂Ph), 73.5 (CH₂Ph), 70.4 (C-2’), 69.8 (C-3’), 35.5 (C-2).

IR: 3446, 3028, 2859, 1656, 1622, 1453, 1362, 1206, 1143, 1070, 732, 696 cm⁻¹ (neat)
[α]D: +26.5 (c 0.1, CHCl₃)


(1R,2R)-1’,3’-bis(benzyloxy)-1-((S)-3-formyl-2H-thiochromen-2-yl)propan-2-yl acetate (171a):

Yield: 129.2 mg, 79%; yellow oil

¹H NMR: (400 MHz, CDCl₃) δH: 9.54 (s, 1H, CHO), 7.43 - 7.10 (m, 13H, Ar and H-4), 6.92 – 6.80 (m, 2H, Ar), 5.20 – 5.03 (m, 1H, H-2’), 4.61 – 4.34 (m, 5H, 2 × CH₂Ph and H-2), 3.88 (t, J = 5.7 Hz, 1H, H-1’), 3.82 (dd, J = 3.5 and 11.0 Hz, 1H, H-3’a), 3.70 (dd, J = 4.8 and 11.0 Hz, 1H, H-3’b), 2.06 (s, 3H, OAc);

¹³C NMR: (100 MHz, CDCl₃) δC: 191.1 (CHO), 169.9 (OCOCH₃), 145.8, 137.9, 137.4, 134.5, 132.2, 131.3, 131.0, 130.3, 128.3, 128.0, 127.6, 127.5, 127.1, 125.6 (Ar, C-3 and C-4), 81.3 (C-1’), 74.5 (CH₂Ph), 73.1 (CH₂Ph), 72.1 (C-2’), 67.8 (C-3’), 35.1 (C-2), 21.12 (OCOCH₃).

IR: 2873, 1737, 1674, 1626, 1367, 1231, 1140, 1069, 732, 696 cm⁻¹ (neat)

[α]D: (c 0.1, CHCl₃) +15.2

HRMS (ESI-TOF): m/z [M + H]^+ Calcd for C₂₉H₂₉O₅S 489.1732; Found: 489.1732.

(1R,2R)-1’,3’-bis(benzyloxy)-1-((S)-3-formyl-6-methyl-2H-thiochromen-2-yl)propan-2-yl acetate (171b):
Yield: 120.1 mg, 73%; yellow oil

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta$: 9.53 (s, 1H, CHO), 7.40 - 6.98 (m, 12H, Ar and H-4), 6.91 - 6.81 (m, 2H, Ar), 5.13 - 4.96 (m, 1H, H-2’), 4.55 - 4.27 (m, 5H, 2 x $\text{C}_2\text{H}_2\text{Ph}$ and H-2), 3.87 - 3.78 (m, 2H, H-1’ and H-3’), 3.69 (dd, $J = 4.8$ and 10.8 Hz, 1H, H-3’), 2.28 (s, 3H, CH$_3$), 2.00 (s, 3H, OAc);

$^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$: 191.2 (CHO), 170.0 ($\text{OCOCH}_3$), 146.0, 138.0, 137.6, 135.5, 132.4, 132.3, 131.6, 131.0, 130.5, 128.3, 128.0, 127.9, 127.7, 127.6, 127.4, 127.1 (Ar, C-3 and C-4), 81.4 (C-1’), 74.4 ($\text{CH}_2\text{Ph}$), 73.2 ($\text{CH}_2\text{Ph}$), 72.3 (C-2’), 68.0 (C-3’), 35.2 (C-2), 21.2 ($\text{OCOCH}_3$), 20.7 (CH$_3$).

IR: 2921, 1737, 1674, 1629, 1566, 1366, 1228, 1143, 1027, 733, 696 cm$^{-1}$ (neat);

$[\alpha]_D$: +18.5 (c 0.1, CHCl$_3$)

HRMS (ESI-TOF): $m/z$ [M + H$^+$]: Calcd 503.1892; Found 503.1878.

$(1R,2R)$-1’,3’-bis(benzyloxy)-1-((S)-3-formyl-6-methoxy-2H-thiochromen-2-yl)propan-2-yl acetate (171c):

Yield: 114.2 mg, 69%; yellow oil

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta$: 9.53 (s, 1H, CHO), 7.39 - 7.12 (m, 10H, Ar and H-4), 6.93 - 6.72 (m, 4H, Ar), 5.14 - 5.01 (m, 1H, H-2’), 4.63 - 4.24 (m, 5H, 2 x $\text{CH}_2\text{Ph}$)
and H-2), 3.86 - 3.79 (m, 2H, H-1' and H-3'a), 3.76 (s, 3H, OMe), 3.69 (dd, J = 6.4 and 12.0 Hz, 1H, H-3'b), 2.01 (s, 3H, OAc);

\[^{13}\text{C NMR:}\] (100 MHz, CDCl\textsubscript{3}) \(\delta\) C: 191.1 (CHO), 170.2 (OCOCH\textsubscript{3}), 158.2, 145.6, 138.2, 133.4, 131.6, 128.3, 128.1, 127.9, 127.7, 127.6, 127.5, 125.1, 117.7, 115.8 (Ar, C-3 and C-4), 81.2 (C-1'), 74.4 (CH\textsubscript{2}Ph), 73.2 (CH\textsubscript{2}Ph), 72.4 (C-2'), 68.0 (C-3'), 55.5 (OMe), 35.1 (C-2), 21.2 (OCOCH\textsubscript{3}).

IR: 1737, 1676, 1596, 1477, 1370, 1229, 1164, 1025, 731, 697 cm\textsuperscript{-1}(neat);

[\(\alpha\)]\text{D}: (c 0.1, CHCl\textsubscript{3}) +12.5

HRMS (ESI-TOF): m/z [M + H]\textsuperscript{+} Calcd for C\textsubscript{30}H\textsubscript{31}O\textsubscript{6}S 519.1841; Found: 519.1833.

\((1R,2R)-1',3'-\text{bis(benzyloxy)-1-}((S)-6-\text{tert-butyl-3-formyl-2H-thiochromen-2-yl})\text{propan-2-yl acetate (171d):}\)

Yield: 125.1 mg, 75%, yellow oil

\[^{1}\text{H NMR:}\] (400 MHz, CDCl\textsubscript{3}) \(\delta\) H: 9.55 (s, 1H, CHO), 7.38 - 7.12 (m, 12H, Ar and H-4), 6.89 - 6.57 (m, 2H, Ar), 4.98 - 4.88 (m, 1H, H-2'), 4.49 - 4.36 (m, 5H, 2 x CH\textsubscript{2}Ph and H-2), 3.91 (dd, J = 5.2 and 6.4 Hz, 1H, H-1'), 3.80 (dd, J = 4.4 and 10.8 Hz, H-3'a), 3.70 (dd, J = 4.4 and 10.8 Hz, 1H, H-3'b), 2.03 (s, 3H, OAC), 1.29 (s, 9H, C(CH\textsubscript{3})\textsubscript{3});

\[^{13}\text{C NMR:}\] (100 MHz, CDCl\textsubscript{3}) \(\delta\) C: 191.3 (CHO), 170.0 (OCOCH\textsubscript{3}), 148.9, 146.9, 138.0, 137.6, 131.9, 131.3, 130.2, 128.9, 128.4, 128.2, 128.1, 128.0, 127.7, 127.6, 127.5, 126.8 (Ar, C-3 and C-4), 81.7 (C-1'), 74.7 (CH\textsubscript{2}Ph), 73.2 (CH\textsubscript{2}Ph), 72.2 (C-2'), 68.0 (C-3'), 35.3 (C-2), 34.4 (C(CH\textsubscript{3})\textsubscript{3}), 31.2 (C(CH\textsubscript{3})\textsubscript{3}), 21.2 (OCOCH\textsubscript{3}).
IR: 2959, 1738, 1674, 1622, 1365, 1229, 1138, 1069, 733, 696 cm\(^{-1}\) (neat);

\([\alpha]_D\): +16.3 (c 0.1, CHCl\(_3\) )

HRMS (ESI-TOF): \(m/z\) [M + H]\(^{+}\) Calcd for C\(_{33}\)H\(_{37}\)O\(_5\)S: 545.2362; Found: 545.2362.

\((1R,2R)-1',3'-bis(benzyloxy)-1-((S)-3-formyl-8-methyl-2H-thiochromen-2-yl)propan-2-yl acetate (171e):

\[
\begin{align*}
\text{Yield:} & \quad 118.5 \text{ mg, 72\%; yellow oil} \\
\text{\(^1\)H NMR:} & \quad (400 \text{ MHz, CDCl}_3) \delta_H: 9.55 (s, 1H, CHO), 7.49 - 7.08 (m, 12H, Ar and H-4), 6.91 - 6.89 (m, 2H, Ar), 5.19 - 5.01 (m, 1H, H-2'), 4.58 - 4.37 (m, 4H, CH\(_A\)H\(_B\)Ph, CH\(_A\)H\(_B\)Ph and H-2), 4.31 (d, \(J = 11.2\) Hz, 1H, CH\(_A\)H\(_B\)Ph), 3.84 - 3.77 (m, 2H, H-1' and H-3'a), 3.70 (dd, \(J = 5.2\) and 10.8 Hz, 1H, H-3'b), 2.35 (s, 3H, CH\(_3\)), 1.98 (s, 3H, OAc);
\text{\(^{13}\)C NMR:} & \quad (100 \text{ MHz, CDCl}_3) \delta_C: 191.2 (CHO), 170.0 (OCOCH\(_3\)), 146.3, 138.0, 137.5, 135.9, 133.9, 132.9, 131.8, 130.3, 128.9, 128.3, 128.1, 127.9, 127.6, 127.5, 124.8 (Ar, C-3 and C-4), 81.4 (C-1'), 74.5 (CH\(_2\)Ph), 73.2 (CH\(_2\)Ph), 72.4 (C-2'), 68.0 (C-3'), 35.2 (C-2), 21.1 (OCOCH\(_3\)), 20.3 (CH\(_3\)). \\
\text{IR:} & \quad 1737, 1674, 1629, 1566, 1366, 1228, 1143, 1027, 733, 696 cm\(^{-1}\) (neat);
\text{[\alpha]_D:} & \quad (c 0.1, CHCl\(_3\) ) +14.0
\end{align*}
\]

HRMS (ESI-TOF): \(m/z\) [M + H]\(^{+}\) Calcd for C\(_{30}\)H\(_{31}\)O\(_5\)S 503.1892; Found: 503.1883.

\subsection*{7.2.7 General procedure for the synthesis of thiochromenes 176a-e}
NaOAc (4 mg, 0.03 mmol) was added to a solution of sulfoxide 168 (0.30 mmol) in acetic anhydride (2 mL) and the reaction mixture was stirred overnight at 140 °C. The reaction mixture was then allowed to cool down to room temperature and diluted with DCM. The
resulting solution was washed successively with saturated aqueous NaHCO₃ and brine, dried over MgSO₄, filtered and evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane, 5:95) to yield the corresponding thiochromene 176:

\[(2R,3S,4R,10bR)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,10b-tetrahydrothiochromeno[4,3-b]pyran (176a):\]

Yield: 161 mg, 63%; white solid

Mp 66 – 68 °C

\[^1\text{H NMR:}\ (\text{CDCl}_3, 400 \text{ MHz}) \delta_H: 7.60 – 7.00 (m, 19H, Ar), 6.75 (d, J = 1.2 \text{ Hz}, 1H, H-5), 5.25 (s, 1H, H-10a), 5.00 – 4.80 (m, 2H, CH₂Ph), 4.71 (d, J = 11.6 \text{ Hz}, 1H, CH₂Ph), 4.60 – 4.40 (m, 3H, CH₂Ph), 4.26 (dd, J = 1.6 and 8.4 \text{ Hz}, 1H, H-4), 3.80 – 3.40 (m, 4H, H-3, H-1’a, H-1’b, H-2)

\[^{13}\text{C NMR:}\ (\text{CDCl}_3, 100 \text{ MHz}): \delta_C: 138.0, 137.8, 129.6, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 128.0, 128.0, 127.9, 127.8, 127.8, 127.8, 127.7, 127.6, 125.6, 125.2 (\text{Ar and C-4a}), 120.4 (\text{C-5}), 85.1 (\text{C-4}), 82.2 (\text{C-2}), 80.6 (\text{C-3}), 75.4 (\text{C-10a}), 75.2, 73.5, 72.8 (\text{CH}_2\text{Ph}), 69.1 (\text{C-1’}).

IR: 696 cm⁻¹ (neat):

[\alpha]_D: -96.5 (c 0.5, CHCl₃);

HRMS (ESI-TOF) m/z: [M + H]^+ Calcd for C₃⁴H₃₃O₄S 537.2100; Found 537.2100.

\[(2R,3S,4R,10bR)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-methyl-2,3,4,10b-tetrahydrothiochromeno[4,3-b]pyran (176b):\]
Yield: 142.1 mg, 86%; white solid

Mp 109 – 111°C

$^1$H NMR: (CDCl$_3$, 400 MHz) δH: 7.60 – 6.90 (m, 18H, Ar), 6.72 (s, 1H, H-5), 5.23 (s, 1H, H-10a), 5.00 – 4.80 (m, 2H, CH$_2$Ph), 4.72 (d, $J = 11.6$ Hz, 1H, CH$_2$Ph), 4.60 – 4.40 (m, 3H, CH$_2$Ph), 4.27 (d, $J = 8.4$ Hz, 1H, H-4), 3.80 – 3.50 (m, 4H, H-4, H-1'a, H-1'b, H-2), 2.30 (s, 3H, ArCH$_3$);

$^{13}$C NMR: (CDCl$_3$, 100 MHz): δC: 138.0, 137.9, 134.9, 130.2, 129.2, 128.5, 128.3, 128.2, 128.0, 127.9, 127.9, 127.7, 127.4, 125.4, 125.0 (Ar and C-4a), 120.5 (C-5), 85.1 (C-4), 82.2 (C-2), 80.5 (C-3), 75.5 (C-10a), 75.2, 73.4, 72.7 (CH$_2$Ph), 69.1 (C-1’), 20.8 (ArCH$_3$).

IR: 696 cm$^{-1}$ (neat)

$[\alpha]$: -95.5 (c 0.5, CHCl$_3$)

HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{35}$H$_{35}$O$_4$S 551.2256; Found 551.2258.

(2$R$,3$S$,4$R$,10b$R$)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-methoxy-2,3,4,10b-tetrahydrothiochromeno[4,3-b]pyran (176c):

Yield: 102 mg, 60%; white solid

Mp 126 – 128 °C
$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta_H$: 7.50 – 7.00 (m, 16H, Ar), 6.85 – 6.75 (m, 2H, Ar), 6.70 (d, $J = 1.6$ Hz, 1H, H-5), 5.20 (s, 1H, H-10a), 4.95 – 4.80 (m, 2H, CH$_2$Ph), 4.72 (d, $J = 11.6$ Hz, 1H, CH$_2$Ph), 4.60 – 4.35 (m, 3H, CH$_2$Ph), 4.27 (dd, $J = 1.2$ and 8.4 Hz, 1H, H-4), 3.90 – 3.40 (m, 7H, OCH$_3$, H-3, H-1’a, H-2’b, H-2)

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta_C$: 157.6, 138.1, 137.9, 129.1, 128.6, 128.4, 128.3, 128.0, 128.0, 127.9, 127.8, 127.6, 126.6, 120.5, 119.3, 115.0, 114.6 (Aromatic, C-4a and C-5), 85.1 (C-4), 82.3 (C-2), 80.6 (C-3), 75.6 (C-10a), 75.3, 73.5, 72.8 (CH$_2$Ph), 69.1 (C-1’), 55.5 (OCH$_3$).

IR: 697, cm$^{-1}$(neat)

$[\alpha]_D$: -99.5 (c 0.5, CHCl$_3$)

HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{35}$H$_{35}$O$_5$S 567.2205; Found 567.2209.

(2$R$,3$S$,4$R$,10b$R$)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-tert-butyl-2,3,4,10b-tetrahydrothiochromeno[4,3-b]pyran (176d):

Yield: 117.3 mg, 66%; white solid

Mp 122 – 124 °C

$^1$H NMR: (CDCl$_3$, 400 MHz) $\delta_H$: 7.60 – 7.00 (m, 18H, Ar), 6.75 (s, 1H, H-5), 5.22 (s, 1H, H-10a), 4.92 (d, $J = 12.0$ Hz, 2H, CH$_2$Ph), 4.72 (d, $J = 112.0$ Hz, 1H, CH$_2$Ph), 4.60 – 4.40 (m, 3H, CH$_2$Ph), 4.26 (d, $J = 8.4$ Hz, 1H, H-4), 3.80 – 3.40 (m, 4H, H-3, H-1’a, H-1’b, H-2), 1.30 (s, 9H, (C(CH$_3$)$_3$);

$^{13}$C NMR: (CDCl$_3$, 100 MHz) $\delta_C$: 148.4, 138.1, 138.0, 128.6, 128.4, 128.3, 128.1, 128.0, 128.0, 127.9, 127.7, 127.5, 127.2, 126.7, 125.7, 125.3, 125.1 (Ar and C-2),
121.0 (C-5), 85.1 (C-4), 82.3 (C-2), 80.6 (C-3), 75.5 (C-10a), 75.2, 73.5, 72.8 (CH₂Ph), 69.2 (C-1’), 34.4 (C(CH₃)₃), 31.3 (C(CH₃)₃).

[α]D: -164.0 (c 0.5, CHCl₃)

IR: 696 cm⁻¹(neat)

HRMS (ESI-TOF) m/z: [M + H]+ Calcd for C₃₈H₄₁O₄S 593.2726; Found 593.2720.

(2R,3S,4R,10bR)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-7-methyl-2,3,4,4a,5,10b-tetrahydrothiochromeno[4,3-b]pyran (176e):

Yield: 140 mg, 85%; colorless oil

¹H NMR: (CDCl₃, 400 MHz) δH: 7.60 – 6.90 (m, 18H, Ar), 6.74 (d, J = 1.6 Hz, 1H, H-5), 5.34 (s, 1H, H-10b), 5.00 – 4.80 (m, 2H, CH₂Ph), 4.71 (d, J = 11.6 Hz, 1H, CH₂Ph), 4.60 – 4.40 (m, 3H, CH₂Ph), 4.25 (dd, J = 1.2 and 8.4 Hz, 1H, H-4), 3.80 – 3.40 (m, 4H, H-3, H-l’a, H-l’b, H-2), 2.32 (s, 3H, ArCH₃);

¹³C NMR: (CDCl₃, 100 MHz): δc: 138.1, 138.0, 137.9, 133.7, 130.0, 128.6, 128.4, 128.3, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 127.6, 127.2, 124.4, 121.0 (C-4a and Ar), 85.0 (C-4), 82.1 (C-2), 80.6 (C-3), 75.3 (C-10b), 75.2, 73.4, 72.8 (CH₂Ph), 69.1 (C-l’), 19.5 (ArCH₃).

[α]D: -88.0 (c 0.5, CHCl₃)

IR: 696 cm⁻¹(neat)

HRMS (ESI-TOF) m/z: [M + H]+ Calcd for C₃₅H₃₅O₄S 551.2256; Found 551.2260.
### 7.2.8 General protocol for the desulfurization of thiochromans 158a-d, 164a and 164b

To a solution of thiochroman 158 and 164 (0.26 mmol) in acetone (2 mL) was added freshly prepared W-1 Raney nickel (1 spatula) and the reaction mixture was stirred at room temperature for 45 min. The reaction mixture was then filtered through a Celite® bed and the filtrate was dried under reduced pressure. The crude product was purified by column chromatography using ethylacetate:hexane (1:9) mixture as eluent to provide the corresponding carbaldehydes:

**Phenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-methyl-α-D-glucopyranoside (180a):**

![180a](image)

Yield 112.4 mg, 85%; colourless oil;

*1H NMR:* (CDCl₃, 400 MHz): δ 7.42-7.16 (m, 20H, Ar), 5.02 (d, J = 3.2 Hz, 1H, H-1), 4.71-4.44 (m, 6H, 3 x CH₂Ph), 4.16-4.02 (m, 1H, H-5), 3.81 (dd, J = 5.2 and 10.4 Hz, H-6a), 3.71 (dd, J = 5.2 and 10.0 Hz, H-6b), 2.30-2.14 (m, 1H, H-2), 0.90 (d, J = 7.6 Hz, 3H, CH₃);

*13C NMR:* (CDCl₃, 100 MHz): δ 138.5, 138.4, 138.3, 128.4, 128.3, 128.0, 127.7, 127.6, 127.5, 127.2, 127.0, 80.8, 75.8, 74.5, 73.6, 73.2, 72.9, 72.8, 68.9, 38.6, 12.3

[α]D: + 15.70 (c 0.1, CHCl₃);

IR: 3030, 2876, 2360, 2116, 1604, 1496, 1453, 1362, 1310, 1065, 1027, 695, 617 cm⁻¹ (neat).

HRMS (ESI-TOF) m/z: [M + H]⁺ Calcd for C₃₄H₃₇O₄ 509.2692; Found 509.2682.
3-Methylphenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-methyl-α-D-glucopyranoside (180b):

Yield 115 mg, 90%; colorless oil

1H NMR: (CDCl₃, 400 MHz): δ 7.42-6.94 (m, 19H, Ar), 4.98 (d, J = 4.0 Hz, 1H, H-1), 4.72-4.43 (m, 6H, 3 x CH₂Ph), 4.14-4.05 (m, 1H, H-5), 3.84-3.67 (m, 4H, H-3, H-4, H-6a and H-6b), 2.33 (s, 3H, ArCH₃), 2.28-2.16 (m, 1H, H-2), 0.91 (d, J = 7.2 Hz, 3H, CH₃);

13C NMR: (CDCl₃, 100 MHz): δ 138.5, 138.3, 137.6, 128.4, 128.3, 128.1, 127.8, 127.7, 127.6, 127.5, 124.3, 80.7, 75.9, 74.4, 73.8, 73.2, 72.9, 72.8, 68.8, 38.6, 21.5, 12.4;

[α]D  +13.20 (c 0.1, CHCl₃)

IR 3029, 2259, 1500, 1453, 1255, 1206, 696, 609 cm⁻¹ (neat).

HRMS (ESI-TOF) m/z: [M + H]⁺ Caled for C₃₅H₃₉O₄ 523.2848; Found 523.2849.

3-Methoxyphenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-methyl-α-D-glucopyranoside (180c):

Yield 133 mg, 95%, colorless oil
$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta$ 7.42-7.7.18 (m, 16H, Ar), 6.93-6.88 (m, 2H, Ar), 6.78 (d, $J = 8.4$ Hz, 1H, Ar), 5.01 (d, $J = 3.2$ Hz, 1H, H-1), 4.4.71-4.43 (m, 6H, 3 x CH$_2$Ph), 4.18-4.07 (m, 1H, H-5), 3.87-3.69 (m, 7H, H-3, H-4, H-6a, H-6b and OCH$_3$), 2.29-2.13 (m, 1H, H-2), 0.93 (d, $J = 7.2$ Hz, 3H, CH$_3$);

$^{13}$C: NMR (CDCl$_3$, 100 MHz): $\delta$ 159.5, 142.0, 138.5, 138.4, 138.3, 128.9, 128.4, 128.3, 127.7, 127.6, 127.5, 119.3, 112.9, 112.4, 80.7, 75.6, 74.6, 73.2, 72.8, 72.7, 68.8, 55.2, 38.6, 12.2; 7.

[$\alpha$]$_D$: +25.60 (c 0.1, CHCl$_3$)

IR: 2900, 2010, 1498, 1434, 1220, 1040, 1019, 696, 634 cm$^{-1}$ (neat).

HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{35}$H$_{39}$O$_5$ 539.2797; Found 539.279

3-tert-Butylphenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-methyl-α-D-glucopyranoside (180d):

Yield 123.4 mg, 84%; colorless oil

$^1$H NMR: (CDCl$_3$, 400 MHz): $\delta$ 7.48-7.11 (m, 19H, Ar), 5.03 (d, $J = 4.0$ Hz, 1H, H-1), 4.73-4.52 (m, 5H, 2 x CH$_A$H$_B$Ph and CH$_A$Ph), 4.49 (d, $J = 12.4$ Hz, 1H, CH$_A$Ph), 4.11-4.06 (m, 1H, H-5), 3.89-3.70 (m, 4H, H-3, H-4, H-6a and H-6b), 2.31-2.14 (m, 1H, H-2), 1.32 (s, 9H, C(CH$_3$)$_3$), 0.95 (d, $J = 7.6$ Hz, CH$_3$);

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $\delta$ 139.6, 138.5, 138.3, 128.4, 128.3, 128.2, 127.9, 127.7, 127.6, 127.5, 125.5, 124.3, 123.9, 80.9, 76.1, 74.3, 74.2, 73.2, 72.9 (x 2), 68.9, 38.8, 34.6, 31.4, 12.5.
IR: 3043, 3056, 2366, 1460, 1450, 1255, 1210, 696, 610 cm\(^{-1}\) (neat).

HRMS (ESI-TOF) m/z: [M + H]\(^+\) Calcd for C\(_{38}\)H\(_{45}\)O\(_4\) 565.3318; Found 565.3329.

Phenyl 3,4,6-tri-\(\text{O}\)-benzyl-2-deoxy-2-\(\text{C}\)-methyl-\(\alpha\)-D-mannopyranoside (181a):

Yield 109.8 mg, 83%; colorless oil

\(^1\)H NMR: (CDCl\(_3\), 400 MHz): \(\delta\) 7.49-7.13 (m, 20H, Ar), 4.95 (d, \(J = 10.8\) Hz, 1H, \(\text{CH}_\text{A}\text{H}_\text{BPh}\)), 4.75 (d, \(J = 12.0\) Hz, 1H, \(\text{CH}_\text{A}\text{H}_\text{BPh}\)), 4.70-4.57 (m, 5H, H-1 and the rest of the \(\text{CH}_\text{Ph}\)), 4.01-3.79 (m, 4H, H-3, H-4, H-6\(_a\) and H-6\(_b\)), 3.64-3.57 (m, 1H, H-5), 2.58-2.36 (m, 1H, H-2), 0.81 (d, \(J = 6.8\) Hz, 3H, \(\text{CH}_3\));

\(^13\)C NMR: (CDCl\(_3\), 100 MHz): \(\delta\) 140.3, 138.6, 138.5, 128.4, 128.3, 128.0, 127.6, 127.4, 126.8, 125.5, 84.3, 79.8, 79.4, 75.1, 74.1, 73.4, 70.6, 69.5, 38.3, 6.5.

[\(\alpha\)]\(_D\): +15.70 (c 0.1, CHCl\(_3\))

IR: 3050, 2874, 2383, 2110, 1496, 1449, 1350, 1067, 1027, 696 cm\(^{-1}\) (neat)

HRMS (ESI-TOF) m/z: [M + H]\(^+\) Calcd for C\(_{34}\)H\(_{37}\)O\(_4\) 509.2692; Found 509.2686.
3-tert-Butylphenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-methyl-α-D-mannopyranoside (181b):

![Chemical Structure](image)

**Yield** 124.8 mg, 85%; colorless oil

**1H NMR:** (CDCl₃, 400 MHz) for the major atropisomer (1:4 ratio): δ 7.57-7.01 (m, 19H, Ar), 4.94 (d, J = 10.4 Hz, 1H, CH₃HaPh), 4.78-4.52 (m, 6H, H-1 and the rest of the CH₂Ph), 3.91-3.52 (m, 5H, H-3, H-4, H-5, H-6a and H-6b), 2.47-2.32 (m, 1H, H-2), 1.32 (s, 9H, C(CH₃)₃), 0.80 (d, J = 6.8 Hz, 3H, CH₃);

**13C NMR:** (CDCl₃, 100 MHz): δ 139.9, 138.8, 138.7, 138.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 123.7, 122.8, 122.5, 84.5, 80.1, 79.9, 75.1, 74.3, 73.5, 70.8, 69.6, 38.4, 34.7, 31.4, 6.6. **1H NMR** (CDCl₃, 400 MHz) for the minor atropisomer: δ 4.77 (d, J = 10.4 Hz, 1H), 4.57-4.46 (m, 2H), 3.26 (t, J = 12.4 Hz, 1H), 2.96 (d, J = 12.8 Hz, 1H), 2.65-2.58 (m, 1H), 1.28 (s, 9H); **13C **{1H} NMR (CDCl₃, 100 MHz) for the minor atropisomer: 83, 74.7, 71.4;

**IR:** 3062, 3029, 2359, 1496, 1453, 1255, 1206, 696, 613 cm⁻¹ (neat)

**HRMS (ESI-TOF) m/z:** [M + H]⁺ Calcd for C₃₈H₄₅O₄ 565.3318; Found 565.3319.

### 7.2.9 General procedure for the synthesis of hemithioacetals 170a-d

A stirred mixture of sulfoxide 167 (0.29 mmol) and sodium acetate (0.05 mmol) in acetic anhydride (1 mL) was refluxed at 140 °C for 3 h. The reaction was allowed to cool to room temperature. Diethyl ether (5 mL) and methanol (1 mL) were added to the reaction mixture and stirred for 1 h. The solution was concentrated under reduced pressure and the residue was diluted with dichloromethane and washed several times with saturated aqueous sodium bicarbonate solution. The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure to give yellow oil. The product was pure enough to be carried through the
next step without further purification. To a solution of the yellow oil (0.285 mmol) in methanol (5 mL) potassium carbonate (0.029 mmol) was added and stirred vigorously at room temperature for 10 min. The white precipitate formed was filtered and washed several times with water. Further crops of the title product were collected by extraction of the aqueous filtrate with ethyl acetate (3 x 10 mL). The combined organic phases were dried over MgSO4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using a mixture of ethyl acetate:hexane (2:8) as an eluent to provide hemithioacetals 170a-d:

\((2R,3S,4R,4aS,5S,10bS)-3,4\text{-bis(benzyloxy)}\text{-}2\text{-}(\text{benzyloxymethyl})\text{-}2,3,4a,5,10b\text{-hexahydrothiochromeno}[4,3-\text{b}]\text{pyran-5-ol} \; (170a)\):

Yield: 122.3 mg, 76%; white solid

Mp: 128-132 °C

\(^1H\text{ NMR:} \; \text{(CDCl}_3, \text{400Hz}) \delta: 7.70-7.62 \; (m, \text{1H, Ar}), \text{7.48-7.21} \; (m, \text{13H, Ar}), \text{7.16-7.04} \; (m, \text{5H, Ar}), \text{5.47} \; (d, \; J = \text{4.0 Hz, 1H, \text{0H-5}}), \text{5.36} \; (d, \; J = \text{6.0 Hz, 1H, H-10b}), \text{4.95} \; (d, \; J = \text{11.2 Hz, 1H, CH}_3\text{H}_3\text{Ph}), \text{4.84-4.71} \; (m, \text{3H, CH}_3\text{H}_3\text{Ph}), \text{4.59} \; (d, \; J = \text{12.4 Hz, 1H, CH}_3\text{H}_3\text{Ph}), \text{4.54} \; (d, \; J = \text{10.8 Hz, CH}_3\text{H}_3\text{Ph}), \text{3.84-3.68} \; (m, \text{4H, H-1’a, H-1’b, H-3 and H-4}), \text{3.59-3.51} \; (m, \text{1H, H-2}), \text{2.78-2.69} \; (m, \text{1H, H-4a})

\(^{13}C\text{ NMR:} \; \text{(CDCl}_3, \text{100 MHz):} \; \delta: \text{138.5, 138.0, 137.9, 131.1, 131.0, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 126.6, 125.4} \; (\text{Ar}), \text{80.8} \; (\text{C-3}), \text{80.1} \; (\text{C-4}), \text{75.7} \; (\text{CH}_2\text{Ph}), \text{74.8} \; (\text{CH}_2\text{Ph}), \text{73.5} \; (\text{CH}_2\text{Ph}), \text{73.1} \; (\text{C-5}), \text{73.0} \; (\text{C-2}), \text{69.2} \; (\text{C-10b}), \text{68.9} \; (\text{C-1’}), \text{44.3} \; (\text{C-4a}).

\([\alpha]D: \; +5.0 \; (c \; 0.1, \text{CHCl}_3)\)
IR: 3320, 3030, 2911, 2361, 1497, 1454, 1355, 1310, 1226, 1158, 696, 673 cm$^{-1}$(neat).

HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{34}$H$_{34}$O$_5$S 555.2205; Found: 555.2203.

(2R,3S,4R,4aS,5R,10bS)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-9-methyl-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-b]pyran-5-ol (170b):

Yield: 117 mg, 71%, light yellow solid,

Mp: 128-131 $^\circ$C

$^1$H NMR: (CDCl$_3$, 400 MHz) $^{\delta}$H: 7.45-7.21 (m, 14H, Ar), 7.13-7.05 (m, 2H, Ar), 6.94 (s, 2H, Ar), 5.79 (d, $J$ = 4 Hz, 1H, H-5), 5.29 (d, $J$ = 5.6 Hz, 1H, H-10b), 4.89 (d, $J$ = 10.8 Hz, 1H, CH$_A$H$_B$Ph), 4.78-4.67 (m, 3H, CH$_A$H$_B$Ph, 2 x CH$_A$H$_A$Ph), 4.58-4.52 (m, 2H, CH$_A$H$_B$Ph), 3.79-3.65 (m, 4H, H-1’a, H-1’b, H-3 and H-4), 3.58-3.50 (m, 1H, H-2), 2.75-2.66 (m, 1H, H-4a), 2.28 (d, $J$ = 4.8 Hz, 1H, OH), 2.25 (s, 3H, CH$_3$);

$^{13}$C NMR: (CDCl$_3$, 100 MHz): $^{\delta}$C: 138.89, 137.9, 135.5, 130.8, 128.9, 128.5, 128.4, 127.9, 127.8, 127.7, 127.6, 127.4, 126.6, (Ar), 81.1 (C-3), 80.3 (C-4), 75.8 (CH$_2$Ph), 74.8 (CH$_2$Ph), 73.5 (CH$_2$Ph), 73.2 (C-5,C-2), 69.3 (C-10b, C-1’), 44.3 (C-4a), 21.0 (CH$_3$);

$\alpha\left[^{\circ}D\right]$ : +15.8 (c 0.1, CHCl$_3$)

IR: 3334.63, 2916, 2851, 1605.89, 1453, 1309, 1294, 1215, 1161 cm$^{-1}$(neat)

HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{35}$H$_{37}$O$_5$S$^+$ 569.2356; Found 569.2347.
(2R,3S,4R,4aS,5R,10bS)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-9-methoxy-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-b]pyran-5-ol (170c):

Yield 123.7 mg, 73%; yellowish solid

Mp: 96-100 °C

1H NMR: (CDCl3, 400 MHz) δH: 7.38-7.00 (m, 15H, Ar), 7.11-7.07 (m, 2H, Ar), 6.95 (d, J = 8.4 Hz, 1H, Ar), 6.76-6.72 (m, 1H, Ar), 5.48 (d, J = 4.0 Hz, 1H, H-5), 5.28 (d, J = 4.4 Hz, 1H, H-10b), 4.90 (d, J = 11.2 Hz, 1H, CH2HasPh), 4.76-4.64 (m, 3H, CH2HasPh, 2 x CH2HasPh), 4.55 (d, J = 12.0 Hz, 1H, CH2HasPh), 4.49 (d, J = 10.8 Hz, CH2HasPh), 3.78-3.68 (m, 4H, H-1’a, H-1’b, H-3 and H-4), 3.66 (s, 3H, OCH3), 3.58-3.52 (m, 1H, H-2), 2.74-2.66 (m, 1H, H-4a);

13C NMR: (CDCl3, 100 MHz) δC: 158.0, 138.5, 138.0, 137.9, 132.2, 128.5, 128.3, 128.0, 127.7, 127.6, 121.5, 115.5, 111.8, (Ar), 80.9 (C-3), 80.2 (C-4), 75.8 (CH2Ph), 74.8 (CH2Ph), 73.6 (CH2Ph), 73.2 (C-5,C-2), 69.4 (C-10b), 69.2 (C-1’), 55.3 (OCH3), 44.2 (C-4a).

IR: 3304, 2914, 2113, 1563, 1454, 1229, 1054, 1029, 696, 634 cm⁻¹ (neat)

[α]D: +14.0 (c 0.1, CHCl3)

HRMS (ESI-TOF) m/z: [M + H]+ Calcd for C35H40NO6S+ 602.2571; Found 602.2568.
(2R,3S,4R,4aS,5R,10bS)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-9-(tert-butyl)-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-b]pyran-5-ol (170d):

Yield: 141.7 mg, 80%; light cream white solid;

Mp: 126-130 °C

$^1$H NMR: (CDCl$_3$, 400 MHz) δH: 7.69 (s, 1H, Ar), 7.48-7.14 (m, 15H, Ar), 7.08-7.03 (m, 2H, Ar), 6.07 (d, $J$ = 8. Hz, 1H, Ar), 5.48 (t, $J$ = 3.4 Hz, 1H, H-5), 5.34 (d, $J$ = 6.0 Hz, 1H, H-10b), 4.91 (d, $J$ = 11.2 Hz, 1H, CH$_A$H$_{a}$Ph), 4.75-4.67 (m, 3H, CH$_A$H$_{b}$Ph, 2 x CH$_A$H$_{b}$Ph), 4.58 (d, $J$ = 12.0 Hz, 1H, CH$_A$H$_{B}$Ph), 4.46 (d, $J$ = 10.4 Hz, CH$_A$H$_{B}$Ph), 3.77-3.64 (m, 4H, H-1’a, H-1’b, H-3 and H-4), 3.56-3.51 (m, 1H, H-2), 2.73-2.69 (m, 1H, H-4a), 2.40 (d, $J$ = 2.8 Hz, 1H, OH), 1.26 (s, 9H, C(CH$_3$)$_3$);

$^{13}$C NMR: (CDCl$_3$, 100 MHz) δC: 148.73, 138.5, 137.9, 137.7, 130.3, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 126.3, 125.1, 124.5, (Ar), 80.9 (C-3), 80.3 (C-4), 75.7 (CH$_2$Ph), 74.98 (CH$_2$Ph), 73.6 (CH$_2$Ph), 73.1 (C-5,C-2), 69.4 (C-10b), 69.0 (C-1’), 44.4 (C-4a), 34.5,31.2 (C(CH$_3$)$_3$);

IR: 3566, 3036, 2901, 2868, 1496, 1454, 1361, 1263, 1207, 1092, 1027, 697, 617 cm$^{-1}$; (neat).

$\lbrack$α$\rbrack_D$: +38.0 (c 0.1, CHCl$_3$)

HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{38}$H$_{43}$O$_6$S$^+$ 611.2826; Found 611.2825.

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7.2.10. General procedure for the synthesis of 1,2-cis-2-C-hydroxymethyl-\(\alpha\)-aryl-C-glucosides 183a-d

To a solution of the hemithioacetal 170 (0.26 mmol) and nickel chloride hexahydrate (2.6 mmol) in a mixture of methanol (11 mL) and tetrahydrofuran (4 mL) at 0 °C was added sodium borohydride (7.8 mmol) in portions. After 10-30 min, the reaction mixture was filtered through a Celite® bed and the filtrate was dried under reduced pressure. The crude product was purified by column chromatography using ethylacetate:hexane (1:9) mixture as eluent to provide the corresponding glucosides 183a-d.

Phenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-hydroxymethyl-\(\alpha\)-D-glucopyranoside (183a):

Yield: 109.1 mg, 80%; colorless oil

\(^1\)H NMR: (400 MHz, CDCl\(_3\)): δ 7.40–7.15 (m, 20H, Ar), 5.10 (d, \(J = 3.6\) Hz, 1H, H-1), 4.68–4.49 (m, 6H, 3 x CH\(_2\)Ph), 4.25–4.16 (m, 1H, H-5), 4.02 (t, \(J = 4.4\) Hz, 1H, H-3), 3.83 (dd, \(J = 6.0\) and 10.0 Hz, 1H, H-6\(_a\)), 3.78–3.68 (m, 3H, H-4, H-6\(_b\), H-7\(_a\)), 3.53–3.44 (m, 1H, H-7\(_b\)), 2.40–2.22 (m, 1H, H-2), 1.79 (bs, 1H, OH);

\(^1\)C NMR: (100 MHz, CDCl\(_3\)): δ 139.8, 138.2, 138.1, 137.7, 128.5, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5, 127.2, 126.2 (Ar), 76.9 (C-3), 74.6 (C-5), 74.3 (C-4), 73.2 (CH\(_2\)Ph), 72.5 (CH\(_2\)Ph), 72.4 (CH\(_2\)Ph), 70.7 (C-1), 68.3 (C-6), 60.4 (C-7), 45.6 (C-2);

IR: 3464, 2862, 1496, 1453, 1070, 1027, 734, 696 cm\(^{-1}\)(neat)

[\(\alpha\)]\(_D\): +2.0 (c 0.1, CHCl\(_3\))

HRMS (ESI-TOF) \(m/z\): [M+H]\(^+\) calcd for C\(_{34}\)H\(_{37}\)O\(_5\) 525.2641; Found 525.2648.

3-Methylphenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-hydroxymethyl-\(\alpha\)-D-glucopyranoside (183b):
Yield: 117.6 mg, 84%; colorless oil

$^1$H NMR: (400 MHz, CDCl$_3$): $\delta$ 7.36-7.21 (m, 15H, Ar), 7.19 (d, $J = 7.6$ Hz, 1H, Ar), 7.16-7.10 (m, 2H, Ar), 7.05 (d, $J = 7.6$ Hz, 1H, Ar), 5.08 (d, $J = 3.6$ Hz, 1H, H-1), 4.65 (d, $J = 11.6$ Hz, 1H, CH$_A$H$_B$Ph), 4.64 (d, $J = 11.6$ Hz, 1H, CH$_A$H$_B$Ph), 4.60 (d, $J = 11.6$ Hz, 1H, CH$_A$H$_B$Ph), 4.60 (d, $J = 11.6$ Hz, 1H, CH$_A$H$_B$Ph), 4.54 (d, $J = 12.0$ Hz, 1H, CH$_A$H$_B$Ph), 4.48 (d, $J = 12.0$ Hz, 1H, CH$_A$H$_B$Ph), 4.22 (dd, $J = 5.6$ and 9.2 Hz, 1H, H-5), 4.02 (t, $J = 4.4$ Hz, 1H, H-3), 3.84 (dd, $J = 6.0$ and 10.0 Hz, 1H, H-6a), 3.79-3.71 (m, 3H, H-4, H-6b and H-7a), 3.51 (dd, $J = 5.6$ and 11.6 Hz, 1H, H-7b), 2.37-2.23 (m, 4H, H-2 and CH$_3$), 1.71 (bs, 1H, OH);

$^{13}$C NMR: (100 MHz, CDCl$_3$): $\delta$ 139.6, 138.1, 138.0, 137.7, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.0, 123.3, 74.5, 74.3, 73.2, 72.5, 70.8, 68.2, 60.5, 45.6, 21.5;

IR: 3474, 2862, 1495, 1453, 1068, 1026, 734, 696 cm$^{-1}$(neat)

$[\alpha]_D$: +4.6 (c 0.1, CHCl$_3$)

HRMS (ESI-TOF) m/z: [M+H]$^+$ calcd for C$_{35}$H$_{39}$O$_5$ 539.2797; Found 539.2795.

3-Methoxyphenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-hydroxymethyl-α-D-glucopyranoside (183c):
Yield  125.5 mg, 87%, Colorless oil

$^1$H NMR:  (400 MHz, CDCl$_3$): $\delta$ 7.38-7.19 (m, 16H, Ar), 6.94-6.86 (m, 2H, Ar), 6.78 (dd, $J = 2.4$ and 8.0 Hz, 1H, Ar), 5.08 (d, $J = 3.6$ Hz, 1H, H-1), 4.68-4.42 (m, 6H, 3 x CH$_2$Ph), 4.26-4.17 (m, 1H, H-5), 4.02 (t, $J = 4.4$ Hz, 1H, H-3), 3.87-3.70 (m, 7H, H-4, H-6a, H-6b, H-7a and OCH$_3$), 3.50 (dd, $J = 5.6$ and 11.6 Hz, 1H, H-7b), 2.38-2.21 (m, 1H, H-2), 1.74 (bs, 1H, OH);

$^{13}$C NMR:  (100 MHz, CDCl$_3$): $\delta$ 159.7, 141.5, 138.2, 138.1, 137.7, 129.3, 128.5, 128.3, 127.8, 127.7, 127.6, 118.4, 112.8, 111.9, 74.6, 74.2, 73.2, 72.5 (x 2), 70.5, 68.3, 60.4, 55.2, 45.7;

IR:   3476, 3030, 2923, 1747, 1601, 1492, 1455, 1436, 1367, 1256, 1069, 696, cm$^{-1}$ (neat)

$\alpha$:  + 5.50 (c 0.1, CHCl$_3$)

HRMS (ESI-TOF) $m/z$: [M+H]$^+$ calcd for C$_{35}$H$_{39}$O$_6$ 555.2747;  Found 555.2741.

3-tert-Butylphenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-hydroxymethyl-$\alpha$-D-glucopyranoside (183d):
Yield: 125.3 mg, 83%; colorless oil

$^1$H NMR: (400 MHz, CDCl$_3$): $\delta$ 7.43-7.11 (m, 19H, Ar), 5.11 (d, $J = 3.6$ Hz, 1H, H-1), 4.71-4.46 (m, 6H, 3 x CH$_2$Ph), 4.24-4.16 (m, 1H, H-5), 4.03 (t, $J = 4.4$ Hz, 1H, H-3), 3.89-3.71 (m, 4H, H-4, H-6a, H-6b, H-7a), 3.52 (dd, $J = 5.4$ Hz, 1H, H-7b), 2.39-2.21 (m, 1H, H-2), 1.78 (s, 1H, OH), 1.30 (s, 9H, C(CH$_3$)$_3$);

$^{13}$CNMR: (100 MHz, CDCl$_3$): $\delta$ 151.2, 139.3, 138.2, 138.1, 137.8, 128.5, 128.3, 127.9, 127.8, 127.7, 127.5, 124.2, 123.4, 123.3, 74.5 (x 2), 73.2, 72.6 (x 2), 71.2, 68.4, 60.6, 45.9, 34.7, 31.4;

[$\alpha$]$_D$: +7.50 (c 0.1, CHCl$_3$)

IR: 3464, 3030, 2952, 2867, 1604, 1585, 1495, 1364, 1027, 1071, 696, 616 cm$^{-1}$ (neat)

HRMS (ESI-TOF) $m/z$: [M+H]$^+$ calcd for C$_{38}$H$_{45}$O$_5$ 581.3267; Found 581.3266.

7.2.11. General procedure for the synthesis of 1,2-$cis$-2-C-formyl-$\alpha$-aryl-C-glucosides 184a-d and mannosides 184a’-d’

To a solution of hemithioacetal 170 (0.18 mmol) in acetone (2 mL) was added freshly prepared W-1 Raney nickel (1 spatula) and the reaction mixture was stirred at room temperature for 45 min. The reaction mixture was then filtered through a Celite® bed and the filtrate was dried under reduced pressure. The crude product was purified by column chromatography using ethylacetate:hexane (1:9) mixture as eluent to provide the corresponding carbaldehydes:

Phenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-carbaldehyde-$\alpha$-D-glucopyranoside (184a) and Phenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-carbaldehyde-$\alpha$-D-mannopyranoside (184a’):
Yield: 73.4 mg, 78%, colorless oil, 67:33 mixture of carbaldehyde 184a and 184a’

$^1$H NMR: (400 MHz, CDCl$_3$) for 184a: $\delta$ 9.58 (d, J = 2.4 Hz, 1H, CHO), 7.60–7.10 (m, 20H, Ar), 5.10 (d, J = 2.8 Hz, 1H, H-1), 4.54–4.33 (m, 5H, 2 x CH$_2$Ph and CH$_3$H$_2$Ph), 4.29 (d, J = 12.0 Hz, 1H, CH$_3$H$_2$Ph), 4.23 (dt, J = 2.2 and 6.8 Hz, 1H, H-5), 4.01 (t, J = 3.8 Hz, 1H, H-3), 3.85 (dd, J = 6.8 and 10.4 Hz, 1H, H-6a), 3.72–3.61 (m, 1H, H-6b). 3.52 (dd, J = 2.2 and 3.8 Hz, 1H, H-1, H-4), 2.71 (dd, J = 2.8 and 6.8 Hz, 1H, H-2);

$^{13}$C NMR: (100 MHz, CDCl$_3$) for 184a: $\delta$ 201.2 (CHO), 139.0, 138.1, 137.6, 137.4, 128.6, 128.5, 128.4, 128.3, 128.0, 127.8, 125.9 (Ar), 75.9 (C-3), 75.5 (C-5), 73.1 (CH$_2$Ph), 72.6 (C-4), 72.5 (CH$_2$Ph), 71.6 (CH$_2$Ph), 67.5 (C-1), 67.4 (C-6), 53.3 (C-2).

$^1$H NMR: (400 MHz, CDCl$_3$) for 184a’: $\delta$ 9.79 (d, J = 2.0 Hz, 1H, CHO), 5.21 (d, J = 5.2 Hz, 1H, H-1), 4.61 (d, J = 11.2 Hz, 1H, CH$_3$H$_2$Ph), 3.93 (dd, J = 4.4 and 6.8 Hz, 1H, H-3), 3.78 (t, J = 6.8 Hz, 1H, H-4) 3.16 (dt, J = 2.0 and 5.2 Hz, 1H, H-2);

$^{13}$C NMR: (100 MHz, CDCl$_3$) for 184a’: $\delta$ 202.0 (CHO), 138.1, 138.0, 137.9, 137.5, 128.5, 128.2, 128.1, 127.8, 127.7, 127.4, 126.7 (Ar), 76.3 (C-3), 74.0 (C-4), 73.8 (CH$_2$Ph), 73.5 (CH$_2$Ph), 73.3 (CH$_2$Ph), 71.8 (C-1), 68.6 (C-6), 52.9 (C-2).

IR: 2859, 1714, 1453, 1634, 1205, 1070, 734, 696 cm$^{-1}$(neat)

HRMS (ESI-TOF) m/z: [M+H]$^+$ calcd for C$_{34}$H$_{35}$O$_5$ 523.2484; Found 523.2777.

3-Methylphenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-carbaldehyde-$\alpha$-$\beta$-glucopyranoside (184b) and 3-Methylphenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-carbaldehyde-$\alpha$-$\beta$-mannopyranoside (184b’):
Yield: 77.3 mg, 80%, colorless oil, 96:4 mixture of carbaldehyde 184b and 184’

$^1$H NMR: (400 MHz, CDCl$_3$) δH: 9.63 (d, $J = 1.6$ Hz, 1H, CHO), 7.31-7.12 (m, 16H, Ar), 7.07 (bs, 1H, Ar), 7.00 (dd, $J = 7.6$ and 16.0 Hz, 2H, Ar), 5.12 (s, 1H, H-1), 4.61-4.24 (m, 7H, 3 x CH$_2$Ph and H-5), 4.09-4.02 (m, 1H, H-3), 3.90 (dd, $J = 7.2$ and 10.0 Hz, H-6a), 3.70 (dd, $J = 6.0$ and 10.0 Hz, 1H, H-6b), 3.59-3.53 (m, 1H, H-4), 2.74 (bs, 1H, H-2), 2.25 (s, 3H, CH$_3$);

$^{13}$CNMR: (100 MHz, CDCl$_3$) δ 201.4, 138.9, 138.2, 138.1, 137.6, 137.3, 128.6, 128.4, 128.3, 128.1, 128.0, 127.8, 127.6, 126.6, 122.9, 75.9, 75.5, 73.1, 72.6, 72.4, 71.5, 67.4, 67.3, 53.1, 21.5.

IR: 2862, 1712, 1453, 1363, 1068, 734, 696 cm$^{-1}$(neat)

$[\alpha]_D$: +12.1 (c 0.1, CHCl$_3$)

HRMS (ESI-TOF) m/z: [M+H]$^+$ calcd for C$_{35}$H$_{37}$O$_5$ 537.2641; Found 537.2657.

3-Methoxyphenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-carbaldehyde-α-D-glucopyranoside (184c) and 3-Methoxyphenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-carbaldehyde-α-D-mannopyranoside (184c’):
Yield: 83.6 mg, 84%; colorless oil, 96:4 mixture of carbaldehyde 184c and 184c’

$^1$H NMR: (400 MHz, CDCl$_3$) for 184c: $\delta$ 9.70 (d, $J = 2.4$ Hz, 1H, CHO), 7.38-7.16 (m, 16H, Ar), 6.93 (d, $J = 7.2$ Hz, 1H, Ar), 6.84 (d, $J = 7.6$ Hz, 1H, Ar), 6.78 (dt, $J = 2.4$ and 6.0 Hz, 1H, Ar) 5.19 (d, $J = 2.4$ Hz, 1H, H-1), 4.69-4.47 (m, 5H, CH$_2$Ph), 4.40 (d, $J = 11.6$ Hz, 1H, CH$_{A\beta}$Ph), 4.37-4.32 (m, 1H, H-5), 4.12 (t, $J = 3.8$ Hz, 1H, H-3), 3.96 (dd, $J = 6.8$ and 10.0 Hz, 1H, H-6a), 3.81-3.75 (m, 4H, H-6b and OCH$_3$), 3.64 (t, 3.0 Hz, 1H, H-4), 2.83-2.77 (m, 1H, H-2);

$^{13}$CNMR: (100 MHz, CDCl$_3$) for 184c: $\delta$ 201.1, 159.9, 140.8, 138.1, 137.6, 137.4, 129.5, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 118.1, 113.1, 111.6, 76.0, 75.6, 73.1, 72.6, 72.5, 71.6, 67.4 (x2), 55.3, 53.3; $^1$H NMR (400 MHz, CDCl$_3$) for 184c’: $\delta$ 9.93 (d, $J = 1.6$ Hz, 1H, CHO), 5.31 (d, $J = 4.8$ Hz, 1H, H-1), 4.73 (d, $J = 11.2$ Hz, 1H, CH$_{A\alpha}$Ph), 4.08-4.02 (m, 1H, H-3), 3.27 (dt, $J = 1.6$ and 4.4 Hz, 1H, H-2);

[α]D: +14.5 (c 0.1, CHCl$_3$)

IR: 2862, 1714, 1600, 1585, 1491, 1453, 1262, 1069, 735, 696 cm$^{-1}$ (neat)

HRMS (ESI-TOF) m/z: [M+H]$^+$ calcld for C$_{35}$H$_{37}$O$_6$ 553.2590; Found 553.2596.

3-tert-Butylphenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-carbaldehyde-α-D-glucopyranoside (184d) and 3-tert-Butylphenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-carbaldehyde-α-D-mannopyranoside (184d’):

Yield: 89.5 mg, 86%, colorless oil 89:11 mixture of carbaldehyde 184d and 184d’
**1H NMR:** (400 MHz, CDCl₃) for 184d δ 9.71 (d, $J = 2.0$ Hz, 1H, CHO), 7.40-7.8 (m, 18H, Ar), 7.12 (d, $J = 6.4$ Hz, 1H, Ar), 5.22 (d, $J = 2.0$ Hz, 1H, H-1), 4.70-4.46 (m, 5H, CH₂Ph), 4.41 (d, $J = 11.6$ Hz, 1H, CH₃H₃Ph), 4.38-4.29 (m, 1H, H-5), 4.13 (t, $J = 4.0$ Hz, 1H, H-3), 3.96 (dd, $J = 6.6$ and 10.4 Hz, 1H, H-6a), 3.80 (dd, $J = 6.0$ and 10.4 Hz, 1H, H-6b), 3.66 (t, $J = 3.2$ Hz, 1H, H-4), 2.82 (bd, $J = 3.2$ Hz, 1H, H-2), 1.29 (s, 9H, C(CH₃)₃);

**13CNMR:** (100 MHz, CDCl₃) for 184d δ 201.3, 151.5, 138.7, 138.2, 137.7, 137.5, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 124.4, 123.2, 122.9, 76.2, 75.5, 73.1, 72.8, 72.7, 71.7, 68.0, 67.6, 53.5, 34.7, 31.4;

**1H NMR:** (400 MHz, CDCl₃) for 184d' δ 9.94 (d, $J = 1.6$ Hz, 1H, CHO), 6.96 (d, $J = 7.6$ Hz, 1H, Ar), 3.41-3.32 (m, 1H, H-2), 1.26 (s, 9H, C(CH₃)₃);

IR: 2864, 1687, 1491, 1453, 1363, 1073, 734, 697 cm⁻¹ (neat);

$[\alpha]_D$: +16.3 (c 0.1, CHCl₃);

HRMS (ESI-TOF) m/z: [M+H]⁺ calcd for C₃₈H₄₃O₅ 579.3110; Found 579.3126.

### 7.2.12. General procedure for the synthesis of 1,2-cis-2,3-unsaturated-2-C-formyl-α-aryl-C-glucosides (187a-c)

To a solution of 2-C-formyl-α-aryl glucoside 184 (0.19 mmol) in methanol (3 mL) was added a catalytic amount of K₂CO₃ and the resulting reaction mixture was stirred for 30 min at room temperature. After completion of the reaction, the reaction mixture was diluted with water (5 mL). The solution was then extracted with ethyl acetate (5 mL) three times. The combined organic layers were dried over MgSO₄, filtered and the filtrate was evaporated to dryness under reduced pressure. The crude product was purified by flash column chromatography using ethyl acetate: hexane (1:9) mixture as eluent to provide the corresponding 2,3-unsaturated carbaldehydes 187a-c.

(1-Phenyl-2,3-dideoxy-C-2-formyl-4,6-di-O-benzyl-1,5-anhydro-α-arabino-hex-2-enitol (187a)
Yield: 72.4 mg, 92%, colorless oil

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta$ 9.46 (s, 1H, CHO), 7.31-7.17 (m, 1H, Ar), 7.01 (s, 1H, H-3), 5.57 (s, 1H, H-1), 4.59 (d, $J = 11.6$ Hz, 1H, CH$_A$H$_B$Ph), 4.50 (d, $J = 12.0$ Hz, 1H, CH$_A$H$_B$Ph), 4.48-4.43 (m, 2H, CH$_A$H$_B$Ph and H-4), 4.37 (d, $J = 12.0$ Hz, 1H, CH$_A$H$_B$Ph), 3.57 (dd, $J = 3.2$ and 10.4 Hz, 1H, H-6$_a$), 3.53-3.42 (m, 2H, H-5 and H-6$_b$);

$^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$ 191.0 (CHO), 147.9, 141.8, 137.7, 137.3, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 126.9, 73.3, 73.2, 72.3, 70.3, 69.5, 68.3;

$\alpha$: +15.6 (c 0.1, CHCl$_3$)

IR: 2856, 1686, 1495, 1453, 1179, 1072, 869, 733, 696 cm$^{-1}$ (neat)

HRMS (ESI-TOF) $m/z$: [M+NH$_4$]$^+$ calcd for C$_{27}$H$_{30}$NO$_4$ 432.2175; Found 432.2167.

1-(m-Tolyl)-2,3-dideoxy-C-2-formyl-4,6-di-O-benzyl-1,5-anhydro- L-arabino-hex-2-enitol (187b)
Yield: 77.3 mg, 95%, colorless oil

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta$ 9.50 (s, 1H, CHO), 7.37-7.13 (m, 11H, Ar), 7.11-7.01 (m, 4H, H-3 and Ar), 5.57 (s, 1H, 5.57 (s, 1H, H-1), 4.64 (d, $J = 10.8$ Hz, 1H, $CH_AH_BPh$), 4.55 (d, $J = 11.6$ Hz, 1H, $CH_AH_BPh$), 4.51-4.45 (m, 2H, H-4 and $CH_AH_BPh$), 4.37 (d, $J = 12.0$ Hz, 1H, $CH_AH_BPh$), 3.64-3.53 (m, 2H, H-5 and H-6a), 3.51 (d, $J = 10.4$ Hz, 1H, H-6b), 2.29 (s, 3H, CH$_3$);

$^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$ 191.0, 147.6, 141.9, 138.0, 137.8, 137.4, 137.2, 129.5, 129.2, 128.5, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 126.9, 125.7, 73.3, 73.2, 72.4, 70.5, 69.6, 68.5, 65.3, 21.4;

$[\alpha]_D$: +14.3 (c 0.1, CHCl$_3$)

IR: 2860, 1686, 1495, 1453, 1179, 1072, 869, 734, 697 cm$^{-1}$ (neat)

HRMS (ESI-TOF) $m/z$: [M+H]$^+$ calcd for C$_{28}$H$_{29}$O$_4$ 429.2066; Found 429.2053.

1-(m-tert-Butylphenyl)-2, 3-dideoxy-C-2-formyl-4,6-di-O-benzyl-1,5-anhydro-D-arabinohex-2-enitol (187c)

![187c]

Yield: 84 mg, 94%, colorless oil

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta$ 9.51 (s, 1H, CHO), 7.37 (s, 1H, Ar), 7.34-7.14 (m, 12H, Ar), 7.04 (s, 1H, H-3), 6.96 (d, $J = 7.2$ Hz, 1H, Ar), 5.61 (s, 1H, H-1), 4.63 (d, $J = 11.6$ Hz, 1H, $CH_AH_BPh$), 4.55 (d, $J = 12.0$ Hz, 1H, $CH_AH_BPh$), 4.53-4.43 (m, 2H, H-4 and $CH_AH_BPh$), 4.36 (d, $J = 12.0$ Hz, 1H, $CH_AH_BPh$), 3.64-3.55 (m, 2H, H-5 and H-6a), 3.52 (d, $J = 10.4$ Hz, 1H, H-6b), 1.26 (s, 9H, C(CH$_3$)$_3$);
13C NMR: (100 MHz, CDCl3) δ 191.0, 151.3, 147.6, 142.3, 137.8, 137.5, 137.0, 128.5, 128.3, 128.1, 128.0, 127.7, 126.0, 125.4, 73.4, 73.3, 72.2, 70.5, 69.6, 68.6, 34.7, 31.3;

[IR: 2856, 1686, 1495, 1453, 1179, 1072, 869, 734, 697 cm⁻¹ (neat)]

[α]D: +17.0 (c 0.1, CHCl3)

HRMS (ESI-TOF) m/z: [M+H]+ calcd for C31H35O4 471.2535; Found 471.2532

7.2.13 Preparation of NaHSO4 Supported on silica gel
4.14 g (0.03 mol) of NaHSO4·H2O dissolved in 20 mL of water was prepared in 100 mL beaker equipped with a stirrer. To this solution was added 10 g of SiO2 (column chromatographic grade, 60 Å, 200-400 mesh). The mixture was stirred for 15 min and then gently heated until the sticky mixture was free flowing. The catalyst was then dried further by putting it in oven at 120 °C for 48 hours.

7.2.14 General procedure for Ferrier rearrangement of glycals using NaHSO4 supported on silica
To a solution of a glycol (1.8 mmol) in CH3CN (1 mL) NaHSO4-SiO2 (12 mg, 3.0 mmol NaHSO4/g) 31 was added. The resulting mixture was stirred at 80°C (room temperature for 3,4,6-tri-O-benzyl-α-D-glucal) until TLC analysis showed complete disappearance of the starting material. After adding silica gel to the reaction mixture at room temperature, the solvent was evaporated under reduced pressure without heating until a free-flowing solid was obtained. The resulting solid was purified by column chromatography using 1:9 ethyl acetate: hexane eluent to afford pure 2,3-unsaturated glycosides.

Benzyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (196a)
Yield: 524.6 mg, 91%; Colorless oil

$^1$H NMR: (400 MHz, CDCl₃): δ 7.4–7.3 (m, 5H), 5.79 (dd, $J = 10.38$ and 0.95 Hz, 1H, H-3), 5.80 (ddd, $J = 10.22$, 2.48 and 1.76 Hz, 1H), 5.23 (ddd, $J = 9.33$, 2.90 and 1.45 Hz, 1H), 5.04 (d, $J = 1.77$ Hz, 1H), 4.71 (d, $J = 11.71$ Hz, 1H), 4.52 (d, $J = 11.71$ Hz, 1H), 4.19–4.13 (m, 1H, H-6), 4.10–4.01 (m, 2H), 2.01 and 1.99 (s, 3H);

$^{13}$C NMR: (100 MHz, CDCl₃): δ 170.7, 170.2, 137.6, 129.2, 128.4, 128.0, 127.8, 127.7, 126.9, 93.6, 70.2, 67.1, 65.3, 62.9, 20.9, 20.7 (spectroscopic data is in agreement with reported values).³

**Allyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (196b)**

![Diagram](attachment:196b.png)

Yield: 350.3 mg, 72%; Crystalline solid

Mp: 40 °C - 42 °C

$^1$H NMR: (400 MHz, CDCl₃): δ 7.51 (d, 2H, $J = 7.2$ Hz), 7.29–7.17 (m, 3H), 6.03 (d, $J = 10.2$ Hz, 1H), 5.83 (d, 1H, $J = 10.8$ Hz), 5.73 (s, 1H), 5.35 (d, 1H, $J = 9.6$ Hz), 4.60–4.13 (m, 3H), 2.07 (s, 3H), 2.03 (s, 3H);

$^{13}$C NMR: (100 MHz, CDCl₃): δ 170.7, 170.2, 134.7, 131.7, 128.9, 128.5, 127.6, 83.6, 67.2, 65.0, 63.0, 20.9, 20.7 (spectroscopic data is in agreement with reported values).³

**2'-Propyn-1'-yl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (196c)**

Yield: 524.6 mg, 91%; Colorless oil

$^1$H NMR: (400 MHz, CDCl₃): δ 7.4–7.3 (m, 5H), 5.79 (dd, $J = 10.38$ and 0.95 Hz, 1H, H-3), 5.80 (ddd, $J = 10.22$, 2.48 and 1.76 Hz, 1H), 5.23 (ddd, $J = 9.33$, 2.90 and 1.45 Hz, 1H), 5.04 (d, $J = 1.77$ Hz, 1H), 4.71 (d, $J = 11.71$ Hz, 1H), 4.52 (d, $J = 11.71$ Hz, 1H), 4.19–4.13 (m, 1H, H-6), 4.10–4.01 (m, 2H), 2.01 and 1.99 (s, 3H);

$^{13}$C NMR: (100 MHz, CDCl₃): δ 170.7, 170.2, 137.6, 129.2, 128.4, 128.0, 127.8, 127.7, 126.9, 93.6, 70.2, 67.1, 65.3, 62.9, 20.9, 20.7 (spectroscopic data is in agreement with reported values).³
Cyclohexyl 4, 6-di-O-acetyl-2, 3-dideoxy-α-D-erythro-hex-2-enopyranoside (196d)

Yield: 502.4 mg, 85%; colorless oil

$^1$H NMR: (400 MHz, CDCl$_3$): $\delta$ 5.87–5.78 (m, 2H), 5.30–5.28 (dd, $J = 1.3$, 9.2 Hz), 5.17 (s, 1H), 4.24–4.16 (m, 3H), 3.68–3.61 (m, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 1.96–1.90 (m, 2H), 1.80–1.67 (m, 2H), 1.57–1.50 (m, 1H), 1.43–1.17 (m, 5H);

$^{13}$C NMR: (100 MHz, CDCl$_3$): $\delta$ 170.74, 170.30, 128.70, 128.50, 92.75, 76.69, 66.71, 65.40, 63.12, 33.73, 32.10, 25.51, 24.35, 24.12, 20.93, 20.70 (spectroscopic data is in agreement with reported values).

$n$-Butyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (196e)

Yield: 434.3 mg, 90%; White solid

Mp: 56 °C - 58 °C

$^1$H NMR: (400 MHz, CDCl$_3$): $\delta$ 5.92 (d, 1H, $J = 10.2$ Hz), 5.84 (ddd, 1H, $J = 10.2$, 2.7, 1.9 Hz), 5.34 (m, 1H), 5.24 (br s, 1H), 4.31 (d, 2H, $J = 2.3$ Hz), 4.27-4.22 (m 1H), 4.20-4.17 (m, 1H), 4.11-4.07 (m, 1H), 2.47 (t, 1H, $J = 2.3$ Hz), 2.10 (s, 3H), 2.08 (s, 3H);

$^{13}$C NMR: (100 MHz, CDCl$_3$) 170.7, 170.2, 129.8, 127.2, 92.8, 79.1, 74.8, 67.2, 65.2, 62.8, 55.0, 20.9, 20.8 (spectroscopic data is in agreement with reported values).
Yield 412.3 mg, 80%; Oily liquid

$^1$H NMR: (400 MHz, CDCl$_3$) 5.89-5.81 (m, 2H), 5.30 (dd, 1H, J = 9.6 and 1.3 Hz), 5.02 (br s 1H), 4.27-4.16 (m, 2H), 4.13-4.08 (m, 1H), 3.81-3.75 (m, 1H), 3.54-3.49 (m, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 1.66-1.53 (m, 2H$_2$), 1.46-1.33 (m, 2H), 0.93 (t, 3H, J = 7.3 Hz)

$^{13}$C NMR: $\delta$C (100 MHz, CDCl$_3$) 170.7, 170.2, 128.9, 127.9, 94.3, 68.5, 66.8, 65.2, 63.0, 31.7, 20.8, 20.7, 19.3, 13.7. (Spectroscopic data is in agreement with reported values).$^8$

Phenyl 4,6-di-O-acetyl-2,3-dideoxy-1-thio-$\alpha$-D-erythro-hex-2-enopyranoside (196f)

Yield 556.6 mg, 96%; Colorles oil

$^1$H NMR: (400 MHz, CDCl$_3$) 7.55-7.53 (m, 2H), 7.32-7.26 (m, 3H), 6.05 (ddd, 1H, J = 10.1, 2.8, 1.8 Hz), 5.86 (dt, 1H, J = 10.1, 1.8 Hz), 5.75 (br s, 1H), 5.37 (ddd, 1H, J 9.5, 1.8 Hz), 4.50-4.44 (m, 1H), 4.33-4.15 (m, 2H), 2.10 (s, 3H), 2.06 (s, 3H$_2$);

$^{13}$C NMR: (100 MHz, CDCl$_3$) 170.7, 170.2, 131.7, 128.9, 128.5, 127.6, 83.6, 67.3, 65.1, 63.0, 20.9, 20.7. (Spectroscopic data is in agreement with reported values).$^9$
2-Mercaptoethyl-4,6-di-O-acetyl-2,3-dideoxy-α-erythro-1-thio-hex-2-enopyranoside (196g):

![Structure of 196g]

Yield 303 mg, 55%; Colorless oil

\(^1\)H NMR: (CDCl\(_3\), 400 MHz): \(\delta\) 5.91 (dd, 1H, \(J = 2.0\) and 9.6 Hz), 5.89 (d, 1H, \(J = 10.0\) Hz), 5.59 (s, 1H), 5.34 (dd, 1H, \(J = 6.6\) and 10.8 Hz), 4.20-4.10 (m, 3H), 2.90-2.68 (m, 4H), 2.08 (s, 3H), 2.05 (s, 3H), 1.65 (t, 1H, \(J = 16.0\) Hz);

\(^{13}\)C NMR: (CDCl\(_3\), 100 MHz): 171.1, 170.6, 128.9, 127.6, 81.3, 67.3, 65.4, 63.4, 36.9, 25.6, 21.3, 21.2; HRMS [M+H]\(^+\) = 307.0665.

Dodecanyl-4,6-di-O-acetyl-2,3-dideoxy-α-erythro-1-thio-hex-2-enopyranoside (196h):

![Structure of 196h]

Yield 311.1 mg, 60%; Yellowish oil,

\(^1\)H NMR: (CDCl\(_3\), 400 MHz): \(\delta\) 5.91 (d, 1H, \(J = 10.4\) Hz), 5.75 (d, 1H, \(J = 10.4\) Hz), 5.52 (s, 1H), 4.35-4.20 (m, 2H), 4.14 (d, 1H, \(J = 11.2\) Hz), 2.75-2.65 (m, 1H), 2.64-2.50 (m, 1H), 2.07 (s, 3H), 2.06 (s, 3H), 1.70-1.50 (m, 2H), 1.40-1.10 (m, 17H), 0.90-0.70 (m, 4H);

\(^{13}\)C NMR: (CDCl\(_3\), 100 MHz): 170.8, 170.3, 129.1, 126.7, 80.4, 66.8, 65.1, 63.0, 32.0, 31.9, 30.0, 29.6 (x 3), 29.5, 29.3, 29.2, 28.9, 22.7, 21.0, 20.8, 14.1.
HRMS (ESI) m/z (M+Na): calcd 437.2338; found 437.2328

5-mercaptopentyl-4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-1-thio-hex-2-enopyranoside (196i):

![Chemical Structure](image)

Yield 313.6 mg, 50%; Colorless oil,

\(^1\)H NMR: (CDCl\textsubscript{3}, 400 MHz) \(\delta\): 5.95 (ddd, 1H, \(J = 2.0, 3.2\) and 10.0 Hz), 5.75 (td, 1H, \(J = 1.6\) and 10.4 Hz), 5.58–5.50 (m, 1H), 5.34 (dd, 1H, \(J = 2.0\) and 9.2 Hz), 4.30–4.20 (m, 2H), 4.13 (d, 1H, \(J = 10.0\) Hz), 2.80–2.55 (m, 2H), 2.50 (q, 2H, \(J = 7.2\) and 14.4 Hz), 2.07 (s, 3H), 2.06 (s, 3H), 1.69–1.59 (m, 4H), 1.49–1.40 (m, 2H), 1.31 (t, 1H, \(J = 7.8\) Hz);

\(^{13}\)C NMR: (CDCl\textsubscript{3}, 100 MHz) \(\delta\)C 170.7, 170.3, 129.0, 126.8, 80.3, 66.8, 65.0, 62.9, 33.4, 31.8, 29.4, 27.5, 24.4, 21.0, 20.8;

HRMS (ESI) m/z (M+Na): calcd 371.4678; found 371.4671

Methyl 4, 6-di-O-benzyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (197a)

![Chemical Structure](image)

Yield 122.5 mg, 20%; colorless oil,

\(^1\)H NMR: (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.67–7.48 (m, 10H), 5.98–5.84 (m, 2H), 5.36–5.33 (dd, 2H, \(J = 1.2, 9.6\) Hz), 5.07 (s, 1H), 4.31–4.12 (m, 3H), 3.88–3.83 (m, 1H), 3.63–3.58 (m, 1H), 1.30–1.25 (t, \(J = 7.2\) Hz, 3H);
\[^{13}\text{C NMR}\] (100 MHz, CDCl\textsubscript{3}): \(\delta\) 170.94, 129.21, 128.21, 94.46, 67.05, 65.53, 64.47, 63.23, 21.15, 20.95, 15.50 (spectroscopic data is in agreement with reported values).\(^{11}\)

**Benzyl 4,6-di-O-benzyl-2,3-dideoxy-\(\alpha\)-\(\text{D-erythro}\)-hex-2-enopyranoside (197b)**

\(197\text{b}\)

**Yield** 674.7 mg, 90%; yellow oil,

\[^{1}\text{H NMR}\] (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.4–7.2 (m, 15H), 6.09 (d, \(J = 10.28\) Hz), 5.79 (dt, \(J = 10.16\) Hz, 2.25Hz, 2.5 Hz and 2.16 Hz), 5.13 (br s, 1H), 4.82–4.40 (m, 6H), 4.19 (d, \(J = 9.41\) Hz, 1H), 4.00 (d, \(J = 10.04\) Hz, 1H), 3.73 (dd, \(J = 10.66\) and 3.84 Hz, 1H), 3.63 (dd, \(J = 10.56\) and 2.0 Hz, 1H);

\[^{13}\text{CNMR}\]: (100MHz, CDCl\textsubscript{3}): \(\delta\) 138.2–137.9, 128.5 127.5, 130.8, 126.5, 93.9, 73.4, 71.0, 70.0, 70.4, 69.3, 68.8 (spectroscopic data is in agreement with reported values).\(^{12}\)

**2-Mercaptoethyl-4,6-di-O-benzyl-2,3-dideoxy-\(\alpha\)-\(\text{D-erythro}\)-1-thio-hex-2-enopyranoside (197c):**

\(197\text{c}\)

Yeld: 463.8 mg, 64%; Colorless oil

\[^{1}\text{H NMR}\]: (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 7.35-7.26 (m, 10H), 6.00 (d, 1H, \(J = 10.0\) Hz), 5.85 (td, 1H, \(J = 5.8\) and 12.4 Hz), 5.60 (s, 1H), 4.65 (d, 1H, \(J = 12.0\) Hz), 4.60 (d, 1H, \(J = 11.2\) Hz), 4.50 (d, 1H, \(J = 12.0\) Hz), 4.40 (d, 1H, \(J = 11.6\) Hz), 4.20 (dd, 1H, \(J = 1.2\) and 9.2 Hz), 4.10 (dd, 1H, \(J = 1.6\) and 9.2 Hz), 3.78 (dd, 1H, \(J = 4.0\) Hz).
and 10.4 Hz), 3.70 (dd, 1H, \( J = 1.2 \) and 10.8 Hz), 3.00-2.70 (m, 4H), 1.66 (t, 1H, \( J = 8.0 \) Hz);


**Dodecanyl-4,6-di-\( O \)-benzyl-2,3-dideoxy-\( \alpha \)-\( \delta \)-erythro-1-thio-hex-2-enopyranoside (197d):**

![197d](image)

Yield: 484.5 mg, 70%, Yellowish oil

\(^{1}\text{H NMR:}\) (CDCl\(_3\), 400 MHz): \( \delta \) 7.40-7.10 (m, 10H), 5.93 (d, 1H, \( J = 10.0 \) Hz), 5.84 (d, 1H, \( J = 11.2 \) Hz), 5.53 (s, 1H), 4.70-4.37 (m, 4H), 4.23(d, 1H, \( J = 9.2 \) Hz), 4.15 (d, 1H, \( J = 9.2 \) Hz), 3.80-3.60 (m, 2H), 2.75-2.50 (m, 2H), 1.70-1.50 (m, 2H), 1.40-1.10 (m, 17H), 0.90-0.70 (m, 4H);

\(^{13}\text{C NMR:}\) (CDCl\(_3\), 100 MHz): \( \delta \) 138.2, 138.1, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 80.6, 73.4, 73.3, 71.1, 70.2, 69.0, 68.9, 32.0, 31.9, 30.1, 29.7, 29.6, 29.5, 29.3, 29.2, 28.9, 22.7

HRMS: (ESI) m/z (M+Na): calcd 533.3065; found 533.3063

**7.2.15. General procedure for the Synthesis of 1,2-cis-2- phosphonate-\( \alpha \)-aryl-C-glucoside.**

To a mixture of the glucoside (0.11 mmol) and triethylamine (0.11 mmol) in dry toluene (10.0 mL) was added drop wise to chlorodiphenylphosphine (24.3 mg, 0.11 mmol) at 0 °C. The ice bath was removed and the reaction mixture was refluxed for 30 minutes. Upon the completion of the reaction (judged by TLC), water (10.0 mL) was added, followed by extraction with DCM (3 x 10.0 mL). The combined organic phase was dried over anhydrous MgSO\(_4\) and the solvent was removed on a rotary evaporator. The crude mixture was purified by column chromatography (silica gel, ethyl acetate/ hexane 2:3) to give the product.
3-tert-Butylphenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-methyl diphenylphosphinate -α-D-glucopyranoside (200)

Yield: 75.6 mg, 88%, colorless oil

H NMR: (400 MHz, CDCl₃): δ 7.45-6.99 (m, 29H, Ar), 5.07 (d, J = 3.2 Hz, 1H, H-1), 4.53-4.48 (m, 6H, 3 x CH₂Ph), 4.46-4.25 (m, 1H, H-5), 4.03 (t, J = 4.3 Hz, 1H, H-3), 3.89-3.70 (m, 4H, H-4, H-6a, H-6b, H-7a), 3.56 (dd, J = 5.4 Hz, 1H, H-7b), 2.59-2.45 (m, 1H, H-2), 1.18 (s, 9H, C(CH₃)₃);

C NMR: (100 MHz, CDCl₃): δ 151, 139.9, 138.2, 138, 132, 131.8, 131.5, 131.4, 128.4 (x2), 128.3, 128.2, 127.9, 127.7, 127.6, 127.5, 124.1, 123.4, 74.9, 74, 73.1, 72.3, 72.2, 70.4, 68.2, 62.4, 62.3, 44.3(x2)34.6, 31.3

P NMR: (121.5 MHz, CDCl₃): δ 31.1

[α]D: +10.50 (c 0.1, CHCl₃)

IR: 2863, 1591, 1453, 1364, 1068, 1225, 1087, 728, 694 cm⁻¹ (neat)

HRMS (ESI-TOF) m/z: [M+H]+ calcd for C₅₀H₅₄O₆P 781.3658; Found 781.3656.

7.2.16 General procedure for the preparation of 1,2-cis-2-thiophosphonate-α-aryl-C-glucoside.

To a mixture of the glucoside (0.11 mmol) and triethylamine (11.0 mmol) in dry toluene (10.0 mL) was added drop wise to chlorodiphenylphosphine (24.3 g, 0.11 mmol) at 0 °C. The ice bath was removed and the reaction mixture was refluxed for 30 minutes and 1.1 equivalence of elemental sulfur dissolved in toluene was added and heated at reflux for 30 minutes. The
progress of the conversion was monitored by TLC analysis. Upon completion of the reaction, the reaction mixture was cooled to room temperature. The excess sulfur was filtered off and the filtrate was concentrated on a rotary evaporator to give a solid crude product, which was further purified by column chromatography (silica gel, ethyl acetate/hexane 1:4).

**3-Methylphenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-methyl diphenylphosphinothioate -α-D-glucopyranoside (201)**

![Structure of 3-Methylphenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-methyl diphenylphosphinothioate -α-D-glucopyranoside (201)](image)

**Yield:** 72.2 mg, 87%, colorless oil

**1H NMR:** (400 MHz, CDCl₃): δ 7.58-6.99 (m, 29H, Ar), 5.03 (d, J = 2.8 Hz, 1H, H-1), 4.58-4.35 (m, 6H, 3 x CH₂Ph), 4.28-4.20 (m, 1H, H-5), 4.02 (t, J = 4.4 Hz, 1H, H-3), 3.87-3.70 (m, 4H, H-4, H-6ₐ, H-6ₐ, H-7ₐ), 3.50 (dd, J = 5.6 and 11.6 Hz, 1H, H-7ₐ), 2.59-2.49 (m, 1H, H-2), 2.29 (s, 1H, CH₃);

**13C NMR:** (100 MHz, CDCl₃): δ 139.3, 138.1, 138, 137.9, 137.7, 134.8, 133.7 (x2), 131.5 (x2), 131 (x2), 130.9 (x2), 128.4, 128.3 (x2), 128.2 (x2) 128.1 (x2), 127.8, 127.7, 127.6 (x2), 125.5, 127.2, 123.6 75.2, 74.9, 74.2, 74.1, 73.1, 72.3, 72.2, 70.1, 68, 62.1 (x2) 60.4, 44.3, 44.2, 21.5

**31P:** (121.5 MHz, CDCl₃): δ 81.5

**IR:** 2859, 2360, 1587, 1453, 1437, 1066, 1007, 993, 727, 692 cm⁻¹ (neat)

[α]D: + 8.50 (c 0.1, CHCl₃)

**HRMS (ESI-TOF) m/z:** [M+H]⁺ calcd for C₄₇H₄₈O₅PS 755.2960; Found 755.2953.
7.3 References