Studies Towards the Synthesis of Tagetitoxin

By

Yannick Gama

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Abstract

The natural product tagetitoxin is a phytotoxin which was first isolated from the bacterium *Pseudomonas syringae* pv. *tagetis* in 1981. Tagetitoxin is an inhibitor of chloroplast and bacteria RNAP and also selectively inhibits RNAP III in eukaryotes. Multiple biological mechanisms of inhibition and several structures have been proposed for tagetitoxin. The structural ambiguity and potential useful biological activity have driven the desire for a total synthesis of tagetitoxin’s proposed structures; none of which of yet have been successful.

This body of research describes the recent developments our group has contributed towards the synthesis of tagetitoxin. The main objective was to synthesize targets 323a and 323b which both contain the oxathiobicyclo[3.3.1]nonane ring system found in two of the proposed structures of tagetitoxin.

Our initial strategy focused on four synthetic routes derived from diacetone mannose (DAM). In this strategy, the route nearest to obtaining the bicyclic core of 323a and 323b was the dithiane-reduction route. In this route, the target precursors 389 and 415 (and analogues) were made, but attempted thioacetate deprotection and concomitant cyclization of the thiol/thiolate onto a ketone or sulfonate ester to yield the oxathiobicyclo[3.3.1]nonane ring system led to either decomposition or complex mixtures. This failure was attributed to the presence of isopropylidene groups hampering the cyclization by imposing steric constraints on ring closure.

We then conducted synthetic routes starting from D-galactose in the D-galactose and *exo*-glycal routes (avoiding the use of any isopropylidene groups). Failure to insert a hydroxyl-methylene group on the C-1 position by anomeric nitrile anion chemistry or ring-opening an anomeric *spiro*-epoxyacetal with TMSCN led us to attempt a hydroboration-oxidation on an *exo*-galactal derivative which was partially successful. Optimization of the hydroboration-oxidation pathway in the *exo*-glycal route is promising for future research.
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### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>1D</td>
<td>One Dimensional</td>
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<tr>
<td>2D</td>
<td>Two Dimensional</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-Borabicyclo[3.3.1]nonane</td>
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<tr>
<td>Ac</td>
<td>Acetyl</td>
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<tr>
<td>aq</td>
<td>Aqueous</td>
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<tr>
<td>ASAP</td>
<td>Atmospheric Solids Analysis Probe</td>
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<tr>
<td>Bn</td>
<td>Benzyl</td>
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<tr>
<td>BOC</td>
<td>tert-Butyloxy carbonyl</td>
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<tr>
<td>Bz</td>
<td>Benzoyl</td>
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<tr>
<td>CI</td>
<td>Chemical Ionization</td>
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<tr>
<td>COLOC</td>
<td>Correlation Through Long Range Spectroscopy</td>
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<tr>
<td>COSY</td>
<td>Correlation Spectroscopy</td>
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<tr>
<td>DAM</td>
<td>Diacetone Mannose</td>
</tr>
<tr>
<td>DBDMH</td>
<td>1,3-Dibromo-5,5-dimethylhydantoin</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
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<tr>
<td>DCC</td>
<td>N,N'-Dicyclohexyl carbodiimide</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-Dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
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<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyano-1,4-benzoquinone</td>
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<tr>
<td>DEAD</td>
<td>Diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DFT</td>
<td>Density Functional Theory</td>
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<tr>
<td>DIBAL</td>
<td>Diisobutylaluminum Hydride</td>
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<tr>
<td>DIPEA</td>
<td>N,N'-Diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
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<tr>
<td>DMF</td>
<td>N,N'-Dimethylformamide</td>
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<td>DMP</td>
<td>Dess-Martin Periodinane</td>
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<tr>
<td>DMPU</td>
<td>N,N'-Dimethylpropyleneurea</td>
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<td>DMS</td>
<td>Dimethyl Sulfide</td>
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<td>DMSO</td>
<td>Dimethyl Sulfoxide</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
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<td>DTT</td>
<td>Dithiothreitol</td>
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<tr>
<td>EI</td>
<td>Electron Ionization</td>
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<td>Equiv.</td>
<td>Equivalent(s)</td>
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<tr>
<td>ESI</td>
<td>Electrospray Ionization</td>
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<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>FAB</td>
<td>Fast Atom Bombardment</td>
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<tr>
<td>FDMS</td>
<td>Field Desorption Mass Spectrometry</td>
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<tr>
<td>FTMS</td>
<td>Fourier Transform Mass Spectrometry</td>
</tr>
<tr>
<td>g</td>
<td>Gram(s)</td>
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<tr>
<td>h</td>
<td>Hour(s)</td>
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<tr>
<td>LiHMDS</td>
<td>Lithium bis(trimethylsilyl)amide</td>
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<tr>
<td>NaHMDS</td>
<td>Sodium bis(trimethylsilyl)amide</td>
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<tr>
<td>HMPA</td>
<td>Hexamethylphosphoramide</td>
</tr>
<tr>
<td>HMQC</td>
<td>Heteronuclear Multiple Quantum Coherence</td>
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<tr>
<td>Acronym</td>
<td>Full Form</td>
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<tr>
<td>TES</td>
<td>Triethylsilyl</td>
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<tr>
<td>Tf</td>
<td>Triflyl</td>
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<tr>
<td>TFA</td>
<td>Trifluoroacetic Acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
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<tr>
<td>THP</td>
<td>Tetrahydropyran</td>
</tr>
<tr>
<td>TIPS</td>
<td>Triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
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<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TOCSY</td>
<td>Total Correlation Spectroscopy</td>
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<tr>
<td>TOF</td>
<td>Time of Flight</td>
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<tr>
<td>Trt</td>
<td>Trityl</td>
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<tr>
<td>Ts</td>
<td>Tosyl</td>
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<tr>
<td>UTP</td>
<td>Uridine Triphosphate</td>
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<tr>
<td>UV</td>
<td>Ultraviolet</td>
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Introduction
Background

The natural product tagetitoxin was first isolated in 1981, and since then research has mostly focused on its interesting inhibitory activity of RNA Polymerase (RNAP), whilst comparatively little research has been carried out on its biosynthesis and chemical synthesis. Despite great developments in its biological research, tagetitoxin has yet to be isolated in a pure crystalline form and therefore no crystal structure of the natural product in its free form has been published. As a result, there has been debate about its structure in the literature. From a synthetic perspective, a total synthesis of tagetitoxin would provide the best means to confirm its structure.

Discovery and Isolation

In 1981, Mitchell and Durbin isolated and purified tagetitoxin from liquid cultures of the plant pathogenic bacterium *Pseudomonas syringae pv. Tagetis*. The steps involved in the isolation, included multiple methanol precipitations and methanol:chloroform:water (MCW) extractions. These steps decreased the amount of unwanted mineral salts and carbohydrates present with the toxin, so that the resultant crude mixture could undergo chromatographic purification. Subsequent chromatographic steps involving gel filtration, ion-exchange and partition chromatography led to the isolation of tagetitoxin as a colourless glassy residue. Mitchell and Durbin, also concluded that the natural product contained a phosphate functional group (by formation of blue-grey colour upon spraying molybdate reagent on TLC plate spotted with the tagetitoxin sample), amino functional group (by ninhydrin staining TLC plate spotted with the tagetitoxin sample) and a sulfur atom (by \(^{35}\text{S}\)-radioactive labelling).

Structure

A difficulty in the structural characterization of tagetitoxin has been the inability to obtain an X-ray crystal structure due to the natural product’s non-crystalline glassy form. Furthermore, while its absolute stereochemical configuration has yet to be determined, several structures of tagetitoxin have been proposed.

Structure 1

The first structure was proposed by Mitchell and Hart in 1983. IR spectroscopic analysis indicated the presence of hydroxyl group(s), carbonyl group(s) and phosphate functional...
group(s) in the molecule. Field Desorption Mass Spectrometry (FDMS) suggested the molecular weight of the natural product to be 435 gmol\(^{-1}\).

In the \(^{31}\)P NMR, the presence of a doublet (\(J = 11.5\) Hz) at 1.0 ppm downfield from a phosphate indicated the presence of a phosphate ester of a secondary alcohol function.

The sulfur atom was deduced to be part of a thiohemiketal functionality. This conclusion was reached firstly on the observation that adding strong acid to tagetitoxin did not liberate a sulfate, indicating the absence of a sulfate ester. Secondly, there was no red-colour observed when reacting tagetitoxin with sodium nitroprusside, suggesting the absence of a thiol in the molecule. Pre-treating the natural product with dilute hydrochloric acid, however, then gave a positive colour test for thiols; this was rationalized as there being a thiohemiketal which ring-opened in dilute acid. Thirdly, there was only one sulfur atom in the molecule because growing \(P.s\) tagetis in the presence of radioactively labelled phosphate (\(^{32}\)PO\(_4^{3-}\)) and sulfate (\(^{35}\)SO\(_4^{2-}\)) produced radiochemically pure tagetitoxin with phosphorous-sulfur ratio of 1:1.

Key conclusions made from the \(^{13}\)C NMR data indicated eleven carbon environments including three carboxyl carbons and five carbons monosubstituted with oxygen. The functionalities on those five carbons were deduced to be an acetate, phosphate and either one hydroxyl and one ether group or three hydroxyl groups based from \(^1\)H and \(^{13}\)C NMR chemical shift data.

Further data from the \(^1\)H NMR (more specifically the well-defined multiplets) gave much structural information about the framework of the natural product.

Using the MS and NMR data, the molecular formula for tagetitoxin was proposed to be C\(_{11}\)H\(_{18}\)O\(_{13}\)SNP. Finally, based on the molecular formula and the absence of any carbon-carbon multiple bond signals in the \(^{13}\)C NMR spectrum, tagetitoxin was hypothesized to be a single ring structure. Combining all these analyses, structure 1 was proposed (Figure 1).
Structures 2 and 3

In 1989, based on more refined NMR experiments and higher resolution MS measurements, four new structures (Figure 2) were proposed by Mitchell et al.  

Fast atom bombardment (FAB) mass spectrograms showed the molecular weight to be 416 leading to the proposition of a new molecular formula, $C_{11}H_{18}O_{11}N_2SP$. The extra nitrogen in the molecular formula was concluded to be of an amide moiety from NMR data. The structure of tagetitoxin was proposed to be bicyclic based on the number of hydrogens in the molecular formula and the absence of any carbon-carbon multiple bond(s) from NMR data. Furthermore, from the data, the authors concluded that the oxygen-containing functional groups were a carboxylic acid and amide, acetate, phosphate and either two hydroxyl or two ether groups.

All four structures were strongly supported by nuclear Overhauser effect (nOe) experiments (for example the significant nOe experienced between H-C-5 and H-C-6). In addition, nOe experiments were critical in disproving structure 1, as the nOe observed between H-C7 and H-C2.
would not be expected for structure 1, since these protons have a too distant spatial proximity from each other.

The authors utilized the Karplus relationship from the coupling constants of the protons in the four-carbon series (C-5 to C-8), to deduce the dihedral angles between them. They found, while this data was in good agreement with structures 2 and 3, it had better supported structures 2. It, for example, showed that H-C-6 and H-C-7 should be in a true diaxial relationship, which is evident for structures 2 but not for structures 3 because of the constraints the five-membered oxathiane ring places on the seven-membered ring. There, however, was not enough evidence to completely discredit structures 3.

COLOC pulse sequences gave further information on the oxathiane ring. For example, a strong correlation between the C-4 and the methylene protons on the oxathiane ring further supported the presence of a thiohemiketal or thioketal.

Finally, the authors preferred structures 2a and 3a where the amide moiety is bonded to C-4, due to the lower $^{13}$C NMR chemical shift of the carboxyl carbon bonded to C-4 than C-1. However, since the chemical shift difference between the carboxyl carbons are low, structures 2b and 3b were not discounted.

In 2005, Gronwald et al. isolated tagetitoxin using a slightly different method. They used the same procedure as Mitchell et al., except that they used partition chromatography instead off the initial methanol precipitation and MCW partitioning steps.

From electrospray ionization (ESI) mass spectrometry, Gronwald et al. concluded that the molecular weight of tagetitoxin was 678 rather than 416 as previously reported by Mitchell et al. This difference was explained by the presence of an ion at $m/z = 679.5216$, which they assigned as the protonated molecular ion. While they found an ion with $m/z = 417.3316$, they identified it as a fragment of their protonated molecular ion. The ion at $m/z = 417.0361$ previously identified as the protonated molecular ion by Mitchell et al., was suggested by Gronwald et al. to be a fragment of minor contaminants.

The $^1$H and $^{13}$C NMR spectra reported by Mitchell et al. were mostly in agreement with the spectra from Gronwald et al., with the only difference seen in the latter being the extra peaks in the $^1$H NMR (1.75ppm and 2.53ppm) and the $^{13}$C NMR (23.2ppm and 181.5ppm) spectra.
To account for the differences in the MS data despite good agreements with the NMR data, Gronwald et al. suggested that the higher molecular weight of 678 may be rationalized by the presence of atoms (such as oxygen, nitrogen and sulfur) and exchangeable protons not detected by 1D NMR experiments.

Furthermore, Structure 2 was supported by many 2D NMR experiments carried out by Gronwald et al. such as COSY, TOCSY and HMQC spectra, but there were some discrepancies with regards to the HMBC spectra.

Despite these conclusions, Gronwald et al. did not propose a new molecular formula nor a revised structure.

**Structure 4**

Later in 2005, Vassylyev et al. published an X-ray crystal structure of the bacterial Thermus thermophilus RNAP-tagetitoxin complex, showing tagetitoxin bound to the enzyme’s active site. Even though the structure of tagetitoxin was not being investigated in this paper, structure 4 was indirectly proposed (Figure 3).

![Structure of tagetitoxin indirectly proposed by Vassylyev et al.](image)

**Figure 3:** Structure of tagetitoxin indirectly proposed by Vassylyev et al.\(^5\)

Whilst structure 4 has the same framework as structure 2, the relative stereochemistry is different, where more specifically the chiral carbon centres bearing the phosphate group and the acetate group (C\(_8\) and C\(_6\)) have inverted.

Despite there being good agreement between the theoretical and experimental electron density maps of structure 4, it is inconsistent with the previously reported NMR data.\(^2,3\) Furthermore, whilst a resolution of 2.4 Å is good for studying a protein structure,\(^6\) it is not deemed sufficient to fully clarify the structure of a small molecule like tagititoxin.\(^7\)
Structure 5

Finally, in 2016, Aliev et al. further analysed a tagetitoxin sample originally isolated and purified by Mitchell. They published more NMR and MS data which led them to propose a new structure (Figure 4) and refute previous structures.

![Figure 4: Structure proposed by Aliev et al.](image)

Aliev et al. concluded that the sample isolated by Gronwald et al., was less pure than that from Mitchell et al. This was rationalized by the absence of the extra peaks Gronwald et al. observed in the $^1$H NMR (1.75ppm and 2.53ppm) and $^{13}$C NMR (181.5ppm).

Moreover, on analysing MS data, no species with a molecular weight of 678 was seen, which disagreed with Gronwald and co-workers’ proposed molecular weight of tagetitoxin.

Key disagreements with the previous structures (1, 2, 3 and 4) were found from the HMBC spectrum and the long range $J_{CH}$ values. These disagreements were:

1. A correlation between C-11 and H-C-8 is seen which is inconsistent with structures 2a, 3a and 4 because of the presence of six bonds between these atoms.
2. The $J_{CH}$ value of 5.0 Hz, between C-10 and H'-C-2 is too large to be a $^4J_{CH}$ correlation. This is not consistent with structures 2b and 3b, since the size of the $J_{CH}$ suggests that this pair of atoms should be closer together.
3. The cross peaks observed for C-7 with H-C-2 ($J_{CH} = 5$ Hz) and with H’-C-2 ($J_{CH} = 3$ Hz) are inconsistent with all structures 1 to 4. This is due to the four-bond separation between these aforementioned atoms.
4. The $J_{CH}$ value of 1.4 Hz for C-4 and H-C-6 is too small to be a $J_{CH}$ correlation for atoms that have a ~180° dihedral angle, which is inconsistent structures 2a and 2b.
The key disagreements for previously reported structures were verified with the authors’ proposed structure 5:

1. C-11 and H-C-8 in structure 5 are 3 bonds apart, and therefore correlate.
2. C-10 and H’-C-2 in structure 5 are 3 bonds apart accounting for the $^3J_{CH}$ value of 5.0 Hz between them.
3. In structure 5, C-7 is 3 bonds apart with H-C-2 and H’C-2 explaining the $^3J_{CH}$ coupling observed.
4. If the 6-membered ring of structure 5 is in a chair confirmation H-C-6 and C-4 will have a dihedral angle of ~60°, which accounts for the low $^3J_{CH}$ value between these.

The authors also concluded that there was trans stereochemistry at the ring junction due to the high coupling constant ($^3J_{HH} = 12.4$Hz) between H-C-6 and H-C-7. Further data from NOESY, vicinal $^3J_{HH}$ coupling constants, HMBC and DFT calculations (the latter was used to explain unexpected missing HMBC correlations), provided further support for structure 5.

**Biological Activity**

Application of tagetitoxin to the stems of plants in the Asteraceae family such as zinnia (*Zinnia elegans* Jacq) and sunflower (*Helianthus annuus*) leads to apical chlorosis (bleaching of apical green plant tissue due to decreased amount of chlorophyll in that tissue).² This effect is due to the translocation of the toxin to apical regions of the plant where it inhibits chloroplast RNAP, suppressing differentiation of proplastids into chloroplasts, preventing new chlorophyll accumulation in these regions.² Two radiolabelling experiments supported this hypothesis.¹⁰ Initially, Matthews and Durbin performed in organello incorporation reactions where tagetitoxin was added to isolated, intact chloroplasts and the rate of incorporation of radiolabelled uridine into RNA was measured.¹⁰ It was observed that tagetitoxin application led to a decrease in the rate of incorporation of $[^3]$H uridine into RNA; indeed at tagetitoxin concentrations of 1mM, there was negligible $[^3]$H uridine incorporation. Furthermore, the addition of tagetitoxin to in vitro transcriptionally active chloroplast protein extracts reduced $[^32]$P UTP incorporation into RNA. Both experiments suggest that RNA synthesis in chloroplasts is suppressed due to tagetitoxin inhibition of chloroplast RNAP.
Moreover, tagetitoxin inhibits RNAP III \textit{in vitro} in many eukaryotes such as yeast, insects and vertebrates.\textsuperscript{11} This is in contrast to the other eukaryotic nuclear RNAPs, RNAP I and RNAP II which appear to be more resistant to inhibition from the toxin.\textsuperscript{12} For example tagetitoxin at low concentrations (0.3-3.0 μm) inhibit RNAP III directed transcription in various organisms but has little effect on RNAP II directed transcription.\textsuperscript{13}

Finally, inhibition of \textit{in vitro} RNA synthesis directed by RNAP from \textit{Escherichia Coli} by tagetitoxin at concentrations less than 1μM has also been reported.\textsuperscript{10,13}

In summary, tagetitoxin inhibits chloroplast and bacterial RNAP. Tagetitoxin is also a selective inhibitor of RNAP III compared to the other nuclear RNAPs in a variety of eukaryotes.

\textbf{Biological Mechanism of Inhibition}

In 1994, Matthews and Durbin conducted abortive initiation assays to primarily investigate the inhibition kinetics of tagetitoxin on \textit{E. Coli} RNAP.\textsuperscript{12} They concluded that tagetitoxin acts an uncompetitive inhibitor of \textit{E. Coli} RNAP which indicates that the toxin does not prevent the nucleotide triphosphate (NTP) substrate from binding with the enzyme. It was also inferred from these studies that tagetitoxin does not affect phosphodiester bond formation between an NTP substrate and the nascent RNA chain. The authors suggested that the inhibition may be due to tagetitoxin affecting the stability of the binding between the nascent RNA chain and the enzyme-DNA template complex. Despite advances in the understanding of the inhibitory effect of tagetitoxin on a RNAP, it was widely acknowledged that the exact mechanism of the toxin and its target site on RNAP were unclear.\textsuperscript{5}

A breakthrough in the inhibition mechanism by tagetitoxin on RNAP was achieved by Vassylyev \textit{et al.} in 2005, where an X-ray crystal structure of the complex between a bacterial RNAP (from \textit{Thermus thermophilus}) and tagetitoxin was published.\textsuperscript{5} Analysis of this structure led to a greater insight of the binding between tagetitoxin and RNAP. This structural analysis along with homology modelling and biochemical analyses allowed the authors to propose a more detailed inhibition mechanism.

The X-ray structure has shown that the RNAP binding site for tagetitoxin is located at the base of the RNAP secondary channel, adjacent to its active site. This suggests that tagetitoxin does not prevent NTP substrate binding, which is in agreement with the conclusions drawn by Matthews.
and Durbin.\textsuperscript{12} Moreover, the binding between tagetitoxin and the RNAP was primarily made up of 18 hydrogen bonds between 9 of the 11 oxygen atoms of the toxin with side chains of adjacent amino acid residues of the RNAP (\textbf{Figure 5}). In addition to the expected catalytic magnesium ions (cMg\textsubscript{1} and cMg\textsubscript{2}) found in a RNAP, a third magnesium ion (tMg) was observed in the RNAP/Tagetitoxin complex. The authors suggested that this well-fixed tMg coordinates to the phosphate group of tagetitoxin stabilizing the toxin further. The tMg is well-fixed because of its coordination to the side chains of two active site amino acid residues of RNAP.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{diagram.png}
\caption{A schematic diagram of the tagetitoxin binding site on RNAP.\textsuperscript{5}}
\end{figure}

Vassylyev and co-workers postulated a two-step mechanism for tagetitoxin inhibition RNAP (\textbf{Figure 6}). They proposed that the mechanism involves the stabilization of an inactive transcription intermediate whilst the NTP substrate is loading into the active site. In this mechanism, whilst tagetitoxin is being bound to its binding site in the enzyme, the NTP substrate enters the pre-insertion site. Due to the coordination of tagetitoxin to tMg, the NTP binds to the tMg rather than cMg\textsubscript{2}; binding to cMg\textsubscript{2} would otherwise occur without tagetitoxin. The NTP substrate is then loaded into the insertion site by a simple rotation forming the insertion complex. In the resulting intermediate, the active site has a more compact conformation leading to tighter binding of the tMg-bound substrate and greater stabilization, locking the intermediate in an inactive state preventing the dissociation of the NTP substrate and the catalytic reaction. The authors also proposed that since the NTP coordinates to the tMg rather the cMg\textsubscript{2}, the positioning of cMg\textsubscript{1} and cMg\textsubscript{2} change. This change in orientation would decrease the stability of the pentavalent transition state formed during phosphodiester formation between the terminal 3’OH
of the nascent RNA chain and the $\alpha$-phosphate functionality of the NTP substrate, further lowering the catalytic activity.

**Figure 6:** Proposed inhibitory mechanism of tagetitoxin on RNAP.$^5$

This mechanism was contested by Artsimovitch *et al.* in 2011.$^{14}$ Based on theoretical modelling using molecular dynamics simulations, they suggested that the inhibitory effect of tagetitoxin on RNAP arises from the interaction between tagetitoxin and the side chains of two amino acid residues of the RNAP trigger loop (a flexible protein domain). During typical transcription, the trigger loop folds into a trigger helix; this leads to the catalytic amino acid residues being in an active configuration. These amino acid residues, then interact with the NTP substrate facilitating phosphodiester bond formation between the NTP and the nascent RNA chain.$^{15}$ However, due to the interaction of tagetitoxin with the trigger loop, instead of folding to a trigger helix, it is stabilized and trapped in an inactive state, which lowers catalytic activity. Klyuyev and Vassylyev later argued that this mechanism was in poor agreement with practical results in favour for theoretical models.$^{16}$

Finally, in 2013, based on multiple transcription assays, the trigger loop mechanism was revised by Yuzenkova *et al.*$^{17}$ The nucleotide addition cycle consists of phosphodiester bond formation
(between the NTP substrate and the nascent RNA chain), a translocation of RNAP on the DNA template strand and then the binding of the next NTP substrate. In between phosphodiester bond formation and translocation, the transcription elongation complex (the RNAP containing complex that additionally includes the DNA template strand and the nascent RNA chain) is in its pre-translocated state. During the subsequent translocation, the trigger loop unfolds. Yuzenkova and co-workers proposed that tagetitoxin stabilizes the folded conformation of the trigger loop when the transcription elongation complex is in its pre-translocated state. As a result the subsequent translocation is slowed down due to the greater difficulty in unfolding the trigger loop; this leads to the overall rate of the RNA chain elongation to decrease.

**Importance of Tagetitoxin**

The importance of tagetitoxin originates from its biological activity. For example, due to the toxin’s inhibition on chloroplast RNAP, its use as a plant growth regulator has been patented. Furthermore, since tagetitoxin inhibits a variety of RNAPs, it can be a useful tool for molecular biologists investigating transcription. Finally, a total synthesis of the natural product would provide opportunities to synthesize a library of analogues; these analogues could be then assessed for herbicidal and antibacterial activity.

**Previous Synthetic Studies of Tagetitoxin**

Since all synthetic studies towards tagetitoxin were conducted prior to 2016, the targets were generally 2a and 2b as these were the accepted structures at the time.

**Sammakia et al.**

In 1996, Sammakia et al. published their attempt to synthesize tagetitoxin. Their retrosynthetic analysis of tagetitoxin involved a precursor 6 that can cyclize to give structures 2a or 2b (Scheme 1). Synthesis of precursor 6 was planned to be an enzymatic aldol-catalysed coupling of dihydroxy acetone phosphate 7 with aldehyde 8. Aldehyde 8 could be made from oxazolidine olefin 9 in three steps: dihydroxylation of the olefin moiety; hydrolysis of the oxazolidine; and selective oxidation of the primary alcohol to an aldehyde.
Scheme 1: Retrosynthetic analysis of proposed targetxin structures 2a and 2b by Sammakia et al.

A range of oxazolidine olefins 9 (Scheme 2 and Table 1) were prepared in a one-pot synthesis. This involved a range of thiolate anions attacking a substituted methyl acrylate phosphonate 10 in a conjugate addition forming an ylide. The ylide, in turn, condensed with the oxazolidine aldehyde 11 to produce the olefins 9a to 9e with varying stereoselectivity.

Scheme 2: One-pot synthesis of oxazolidine olefins 9.

Reagents and conditions: a) RSH, NaH, THF, 0 °C. See Table 1.
<table>
<thead>
<tr>
<th>R</th>
<th>Ethyl 9a</th>
<th>i-Propyl 9b</th>
<th>t-Butyl 9c</th>
<th>Phenyl 9d</th>
<th>Benzyl 9e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z:E</td>
<td>60:40</td>
<td>70:30</td>
<td>100:0</td>
<td>20:80</td>
<td>30:70</td>
</tr>
</tbody>
</table>

**Table 1:** Effect of the sulfur protecting group on the Z:E ratio of olefins 9a-e

The authors then attempted a range of dihydroxylation methods on olefins 9 (Scheme 3 and Table 2).

**Scheme 3:** Dihydroxylation attempts of olefins 9.

<table>
<thead>
<tr>
<th>Olefin</th>
<th>Conditions</th>
<th>Recovered 9 (%)</th>
<th>Yield of 12 (%)</th>
<th>Yield of 13 (%)</th>
<th>Yield of 14 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>a</td>
<td>54</td>
<td>-</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>30</td>
<td>-</td>
<td>70</td>
<td>-</td>
</tr>
<tr>
<td>9b</td>
<td>a</td>
<td>56</td>
<td>6</td>
<td>28</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>39</td>
<td>15</td>
<td>44</td>
<td>-</td>
</tr>
<tr>
<td>9c</td>
<td>a</td>
<td>86</td>
<td>14</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>32</td>
<td>55</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>9d</td>
<td>a</td>
<td>99</td>
<td>-</td>
<td>&lt;1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>34</td>
<td>27</td>
<td>-</td>
<td>39</td>
</tr>
<tr>
<td>9e</td>
<td>a</td>
<td>82</td>
<td>-</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>22</td>
<td>6</td>
<td>72</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 2:** Yields reported for compounds 12, 13 and 14 from the dihydroxylations of olefins 9

When using conventional methods of stoichiometric or catalytic amounts of osmium tetroxide, only sulfur oxidized products were isolated. This then led them to use AD-mix-β or
stoichiometric amounts of osmium tetroxide and potassium ferricyanide. However, for most of the olefins 9, starting material and sulfur oxidized products (mainly sulfoxides) were the major compounds isolated. The most promising result was the dihydroxylation of the bulky t-butyl thioether substrate 9c using stoichiometric osmium tetroxide and potassium ferricyanide. Despite this promising result, the synthesis to structures 1 and 2a were not pursued and no research related to this synthetic strategy has yet to be reported.

Dent et al.

Due to tagetitoxin’s reported biological activity, Dent et al. aimed to synthesize related analogues of the natural product for evaluation as herbicides and plant growth regulators.\textsuperscript{21} Based on structures 2a and 2b, the authors thought that the acetate, amine and phosphate groups were key for the biological activity. They also suggested that the sulfur bridge was important to impose the desired stereochemistry on the pyranoid ring. As a result, structures 15 and 16 were their synthetic targets (Figure 7). To achieve their main goal of gaining greater knowledge on structure-activity relationships of tagetitoxin, Dent et al. would have to make carbohydrate-based vicinal cis-amino phosphates (where the latter in itself is useful synthetic methodology).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{synthetic_targets.png}
\caption{Synthetic targets for Dent et al.}
\end{figure}

The authors were able to synthesize structure 15 (X=O) in a twelve-step route starting from dialdehyde 17 (Scheme 4), which is readily available from periodate oxidation of levoglucosan. The cyclic framework of their synthetic target was achieved by the cyclization of dialdehyde 17 with nitromethane furnishing 18. After hydrogenolytic reduction of the nitro group to produce 19, the formed amine was then N-Boc protected to give 20. The authors then exploited the syn-stereochemistry of the C-2 and C-3 substituents; this would eventually allow them to esterify the C-2 and C-4 hydroxyl groups selectively. The N-Boc derivative 20 was then treated with bis(tributyltin) oxide in toluene under reflux, followed by addition of tetra-n-butylammonium
bromide and benzyl bromide to form the N-benzyloxazolidinone derivative 21. The authors then carried out a three-step sequence of protections and deprotections of various groups to afford 24. Compound 24 then underwent a phosphitylation using o-xylene-N,N-diethylphosphoramidite and 1H-tetrazole, which was followed by an oxidation using m-CPBA yielding phosphate ester 25. The authors subsequently deprotected the tetrahydropyranly acetal (THP) and then acetylated the C-4 hydroxyl group, which formed compound 27. Hydrogenolysis of the phosphate ester and benzyl amine moieties in 27 were performed leading to synthetic target 15. Hydrogenolysis of intermediate 26 led to an additional analogue 28 which along with 15 were tested for herbicidal activity.
Scheme 4: Dent and co-workers’ synthesis of analogues 15 and 28.
Biological testing showed compound 15 and its deacylated analogue 28 to have no herbicidal activity against a variety of agriculturally important weeds:

*Avena Fatua* (wild oat), *Setaria viridis* (green foxtail), *Amaranthus retroflexus* (redroot pigweed) and *Chenopodium album* (fat hen).

A second set of analogues based on structure 15, were then targeted by the authors using different synthetic methodology, whereby the insertion of the amino functionality at C-3 would be different. This would be achieved by forming a good leaving group at the C-3 position followed by a S_N2 reaction using a nitrogen-based nucleophile which could later be transformed to an amino functional group (e.g. azide nucleophile).

Their first attempted synthesis following the above methodology started from 1,6-anhydro-D-galactose 29 and it sulfur analogue 30 (Scheme 5). Acetonide formation of the hydroxyl groups on C-3 and C-4 in 29 and 30, allowed subsequent selective phosphate ester formation on the C-2 position forming 32, 33 and 35. Phosphate ester formation was achieved using either a dialkyl chlorophosphate in pyridine or a pyrophosphate with a strong base (only the latter strategy was used on the sulfur analogue 34). Subsequent steps (d, e and f) involved successive protections and deprotections of various groups in order to reach 38 or 40. The authors began this sequence with an acetonide deprotection affording 36 and 37. They, however, could not isolate the required diol from acetonide hydrolysis of sulfur species 35 (presumed to be because of the sulfur atom participating in reactions involving carbocations generated in these acidic conditions). Under a variety of conditions, Dent and co-workers, then unsuccessfully attempted to selectively acetylate the C-4 hydroxyl group over the C-3 hydroxyl group in 36 and 37, since they only isolated inseparable mixtures of the monoacetates 38 and 39 or 40 and 41 respectively. The origin of this poor selectivity was attributed to either an inherent unselective reaction or ester migration occurring during the reaction.
Scheme 5: Dent and co-workers’ second route to analogues based on structure 15.

As a result, the authors changed their approach in an attempt to isolate 40 (Scheme 6). This involved forming a cyclic brominated orthoacetate 42 (from 37) and then subjecting this to mild acidic hydrolysis. This methodology was hypothesized to lead to bromoacetate 43. Compound 43 could then be acetylated on the C-4 position, then deprotection of the C-3 bromoacetate in the presence of the C-4 acetate would lead to the desired 40. Although brominated orthoacetate 42 was successfully synthesized, when subjected to mild hydrolysis an inseparable mixture of bromoacetates 43 and 44 were formed causing the authors to abandon this methodology.

Scheme 6: Dent and co-workers’ alternative route to structure 40.

Dent and co-workers’ second attempted route in selectively functionalizing 29 and 30 exploited the regioselective reductive cleavage of a methoxybenzylidene acetal (Scheme 7). After forming a methoxybenzylidene acetal on the C-3 and C-4 position and successively silyl protecting the C-2
hydroxyl group to form 47 and 48 respectively, treatment with LiAlH$_4$-AlCl$_3$ produced only the 3-O-p-methoxybenzyl ethers 49 and 50. Subsequently via a series of protections and deprotections, compounds 53 and 54 were made where the hydroxyl group on C$_{3}$ was unprotected. This therefore allowed introduction of a good leaving group on the C$_{3}$ position (triflate, tosylate and mesylate) and displacement of that leaving group with an azide nucleophile. However, despite successfully synthesizing sulfonate esters 55 – 60, treatment with sodium azide in DMF, HMPA or DMSO failed to yield compounds 61 and 62 as only starting material or decomposition was seen. The rationale for these observations was steric hindrance from the adjacent bulky silyl ether.

Scheme 7: Attempted synthesis of compounds 61 and 62 by Dent et al.

Dent et al. then focused on synthesizing compounds based on structure 16 starting from pentaprotected carbohydrates. Their strategy involved a one carbon chain extension at the C$_{1}$ position of a D-galactopyranose derivative, followed by ring closure linking this new carbon atom with the C$_{6}$ by a sulfur or oxygen atom. Following this, phosphorylation, acetylation and
introduction of the amino functionality (latter by S\textsubscript{N}2 chemistry) would then yield 16 (Scheme 8).

**Scheme 8:** Dent and co-workers’ methodology to synthesize analogue 16.

In this strategy, the authors started with the bromination of D-galactose pentaacetate 63 to give the α-glycosyl bromide, which was then treated with mercuric cyanide in nitromethane to furnish the β-nitrile 64 (Scheme 9). Two approaches to synthesize 66 from 64 were successfully achieved. The first approach involved a reductive hydrolysis of a nitrile to an aldehyde using Raney nickel with the hydrogen source sodium hypophosphite in aqueous acetic acid and pyridine, followed by the *in-situ* trapping of that aldehyde with a diamine to form imidazolidine 65. The success of this reaction was variable due to the occurrence of undesired side-reactions. The aldehyde was then regenerated by hydrolysis of the imidazolidine and then reduced using sodium borohydride. The resultant crude product was then acetylated to form 66. The second approach involved deacylation of 64, basic nitrile hydrolysis and then acetylation of the crude hydrolysis product which gave a mixture of γ-lactone 67 and hydroxy carboxylic acid 68. However, under strong acetylation conditions, 68 was cleanly reconverted into γ-lactone 67. Lithium aluminium hydride (LAH) reduction of the lactone and subsequent peracetylation gave
66. After compound 69 was formed from deacetylation of 66, selective tosylation on the methylene alcohols produced compounds 70 and the undesired tri-tosylate 71. Acetonide formation on ditosylate 70, led to the bicyclic precursor 72. Attempts at ring closure in 72 using sulfide nucleophiles (lithium or sodium sulfide) in DMF failed to produce the bicyclic structure 73. However, thiol 74 was isolated where only one of the tosylates was displaced by the sulfide nucleophile. The authors attributed this result to the isopropylidene groups placing steric constraints on the ring closure.
Scheme 9: Dent and co-workers’ attempted synthesis of bicyclic structure 73.

As the synthesis of 73 was unsuccessful, Dent et al. decided to replace the isopropylidene group with benzyl groups when forming further precursors for target 16 (X=O). Hence, starting from
compound 65, they performed a sequence of deprotections and protections of various groups to reach the tri-benzylated compound 76 (Scheme 10). After unmasking the aldehyde in 76, sodium borohydride reduction and trityl deprotection, diol 77 was isolated. Two different methods on 77 were undertaken in an attempt to isolate the desired cyclic ether 78:

1. An acidic cyclodehydration in toluene under reflux.
2. Treatment with triphenylphosphine and diethyl azodicarboxylate (DEAD).

In both methods, however, starting material was only recovered. The authors then tried a mono-tosylation on diol 77 but this led to a mixture of the regiomeric mono-tosylates 79 and 80 in addition to di-tosylate 81. Nevertheless, since they were able to isolate 79, they attempted the cyclization using sodium hydride, but this gave a complex mixture.

Scheme 10: Dent and co-workers’ attempted synthesis of bicyclic structure 78.

Finally, Dent et al. wanted to introduce a nitrogen functional group attached to the C-3 position prior to the ring closure to assess whether the substituent on this position in the previous routes sterically hindered the cyclization. They, therefore synthesized the di-benzylidene acetal 82 from 69 (Scheme 11). This allowed subsequent transformation of the C-3 hydroxyl group in 82 to a variety of sulfonate esters (compounds 83-86). However, nucleophilic displacement of these sulfonate esters with an azide nucleophile under a range of conditions led to either no reaction or
decomposition of the starting material, except for tosylate 85 which furnished azide 87 but at only 10% yield. Due to the low yield, the synthesis was abandoned at this stage.

Scheme 11: Synthesis of azide 87 by Dent et al.

In summary, Dent et al. were successful in making the analogue 15 (Scheme 4) but only with an oxygen bridge rather than a sulfur bridge. They were also unsuccessful in the synthesis of analogue 17, which is more closely related to tagetitoxin structures 2a and 2b.

Porter and Plet 2006

In 2006, Porter and Plet published the first synthesis of the bicyclic core of tagetitoxin from a carbohydrate precursor.24

Their first strategy, was based on a carbene-mediated ring expansion of a 1,3-oxathiolane moiety (Scheme 12). In this approach a metallocarbene would be generated from a transition metal catalysed decomposition of a diazo derivative. The nucleophilic sulfur atom would then attack the electrophilic carbon of the metallocarbene forming a sulfur ylide. This would cause the 1,3-oxathiolane moiety to ring open followed by a ring closure to form a 1,4-oxathiane moiety in a Stevens rearrangement.
Scheme 12: Carbene mediated ring expansion strategy of 1,3-oxathiolones to form the tagetitoxin bicyclic structure envisaged by Porter and Plet.

In order to test their ring expansion strategy towards the synthesis of the bicyclic core of tagetitoxin, the investigators firstly synthesized compound 88 (Scheme 13). Compound 88 was synthesized from D-glucose by selective tosylation on the C-6 hydroxyl group, peracetylation, bromination on the anomeric position and substitution of the two leaving groups using a xanthate species. They then attempted the ring expansion of 88 using ethyl diazo(triethylsilyl)acetate and catalytic rhodium(II)acetate, but only glycal 91 was formed rather than the intended sulfur bridged bicyclic structure. The authors explained this result from the behaviour of the zwitterion intermediate 90; instead of 90 undergoing the desired C-C bond formation, it ring-flipped to the more stable conformer which was followed by a proton transfer affording 91. Thus, Porter et al. synthesized the more constrained precursor 92, in five steps from 3-methyl-D-glucose for the ring expansion, because the consequent zwitterion (analogous to 90) would have a locked conformation preventing any ring flipping. Yet, when subjecting 92 to ethyl diazo(triethylsilyl)acetate and rhodium(II) heptafluorobutyrate, only alcohol 94 at low yield was isolated. This probably occurred because of nucleophilic ring opening of ylide 93 with a water molecule followed by a proton transfer.
Scheme 13: Porter and Plet’s attempt to synthesize the bicyclic core of tagetitoxin using their ring expansion strategy.

As a result, to synthesize the 1,4-oxathiane ring of tagetitoxin, the investigators altered their approach from a ring expansion strategy to cyclization of a thiol onto an electrophilic ketone. The key methodology for this approach, involved the insertion of a bromoalkyne (masks an α-ketoester) and a thioacetate moiety (masks a thiol) onto a carbohydrate derivative, followed by the unmasking of these groups leading to cyclization.

Starting from the β-thioglycoside 95, selective silyl protection of the primary alcohol and subsequent perbenzylation furnished 96 (Scheme 14). Compound 96 was then transformed into δ-lactone 97 by hydrolysis of the thioglycosidic linkage using N-bromosuccinimide (NBS), followed by oxidation when treated with Dess-Martin periodinane (DMP). Silyl alkyne 98 was then formed after cerium-mediated addition of trimethylsilylacetylene onto the lactone and sequent hydrosilane reduction on the C-1 position. The silyl alkyne moiety was then transformed
into a bromoalkyne by protodesilylation and bromination of the terminal alkyne. Oxidation of the bromoalkyne to an α-ketoester was achieved using potassium permanganate in aqueous methanol yielding 101. Deprotection of the primary silyl ether in 101, would then allow activation of the primary alcohol into a good leaving group and its displacement with a thioacetate nucleophile. However, when attempting to cleave the silyl ether with tetra-n-butylammonium fluoride (TBAF), elimination of the 2-benzyloxy group occurred forming glycal 102 in most likely an E1cb reaction. The authors therefore changed the conditions and used hydrogen fluoride – pyridine complex, but instead tricyclic ketal 103 was formed. To reach 103, the silyl ether and the benzyl ethers on the C₃ and the C₄ in 101 must have been cleaved, which was followed by a ketal formation between the ketone and the liberated hydroxyl groups on the C₃ and C₆ centres.

Scheme 14: Synthesis of intermediate 101 by Porter and Plet.
To overcome the difficulty in deprotecting the silyl ether on the C-6 position in the presence of the α-ketoester, the authors altered the sequence of the route; specifically, they planned to incorporate the sulfur functionality before the α-ketoester synthesis. Starting from 98, double desilylation of the silyl alkyne and silyl ether occurred forming 104 (Scheme 15). The hydroxyl group on the C-6 centre transformed into a mesylate and was subsequently displaced with a potassium thioacetate nucleophile in DMF. Using the same previous methods, bromination of the alkyne and subsequent oxidation with potassium permanganate gave the α-ketoester bicyclic precursor 106. Thioacetate deprotection and in-situ cyclization of the thiolate onto the ketone led to bicyclic thiohemiketal 107.

Scheme 15: Porter and Plet’s synthesis of the bicyclic core of tagetitoxin (107).

In summary Porter and Plet attempted two strategies to synthesize the bicyclic core of tagetitoxin. Although the carbene-mediated ring expansion approach failed, they were successful in their methodology involving a thiolate cyclizing onto an electrophilic ketone. This was only achieved with inserting the thioacetate moiety before forming the α-ketoester, illustrating the importance in the order of the steps in the route. However, a carboxylic acid derivative on the anomeric position on the bicyclic core was still missing.
Porter et al. 2008

In 2008, Porter and co-workers again synthesized the core structure of tagetitoxin. This was achieved by building on their previous work regarding the carbene-mediated ring expansion of a 1,3-oxathiolane moiety to a 1,4-oxathiane moiety. The authors concluded, that their previous ring expansion attempts did not work because of the conformational flexibility of the zwitterion 90 leading to the undesired glycal 91. However, even when they incorporated a di-tert-butylsilane bridge on the C-2 and C-4 hydroxyl groups to form the more constrained precursor 92, no ring expansion products were still observed (Scheme 13). Nevertheless, Porter et al. still postulated that the conformational flexibility rationale was the cause for the ring expansion failure. They therefore aimed to synthesize the ylide in an intramolecular reaction (rather than intermolecular fashion as previously). This would lead to a more constrained ylide and subsequent zwitterion intermediate, which would favour the desired C-C bond formation.

To test their postulate, the authors made thioanhydroglucose 108 in a four-step route according to the literature. They then devised a synthetic route to tetracyclic structure 109 from thioanhydroglucose 108 (Scheme 16). Selective protection of the C-2 and C-4 hydroxyl groups with a di-tert-butylsilane bridge furnished 110. This was followed by acetoacetylation and subsequent diazo transfer yielding 111. Treatment of 111 with rhodium(II) acetate dimer formed isolable tetracyclic ylide 112 (further confirmed with X-ray crystallography). However, despite heating 112 in an array of solvents of different polarities such as xylene, methanol and DMSO, only starting material or decomposition (latter only observed at extended reaction times) were seen.
Scheme 16: Attempted synthesis of tetracyclic 109 by a thermal promoted Stevens rearrangement by Porter et al.

Porter et al. proposed two mechanisms for the thermally promoted Stevens rearrangement (Scheme 17). The homolysis mechanism a, is the general favoured mechanism for the Stevens rearrangement.\textsuperscript{28,29} However, to account for the isolation of glycal 91 from their previous attempted ring expansion on 88,\textsuperscript{24} they suggested that heterolytic mechanism b would be favoured for these substrates under thermal conditions. Thus, they found it surprising when the ylide was generally stable under these conditions (dependent on reaction times). They also thought pathway b would be more favoured with acidic conditions (due to increased polarization of the C-S bond). Therefore, protic acids (such as trifluoroacetic acid and triflic acid) and Lewis acids (such as [Cu(acac)\textsubscript{2}]) were then added to ylide 112 but these failed to induce the desired Stevens rearrangement.
Since, a Stevens rearrangement did not occur on ylide 112 under acidic or thermal conditions, Porter et al. attempted a photochemical variant of the Stevens rearrangement. They subjected ylide 112 to photolysis in acetonitrile, affording the tetracycle target 109 (Scheme 18).

Scheme 17: Porter and co-workers’ proposed mechanisms for the thermally promoted Stevens rearrangement.

Scheme 18: Porter and co-workers’ synthesis of target 109 by a photo-Stevens reaction of 112.

Reagents and conditions: a) hv (> 290 nm), MeCN, 69%.
Having made the tetracyclic structure 109, the authors explored the scope of their methodology. More specifically, they synthesized further substrates to assess which structural features were important for ylide formation and the photo-Stevens rearrangement.

The first structural feature investigated was the effect the di-tert-butylsilylene protecting group (on the C-2 and C-4 hydroxyl groups) had on ylide formation or the photo-Stevens rearrangement. Hence, via a sequential deprotection-protection, the authors formed 114 from 113 where the bridged silyl ether on the C-2 and C-4 was replaced with two triethylsilyl (TES) ethers (Scheme 19). A Diazo transfer and subsequent rhodium-catalysed diazodecomposition led to ylide 116 (analogous to ylide 112 except with the non-bridged silyl ether protecting group). Photolysis of 116 yielded the tricyclic product 117 (with similar rates and yields to the previous example 109).

Scheme 19: Porter and co-workers’ synthesis of tricyclic structure 117.

Finally, the authors wanted to examine whether the acetyl group alpha to the carbon centre of the ylide was important in this methodology. Diazoacetate 120 was therefore made in three steps from alcohol 110, via acetylation, acetoacetylation and a diazo transfer (Scheme 20). Attempted
ylide formation using rhodium(II)acetate dimer in benzene failed and instead furnished 121; this compound must have been produced from the formed rhodium carbenoid reacting with the benzene solvent.\textsuperscript{30} As a result, the authors changed the solvent to dichloromethane which gave the desired ylide 122. Since, 122 was unstable to column chromatography, the crude reaction mixture was directly subjected to photolysis yielding target compound 123.

![Scheme 20](image)

**Scheme 20**: Porter and co-workers’ synthesis of tetracyclic 123.

To summarize, Porter et al. developed another route to make the core structure of tagetitoxin. The key steps in this route were the intramolecular ylide formation, between the sulfur atom and an \textit{in-situ} formed metallocarbenoid, followed by a photo-Stevens rearrangement. They additionally inferred that the silyl bridge tether between the oxygens on the C-2 and C-4 position as well as the acetyl group alpha to the nucleophilic carbon on the ylide were not important factors for this methodology to be successful. This strategy, however, would need to be explored further and adapted to achieve a total synthesis of tagetitoxin.
**Porter et al. 2009**

In 2009, Porter et al. adapted their previous strategy of forming the tagetitoxin bicyclic core (from a thiol/thiolate cyclizing onto an electrophilic ketone),\textsuperscript{24} to attempt a total synthesis of tagetitoxin \textbf{124} and decarboxytagetitoxin \textbf{125} (Figure 8).\textsuperscript{31}

![Figure 8: Synthetic targets for Porter et al.](image)

Their initial target was decarboxytagetitoxin \textbf{125}, starting from D-glucose. The key methodology of this route was to invert the stereogenic centres at the C-2 and the C-3 positions with the incorporation of a nitrogen functionality at the C-3, via the formation and subsequent trans-diaxial ring opening of a 2,3-β-epoxide with an azide nucleophile.

The diol \textbf{126} was prepared from D-glucose in two steps according to the literature (Scheme 21).\textsuperscript{32} Diol \textbf{126} was doubly deprotonated using sodium hydride and then underwent selective tosylation at the O-2 position, which triggered the O-3 alkoxide to intramolecularly displace the tosylate to form the 2,3-β-epoxide. The epoxide was then ring-opened with sodium azide to form \textbf{127}. After silyl protection of the hydroxyl group on the C-2, the anomic allyl ether was deprotected to form a lactol, which in turn underwent a DMP oxidation yielding lactone \textbf{128}. 
Scheme 21: Attempted synthesis of compound 129 by Porter et al.

Treatment of lactone 128 with an in-situ generated cerium-acetylide did not lead to the desired addition product; this was surprising, given the success when subjecting the related lactone 97 to these conditions in their previous work. Instead the only compound isolated was the double addition product 130. The authors hypothesized that after the desired nucleophilic attack of the cerium-acetylide onto the lactone, a ring opening to a ketone occurred, which then underwent a second organometallic addition. This was followed by a silyl migration from the O-2 position to the formed tertiary alkoxide producing 130. As a result, Porter and co-workers carried out the reaction with ytterbium triflate instead of cerium chloride, so that an organoytterbium instead of an organocerium species would react with lactone 128. Compound 131, however, was formed instead of 129. Porter and co-workers proposed a mechanism for this transformation (Scheme 22). Initially the ytterbium acetylide attacks the lactone to form 132 which ring opens to 133.
Subsequently a transannular hydride shift occurs forming 134 which then cyclized to 131 upon workup.

\[
\begin{align*}
&\text{Ph} \quad \text{O} \quad \text{O} \quad \text{OTBS} \quad \text{TMS} \\
&\text{N}_3 \quad \text{OM} \\
&132 \\
\rightleftharpoons \\
\text{Ph} \quad \text{O} \quad \text{O} \quad \text{OTBS} \quad \text{TMS} \\
&\text{N}_3 \quad \text{H} \\
&133 \\
\downarrow \\
\text{Ph} \quad \text{O} \quad \text{O} \quad \text{OH} \quad \text{TMS} \\
&\text{OM} \\
&131 \\
\text{H}_2\text{O} \\
\rightleftharpoons \\
\text{Ph} \quad \text{O} \quad \text{O} \quad \text{OTBS} \quad \text{TMS} \\
&\text{N}_3 \quad \text{H} \\
&134
\end{align*}
\]

**Scheme 22**: Porter and co-workers’ proposed mechanism for the formation of 131.

To overcome problems arising from the introduction of the acetylene moiety at the anomeric position on 128, the authors decided changed the order of the route. Specifically, they planned to incorporate the alkyne moiety prior to the inversion of the C-2 and C-3 chiral centres (i.e. to insert the alkyne moiety before they form the 2,3-β-epoxide). They rationalized that by carrying out the synthesis in this order, the acetylide would add to a glucose configured substrate (rather than an altrose configured substrate) which is more similar to the lactone 97 used for this analogous reaction in their previous successful strategy (**Scheme 14**).\(^{24}\)

Porter et al. synthesized 1,6-anhydroglucose 135 from D-glucose in four steps from the literature.\(^{33}\) Following selective silyl protection of the O-2 and O-4 to form 136, the authors introduced an alkyne moiety on the anomeric position using Vasella’s method (**Scheme 23**).\(^{34}\) This method involved the reaction between a lithium acetylide and aluminium trichloride to form a Al(C≡CTMS)\(_3\) species which upon treatment with 136, led to 137. Formation of 138 was then achieved by deprotection of the silyl ethers and sequent protection of the O-5 and O-6 in the form of a p-methoxybenzylidene acetal. Synthesis of epoxide 139 was, however, not achieved
using their previous strategy. This is because despite trying a range of conditions (TsCl, Ts-imidazole, Ts₂O and MsCl with either pyridine or sodium hydride as base) no regioselectivity was accomplished for the sulfonylation of one of the hydroxyl groups on C₂ or C₃ centres over the other (since only inseparable 1:1 mixtures of the respective mono-sulfonates were obtained).

![Chemical Structures](image)

**Scheme 23**: Attempted synthesis of epoxide 139 by Porter et al.

To solve this regioselective problem, the route was altered to make a substrate analogous to 138 with the exception of O-3 being protected (**Scheme 24**). Acetate 140 was therefore synthesized from 137 by a selective silyl protection on O-6 and sequent acetyl protection on O-3. Silyl ether cleavage and acetal formation then followed yielding 141. Tosylation of the free hydroxyl group on C₂ was accomplished and then epoxide formation was attempted. Under basic conditions, deacetylation of O-3 and concomitant displacement of the tosylate as well as removal of the silyl group on the alkyne led to the epoxide 142 being formed. Yet, when attempting to ring open the epoxide with an azide nucleophile in acidic conditions, only partial hydrolysis of the acetal was seen. Thus, the authors tried non-acidic conditions such as heating the epoxide with sodium azide in DMF, but only elimination product 143 was observed. Trans-diaxial ring opening of epoxide 142 to azide 144 was eventually achieved using Yamamoto’s procedure.³⁵ In this procedure, ytterbium triisopropoxide (formed in-situ from ytterbium triflate and lithium isopropoxide) activates the epoxide for nucleophilic attack from the azide.
The next target was to install the thioacetate on the C-6 position. To achieve this, they protected the 2-O with an acetyl group, hydrolysed the acetal and then performed a selective tosylation on the primary alcohol. This was followed by a displacement of the tosylate with a thioacetate nucleophile furnishing 145. After silylation of the O-4, bromination of the terminal alkyne was achieved using NBS and catalytic AgNO₃. However, oxidation of the bromoalkyne moiety in 146 to an α-ketoester using potassium permanganate in methanol (as similarly carried out in the synthesis of 106 in their earlier work)²⁴ failed for this substrate as only decomposition was observed; this prevented the synthesis of decarboxytagetitoxin 2 being achieved.

Scheme 24: Attempted synthesis of bicyclic precursor 147 by Porter et al.

Porter et al. also focused on the total synthesis of tagetitoxin 124. They adapted their previous strategy (shown in Scheme 23) to include the installation of a vinyl group on the C-5 of the glucose configured backbone, envisaging later oxidation of this group to a carboxylic acid derivative. Incorporation of the vinyl group, was based on an strategy described by Rao et al.,³⁶
with the key step being stereoselective addition of a vinyl Grignard reagent to a 5-keto derivative of glucose.

Porter and co-workers synthesized a similar 5-keto derivative of glucose 149 to Rao et al. (the only difference being the protecting group on the O-3). This was accomplished in four steps from compound 148 (Scheme 25): protection of the 3-O with a PMB group; hydrolysis of the 5,6-acetonide; selective silyl protection of the O-6; and finally a Swern oxidation of the remaining free hydroxyl group on the C-5 position. Subsequent stereoselective Grignard addition afforded 150. Upon heating 150 in a mixture of acetic and trifluoracetic acid, global deprotection and concomitant cyclization occurred to give the desired 1,6-anhydroglucose derivative; it was also vital to have a thioanisole cation scavenger in the reaction mixture as it prevented unwanted side reactions. Due to the nature of the conditions (heat and acid), Fischer esterification side products were formed in addition. Thus, the investigators subjected the crude mixture to sodium methoxide in methanol to deacetylate the mixture of acetates producing 151 in high yield. Via the same methodology in their previous synthetic studies towards decarboxytagetitoxin (synthesis of 137 from 135 shown in Scheme 23), the authors performed two further steps to yield 152. No further work on this route, however, has been published.
Reagents and conditions: a) NaH, PMBCl, THF, rt, 86%; b) 60% aq ACOH, rt, 80%; c) TBSCl, imidazole, DMF, rt, 81%; d) (COCl)$_2$, DMSO, Et$_3$N, DCM, -78°C, 79%; e) vinylmagnesium bromide, THF, rt, 76%; f) 80% aq AcOH, TFA, PhSMe, reflux then NaOMe, MeOH, rt, 73%; g) TESCl, pyridine, rt, 68%; h) TMS-Acetylene, BuLi, AlCl$_3$, 2,4,6-collidine, toluene-THF, sonicate, -15°C to 50°C, then added substrate, 130°C, 70%.

**Scheme 25**: Synthesis of compound 152 by Porter et al.

In summary, whilst Porter et al. have previously developed a successful synthetic route to the bicyclic core of tagetitoxin from thiol/thiolate cyclizing onto a ketone, applying and adapting this methodology towards a total synthesis of the natural product and its non-natural decarboxy analogue have proved difficult despite isolating promising intermediates 146 and 152. In fact, since this paper, no further research related to this synthetic approach has yet to be reported.

**Porter et al. 2012**

In 2012, Porter and co-workers published another paper building on their earlier research concerning ring expansions of a 1,3-oxathiolane moiety in thioanhydrosugars to a 1,4-oxathiane moiety and its application towards tagetitoxin synthesis. Although Porter and co-workers were previously successful in forming a sulfonium ylide from the reaction of a sulfur atom of a thioanhydrosugar with a metallaoacarbonoid (generated in situ from a transition metal complex and α-diazoester), they explored methods of forming the ylide without the use of a transition metal complex. Furthermore, the authors aimed to adapt their previous successful ring
expansion methodology in synthesizing the tagetitoxin bicyclic core (based on a carbene-mediated intramolecular sulfonium ylide formation followed by a photochemical 1,2-Stevens rearrangement) to a closer related analogue of decarboxytagetitoxin. Using compound 92 (made in their earlier studies), Porter et al. planned to carry out an S-alkylation to form a sulfonium bromide salt 153 followed by a deprotonation to form the ylide 154 (Scheme 26).

![Scheme 26: Porter and co-workers’ retrosynthetic analysis of ylide 154.](image)

Reaction of 92 with ethyl bromoacetate produced no trace of sulfonium salt 153, instead only compound 155 was isolated (Scheme 27); this was formed from nucleophilic attack of the bromide ion on the formed sulfonium ion. To prevent this undesired reaction, the authors added either silver salts (to form insoluble silver bromide removing the bromide nucleophile) or replaced the bromide leaving group on the alkylating agent with a non-nucleophilic group (such as a triflate). However, neither of these attempts yielded 153.

![Scheme 27: Synthesis of compound 155 by Porter et al.](image)

Reagents and conditions: a) EtO₂CCH₂Br, MeCN, 72%.
The authors considered another method of generating an ylide considered by forming a free carbene (rather than a metallocarbene) from diazo compound 111 under photolytic conditions (Scheme 28). If successful, ylide formation and the subsequent photochemical 1,2-Stevens rearrangement could be done in one-pot. However, irradiation of 111 with UV light in acetonitrile only formed compounds 156 and 157. Compound 156 was most likely formed by a Wolf rearrangement of the generated free carbene, followed by hydrolysis on the formed ketene intermediate. Whilst oxazole 157 was most likely produced by the reaction between the free carbene and acetonitrile. On changing the solvent to dichloromethane or chloroform, the major product malonate 156.

![Scheme 28: Synthesis of compounds 156 and 157 from 111 by Porter et al.](image)

To further expand the scope of their methodology, the authors wanted to make 158 (Scheme 29); this is an analogue of compound 109 which they had successfully synthesized in their previous study. The key difference between these congeners is the presence sulfoxide functionality in 158 rather than a thioether. The oxosulfonium ylide 161 was synthesized from compound 113 (made in their previous studies) in three steps: controlled thioether oxidation; diazo transfer; and diazodecomposition using rhodium acetate. Only decomposition, however, was observed when irradiating tetracyclic ylide 161 with UV light.
Finally, Porter et al. tried to make a closely related analogue of decarboxytagetitoxin using their methodology on a photochemical 1,2-Stevens rearrangement of a sulfonium ylide. To achieve this, Porter and co-workers made key changes to their previously successful routes in synthesizing the tagetitoxin bicyclic core (Schemes 18, 19 and 20). One modification was to tether the diazo functionality through an equatorial oxygen at the C-2 position rather than the axial position at C-3. This would affect the intramolecular ylide formation which would now occur between the sulfur atom of the 1,3-oxathiolane with the diazo functionality on the C-2 position instead of the C-3 position. This modification would allow the installation of a nitrogen functionality at the C-3 position as is the case with decarboxytagetitoxin.

The authors started the synthesis by making a 2,3-β-epoxy derivative in two steps from compound 162, which was then ring opened with sodium azide to yield 163 (Scheme 30).
Subsequently, a Hanessian-Hullar oxidative ring opening of the benzylidene acetal moiety led to 164.\textsuperscript{38,39} A S\textsubscript{N}2 displacement of the bromide with a thioacetate nucleophile followed to afford thioester 165. Under strong acidic acetylation conditions, acetylation of the 2-OH, thioacetate cleavage and concomitant cyclization (where the formed thiol displaced the 1-OMe in a 5-exo-tet reaction) were all accomplished in one step, yielding 166.

![Chemical Diagram]

Reagents and conditions: a) NaOMe, Ts-imidazole, DCM, reflux b) NaOMe, MeOH, Reflux, 81% (2steps); c) NaN\textsubscript{3}, NH\textsubscript{4}Cl, MeOCH\textsubscript{2}CH\textsubscript{2}OH, H\textsubscript{2}O, reflux, 83%; d) NBS, BaCO\textsubscript{3}, CHCl\textsubscript{3}, reflux, 79%; e) KSAc, DMF, 95%; f) Ac\textsubscript{2}O, AcOH, H\textsubscript{2}SO\textsubscript{4}, 60%.

**Scheme 30:** Synthesis of 166 by Porter et al.

The next goal for the authors, was to trifluoroacetyleate the 2-OAc in 166 and to subsequently perform a detrifluoroacetylating diazo transfer to form 170 (Scheme 31). The trifluoroacetylation of 166 using LDA and trifluoroethyl trifluoroacetate, however, proved troublesome, because the only products observed were alcohol 167 and acetoacetate 168. Since, only these products were seen without even adding the electrophile, the authors postulated that after the deprotonation of 166 by LDA, a Claisen condensation followed by an elimination took place to form a ketene and 167 (in its alkoxide form). The ketene then reacted with the ester enolate species forming 168. Despite varying the base and temperature, compound 169 was not seen. The authors therefore attempted an alternative route whereby they deacetylated 166 to form 167, which was then subjected to the 2-fluoroacetylnderivative of Meldrum’s acid under reflux furnishing 169. Compound 169 then underwent a detrifluoroacetylating diazo transfer to form 170.
Diazodecomposition and consequent intramolecular ylide formation from 170 was unsuccessful despite performing a range of conditions with various catalysts [Rh$_2$(OAc)$_4$, CuPF$_6$(MeCN)$_4$, AgOTf, Cu(acac)$_2$].

Scheme 31: Attempted synthesis of ylide 171 by Porter et al.

As a result, the authors changed their strategy for the synthesis of ylide 171 from a transition metal catalysed diazodecomposition to an intramolecular S-alkylation followed by deprotonation. Hence, 172 was made by acylation of the 2-OH in 167 with bromoacetyl bromide (Scheme 32). However, intramolecular displacement of the bromide by the sulfur atom to form sulfonium salt 173 was not observed with or without the presence of silver salts.
Scheme 32: Attempted synthesis of sulfonium salt 173 by Porter et al.

As the authors previously made the thermally stable acetyl-substituted ylides 112 and 116,²⁵ they aimed to synthesize ylide 175 (Scheme 33). To achieve this, acetoacetylation of 167 was performed to give 168, which then underwent a diazo transfer to form 174. Although ylide 175 was formed from 174 by diazodecomposition, it was impure and in low yield. Furthermore, irradiation of impure ylide 174 did not furnish the desired ring expansion product 176.

Scheme 33: Attempted synthesis of tricyclic 176 by Porter et al.
In summary, alternative methods to transition metal catalysed diazodecomposition for ylide formation such as photolytic conditions or S-alkylation followed by deprotonation failed due to undesired side reactions. Moreover, modifying their earlier successful methodology in making the tagetitoxin bicyclic core,25 to closer related analogues of tagetitoxin by either sulfoxide incorporation instead of a thioether or to tether the diazo functionality through an equatorial linkage at the C-2 proved unsuccessful; the latter of which was explained by increased strain in the ylide. These results highlight the difficulty in expanding the scope of the ring expansion strategy and its applicability to a total synthesis of tagetitoxin. Thus, since this paper, no further related work to this strategy has been published.

Nishikawa et al.

In 2013, Nishikawa and co-workers synthesized a fully functionalized tagetitoxin core structure.7

The first step in their synthesis of a tagetitoxin core structure was a Ferrier-type α-selective C-glycosylation of galactal 177 with tin acetylene and TMSOTf, producing 178 (Scheme 34). The yield and the selectivity in these conditions were much higher than using conventional methods, such as with bis(trimethylsilyl)acetylene and Lewis acids like SnCl4.40,41 After cleavage of the two acetates and TMS group using methanolic sodium methoxide, the primary alcohol was selectively silyl protected forming 179. This allowed selective carbamoylation to then take place on the remaining free hydroxyl group via trichlorocetyl carbamoylation and subsequent hydrolysis to form 180.
The next target in the synthesis was the stereocontrolled installation of a nitrogen functionality at the C-3 position and an oxygen functionality at the C-2 position in a stereocontrolled manner. The authors envisaged that this could be accomplished by the synthesis of a 2,3-β-aziridine derivative and subsequent regioselective opening with an oxygen nucleophile (Scheme 35).

Treatment of 180 under typical aziridination conditions of catalytic amounts of Rh$_2$(OAc)$_4$ and PhI(OAc)$_2$ with magnesium oxide, afforded aziridine 181, albeit in low yield (17%). However, upon modification of the conditions, namely using Rh$_2$(OAc)$_4$, PhIO and 4Å molecular sieves, the reaction was optimized to 70% yield. Aziridine 181 was then ring-opened regioselectively with an acetate nucleophile to furnish 182. The carbamate was then benzylated under typical conditions, which was then followed by a silyl ether deprotection to afford 183.

**Scheme 34**: Synthesis of compound 180 by Nishikawa et al.

Reagents and conditions: a) tributylstannyl(trimethylsilyl)ethyne, TMSOTf, DCM, 0°C; b) NaOMe, MeOH, 0°C; then Dowex®, 95% in 2 steps; c) TBSCI, Et$_3$N, DMAP, DCM, rt, 85%; d) trichloroacetyl isocyanate, DCM, 0°C; then K$_2$CO$_3$, MeOH, H$_2$O, 0°C, 73%.
The investigators then aimed to incorporate a carboxylic acid derivative on the C-5 position. To achieve this, the authors planned to make an *exo*-glycal, carry out an epoxidation on it and finally ring open the *spiro*-epoxyacetal with a cyanide-based nucleophile in a regioselective and stereoselective fashion. The authors firstly activated the primary hydroxyl group as a triflate and displaced it with lithium phenylselenide (generated from diphenyldiselenide and *n*-BuLi) to produce selenide 185 ([Scheme 36](#)). Using mCPBA, 185 was then oxidized to give the selenoxide which then underwent a selenoxide elimination to give *exo*-glycal 186. Electrophilic epoxidation was then successfully carried out on 186 to yield *spiro*-epoxyacetal 187. When attempting to ring open the epoxide using TMSCN and a range of Lewis acids, the desired nitrile 188 was not observed. Treatment, however, with Et₂AlCN did produce 188 as a single diastereomer but only in an 8% yield. Eventually the authors found optimal conditions for this reaction using TMSCN and molecular iodine in toluene and hexane at 0 °C; this led to the isolation of 188 in sufficient yield (44%) after acidic hydrolysis of the TMS ether.
Having succeeded in making a fully functionalized pyranoid framework of tagetitoxin (188), the authors then aimed to construct the 1,4-oxathiane moiety of the natural product. In order to achieve this, they firstly incorporated a sulfur functionality into the structure in the form of a thioacetyl group, using similar methodology to Porter et al., whereby the primary alcohol of 188 was transformed into a triflate and then displaced with a thioacetate nucleophile to afford 189 (Scheme 37). The authors then planned to deprotect the thioacetate group to release the thiolate which would then undergo a concomitant 6-exo-dig cyclization. Although treatment of 189 with LiSMe did cause the intended thioacetyl deprotection, only the undesired 7-endo-dig cyclization from the generated thiolate occurred. Therefore, Nishikawa and co-workers planned to modify their cyclization strategy; instead of an in-situ generated thiolate undergoing a 6-exo-dig cyclization, they envisaged that it would undergo a conjugate addition on an α,β-unsaturated sulfoxide in a 6-exo-trig cyclization. Thus, the authors synthesized the α,β-unsaturated sulfoxide 190 in two steps from 189 by a radical addition of thiophenol to the alkyne moiety and subsequent oxidation of the vinyl thioether with mCPBA. Treatment of 190 with lithium hydride in methanol led to initial thioester cleavage and an in-situ conjugate addition of the formed...
thiolate on the vinyl sulfoxide, but deacetylation and nitrile transformation into an imidate were additionally observed leading to 191 forming. Subsequent acidic hydrolysis on the imidate was then carried out to give methyl ester 192, which in turn was acetylated to form 193.

Scheme 37: Synthesis of compound 193 by Nishikawa et al.

Transformation of the sulfoxide moiety of 193 into an aldehyde via the Pummerer rearrangement to form 194 was attempted (Scheme 38). However, the use of conventional conditions such as acetic anhydride and sodium acetate only led to unreacted starting material. This prompted the authors to use the more electrophilic trifluoracetic anhydride instead. This led to starting material being recovered, although, epimerization of the chiral sulfoxide was observed (diastereomeric ratio changed from 1:7 to 2:1); this indicates that the sulfoxide must have been trifluoroacetylated initially but then underwent an intermolecular displacement with a trifluoroacetate nucleophile. In order to solve the aforementioned difficulties encountered in this transformation, a strong electrophilic activating agent with a poor nucleophilic leaving group (TMSOTf) and a non-nucleophilic base (Et$_3$N) were used; the former led to successful sulfoxide
activation and the latter led to successful elimination of the generated silylated sulfoxide to the thonium ion, which in turn underwent hydrolysis to form aldehyde 194.

![Diagram](image)

Reagents and conditions: a) NaOAc, Ac₂O; b) TMSOTf, Et₃N, DCM, 0 °C, 63%; c) (CF₃CO)₂O.

**Scheme 38:** Synthesis of compound 194 by Nishikawa et al.

The final objectives to synthesize the core structure of tagetitoxin was the conversion of the aldehyde into an amide and formation of a thioketal functionality. Surprisingly, the authors accomplished both these goals in one step (**Scheme 39**). Oxidative amidation of aldehyde 194 with benzylamine and iodine in methanol produced thioketal 195 rather than the expected compound 196. It was postulated, that during the reaction, 196 was produced but then underwent acetate cleavage. Additionally, under these conditions, the sulfide was activated with iodine to form a sulfonium ion which was then trapped by a methanol molecule furnishing 195. Acetylation of 195 gave the tagetitoxin core structure 197.
Scheme 39: Synthesis of the core structure of tagetitoxin (197) by Nishikawa et al.

In summary, Nishikawa et al. synthesized the first fully functionalized tagetitoxin core. Their key methodology in constructing the bicyclic ring system involved the deprotection of a thioacetate and concomitant intramolecular conjugate addition of the free thiolate on a vinyl sulfoxide. Moreover, compared to previously synthesized tagetitoxin core structures,\textsuperscript{24,31} compound 197 is the only one which has a carboxylic derivative on the pyranoid core of the natural product (which was accomplished by the synthesis and subsequent ring opening of a spiro-epoxyacetal).

Previous Work in The Page Group

The targets in all previous studies in the Page group towards the synthesis of tagetitoxin have been structures 2a and 2b.\textsuperscript{43–45} There have been several routes attempted by the Page group to make the bicyclic core of structures 2a and 2b. In all routes, the planned synthesis of the 1,4-oxathiane moiety in the bicyclic core has been based upon Porter and co-workers’ methodology where a thioacetyl functionality is deprotected leading to an in-situ cyclization of a free thiol or thiolate onto a ketone.\textsuperscript{24}
Roy

Early studies in the Page group towards the synthesis of tagetitoxin were carried out by Claud-Éric Roy. Their synthetic pathways generally started from non-cyclic materials (such as mucic acid or meso-tartaric acid) before moving on to cyclic starting materials such as D-mannose.

Mucic Acid Route

The first strategy of the group began from a non-cyclic starting material mucic acid (Scheme 40).

![Scheme 40: Retrosynthesis of the target bicyclic structure 198 from mucic acid.](image)

In this strategy, bicyclic precursor 199 could be derived from 200 by activating the hydroxyl into a good leaving group and then displacing it with a thioacetate nucleophile. The fully functionalized pyranoid core 200, could be made from cyclization in terminal epoxide 201. This
epoxide intermediate 201 could be synthesized from di-ketoester 202 via a Wittig or Tebbe olefination-epoxidation sequence or a Corey-Chaykovsky reaction on one of the ketones.\textsuperscript{46–48} Compound 202 could be formed by a Krapcho decarboxylation of the two esters, other than the two α-ketoesters in 203. Enolization of both esters in 204, which then undergo nucleophilic attack on an esterified derivative of oxalic acid could then lead to the installation of the two α-ketoester moieties seen in 203. Finally, 204 could be synthesized from readily available mucic acid 205 by esterification of the two carboxylic acid moieties followed by relevant hydroxyl group protection.

Roy began the route by synthesizing compound 207 in two steps from mucic acid 205 (Scheme 41) as described by Hirsch et al.\textsuperscript{49} These steps were a Fischer esterification to form bis-methyl ester 206 which was then treated with acid in acetone to furnish bis-acetonide 207. However, only low yields (17-25%) of 207 were obtained; changing the acid catalyst led to either lower yields or decomposition.

Scheme 41: Two-step synthesis of 207 from mucic acid 205.

The next planned step in the synthesis was the insertion of the two α-ketoester moieties to give 208 (Scheme 42 and Table 3).

Scheme 42: Acylation attempts of 207.
Table 3: Conditions reported for the acylation attempts of compound 166

This was initially attempted using Kagan’s conditions,\textsuperscript{50} where sodium ethoxide was used as a base (to form the ester enolates), and diethyl oxalate used as the electrophile. Under these conditions, however, only starting material was recovered (entry 1). Consequently, the group used stronger bases such as sodium hydride and lithium diisopropylamide (LDA) but this similarly led to full starting material recovery (entries 2 to 4).

To investigate the failure of this reaction, the group attempted to alkylate 207 to assess the reactivity of the carbon being deprotonated. Only starting material, however, was observed when using ethyl iodide as the alkylating agent with the same bases used in the attempted acylation (LDA and sodium hydride). This unexpectedly suggests that under these conditions, the ester enolate of 207 is not generated or not reactive enough to attack the diethyl oxalate in a nucleophilic manner.

This route was therefore abandoned due to the low yields obtained with bis-acetonide 207 as well as the failure in producing bis-ketoester 208.

Tartaric Acid Route

The group then moved onto a different strategy starting from meso-tartaric acid (Scheme 43).
Scheme 43: Retrosynthesis of the target bicyclic structure 198 from meso-tartaric acid.

In this route, bicyclic precursor 199 could be formed from 209 by deprotection of the exo-cyclic secondary hydroxyl group and then subsequent oxidation of the α-hydroxyester to an α-ketoester. Similarly to the retrosynthetic analysis in the mucic acid route, the thioacetate moiety could be incorporated into the structure 210 by displacement chemistry. Intermediate 210 could be derived by reaction between the anomeric ester enolate of 211 with formaldehyde. The functionalized pyranoid core 211 could be made by a 6-exo-tet cyclization from attack of a nucleophilic hydroxyl onto an activated hydroxyl group (e.g. sulfonate ester) in the cyclic
precursor 212, which in turn could be made by the bis-dihydroxylation of 213. The bis-alkenylcarboxylic ester 213 could be synthesized by a Wittig olefination on both aldehydes of 214. Finally, esterification and relevant hydroxyl group protection on meso-tartaric acid followed by ester reduction would furnish dialdehyde intermediate 214.

It was planned that the synthesis would be first attempted with racemic tartaric acid and then the optimized conditions would be applied to meso-tartaric acid (due to the high cost of the latter).

Using Carmack’s procedure, Roy synthesized intermediate (±)-218 from racemic tartaric acid 217 (Scheme 44). In this one-pot reaction, under acidic conditions (p-toluenesulfonic acid) in methanol and 2,2-dimethoxypropane under reflux, both carboxylic acids underwent a Fischer esterification in addition to the ketalization of the diol functionality. Although it was advantageous to have both the esterification and ketalization in one pot, the reaction was capricious, since results varied from quantitative yields of (±)-218 to complex mixtures with undesired side products such as acid (±)-219 and (±)-220.

![Scheme 44: Synthesis of (±)-218 from racemic tartaric acid (±)-217.](image)

The next target in this strategy was the synthesis of dialkene (±)-222 from (±)-218 by a one-pot bis-[ester reduction/Wittig olefination] (Scheme 45). In this step, the diester was reduced to the dialdehyde (±)-221 using diisobutylaluminium hydride (DIBAL) which was followed by a Wittig olefination of the formed aldehydes. It was observed that for the reduction, the addition rate of the hydride and reaction time were significant variables that required optimization to avoid starting material decomposition or full reduction of the esters to alcohol moieties. After 3 hours at -78 °C, the Wittig ylide was then added to the reaction mixture, which led to an inseparable mixture of the (E,E)-dialkene (±)-222 and its geometric isomer (Z,Z)-dialkene (±)-223. Since, however, it was important to perform the next steps with only one isomer (to help
with the potential isolation of cyclized compound 211 later on in the synthesis), this mixture was not used further in the synthesis.

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{a} \quad \begin{bmatrix}
\text{O} & \quad \text{O} \\
\text{OHC} & \quad \text{CHO}
\end{bmatrix} \quad \text{b} \quad \begin{bmatrix}
\text{EtO}_2\text{C} \\
\text{CO}_2\text{Et}
\end{bmatrix} + \\
\text{EtO}_2\text{C} & \quad \text{O} \quad \text{CO}_2\text{Et}
\end{align*}
\]

\((\pm)-218\) \[ \Rightarrow \] \((\pm)-221\) \[ \Rightarrow \] \((\pm)-222\) \[ \pm \] \((\pm)-223\)

Reagents and conditions: a) DIBAL (1M in PhMe) over 30 min, PhMe, -78 °C, 3 h; b) \(\text{Ph}_3\text{PCHCO}_2\text{Et}\), -78 °C to rt, 16 h.

Scheme 45: One-pot bis-[ester reduction/Wittig olefination] of intermediate \((\pm)-218\)

With the goal being to isolate only one geometric isomer of the dialkene, Roy planned to adapt a synthesis carried out by Saito \textit{et al.},\textsuperscript{53} since they succeeded in making the \((E,E)\)-dialkene \((\pm)-222\) from a one-pot bis-[ester reduction/Horner Wadsworth-Emmons olefination] on \((\pm)-224\) (Scheme 46). Saito \textit{et al.} conclude that this type of diester starting material (with acetonide protecting group and isopropyl esters) in a toluene-hexane solvent system with diisopropylphosphonate as the Horner Wadsworth-Emmons (HWE) olefination reagent were key features for the success of the reaction.\textsuperscript{53}

\[
\begin{align*}
\text{iPrO}_2\text{C} & \quad \text{CO}_2\text{iPr} \quad \text{a} \quad \begin{bmatrix}
\text{EtO}_2\text{C} \\
\text{CO}_2\text{Et}
\end{bmatrix}
\end{align*}
\]

\((\pm)-224\) \[ \Rightarrow \] \((\pm)-222\)

Reagents and conditions: a) DIBAL (1M in PhMe) over 30 min, PhMe/hexane, -78 °C, 3 h; then \((\text{iPrO})_2\text{P(O)CHCO}_2\text{Et}\), -78 °C to rt, 78%.

Scheme 46: Saito and co-workers’ synthesis of dialkene 222 from compound 224.\textsuperscript{53}

However, Roy intended to perform this bis-[ester reduction/HWE] on isopropyl diester 225 rather than \((\pm)-224\). The synthesis would, therefore, be started from \textit{meso}- rather than \textit{rac}-tartaric acid (despite the high cost of the former). Thus, isopropyl diester 226 was synthesized in two steps from \textit{meso}-tartaric acid 216 by a Fischer esterification and subsequent ketalization (Scheme 47).
Scheme 47: Two-step synthesis of 226 from meso-tartaric acid 216.

Roy then attempted the bis-[ester reduction/HWE] on 225 using conditions reported from Saito et al. (Scheme 48). However, only low yields (13-15%) of dialkene 227 were obtained. Changing reaction times, rate of addition of reagents as well as the base that deprotonates the phosphonate from n-BuLi to non-nucleophilic LDA led to no improvement in yield.

Scheme 48: One-pot bis-[ester reduction/HWE olefination] of 226.

Despite the poor yields for dialkene 227, the bis-dihydroxylation using AD mix-β was attempted (Scheme 49). The crude \(^1\)H NMR spectrum, however, showed a resultant complex mixture. Purification attempts by chromatography on silica gel or alumina proved futile because the mixture was lost with no recovery possibly due to its polarity.

Scheme 49: Failed synthesis of 228 by bis-dihydroxylation of 227.
The low yields of the dialkene 227 in addition to no single isolable product from the bis-dihydroxylation, led the group to focus on a different strategy.

**Darzens Route**

Roy then moved onto a strategy with the cyclic starting material D-mannose (Scheme 50).

![Scheme 50: Retrosynthesis of target structure 229 from D-mannose 235 in the Darzens route.](image)

In this strategy, structure 229 is the synthetic target. If 229 were successfully made, the strategy would then be modified to install an ester on the thiohemiketal centre. The target precursor 230 could be synthesized from 231 in three-steps: selective acetonide hydrolysis; primary hydroxyl protection; and oxidation of the secondary alcohol. The insertion of the thioacetyl-methylene moiety on 232 to afford 231 is identical to the aforementioned methodology in the meso-tartaric acid route. The synthesis of the pyranoid core in 232 could be achieved by a 6-endo-tet
cyclization in glycidic ester 233 followed by a protection of the OH on C-2. This glycidic ester 233 could form from a Darzens reaction between an α-haloester and diacetone mannose (DAM) 234. Finally, DAM 234 could be synthesized from D-mannose 235 using acid catalysis in an acetone solvent.

The key feature in this route is the proposed Darzens condensation reaction involving a nucleophilic addition of an α-haloester (using enolate chemistry) on the acyclic hydroxy-aldehyde form of DAM 234 followed by a 3-exo-tet cyclization to give epoxide 233 (Scheme 51). This reaction exploits the aldehyde chemical properties that most cyclic carbohydrate derivatives have, arising from the equilibrium between the ‘closed’ lactol form and the ‘open’ hydroxy-aldehyde form. Furthermore, in intermediate 236, competing with the 3-exo-tet cyclization for epoxide formation, a 6-exo-tet cyclization could occur to give the desired glycoside 237. Alternatively, even if epoxide formation occurs in the reaction, the formed epoxide intermediate could undergo a concomitant 6-endo-tet cyclization (although in competition with the more favourable undesired 5-exo-tet cyclization) to give the C-glycosyl ester 237.

Scheme 51: Proposed mechanism for the Darzens reaction on DAM 234.

For the first step of the route, Roy synthesized DAM from D-mannose using a literature procedure from Schmidt et al. (Scheme 52). The reaction occurred by the protection of the cis-
hydroxyl groups in the furanose form of D-Mannose with isopropylidene groups. It was observed that neutralization of the crude reaction mixture prior to second stage of the reaction was critical, since without doing this only decomposition was observed.

Scheme 52: Synthesis of DAM 234 from D-mannose 235.

Subsequently the Darzens reaction on DAM was attempted (Scheme 53). However, only starting material was observed in the reaction, despite trying different deprotonation conditions for the addition of the α-haloester.

Scheme 53: Attempted Darzens reaction on DAM 234.

As a result, the group modified their strategy (Scheme 54). In this approach, the Darzens reaction would occur on a protected derivative of the ‘open’ form of DAM. Then basic deprotection and concomitant 6-endo-tet cyclization would then eventually lead to glycoside 237.
To make this protected derivative, Roy followed a synthesis performed by Hashimoto et al. (Scheme 55).\textsuperscript{55} In this synthesis diol 241, was synthesized by the total reduction of the lactol functionality in DAM 234 using LAH. A selective benzoylation on the primary hydroxyl group and subsequent silylation on the secondary alcohol then afforded 243. Deprotection of the benzoyl group and subsequent oxidation of the resulting primary alcohol furnished aldehyde 245.

Although benzoyl 242 was reached easily by Roy using Hashimoto and co-workers’ conditions, difficulties were encountered in the ensuing silylation of the secondary alcohol. The use of TBSCI was concluded to be ineffective under the conditions reported by Hashimoto et al.,\textsuperscript{55} as
only decomposition was observed. The use of the more electrophilic silylating agent TBSOTf, with N,N-Diisopropylethylamine (DIPEA) in Et₂O, however, did furnish compound 243 but in low yield (37%). After Roy successfully isolated alcohol 244 in quantitative yield from the saponification of the benzoyl functionality in 243, the oxidation to the target aldehyde 245 was then attempted. Surprisingly when using Moffatt-Pfitzner methodology as reported in Hashimoto and co-workers’ synthesis, only a mixture of starting material and decomposition was seen. Even applying range of other oxidations (Parikh-Doering, Swern and hypervalent iodine mediated oxidations) were similarly unsuccessful.

As a result, Roy planned to follow a synthesis towards an alternate protected aldehyde species with an acetyl protected secondary hydroxyl group published by López-Herrera et al. (Scheme 56). The route consisted of a Wittig olefination of DAM forming terminal alkene 246, then acetyl protection followed by ozonolysis yielding aldehyde 248. An advantage of this synthesis was fewer steps compared to the synthesis of aldehyde 245 reported by Hashimoto and co-workers.55

The Wittig olefination on DAM 234 carried out by Roy, appeared capricious as terminal alkene 246 was formed in yields varying from 47% to 76%. Acetylation (84-97% yield) and consequent ozonolysis (up to 100% yield), however, proceeded smoothly to afford the desired aldehyde 248.

The next step in the synthesis was the Darzens condensation on aldehyde 248 (Scheme 57). In both conditions attempted, glycidic ester 249 was not isolated. When the reaction was performed with LDA, only DAM was recovered. When using the milder base t-BuOK, mainly starting material and a small amount of DAM was isolated. The formation of DAM in both conditions

\[ \text{Scheme 56: Lopéz-Herrera and co-workers’ three-step synthesis of aldehyde 248 from DAM 234.} \]
could be explained by an *in-situ* deprotection of the acetate by the deprotonated bromoacetate nucleophile liberating an anionic oxygen which could attack the aldehyde yielding DAM.

Scheme 57: Failed Darzens reactions of aldehyde 248.

This route was abandoned due to the inability to isolate glycidic ester 249.

Pearce

Continuing the work of Claude-Eric Roy, Pearce undertook a variety of routes starting from DAM 234.\(^{44}\)

**Dithioacetal Route**

The first route attempted by Pearce involved the nucleophilic addition of a masked α-ketoester onto DAM 234 (Scheme 58).
Scheme 58: Retrosynthesis of target structure 229 from DAM 234 in the dithioacetal route.

The synthetic target 229 could be derived from intermediate 232 by the same methodology mentioned in the Darzens route. Pearce proposed that pyranose 250 could lead to 232 in a three-step sequence involving selective protection of the C_2 hydroxyl group, activation of the anomeric alcohol into a good leaving group and displacement of the latter with a hydride source. Pyranose 250 could be obtained by dethioketalization of 251, which in turn, would trigger a 6-exo-trig cyclization. The nucleophilic addition of a deprotonated 1,3-dithiane-2-carboxylate ester derivative on DAM 234 would yield intermediate 251. Finally DAM 234 would be made from D-mannose 235 in identical fashion to previous work in the group.
This route was largely inspired by the synthesis of intermediate 253 from DAM 234 reported by Reiner and Schmidt (Scheme 59).\textsuperscript{57} Pearce planned to reproduce this synthesis except but without performing the transesterification after the dethioketalization.

\begin{center}
\includegraphics[scale=0.5]{scheme59}
\end{center}

Reagents and conditions: a) ethyl 1,3-dithiane-2-carboxylate, LDA, MgBr\textsubscript{2}, THF, 76%; b) NBS, acetone; c) NaOMe, MeOH, 30% over 2 steps

**Scheme 59**: Reiner and Schmidt’s two-step synthesis of pyranose 253 from DAM 234.

After synthesizing DAM 234 from D-mannose 235, Pearce then attempted the nucleophilic addition of ethyl 1,3-dithiane-2-carboxylate onto DAM with the goal of making 252. The group decided to modify Reiner and Schmidt’s procedure by not using MgBr\textsubscript{2} (for practicality reasons); therefore DAM 234 was added to a lithiated 1,3-dithiane derivative rather than a Grignard reagent 1,3-dithiane derivative, but only DAM was recovered. The group rationalized this observation by suggesting that the lithiated dithiane acted as a base rather than a nucleophile on the open hydroxy-aldehyde form of DAM to reform the closed lactol form. When repeating the conditions from the literature,\textsuperscript{57} high yields of up to 98\% of 252 were obtained, though the yields did decrease on a scale less than 10g of DAM.

The next step in this strategy involved the dethioketalization and \textit{in-situ} cyclization of the hydroxyl group onto the formed ketone (Scheme 60 and Table 4).

\begin{center}
\includegraphics[scale=0.5]{scheme60}
\end{center}

Reagents and conditions: a) see Table 4.

**Scheme 60**: Dethioketalization attempts of 252.
Table 4: Conditions and results reported for dethioketalization attempts of compound 252.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (^{57})</td>
<td>NBS, 97% aqueous acetone, 0 °C, 3 min</td>
<td>40% 254</td>
</tr>
<tr>
<td>2</td>
<td>NIS, Acetone, 0 °C, 3 min</td>
<td>40% 254</td>
</tr>
<tr>
<td>3</td>
<td>NCS, Acetone, 0 °C, 3 min</td>
<td>10% 254</td>
</tr>
<tr>
<td>4</td>
<td>DBDMH, Acetone, 0 °C, 3 min</td>
<td>40% 254</td>
</tr>
<tr>
<td>5 (^{58})</td>
<td>HgCl₂, (MeOH/H2O 9:1) reflux, 18 h</td>
<td>DAM 234</td>
</tr>
<tr>
<td>6 (^{59})</td>
<td>HgO, (MeOH/H2O 9:1) reflux, 18 h</td>
<td>DAM 234</td>
</tr>
<tr>
<td>8 (^{60})</td>
<td>H₂O₂ (MeOH/H2O 5:1) 6 h</td>
<td>DAM 234</td>
</tr>
<tr>
<td>9 (^{61})</td>
<td>mCPBA, DCM, RT, 4 h</td>
<td>DAM 234</td>
</tr>
<tr>
<td>10 (^{62})</td>
<td>Oxone® DCM, RT, 4 h</td>
<td>DAM 234</td>
</tr>
<tr>
<td>11</td>
<td>MeI, DCM, reflux, 2 h</td>
<td>SM</td>
</tr>
</tbody>
</table>

When using NBS in aqueous acetone (entry 1) as reported by Reiner and Schmidt,\(^ {57}\) pyranose 254 was isolated albeit in low yields (up to 40%). In addition to poor yields, there were scalability issues, where masses greater than ~200 mg of 252 led to little or no product and purification issues, due to the production of vast impurities in comparison to small yields of 254. The stereochemistry of the resulting pyranose was confirmed by X-ray crystallography. To improve the yields, a variety of other dethioketalization procedures were attempted, such as the use of different halide donors (entries 2-4), mercury reagents (entries 5-6),\(^ {58,59}\) oxidants (entries 8-10)\(^ {60-62}\) and the use of methyl iodide (entry 11). None of these methods, however, led to any improvements; the only one with comparable success to NBS (entry 1) were the use of NIS (entry 2) and DBDMH (entry 4), presumably because of the dithiane deprotection mechanism of all three reagents being identical.

It was noticeable that in many dethioketalization conditions, DAM 234 was isolated which led the group to propose a mechanism for this (Scheme 61).
Scheme 61: Proposed mechanism for DAM 234 production in the dethioketalization attempts of 252.

Despite the low yields of the dethioketalization, Pearce decided to continue the route with the next step being the selective protection of the hydroxyl group on the C₂ position in 254. Attempts to protect the hydroxyl group as a TBDPS ether failed even after refluxing for several days; this failure was attributed to a steric rationale. Nevertheless, TBS and TIPS protection of the C₂ hydroxyl were achieved (Scheme 62), though only at low yields for the former.

Scheme 62: Synthesis of silyl ethers 255 and 256.

Pearce then attempted to activate the anomeric hydroxyl group. Initially, the hydroxyl group was methylated (Scheme 63), since there was literature precedent for the reductive cleavage of anomeric methoxy groups using triethylsilane and TMSOTf from Gray et al. The group also mesylated and acetylated the anomeric alcohol as they thought the reduction of the mesylated compound would be easier to achieve due to better leaving group ability of the mesylate and acyl groups compared to the methoxy group.
Scheme 63: Activation of anomeric hydroxyl group in 255 and 256.

The reduction of the methylated, acetylated and mesylated products (257-260) using Et$_3$SiH and TMSOTf according to the literature$^{63}$ was unsuccessful (Scheme 64). Consequently, the group tried a range of combinations of Lewis acids (BF$_3$.Et$_2$O, AlCl$_3$ and TiCl$_4$) and hydride reductants (Et$_3$SiH and NaBH$_3$CN) but only starting material was recovered.

Scheme 64: Failed reductions of anomeric centre in compounds 257 – 260.

Due to the low yields obtained in the dethioketalization and the failure of the reductions, the group decided to develop a new route.

Reduction Route

In order to synthesize target 229, Pearce persevered with the dethioketalization strategy but aimed to reduce and thereby effectively remove the ester moiety. This would lead to the
dethioketalization and removal of the anomeric hydroxyl group being attempted on different substrates, as compared to the dithioacetal route (Scheme 65).

**Scheme 65**: Retrosynthesis of target structure 229 from DAM 234 in the Reduction route.

The retrosynthetic analysis for target 229 from intermediate 232 is identical to previous routes (i.e. the dithioacetal and Darzens routes). Structure 232 could derive from 261 in three steps: a selective deprotection of the methylene alcohol; primary alcohol oxidation to the carboxylic acid; followed by esterification. Activation and subsequent removal of the anomeric hydroxyl group in pyranose 262 could form intermediate 261. Pyranose 262 could be formed from dethioketalization of intermediate 263, which in turn could be made by the reduction of the ester moiety in 251 and then protection of the primary alcohol. Structure 251 could be synthesized...
from D-mannose in 2 steps as previously achieved by Pearce in the dithioacetal route (where ester 252 was made).

Starting from compound 252, the group successfully reduced the ethyl ester moiety using LAH to afford triol 264 (Scheme 66). Selective protection of the primary alcohol in 264 with an acetyl group proved challenging in any conditions using DMAP, since only the tri-acetylated compound 265 and starting material were recovered. Standard acetylation conditions without DMAP, however, afforded compound 266 in good yield. Pearce also formed the tert-butyldiphenylsilyl (TBDPS) ether of primary hydroxyl group albeit in low yield (18%).

Scheme 66: Synthesis of compounds 266 and 267.

Compounds 266 and 267 were then subjected to the dethioketalization reaction (Scheme 67). Treatment with NBS in aqueous acetone led to no desired product, although replacing NBS with DBDMH gave pyranoses 268 and 269 in good yield.
The next step of the route was the reduction of the anomeric position in 268 and 269 using Gray’s conditions (Scheme 68). Unfortunately, under these conditions only decomposition of 268 and 269 observed.

As a result, the group opted to methylate the anomeric and C-2 hydroxyl groups in 268 and 269 in anticipation that this would aid removal of the anomeric hydroxyl group in the later reduction. However attempted methylations on 268 and 269 only led to decomposition (Scheme 69).
The unsuccessful attempted reductions of the anomeric centre and dimethylations steered the group away from the dethioketalization strategy in developing a new route.

**Wittig Route**

Pearce then opted for a different approach to reach target 229; this involved a Wittig reaction on DAM to introduce the ester moiety instead of the nucleophilic addition of a deprotonated functionalized dithiane in his previous routes (Scheme 70).
As explained in previous routes, target 229 could be derived from 232. Similarly to the Darzens route performed by Roy,\textsuperscript{43} the pyranoid core of 232 could be made by the deprotection of the secondary alcohol in glycidic ester 240 and concomitant 6-\textit{endo}-tet cyclization. Glycidic ester 240 could originate from epoxidation of alkene 274, which in turn could be made from a Wittig olefination of DAM 234 using an ester-stabilized ylide.

After synthesizing, the ethyl ester-stabilized ylide (from refluxing ethyl bromoacetate and triphenylphosphine in toluene followed by a NaOH wash), the Wittig olefination on DAM was attempted using previously published conditions (\textbf{Scheme 71}).\textsuperscript{64} Under these conditions, the major \textit{E}-alkene 275 and minor \textit{Z}-alkene 276 products were isolated. The minor \textit{Z}-alkene 276 was
discarded, presumably due to the low yields of the latter (10–20%). Hence, Pearce proceeded to the next step only with $E$-alkene 275.

**Scheme 71**: Wittig olefination of DAM 234.

Acetylation of the secondary alcohol in $E$-alkene 275 was then achieved to afford compound 277 (Scheme 72).

**Scheme 72**: Acetylation of compound 275.

The group then aimed to synthesize glycidic ester 278 (Scheme 73). However, despite trying a range of epoxidation conditions, the glycidic ester was not isolated nor even observed.

**Scheme 73**: Failed epoxidations of alkene 277.
The disappointing epoxidation results, led the group to slightly modify their methodology by devising other cyclization methods (Scheme 74). In this new strategy, a bromination on the unprotected E-alkene 275 would be performed; this could cause a 6-endo-tet cyclization (albeit in competition with the more favourable 5-exo-tet cyclization) of the secondary alcohol onto the bromonium ion to afford 279. Subsequent displacement of the bromine on the C₂ with an oxygen nucleophile could afford pyranoid 280.

Scheme 74: Proposed synthetic approach to pyranoid 280.

Regrettably, the attempted bromination involving the addition of neat bromine to a solution of 275 in DCM at 0 °C led to a complex mixture, from which neither pyranoid 279 nor the 1,2-dibrominated compound were isolated.

Finally, Pearce planned one last strategy starting from the acetyl-protected alkene 277, whereby instead of functionalizing the alkene, a reduction would be attempted (Scheme 75).
Scheme 75: Retrosynthesis of target structure 281 from alkene 277.

The only disadvantage of this strategy was the absence of a functionality on the C₂ position. If, however, synthetic target 281 was successfully made, however, methods to functionalize the C₂ position would be revisited. The retrosynthetic analysis for target 281 from 284 is identical in methodology to the previous target 229 from compound 232 (as mentioned in earlier routes). Compound 284 could be made from alkene 277 in three steps. Alkene 277 could firstly be reduced by a hydrogenation to give compound 286. Then the ester in 286 could undergo an α-halogenation to form 285, offering a good leaving group alpha to the ester and thus subsequent cleavage of the acetate group could trigger a 6-exo-tet cyclization to afford C-glycoside 284.
Pearce successfully reduced alkene 277 with hydrogen gas over palladium on carbon to yield 286. The following α-halogenation of the ester, however, proved difficult (Scheme 76 and Table 5).

\[ \text{Reagents and conditions: a) see Table 5.} \]

**Scheme 76: α-Halogenations of ester 286.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{65}</td>
<td>I\textsubscript{2}, LDA, THF, -78 °C to rt</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>Br\textsubscript{2}, LDA, THF, -20 °C to rt</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>Br\textsubscript{2}, t-BuLi, HMPA, THF, -78 °C to rt</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>I\textsubscript{2}, DBU, DCM, rt</td>
<td>SM</td>
</tr>
<tr>
<td>5</td>
<td>NBS, NEt\textsubscript{3}, DCM, rt</td>
<td>SM</td>
</tr>
<tr>
<td>6</td>
<td>NCS, LDA, THF, -78 °C to rt</td>
<td>SM</td>
</tr>
</tbody>
</table>

*Table 5: Conditions and results reported for ester α-halogenation attempts of 286.*

Initially the group used Rathke’s conditions which involved the use of LDA and iodine as the halogen donor but only starting material was isolated from the reaction (entry 1).\textsuperscript{65} The group then tested a variety of other bases and halogen donors (entries 2 to 6), though again only starting material was recovered.

To identify the failure of these ester α-halogenation reactions, the group tried to alkylate 286 with methyl iodide using LDA as the base (Scheme 77). This would establish whether the lithium ester enolate of 286 is generated prior to the addition of the halogen donor. Surprisingly, no trace of compound 287 was observed suggesting the lithium ester enolate was not formed.
Scheme 77: Attempted alkylation of ester 286.

The lack of success in functionalizing alkenes 275 and 277 and incorporating a halide leaving group alpha to the ester in 286, led to the abandonment of this route.

Mahoney

Following Pearce, Mahoney generally attempted a range of strategies to optimise the dithioacetal route (previously established by Pearce), to improve the route’s feasibility and to progress further in the synthesis of the target 229.

Samarium Diiodide Route

This first route carried out by Mahoney, specifically targeted the main problems encountered by Pearce in the dithioacetal route. These were poor yields, scalability and purification issues in the dethioketalization of compound 252 and the inability to remove the anomeric hydroxyl group from 255 and 256. It was hoped that in the samarium diiodide route would overcome these problems (Scheme 78). This is because the dethioketalization would be attempted on a different compound as compared to the dithioacetal route. Additionally, instead of the reductive cleavage of a methoxy or mesylate group on the anomeric position using a hydride or hydrosilane reductant endeavoured in the dithioacetal route, a samarium diiodide promoted coupling between the anomeric acetate 289 and formaldehyde would be attempted. If this coupling reaction were successful, then the removal of the anomeric oxygen functionality and the introduction of a methylene alcohol group could be achieved in one step.
Scheme 78: Retrosynthesis of target 229 from DAM 234 in the samarium diiodide route.

The retrosynthesis for target 229 from intermediate 231 is identical to previous routes undertaken in the group, for example the Darzens and dithioacetal routes. Intermediate 231 could form by activation of the primary alcohol in 288 followed by a displacement with a thioacetate nucleophile. Using samarium diiodide and a formaldehyde electrophile, alcohol 288 could be made from anomeric acetate 289, which could be obtained from acetylation of pyranose 290. The selective deprotection of OR' in the α-ketoester 291 should trigger a 6-exo-trig cyclization affording pyranose 290. The dethioketalization in this route would be attempted on dithioketal 292 to yield compound 291. Moreover, compound 292 could be formed from the nucleophilic addition of a deprotonated derivative of ethyl 1,3-dithiane-2-carboxylate onto aldehyde 239 followed by the protection of the formed secondary alcohol. The synthesis of aldehyde 239 could be achieved by a sequence of protections and deprotections on diol 241 followed by an oxidation of the primary alcohol. The LAH reduction of DAM using previous conditions in the group, would furnish diol 241.
The key feature of this route is the samarium diiodide mediated coupling reaction between formaldehyde and compound 289. This was inspired by Malapelle et al. who succeeded in the transformation of the anomeric acetate in their N-acetylneuraminic acid derivative to the corresponding alcohol using samarium diiodide and a range of aldehydes and ketones (Scheme 79). Malapelle and co-workers proposed that a samarium ester enolate was formed on the anomeric position which then reacted with an aldehyde or ketone electrophile to eventually furnish the resultant alcohols 294. Mahoney planned to apply this methodology to anomeric acetate 289 with a formaldehyde electrophile.

Scheme 79: Malapelle and co-workers’ synthesis of compounds 294 from 293 using samarium diiodide and a range of aldehydes and ketones.

The synthesis began, with the LAH reduction of DAM using previous conditions employed by the group (Scheme 80). The following steps comprised of successive selective protections and deprotections of both alcohols to ultimately reach alcohol 297.
Mahoney, then attempted a Swern oxidation on 297 followed by a nucleophilic addition of the functionalized dithiane derivative (Scheme 81), but in the latter step only DAM 234 was isolated. To explain this result, Mahoney proposed that the MOM ether was surprisingly deprotected in these conditions, producing the alkoxide form of the hydroxy aldehyde, which is in equilibrium with DAM 234.

Scheme 80: Four-step synthesis of compound 297 from DAM 234.

Scheme 81: Failed synthesis of 298 from 297.
Due to this setback, Mahoney decided to form pyranose 254 from DAM 234 in two steps using the same synthesis previously completed by Pearce in the dithioacetal route (Scheme 59). Then after acetyling both hydroxyl groups in 254 (Scheme 82), Mahoney planned to apply the samarium diiodide methodology on the anomeric acetate 299. Despite numerous attempts, the group failed to isolate 300 in the presence of samarium diiodide and paraformaldehyde. They attributed this failure to possible poor quality of the commercially available samarium diiodide solution in THF (since they noticed significant degradation over time). Attempts to synthesize their own samarium diiodide solution, however, were unsuccessful.

![Diagram](image)

Scheme 82: Attempted synthesis of 300.

The failure to couple formaldehyde with 299 using samarium diiodide led Mahoney to investigate alternate strategies to synthesize the tagetitoxin bicyclic core 229.

**Nitrile-Dithiane and Methyl Ester-Dithiane Route**

Mahoney’s next route was identical to the dithioacetal route performed by Pearce with the exception of having a nitrile or methyl ester instead of an ethyl ester moiety (Scheme 83). It was hoped, that this change could improve the yields of the dethioketalization and aid in the removal of the anomeric hydroxyl group in 305.
Scheme 83: Retrosynthesis of target 301 from DAM 234 in the nitrile-dithiane and methyl ester-dithiane route.

The retrosynthetic analysis for 301 from DAM 234 is identical in methodology to the retrosynthesis of 229 in the dithioacetal route (the only difference being the nature of the carboxylic acid derivative on the C-1 position).

In order to incorporate the nitrile or methyl ester functionality in the target 301, the functionalized dithiane derivative undergoing nucleophilic addition on DAM would have a nitrile or methyl ester moiety instead of an ethyl ester moiety. Since these particular dithiane derivatives are not commercially available (unlike ethyl 1,3-dithiane-2-carboxylate), the first goal of the route was to synthesize these derivatives.
Using conditions previously published by the Page group in the literature, the synthesis of 2-cyano-1,3-dithiane 309 was accomplished in two steps from 1,3-dithiane 307 (Scheme 84). The first step involved a hydride abstraction of 1,3-dithiane 307 when treated with triphenylcarbenium tetrafluoroborate in DCM under reflux to furnish salt 308. Addition of TMSCN to the salt 308 afforded the desired functionalized dithiane 309.

\[
\begin{align*}
307 & \quad \text{a} \quad 308 \quad \text{b} \quad 309 \\
\text{Reagents and conditions:} & \quad \text{a) } \text{Ph}_3\text{CBF}_4, \text{ DCM, reflux, 45 min;} \\
& \quad \text{b) } \text{TMSCN, DCM, -20 °C, 1 h, 58% over two steps.}
\end{align*}
\]

**Scheme 84: Two-step synthesis of 2-cyano-1,3-dithiane 309 from 1,3-dithiane 307**

The synthesis of methyl 1,3-dithiane-2-carboxylate 311 was also achieved in two steps from 1,3-dithiane 307 (Scheme 85). This synthesis involved the lithiation of the 1,3-dithiane and ensuing nucleophilic addition onto solid carbon dioxide to furnish carboxylic acid 310 after acidic work-up. This was followed by a Fischer esterification to yield 311.

\[
\begin{align*}
307 & \quad \text{a} \quad 310 \quad \text{b} \quad 311 \\
\text{Reagents and conditions:} & \quad \text{a) } \text{n-BuLi, CO}_2\text{(g), THF, -78 °C to rt, 68%;} \\
& \quad \text{b) } \text{HCl(g), MeOH, 10 min, 85%}.
\end{align*}
\]

**Scheme 85: Two-step synthesis of ethyl 1,3-dithiane-2-carboxylate 311 from 1,3-dithiane 307**

The next aim of the group was to perform the nucleophilic addition of these functionalized dithiane derivatives 309 and 311 on DAM 234 (Scheme 86). Regrettably, under the same conditions used previously to synthesize 252 in the dithioacetal route, compounds 306 were not formed.
These unsuccessful results led Mahoney to devise a new synthetic route away from the dithiane strategy.

**KDO Route**

The group devised a new synthesis to target 312 from DAM 234; although, there would be and absent functionality on the C-2 position (Scheme 87). If successful, however, this methodology would be revised to install an oxygen functionality on this position.
Scheme 87: Retrosynthesis of target 312 from DAM 234 in the KDO route.

The target bicyclic core 312 could be derived from 315 by the same methodology mentioned in aforementioned earlier routes for 229 from 232. The pyranoid core 315 could be constructed by the formation of an ester enolate of 316, which could consequently displace a leaving group in a cyclization reaction. Deprotection of the primary alcohol in 317 and subsequent transformation into a good leaving group (e.g. halide or sulfonate ester) would furnish 316. The ester moiety would be introduced into the structure by selective protection of the primary alcohol in diol 241 followed by alkylation of the secondary alcohol with an α-halo ester. As already synthesized in the samarium diiodide route and Darzens route, diol 241 would be formed by the LAH reduction of DAM 234 (e.g. Scheme 80).
This route was largely inspired by the production of intermediate 322 part of Ohrui and co-workers’ synthetic route towards 3-deoxy-D-manno-oct-2-ulosonic acid (KDO).\textsuperscript{68} In this route, Ohrui et al. made pyranoid 322 from diol 241 in 5 steps using the methodology outlined in the above retrosynthetic analysis (Scheme 88).

\begin{center}
\includegraphics[width=0.8\textwidth]{Scheme88.png}
\end{center}

Reagents and conditions a) NaH, BnBr, DMF, 0 °C to rt, 85%; b) NaH, ethyl bromoacetate, oxolane 0 °C to rt, 78%; c) Pd(OH)$_2$, MeOH, H$_2$, 97%; d) PPh$_3$, imidazole, I$_2$, 0 °C, 77%; e) LDA, oxolane, -75 °C, 84%.

\textbf{Scheme 88}: Ohrui and co-workers’ five step synthesis of pyranoid 322 from diol 241.\textsuperscript{68}

Mahoney intended, therefore, to replicate this synthesis to reach pyranoid 322. Initially, Mahoney was successful in benzylating the primary alcohol in 241 to afford 318 in 90% yield. However, after numerous efforts, the ensuing alkylation with ethyl bromoacetate under Ohrui and co-workers’ conditions failed to furnish compound 319. Attempts to modify the conditions such as varying the amounts of sodium hydride or ethyl bromoacetate proved unsuccessful.

The failure to synthesize ester 319 led Mahoney to discard this route.
Overall, work by the Page Group on the synthesis towards tagetitoxin led to a number of noteworthy intermediates via a range of strategies, and some of these routes will be explored further (described later within this thesis).

Project

Synthetic Target

Despite Aliev et al. contesting the proposed tagetitoxin structures 1 – 4 due to inconsistencies with NMR and MS data, the aim of this project was to complete a total synthesis of structures 2a and 2b (Figure 9).

![Proposed tagetitoxin structures 2a and 2b.](image)

**Figure 9:** Proposed tagetitoxin structures 2a and 2b.

The two significant reasons for synthesizing structures 2a and 2b are:

1) Contributing to the debate surrounding the structure of the natural product. There are no published total syntheses of any of the proposed tagetitoxin structures 1 – 5, and if we were to chemically synthesize structures 2a and 2b, their characterization data would be compared with the data collated from Aliev et al. This would provide evidence to support or refute the conclusions made in the literature regarding the structure of tagetitoxin.

2) From a synthetic perspective, the large number of complex functionalities in 2a and 2b, make these structures interesting and challenging targets.

Complex Functionalities

The primary aim of this project was to firstly synthesize intermediates 323a and/or 323b (Figure 10).
Intermediates 323a and 323b each contain the bicyclic core of structures 2a and 2b as well as key functionalities such as the thiohemiketal and carboxylic acid derivatives. We then envisaged phosphate, amino and acetate functionalities could be incorporated into the bicyclic structures 323a and 323b to achieve a total synthesis (Scheme 89).

Scheme 89: Retrosynthetic analysis of the functional groups on pyranoid core in structures 2a and 2b.

The easiest functionality to install in the structure would be the acetate group by simple esterification of a free hydroxyl group on the C-4 centre with a range of acetylating agents (e.g. AcCl and Ac₂O) under various conditions.

Incorporation of the amino group would be more challenging since, in addition, the stereochemical configuration of the C-3 position has to be inverted. This could be achieved using displacement chemistry; the C-3 hydroxyl group could be activated into a good leaving group which could be substituted by an azide nucleophile in S₈2 fashion. The azide moiety could then be reduced into an amino group by a Staudinger reaction or hydrogenation.
The phosphorylation of the C-2 hydroxyl group could be achieved by numerous methods with the most common being:

1) Esterification using activated phosphonates (e.g. phosphoric acid chlorides or anhydrides).
2) Esterification using phosphoric acid or a derivative with activating agents such as DCC, trichloroacetonitrile or arylsulfonyl chlorides.
3) Phosphitylation using a phosphoramidite followed by oxidation with a peracid or a peroxide (e.g. mCPBA or H₂O₂).

The order and the methods in which these three functionalities would be selectively installed onto the structure would depend on the type of the protecting groups present on bicyclic structures 323a and 323b, in addition to the exact nature of the synthetic route from these compounds to structures 2a or 2b. The exact synthetic route would be determined once bicyclic 323a and/or 323b was synthesized.

**Bicyclic Skeleton**

To reach our ultimate bicyclic targets 323a and 323b (**Figure 10**), we attempted a variety of routes starting from readily available cyclic sugars such as D-mannose and D-galactose.
References for Introduction Chapter


Results and Discussion
Nitrile-Wittig Route

Our first synthetic route was similar to the Wittig route previously performed by Pearce,¹ with the main difference being the presence of a nitrile instead of an ethyl ester functionality (Scheme 90).

Scheme 90: Retrosynthesis of target structure 324 from D-mannose in the nitrile-Wittig route.

If this route to target 324 were successful, then this strategy would be adapted to incorporate a carboxylic acid derivative alpha to the thiohemiketal centre in order to reach our ultimate bicyclic targets 323a and 323b.

As planned in all previous routes from the Page group,¹⁻³ the synthesis of the 1,4-oxathiane moiety in target 324 is based on the strategy established by Porter and co-workers,⁴ involving the
deprotection of the thioacetate moiety in 325 followed by an in-situ cyclization of the free thiol/thiolate onto the ketone. Intermediate 325 could be made from the selective hydrolysis of the exo-cyclic isopropylidene group in 326, followed by protection of the primary alcohol and oxidation of the secondary alcohol. The installation of the thioacetyl-methylene moiety in 326 could be achieved in three steps: condensation between the anomeric nitrile anion of 327 with a formaldehyde electrophile would introduce the hydroxyl methylene functional group; activation of the aforementioned hydroxyl into a good leaving group (e.g. halide or sulfonate ester); and displacement of the leaving group with a thioacetate nucleophile. A 6-endo-tet cyclization of the hydroxyl group on the epoxide in glycidic nitrile 328 would construct the pyranoid core in 327. Glycidic nitrile 328 could be formed by an epoxidation of alkene 329, which in turn could be derived from a Wittig olefination on DAM 234 with a nitrile stabilized ylide. As previously achieved in the Page group, DAM 234 could be synthesized from D-mannose 235 in acetone under acidic catalysis.1–3

The key feature of this route is the epoxidation of alkene 327. Since the alcohol in alkene 327 is not protected, we were hopeful that during the epoxidation step, the intramolecular 6-endo-tet cyclization (although in competition with the faster 5-exo-tet cyclization) in glycidic nitrile 328 would occur to form pyranoid 329. If successful, pyranoid 329 could be reached potentially in at least two steps less than if we protected the hydroxyl group prior to the epoxidation, as carried out previously by Pearce in the Wittig route.1

The project began with the synthesis of DAM 234 from D-mannose 235 in 92% yield using conditions established from earlier work in the Page group (Scheme 91).1–3 As discovered previously, this procedure did not afford 100% of a single anomer; though this was not important since the subsequent Wittig reaction only involves the ‘open’ hydroxy-aldehyde form of DAM 234 (thus negating the stereochemistry on the anomeric position).
Before the Wittig reaction could be attempted, the nitrile stabilized ylide $332$ had to be synthesized in two steps from triphenylphosphine $330$; this was achieved using conditions from Aitken et al.\(^5\) Firstly, the phosphonium chloride salt $331$ was synthesized in 91% yield via displacement chemistry using triphenylphosphine and chloroacetonitrile in ethyl acetate under reflux (Scheme 92). The ylide $332$ was then isolated in 74% yield by deprotonation of the phosphonium ion with a triethylamine base.

\[
\begin{align*}
&\text{Ph}_3\text{P} \overset{a}{\rightarrow} \text{Ph}_3\text{P}^+\text{Cl}^{-} \overset{b}{\rightarrow} \text{Ph}_3\text{P} \equiv \text{CN} \\
\end{align*}
\]

Reagents and conditions: a) chloroacetonitrile, EtOAc, reflux, 3h, 91%; b) Et$_3$N, DCM, 30 mins, 74%.

**Scheme 92:** Two-step synthesis of ylide $332$ from triphenylphosphine.

The Wittig reaction between stabilized ylide $332$ and DAM $234$ was then carried out (Scheme 93 and Table 6).

\[
\begin{align*}
&\text{Ph}_3\text{P}=\text{CHCN} (1.1 \text{ equiv.}), \text{ solvent, reflux, 24 h. See Table 6.} \\
\end{align*}
\]

**Scheme 93:** Wittig olefination attempts on DAM $234$. 

---

Reagents and conditions: a) H$_2$SO$_4$, Acetone, overnight; b) Na$_2$CO$_3$, activated charcoal, reflux, 2h, 92%.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Result $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>77% SM, 18% 333 ($\beta:\alpha$, 63:37)</td>
</tr>
<tr>
<td>2</td>
<td>MeCN</td>
<td>46% SM, 45% 333 ($\beta:\alpha$, 2:1)</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>26% SM, 66% 333 ($\beta:\alpha$, 2:1)</td>
</tr>
</tbody>
</table>

$^a$ The number of moles of recovered DAM 234 and C-glycosides 333 in the inseparable mixture were calculated from molar ratios observed in the $^1$H NMR spectrum.

**Table 6**: Conditions and results reported for the attempted Wittig olefinations of DAM 234.

We initially tried standard conditions, whereby DAM 234 and the ylide 332 were heated under reflux in THF, MeCN or toluene for 24 h (entries 1 to 3). In each case, TLC appeared to indicate no change during the reaction. After work-up and purification by column chromatography, an inseparable mixture of starting material DAM 234 and C-glycosides $\alpha$- and $\beta$-333 was isolated (explaining why no change appeared on TLC).

The formation of C-glycosides 333 does at least indicate that the Wittig reaction was successful in synthesizing alkenes 329. This is because compounds 333 were probably formed from a 5-exo-trig conjugate addition in alkenes 329 (Scheme 94).

![Scheme 94](image)

**Scheme 94**: Proposed mechanism for the synthesis of C-glycosides 333.

The conversion of DAM 234 was fairly poor in all the Wittig attempts, but it did increase upon changing solvent from THF to MeCN to toluene (possibly due to the higher temperatures at which these solvents reflux at). Longer reaction times, though, made no significant difference in conversion.

As a result, alternative methods were sought to synthesize alkenes 329. We envisaged the use of the Horner-Wadsworth-Emmons olefination (HWE) on DAM 234, though the more basic
conditions in this reaction would even more likely promote the conjugate addition. Nevertheless, an HWE reaction with diethyl cyanomethylphosphonate was attempted (Scheme 95 and Table 7).

![Scheme 95: HWE olefination attempts on DAM 234.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diethyl cyanomethylphosphonate, t-BuOK (1.5 equiv.), THF, 0 °C, 30 mins, then DAM 234, 0 °C to rt, overnight</td>
<td>98% 333 (β:α, 3:1)</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Diethyl cyanomethylphosphonate, K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (1 equiv.), THF, rt 30 mins, then DAM 234, overnight</td>
<td>81% SM, 11% 333 (β:α, 66:34)</td>
</tr>
</tbody>
</table>

<sup>a</sup> The number of moles of recovered DAM 234 and C-glycosides 333 in the inseparable mixture were calculated from molar ratios observed in the <sup>1</sup>H NMR spectrum.

Table 7: Conditions and results reported for the attempted HWE olefinations of DAM 234.

Unsurprisingly, when using common conditions (entry 1) only C-glycosides 333 were observed. With the goal of making the conditions less basic to suppress any conjugate additions, we replaced potassium tert-butoxide with the weaker base potassium carbonate (entry 2). These milder conditions, however, only caused a decrease in yield of the C-glycosides 333 (because of a lower conversion of DAM 234).

The C-1 stereochemistry in C-glycosides α-333 and β-333 were assigned from NMR analysis. For example, the lower <sup>13</sup>C chemical shift of C-1 in β-333 (76.9 ppm) compared to α-333 (80.3 ppm) signifies a cis relationship between the substituents on the C-1 and C-2 positions.\(^6\)\(^7\)
Furthermore, the small vicinal coupling constant between the H-C\textsubscript{1} and H-C\textsubscript{2} ($^3J_{1,2}$) in \textit{α-333} (1.3 Hz) suggests that these protons have a \textit{trans} relationship.\textsuperscript{8} Finally from the NOESY spectra, there was a significant nOe between H-C\textsubscript{1} and H-C\textsubscript{4} in \textit{β-333}, suggesting a \textit{cis} relationship. This was unlike \textit{α-333} where such a nOe was not observed (Figure 11). Additionally, in contrast to \textit{β-333}, a nOe was observed between the methylene protons of the CH\textsubscript{2}CN moiety and H-C\textsubscript{4} in \textit{α-333}, which suggests a \textit{cis} relationship.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{scheme11.png}
\caption{NOESY analysis to assign stereochemistry at the C\textsubscript{1} position in β-333 and α-333.}
\end{figure}

The failure of the Wittig and HWE olefinations, led us to investigate alternative strategies to synthesize alkene 329. This led us to attempt a retro-Michael reaction of the C-glycosides 333, which was inspired by the research conducted by Fleming \textit{et al.}\textsuperscript{9} In this work, Fleming and co-workers performed a retro-Michael reaction (i.e. a β-elimination of the ring oxygen) on a variety of compounds including 334 (Scheme 96).

The authors attributed the success of the reaction to three specific features of the conditions:

1. Use of a strong lithium base (i.e. LDA).
2. Low concentrations of 334 in THF (0.0018 M).
3. Shortest possible reaction time.
Using a lithium base will lead to the formation of a lithium alkoxide intermediate. The authors stated that the interaction between the lithium and the oxygen in this intermediate is strong enough to suppress unwanted intramolecular and intermolecular conjugate additions to the nitrile functionality, which could otherwise trigger an unwanted polymerization.\(^9\) The low concentration and short reaction time would additionally help to suppress conjugate additions and thus polymerizations.

We therefore applied this retro-Michael methodology to C-glycosides 333 (Scheme 97).

![Scheme 97](image)

**Scheme 97**: Synthesis of alkene \(E\)-329 by a retro-Michael reaction on 333.

To our delight, the reaction did afford alkene \(E\)-329 in yields of up to 56% after optimization. The high vicinal coupling constant between the alkene protons (16.2 Hz) indicated the \(E\)-stereochemistry of the formed double bond. The \(Z\)-alkene was also formed in the reaction but could not be isolated pure from column chromatography as it co-eluted with a number of other compounds and was thus discarded. The reaction was stereoselective towards the \(E\)-alkene, since analysis from the \(^1\)H NMR spectrum of the crude material showed that the \(E:Z\) ratio always varied from 68:32 to 76:24.

The required low concentrations of 333 in THF provided practical and scalability issues. Increasing the concentration to 0.02 M had no effect on yield, though any further increase led to a 0% yield of \(E\)-329 possibly due to decomposition or polymerization.

With alkene \(E\)-329 in hand, we proceeded with the epoxidations using a range of conditions from the literature (Scheme 98 and Table 8).
Table 8: Conditions and results reported for the attempted epoxidations of alkene 329.

We initially tried a standard nucleophilic epoxidation with hydrogen peroxide and sodium hydroxide in methanol, but only C-glycosides 333 were observed (entry 1). This suggests that, under these oxidizing conditions, deprotonation and intramolecular conjugate addition of the hydroxyl group in 329 were favoured compared to the desired nucleophilic attack of the perhydroxyl anion onto the alkene. Consequently, our next epoxidation attempt was carried out under less basic conditions, by repeating our initial entry with the exception of using the more dilute 2 M aqueous NaOH instead of 6 M (entry 2); we hoped that under these less basic conditions, the epoxidation would be preferred to the intramolecular conjugate addition. Once again, however, only compounds 333 were recovered. The same result occurring in an alternative
nucleophilic epoxidation using sodium hypochlorite (entry 3), prompted us to try electrophilic epoxidations.

Epoxidation using $m$CPBA only led to recovery of starting material (entry 4), possibly because of the alkene not being reactive enough as it too electron-deficient. We therefore next tested a more powerful electrophilic oxygen transfer reagent by using hydrogen peroxide in acetonitrile (entry 5), which should trigger the formation of the more reactive peroxyimidic species, but again only starting material was observed.

Finally, using a slightly modified procedure from the literature, we tried epoxidations using oxone. Although this initially led to only starting material being recovered (entry 6). Upon increasing the temperature from 0 °C to rt, however, starting material and compound 333 were isolated (entry 7). This suggests that the electron-deficient nature of the alkene in 329 makes it too unreactive with the peroxymonosulfate anion of oxone, leading to the base promoted conjugate addition being more favoured over the epoxidation.

We concluded that no nucleophilic epoxidations under basic conditions could occur without triggering the intramolecular conjugate addition, while all electrophilic epoxidations failed, presumably to do with the poor nucleophilicity of the electron-deficient alkene.

As a result, we planned to protect the hydroxyl group in 329 and only then perform the nucleophilic epoxidation, since this would prevent the intramolecular conjugate addition happening under basic oxidizing conditions. This strategy would differ from that first envisaged, since the epoxidation step would now lead to the O-protected epoxide 338 (Scheme 99). The removal of the protecting group under basic conditions would hopefully cause a concomitant 6-endo-tet cyclization to give pyranoid 336.

![Scheme 99: Proposed synthetic approach to pyranoid 336 from alkene 329.](image-url)
We opted to protect the free hydroxyl group in 329 with a silyl and benzoyl group. Surprisingly, this protection step proved much more challenging than initially anticipated (Scheme 100 and Table 9).

![Scheme 100: Protection of alkene 329.](image)

Table 9: Conditions and results reported for the attempted silyl ether- and benzoyl- protections of alkene 329.
Using a slightly modified procedure from Trost,\textsuperscript{16} we failed to protect the alcohol with a TIPS group, only starting material was recovered despite the long reaction time and the presence of the nucleophilic catalyst DMAP (entry 1). Given that the alcohol in 329 is secondary and surrounded by fairly bulky substituents, we attributed this failure to steric factors. We therefore tried to protect the alcohol with the smaller TBS group (entries 2 and 3). Yet, using TBSCl (entry 2) or even the more electrophilic TBSOTf (entry 3) did not make any difference. We were, however, successful in protecting the alcohol with the less bulky IPDMS group affording alkene 340 in 81\% yield (entry 4). The success of the IPDMS protection provides further support to steric factors accounting for the failure of the TBS and TIPS protections.

Furthermore, we found that the order of addition of reagents was vital for the benzoylations. For example, under typical conditions from the literature,\textsuperscript{17} when the triethylamine base was added to alkene 329 before benzoyl chloride and DMAP, only the cyclization products 333 were isolated (entry 5). However, when modifying the addition order (by adding alkene 329 to a solution of triethylamine, benzoyl chloride and DMAP), the desired benzoyl-protected alkene 340 was produced in various yields (entries 6 and 7) and the conjugate addition side-reaction reduced. In entry 5, the alkene was in a basic solution prior to the addition of the electrophile and nucleophilic catalyst. This meant that the conjugate addition was probably already triggered before the electrophile and nucleophile catalyst were even added. This was not the case in entries 6 and 7 because the alkene was never in a basic solution in the absence of the electrophile and DMAP catalyst. Once finding optimal conditions (e.g. addition order as well as equivalents of triethylamine and benzoyl chloride) this reaction did proceed smoothly in high yields of up to 85\% of 340 with no sign of the unwanted intramolecular conjugate addition (entry 7).

Interestingly, in contrast to the benzoylations, the order of addition of reagents was not significant in the silyl ether protections. A possible reason for this could be due to imidazole and 2,6-lutidine being weaker bases than triethylamine; alkene 329 would thus be more likely to undergo a base-promoted intramolecular conjugate addition in the presence of triethylamine rather than 2,6-lutidine or imidazole.

Having successfully obtained protected derivatives 339 and 340, our next goal was to form epoxides 341 and/or 342 (Scheme 101 and Table 10).
Scheme 101: Epoxidation attempts on alkenes 339 and 340.

<table>
<thead>
<tr>
<th>Method</th>
<th>R</th>
<th>Reagents and Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;10&lt;/sup&gt;</td>
<td>IPDMS, Bz</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt; (35% wt. in H&lt;sub&gt;2&lt;/sub&gt;O), 6M NaOH (0.83eq), MeOH, 48 h</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>IPDMS, Bz</td>
<td>t-BuOOH (70% wt. in H&lt;sub&gt;2&lt;/sub&gt;O), 6M NaOH (0.83eq), MeOH, 48 h</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>IPDMS</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt; (35% wt. in H&lt;sub&gt;2&lt;/sub&gt;O), 6M NaOH (1eq), MeOH, 72 h</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>IPDMS</td>
<td>t-BuOOH (70% wt. in H&lt;sub&gt;2&lt;/sub&gt;O), 6M NaOH (1eq), MeOH, 72 h</td>
<td>SM</td>
</tr>
<tr>
<td>5</td>
<td>Bz</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt; (35% wt. in H&lt;sub&gt;2&lt;/sub&gt;O), 6M NaOH (1eq), MeOH, 72 h</td>
<td>329</td>
</tr>
<tr>
<td>6</td>
<td>Bz</td>
<td>t-BuOOH (70% wt. in H&lt;sub&gt;2&lt;/sub&gt;O), 6M NaOH (1eq), MeOH, 72 h</td>
<td>329</td>
</tr>
<tr>
<td>7&lt;sup&gt;11&lt;/sup&gt;</td>
<td>IPDMS, Bz</td>
<td>NaOCl (from bleach), MeCN, 72 h&lt;sup&gt;b&lt;/sup&gt;</td>
<td>SM</td>
</tr>
</tbody>
</table>

<sup>a</sup> temperature: 0 °C to rt; <sup>b</sup> room temperature.

Table 10: Conditions and results reported for the attempted epoxidations of alkenes 339 and 340.

We first attempted standard nucleophilic epoxidation conditions on the benzoyl- and IPDMS-protected alkenes with hydrogen peroxide and tert-butylperoxide (methods 1 and 2). Regrettably, neither set of conditions with each alkene furnished the desired epoxides, as only starting material was recovered. This influenced us to use more basic conditions by increasing the number of equivalents of sodium hydroxide (methods 3 – 6). While only starting material was recovered for the IPDMS-protected alkene 339 (methods 3 and 4), these stronger basic conditions did lead to the benzoyl ester being cleaved, yielding the unprotected alkene 329.
Further attempts were made using sodium hypochlorite (entry 7), though for each alkene 339 and 340 only starting material was recovered.

Confronted with these disappointing epoxidation results, we devised an alternative strategy to pyranoid 327. In this strategy, we would directly brominate alkene 329 to form a bromonium ion intermediate 343 which could then undergo an intramolecular 6-endo-tet cyclization (but competing with an undesired faster 5-exo-tet cyclization) to afford compound 344 (Scheme 102). Displacement of the bromine with a nucleophilic oxygen species would then form pyranoid 327. This methodology was identical to the approach followed by Pearce in the Wittig route (Scheme 72) with the only difference being the presence of a nitrile rather than an ethyl ester.\(^1\)

\[\text{Scheme 102: Proposed bromination strategy to pyranoid 327.}\]

Unfortunately, when subjected to standard bromination conditions, neither pyranoid 344 nor even the 1,2-dibrominated compound 345 were detected; only decomposition of the starting materials was observed (Scheme 103).

\[\text{Scheme 103: Attempted bromination on alkene 327.}\]

After having no success in our bromination strategy, we decided to try another alternative synthetic approach to pyranoid 307 (Scheme 104). In this approach, an oxymercuration-
demercuration would be attempted on the IPDMS- and benzyol-protected alkene derivatives 339 and 340. Then, following a protection of the product alcohol (e.g. benzyl or trityl protection), halogenation alpha to the nitrile would be performed; this would install a good leaving group alpha to the nitrile. Finally, selective deprotection of the IPDMS or benzyol protecting group in 350 or 351 would liberate the nucleophilic oxygen (in the form of an alcohol or alkoxide depending on the deprotection conditions), which in turn could displace the halide in a 6-exo-tet cyclization to afford pyranoid 327.

In this oxymercuration-demercuration strategy, there are more steps required to synthesize pyranoid 327 as compared to the epoxidation or bromination pathways. However, in contrast to the previous pathways, there would be no regioselective issues in the cyclization. This is because in this pathway, the 5-exo-tet cyclization would be much slower and unfavourable compared to the 6-exo-tet cyclization since the former process requires an alkoxide leaving group instead of a good halide leaving group as in the latter.

Consequently, the protected derivatives 339 and 340 were subjected to a range of oxymercuration-demercuration conditions (Scheme 105 and Table 11).
Scheme 105: Oxymercuration-demercuration attempts on compounds 339 and 340.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mercuric Reagent</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^{18})</td>
<td>Hg(OAc)(_2)</td>
<td>None</td>
<td>1:1, THF:Water</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>Hg(OAc)(_2)</td>
<td>70% HClO(_4)(aq) (0.2 equiv.)</td>
<td>1:1, THF:Water</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>Hg(TFA)(_2)</td>
<td>None</td>
<td>1:1, THF:Water</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>Hg(TFA)(_2)</td>
<td>70% HClO(_4)(aq) (0.2 equiv.)</td>
<td>1:1, THF:Water</td>
<td>SM</td>
</tr>
<tr>
<td>5</td>
<td>Hg(OAc)(_2)</td>
<td>None</td>
<td>1:1, Acetone:Water</td>
<td>SM</td>
</tr>
</tbody>
</table>

Table 11: Conditions and results reported for oxymercuration-demercuration attempts of compounds 339 and 340.

When applying standard literature conditions on 339 and 340 (entry 1),\(^{18}\) only starting material was isolated. This prompted us to use more powerful conditions by also adding 70% perchloric acid (entry 2); the presence of perchloric acid should trigger the formation of the more electrophilic acetoxymercuric cation (part of the acetoxymercury perchlorate ion pair).\(^{19,20}\) Unfortunately these powerful conditions still made no difference to the result. Attempts using the more electrophilic mercuric trifluoroacetate with or without perchloric acid were also unsuccessful (entries 3 and 4). Finally, in one last attempt the solvent system was modified whereby THF was replaced with acetone, but as expected this again made no difference (entry 5).
As with the attempted bromination and electrophilic epoxidations on alkene 327, the probable reason for the failure of these oxymercuration-demercurations on 339 and 340 is the poor nucleophilicity of the electron-deficient alkene.

Considering the failures of the epoxidations, bromination and oxymercuration-demercurations we abandoned this route.

**Vinyl-Transetherification Route**

Following on from the disappointments of the nitrile-Wittig Route, in order to reach target 324, we proposed an alternative strategy to synthesize intermediate pyranoid 327 (Scheme 106).

![Scheme 106: Retrosynthesis of target structure 324 from DAM 234 in the vinyl-transetherification route.](image)

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The retrosynthesis of target **324** from **327** is identical to the nitrile-Wittig Route. In this route, pyranoid **327** could be made from diol **352** in a two-step sequence involving esterification of both hydroxyl groups (e.g. acetylation or benzoylation) followed by a C-glycosylation reaction with TMSCN. The esterification of the anomeric hydroxyl group will incorporate a good leaving group on the anomeric centre which would help to activate the molecule for the subsequent C-glycosylation reaction. Furthermore, esterification of the neighbouring C-2 hydroxyl group should additionally activate the molecule for the C-glycosylation due to its role in anchimeric assistance.\(^{21}\) Diol **352** could derive from the dihydroxylation of glycal **353**. A mercuric acetate catalysed intramolecular vinyl-transetherification of enol ether **354** would construct the pyranoid framework in glycal **353**. Finally, enol ether **354** could be made by a Wittig olefination of DAM **234** with an ylide derived from (methoxymethyl)triphenylphosphonium chloride.

The pivotal steps of this route were the Wittig olefination of DAM **234** and subsequent intramolecular vinyl-transetherification to afford glycal **353**. This exact synthesis has already been achieved by Wardrop *et al.* in 58% yield (over both steps) during their synthesis of KDO (Scheme 107); though characterization data for enol ether **354** and glycal **353** were not reported.\(^{22}\)

![Diagram](image-url)

**Scheme 107**: Two-step synthesis of glycal **353** from DAM **234** by Wardrop *et al.*\(^{22}\)

The route started with the attempted Wittig olefination of DAM **234** (Scheme 108 and Table 12).
Scheme 108: Wittig olefination attempts on DAM 234.

Table 12: Conditions and results reported for the Wittig olefination attempts on DAM 234.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Reaction Temperature</th>
<th>Product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-BuOK</td>
<td>Reflux</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>n-BuLi</td>
<td>rt</td>
<td>9-36% 354 (E:Z, 7:3), 0-17% 355</td>
</tr>
<tr>
<td>3</td>
<td>NaHMDS</td>
<td>rt</td>
<td>11% 354 (E:Z, varied from 1:0 to 4:1), 30% SM</td>
</tr>
<tr>
<td>4</td>
<td>LDA</td>
<td>rt</td>
<td>19% 354 (E:Z, 9:1), 61% SM</td>
</tr>
<tr>
<td>5</td>
<td>LDA</td>
<td>reflux</td>
<td>57% (E:Z, varied from 5:1 to 3:2)</td>
</tr>
</tbody>
</table>

Surprisingly, when using conditions from Wardrop et al., no reaction seemingly occurred as only starting material was recovered (entry 1). This happened despite the mixture even being heated under reflux for very long reaction times (~72 h).

We therefore aimed to apply more powerful conditions and replaced the potassium tert-butoxide base with n-BuLi (entry 2). This change did considerably improve the conversion (no trace of starting material observed in the crude mixture) but a complex mixture was formed (hinting at many undesired side reactions) with the only products isolated after purification being the desired enol ether 354 (38% yield) and the side product 355 (17%). Compound 355 was probably formed from the nucleophilic addition of n-BuLi to the ‘open’ hydroxy aldehyde form of DAM 234, followed by a dehydration of the formed alcohol. We also found, that when using n-BuLi, the reaction had scalability issues; for example, scaling up the reaction beyond 1 g of DAM 234 led to yields of 354 as low as 9%. The capricious nature of this reaction influenced us to change
the base to strong non-nucleophilic bases like NaHMDS (entry 3) or LDA (entry 4), but in these cases only low yields of enol ether 354 were obtained due to the occurrence of many side reactions (inferred from the presence of crude complex mixtures) and poor conversion of DAM 234. When using LDA as the base, however, satisfactory yields of enol ether 354 (up to 57%) were obtained when increasing the reaction temperature (entry 5) due to a greater conversion of DAM 234 (inferred from no trace of DAM 234 being seen in crude mixture).

The next step involved the intramolecular vinyl-transetherification of 354 (Scheme 109). This was accomplished by subjecting enol ether 354 to catalytic mercuric acetate at 110 ºC under reduced pressure using Kugelrohr distillation apparatus, which furnished glycal 353 in yields up to 57%.

![Scheme 109: Synthesis of glycal 353 from enol ether 354.](image)

Reagents and conditions: a) Hg(OAc)$_2$, 110 ºC, 20 mmHg, 3 h, 57%.

**Scheme 109**: Synthesis of glycal 353 from enol ether 354.

The dihydroxylation of glycal 353 was then attempted (Scheme 110 and Table 13).

![Scheme 110: Dihydroxylation attempts on glycal 353.](image)

Reagents and conditions a) see Table 13.

**Scheme 110**: Dihydroxylation attempts on glycal 353.
Table 13: Conditions and results reported for the dihydroxylation attempts on glycal 353.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{24}</td>
<td>AD-Mix-α, 1:1 r-BuOH:H\textsubscript{2}O</td>
<td>SM</td>
</tr>
<tr>
<td>2\textsuperscript{24}</td>
<td>AD-Mix-β, 1:1 r-BuOH:H\textsubscript{2}O</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>OsCl\textsubscript{3}, NMO, 1:1 THF:H\textsubscript{2}O, overnight</td>
<td>64% 352 (α:β, 14:1)</td>
</tr>
</tbody>
</table>

Our first attempts were Sharpless asymmetric dihydroxylations using AD-mix-α (entry 1) and AD-mix-β (entry 2) since these had the easiest osmium reagent (potassium osmate) to handle (i.e. least volatile).\textsuperscript{24,25} We initially tried both AD-mixes, because it was difficult to predict which face of the alkene in 353 would preferentially be dihydroxylated by each AD-mix. This was due to the similar steric environment on both sides of the alkene moiety in 353 as well as the presence of four stereogenic centres in 353 that could also influence the stereoselectivity. Despite long reaction times (7 days) only starting material was observed for each AD-mix reaction. A possible reason for these results could arise from the bulky osmium-ligand complex formed in these conditions being sterically demanding in addition to glycal 353 being fairly bulky; this would cause the 1,3-dipolar cycloaddition between these species to be too slow because of the sterically congested transition state for this step.\textsuperscript{26}

We then performed the dihydroxylation using osmium trichloride (entry 3). Under these conditions, we successfully isolated diols 352 (14:1, α:β). These anomers were inseparable in flash column chromatography. Consequently, several recrystallizations were attempted to separate the anomers, without success.

Theoretically from the dihydroxylation of glycal 353, there are four possible stereoisomers that could be formed (Figure 12).
Figure 12: Every possible product from the dihydroxylation of glycal 353.

From NMR analysis (see below), we assigned the stereochemical configuration on the C-1 and C-2 and deduced that the major stereoisomer isolated was diol \( \alpha-352 \). We also suggest that the minor product, which co-eluted with diol \( \alpha-352 \) from column chromatography, was its anomer \( \beta-352 \).

From a range of similar compounds in the literature whose conformations have been determined from NMR and/or X-ray analysis, the most likely conformation(s) adopted by diols 352 and 356 is a hybrid between a twist-boat (\( \alpha S_2 \)) and boat conformation (\( B_{2,5} \)),\(^{27-30}\) ideal \( \alpha S_2 \) or \( B_{2,5} \) conformations,\(^{31-34}\) or a slightly flattened chair conformation (Figure 13).\(^{34}\) The reason that the usual chair conformer is generally not the preferred conformation of the galactose ring originates from constraints imposed by the 3,4-O-isopropylidene group.\(^{32}\)

Figure 13: Proposed conformations of diol \( \alpha-352 \).

From the NOESY spectrum, for the major product, a strong nOe was observed between one of the methyl groups on the 3,4-O-isopropylidene group with both H-C-1 and H-C-2 of the major product, implying that these are close in space. No matter what conformation is adopted, it is...
very unlikely for these atoms to be close in space in diastereomers β-352, α-356 or β-356, supporting the suggestion that the major product is diol α-352.

Furthermore, for the major product there were no nOes observed that would be expected for the diastereomers β-352, α-356 or β-356. For example, if either diol α-356 or β-356 were the major products, a nOe between H-C-2 and H-C-5 should be observed if the °S₂, B₂, or a hybrid between these conformations, were adopted. Moreover, if diol β-352 or β-356 were the major products, a nOe should be observed between H-C-1 and H-C-5 if a chair, flattened chair, B₂, °S₂, or hybrid between these conformations, were adopted. Likewise, for β-352 or β-356, a nOe should be observed between H-C-1 and H-C-3 if a chair or flattened chair conformation were adopted. As a result, since all these aforementioned nOes were absent, there is greater support that diol α-352 is the major product.

With regards to the minor product, from the NOESY spectrum, there was an observed nOe between H-C-1 and H-C-5. Also, there was no nOe observed between H-C-1 and the methyl group on the 3,4-O-isopropylidene. These nOe results suggest that H-C-1 is cis to H-C-5 and trans to the 3,4-O-isopropylidene group, which means that there is a β stereochemical configuration on the anomeric C-1 position. Hence, these observations from the NOESY spectrum indicate the minor product is β-352 or β-356.

Additionally, in both the minor and the major product (to a lesser extent in the major product) the stereochemical configuration on C-2 can be assigned from the magnitude of the vicinal coupling constant between H-C-2 and H-C-3 (3J2,3) using the Karplus relationship.35 The 3J2,3 values for the minor (7.9 Hz) and the major (6.4 Hz) products seem too high for the H-C-2 being cis with H-C-3 (no matter which of the previously mentioned conformations are adopted). This indicates that H-C-2 is trans to H-C-3 and gives further evidence that the major product is α-352 and minor product is β-352.

Finally, the vicinal coupling constant between H-C-1 and H-C-2 (3J1,2) in the major product is only 3.4 Hz whereas in the minor product it is 7.8 Hz. The larger 3J1,2 for the latter suggests a trans relationship between H-C-1 and H-C-2 (providing further evidence that the minor product is 356) while the former indicates a cis relationship between H-C-1 and H-C-2 (giving further indication that the major product is α-352).
From observing the stereochemistry of the major product α-352, it appears that the 1,3-dipolar cycloaddition with the osmium tetroxide occurs preferentially on the bottom face of glycal 353. To rationalize the stereoselectivity of the dihydroxylation, the conformation of glycal 353 must be considered. The most likely conformations adopted are the half chair conformations $^5H_4$ and $^4H_5$ (with the former being less stable due to the significant destabilizing 1,3-pseudo axial – axial interaction between the axial substituent on C-5 and the pseudo-axial substituent on C-3).\textsuperscript{36,37} Attack on the bottom face by the osmium species in both conformations are each less sterically hindered compared to top face attack (Figure 14). Hence, the 1,3-dipolar cycloaddition on the bottom face is faster as it leads to a less sterically congested and thus more stable transition state.

\textbf{Figure 14:} Rationale for stereoselectivity of dihydroxylation on glycal 353. The osmium tetroxide species is denoted as Os*. 
The minor product $\beta$-352 was probably formed by the major product $\alpha$-352 undergoing mutarotation during the reaction.

Using a slightly modified procedure from the literature, the diol was then diacetylated to afford 357 (Scheme 111).

\[
\begin{align*}
\text{Reagents and conditions: } & \text{a) PY, Ac}_2\text{O, } 0 \, ^\circ\text{C to rt, overnight, 68\%.} \\
\text{Scheme 111: Synthesis of compounds 357.}
\end{align*}
\]

The diacetate 357 was isolated as an anomeric mixture because of the isomers being inseparable after column chromatography. The stereochemical configuration of the major product $\alpha$-357 was deduced to be identical to diol $\alpha$-352 because of the great similarities of the NOESY spectra and vicinal coupling constants (around the pyranoid ring) between these compounds.

We then aimed to perform the C-glycosylation of diacetate 357 with TMSCN to introduce the nitrile functionality onto the anomeric position (Scheme 112 and Table 14).

\[
\begin{align*}
\text{Reagents and conditions: } & \text{a) see Table 14.} \\
\text{Scheme 112: Attempted C-glycosylation of 357 with TMSCN.}
\end{align*}
\]
<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;39&lt;/sup&gt;</td>
<td>TMSCN, BF&lt;sub&gt;3&lt;/sub&gt;OEt&lt;sub&gt;2&lt;/sub&gt;, NO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2&lt;sup&gt;40&lt;/sup&gt;</td>
<td>TMSCN, BF&lt;sub&gt;3&lt;/sub&gt;OEt&lt;sub&gt;2&lt;/sub&gt;, MeCN</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3&lt;sup&gt;41,42&lt;/sup&gt;</td>
<td>TMSCN, SnCl&lt;sub&gt;4&lt;/sub&gt;, MeCN</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4</td>
<td>TMSCN, SnCl&lt;sub&gt;4&lt;/sub&gt;, NO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5&lt;sup&gt;43&lt;/sup&gt;</td>
<td>TMSCN, SnCl&lt;sub&gt;4&lt;/sub&gt;, DCM&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Decomposition</td>
</tr>
<tr>
<td>6&lt;sup&gt;44&lt;/sup&gt;</td>
<td>TMSCN, HgBr&lt;sub&gt;2&lt;/sub&gt;, NO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>7&lt;sup&gt;39&lt;/sup&gt;</td>
<td>TMSCN, TMSOTf, NO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>8</td>
<td>TMSCN, MeCN</td>
<td>SM</td>
</tr>
<tr>
<td>9</td>
<td>TMSCN, MeCN, Reflux</td>
<td>SM</td>
</tr>
</tbody>
</table>

<sup>a</sup>The reaction was performed at rt rather than at reflux as reported in the literature.<sup>43</sup>

Table 14: Conditions and results reported for the attempted C-glycosylation of 357 with TMSCN.

Unfortunately, under common literature conditions involving TMSCN with a Lewis acid in a polar aprotic solvent (entries 1 to 7), no trace of the desired glycosyl nitrile 358 was detected. Instead only decomposition or the formation of complex mixtures were observed.

These poor results led us to try milder conditions by performing the reaction in the absence of any Lewis acid (entry 8); while this did not lead to any decomposition or complex mixtures, the conditions were unsurprisingly too mild for any reaction to occur, as only starting material was recovered. Repeating the reaction under these neutral conditions at higher temperatures (entry 9) for longer reaction times (72 h) was also not sufficient to trigger the reaction.

Since glycosyl nitrile 358 was not obtained, we decided to try the C-glycosylation with benzoyl ester groups on C<sub>1</sub> and C<sub>2</sub> instead of acetates, to see if this could influence the reaction. Therefore, from a modified procedure in the literature,<sup>45</sup> the diol was esterified using an excess of benzoyl chloride in a pyridine solvent (Scheme 113).
Attempts to grow a crystal of 359 for X-ray analysis failed. However, since the NMR data (i.e. vicinal coupling constants and NOESY spectra) were very similar to those of α-357 and the diol α-352, the stereochemistry of the dibenzoylated compound 359 was inferred to be identical with these respective compounds.

We then moved onto the C-glycosylation reactions of the dibenzoylated compound 359 with TMSCN (Scheme 114 and Table 15). Unfortunately, when subjecting dibenzoyl 359 to the same conditions as diacetyl 359, the results were effectively identical, with no trace of desired nitrile 360 being observed.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSCN, BF₃.OEt₂, NO₂Me</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>TMSCN, BF₃.OEt₂, MeCN</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3</td>
<td>TMSCN, SnCl₄, MeCN</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4</td>
<td>TMSCN, SnCl₄, NO₂Me</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5</td>
<td>TMSCN, SnCl₄, DCM a</td>
<td>Decomposition</td>
</tr>
<tr>
<td>6</td>
<td>TMSCN, HgBr₂, NO₂Me</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>7</td>
<td>TMSCN, TMSOTf, NO₂Me</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>8</td>
<td>TMSCN, MeCN</td>
<td>SM</td>
</tr>
<tr>
<td>9</td>
<td>TMSCN, MeCN, Reflux</td>
<td>SM</td>
</tr>
</tbody>
</table>

a The reaction was performed at rt rather than at reflux as reported in the literature.43

Table 15: Conditions and results reported for the C-glycosylation attempts of 359 with TMSCN.

Due to the inability to synthesize glycosyl nitriles 358 and 360, we abandoned this route.

**Silyl Enol Ether Route**

In our next approach, we planned to synthesize a silyl enol ether from DAM 234 (Scheme 115).
If target 229 were successfully prepared, this strategy would be tailored to synthesize our ultimate bicyclic targets 323a and 323b.

Target 229 could derive from compound 232, using the same retrosynthetic analysis described above for the previous target 324 from 327 (in the nitrile-Wittig and vinyl-transetherification routes) with the only difference being the presence of an ester instead of a nitrile functionality on the C-1 position. Pyranoid 232 could be synthesized by the regioselective hydration of glycal 361 and subsequent protection of the formed alcohol. Glycal 361 could be synthesized by the dehydration of pyranose 362. The deprotection of the silyl enol ether in 363 should trigger an intramolecular 6-\textit{exo}-trig cyclization of the hydroxyl group on the formed \( \alpha \)-ketoester to furnish
pyranose \textbf{362}. Silyl enol ether \textbf{363} could be synthesized from DAM \textbf{234} by a Wittig or HWE olefination with an appropriate ylide or phosphonate anion.

This route was inspired by the successful three-step synthesis of glycal \textbf{366} from DAM \textbf{234} executed by Chai \textit{et al}. (Scheme 116).\textsuperscript{46}

\begin{center}
\includegraphics[width=\textwidth]{Scheme116.png}
\end{center}

\textbf{Scheme 116}: Three-step synthesis of glycal \textbf{366} from DAM \textbf{234} by Chai \textit{et al}.\textsuperscript{46}

In this synthesis, the authors performed an HWE reaction between phosphonate \textbf{367} and DAM \textbf{234} to afford a mixture of \textit{E} and \textit{Z} silyl enol ethers \textbf{\textit{E}-364} and \textbf{\textit{Z}-364}. Subsequent treatment of the silyl enol ethers with TBAF and 20% AcOH led to desilylation and an \textit{in-situ} 6-\textit{exo}-trig cyclization to form an anomeric mixture of pyranoses \textbf{365}. Finally, glycal \textbf{366} was formed by dehydration of anomers \textbf{365}; this was achieved by mesylation of the anomeric hydroxyl group in \textbf{365} and subsequent elimination using MsCl and Et\textsubscript{3}N.

Phosphonate \textbf{367}, however, had to be synthesized as it is not commercially available. Chai and co-workers synthesized \textbf{367} in two steps from ethyl glyoxylate hydrate \textbf{368} and dimethyl phosphite (Scheme 117).\textsuperscript{46}
We therefore decided to replicate their synthesis to obtain glycal 366.

Our first task in this route was to synthesize the TBS-protected phosphonate 367. In order to achieve this feat, we had to first synthesize ethyl glyoxylate hydrate 368. We aimed to do this by using Bailey and co-workers’ conditions, where a periodate oxidative cleavage of the 1,2-diol in L-diethyl tartrate 369 was carried out (Scheme 118).47

However, our attempts at applying these conditions, were of limited success. The $^1$H NMR spectrum of the crude material, showed a mixture of multiple compounds. Due to the complexity of the $^1$H NMR spectrum, we were unable to confirm the presence of the hydrate 368, although the presence of the ethyl glyoxylate as a free aldehyde was observed. Attempts to isolate the aldehyde or the hydrate (if latter was even formed) using column chromatography proved futile. Hence, the crude mixture was used directly for the next step.

We carried out the nucleophilic addition of dimethyl phosphite to our impure sample of the ethyl glyoxylate aldehyde using Chai and co-workers’ conditions (Scheme 119).46
**Scheme 119**: Two-step synthesis of α-hydroxyphosphonate 370 from L-diethyl tartrate 369.

We were able to isolate the α-hydroxyphosphonate 370, albeit in poor yield (41% over two steps). The mediocre yield is probably the result of the use of an impure sample of the ethyl glyoxylate aldehyde as well as the production of the undesired organophosphate side-product 371 (31% yield over 2 steps). This compound was probably formed by a base-catalysed phospha-Brook rearrangement of α-hydroxyphosphonate 370 occurring during the reaction (Scheme 120).

**Scheme 120**: Proposed mechanism to account for the production of organophosphate 371.

Finally, protection of the hydroxyl group in 370 with a TBS group under standard conditions gave phosphonate 367 in 91% yield (Scheme 121).

**Scheme 121**: Silyl protection of α-hydroxyphosphonate 367.
The following step in the route involved the HWE condensation of DAM 234 with phosphonate 367 (Scheme 122 and Table 16). Despite this reaction being carried out by Chai et al., this HWE olefination proved troublesome.

Scheme 122: HWE olefination attempts between DAM 234 and phosphonate 367.
| Entry | Base       | Deprotonation Temperature/ °C | Reaction Temperature/ °C | Products **| **
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-BuOK</td>
<td>rt</td>
<td>50</td>
<td>SM</td>
</tr>
<tr>
<td>2**</td>
<td>t-BuOLi</td>
<td>rt</td>
<td>50</td>
<td>SM</td>
</tr>
<tr>
<td>3 b</td>
<td>t-BuOLi</td>
<td>rt</td>
<td>Reflux</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>t-BuOLi</td>
<td>50</td>
<td>50</td>
<td>2% Z-364, 8% E-364, 2% 372, 60% SM</td>
</tr>
<tr>
<td>5</td>
<td>t-BuOLi</td>
<td>50</td>
<td>Reflux</td>
<td>3% Z-364, 15% E-364, 7% 372, 51% SM</td>
</tr>
<tr>
<td>6</td>
<td>n-BuLi</td>
<td>0</td>
<td>50</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>7</td>
<td>LDA</td>
<td>0</td>
<td>50</td>
<td>15% Z-364, 7% E-364, 24% 372</td>
</tr>
<tr>
<td>8</td>
<td>LDA</td>
<td>0</td>
<td>rt</td>
<td>3% Z-364, 12% E-364, 3% 372, 40% SM</td>
</tr>
<tr>
<td>9</td>
<td>NaH</td>
<td>0</td>
<td>50</td>
<td>17% Z-364, 28% E-364, 1% 372, 11% SM</td>
</tr>
<tr>
<td>10 c</td>
<td>NaH</td>
<td>0</td>
<td>50</td>
<td>18% Z-364, 36% E-364, trace 372</td>
</tr>
</tbody>
</table>

**Compounds E-364 and 372 were inseparable in column chromatography. The number of moles of E-364 and 372 in the inseparable mixture were calculated from molar ratios observed in the 1H NMR spectrum. Since the yield of the E-364 is based on the number of moles of E-364 in the inseparable mixture, the yield of E-364 derives from the aforementioned molar ratios seen in the 1H NMR spectrum (same applies to 372); b Reaction time: 72 h; c 1.5 equiv. of base and 367 were added.**

Table 16: Conditions and results reported for HWE olefination attempts between DAM 234 and phosphonate 367.

Unexpectedly, when using the conditions from Chai et al.** with the exception of using t-BuOK instead of t-BuOLi (entry 1), only starting material was observed. Though we did not expect any difference, we decided to copy fully the conditions in the literature,** and hence changed the base to t-BuOLi (entry 2), but again only starting material was seen. Therefore, the HWE
condensation was carried out under more forceful conditions by firstly refluxing the reaction mixture and allowing longer reaction times (entry 3), but this made no difference.

Since we have already tried using more forceful reaction conditions, we attempted to use more powerful deprotonation conditions. Therefore prior to DAM 234 addition, the t-BuOLi base and the phosphonate 364 were heated at 50 ºC for 1 h (entry 4). After work-up, this led to a messy crude mixture with the only isolable products after column chromatography being starting material 234 (60%), Z-364 (2%) and an inseparable mixture of the E-364 (8%) and an unknown side product which we later identified as 372 (2%). The yields of the silyl enol ethers Z-364 and E-364 were still very low (10%) due to the large amount of unreacted starting material. We therefore repeated this more vigorous deprotonation in addition to subsequently heating the HWE reaction mixture at a higher temperature (entry 5). While this slightly improved the conversion and the yields of silyl enol ethers Z-364 and E-364, this also caused the yield of the unwanted side product 372 to increase as well; there was also still a great amount of unreacted starting material (51%).

At this time, we attributed the low yields of the silyl enol ethers Z-364 and E-364 to the presence of large amounts of unreacted starting material. We postulated that there could be three possible reasons to explain the high amounts of unreacted starting material:

1. Issues regarding the deprotonation step of the phosphonate 367 by the tert-butoxide base.
2. Issues regarding the betaine-forming step involving the hydroxy-aldehyde form of DAM and the phosphonate ion of 367;
3. Occurrence of unwanted side reactions of the phosphonate 367 and/or DAM 234 under the applied conditions (such as the one that leads to the undesired side product 372).

However, considering the success of this HWE reaction by Chai et al.,46 each of these rationales appear surprising and unlikely. Nevertheless, since there was an improvement in conversion when using more powerful deprotonating conditions (entries 3 to 5) we therefore decided to use stronger bases than the tert-butoxide anion.

The first strong base that we used was n-BuLi (entry 6), but only a complex mixture was observed with no isolable products, suggesting many unwanted side reactions occurred which most likely have arisen from the nucleophilic character of n-BuLi.
This led us to use the strong non-nucleophilic base LDA (entry 7). This gave a complex crude mixture, with the only isolable products after purification being the silyl enol ethers Z-364 and E-364 as well as the side product 372. While there was no trace of starting material seen in the \(^1\)H NMR spectrum of the crude mixture (indicating an improved conversion), the yield of the silyl enol ethers 364 (22%) was still low (albeit higher than previous entries), and the yield of the undesired side product 372 increased to 24%. In order to reduce the number of unwanted side reactions, we repeated the HWE olefination with LDA, except under milder conditions, by lowering the reaction temperature from 50 °C to rt (entry 8). However, the only significant effect this had was a decrease in the conversion of the starting material and yields of the silyl enol ethers Z-364 and E-364.

When using NaH as the base (entry 9), much higher yields of the silyl enol ethers Z-364 and E-364 (46%) were obtained and there were only trace amounts of the unwanted side-product 372. Additionally, increasing the equivalents of NaH and the phosphonate 367 to 1.5 equiv. (entry 10) gave greater yields of the silyl enol ethers Z-364 and E-364 (probably due to a greater conversion of starting material). We generally found that, as in entries 9 and 10, the \(^1\)H NMR spectra for the crude material were cleaner, hinting that there were fewer unwanted side reactions (including the side reaction that produces 372).

The most likely mechanism to account for the formation of the 372 would involve a silyl migration between the phosphonate 367 and DAM 234 (Scheme 123). A possible reason for this undesired reaction could arise from phosphonate 367 being bulky, and rather than attacking the hydroxy-aldehyde form of DAM in nucleophilic fashion to make the betaine intermediate, it acts as a base, deprotonating DAM, as there is greater steric hindrance in the former process. However, considering the success of this HWE reaction reported by Chai et al., this explanation seems unlikely. Furthermore, it is unclear why the yield of 372 varies considerably when different bases are used.
Scheme 123: Proposed mechanism to account for the formation of by-product 372.

As mentioned above, when performing these HWE reactions, we did not know that the side-product inseparable from \( E-364 \) was compound 372. We were only able to identify compound 372 when performing the subsequent TBAF-based silyl ether and silyl enol ether deprotection step on the inseparable mixture containing \( E-364 \) and 372 (Scheme 124).

Scheme 124: Treatment of the inseparable mixture of \( E-364 \) and 372 with TBAF.

We found that the silyl enol ether \( E-364 \) was UV active whereas 372 was not. We also discovered that \( E-364 \) was desilylated faster than 372. Hence, we ceased/quenched the reaction once \( E-364 \) was consumed as shown by TLC (by UV visualization). As a result, after purification, compound 372, DAM 234, and the desired pyranoses 365 were isolated. This allowed us to fully characterize compound 372. Furthermore, the production of DAM 234 from this silyl ether deprotection step provided further evidence of the presence of 372 in the starting inseparable mixture.

The next task in the route was deprotection of the silyl enol ethers to trigger the concomitant 6-exo-trig intramolecular cyclization to produce pyranoses 362. Using Chai and co-workers’
conditions, the silyl enol ethers \( Z-364 \) and \( E-364 \) were successfully transformed into pyranoses 362 (\( \alpha:\beta \) varying from, 5:1 to 4:1) in yields of up to 79% (Scheme 125). As indicated above, due to \( E-364 \) being inseparable from 372, this additionally led to the production of DAM 234 in the reaction.

![Scheme 125: Synthesis of pyranoses 365 from the deprotection of silyl enol ethers \( Z-364 \) and \( E-364 \).](image)

In order to synthesize glycal 366, we next attempted the dehydration of pyranoses 365 (Scheme 126 and Table 17).

![Scheme 126: Attempted dehydration of pyranoses 366.](image)
Table 17: Conditions and results reported for the dehydration attempts of pyranoses 365.

We initially used Chai and co-workers’ conditions, where an excess of base (3 equiv.) was used to trigger mesylation of the anomeric hydroxyl group in pyranoses 365 in addition to the consequent in-situ elimination of the anomeric mesylates 373 (entry 1). However, despite numerous efforts, we were unable to replicate the yields (80%) reported by Chai et al., as we only could isolate glycal 366 in low yields of up to 8%. From the $^1$H NMR spectrum of the crude material, there was a mixture of unknown compounds present alongside glycal 366. Interestingly, these unknown compounds appeared to be very polar because they could only be isolated from flash column chromatography on silica gel using a very polar solvent system (9:1, DCM:methanol). We speculated that the intermediate anomeric mesylates 373 could be in the undesired mixture, though considering the high polarity of this mixture it seemed unlikely (the complexity of the NMR spectrum for this mixture made it difficult to interpret). As a result, we concluded that the production of this polar mixture arises from undesired side-reactions, reducing the yield of glycal 366.

Applying more basic conditions by increasing the equivalents of triethylamine slightly decreased production of these polar products (as seen in the $^1$H NMR spectrum of the crude material), which may explain the higher yield of glycal 366 (entry 2); though since the yield was still low, further improvement was required.

To our delight, from an alternative procedure in the literature involving even stronger basic conditions using DBU (entry 3), there was no trace of the polar unknown mixture in the $^1$H NMR spectrum of the crude material, and provided us higher yields of glycal 366 (up to 71%).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Yield of Glycal 366/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et$_3$N (3 equiv.), MsCl (1.5 equiv.), DCM, 0°C, overnight</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>Et$_3$N (5 equiv.), MsCl (1.5 equiv.), DCM, 0°C, overnight</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>Et$_3$N (3.4 equiv.), MsCl (3 equiv.), DCM, 0°C to rt, 3 h, then DBU (3 equiv.), overnight</td>
<td>64 - 71</td>
</tr>
</tbody>
</table>
Our next goal was the hydration of the alkene in glycal 366. There are three common methods for this transformation: an oxymercuration-demercuration; an aqueous acid catalysed hydration; and a hydroboration-oxidation reaction.

In an aqueous acid-catalysed hydration, we anticipated numerous issues such as possible unwelcome hydrolysis of the isopropylidene groups and the ethyl ester, and hence we discarded this method.

The choice between an oxymercuration-demercuration or hydroboration-oxidation of glycal 366 was based upon their predicted regioselectivity. From an electronics rationale, predicting the regiochemistry would depend on the ‘victor’ in the competition between the electron-withdrawing ability (by mesomeric and inductive effect) of the ethyl ester and ring oxygen (by inductive effect) against the electron-donating ability of the ring oxygen (by mesomeric effect) in glycal 366.

Yamaguchi et al. performed an oxymercuration-demercuration on a range of compounds with a generic structure 374 (Scheme 127). These compounds 374 have similar features to glycal 366 in that they both have an electron-withdrawing group on the C-1 position.

![Scheme 127: Yamaguchi and co-workers’ syntheses of compounds 375 by an oxymercuration-demercuration process.](image)

In oxymercurations, the regioselectivity is generally governed by electronic factors, that is by nucleophilic attack of a water molecule onto the carbon of the mercurinium ion that can best accommodate a partial positive charge; the regioselectivity observed in Yamaguchi and co-workers’ example indicates that this carbon in question is C-2. Hence, this observed regiochemistry suggests that the electron-withdrawing ability of the ester and ring oxygen is more powerful than the electron-donating ability of the ring oxygen. This literature example
therefore indicates that performing an oxymercuration-demercuration on glycal 366 would lead to the desired compound 376 as the major regioisomer (Scheme 128).

**Scheme 128:** Predicted major regioisomer for an oxymercuration-demercuration of glycal 366.

In contrast, the regioselectivity for hydroborations is based on steric and electronic factors. When based on electronic factors, presuming the electron-withdrawing ability of the ester and ring oxygen is more powerful than the electron-donating ability of the ring oxygen (as inferred from the regiochemistry seen in Scheme 127), the major expected product would be the unwanted 365. This is because the regioselectivity would be dependent upon the relative stabilities of the four-centred transition states in the hydroboration (Figure 15) - since C-2 can stabilize a partial positive charge to a greater extent than C-1, transition state 377 (which after oxidation would eventually lead to 365) would be more stable than the transition state 378 (which after oxidation would eventually lead to the desired 376).52-54

**Figure 15:** Transition states for the hydroboration of glycal 366.

However, from a steric rationale, the desired compound 376 would be the major expected product since the trisubstituted C-1 position is more sterically hindered than the C-2 position; this effect would become more pronounced with bulkier boranes (Scheme 129).55
Scheme 129: Predicted major regioisomer for a hydroboration-oxidation (with steric factors or electronic factors controlling regioselectivity) on glycal 366.

As a result, due to a greater predicted regioselectivity for the desired product 376, we chose to perform an oxymercuration-demercuration sequence on glycal 366 (Scheme 130 and Table 18).

Reagents and conditions: a) see Table 18.

Scheme 130: Oxymercuration-demercuration attempts on glycal 366.
Table 18: Conditions and results reported for the oxymercuration-demercuration attempts of glycal 366.

Similarly to the oxymercurations-demercuration processes previously attempted in the nitrile-Wittig route, we initially applied standard literature conditions to glycal 366 (entry 1). However, even after very large reaction times (72 h), no change was observed by TLC. Although it would be unlikely for the organomercury compound and starting material to have the same retention factor (Rf) on silica gel, we still attempted the demercuration step, but after work-up, $^1$H NMR analysis of the crude material indeed confirmed only starting material 366 was present. Even under greater activating conditions, such as the use of catalytic 70% perchloric acid and/or use of mercuric trifluoroacetate (entries 2-4), no change in result occurred. An alternative solvent system also made no difference (entry 5).

These negative results suggest that despite the electron-donating ability of the ring oxygen, the alkene of 366 still seems to be too electron-deficient (due to the effects from the electron-withdrawing ester and ring oxygen) to react with the electrophilic mercuric reagents. However, this is perhaps surprising given of Yamaguchi and co-workers’ successful oxymercuration-demercuration of their glycal 374 (Scheme 127).
We ceased further work on this route as our oxymercuration-demercuration reactions were unsuccessful, but future work regarding hydroboration-oxidations on glycal 366 was not excluded.

**Dithiane-Reduction Route**

The lack of success in the nitrile-Wittig, vinyl-transetherification and silyl enol ether routes prompted us to revisit the dithiane strategy established previously by the group (Scheme 131).1,3

![Diagram of the Dithiane-Reduction Route]

Scheme 131: The retrosynthesis of target 379 from DAM 234 in the Dithiane-Reduction route.

If target 379 were successfully synthesized, this route would be modified to install carboxylic acid derivatives on the C₁ and thiohemiketal centres.
As planned in previous routes, thioacetate cleavage of 380 should trigger the thiol/thiolate to cyclize onto the ketone to afford target 379. The cyclization precursor 380 could be made by selective acetonide hydrolysis of 381 followed by selective protection of the primary alcohol and subsequent oxidation of the secondary alcohol. Similar to all previous routes, the thioacetyl functionality can be incorporated into the structure from 382 through a sequence involving displacement chemistry (i.e. activation of the primary hydroxyl group into a good leaving group and substitution of that leaving group with a thioacetate nucleophile in S\textsubscript{N}2 fashion). Protection of the diol in pyranose 268 followed by deacetylation would afford intermediate 382.

As already accomplished previously in the Page group, pyranose 268 could be synthesized from DAM 234 in four steps (Schemes 64 and 65).\textsuperscript{1} We therefore planned to copy this four-step synthesis to 268.

The route started with the nucleophilic addition of ethyl 1,3-dithiane-2-carboxylate (in the form of a functionalized Grignard reagent) to DAM 234 affording ester 252 in 97% yield (Scheme 132). Using LAH, the ester was then reduced to a primary alcohol, which in turn was selectively acetylated using acetic anhydride and triethylamine in DCM to form compound 266 in yields up to 75%.

![Scheme 132: Three step synthesis of 266 from DAM 234.](image)

We then intended to cleave the dithioketal in 266 and trigger the cyclization to form pyranose 268 using commercially available DBDMH in reagent grade acetone (Scheme 133 and Table 19).
Scheme 13: Dethioketalization attempts on 266 using DBDMH.

<table>
<thead>
<tr>
<th>Entry</th>
<th>DBDMH equiv.</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.83</td>
<td>10% 383</td>
</tr>
<tr>
<td>2 (^a)</td>
<td>2.83</td>
<td>268</td>
</tr>
<tr>
<td>3 (^a)</td>
<td>1</td>
<td>43% 383</td>
</tr>
<tr>
<td>4 (^a)</td>
<td>2</td>
<td>80-89% 383</td>
</tr>
</tbody>
</table>

\(^a\) Sample of DBDMH was recrystallized prior to use.

Table 19: Conditions and results obtained for the dethioketalization of 266.

We initially performed the reaction in identical conditions to Pearce’s successful dethioketalization of 266 (Scheme 67),\(^1\) except for the solvent, where we used reagent grade acetone instead of 95% aqueous acetone (entry 1). The \(^1\)H NMR spectrum of the crude material showed a complex mixture of compounds (indicating many side reactions and/or decomposition occurred). After purification, however, the triacetonide 383 was isolated in 7% yield. The formation of 383 could be explained by acetonide formation between the C-1 and C-2 hydroxyl groups in the intended product 268 (Scheme 134). This was possibly caused by the presence of catalytic quantities of HBr (possibly due to impure sample of DBDMH containing trace amounts of HBr and/or generated from reaction between DBDMH and water as the reaction was not under anhydrous conditions) accompanied by a large excess of acetone.
In the retrosynthetic analysis for this route, pyranose 268 was initially planned to be synthesized from 266 by a dethioketalization and concomitant cyclization, then in a subsequent step, the C-1 and C-2 hydroxyl groups were to be protected with suitable groups. Hence, the formation of triacetonide 383 is very beneficial because it means the dethioketalization, cyclization and the protection of the C-1 and C-2 hydroxyl groups were achieved in one step rather than two. We therefore tried to optimize the conditions in order to achieve a high yield of triacetonide 383.

With the aim of reducing the number of side reactions and/or decomposition, we repeated the reaction with purified DBDMH (recrystallized from water prior to use), but only 268 was observed in the $^1$H NMR spectrum of the crude material (entry 2). However, by tailoring the equivalents of DBDMH (entries 3 and 4) we eventually produced 383 in yields as high as 89%.

Our next aim was to deprotect the acetyl group in 383; this would allow us to activate the formed primary alcohol into a good leaving group, which would be needed subsequently to install the thioacetyl moiety into the structure by displacement chemistry. Deacetylation of 383 was achieved in 97% yield using $\text{K}_2\text{CO}_3$ in methanol according to a modified procedure from the literature (Scheme 135). We planned to activate the primary alcohol as a triflate as these are known to be excellent leaving groups. Hence, a triflation of the primary alcohol was carried out to furnish 385 in 99% yield.

**Scheme 134:** Possible pathway for the production of triacetonide 383.
Scheme 135: Two-step synthesis of triflate 385 from 383.

We proceed to the displacement of the triflate in 385 with a thioacetate nucleophile. Using slightly altered conditions to those of Repetto et al., we initially attempted the reaction using potassium thioacetate in acetonitrile for 16 h at rt (Scheme 136). However, the conversion of triflate 385 to 386 was quite low. When repeating the reaction under refluxing conditions for 16 h, however, 386 was isolated in quantitative yield after work-up and purification.

Scheme 136: Synthesis of 386 from 385.

The next step involved the regioselective deprotection of the exo-cyclic acetonide. The conditions used were reported by Ma et al., who successfully carried out a selective deprotection of a primary acetonide on a different substrate using 90% aqueous acetic acid at 40 °C. Subjecting 386 to these conditions led us to obtain diol 387 in 80% yield (Scheme 137).
After successfully obtaining \( \text{387} \), the next objective was to synthesize the precursor to target \( \text{379/391} \). In order to do this, we then moved onto the selective protection of the primary alcohol in \( \text{387} \); this would allow us subsequently to selectively oxidize the secondary alcohol into a ketone. Thus, the primary alcohol was selectively protected with the TBS group using standard conditions (Scheme 138). This was followed by a Swern oxidation, which provided the target precursor \( \text{389} \) in 86% yield.

We were next tasked with the deprotection of the thioacetate in \( \text{389} \) to provide the thiol/thiolate intermediate \( \text{390} \), which was expected to cyclize in-situ to furnish the synthetic target \( \text{391} \) (Scheme 139 and Table 20).
Scheme 139: Thioacetate deprotection attempts of compound 389.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOMe, MeOH</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>NaHCO₃, MeOH, reflux</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3</td>
<td>NaHCO₃, MeOH, rt</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4</td>
<td>K₂CO₃, MeOH</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5</td>
<td>NaSMe, MeOH</td>
<td>Decomposition</td>
</tr>
<tr>
<td>6</td>
<td>N₂H₄·H₂O, MeOH</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>7</td>
<td>N₂H₄, THF</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>8</td>
<td>N₂H₄·H₂O, AcOH, DMF</td>
<td>Decomposition</td>
</tr>
<tr>
<td>9</td>
<td>N₂H₅·OAc, THF</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

Table 20: Conditions and results obtained for the thioacetate deprotections of 389.

Unfortunately, despite testing a large variety of deprotection procedures from the literature, including common basic (entries 1 to 4), transthioesterification (entry 5) and hydrazinolysis (entries 6 to 9) conditions, only decomposition or complex mixtures were observed.

Since we were unable to obtain target 390 or even thiol 391, we also used silyl protecting groups other than TBS, such as the TIPS and TBDPS groups. Hence, we selectively protected the primary alcohol in 387 with TIPS and TBDPS groups under standard conditions (Scheme 140).
Swern oxidations of the protected derivatives \(392\) and \(393\) were then carried out, allowing us to obtain ketones \(394\) and \(395\) (Scheme 141).

Thioacetate deprotections of the TIPS and TBDPS-protected ketones \(394\) and \(395\) were then attempted. Regrettably, despite trying all the same procedures as previously carried out with the TBS ketone \(381\), only decomposition or complex mixtures were seen (Scheme 142).
Confronted with these disappointing results, we decided to modify our cyclization strategy. In this strategy, instead of oxidizing the secondary alcohol in 388 to a ketone, we planned to activate it as a good leaving group such as a sulfonate ester (Scheme 143). The presence of a good leaving group in this position should aid the in-situ cyclization during the thioacetate deprotection. The major drawback to this strategy is the absence of a thiohemiketal functionality in target 400. If 400 were successfully synthesized, however, the route would be revised to install a thiohemiketal functionality (for example using Pummerer reaction methodology).

![Scheme 143: Proposed synthetic approach to target 400.](image)

We initially aimed to activate the hydroxyl group in 388 as a tosylate (Scheme 144 and Table 21).
Scheme 14: Attempted tosylation of alcohol 388.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions (^a)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^{67})</td>
<td>Et(_3)N (1.5 equiv.), TsCl (1.1 equiv.), DCM</td>
<td>SM</td>
</tr>
<tr>
<td>2(^{68})</td>
<td>DMAP (1.9 equiv.), TsCl (1.46 equiv.), DCM</td>
<td>SM</td>
</tr>
<tr>
<td>3(^{69})</td>
<td>Et(_3)N (7 equiv.), DMAP (1 equiv.), TsCl (2 equiv.), DCM</td>
<td>SM</td>
</tr>
<tr>
<td>4(^{70})</td>
<td>DMAP (0.1 equiv.), TsCl (2 equiv), pyridine (^b)</td>
<td>SM</td>
</tr>
</tbody>
</table>

\(^a\) reaction time: 72 h, temperature: 0 °C to rt; \(^b\) 60 °C

Table 21: Conditions and results obtained for the attempted tosylation of alcohol 388.

Using methods outlined in the literature (conditions increasing in severity from entries 1 to 4),\(^{67-70}\) we did not obtain tosylate 401, as only starting material was recovered. A possible reason for this failure could be steric hindrance in compound 401. This is because the tosylation requires a secondary alcohol (adjacent to a large TBS group and pyranoid ring) to react with a bulky tosyl chloride electrophile, leading to a sterically congested transition state.

The lack of success in the tosylation prompted us to transform the secondary alcohol into a triflate (Scheme 145); this was accomplished in 96% yield under the same conditions used previously in the route (for the synthesis of 385 – Scheme 135).
We proceeded to the thioacetate deprotection of triflate 402 (Scheme 146 and Table 22). Similarly, to the previously attempted thioacetate deprotections of the ketone substrates 389, 394 and 395, however, the reaction was a failure as neither the thiol 403 or target 400 were isolated, only decomposition or complex mixtures were observed.

Scheme 146: Thioacetate deprotection attempts of compound 402.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1⁵⁹</td>
<td>NaOMe, MeOH</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>2⁶⁰</td>
<td>NaHCO₃, MeOH, rt</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3⁶¹</td>
<td>K₂CO₃, MeOH</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>4⁶²</td>
<td>NaSMe, MeOH</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5⁴,⁶³</td>
<td>N₂H₄.H₂O, MeOH</td>
<td>Decomposition</td>
</tr>
<tr>
<td>6⁶⁴</td>
<td>N₂H₄, THF</td>
<td>Decomposition</td>
</tr>
<tr>
<td>7⁶⁵</td>
<td>N₂H₄.H₂O, AcOH, DMF</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>8⁶⁶</td>
<td>N₂H₅.OAc, THF</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

**Table 22:** Conditions and results obtained for the thioacetate deprotections of 402.

We next decided to use a mesylate leaving group instead of a triflate to see if this could make any difference to the result of the thioacetate deprotections. We successfully synthesized mesylate 404 from compound 388 in 66% yield according to the conditions of Hoveyda et al. (Scheme 147).

![Scheme 147: Mesylation of 388.](image)

Reagents and conditions: a) Et₃N, MsCl, 0 °C to rt, 66%.

**Scheme 147:** Mesylation of 388.

We attempted the thioacetate deprotection of 404, but once again only decomposition and complex mixtures were observed (Scheme 148 and Table 23).
Scheme 148: Thioacetate deprotection attempts of compound 404.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^{59})</td>
<td>NaOMe, MeOH</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2(^{60})</td>
<td>NaHCO(_3), MeOH, rt</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3(^{61})</td>
<td>K(_2)CO(_3), MeOH</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>4(^{62})</td>
<td>NaSMe, MeOH</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5(^{4,63})</td>
<td>N(_2)H(_4).H(_2)O, MeOH</td>
<td>Decomposition</td>
</tr>
<tr>
<td>6(^{64})</td>
<td>N(_2)H(_4), THF</td>
<td>Decomposition</td>
</tr>
<tr>
<td>7(^{65})</td>
<td>N(_2)H(_4).H(_2)O, AcOH, DMF</td>
<td>Decomposition</td>
</tr>
<tr>
<td>8(^{66})</td>
<td>N(_2)H(_5).OAc, THF</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

Table 23: Conditions and results obtained for the thioacetate deprotection of 404.

With the lack of success using the TBS group in the attempted thioacetate deprotections of triflate 402 and mesylate 404, we planned to use the TIPS group instead. As a result, under the same conditions used previously (for the synthesis of 402 and 404) we synthesized the TIPS triflate 405 and mesylate 406 from 392 in yields of 98% and 64% respectively (Scheme 149).
We then attempted the thioacetate deprotections (under all the same conditions previously tried for the TBS triflate 402 and mesylate 404) of 405 and 406. To our disappointment, only decomposition occurred.

The failure of the thioacetate deprotections in all the ketone, triflate and mesylate substrates, led us to consider a new route with a different cyclization strategy (Scheme 150).

The 1,4-oxathiane moiety in target 407 could be made from the reaction between the disulfonate ester 408 and a sulfide anion (deriving from Li2S or Na2S). Sulfonylation of both hydroxyl...
groups in 409 would lead to the target precursor 408. Diol 409 could be made from deacetylation of compound 410, which in turn could be synthesized from selective protection of the primary hydroxyl group in 411. Regioselective isopropylidene hydrolysis of 383 could afford compound 411. Compound 383 has already been made earlier in the route (in four synthetic steps from DAM 234).

The key step in this strategy is the cyclization to target 407. This step would involve two consecutive S_N2 reactions: the first being the substitution of the primary sulfonate ester with the sulfide ion, forming a thiolate, which in turn would intramolecularly displace the secondary sulfonate ester in-situ (Scheme 151).

Scheme 151: Proposed mechanism for the synthesis of target 407 from disulfonate ester 408.

This route started with a selective acetonide hydrolysis of 383 using aqueous acetic acid (Scheme 152). The reaction afforded diol 411 in 90% yield, though a diacetylated side product 412 was also isolated in low yields (the extra acetylation was probably formed by Fischer esterification of the primary alcohol).

Scheme 152: Regioselective isopropylidene hydrolysis of 383.
The next step involved the selective protection of the primary alcohol; we chose to use the trityl protecting group. Regioselective tritylation of 411 was achieved in 89% yield using conditions from Peyrat et al.\textsuperscript{72} Treatment of the trityl-protected compound 413 with sodium methoxide in methanol led to deacetylation, which furnished 414 in 94% yield (Scheme 153).

Scheme 153: Two-step synthesis of 414 from 411.

We then aimed to activate both hydroxyl groups in 414 as mesylates. The dimesylation was carried out under conditions according to the literature,\textsuperscript{73} which afforded 415 in 70% yield (Scheme 154).

Scheme 154: Dimesylation of 414.

With dimesylate 415 in hand, we then attempted the cyclization to target 416 using an array of conditions from the literature (Scheme 155 and Table 24).
Table 24: Conditions and results obtained for the attempted cyclization of $415$.

When $415$ was subjected to conventional conditions such as lithium or sodium sulfide in a polar aprotic solvent (entries 1 to 5), only starting material was observed despite long reaction times. Repeating entries 1 to 3 at higher temperatures made no difference. Attempting other literature conditions (entries 4 to 8) led to the same unwanted outcome. Given the previous success of the thioacetate displacement of the triflate in $385$, these results were perhaps surprising, since we expected that at least the relatively unhindered primary mesylate of $415$ would be displaced fairly easily by the sulfide anion.

Due to the lack of reactivity of dimesylate $415$ with sulfide anions, we decided to transform both hydroxyl groups in $414$ to triflates (as these are better leaving groups than mesylates). Hence, using a modified procedure from the literature, $414$ was treated with pyridine and triflic anhydride, giving ditriflate $417$ (Scheme 156).
The cyclization of 417 into target 416 was then attempted under a range of conditions (Scheme 157 and Table 25). Unfortunately, in each attempt only decomposition or complex mixtures were observed. We also attempted the cyclization under milder conditions (entry 8) whereby the reaction was carried out at 0 °C, but a complex mixture still resulted.

Scheme 156: Ditriflation of 414.

Scheme 157: Attempted synthesis of target 416 from ditriflate 417.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{74}</td>
<td>Li\textsubscript{2}S, DMF, rt</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2\textsuperscript{74}</td>
<td>Li\textsubscript{2}S, DMSO, rt</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3\textsuperscript{75}</td>
<td>Na\textsubscript{2}S, DMSO, rt</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4\textsuperscript{76}</td>
<td>Na\textsubscript{2}S, DMF, 80 °C</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>5\textsuperscript{75}</td>
<td>Na\textsubscript{2}S, DMSO:MeOH (2:1), 60 °C</td>
<td>Decomposition</td>
</tr>
<tr>
<td>6\textsuperscript{78}</td>
<td>Na\textsubscript{2}S, MeOH, reflux</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>7\textsuperscript{79}</td>
<td>Na\textsubscript{2}S, EtOH, reflux</td>
<td>Decomposition</td>
</tr>
<tr>
<td>8</td>
<td>Na\textsubscript{2}S, DMF, 0 °C</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

Table 25: Conditions and results obtained for the attempted cyclization of 417.
We considered that one possible reason for the failures of the cyclizations to target 416 from dimesylate 415 and ditriflate 417 could be due to the large trityl group sterically hindering the secondary sulfonate ester. As a result, we decided to use a slightly less bulky TIPS group to protect the primary alcohol in 411 instead; this was accomplished in 89% yield (Scheme 158) under the same conditions previously used for the TIPS-protection of 387.

![Reagents and conditions: a) imidazole, DMAP, TIPSCI, DCM, 0 °C to rt, 24 h, 89%.

Scheme 158: Regioselective TIPS protection of the primary hydroxyl group in 411.

The next step involved the deacetylation of 418 (Scheme 159 and Table 26). Surprisingly, this deacetylation step appeared more problematic than initially envisaged.

![Reagents and conditions: a) see Table 26.

Scheme 159: Deacetylation attempts of 418.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions a</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOMe, MeOH, 3 h</td>
<td>77% A, 18% B</td>
</tr>
<tr>
<td>2</td>
<td>K₂CO₃, MeOH, 4 h</td>
<td>77% A, 13% B</td>
</tr>
<tr>
<td>3</td>
<td>DIBAL, THF</td>
<td>69% A</td>
</tr>
</tbody>
</table>

a room temperature

Table 26: Conditions and results reported for the attempted deacetylations of 418
We initially attempted the deacetylation using sodium methoxide in methanol (entry 1). However, we isolated two isomeric products; a major product A and a minor product B. From NMR, IR and MS analysis we concluded that either of these products could be the desired compound 419. When performing another base-promoted deacetylation using K$_2$CO$_3$ in methanol (entry 2), the same two isomeric products were isolated in similar yields to entry 1.

In order to diagnose whether product A or B is the desired compound 419, we planned to mono-acetylate A and B respectively; If A is 419, then mono-acetylation of A should lead to 418 (418 has previously been made earlier in the route) and mono-acetylation of B will not lead to 418 (or vice versa). We found that in contrast to B, mono-acetylation of A produced 418 (Scheme 160); thus, we concluded that A is the desired product 419.

![Scheme 160: Mono-acetylation of products A and B.](image)

When performing the deacetylation under reductive rather than basic conditions (entry 3), only 419 (i.e. product A) was isolated. This indicates that the side reaction leading to the production of B requires basic conditions. Therefore, we speculate that B is formed from a base-promoted 1,4-intramolecular migration of the TIPS group in 419 (though more experiments would be required to confirm this).

Using the same conditions previously carried out (for 415), both hydroxyl groups in 419 were then transformed into mesylates (Scheme 161).
We then attempted the cyclization of 420 to give target 421 under a range of conditions (Scheme 162 and Table 27). Yet, as with the attempted cyclizations with the trityl protected dimesylate 415, only starting material was recovered with no trace of target 421 seen.

**Scheme 161**: Dimesylation of 419.

**Scheme 162**: Attempted synthesis of target 421 from dimesylate 420.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^74)</td>
<td>Li(_2)S, DMF, rt</td>
<td>SM</td>
</tr>
<tr>
<td>2(^74)</td>
<td>Li(_2)S, DMSO, rt</td>
<td>SM</td>
</tr>
<tr>
<td>3(^75)</td>
<td>Na(_2)S, DMSO, rt</td>
<td>SM</td>
</tr>
<tr>
<td>4(^76)</td>
<td>Na(_2)S, DMF, 80 °C</td>
<td>SM</td>
</tr>
<tr>
<td>5(^77)</td>
<td>Na(_2)S, DMF, 100 °C</td>
<td>SM</td>
</tr>
<tr>
<td>6(^75)</td>
<td>Na(_2)S, DMSO:MeOH (2:1), 60 °C</td>
<td>SM</td>
</tr>
<tr>
<td>7(^78)</td>
<td>Na(_2)S, MeOH, reflux</td>
<td>SM</td>
</tr>
<tr>
<td>8(^79)</td>
<td>Na(_2)S, EtOH, reflux</td>
<td>SM</td>
</tr>
</tbody>
</table>

**Table 27**: Conditions and results obtained for the attempted cyclization of 420.
Due to the failure of the cyclizations with the TIPS-protected dimesylate 420, we planned to attempt the cyclizations with a ditriflate instead. Consequently, a ditriflation on 419 was completed, affording 422 in near quantitative yield (Scheme 163).

Scheme 163: Ditriflation of 419.

With ditriflate 422 in hand we attempted the cyclizations with the sulfide anion, again under a range of conditions (Scheme 164 and Table 28).

Scheme 164: Attempted synthesis of target 421 from ditriflate 422.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;74&lt;/sup&gt;</td>
<td>Li₂S, DMF, rt</td>
<td>Trace unknown product</td>
</tr>
<tr>
<td>2&lt;sup&gt;74&lt;/sup&gt;</td>
<td>Li₂S, DMSO, rt</td>
<td>Unknown product</td>
</tr>
<tr>
<td>3&lt;sup&gt;75&lt;/sup&gt;</td>
<td>Na₂S, DMSO, rt</td>
<td>Trace unknown product</td>
</tr>
<tr>
<td>4&lt;sup&gt;76&lt;/sup&gt;</td>
<td>Na₂S, DMF, 80 °C</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5&lt;sup&gt;75&lt;/sup&gt;</td>
<td>Na₂S, DMSO:MeOH (2:1), 60 °C</td>
<td>Decomposition</td>
</tr>
<tr>
<td>6&lt;sup&gt;78&lt;/sup&gt;</td>
<td>Na₂S, MeOH, reflux</td>
<td>Decomposition</td>
</tr>
<tr>
<td>7&lt;sup&gt;79&lt;/sup&gt;</td>
<td>Na₂S, EtOH, reflux</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>8&lt;sup&gt;79&lt;/sup&gt;</td>
<td>Na₂S, DMF, 0 °C</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

**Table 28:** Conditions and results obtained for the attempted cyclization of 422.

Interestingly, in three sets of conditions (entries 1 to 3), the same unknown product was isolated in variable yields; thorough NMR and MS analysis ruled out this product from being target 421 or an intermediate thiol. Decomposition and complex mixtures were observed in the rest of the attempts (entries 4 to 8).

We concluded any future work with this cyclization strategy due to the failure of the cyclizations with the trityl-protected and TIPS-protected sulfonate esters 415, 417, 420 and 422.

In the dithiane-reduction route, three cyclization strategies were attempted on numerous substrates:

1. Thioacetate deprotection and *in-situ* cyclization of the liberated thiol/thiolate onto a ketone.
2. Thioacetate deprotection and *in-situ* cyclization of the liberated thiol/thiolate onto a sulfonate ester.
3. Displacement of two sulfonate esters using a sulfide anion.

A common trait that all the substrates for these cyclization strategies have, are the two cyclic isopropylidene groups. Given that all three strategies failed, we postulated that maybe the presence of isopropylidene groups hinder the cyclization as they lead to steric constraints being
placed on ring closure. A consequence for the failure of the cyclization could lead to a whole host of side reactions occurring instead (leading to decomposition or complex mixtures being observed). We therefore aimed to attempt our initial cyclization approach with a substrate without any acetonide groups; we postulated that this could be achieved in three steps from either of the ketone substrates 389, 394 or 395 (Scheme 165).

![Proposed synthetic approach to target 426 from ketones 389, 394 or 395.](image)

Methodologies: a) isopropylidene hydrolysis; b) protection with benzyl or silyl groups; c) thioacetate deprotection; d) in-situ cyclization.

**Scheme 165**: Proposed synthetic approach to target 426 from ketones 389, 394 or 395.

We chose to attempt this synthesis starting from the TIPS-protected ketone substrate 394. Hence, our initial objective was to hydrolyse both acetonide groups in 394 (Scheme 166 and Table 29).
Reagents and conditions: a) see Table 29.

Scheme 166: Acetonide hydrolysis attempts on 394.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{81}</td>
<td>80% AcOH\textsubscript{(aq)}, 70 °C</td>
<td>66% 427</td>
</tr>
<tr>
<td>2</td>
<td>80% AcOH\textsubscript{(aq)}, 90 °C</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3\textsuperscript{82}</td>
<td>90% TFA\textsubscript{(aq)}, rt,</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4\textsuperscript{83}</td>
<td>H\textsubscript{2}O:AcOH:TFA (2:3:5), rt</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5\textsuperscript{84}</td>
<td>DCM:TFA (2:1), rt</td>
<td>Decomposition</td>
</tr>
<tr>
<td>6\textsuperscript{85}</td>
<td>BF\textsubscript{3}.OEt\textsubscript{2}, DCM:MeOH (1:1), rt</td>
<td>Decomposition</td>
</tr>
<tr>
<td>7\textsuperscript{85}</td>
<td>BF\textsubscript{3}.OEt\textsubscript{2}, DCE:MeOH (1:1), rt</td>
<td>Decomposition</td>
</tr>
<tr>
<td>8\textsuperscript{86}</td>
<td>1M HCl\textsubscript{(aq)}:THF (1:1), rt</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

Table 29: Conditions and results reported for the attempted acetonide hydrolysates of 427.

In our first attempt (entry 1), we attempted hydrolysis of both acetonide groups using 80% aqueous acetic acid at 70 °C according to a procedure by Komizo \textit{et al.}\textsuperscript{81} However, these conditions were not strong enough to hydrolyse the acetonides because only TIPS deprotection occurred, affording compound 427 in 66% yield. Heating at longer reaction times (~72 h) made no difference. We therefore heated the reaction mixture at higher temperatures (entry 2), but only decomposition was observed. Following this, we tested a range of conditions from the literature,\textsuperscript{82–86} such as TFA, Lewis acid and aqueous HCl based procedures (entries 3 to 8), but only decomposition was found.

The lack of success in the three cyclization strategies and in the subsequent acetonide deprotections led us to abandon this route. However, in any future route we decided to not
incorporate any isopropylidene groups in the synthesis, as they could be hindering the cyclization to the bicyclic core by imposing steric constraints on ring closure.

**D-Galactose Route**

In this route, we planned to synthesize target 428 from D-galactose 433, without any use of isopropylidene protecting groups (Scheme 167).

**Scheme 167**: Retrosynthesis of target structure 428 from D-galactose 433 in the D-galactose route.

If successful, this route would be revised and altered to install a carboxylic acid derivative on the thiohemiacetal centre in target 428.
The bicyclic target structure 428 could be made from thioacetate deprotection of 429 and consequent \textit{in-situ} cyclization of the thiol/thiolate onto the aldehyde. The target precursor 429 could be made from selective deprotection of the primary hydroxyl group in 430, followed by oxidation into an aldehyde. Activation of the primary alcohol in 431 and subsequent substitution with a thioacetate nucleophile could form thioacetate 430. Reaction between the anomic nitrile anion of 432 with a formaldehyde electrophile would introduce the hydroxy methylene functional group. Intermediate 432 could be made from compound 64 in three steps: deacetylation of 64; selective protection of the primary hydroxyl group (e.g. silyl protection); and protection of the three secondary hydroxyl groups (e.g. perbenzylation). Compound 64 could be made from D-galactose 433 in two steps. The first step would be a peracetylation of D-galactose to form D-galactose pentaacetate 63, which in turn can then undergo a C-glycosylation reaction with TMSCN to form 64; both these steps have already been accomplished in the literature.\textsuperscript{87–89}

The route started with the peracetylation of D-galactose 433 (Scheme 168). Subjecting D-galactose 433 to typical literature conditions of NaOAc in Ac\textsubscript{2}O at 120 °C\textsuperscript{87} led to the isolation of \(\beta\)-63 in 64% yield.

\begin{equation}
\begin{array}{c}
\text{433} \\
\text{a} \\
\text{\beta-63}
\end{array}
\end{equation}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{scheme168.png}
\caption{Scheme 168: Synthesis of \(\beta\)-63.}
\end{figure}

Reagents and conditions: a) NaOAc, Ac\textsubscript{2}O, 120 °C, 3 h, 64%.

The production of three other isomeric pentaacetate compounds (Figure 16) in this reaction contributed to the lower than expected yield of \(\beta\)-63. Nevertheless, \(\beta\)-63 was still isolated from the mixture using a recrystallization procedure reported by Liu \textit{et al.}\textsuperscript{90}
Figure 16: Other pentaacetate derivatives formed in peracetylation of D-galactose 433.

It was also inferred that the reaction time was critical in achieving sufficient yields for β-63. For example, a reaction time too long (e.g. greater than 5 hours) generated increased amounts of the undesired pentaacetate furanosides at the expense of β-63, leading to yields being as low as 5%. Conversely, too short reaction times additionally led to low yields because of poor conversion to the penta-acetylated derivatives. It was found that the optimum reaction time was 3 hours.

Compound α-63 was not isolated even though it could be used in the subsequent C-glycosylation step. This is because purification and isolation of α-63 from the pentaacetate furanosides α-434 and β-434 by recrystallization and column chromatography proved difficult. Furthermore, from the molar ratios between α-63, β-63, α-434 and β-434 in the 1H NMR spectrum of the crude material, if isolated, maximum yields of α-63 would only be ~10-15%.

The C-glycosylation of β-63 was then performed. According to conditions outlined in the literature,88,89 β-63 was treated with TMSCN and a Lewis acid (BF₃.OEt₂) in a polar aprotic solvent, furnishing glycosyl nitrile 64 in 67% yield (Scheme 169).

Scheme 169: C-glycosylation of β-63 with TMSCN.

The next goal in the route was the deprotection of the acetate groups in 64 followed by the selective protection of the primary alcohol (Scheme 170 and Table 30).
Scheme 170: Deacetylation of 64 and selective protection of the primary alcohol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Reagents and conditions $^a$</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^{91}$</td>
<td>PMB</td>
<td>NaH (1 equiv.), PMBCl (1 equiv.), DMF, 24 h</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>2$^{92}$</td>
<td>TIPS</td>
<td>Imidazole (2.5 equiv.), TIPSCl (1.5 equiv.), DMF, 72 h</td>
<td>26% 436b (over 2 steps)</td>
</tr>
<tr>
<td>3</td>
<td>TIPS</td>
<td>Imidazole (4 equiv.), TIPSCl (2 equiv.), DMF, 72 h</td>
<td>42% 436b (over 2 steps)</td>
</tr>
</tbody>
</table>

$^a$Temperature: 0 °C to rt.

Table 30: Conditions and results reported for the regioselective protection.

From the literature,$^{92}$ we used sub-stoichiometric quantities of sodium methoxide in methanol for the deacetylation. The $^1$H and $^{13}$C NMR spectra of the crude material confirmed that all the acetates have been cleaved successfully and that the major product in the mixture was 435. There were, however, a number of signals in the spectra belonging to impurities. Purification attempts by column chromatography on silica gel or alumina failed because the mixture was ‘lost’ with no recovery (perhaps due to its high polarity). We also tried to purify the mixture by recrystallization using numerous solvents, but this failed as well. Consequently, the crude mixture was used directly for the next step.

We initially tried to protect the primary alcohol selectively with a PMB group using modified conditions from the literature,$^{91}$ but only a complex mixture was observed (entry 1). We therefore tried a protection with the larger TIPS group (entries 2 and 3). Using conditions from Balmond et al.$^{92}$ we successfully isolated compound 436b, albeit only in 26% yield (entry 2). This low yield occurred due to the poor conversion of 435 (since unreacted 435 was isolated.
from the aqueous layer in the work-up). By increasing the equivalents of TIPSCI and imidazole, however, higher yields (42%) were reached (entry 3). Regrettably, increasing the equivalents further or adding DMAP in catalytic quantities (0.2 equiv.) made no significant improvement to the yield.

We then moved onto the perbenzylolation of the TIPS silyl ether 436b (Scheme 171 and Table 31).

Scheme 171: Perbenzylolation attempts of 436b.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^{93}$</td>
<td>NaH (3.7 equiv.), BnBr (4.5 equiv.), DMF</td>
<td>44% 437, 15% mono- and di-benzylated products (6% 438, 3% 439, 2% 440, 4% 441)</td>
</tr>
<tr>
<td>2</td>
<td>NaH (8 equiv.), BnBr (10 equiv.), DMF</td>
<td>41% 437, 20% mono- and di-benzylated products (8% 438, 7% 439, 2% 440, 3% 441)</td>
</tr>
<tr>
<td>3</td>
<td>NaH (8 equiv.), BnBr (10 equiv.), THF</td>
<td>57% 437, 20% mono- and di-benzylated products (7% 438, 3% 439, 2% 440, 8% 441)</td>
</tr>
<tr>
<td>4</td>
<td>NaH (8 equiv.), BnBr (10 equiv.), THF$^{b}$</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5$^{94}$</td>
<td>NaH (4.95 equiv.), BnBr (4.5 equiv.), THF, TBAI (0.08 equiv.)</td>
<td>71% 437</td>
</tr>
<tr>
<td>6</td>
<td>NaH (4.95 equiv.), BnBr (4.5 equiv.), THF</td>
<td>39% 437, 36% mono- and di-benzylated products (23% 438, 3% 439, 3% 440, 7% 441)</td>
</tr>
</tbody>
</table>

$^{a}$Reaction time: 72 h, temperature: 0 °C to rt; $^{b}$0 °C to heat under reflux for 4 h.

**Table 31:** Conditions and results reported for the attempted perbenzylations of 436b.

We initially tried standard conditions using sodium hydride and benzyl bromide in DMF,$^{93}$ but got poor yields of the tribenzylated derivative 437 (entry 1). The isolation of mono- and di-benzylated intermediates accounted for the poor yield, and also indicates that these conditions were not powerful enough to induce complete perbenzylation.

To increase the conversion of these intermediates to the desired tribenzylated compound 437, we tried more vigorous conditions by increasing the equivalents of the base and benzyl bromide electrophile, but no significant difference was observed (entry 2). Surprisingly, changing the solvent from DMF to THF slightly improved the yield for the tribenzylated derivative 437 (entry 3), though the presence of the mono and di-benzylated intermediates still suggested that more forcing conditions were needed. Consequently, we repeated the reaction using THF again but instead heated the reaction mixture under reflux (entry 4). These conditions seemed too strong, as only decomposition was observed after only a relatively short reaction time (4 h rather than 72 h).
In order to further improve the yield of 437, from a modified procedure in the literature, we decided to use TBAI as a catalyst in a THF solvent (entry 5). Gratifyingly, under these conditions, 437 was isolated in 71% yield. Since the equivalents of sodium hydride and benzyl bromide in this reaction (entry 5) were different from all previous attempts (entries 1 to 4), we wanted to prove whether the change in equivalents or the use of TBAI were pivotal in optimizing the reaction. We therefore repeated the reaction again without the use of TBAI (entry 6) and obtained a much lower yield of 437; this result showed that using catalytic TBAI was critical to the success of the perbenzylation. The success of the reaction when using TBAI is most likely due to the displacement of the bromide in benzyl bromide with an iodide, generating a much more reactive benzyl iodide electrophile in-situ.

The next step was the attempted formation and reaction of the nitrile anion of 437 with formaldehyde (Scheme 172 and Table 32).

Scheme 172: Attempted synthesis of 442 from 437.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiHMDS</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>NaH</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>LDA</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>t-BuLi</td>
<td>SM</td>
</tr>
<tr>
<td>5</td>
<td>t-BuLi&lt;sup&gt;a&lt;/sup&gt;</td>
<td>SM</td>
</tr>
</tbody>
</table>

<sup>a</sup> DMPU (3 equiv.) additive was used in addition.

Table 32: Conditions and results reported for the attempted synthesis of 442 from 437.

Unfortunately, despite using an array of strong bases (increasing in strength from entries 1 to 4), only starting material 437 was recovered in each attempt. Even when using a DMPU additive to
further increase the reactivity of (the already very strong base) t-BuLi,\textsuperscript{96} the same result occurred.

In order to identify the failure of this reaction, we decided to repeat all the above attempts (entries 1 to 5) but replace the formaldehyde electrophile with D\textsubscript{2}O (Scheme 173). This would establish whether a nitrile anion is formed prior to the addition of formaldehyde. Surprisingly in all cases, only starting material (with no diminishment of the anomeric proton signal) was recovered. These results suggest, that under each attempted set of conditions (entries 1 to 5 in Table 32), the nitrile anion was not formed. While this explains why the reaction with formaldehyde failed, it is unclear as to why the nitrile anion not formed.

\[
\text{Scheme 173: Deuteration attempts of 437.}
\]

We also repeated all the previous attempts with D\textsubscript{2}O at a higher deprotonation temperature (\(-20 \, ^\circ C\)), but the same results were seen.

Confronted with these failures, we decided to replace the nitrile in 437 with an ester (Scheme 174). If successful, this would allow us to attempt a reaction with formaldehyde using an anomeric ester enolate of 445 (instead of an anomeric nitrile anion of 437). Compound 445 could derive from 446 by selective TIPS protection of the primary hydroxyl group followed by perbenzylation. Esterification of carboxylic acid 447 would form compound 446. Finally, carboxylic acid 447 could be made by deacetylation and nitrile hydrolysis of 64.
By the methodology mentioned in the above retrosynthetic analysis, we successfully synthesized the C-glycosyl ester derivative 446 in three steps from 64 (Scheme 175). These involved acetyl cleavage of 64, followed by basic nitrile hydrolysis to afford carboxylate 448 in 60% yield (over two steps)\(^8\). Subsequent treatment of the carboxylate with hydrogen chloride-methanol solution (prepared from addition of acetyl chloride to methanol) under reflux then led to Fischer esterification yielding 446\(^8\).

**Scheme 175:** Three-step synthesis of 446 from 64.

Under the optimized conditions previously applied to C-glycosyl nitrile 435, the primary alcohol in 446 was successfully protected with a TIPS group, albeit in low yield (Scheme 176).
We then moved onto the perbenzylation of compound 449 (Scheme 177 and Table 33).

**Scheme 177:** Perbenzylation attempts of compound 449.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NaH (4.95 equiv.), BnBr (4.5 equiv.), THF, TBAI (0.08 equiv.), 0 °C to rt</td>
<td>59% 451</td>
</tr>
<tr>
<td>2</td>
<td>NaH (3 equiv.), BnBr (4.5 equiv.), THF, TBAI (0.08 equiv.), 0 °C to rt</td>
<td>51% 451</td>
</tr>
<tr>
<td>3</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (4.5 equiv.), BnBr (4.5 equiv.), MeCN, reflux</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (4.5 equiv.), BnBr (4.5 equiv.), DMF, 90 °C</td>
<td>SM</td>
</tr>
<tr>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Ag&lt;sub&gt;2&lt;/sub&gt;O (6 equiv.), BnBr (9 equiv.), DMF, 0 °C to rt</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction time: 72 h.

**Table 33:** Conditions and results reported for the attempted perbenzyltion of 449.

We initially tried the same optimized conditions previously used for the perbenzyltion of the C-glycosyl nitrile 436 (entry 1), but no trace of the desired tribenzylated compound 450 was observed. In fact, the only compound isolated after work-up and purification was the dibenzylated glycal 451. Glycal 451 was probably formed by an E1cB elimination of the desired
tribenzylated compound 450. In order to suppress the undesired β-elimination, we made the conditions less basic by decreasing the equivalents of the sodium hydride base, but again only glycal 451 was isolated (entry 2). These disappointing results indicated that milder conditions were required to suppress the elimination. We therefore replaced sodium hydride with the weaker base, potassium carbonate (entries 3 and 4), but despite heating for prolong times, these conditions were too mild for any benzylation to take place. Finally, when the benzylation was carried out in near neutral conditions,95 using silver(1)oxide with benzyl bromide in DMF (entry 6),97 only a complex mixture was observed.

The lack of success in the perbenzylation of methyl ester 449 and reaction between formaldehyde and the tribenzylated nitrile 437, led us to modify the strategy (Scheme 178).

![Scheme 178: Retrosynthetic analysis for target 452 from 437.](image)

The retrosynthesis for target 452 from compound 455 is identical in methodology for the previous target 428 from 431, with the only difference being the absence of a nitrile on the C-1 position (Scheme 167). Compound 455 can be synthesized from 437 by two consecutive reduction steps (reductive hydrolysis of the nitrile to an aldehyde and subsequent aldehyde reduction to an alcohol). A key disadvantage to this approach is that target 452 has carboxylic acid derivatives missing on the C-1 and thiohemiacetal centre, but if this strategy were successful, it would be revised to include both carboxylic acid derivatives.
We started this sequence with the attempted reduction of the nitrile moiety in 437 to an aldehyde using a range of metal hydride reagents (Scheme 179 and Table 34).

![Chemical structures](image)

**Scheme 179**: Attempted nitrile reductions of 437.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^{98})</td>
<td>DIBAL (1M in DCM, 1 equiv.), DCM, -78 °C, 3 h, then 1M NH(<em>4)Cl(</em>{aq})</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>2(^{99})</td>
<td>LiAlH(_4) (1 equiv.), EtOH (3 equiv.), Et(_2)O, 0 °C, 437, 0 °C to rt, 16 h, then 1M NH(<em>4)Cl(</em>{aq})</td>
<td>SM</td>
</tr>
<tr>
<td>3(^{100})</td>
<td>Red-Al(^\circledR) (3.5 M in toluene, 1 equiv.), toluene, -78 °C to 0 °C, 2 h, then 1M tartaric acid(_{aq})</td>
<td>78% 457, 4% 458</td>
</tr>
</tbody>
</table>

**Table 34**: Conditions and results tested for the attempted nitrile reductions of 437.

Initially, from a modified procedure in the literature,\(^ {98}\) a diisobutylaluminium hydride (DIBAL) based reduction was attempted (entry 1). Unfortunately, despite the relatively mild conditions (low temperature and limited equivalents of DIBAL), a complex mixture resulted. Though there were distinctive aldehyde proton signals (H-COR) in the \(^1\)H NMR spectrum of the crude complex mixture, there were no pure isolated products after purification by column chromatography.

We then tried an alkoxyaluminate hydride-based reduction (entry 2).\(^ {99}\) In this reaction, we had to first synthesize lithium tris(ethoxy)aluminium hydride (LTEA) *in-situ* (from reaction between
absolute ethanol and LAH) prior to the addition of nitrile 437. However, these conditions were too mild for any reduction to take place as only starting material was observed.

Finally, we used Red-Al® for the nitrile reduction according to a modified procedure from Balskus and Jacobsen. Unfortunately, the production of amines 457 and 458 showed that under these conditions over-reduction readily occurred (i.e. reduction did not cease at the imine stage). The formation of amine 457 can be explained by silyl ether cleavage of 458 occurring during the acidic work-up.

These disappointing reductive hydrolysis results led us to abandon this route.

**Exo-Glycal Route**

The failure to synthesize compound 442 by the reaction between formaldehyde and the tribenzylated nitrile 437 using nitrile-anion chemistry steered us to an alternative synthetic strategy. In this strategy, we aimed to synthesize 442 by the functionalization of an exo-glycal (Scheme 180).
Scheme 180: Retrosynthesis for target 459 from D-galactose 433 in the Exo-Glycal route.

The retrosynthetic analysis for target 459 from compound 442 is identical to 428 from 431 in the D-galactose route (Scheme 167). Compound 442 could be made by ring opening of the anomeric epoxy acetal in 462 using a cyanide nucleophilic source (e.g. TMSCN) and a Lewis acid. Compound 462 could derive from an electrophilic epoxidation of the exo-glycal 463, which in turn could be made by a Bamford-Stevens reaction of tosylhydrazone 464. Reductive hydrolysis of the nitrile in 437 to an aldehyde, followed by trapping with tosylhydrazide, could form hydrazine 464. Finally compound 437 has already been synthesized from D-galactose in five steps in the D-galactose route.

This synthetic approach was largely inspired by the research carried out by Tóth et al. In their work, they successfully synthesized exo-glycal 466 from compound 64 in two steps (Scheme 181). In the first step, the authors subjected 64 to Raney-nickel and sodium
hypophosphite in aqueous acetic acid and pyridine alongside tosylhydrazide. These conditions caused the reduction of the nitrile moiety to an imine, which was then hydrolysed *in-situ* to an aldehyde. Due to the presence of tosylhydrazide, the aldehyde was then trapped with this reagent to form tosylhydrazone 465. In the second step, tosylhydrazone 465 was treated with an excess of sodium hydride (10 equiv.) in 1,4-dioxane under reflux, which triggered an *in-situ* generation of a C-glycosylmethylene carbene, which eventually yielded *exo*-glycal 466 in an aprotic Bamford-Stevens reaction.

![Scheme 181: Tóth and co-workers’ two-step synthesis of *exo*-glycal 466 from 64.](image)

We therefore aimed to apply Tóth et al.’s methodology to compound 437. Unfortunately, when subjecting 437 to Tóth and co-workers’ reductive hydrolysis conditions, the desired tosylhydrazone 464 was not isolated due to the production of a complex mixture (Scheme 182).

![Scheme 182: Attempted synthesis of tosylhydrazone 464 from 437.](image)

Confronted with these failures, we devised an alternative route (simply by changing the order of steps) to the tribenzylated *exo*-glycal 463 (Scheme 183). In this route, we planned to copy Tóth and co-workers’ two-step synthesis of 466 from glycosyl cyanide 64 (64 has already been
successfully synthesized in the D-galactose route). Then compound 466 would be deacetylated to form 467. Selective silyl protection of the primary hydroxyl group in 467 followed by perbenzylation would furnish the tribenzylated exo-glycal 463.

Scheme 183: Proposed five-step synthesis of the tribenzylated exo-glycal 463 from 64.

Using Tóth and co-workers’ conditions, we firstly synthesized tosylhydrazone 465 in 83% yield (Scheme 184). We then performed a Bamford-Stevens reaction on 465 to form exo-glycal 466 in yields up to 72%. The reaction time was concluded to be pivotal for the yield (of both the final product after purification and the crude). For example, reaction times longer than 30 minutes led to a decrease in yield, hinting at possible product decomposition under the reaction conditions, whereas reaction times that were too short led to poor conversion. Treatment of compound 466 with sodium methoxide in methanol afforded the deacetylated product 467 in quantitative yield.

Scheme 184: Three-step synthesis of 467 from 64.
With compound 467 in hand, we proceeded to the regioselective TIPS protection (Scheme 185 and Table 35).

Scheme 185: Selective silyl protection attempts of 467.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions a</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Imidazole (4 equiv.), TIPSCI (2 equiv.), DMF</td>
<td>43% 469, 19% 470, 11% 471</td>
</tr>
<tr>
<td>2</td>
<td>Imidazole (3 equiv.), TIPSCI (1.5 equiv.), DMF</td>
<td>67% 471, 13% 468</td>
</tr>
<tr>
<td>3</td>
<td>Imidazole (2.2 equiv.), TIPSCI (1.1 equiv.), DMF</td>
<td>64% 471, 11% 468</td>
</tr>
<tr>
<td>4</td>
<td>K₂CO₃ (2.2 equiv.), TIPSCI (1.1 equiv.), DMF</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>TIPSCI (1.1 equiv.), Pyridine</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>6</td>
<td>2,6-lutidine (2 equiv.), TIPSOTf (1.1 equiv.), DMF</td>
<td>3% 472</td>
</tr>
</tbody>
</table>

a reaction time: 24 h, temperature: 0 °C to rt.

Table 35: Conditions and results reported for the attempted TIPS protection of 467.

We initially applied the same optimized conditions used previously for the synthesis of 436 in the D-galactose route (entry 1). Under these conditions, however, no trace of the desired 468 was
observed; instead compounds 469, 470 and 471 were isolated. The disilylated compounds 469 and 471 were formed due to the large number of equivalents of TIPSCI used (2 equiv.). The probable mechanism to account for these side products arise from the basicity of the exo-glycal (Scheme 186).

**Scheme 186:** Proposed mechanism for the formation of side-products 469, 470 and 471.

The silylation of alcohol leads to the formation of acid (effectively HCl), although it would be expected that the imidazole would neutralize these acidic conditions. Nevertheless, under these conditions, the exo-glycal was protonated to form an oxocarbenium ion. The imidazole then attacked the oxocarbenium ion in nucleophilic fashion to form the undesired side-products 469, 470 and 471 after proton transfer.

The number of equivalents of imidazole and TIPSCI were then reduced (entries 2 and 3). The use of lower equivalents of TIPSCI (1.5 equiv. and 1.1 equiv.) led to no disilylated products being produced. While we isolated the desired product 468 in these entries, the yields were still very low (13% and 11% respectively) because of the large production of compound 471.

In order to suppress this side reaction, we replaced the imidazole base with potassium carbonate (entry 4). This is because potassium carbonate is a stronger base (will more likely neutralize any acid and reduce the risk of the exo-glycal being protonated), and also the carbonate or
bicarbonate ion is a poor nucleophile (to prevent any nucleophilic addition on the oxocarbenium ion if it forms). However, under these conditions, only a complex mixture was formed.

The TIPS protection was then attempted in a pyridine solvent (entry 5). We anticipated that the large excess of pyridine would ‘mop-up’ any protons in solution decreasing the likelihood of the exo-glycal being protonated (entry 5). Unfortunately, since a complex mixture resulted, the desired product 468 was not isolated.

Finally, a standard TIPS protection using the more electrophilic TIPSOTf and non-nucleophilic base 2,6-lutidine was attempted (entry 6). These conditions led to a complex mixture with the only product isolated being compound 472 in 3% yield. The production of a complex mixture in these conditions suggests that many undesired side-reactions occurred. We speculate that the formation of 472 was due to the exo-glycal being protonated under the TIPS protection conditions to form the oxocarbenium ion, which in turn during the work-up underwent nucleophilic attack by water.

The assignment of the stereochemical configuration on the C-1 position in by-products 469, 470, 471 and 472 was inferred from NOESY spectra analysis (see below).

In compounds 469, 471 and 472, a nOe was observed between the methyl group of C-1 and H-C-2 (Figure 17), which suggests a cis relationship between the methyl group and H-C-2. Furthermore, with respect to 469 and 471, a nOe was seen between protons of the imidazole moiety and H-C-5, which suggests that these also have a cis relationship. This was unlike compound 470, where the observed nOes (between H-C-2 and protons of the imidazole moiety as well as between the methyl group and H-C-2) suggested a trans relationship between the methyl group and H-C-2.

![Figure 17](image-url): NOESY spectra analysis to assign stereochemistry on the C-1 position in 469, 470, 471 and 472.
The yield for 469 was higher than its epimer 470. Likewise, the epimers (defined in this context as opposite stereochemistry on the C1 position) for 471 and 472 were not even isolated. These results imply that the nucleophile (e.g. imidazole or a water molecule) attacks the bottom face of the oxocarbenium ion more favourably than the top face.

The stereoselectivity can be explained by considering the conformations of the oxocarbenium ion (Figure 18). The most stable conformations of the oxocarbenium ion would be the $^3$H$_4$ and $^4$H$_3$ half chairs (with the former being less stable due to the 1,3-pseudo axial – axial interactions between the OR and CH$_2$OTIPS groups). The selectivity is under kinetic control. There is less steric hindrance to the nucleophile when it attacks the bottom face of the more stable $^4$H$_3$ conformation (leading to a less sterically-congested chair-like transition state); hence bottom face attack is faster than top face attack. Under these conditions, bottom face attack on the $^3$H$_4$ conformation and top face attack on the $^4$H$_3$ conformation contribute little to the product distribution. This is because these non-axial nucleophilic attacks lead to high energy unstable twist-boat like transition states.

**Figure 18:** Proposed rationale for the stereoselectivity of nucleophilic attack on the oxocarbenium ion formed in the TIPS protections.

We pondered whether to try protecting groups other than TIPS (e.g. Trt, Bn, PMB etc.), but we anticipated the same problems regarding the basicity/reactivity of the exo-glycal in the protection conditions.
We concluded that due to the reactivity of the \textit{exo}-glycal in these TIPS protection conditions, the \textit{exo}-glycal 466 should be functionalized (i.e. epoxidation on the \textit{exo}-glycal followed by ring opening the epoxide) prior to any of the protections; hence the route to compound 442 was modified (Scheme 187).

![Scheme 187: Proposed alternative synthetic route to compound 442.](image)

Methodologies: a) epoxidation; b) epoxide ring-opening; c) tritylation; d) deacetylation; e) selective TIPS protection; f) perbenzylolation; g) detritylation.

We subjected 466 to standard electrophilic epoxidation conditions using mCPBA in dichloromethane and aqueous sodium bicarbonate,\textsuperscript{103} which furnished epoxide \textit{\alpha}-473 in 98% yield (Scheme 188).
The stereochemistry on the anomeric centre of epoxide $\alpha$-473 was determined from the NOESY spectrum (Figure 19). The significant nOe between one of the methylene protons of the epoxide and H-C₂ indicated a cis relationship between these.

**Figure 19:** NOESY spectrum analysis to assign stereochemistry on the anomeric centre of epoxide $\alpha$-473.

The epoxide ring-opening reaction with TMSCN was then attempted using the same conditions that Nishikawa et al. applied for their anomeric epoxy acetal 187 (Scheme 36). When subjecting $\alpha$-473 to these conditions, however, only a complex mixture formed, with 479 being the only product isolated in 4% yield after purification (Scheme 189).

**Scheme 189:** Attempted synthesis of 474.
Unfortunately, due to the stereochemistry at the C-1 position, we could not continue the route with 479. The stereochemistry on the C-1 position in 479 was deduced by analysis from its NOESY spectrum. The strong nOe observed between the methylene protons of the CH₂OTMS moiety with H-C-3 and H-C-5 suggested that these have a cis relationship (Figure 20).

![Image of structure 479]

**Figure 20:** NOESY spectrum analysis to assign stereochemistry on the C-1 position in 479.

We then tried conventional epoxide ring-opening reactions of α-473 with TMSCN using a range of Lewis acids (Scheme 190 and Table 36).

![Image of reaction scheme]

**Scheme 190:** Epoxide ring opening attempts of α-473.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;105&lt;/sup&gt;</td>
<td>SnCl₄</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>AlCl₃</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>ZnCl₂</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>BF₃·Et₂O</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>SM</td>
</tr>
</tbody>
</table>

**Table 36:** Conditions and results reported for the epoxide ring-opening attempts of α-473.
Regrettably, with each Lewis acid (entries 1 to 4), only complex mixtures were observed, which implied that many side-reactions occurred. In an attempt to reduce the number of side reactions, we performed the reaction without any Lewis acid (entry 5), though these conditions seemed too mild to trigger any reaction, since only starting material was recovered.

The lack of success in the ring-opening epoxide reaction forced us to once again re-evaluate the methodology. A new synthetic strategy towards target 452 was postulated, which involved a hydroboration-oxidation reaction on exo-glycal 466 instead of an epoxidation (Scheme 191).

![Scheme 191: Retrosynthesis for target 452 from 466.](image)

The retrosynthesis for target 452 from 455 has already been analysed in a previous route (Scheme 178). Compound 455 could be made from 480 in three steps: selective TIPS protection;
perbenzylolation; and detritylation. Deacetylation and tritylation of compound 481 could yield 480. Finally, a hydroboration-oxidation reaction on 466 could afford 481.

Thus, we attempted the hydroboration-oxidation reaction on 466 (Scheme 192 and Table 37).

![Scheme 192: Hydroboration-oxidation attempts of 466.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydroboration Reagent</th>
<th>Oxidative Work-Up a</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 106</td>
<td>BH3,THF</td>
<td>30% H2O2 (aq)</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>BH3,DMS</td>
<td>30% H2O2 (aq)</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3</td>
<td>9-BBN</td>
<td>30% H2O2 (aq)</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>BH3,THF</td>
<td>1:1 EtOH:THF, phosphate buffer (0.1 M, pH 7), 30% H2O2 (aq)</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5</td>
<td>BH3,DMS</td>
<td>1:1 EtOH:THF, phosphate buffer (0.1 M, pH 7), 30% H2O2 (aq)</td>
<td>Decomposition</td>
</tr>
<tr>
<td>6</td>
<td>9-BBN</td>
<td>1:1 EtOH:THF, phosphate buffer (0.1 M, pH 7), 30% H2O2 (aq)</td>
<td>10% 481 b</td>
</tr>
</tbody>
</table>

aReaction time: 3 h; temperature: 0 °C to rt. b 481 was part of an inseparable mixture with an unknown compound (481:unknown compound, 7:1). Assuming the unknown compound is an isomer of 481, the number of moles of 481 in the inseparable mixture (used for the yield calculation) were calculated from molar ratios seen in the 1H NMR spectrum of the inseparable mixture.

**Table 37**: Conditions and results reported for the hydroboration-oxidation attempts of 481.

We firstly tried the hydroboration using BH3,THF (entry 1) according to a procedure from the literature.106 Once full consumption of the starting material was observed by TLC visualization
(hinting that the organoborane intermediate was synthesized), we then performed the oxidative work-up. Surprisingly, after work-up, a complex mixture was observed with a very low crude yield (7%). Replacing the hydroboration agent with BH$_3$.DMS made no difference to the result (entry 2). We pondered whether acetate hydrolysis occurred during the oxidative work-up in both entries 1 and 2; this would lead to the hydrolysed product dissolving in the aqueous layer rather than the organic layer in the work-up, which would account for the very low crude yields. Hence, we evaporated the aqueous layer (after quenching any remaining H$_2$O$_2$ with sodium sulfite) under reduced pressure, but no acetyl-hydrolysed products were observed.

9-BBN was then used as the hydroboration agent (entry 3). In this entry, while the crude yield increased dramatically (82%), there was no trace of the desired product 481 observed in the crude complex mixture. A possible reason for the apparent increase in crude yield could be due to the production of cis-1,5-cyclooctanediol (a by-product from 9-BBN hydrolysis).

The absence of any hydrolysed products upon evaporation of the aqueous layer of the work-up under reduced pressure for entries 1 and 2, and the higher crude yield when using 9-BBN in entry 3, each suggest that acetate hydrolysis may not have occurred in the work-up. Nevertheless, we aimed to repeat all the hydroboration-oxidations using milder oxidative work-up conditions involving a phosphate buffer according to the literature (entries 4 to 6), in order to see if that could make a positive difference to the result.

The milder oxidative work-up for the hydroboration-oxidations using BH$_3$.THF and BH$_3$.DMS unfortunately made no difference (entries 4 and 5). For the 9-BBN hydroboration-oxidation, a complex mixture still resulted (entry 6), but the desired product was isolated after column chromatography in the form of an inseparable mixture with an unknown compound (481:unknown compound, 7:1), albeit in very low yields (10%). We speculate that the unknown compound is a stereoisomer of 481.

NMR analysis was used to assign the stereochemistry at the C-1 position in 481. For example, the high $^3$J$_{1,2}$ (10 Hz) suggested a diaxial and thus trans relationship between H-C-1 and H-C-2. Furthermore, the observed nOes between H-C-1 with H-C-3 and H-C-5 from the NOESY spectrum suggested that these protons are cis (Figure 21).
Figure 21: NOESY spectrum analysis to assign stereochemistry at the C₁ position in 481.

Conclusion

At the end of our studies towards the synthesis of tagetitoxin, numerous synthetic routes were investigated, leading to several interesting intermediates (Figure 22).
In the nitrile-Wittig route, we eventually formed alkene $329$ from retro-Michael methodology after difficulties in directly synthesizing it from Wittig and HWE olefinations of DAM $234$. Reactivity issues, though, arose with $329$ and the protected derivatives $339$ and $340$ in

*Figure 22: The key intermediates formed during the project.*
electrophilic epoxidations, halogenations and/or oxymercuration-demercuration reactions presumably due to the alkene being too electron-deficient. The lack of reactivity of these electron-deficient alkenes in the nucleophilic epoxidations, however, was surprising and not clearly understood.

In the vinyl-transetherification route, the diacetyl 357 and dibenzoyl α-359 were each obtained after four steps from DAM 234. Regrettably, the C-glycosylation reactions of these intermediates with TMSCN failed (with or without the use of Lewis acids), prompting us to reject this strategy.

In the silyl enol ether route, we replicated Chai and co-workers’ three-step synthesis of glycal 366 from DAM 234 (though with modification of the conditions in the HWE olefination and anomeric dehydration steps). Similarly to the nitrile-Wittig route, however, the failure in hydrating glycal 366 in an oxymercuration-demercuration reaction, led us to conclude that the alkene in glycal 366 was too unreactive with electrophilic mercuric reagents. This was surprising considering Yamaguchi and co-workers’ success in their oxymercuration-demercuration of glycals 374.

The dithiane-reduction route was the strategy that was closest in obtaining the synthetic targets 379, 400 and 407. The lack of success in the thioacetate deprotections and concomitant cyclizations of the liberated thiol/thiolate onto a ketone or sulfonate ester in substrates 389 (and analogues) and 402 (and analogues) was a major setback. Changing the cyclization strategy to the nucleophilic displacement of two sulfonate esters in substrate 415 (and analogues) with a sulfide anion also failed. The failure of these three cyclization strategies was attributed to the presence of the isopropylidene groups hindering the cyclization by placing steric constraints on ring closure. We therefore aimed to deprotect the thioacetate functionality on a substrate without the isopropylidene groups. However, since efforts to hydrolyse both isopropylidene groups in ketone 394 were unsuccessful, we ceased work on this route and focused our efforts on a new strategy not involving isopropylidene groups.

In the D-galactose route, the tribenzylated nitrile 437 was isolated after five synthetic steps from D-galactose 433. To our disappointment, we were unable to form the nitrile anion of 437 under a variety of conditions, which prevented any reaction with formaldehyde. These poor results, prompted us to synthesize the tribenzylated methyl ester 449, but after trying numerous conditions, benzylations of 449 failed because of either undesired side-reactions or no reactions.
taking place at all. Endeavours to reductively hydrolyse the nitrile of 437 using a variety of metal hydride reagents did not afford the desired aldehyde, which forced us to abandon this route.

Finally, in the exo-glycal route, compound 467 was successfully synthesized in five steps from D-galactose. Attempts to protect exo-glycal 467 proved difficult, however, due to the basic nature of the exo-glycal under these conditions leading to many undesired side-reactions. We therefore aimed to functionalize the exo-glycal prior to any protections. This allowed us to isolate epoxide α-473, but we were unsuccessful in ring opening the epoxide with TMSCN and a Lewis acid. We thus performed a hydroboration on exo-glycal 466, which furnished 481, though in low yield and inseparable with an unknown compound.

**Future Work**

The main objective of this project was the synthesize targets 323a and 323b (Figure 10) which both contain the bicyclic core of the proposed structure of tagetitoxin. While we did not achieve this feat, the hydroboration-oxidation pathway in the exo-glycal route is promising for future research.

Due to the poor yield (and purity) of 381 (10%), the initial goal in any future work should be the optimization of the hydroboration-oxidation of 466 using 9-BBN (Scheme 193). This might involve changing the equivalents of 9-BBN and/or temperature of the reaction.

![Reaction diagram](image)

**Scheme 193**: Synthesis of 481 by the hydroboration-oxidation of 466 using 9-BBN.

If this reaction can be optimized, the route to target 452 should be continued (Schemes 191 and 194). If target 452 were to be synthesized, the route should be revised and altered to install carboxylic acid derivatives on the C₁ position and thiohemiacetal centre.
If, however, the hydroboration-oxidation reaction cannot be optimized, then an alternative route towards intermediate 455 should be investigated (Scheme 195).
We have already made compound 64 from 433 in the D-galactose route. Furthermore, Dent et al. have previously synthesized the imidazolidine derivative 65 from 64 by a Raney-nickel and sodium hypophosphate-based reductive hydrolysis alongside N,N′-Diphenylethylediamine (Scheme 9). A subsequent three-step sequence of deprotections and protections would lead to compound 489. Unmasking of the aldehyde in 489 could then be achieved by imidazolidine hydrolysis; typical conditions would involve using p-TsOH (2-3 equiv.) in DCM at 0 °C to rt. Finally, reduction of the aldehyde 490 to alcohol 455 could be achieved using a metal hydride reductant such as NaBH₄.

Scheme 195: Alternative synthetic route towards intermediate 455.
References for Results and Discussion Chapter


Experimental
General Experimental Details

Reagents and Solvents

All reagents obtained commercially were used without any further purification, unless otherwise stated. Triethylamine was stored over sodium hydroxide pellets.

For reactions performed under anhydrous conditions, solvents were obtained commercially dry except for: dichloromethane which was distilled over calcium hydride, tetrahydrofuran which was distilled under an argon atmosphere from the sodium/benzophenone ketyl radical, toluene which was dried over sodium and then distilled, acetonitrile which was stored under an argon atmosphere over activated MS 3Å for 24 hours, methanol which was stored under an argon atmosphere over activated MS 3Å for 24 hours, and N,N-dimethylformamide which was dried over activated MS 4Å overnight, vacuum distilled and then stored over activated MS 4Å under an argon atmosphere. Petroleum ether 40/60 was distilled before use to remove higher boiling point impurities. Petroleum ether 40/60 has been denoted as petrol.

Extractions were carried out using the reported organic solvent equivolumetric, unless stated otherwise.

Apparatus

For reactions requiring anhydrous conditions, glassware was flame-dried and allowed to cool to room temperature under a stream of argon or nitrogen. The reaction was then performed under an atmosphere of argon or nitrogen.

All reactions were carried out at room temperature unless otherwise stated.

Chromatography

Flash column chromatography on silica gel was carried out using Material Harvest Silica Gel 60 with 40-63 μm particle size. Individual solvent systems are reported in the experimental procedures.

Thin layer chromatography (TLC) was carried out on Merck aluminium backed plates coated with Kieselgel 60 F254 silica gel. The plates were visualized by irradiation of UV light (254nm)
and/or staining by aqueous potassium permanganate solution, ethanolic solution of phosphomolybdic acid or ethanolic solution of vanillin.

**Compound Characterization Analysis**

Infrared spectra were obtained using a Perkin Elmer Spectrum 100 Fourier Transformation-Infrared Spectrometer. Samples were dissolved in dichloromethane and applied onto sodium chloride plates as thin films.

High resolution mass spectra were acquired from the EPSRC UK National Mass Spectrometry Facility at the University of Swansea.

Melting points were carried out on a Büchi B-545 instrument.

Optical rotation measurements were obtained with a Bellingham and Stanley ADP-440 polarimeter operating at the sodium (D) line emission ($\lambda=589$ nm) at the reported temperature. The cell path length was 0.25 dm. The solutions for these measurements were prepared in volumetric flasks using solvents of spectrophotometric grade.

Proton, carbon and fluorine NMR experiments were carried out at 500, 126 and 471 MHz respectively using a Bruker Advance III 500 MHz NMR spectrometer or at 400, 101 and 376 MHz using a Bruker Ultrashield 400 MHz NMR spectrometer. Chemical shifts were reported in parts per million (ppm) relative to the residual solvent peak. Abbreviations for signals in proton NMR are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants (J values) are reported in Hertz (Hz).

**Numbering System**

The assignments of the NMR spectroscopy measurements for any compound with a pyranose or furanose core, follow the standard numbering system ([Figure 23](#)).

![Figure 23: Numbering system used in experimental detail.](#)

For all other compounds, the numbering system is designed by the author.
Concentrated sulfuric acid (14 ml) was added to a stirred suspension of D-mannose 235 (20 g, 110 mmol) in anhydrous acetone (600 ml). After stirring the reaction mixture overnight, the red coloured solution was neutralized with anhydrous sodium carbonate and filtered. The filtrate was heated under reflux for 1 hour with activated charcoal and sodium carbonate (2-3 g). After filtration through a pad of celite, the filtrate was evaporated under reduced pressure to give a crude colourless solid. Recrystallization from diethyl ether and petrol furnished the title compound as a colourless solid (26.652 g, 92%); IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3432, 2978, 2947, 2900, 1458, 1438, 1373, 1227, 1203, 1070; $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 1.32 (s, 3H, CH$_3$ Isopropylidene), 1.37 (s, 3H, CH$_3$ Isopropylidene), 1.45 (s, 3H, CH$_3$ Isopropylidene), 1.46 (s, 3H, CH$_3$ Isopropylidene), 3.04 – 3.13 (m, 1H, OH), 4.04 (dd, $J$ = 8.7, 4.8 Hz, 1H, H’-C$_6$), 4.08 (dd, $J$ = 8.7, 6.2 Hz, 1H, H’-C$_6$), 4.18 (dd, $J$ = 7.2, 3.6 Hz, 1H, H-C$_4$), 4.40 (ddd, $J$ = 7.2, 6.2, 4.8 Hz, 1H, H-C$_5$), 4.61 (d, $J$ = 5.9 Hz, 1H, H-C$_2$), 4.80 (dd, $J$ = 5.9, 3.6 Hz, 1H, H-C$_3$), 5.37 (d, $J$ = 2.5 Hz, 1H, H-C$_1$); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 24.6 (1C, CH$_3$ Isopropylidene), 25.2 (1C, CH$_3$ Isopropylidene), 26.0 (1C, CH$_3$ Isopropylidene), 27.0 (1C, CH$_3$ Isopropylidene), 66.7 (1C, C$_6$), 73.4 (1C, C$_5$), 79.8 (1C, C$_4$), 80.4 (1C, C$_3$), 85.6 (1C, C$_2$), 101.4 (1C, C$_1$), 109.2 (1C, C$_q$ Isopropylidene), 112.8 (1C, C$_q$ Isopropylidene).

The data is in agreement with literature reference.\(^1\)
Chloroacetonitrile (2.4 ml, 38.2 mmol, 1 equiv.) was added dropwise to a stirred mixture of triphenylphosphine 330 (10 g, 38.2 mmol) in EtOAc (30 ml) at rt. The reaction mixture was then heated under reflux for 3 hours. After cooling to rt, the mixture was filtered and the precipitate was washed with Et₂O to afford a pure colourless solid (11.73 g, 91%); mp 260 – 264 °C decomposition [lit. 268 – 270 °C],² [lit. 263 °C decomposition]³; IR ν_{max} (film)/cm⁻¹: 3056, 3010, 2972, 2715, 2251, 1586, 1439, 1113, 723; ¹H NMR (500 MHz, DMSO) δ 6.07 (d, J = 15.9 Hz, 2H, CH₂), 7.81 – 7.93 (m, 12H, 12 X H-C₅), 7.96 – 8.02 (m, 3H, 3 X H-C₅). ¹³C NMR (126 MHz, DMSO) δ 14.3 (d, J = 55.1 Hz, 1C, CH₂), 112.9 (d, J = 9.2 Hz, 1C, C₅₃ Nitrile), 116.3 (d, J = 88.7 Hz, 3C, 3 X C₅), 130.6 (d, J = 13.2 Hz, 6C, 6 X C₅), 133.8 (d, J = 10.9 Hz, 6C, 6 X C₅), 136.0 (d, J = 3.0 Hz, 3C, 3 X C₅).

The data is in agreement with literature reference.²
2-((Triphenylphosphoranylidene)acetonitrile (332)$^2$

Et$_3$N (12.3 ml, 87.9 mmol, 2.53 equiv.) was added to a stirred suspension of 331 (11.73 g, 34.8 mmol) in dry DCM (160 ml). After stirring the suspension for 30 minutes, water (20 ml) was then added. The layers were then separated, and the organic phase was washed with water (2 x 20 ml). The organic phase was dried over anhydrous Na$_2$SO$_4$, filtered and the solvents were removed under reduced pressure. Recrystallization from toluene gave the title compound as a colourless solid (8.70 g, 74%); mp 188 – 190 ºC [lit. 195 – 197 ºC]$^2$, [190 – 192 ºC]$^4$; IR $\nu$$_{\text{max}}$(film)/cm$^{-1}$: 3052, 2138, 2972, 1435, 1105, 714; $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 1.58 (s, 1H), 7.44 – 7.71 (m, 15H); $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ -2.0 (d, $J$ = 136.2 Hz, 1C, CH), 127.5 (d, $J$ = 91.8 Hz, 3C, 3 X C$_{AR}$), 129.2 (d, $J$ = 12.3 Hz, 6C, 6 X C$_{AR}$), 132.7 (3C, 3 X C$_{AR}$), 132.9 (d, $J$ = 10.1 Hz, 6C, 6 X C$_{AR}$).

The data is in agreement with the literature reference.$^2$
t-BuOK (3.88 g, 34.6 mmol, 1.5 equiv.) was added to a stirred solution of diethyl cyanomethylphosphonate (5.6 ml, 34.6 mmol, 1.5 equiv.) in dry THF (115 ml) at 0 °C. The mixture was stirred for 30 minutes at 0 °C. To this solution was added a solution of 234 (6.0 g, 23.1 mmol) in dry THF (156 ml) slowly. The reaction mixture was then warmed to rt and stirred overnight. The mixture was then treated with water (ca. 120 ml) and DCM (ca. 120 ml). The layers were separated and the aqueous layer was extracted with DCM twice. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO₄. Filtration and removal of the solvent under reduced pressure furnished a crude colourless solid. Purification by flash column chromatography on silica gel (petrol:EtOAc, 3:1) afforded an inseparable mixture (α:β, 1:3) of diastereomers 333 (6.429 g, 98%); IR ν max (film)/cm⁻¹: 2987, 2938, 2878, 2253, 1373, 1068; ¹H NMR (400 MHz, Chloroform-d) δ 1.33 (s, 3H, CH₃ Isopropylidene, β isomer), 1.35 (s, 3H, CH₃ Isopropylidene, α isomer), 1.37 (s, 6H, CH₃ Isopropylidene, both isomers), 1.44 (s, 6H, CH₃ Isopropylidene, both isomers), 1.48 (s, 3H, CH₃ Isopropylidene, β isomer), 1.50 (s, 3H, CH₃ Isopropylidene, α isomer), 2.54 (d, J = 6.4 Hz, 2H, CH₂, α isomer), 2.72 (d, J = 6.7 Hz, 2H, CH₂, β isomer), 3.58 (dd, J = 7.4, 3.6 Hz, 1H, H-C-4, β isomer), 3.83 (td, J = 6.7, 3.7 Hz, 1H, H-C-1, β isomer), 3.98 (dd, J = 7.4, 3.7 Hz, 1H, H-C-4, α isomer), 4.01 – 4.11 (m, 4H, H-C-6, H'-C-6, both isomers), 4.34 (td, J = 6.4, 1.3 Hz, H-C-1 α isomer), 4.36 - 4.41 (m, 2H, H-C-5 both isomers), 4.66 - 4.72 (m, 2H, H-C-2, both isomers), 4.80 (dd, J = 6.0, 3.6 Hz, 1H, H-C-3, β isomer), 4.87 (dd, J = 6.0, 3.7 Hz, 1H, H-C-3, α isomer). ¹³C NMR (101 MHz, CDCl₃) δ 17.7 (1C, CH₂, α isomer), 20.8 (1C, CH₂, β isomer), 24.6 (1C, CH₃ Isopropylidene, β isomer), 24.8 (1C, CH₃ Isopropylidene, α isomer), 25.2 (1C, CH₃ Isopropylidene, α isomer), 25.3 (1C, CH₃ Isopropylidene, β isomer), 25.7 (1C, CH₃ Isopropylidene, β isomer), 26.9 (1C, CH₃ Isopropylidene, α isomer), 27.0 (1C, CH₃ Isopropylidene, both isomers), 66.8 (1C, C-6, β isomer), 66.9 (1C, C-6, α isomer), 73.0 (1C, C-5, β isomer), 73.3 (1C, C-5, α isomer), 76.9 (1C, C-1, β isomer), 80.3 (1C, C-1, α isomer), 80.6 (1C, C-2, β isomer), 80.8 (1C, C-3, β isomer), 80.9 (1C, C-3,
\( \alpha \) isomer, 81.6 (1C, C-4, \( \alpha \) isomer), 82.2 (1C, C-4, \( \beta \) isomer), 84.6 (1C, C-2, \( \alpha \) isomer), 109.3 (1C, C\textsubscript{q} Isopropylidene, \( \beta \) isomer), 109.5 (1C, C\textsubscript{q} Isopropylidene, \( \alpha \) isomer), 113.4 (1C, C\textsubscript{q} Isopropylidene, \( \beta \) isomer), 113.7 (1C, C\textsubscript{q} Isopropylidene, \( \alpha \) isomer), 116.9 (1C, C\textsubscript{q} Nitrile, \( \alpha \) isomer), 117.2 (1C, C\textsubscript{q} Nitrile, \( \beta \) isomer); HRMS (NSI-FTMS) \( m/z \) found for [M+NH\(_4\)]\(^+\): 301.1757; [C\(_{14}\)H\(_{21}\)NO\(_5\)+NH\(_4\)]\(^+\) requires 301.1758.
\((E)-3-((4R,5S)-5-((R)-2,2\text{-dimethyl}-1,3\text{-dioxolan-4-yl})(hydroxy)methyl)-2,2\text{-dimethyl}-1,3\text{-dioxolan-4-yl})\text{acrylonitrile} (E-329)\)

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\(n\text{-Butyl lithium (4.3 ml, 2.5 M in hexanes, 10.6 mmol, 3 equiv.) was added dropwise to a stirred solution of diisopropylamine (1.9 ml, 10.6 mmol, 3 equiv.) in dry THF (64 ml) at -78 °C. The solution was stirred for 1 hour at this temperature. A solution of 333 (1.008 g, 3.56 mmol) in dry THF (108 ml) at -78 °C was cannulated into the LDA solution. The dark orange solution was then stirred at -78 °C until TLC showed complete consumption of the starting material (~45 minutes). Glacial acetic acid (0.8 ml) and ethyl acetate (240 ml) were then added. The mixture was then warmed to rt slowly and then concentrated \textit{in vacuo}. Purification by flash column chromatography on silica gel (petrol:EtOAc, 5:1) afforded the title compound as a colourless oil (0.564 g, 56%); \([\alpha]_D^{25} = +31.1 \text{ (c 1.31 in CHCl}_3\text{); IR } \nu_{\text{max}} \text{(film)/cm}^{-1}: 3486, 2988, 2937, 2265, 1638, 1376, 1215, 1070; ^1\text{H NMR (400 MHz, Chloroform-d)} \delta 1.35 \text{ (s, 3H, CH}_3\text{Isopropylidene), 1.41 (s, 6H, 2 X CH}_3\text{Isopropylidene), 1.53 (s, 3H, CH}_3\text{Isopropylidene), 2.15 (d, } J = 8.3 \text{ Hz, 1H, OH), 3.40 (td, } J = 8.3, 2.3 \text{ Hz, 1H, H-C}_5\text{), 3.92 - 4.01 (m, 2H, H-C}_7\text{, H-C}_8\text{), 4.06 - 4.16 (m, 1H, H'-C}_7\text{), 4.47 (dd, } J = 7.4, 2.4 \text{ Hz, 1H, H-C}_4\text{), 4.76 (ddd, } J = 7.4, 5.4, 1.7 \text{ Hz, 1H, H-C}_3\text{), 5.66 (dd, } J = 16.2, 1.7 \text{ Hz, 1H, H-C}_1\text{), 6.88 (dd, } J = 16.2, 5.4 \text{ Hz, 1H, H-C}_2\text{); } ^{13}\text{C NMR (101 MHz, CDCl}_3\text{)} \delta 24.9 (1C, CH}_3\text{Isopropylidene), 25.3 (1C, CH}_3\text{Isopropylidene), 26.9 (1C, CH}_3\text{Isopropylidene), 27.0 (1C, CH}_3\text{Isopropylidene), 67.5 (1C, C}_7\text{), 70.5 (1C, C}_5\text{), 76.2 (1C, C}_6\text{), 76.6 (1C, C}_3\text{), 77.5 (1C, C}_4\text{), 101.7 (1C, C}_1\text{), 109.8 (1C, C}_q\text{Isopropylidene), 109.8 (1C, C}_q\text{Isopropylidene), 116.9 (1C, C}_q\text{Nitrile), 150.8 (1C, C}_2\text{); HRMS (NSI-FTMS) } m/z \text{ found for } [M+NH}_4^+ : 301.1758; [C}_{14}H_{21}NO_3+NH}_4^+ \text{ requires 301.1758.}
(E)-3-(((4R,5R)-5-((R)-(R)-2,2-dimethyl-1,3-dioxolan-4-yl)((isopropyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylonitrile (339)

IPDMSCI (0.67 ml, 3.97 mmol, 2.0 equiv.) was added dropwise to a mixture of alkene E-329 (0.562 g, 1.99 mmol) and imidazole (0.270 g, 3.97 mmol, 2.0 equiv.) in dry DCM at 0 °C. The reaction mixture was stirred for 24 hours at rt. The reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with DCM three times. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO₄. After filtration, the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 6:1) to furnish 339 as a pure colourless oil (0.622 g, 82%); [α]D²⁵ = + 64.2 (c 0.9 in CHCl₃); IR νmax (film)/cm⁻¹: 2988, 2940, 2866, 2226, 1635, 1372, 1079; ¹H NMR (500 MHz, Chloroform-d) δ 0.06 (s, 3H, CH₃ IPDMS), 0.07 (s, 3H, CH₃ IPDMS), 0.75 – 0.84 (m, 1H, H-CMe₂ IPDMS), 0.95 – 0.90 (m, 6H, 2 X CH₃ iPr(IPDMS)), 1.33 (s, 3H, CH₃ Isopropylidene), 1.37 (s, 3H, CH₃ Isopropylidene), 1.42 (s, 3H, CH₃ Isopropylidene), 1.50 (s, 3H, CH₃ Isopropylidene), 3.63 (dd, J = 8.9, 7.9 Hz, 1H, H-C-5), 3.77 (dd, J = 8.3, 7.4 Hz, 1H, H-C-7), 3.92 – 3.99 (m, 1H, H-C-6), 4.10 – 4.18 (m, 2H, H'-C-7, H-C-4), 4.69 (dd, J = 6.2, 4.4, 1.9 Hz, 1H, H-C-3), 5.67 (dd, J = 16.3, 1.9 Hz, 1H, H-C-1), 6.95 (dd, J = 16.3, 4.4 Hz, 1H, H-C-2); ¹³C NMR (126 MHz, CDCl₃) δ -3.6 (1C, CH₃ Me (IPDMS)), -3.0 (1C, CH₃ Me (IPDMS)), 15.4 (1C, CHMe₂ iPr (IPDMS)), 17.0 (1C, CH₃ iPr (IPDMS)), 17.1 (1C, CH₃ iPr (IPDMS)), 25.3 (1C, CH₃ Isopropylidene), 25.4 (1C, CH₃ Isopropylidene), 26.4 (1C, CH₃ Isopropylidene), 27.8 (1C, CH₃ Isopropylidene), 68.6 (1C, C-7), 72.9 (1C, C-5), 76.5 (1C, C-3), 77.4 (1C, C-6), 81.4 (1C, C-4), 101.5 (1C, C-1), 109.0 (1C, Cq Isopropylidene), 110.2 (1C, Cq Isopropylidene), 117.4 (1C, Cq Nitrile), 152.6 (1C, C-2); HRMS (NSI-FTMS) m/z found for [M+H]⁺: 384.2203; [C₁₉H₃₃NO₅Si+H]⁺ requires 384.2201.
(R)-((4R,5R)-5-((E)-2-cyanovinyl)-2,2-dimethyl-1,3-dioxolan-4-yl)((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl benzoate (340)

DMAP (0.039 g, 0.32 mmol, 0.2 equiv.) was added to a stirred solution of Et₃N (0.99 ml, 7.07 mmol, 4.42 equiv.) in dry DCM (12 ml) at 0 °C. Benzoyl chloride (0.62 ml, 5.30 mmol, 3.31 equiv.) was then added dropwise. To this solution at 0 °C, was then added a solution of E-329 (0.454 g, 1.60 mmol) in dry DCM (4 ml) dropwise. The reaction mixture was stirred at rt overnight. The reaction mixture was quenched with saturated aqueous NaHCO₃ and extracted with DCM three times. The combined organic extracts were washed with water, then brine, and dried over anhydrous Na₂SO₄. Filtration and removal of the solvent under reduced pressure afforded a crude residue. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 3:1) to furnish the title compound as a pure yellow oil (0.620 g, quant.); [α]₂⁵D = -29.7 (c 0.9 in CHCl₃); IR νmax (film)/cm⁻¹: 3072, 2988, 2229, 1724, 1372, 1268; ¹H NMR (500 MHz, Chloroform-d) δ 1.36 (s, 6H, 2 x CH₃ Isopropylidene), 1.42 (s, 3H, CH₃ Isopropylidene), 1.61 (s, 3H, CH₃ Isopropylidene), 3.98 (dd, J = 8.8, 6.2 Hz, 1H, H-C₇), 4.03 (dd, J = 8.8, 6.2 Hz, 1H, H-C₅), 4.34 (dt, J = 7.2, 6.2 Hz, 1H, H-C₆), 4.67 (dd, J = 7.6, 2.3 Hz, 1H, H-C₄), 4.85 (ddd, J = 7.6, 4.1, 2.1 Hz, 1H, H-C₁), 5.27 (dd, J = 7.2, 2.3 Hz, 1H, H-C₃), 5.47 (dd, J = 16.1, 2.1 Hz, 1H, H-C₁), 6.44 (dd, J = 16.1, 4.1 Hz, 1H, H-C₂), 7.43 – 7.50 (m, 2H, 2 x H-C₉AR), 7.56 – 7.64 (m, 1H, H-C₉AR), 8.01 – 8.06 (m, 2H, 2 x H-C₉AR); ¹³C NMR (126 MHz, CDCl₃) δ 25.0 (1C, CH₃ Isopropylidene), 25.5 (1C, CH₃ Isopropylidene), 26.6 (1C, CH₃ Isopropylidene), 26.9 (1C, CH₃ Isopropylidene), 66.5 (1C, C-₇), 71.0 (1C, C-₅), 75.2 (1C, C-₆), 75.6 (1C, C-₃), 76.8 (1C, C-₄), 101.0 (1C, C-₁), 109.7 (1C, C-₉ Isopropylidene), 109.8 (1C, C-₉ Isopropylidene), 116.2 (1C, C-₉ Nitrile), 128.6 (2 x C₉AR), 129.5 (1C, C₉AR), 129.9 (2C, 2 x C₉AR), 133.6 (1C, C₉AR), 148.2 (1C, C-₂), 165.7 (1C, C- Benzoyloxy); HRMS (NSI-FTMS) m/z found for [M+H]+: 388.1756; [C₂₁H₂₅NO₆+H]+ requires 388.1755.
(R)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)((4S,5R)-5-(2-methoxyvinyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (354)

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\text{OH} \quad \xrightarrow{\text{234}} \quad \text{OMe}
\]

\(\text{n-Butyl lithium (36.0 ml, 1.6M in hexanes, 57.6 mmol, 3 equiv.) was added dropwise to a stirred solution of diisopropylamine (8.1 ml, 57.6 mmol, 3 equiv.) in dry THF (140 ml) at -78 °C. After}
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\(\text{stirring for 1 hour at this temperature methoxymethyltriphenylphosphonium chloride (19.76 g,}
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\(\text{57.6 mmol, 3 equiv.) was then added cautiously portion wise. The red-coloured solution was}
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\(\text{then stirred for 1 hour at -78 °C. A solution of 234 (5.0 g, 19.2 mmol) in dry THF (40 ml) at -78 °C was added to the ylide-solution slowly via a cannula transfer. The resultant mixture was then}
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\(\text{warmed to rt gradually before being refluxed overnight. The reaction mixture was then cooled to}
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\(\text{rt and quenched with brine (ca. 60 ml), and the layers were then separated. The aqueous layer}
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\(\text{was extracted with Et}_2\text{O three times. The combined organic extracts were dried over anhydrous MgSO}_4\text{. Filtration and removal of the solvent in vacuo furnished a crude dark brown oil. The}
\]
\(\text{crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 6:1) furnishing an inseparable mixture (E:Z, 5:1) of geometric isomers of vinyl ether 354 as a yellow oil (3.125 g, 57%); IR }\nu_{\text{max}}\text{(film)/cm}^{-1}: 3530, 2987, 2937, 1655, 1372, 1212, 1070; \text{ }^1\text{H NMR (500 MHz, Chloroform}-d\text{)} \delta 1.35 \text{ (s, 6H, CH}_3\text{Isopropylidene, Both Isomers), 1.38 – 1.41 (m, 12H, 2 X CH}_3\text{Isopropylidene, Both Isomers), 1.50 (s, 3H, CH}_3\text{Isopropylidene, Z Isomer), 1.51 (s, 3H, CH}_3\text{Isopropylidene, Z Isomer), 2.17 (d, }J\text{ = 8.1 Hz, 1H, OH, Z Isomer), 2.20 (d, }J\text{ = 8.7 Hz, 1H, OH, E Isomer), 3.45 – 3.51 (m, 2H, H-C}_6\text{, Both Isomers), 3.61 (s, 3H, CH}_3\text{Methoxy, E Isomer), 3.63 (s, 3H, CH}_3\text{Methoxy, Z Isomer), 3.98 – 4.13 (m, 6H, H-C}_7\text{, H}^1\text{-C}_7\text{, H-C}_5\text{, Both Isomers), 4.30 (dd, }J\text{ = 7.4, 1.1 Hz, 1H, H-C}_4\text{, E Isomer), 4.34 (dd, }J\text{ = 7.4, 1.4 Hz, 1H, H-C}_4\text{, Z Isomer), 4.66 (dd, }J\text{ = 9.6, 7.4 Hz, 1H, H-C}_3\text{, E Isomer), 4.74 (dd, }J\text{ = 8.7, 6.3 Hz, 1H, H-C}_2\text{, Z Isomer), 5.05 (dd, }J\text{ = 12.7, 9.6 Hz, 1H, H-C}_2\text{, E Isomer), 5.27 (ddd, }J\text{ = 8.7, 7.4, 1.2 Hz, 1H, H-C}_3\text{, Z Isomer), 6.13 (dd, }J\text{ = 6.3, 1.2 Hz, 1H, H-C}_1\text{, Z Isomer), 6.64 (d, }J\text{ = 12.7 Hz, 1H, H-C}_1\text{, E Isomer); }^{13}\text{C NMR (126 MHz, CDCl}_3\text{) }\delta\text{ 24.4 (1C, CH}_3\text{Isopropylidene, E isomer), 24.5 (1C, CH}_3\text{Isopropylidene, Z isomer), 25.4 (1C, CH}_3\text{Isopropylidene, E isomer), 25.5 (1C, CH}_3\text{Isopropylidene, Z isomer), 26.8 (2C,}
CH₃ Isopropylidene, Both isomers), 26.9 (1C, CH₃ Isopropylidene, Z isomer), 27.0 (1C, CH₃ Isopropylidene, E isomer), 56.3 (1C, CH₃, Methoxy, E Isomer), 60.2 (1C, CH₃, Methoxy, Z Isomer), 67.0 (1C, C-7, Z Isomer), 67.2 (1C, C-7, E Isomer), 70.9 (1C, C-6, Z isomer), 71.0 (1C, C-6, E Isomer), 71.4 (1C, C-3, Z Isomer), 76.1 (1C, C-4, Z Isomer), 76.3 (1C, C-5, Z Isomer), 76.3 (1C, C-5 or C-4, E Isomer), 76.4 (1C, C-5 or C-4, E Isomer), 76.9 (1C, C-3, E Isomer), 98.1 (1C, C-2, E Isomer), 102.1 (1C, C-2, Z Isomer), 107.9 (1C, C₉ Isopropylidene, E Isomer), 108.0 (1C, C₉ Isopropylidene, Z Isomer), 109.3 (1C, C₉ Isopropylidene, Z Isomer), 109.4 (1C, C₉ Isopropylidene, E Isomer), 150.3 (1C, C-1, Z Isomer), 153.2 (1C, C-1, E Isomer); HRMS (ESI-TOF) m/z found for [M+Na]^+: 311.1465; [C₁₄H₂₄O₆Na]^+ requires 311.1465.
(2R,3R,4R,5R)-3-Hydroxy-1,2;4,5-di-O-isopropylidene-6-decene (355)\(^5\)

\[
\begin{align*}
\text{234} & \quad \rightarrow \quad \text{355} & \quad + \quad \text{354}
\end{align*}
\]

\(n\)-Butyl lithium (2.08 ml, 2.5M in hexanes, 5.21 mmol, 3 equiv.) was added dropwise to a stirred mixture of methoxymethyltriphenylphosphonium chloride (1.786 g, 5.21 mmol, 3 equiv.) in dry THF (15.6 ml) at -78 °C. The red-coloured solution was then stirred for 1 hour at -78 °C. A solution of 234 (0.5 g, 1.96 mmol) in dry THF (3.1 ml) at -78 °C was added to the ylide-solution slowly via a cannula transfer. The resultant mixture was then warmed to rt gradually and left to stir overnight. The reaction mixture was then cooled to rt and quenched with brine, and the layers were then separated. The aqueous layer was extracted with Et\(_2\)O three times. The combined organic extracts were dried over anhydrous MgSO\(_4\). Filtration and removal of the solvent in vacuo furnished a crude dark brown oil. The crude mixture was purified by flash column chromatography on silica gel (petrol:EtOAc, 8:1) furnishing compound 355 as a colourless oil (0.099 g, 17\%);\(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 0.91 (t, \(J = 7.4\) Hz, 3H, CH\(_3\) Propyl), 1.35 (s, 3H, CH\(_3\) Isopropylidene), 1.39 (s, 3H, CH\(_3\) Isopropylidene), 1.40 (s, 3H, CH\(_3\) Isopropylidene), 1.41 – 1.46 (m, 2H, CH\(_2\) Propyl), 1.52 (s, 3H, CH\(_3\) Isopropylidene), 2.12 – 2.13 (m, 2H, CH\(_2\) Propyl), 3.43 – 3.49 (m, 1H, H\(-\)C\(-5\)), 3.97 – 4.05 (m, 2H, H-C\(_6\), H-C\(_7\)), 4.06 – 4.12 (m, 1H, H'-C\(_7\)), 4.33 (dd, \(J = 7.4, 1.3\) Hz, 1H, H-C\(_4\)), 4.69 (t, \(J = 7.8\) Hz, 1H, H-C\(_3\)), 5.73 (ddt, \(J = 15.4, 8.4, 1.3\) Hz, 1H, H-C\(_2\)), 5.84 (dt, \(J = 15.5, 6.7\) Hz, 1H, H-C\(_1\));\(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 13.7 (1C, CH\(_3\) Propyl), 22.2 (1C, CH\(_2\) Propyl), 24.5 (1C, CH\(_3\) Isopropylidene), 25.3 (1C, CH\(_3\) Isopropylidene), 26.7 (1C, CH\(_3\) Isopropylidene), 26.8 (1C, CH\(_3\) Isopropylidene), 34.4 (1C, CH\(_2\) Propyl), 67.0 (1C, C\(_7\)), 70.7 (1C, C\(_5\)), 76.1 (1C, C\(_6\)), 76.6 (1C, C\(_4\)), 79.1 (1C, C\(_3\)), 108.3 (1C, C\(_q\) Isopropylidene), 109.3 (1C, C\(_q\) Isopropylidene), 125.5 (1C, C\(_2\)), 137.8 (1C, C\(_1\)).

The data is in agreement with the literature reference.\(^5\)

Further elution (petrol:EtOAc, 5:1) gave vinyl ether 354 as an inseparable mixture of geometric isomers (E:Z, 7:3) as a yellow oil (0.2 g, 36\%).
Mercuric acetate (0.135 g, 0.42 mmol, 0.2 equiv.) was added to a solution of 354 (0.610 g, 2.12 mmol) in a minimal volume of dry DCM in a Kugelrohr flask. The solution was evaporated to give a crude viscous oil (in a Buchi Kugelrohr apparatus) when heated at 110 °C and 20 mm Hg for 2 hours. The crude product was purified by flash column chromatography (petrol:EtOAc, 2:1) to yield the title compound as a pure colourless solid (0.312 g, 57%); mp 38–39 °C; [α]D21 = -6.8 (c 1.18 in CHCl3); IR νmax (film)/cm⁻¹: 2986, 2935, 1648, 1371, 1084; ¹H NMR (400 MHz, Chloroform-d) δ 1.38 (s, 6H, CH₃Isopropylidene), 1.43 (s, 3H, CH₃Isopropylidene), 1.45 (s, 3H, CH₃Isopropylidene), 3.77 (dd, J = 8.0, 1.2 Hz, 1H, H-C-δ), 4.03 – 4.15 (m, 2H, H-C-7, H’-C-7), 4.37 (ddd, J = 8.0, 6.1, 5.0 Hz, 1H, H-C-δ), 4.41 – 4.45 (dt, J = 6.2, 1.2 Hz, 1H, H-C-δ), 4.66 (dd, J = 6.2, 2.8 Hz, 1H, H-C-δ), 4.76 – 4.82 (ddd, J = 6.3, 2.8, 1.2 Hz, 1H, H-C-δ), 6.35 (d, J = 6.3 Hz, 1H, H-C-1); ¹³C NMR (101 MHz, CDCl3) δ 25.4 (1C, CH₃Isopropylidene), 27.0 (1C, CH₃Isopropylidene), 27.2 (1C, CH₃Isopropylidene), 28.3 (1C, CH₃Isopropylidene), 66.8 (1C, C-7), 68.6 (1C, C-3), 72.2 (1C, C-4), 74.3 (1C, C-δ), 75.2 (1C, C-5), 103.2 (1C, C-δ), 109.6 (1C, CqIsopropylidene), 110.7 (1C, CqIsopropylidene), 144.6 (1C, C-1); HRMS (ESI-TOF) m/z found for [M+Na]+: 279.1203; [C₁₃H₂₀O₅+Na]+ requires 279.1203.
OsCl₃ (0.012 g, 0.04 mmol, 0.0167 equiv.) and NMO (0.832 g, 7.10 mmol, 2.9 equiv.) were added to a stirred solution of glycal 353 (0.628 g, 2.45 mmol) in 1:1 THF:HzO (32.6 ml). The mixture was stirred overnight. Excess anhydrous Na₂SO₃ was then added to the mixture. After 1 hour, water and CHCl₃ were added to the mixture. The layers were separated and the aqueous layer was extracted with CHCl₃ twice. The combined organic extracts were washed with saturated aqueous Na₂SO₃, water, brine, and dried over anhydrous MgSO₄. Filtration and evaporation of the solvent under reduced pressure gave a crude residue. Purification by column chromatography on silica gel (petrol:EtOAc, 1:2) furnished an inseparable anomeric mixture 352 (α:β, 14:1) as a colourless solid (0.453 g, 64%); mp 133 - 135 °C; [α]D₂¹ = + 65.1 (c 0.99 in MeOH); IR νmax (film)/cm⁻¹: 3363, 2988, 1378, 1220, 1065; ¹H NMR (500 MHz, DMSO-d₆) δ 1.26 (s, 3H, CH₃ Isopropylidene α-352), 1.27 (s, 6H, CH₃ Isopropylidene α-352, CH₃ Isopropylidene β-352), 1.32 (s, 3H, CH₃ Isopropylidene α-352), 1.34 (s, 3H, CH₃ Isopropylidene β-352), 1.38 (s, 3H, CH₃ Isopropylidene α-352), 1.39 (s, 6H, 2 X CH₃ Isopropylidene β-352), 3.15 (td, J = 7.9, 4.8 Hz, 1H, H-C-2 β-352), 3.44 (td, J = 6.4, 3.4 Hz, 1H, H-C-2 α-352), 3.65 (dd, J = 7.7, 2.1 Hz, 1H, H-C-5 β-352), 3.82 (dd, J = 8.4, 5.2 Hz, 1H, H-C-7 α-352), 3.86 (dd, J = 8.4, 5.3 Hz, 1H, H-C-7 β-352), 3.90 – 3.93 (m, 1H, H-C-3 β-352), 3.94 – 4.01 (m, 3H, H-C-5 α-352, H'-C-7 α-352, H'-C-7 β-352), 4.06 – 4.12 (m, 2H, H-C-3 α-352, H-C-4 β-352), 4.12 – 4.16 (m, 2H, H-C-3 α-352, H-C-6 β-352), 4.17 (dd, J = 6.0, 2.2 Hz, 1H H-C-4 α-352), 4.29 (dd, J = 7.9, 6.8 Hz, 1H, H-C-1 β-352), 4.88 (dd, J = 5.5, 3.4 Hz, 1H, H-C-1 α-352), 4.97 (d, J = 6.4 Hz, 1H, C-2-OH α-352), 5.10 (d, J = 4.8 Hz, 1H, C-2-OH β-352), 6.39 (d, J = 5.5 Hz, 1H, C-1-OH α-352), 6.70 (d, J = 6.8 Hz, 1H, C-1-OH β-352); ¹³C NMR (126 MHz, DMSO) δ 25.2 (1C, CH₃ Isopropylidene α-352), 26.1 (1C, CH₃ Isopropylidene α-352), 26.6 (2C, 2 X CH₃ Isopropylidene β-352), 26.7 (1C, CH₃ Isopropylidene α-352), 27.8 (1C, CH₃ Isopropylidene α-352), 28.1 (1C, CH₃ Isopropylidene β-352), 28.5 (1C, CH₃ Isopropylidene β-
352), 66.3 (1C, C-7 β-352), 66.4 (1C, C-7 α-352), 67.9 (1C, C-5 α-352), 69.2 (1C, C-2 α-352), 72.4 (1C, C-4 α-352), 72.4 (1C, C-5 β-352), 73.1 (1C, C-4 β-352), 73.7 (1C, C-2 β-352), 73.8 (2C, C-6 α-352, C-6 β-352), 75.7 (1C, C-3 α-352), 79.3 (1C, C-3 β-352), 91.6 (1C, C-1 α-352), 96.7 (1C, C-1 β-352), 107.8 (1C, C_q Isopropylidene α-352), 108.3 (1C, C_q Isopropylidene α-352), 108.5 (1C, C_q Isopropylidene β-352), 108.5 (1C, C_q Isopropylidene β-352); HRMS (NSI-FTMS) m/z found for [M+Na]+: 313.1257; [C_{13}H_{27}O_{7}+Na]^+ requires 313.1258.
Ac₂O (0.49 ml, 5.17 mmol, 7.5 equiv.) was added dropwise to a stirred solution of 352 (0.200 g, 0.69 mmol) in pyridine (2.5 ml) at 0 °C. The reaction mixture was stirred at rt overnight. The mixture was then concentrated in vacuo. The residue was dissolved in DCM and treated with water. The layers were separated and the aqueous layer was extracted with DCM twice. The combined organic layers were washed with saturated aqueous copper (II) sulfate, saturated aqueous NH₄Cl, saturated aqueous NaHCO₃, water, brine, and dried over anhydrous MgSO₄. Filtration and removal of the solvent under reduced pressure gave a crude colourless oil. Purification by flash column chromatography on silica gel (petrol:EtOAc, 9:2), furnished 357 (α:β, 14:1) as a colourless oil (0.176 g, 68%); [α]D²¹ = +72.4 (c 1.15 in CHCl₃); IR νmax (film)/cm⁻¹: 2988, 2937, 1758, 1216, 1150, 1069; ¹H NMR (500 MHz, Chloroform-d) δ 1.37 (s, 3H, CH₃ Isopropylidene), 1.38 (s, 3H, CH₃ Isopropylidene), 1.43 (s, 3H, CH₃ Isopropylidene), 1.52 (s, 3H, CH₃ Isopropylidene), 2.08 (s, 3H, CH₃ Acetate), 2.10 (s, 3H, CH₃ Acetate), 3.92 – 4.00 (m, 2H, H-C-5, H-C-7), 4.07 (dd, J = 8.9, 6.2 Hz, 1H, H'-C-7), 4.29 – 4.41 (m, 3H, H-C-3, H-C-4, H-C-6), 5.13 (dd, J = 6.7, 3.8 Hz, 1H, H-C-2), 6.20 (d, J = 3.8 Hz, 1H, H-C-1); ¹³C NMR (126 MHz, CDCl₃) δ 20.9 (1C, CH₃ Acetate), 21.0 (1C, CH₃ Acetate), 25.3 (1C, CH₃ Isopropylidene), 26.6 (1C, CH₃ Isopropylidene), 27.1 (1C, CH₃ Isopropylidene), 27.6 (1C, CH₃ Isopropylidene), 66.9 (1C, C-7), 69.3 (1C, C-2), 70.8 (1C, C-5), 72.7 (1C, C-3 or C-4 or C-6), 72.8 (1C, C-3 or C-4 or C-6), 74.0 (1C, C-3 or C-4 or C-6), 89.4 (1C, C-1), 109.6 (1C, Cq Isopropylidene), 110.4 (1C, Cq Isopropylidene), 169.1 (1C, Cq Acetate), 170.1 (1C, Cq Acetate); HRMS (NSI-FTMS) m/z found for [M+NH₄]⁺: 392.1915; [C₁₇H₂₆O₉+NH₄]⁺ requires 392.1915.
BzCl (0.24 ml, 2.087 mmol, 3 equiv.) was added dropwise to a stirred solution of 352 (0.201 g, 0.69 mmol) in pyridine (1 ml) at 0 °C. After 24 hours stirring at rt, the reaction mixture was diluted with DCM and quenched with water. The layers were separated and the aqueous layer was extracted with DCM twice. The combined organic extracts were washed with saturated aqueous copper (II) sulfate, saturated aqueous NH₄Cl, saturated aqueous NaHCO₃, water, brine, and dried over anhydrous MgSO₄. Filtration and removal of the solvent under reduced pressure gave a crude residue. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 8:1), yielding 359 as a pure colourless solid (0.223 g, 65%); mp 114 – 116 °C; [α]D²¹ = +104.3 (c 0.97 in CHCl₃); IR νmax (film)/cm⁻¹: 3063, 2988, 2937, 1732, 1602, 1452, 1248, 1068; H NMR (500 MHz Chloroform-d) δ 1.37 (s, 3H, CH₃ Isopropylidene), 1.43 (s, 6H, 2 X CH₃ Isopropylidene), 1.61 (s, 3H, CH₃ Isopropylidene), 4.00 (dd, J = 9.0, 4.4 Hz, 1H, H-C-7), 4.06 – 4.16 (m, 2H, H'-C₇, H-C₅), 4.41 (ddd, J = 7.9, 6.2, 4.4 Hz, 1H, H-C-6), 4.54 (dd, J = 6.3, 2.3 Hz, 1H, H-C-4), 4.67 (t, J = 6.3 Hz, 1H, H-C-3), 5.57 (dd, J = 6.3, 3.8 Hz, 1H, H-C-2), 6.56 (d, J = 3.8 Hz, 1H, H-C-1), 7.38 – 7.43 (m, 4H, 4 X H-CAR), 7.53 – 7.60 (m, 2H, 2 X H-CAR), 7.93 – 8.00 (m, 4H, 4 X H-CAR); ¹³C NMR (126 MHz, CDCl₃) δ 25.4 (1C, CH₃ Isopropylidene), 26.1 (1C, CH₃ Isopropylidene), 27.1 (1C, CH₃ Isopropylidene), 27.5 (1C, CH₃ Isopropylidene), 67.1 (1C, C-7), 69.5 (1C, C-2), 71.5 (1C, C₅), 72.8 (1C, C₄), 73.1 (1C, C-₃), 74.0 (1C, C₆), 90.2 (1C, C-₁), 109.6 (1C, C₉ Isopropylidene), 110.7 (1C, C₉ Isopropylidene), 128.6 (2C, 2 X CAR), 128.7 (2C 2 X CAR), 129.4 (1C, CAR), 129.4 (1C, CAR), 130.0 (2C, 2 X CAR), 130.0 (2C, 2 X CAR), 133.6 (1C, C₉ AR), 133.7 (1C, C₉ AR), 164.6 (1C, C₉ Benzoyl), 165.6 (1C, C₉ Benzoyl); HRMS (ASAP-TOF) m/z found for [M+NH₄]+: 516.2231; [C₂₇H₃₀O₆₉+NH₄]+ requires 516.2233.
Sodium periodate (10.37 g, 48.5 mmol, 2 equiv.) and water (10 ml) were added to a stirred solution of diethyl-L-tartrate (4.15 ml, 24.3 mmol) in DCM (50 ml). The biphasic mixture was then heated under reflux for 3 hours. The solution was then cooled to 0 °C before anhydrous MgSO₄ was added portion wise. Filtration and removal of the solvent under reduced pressure afforded ethyl glyoxylate in an unpurified state (4.433 g) and was used directly in the next step without any purification.

Et₃N (15.9 ml, 114.1 mmol, 3.09 equiv.) was added dropwise to a solution of dimethyl phosphite (3.99 ml, 43.6 mmol, 1.18 equiv.) in dry toluene (40 ml) at 0 °C. After leaving the solution to stir for 15 minutes at 0 °C, a solution of crude ethyl glyoxylate (4.433 g) in dry toluene (20 ml) was added. The reaction mixture was then warmed to rt and stirred overnight. The mixture was concentrated in vacuo forming a pale-yellow crude residue. Purification by flash column chromatography on silica gel (petrol:EtOAc, 1:3) afforded phosphonate 370 as a colourless solid (4.262 g, 41% over two steps); IR ν max (film)/cm⁻¹: 3269, 2963, 2858, 1745, 1250, 1103, 1035; ¹H NMR (500 MHz, CDCl₃) δ 1.32 (t, J = 7.1 Hz, 3H, CH₃Ester), 3.83 (d, J = 6.7 Hz, 3H, OCH₃), 3.86 (d, J = 6.6 Hz, 3H, OCH₃), 4.29 – 4.37 (m, 2H, CH₂Ester), 4.57 (d, J = 16.1 Hz, 1H, H-COH). ¹³C NMR (126 MHz, CDCl₃) δ 14.1 (1C, CH₃Ester), 54.0 (d, J = 6.9 Hz, 1C, OCH₃), 54.4 (d, J = 6.8 Hz, 1C, OCH₃), 63.1 (1C, CH₂Ester), 68.6 (d, J = 156.1 Hz, 1C, CHOH), 169.3 (d, J = 1.2 Hz, 1C, C_qEster); HRMS (ASAP-TOF) m/z found for [M+H]⁺: 213.0527; [C₆H₁₃O₆P+H]⁺ requires 213.0528.

Organophosphate 371 was also isolated as a pure colourless oil (3.233g, 31% over two steps); ¹H NMR (500 MHz, Chloroform-d) δ 1.27 (t, J = 7.1 Hz, 3H, CH₃Ester), 3.80 (d, J = 11.3 Hz, 6H, 2X OCH₃), 4.23 (q, J = 7.1 Hz, 1H, CH₂Ester), 4.55 (d, J = 11.4 Hz, 2H, CH₂); ¹³C NMR (126 MHz, CDCl₃) δ 14.2 (1C, CH₃Ester), 54.8 (d, J = 6.1 Hz, 2C, 2X OCH₃), 61.7 (1C, CH₂Ester), 63.6 (d, J = 5.0 Hz, 1C, OCH₂), 167.9 (d, J = 5.6 Hz, 1C, C_qEster); HRMS (Cl) m/z found for [M+H]⁺: 213.0525; [C₆H₁₃O₆P+H]⁺ requires 213.0528.
Imidazole (0.949 g, 13.9 mmol, 1.6 equiv.) and then TBSCl (1.580 g, 10.46 mmol, 1.2 equiv.) were added to a stirred solution of 370 (1.848 g, 8.71 mmol) in dry DCM (15.8 ml) at 0 °C. The resultant heterogenous mixture was stirred overnight at rt. The reaction mixture was then quenched with saturated aqueous NH₄Cl and extracted with DCM three times. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO₄. Filtration and removal of the solvent under reduced pressure gave a crude yellow oil. The crude oil was purified by flash column chromatography on silica gel (petrol:EtOAc, 3:2) to furnish the title compound as a pure colourless oil (2.60 g, 91%); IR ν_{max} (film)/cm⁻¹: 2958, 2931, 2897, 2858, 1754, 1262, 1139, 1035; ¹H NMR (500 MHz, CDCl₃) δ 0.11 (s, 3H, CH₃ Me (TBS)), 0.12 (s, 3H, CH₃ Me (TBS)), 0.92 (s, 9H, 3 X CH₃ tBu (TBS)), 1.30 (t, J = 7.1 Hz, 3H, CH₃ ester), 3.83 (d, J = 8.5 Hz, 3H, OCH₃), 3.85 (d, J = 8.5 Hz, 3H, OCH₃), 4.21 – 4.33 (m, 2H, CH₂ ester), 4.61 (d, J = 18.1 Hz, 1H, H-COTBDMS). ¹³C NMR (126 MHz, CDCl₃) δ -5.2 (1C, CH₃ Me (TBS)), -5.4 (1C, CH₃ Me (TBS)), 14.2 (1C, CH₃ ester), 18.5 (1C, C₃tBu (TBS)), 25.7 (3C, 3 X CH₃ tBu (TBS)), 54.2 (d, J = 6.9 Hz, 1C, OCH₃), 54.3 (d, J = 6.7 Hz, 1C, OCH₃), 62.0 (1C, CH₂ ester), 70.8 (d, J = 162.1 Hz, 1C, CHOTBS), 168.6 (d, J = 2.8 Hz, C₇ ester).

The data is in agreement with the literature reference.⁶
A solution of phosphonate 367 (1.158 g, 7.78 mmol, 1.5 equiv.) in dry THF (12.5 ml) was added dropwise to a stirred suspension of NaH (0.187 g, 7.78 mmol, 1.5 equiv.) in dry THF (12.5 ml) at 0 °C. The mixture was stirred at 0 °C for 1 hour. A solution of 234 (1.35 g, 5.19 mmol) in dry THF (12.5 ml) was then added dropwise to the suspension. The mixture was then warmed to rt and heated at 50 °C for 24 hours. The reaction was then cooled to rt and quenched with saturated aqueous NH₄Cl. Most of the THF was removed under reduced pressure. The aqueous layer was extracted with EtOAc three times. The combined organic extracts were dried over anhydrous MgSO₄. Filtration and removal of the solvent in vacuo gave the crude product. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 15:2) to give an inseparable mixture (0.878 g, E-364:372, 50:1) of E-364 (0.864 g, 36%) and by-product 372 (0.014 g, 1%) as a colourless oil.**

Characterization data for E silyl enol ether E-364; IR νmax (film)/cm⁻¹: 3510, 2986, 2934, 2887, 2860, 1714, 1639, 1473, 1212, 1179, 1033; ¹H NMR (500 MHz, Chloroform-d) δ 0.17 (s, 6H, 2X CH₃ Me (TBS)), 0.95 (s, 9H, 3X CH₃ tBu (TBS)), 1.34 (s, 3H, CH₃ Isopropylidene), 1.37 (s, 3H, CH₃ Isopropylidene), 1.40 (s, 3H, CH₃ Isopropylidene), 1.52 (s, 3H, CH₃ Isopropylidene), 3.35 (t, J = 7.5 Hz, 1H, H-C-7), 3.96 – 4.01 (m, 2H, H-C-5, H’-C-7), 4.03 – 4.08 (m, 1H, H-C-6), 4.16 – 4.24 (m, 2H, CH₂ Ester), 4.64 (dd, J = 7.4, 1.1 Hz, 1H, H-C₄), 5.48 (t, J = 7.4 Hz, 1H, H-C₃), 5.73 (d, J = 7.4 Hz, 1H, H-C₂), 13C NMR (126 MHz, CDCl₃) δ -4.8 (1C, CH₃ Me (TBS)), -4.7 (1C, CH₃ Me (TBS)), 14.3 (1C, CH₃ Ester), 18.3 (1C, C₉ tBu (TBS)), 24.2 (1C, CH₃ Isopropylidene), 25.5 (1C, CH₃ Isopropylidene), 25.7 (3C, 3X CH₃ tBu (TBS)), 26.8 (1C, CH₃ Isopropylidene), 27.0 (1C, CH₃ Isopropylidene), 61.3 (1C, CH₂ Ester), 67.1 (1C, C-7), 70.3 (1C, C-5), 74.3 (1C, C₃), 76.4 (1C, C-6), 77.2 (1C, C-4), 108.4 (1C, C₉ Isopropylidene), 109.4 (1C, C₉ Isopropylidene), 122.9 (1C, C-2), 141.8 (1C, C-1), 164.4 (1C, C₉ Ester).
Characterization data for by-product 372; [α]D22 = -13.8 (c 1.45 in CHCl3); IR Vmax (film)/cm⁻¹: 2985, 2931, 2858, 1372, 1252, 1212, 1048; ¹H NMR (400 MHz, Chloroform-d) δ 0.13 (s, 6H, 2X CH3 Me(TBS)), 0.92 (s, 9H, 3X CH3tBu(TBS)), 1.36 (s, 3H, CH3 Isopropylidene), 1.38 (s, 3H, CH3 Isopropylidene), 1.44 (s, 3H, CH3 Isopropylidene), 1.51 (s, 3H, CH3 Isopropylidene), 3.55 (dd, J = 7.7, 3.8 Hz, 1H, H-C-4), 4.03 – 4.11 (m, 2H, H-C6, H'-C6), 4.44 (dddd, J = 7.7, 5.9, 4.9 Hz, 1H, H-C-5), 4.49 (dd, J = 6.1, 3.6 Hz, 1H, H-C2), 4.69 (dd, J = 6.1, 3.8 Hz, 1H, H-C-3), 5.01 (d, J = 3.6 Hz, 1H, H-C-1). ¹³C NMR (126 MHz, CDCl3) δ -4.5 (1C, CH3 Me(TBS)), -4.3 (1C, CH3 Me(TBS)), 18.4 (1C, Cq tBu(TBS)), 25.5 (1C, CH3 Isopropylidene), 25.7 (1C, CH3 Isopropylidene), 25.9 (3C, 3X CH3 tBu(TBS)), 26.0 (1C, CH3 Isopropylidene), 27.2 (1C, CH3 Isopropylidene), 67.1 (1C, C-6), 73.5 (1C, C-5), 76.9 (1C, C-4), 79.6 (1C, C-3), 80.7 (1C, C-2), 98.1 (1C, C-1), 109.3 (1C, Cq Isopropylidene), 113.7 (1C, Cq Isopropylidene); HRMS (ASAP-TOF) m/z found for [M-H]: 373.2047; [C18H34O8Si-H⁺] requires 373.2040.

Further elution (petrol:EtOAc, 5:1) gave the Z silyl enol ether Z-364 as a pure colourless oil (0.440 g, 18%); [α]D22 = +40.8 (c 0.93 in CHCl3); IR Vmax (film)/cm⁻¹: 3513, 2995, 2933, 2859, 1726, 1650, 1251, 1130, 1071; ¹H NMR (500 MHz, Chloroform-d) δ 0.21 (s, 3H, CH3 Me(TBS)), 0.95 (s, 9H, 3X CH3 tBu(TBS)), 1.31 (t, J = 7.1 Hz, 3H, CH3 Ester), 1.34 (s, 3H, CH3 Isopropylidene), 1.38 (s, 3H, CH3 Isopropylidene), 1.40 (s, 3H, CH3 Isopropylidene), 1.53 (s, 3H, CH3 Isopropylidene), 2.10 (d, J = 8.4 Hz, 1H, OH), 3.37 – 3.42 (m, 1H, H-C-5), 3.97 – 4.03 (m, 2H, H-C-7, H'-C-7), 4.08 (td, J = 8.0, 2.6 Hz, 1H, H-C-6), 4.18 (dq, J = 10.8, 7.1 Hz, 1H, 1H of CH2 Ester), 4.27 (dq, J = 10.8, 7.1 Hz, 1H, 1H of CH2 Ester), 4.45 (dd, J = 7.5, 1.3 Hz, 1H, H-C-4), 5.30 (dd, J = 8.6, 7.5 Hz, 1H, H-C-3), 6.21 (d, J = 8.6 Hz, 1H, H-C-2). ¹³C NMR (126 MHz, CDCl3) δ -4.2 (1C, CH3 Me(TBS)), -4.0 (1C, CH3 Me(TBS)), 14.3 (1C, CH3 Ester), 18.7 (1C, Cq tBu(TBS)), 24.4 (1C, CH3 Isopropylidene), 25.4 (1C, CH3 Isopropylidene), 26.0 (3C, 3X CH3 tBu(TBS)), 26.7 (1C, CH3 Isopropylidene), 26.9 (1C, CH3 Isopropylidene), 61.6 (1C, CH2 Ester), 67.0 (1C, C-7), 70.9 (1C, C-5), 72.3 (1C, C-3), 76.2 (1C, C-6), 76.6 (1C, C-4), 108.8 (1C, Cq Isopropylidene), 109.4 (1C, Cq Isopropylidene), 116.3 (1C, C-2), 143.7 (1C, C-1), 164.1 (1C, Cq Ester); HRMS (ESI-TOF) m/z found for [M+Na]⁺: 483.2377; [C22H40O8Si+Na⁺] requires 483.2390.

*In the subsequent silyl enol ether deprotection step using TBAF, the by-product 372 was isolated and therefore fully characterized. The ¹H and ¹³C NMR spectral interpretations of E-364 were determined by comparison between the NMR spectra of the inseparable mixture of E silyl E-364 and 372 with the NMR spectra for pure 372.
* The number of moles of \textit{E-364} and 372 in the inseparable mixture were calculated from molar ratios observed in the $^1$H NMR spectrum. Since the yield of the \textit{E-364} is based on the number of moles of \textit{E-364} in the inseparable mixture, the yield of \textit{E-364} derives from the aforementioned molar ratios seen in the $^1$H NMR spectrum (same applies to 372); \textsuperscript{b} Reaction time: 72 h; \textsuperscript{c} 1.5 equiv. of base and 367 were added.
(3aR,4R,7aR)-ethyl 4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-hydroxy-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-carboxylate (365) \(^6\)

\[
\begin{align*}
\text{Z-364} & \quad + \quad \text{E-364} \quad \rightarrow \quad 365 \\
\text{372}
\end{align*}
\]

Compound **Z-364** (0.339 g, 0.76 mmol) and an inseparable mixture (0.601 g, **E-364:372**, 50:1) of **E-364** (0.591 g, 1.28 mmol) and **372** (0.01 g, 0.026 mmol) were dissolved in THF (2.1 ml). After cooling the stirred solution to 0 °C, 20% acetic acid (2.7 ml, 9.38 mmol, 4.6 equiv.) was added, followed by the dropwise addition of TBAF (2.04 ml, 1M in THF, 2.04 mmol, 1 equiv.). The reaction mixture was stirred at rt until the starting material was fully consumed (monitored by TLC). The reaction mixture was then neutralized with NaHCO\(_3\), filtered and concentrated in vacuo. The residue was then treated with saturated aqueous NaHCO\(_3\) and EtOAc. After separating the layers, the aqueous layer was extracted with EtOAc twice. The combined organic extracts were dried over anhydrous MgSO\(_4\). Filtration and removal of the solvent under reduced pressure gave a crude residue. Purification by flash column chromatography on silica gel (petrol:EtOAc, 3:1) furnished an inseparable mixture (α:β, 5:1) of anomers **365** as a colourless oil (0.558 g, 79%)*; IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 3401, 2986, 2937, 1745, 1457, 1371, 1218, 1070; \(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 1.30 (t, \(J = 7.1\) Hz, 3H, CH\(_3\) Ester, α anomer), 1.33 (t, \(J = 7.2\) Hz, 3H, CH\(_3\) Ester, β anomer), 1.35 (s, 3H, CH\(_3\) Isopropylidene, both anomers), 1.36 (s, 3H, CH\(_3\) Isopropylidene, α anomer), 1.38 (s, 3H, CH\(_3\) Isopropylidene, β anomer), 1.41 (s, 3H, CH\(_3\) Isopropylidene, β anomer), 1.42 (s, 3H, CH\(_3\) Isopropylidene, α anomer), 1.46 (s, 3H, CH\(_3\) Isopropylidene, α anomer), 1.56 (s, 3H, CH\(_3\) Isopropylidene, β anomer), 1.88 (dd, \(J = 14.4, 4.9\) Hz, 1H, H-C-2, α anomer), 2.33 (d, \(J = 2.9\) Hz, 2H, H-C-2, H\(^{1}\)C-2, β anomer), 2.49 (dd,
$J = 14.4, \ 6.7 \text{ Hz}, \ 1\text{H}, \ H'\text{-C}-2, \ \alpha \text{ anomer}$), 3.44 (dd, $J = 8.7, \ 1.8 \text{ Hz}, \ 1\text{H}, \ H\text{-C}-5, \ \beta \text{ anomer}$), 3.61 (br, $1\text{H}, \ \text{OH}, \ \alpha \text{ anomer}$), 3.90 (dd, $J = 8.0, \ 2.2 \text{ Hz}, \ 1\text{H}, \ H\text{-C}-5, \ \alpha \text{ anomer}$), 3.97 – 4.02 (m, $1\text{H}, \ H\text{-C}-7, \ \text{both anomers}$), 4.05 – 4.11 (m, $1\text{H}, \ H'\text{-C}-7, \ \text{both anomers}$), 4.21 – 4.31 (m, 3H, CH$_2$ Ester, H-C-4, both anomers), 4.32 – 4.37 (m, $1\text{H}, \ H\text{-C}-6, \ \alpha \text{ anomer}$), 4.43 (dd, $J = 8.0, \ 1.8 \text{ Hz}, \ 1\text{H}, \ H\text{-C}-6, \ \beta \text{ anomer}$), 4.48 – 4.53 (m, $1\text{H}, \ H\text{-C}-3, \ \alpha \text{ anomer}$), 4.72 – 4.75 (m, 2H, H-C-3, OH, $\beta \text{ anomer}$). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 14.2 (1C, CH$_3$ ester, $\alpha \text{ anomer}$), 14.3 (1C, CH$_3$ ester, $\beta \text{ anomer}$), 24.4 (1C, CH$_3$ Isopropylidene, $\beta \text{ anomer}$), 25.2 (1C, CH$_3$ Isopropylidene, $\beta \text{ anomer}$), 25.5 (1C, CH$_3$ Isopropylidene, $\alpha \text{ anomer}$), 25.9 (1C, CH$_3$ Isopropylidene, $\alpha \text{ anomer}$), 26.2 (1C, CH$_3$ Isopropylidene, $\beta \text{ anomer}$), 27.1 (1C, CH$_3$ Isopropylidene, $\alpha \text{ anomer}$), 27.2 (1C, CH$_3$ Isopropylidene, $\beta \text{ anomer}$), 27.3 (1C, CH$_3$ Isopropylidene, $\alpha \text{ anomer}$), 31.1 (1C, C-2, $\beta \text{ anomer}$), 32.4 (1C, C-2, $\alpha \text{ anomer}$), 62.1 (1C, CH$_2$ Ester, $\beta \text{ anomer}$), 62.5 (1C, CH$_2$ Ester, $\alpha \text{ anomer}$), 67.0 (1C, C-7, $\alpha \text{ anomer}$), 67.3 (1C, C-7, $\beta \text{ anomer}$), 70.0 (1C, C-3, $\alpha \text{ anomer}$), 70.8 (1C, C-3, $\beta \text{ anomer}$), 71.4 (1C, C-4, $\alpha \text{ anomer}$), 72.5 (1C, C-6, $\beta \text{ anomer}$), 73.5 (1C, C-4, $\beta \text{ anomer}$), 74.0 (1C, C-5, $\beta \text{ anomer}$), 74.1 (1C, C-6, $\alpha \text{ anomer}$), 94.5 (1C, C-1, $\alpha \text{ anomer}$), 95.7 (1C, C-1, $\beta \text{ anomer}$), 109.3 (1C, C$_q$ Isopropylidene, $\alpha \text{ anomer}$), 109.5 (1C, C$_q$ Isopropylidene, $\alpha \text{ anomer}$), 109.7 (1C, C$_q$ Isopropylidene, $\beta \text{ anomer}$), 109.7 (1C, C$_q$ Isopropylidene, $\beta \text{ anomer}$), 169.0 (1C, C$_q$ Ester, $\beta \text{ anomer}$), 169.75 (1C, C$_q$ Ester, $\alpha \text{ anomer}$).

*The number of moles of E-364 and 372 in the starting material inseparable mixture were calculated from molar ratios seen in the $^1$H NMR spectrum. Yield of 365 is based on the total number of moles of E-364 in the inseparable mixture and Z-364.
An inseparable mixture (0.4964 g, \textit{E}-364:372, 4:1) of \textit{E}-364 (0.390 g, 0.85 mmol) and 372 (0.106 g, 0.21 mmol) were dissolved in THF (1.1 ml). After cooling the stirred solution to 0 °C, 20% acetic acid (1.12 ml, 3.90 mmol, 4.6 equiv.) was added, followed by the dropwise addition of TBAF (0.85 ml, 1M in THF, 0.85 mmol, 1 equiv.). The reaction mixture was stirred at rt until \textit{E}-364 was fully consumed (monitored by TLC with UV visualization). The reaction mixture was then neutralized with NaHCO$_3$, filtered and concentrated \textit{in vacuo}. The residue was then treated with saturated aqueous NaHCO$_3$ and EtOAc. After separating the layers, the aqueous layer was extracted with EtOAc twice. The combined organic extracts were dried over anhydrous MgSO$_4$. Filtration and removal of the solvent under reduced pressure gave a crude residue. Purification by flash column chromatography on silica gel (petrol:EtOAc, 7:2) furnished the unreacted 372 (0.054 g), 234 (0.017 g, 31%) and an inseparable mixture (α:β, 4:1) of anomers 365 as a colourless oil (0.166 g, 57%). *

*The number of moles of \textit{E}-364 and 372 in the starting material inseparable mixture were calculated from molar ratios seen in the $^1$H NMR spectrum. Yield of 365 is based on the total number of moles of \textit{E}-364 in the inseparable mixture. Yield of DAM 234 is based on the moles of 372 in inseparable mixture.
(3aR,4R,7aR)-ethyl 4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-4,7a-dihydro-3aH-
[1,3]dioxolo[4,5-c]pyran-6-carboxylate (366)\textsuperscript{6}

MsCl (0.12 ml, 1.55 mmol, 3 equiv.) was added dropwise over 5 minutes to a stirred solution of 365 (0.179 g, 0.52 mmol) and Et\textsubscript{3}N (0.24 ml, 1.76 mmol, 3.4 equiv.) in dry DCM (5 ml) at 0 °C. After 3 hours stirring at rt (i.e. monitored by TLC until full consumption of starting material was observed), DBU (0.23 ml, 1.55 mmol, 3 equiv.) was added dropwise and the mixture was stirred at rt overnight. The mixture was then concentrated \textit{in vacuo} furnishing a crude residue.

Purification by flash column chromatography on silica gel (petrol:EtOAc, 4:1) gave glycal 366 as a colourless solid (0.120 g, 71%); mp 68-70 °C [lit. 69-71 °C]\textsuperscript{2}; \([\alpha]\)\textsubscript{D}\textsuperscript{22} = +38.4 (c 1.24 in CHCl\textsubscript{3}) [lit. \([\alpha]\)\textsubscript{D}\textsuperscript{20} = +40.4 (c 0.47 in CHCl\textsubscript{3})]\textsuperscript{2}; IR \nu\textsubscript{max} (film)/cm\textsuperscript{-1}: 2986, 2918, 2854, 1733, 1652, 1221, 846; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \delta 1.30 (t, \(J = 7.2\) Hz, 3H, CH\textsubscript{3} Ester), 1.39 (s, 9H, 3 CH\textsubscript{3} Isopropylidene), 1.45 (s, 3H, CH\textsubscript{3} Isopropylidene), 3.83 (dd, \(J = 8.1, 1.0\) Hz, 1H, H-C-5), 4.14 – 4.27 (m, 4H, CH\textsubscript{2} Ester, H-C-7, H'-C-7), 4.42 – 4.47 (m, 2H, H-C-4, H-C-6), 4.78 (dd, \(J = 6.1, 3.3\) Hz, 1H, H-C-3), 5.97 – 6.01 (m, 1H, H-C-2). \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) \delta 14.2 (1C, CH\textsubscript{3} Ester), 25.5 (1C, CH\textsubscript{3} Isopropylidene), 26.8 (1C, CH\textsubscript{3} Isopropylidene), 27.1 (1C, CH\textsubscript{3} Isopropylidene), 28.2 (1C, CH\textsubscript{3} Isopropylidene), 61.6 (1C, CH\textsubscript{2} Ester), 66.8 (1C, C-7), 68.9 (1C, C-3), 71.4 (1C, C-6), 74.1 (1C, C-4), 76.5 (1C, C-5), 109.8 (1C, C\textsubscript{q} Isopropylidene), 110.2 (1C, C-2), 111.2 (1C, C\textsubscript{q} Isopropylidene), 144.3 (1C, C-1), 162.2 (1C, C\textsubscript{q} Ester).

The data is in agreement with the literature reference.\textsuperscript{6}
Ethyl 2-((R)-((4R,5S)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-1,3-dithiane-2-carboxylate (252)

\[ \text{234} \rightarrow \text{252} \]

\( n\)-Butyl lithium (50.7 ml, 2.5M in hexanes, 126.8 mmol, 3.3 equiv.) was added dropwise to a stirred solution of diisopropylamine (17.8 ml, 126.8 mmol, 3.3 equiv.) in dry THF (200 ml) at -20 °C. After 30 minutes, ethyl 1,3-dithiane-2-carboxylate (18.2 ml, 115.3 mmol, 3.0 equiv.), was added dropwise to the solution at -20 °C. The solution was stirred for 2 hours at -20 °C. This dark-red solution was then cannulated slowly into a suspension of MgBr\(_2\) in dry THF (250 ml) at -20 °C, prepared from magnesium (4.2 g, 173.0 mmol, 4.5 equiv.) and 1,2-dibromoethane (13.3 ml, 153.7 mmol, 4.0 equiv.). Compound 234 (10 g, 38.4 mmol) was then added to the solution in one portion. The stirred reaction mixture was warmed to rt gradually overnight and then heated for 5 hours at 50 °C. After cooling to rt, the reaction mixture was poured into ice-cold saturated aqueous NH\(_4\)Cl (450 ml). After adding EtOAc (300 ml), the layers were then separated. The aqueous layer was then extracted with EtOAc (2 x 300 ml). The combined organic extracts were washed with water and dried over anhydrous MgSO\(_4\). Filtration and removal of the solvent in vacuo gave a crude yellow oil. The crude product was purified by flash column chromatography on silica gel (toluene:EtOAc, 3:1) to yield the title compound as a pure yellow oil (16.932 g, 97%); \( [\alpha]_D^{25} = -1.4 \) (c 1.12 in CHCl\(_3\)) [lit. \( [\alpha]_D = -1.8 \) (c 1.0 in CHCl\(_3\))]\(^7\); IR \( \nu_{\text{max}} \) (film)/cm\(^{-1}\): 3454, 3054, 2988, 2935, 1728, 1424, 1381, 1215, 1064; \(^1\)H NMR (500 MHz, Chloroform-d) \( \delta \)

\begin{align*}
1.33 & (t, J = 7.1 \text{ Hz}, 3H, \text{CH}_3 \text{ Ester}) \\
1.35 & (s, 3H, \text{CH}_3 \text{ Isopropylidene}) \\
1.37 & (s, 3H, \text{CH}_3 \text{ Isopropylidene}) \\
1.41 & (s, 3H, \text{CH}_3 \text{ Isopropylidene}) \\
1.50 & (s, 3H, \text{CH}_3 \text{ Isopropylidene}) \\
1.84 & (m, 1H of \text{CH}_2 \text{ Dithiane}) \\
2.05 & (m, 1H, \text{CH}_2 \text{ Dithiane}) \\
2.14 & (m, 1H, 1H of \text{CH}_2 \text{ Dithiane}) \\
2.72 & (m, 2H, \text{CH}_2 \text{ Dithiane}) \\
3.02 & (ddd, J = 14.4, 11.5, 2.8 \text{ Hz}, 1H of \text{CH}_2 \text{ Dithiane}) \\
3.22 & (ddd, J = 14.4, 11.3, 3.0 \text{ Hz}, 1H, 1H of \text{CH}_2 \text{ Dithiane}) \\
3.64 & (ddd, J = 8.1, 3.1, 1.1 \text{ Hz}, 1H, \text{H-C-6}) \\
4.01 & (m, 1H, \text{H-C-7}) \\
4.09 & (m, 2H, H’-C-2, H-C-5) \\
4.23 & (m, 3H, \text{CH}_2 \text{ Ester, H-C-4}) \\
4.43 & (dd, J = 7.5, 1.1 \text{ Hz}, 1H, \text{H-C-3}) \\
4.58 & (d, J = 7.5 \text{ Hz}, 1H, \text{H-C-2}) \\
13C NMR (126 MHz, CDCl\(_3\)) \( \delta \)
\end{align*}

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Isopropylidene), 25.5 (1C, CH$_3$ Isopropylidene), 26.2 (1C, CH$_3$ Isopropylidene), 27.0 (1C, CH$_3$ Isopropylidene), 27.4 (1C, CH$_2$ Dithiane), 27.7 (1C, CH$_2$ Dithiane), 58.8 (1C, C-1), 62.8 (1C, CH$_2$ Ester), 67.7 (1C, C-7), 70.7 (1C, C-6), 72.6 (1C, C-4), 77.1 (1C, C-2), 74.3 (1C, C-5), 75.8 (1C, C-3), 109.3 (1C, C$_q$ Isopropylidene), 109.4 (1C, C$_q$ Isopropylidene), 170.0 (1C, C$_q$ Ester).

The data is in agreement with the literature references.$^{1,7}$
(R)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)((4S,5R)-5-((R)-hydroxy(2-(hydroxymethyl)-1,3-dithian-2-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (264)\(^1\)

![Chemical Structure](image)

LiAlH\(_4\) (1.104 g, 29.10 mmol, 2 equiv.) was added cautiously portion wise to a solution of 252 (6.584 g, 14.55 mmol) in dry THF (100 ml) at 0 °C. The grey suspension was stirred at rt overnight. Then the excess LiAlH\(_4\) was carefully quenched by the addition of anhydrous Na\(_2\)SO\(_4\) (ca. 2 g), followed carefully by the dropwise addition of water until no effervescence was observed. The solution was then filtered through a pad of celite and the solvent was evaporated under reduced pressure. The crude residue was purified by flash column chromatography (petrol:EtOAc, 1:1) to afford 264 as a colourless gum (5.714 g, 96%); \([\alpha]_D^{25} = -2.7\) (c 1.10 in CHCl\(_3\)); IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 3410, 2984, 2934, 1371, 1245, 1214, 1138, 1064, 853; \(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 1.36 (s, 3H, CH\(_3\)Isopropylidene), 1.42 (s, 3H, CH\(_3\)Isopropylidene), 1.43 (s, 3H, CH\(_3\)Isopropylidene), 1.57 (s, 3H, CH\(_3\)Isopropylidene), 1.98 – 2.06 (m, 2H, CH\(_2\)Dithiane), 2.72 – 2.84 (m, 4H, 2 X CH\(_2\)Dithiane), 3.35 (t, \(J = 7.4\) Hz, 1H, OH), 3.61 – 3.65 (m, 1H, H-C\(_4\)), 3.87 – 3.94 (m, 2H, 2 X OH), 3.94 – 3.98 (m, 2H, CH\(_2\)OH), 4.02 – 4.07 (m, 1H, H-C\(_7\)), 4.08 – 4.11 (m, 1H, H-C\(_6\)), 4.11 – 4.18 (m, 2H, H\(^\prime\)-C\(_7\), H-C\(_5\)), 4.46 (dd, \(J = 7.4, 0.9\) Hz, 1H, H-C\(_3\)), 4.83 (d, \(J = 7.4\) Hz, 1H, H-C\(_2\)); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 24.6 (1C, CH\(_2\)Dithiane), 25.1 (1C, CH\(_2\)Dithiane), 25.4 (1C, CH\(_2\)Dithiane), 25.6 (1C, CH\(_3\)Isopropylidene), 25.6 (1C, CH\(_3\)Isopropylidene), 26.1 (1C, CH\(_3\)Isopropylidene), 27.1 (1C, CH\(_3\)Isopropylidene), 58.5 (1C, C\(_1\)), 65.1 (1C, CH\(_2\)OH), 67.5 (1C, C\(_7\)), 70.7 (1C, C\(_4\)), 71.2 (1C, C\(_6\)), 73.5 (1C, C\(_2\)), 75.9 (1C, C\(_5\)), 77.0 (1C, C\(_3\)), 109.4 (1C, C\(_q\)Isopropylidene), 109.5 (1C, C\(_q\)Isopropylidene).

The data is in agreement with the literature reference.\(^1\)
Acetic anhydride (0.32 ml, 3.36 mmol, 1.12 equiv.) was added to a stirred solution of 264 (1.230 g, 3.00 mmol) and Et₃N (0.47 ml, 3.36 mmol, 1.12 equiv.) in DCM (12 ml) at 0 °C. The reaction mixture was stirred overnight at rt. Saturated aqueous NaHCO₃ solution was then added, and the layers were separated. The aqueous layer was then extracted with DCM two times. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO₄. After filtration, the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 3:1) to yield the title compound as a pure colourless oil (1.022 g, 75%); [α]D²⁵ = -6.1 (c 1.05 in CHCl₃); IR νmax (film)/cm⁻¹: 3456, 2985, 2941, 1743, 1379, 1218, 1066; ¹H NMR (500 MHz, Chloroform-d) δ 1.36 (s, 3H, CH₃ Isopropylidene), 1.42 (s, 6H, 2 X CH₃ Isopropylidene), 1.54 (s, 3H, CH₃ Isopropylidene), 1.84 – 1.93 (m, 1H, 1H of CH₂ Dithiane), 2.03 – 2.10 (m, 1H of CH₂ Dithiane), 2.12 (s, 3H, CH₃ Acetate), 2.65 – 2.79 (m, 2H, CH₂ Dithiane), 2.88 – 3.01 (m, 2H, CH₂ Dithiane), 3.51 (d, J = 8.8 Hz, 1H, OH), 3.59 – 3.64 (m, 2H, OH, H-C₄), 3.98 – 4.02 (m, 1H, H-C₆), 4.06 (dd, J = 7.2, 4.2 Hz, 1H, H-C₇), 4.10 – 4.16 (m, 2H, H'-C₇, H-C₅), 4.41 – 4.49 (m, 2H, 1H of CH₂OAc, H-C₃), 4.69 – 4.74 (m, 1H, H-C₂), 4.80 (d, J = 11.9 Hz, 1H, 1H of CH₂OAc); ¹³C NMR (101 MHz, CDCl₃) δ 21.2 (1C, CH₃ Acetate), 24.5 (1C, CH₂ Dithiane), 25.2 (1C, CH₃ Isopropylidene), 25.4 (1C, CH₃ Isopropylidene), 25.9 (1C, CH₂ Dithiane), 26.0 (1C, CH₂ Dithiane), 26.2 (1C, CH₃ Isopropylidene), 27.1 (1C, CH₃ Isopropylidene), 56.7 (1C, Cq Dithiane), 63.8 (1C, CH₂OAc), 67.5 (1C, C₇), 70.7 (1C, C₄), 72.3 (1C, C₆), 73.7 (1C, C₂), 75.9 (1C, C₅), 77.1 (1C, C₅), 109.2 (1C, Cq Isopropylidene), 109.4 (1C, Cq Isopropylidene), 170.4 (1C, Cq Acetate).

The data is in agreement with the literature reference.¹
Freshly recrystallized DBDMH (1.166 g, 4.08 mmol, 2 equiv.) was added to a stirred solution of 266 (0.923 g, 2.04 mmol) in reagent grade acetone (34 ml) at 0 °C which formed a yellow coloured solution. After stirring at 0 °C for 30 mins, saturated aqueous solutions of Na$_2$S$_2$O$_3$ and NaHCO$_3$ were added. The mixture was then extracted four times with EtOAc. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO$_4$. Filtration and removal of the solvent under reduced pressure gave a crude residue. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 5:1) to furnish 383 as a pure colourless oil (0.678 g, 83%); [α]$_D^{25}$ = -8.7 (c 1.01 in CHCl$_3$); IR $\nu$$_{max}$ (film)/cm$^{-1}$: 2989, 2937, 1752, 1259, 1224, 1073; $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 1.35 (s, 6H, 2 X CH$_3$ Isopropylidene), 1.39 (s, 3H, CH$_3$ Isopropylidene), 1.41 (s, 3H, CH$_3$ Isopropylidene), 1.43 (s, 3H, CH$_3$ Isopropylidene), 2.08 (s, 3H, CH$_3$ Acetate), 3.71 (dd, $J$ = 8.8, 1.9 Hz, 1H, H-C-5), 3.94 (d, $J$ = 11.7 Hz, 1H, 1H of CH$_2$OAc), 3.99 (dd, $J$ = 8.8, 3.8 Hz, 1H, H-C-7), 4.05 (dd, $J$ = 8.8, 6.0 Hz, 1H, H'-C-7), 4.20 – 4.26 (m, 1H, H-C-6), 4.34 (d, $J$ = 2.7 Hz, 1H, H-C-2), 4.38 (dd, $J$ = 7.9, 1.9 Hz, 1H, H-C-4), 4.43 (d, $J$ = 11.7 Hz, 1H, 1H of CH$_2$OAc), 4.65 (dd, $J$ = 7.9, 2.7 Hz, 1H, H-C-3); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 21.0 (1C, CH$_3$ Acetate), 24.4 (1C, CH$_3$ Isopropylidene), 25.3 (1C, CH$_3$ Isopropylidene), 25.4 (1C, CH$_3$ Isopropylidene), 25.9 (1C, CH$_3$ Isopropylidene), 26.7 (1C, CH$_3$ Isopropylidene), 27.3 (1C, CH$_3$ Isopropylidene), 64.8 (1C, CH$_2$OAc), 67.2 (1C, C-7), 69.6 (1C, C-5), 70.7 (1C, C-4), 70.8 (1C, C-2), 70.9 (1C, C-3), 73.4 (1C, C-6), 102.3 (1C, C-1), 109.1 (1C, C$_q$ Isopropylidene), 109.6 (1C, C$_q$ Isopropylidene), 109.7 (1C, C$_q$ Isopropylidene), 170.2 (1C, C$_q$ Acetate); HRMS (ESI-TOF) $m$/z found for [M+Na]$^+$: 425.1786; [C$_{19}$H$_{30}$O$_9$+Na]$^+$ requires 425.1782.
((3aR,5R,5aS,8aS,8bR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,7,7-tetramethylytetrabhydro-3aH-bis[(1,3]dioxolo)[4,5-b:4',5']-pyran-3a-yl)methanol (384)

Anhydrous K$_2$CO$_3$ (0.38 g, 2.74 mmol, 1.21 Equiv.) was added to a stirred solution of 383 (0.912 g, 2.27 mmol) in dry methanol (23 ml). The mixture was stirred at rt overnight. The solvent was then removed under reduced pressure. The residue was treated with water (ca. 25 ml) and Et$_2$O (ca. 25 ml), and the layers were separated. The aqueous layer was then extracted with Et$_2$O two times. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO$_4$. Filtration and removal of the solvent under reduced pressure gave a crude residue. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 2:1) to yield the title compound as a pure colourless oil (0.792 g, 97%); [α]$_{D}^{25}$ = -25.6 (c 0.78 in CHCl$_3$); IR $ν_{max}$ (film)/cm$^{-1}$: 3501, 2989, 2941, 1372, 1211, 1072; $^1$H NMR (400 MHz, Chloroform-d) δ 1.36 (s, 3H, CH$_3$ Isopropylidene), 1.37 (s, 3H, CH$_3$ Isopropylidene), 1.39 (s, 3H, CH$_3$ Isopropylidene), 1.42 (s, 3H, CH$_3$ Isopropylidene), 1.45 (s, 3H, CH$_3$ Isopropylidene), 1.54 (s, 3H, CH$_3$ Isopropylidene), 3.59 – 3.69 (m, 2H, 2H of CH$_2$OAc), 3.68 – 3.75 (m, 1H, H-C$_7$), 3.99 (dd, $J = 8.8, 3.7$ Hz, 1H, H-C$_5$), 4.06 (dd, $J = 8.8, 6.0$ Hz, 1H, H-C$_7$), 4.25 (ddd, $J = 9.2, 6.0, 3.7$ Hz, 1H, H-C$_6$), 4.36 (d, $J = 2.7$ Hz, 1H, H-C$_2$), 4.40 (dd, $J = 7.9, 1.9$ Hz, 1H, H-C$_4$), 4.66 (dd, $J = 7.9, 2.7$ Hz, 1H, H-C$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 24.3 (1C, CH$_3$ Isopropylidene), 25.4 (1C, CH$_3$ Isopropylidene), 25.8 (1C, CH$_3$ Isopropylidene), 26.7 (1C, CH$_3$ Isopropylidene), 27.4 (1C, CH$_3$ Isopropylidene), 65.4 (1C, CH$_2$OH), 67.3 (1C, C$_7$), 69.7 (1C, C$_5$), 70.8 (1C, C$_2$), 70.9 (1C, C$_3$), 71.5 (1C, C$_4$), 73.4 (1C, C$_6$), 103.9 (1C, C$_1$), 109.0 (1C, C$_q$ Isopropylidene), 109.6 (1C, C$_q$ Isopropylidene), 109.7 (1C, C$_q$ Isopropylidene); HRMS (ESI-TOF) $m/z$ found for [M+Na]$^+$: 383.1677; [C$_{17}$H$_{28}$O$_8$+Na]$^+$ requires 383.1676.
Pyridine (0.34 ml, 4.21 mmol, 1.5 equiv.) was added to a stirred solution of 384 (1.011 g, 2.81 mmol) in dry DCM (28 ml). After cooling the solution to 0 °C, trifluoromethanesulfonic anhydride (0.47 ml, 2.81 mmol, 1.0 Equiv.) was added dropwise over 15 minutes. The reaction mixture was stirred at 0 °C for 30 minutes then allowed to warm up to rt and monitored by TLC until full consumption of the starting material was observed. The mixture was diluted with DCM and was treated with ice-cold water (ca. 30 ml), and the layers were separated. The aqueous layer was then extracted with DCM twice. The combined organic extracts were then washed with water and dried over anhydrous MgSO₄. Filtration and removal of the solvent under reduced pressure gave the title compound as a pure yellow oil (1.374 g, 99%); $[\alpha]_D^{25} = -6.0$ (c 1.68 in CHCl₃); IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2991, 2939, 1383, 1210, 1146, 1074, 983; $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 1.36 (s, 3H, CH$_3$ Isopropylidene), 1.37 (s, 3H, CH$_3$ Isopropylidene), 1.40 (s, 3H, CH$_3$ Isopropylidene), 3.74 (dd, $J = 8.8$, 1.9 Hz, 1H, H-C-5), 3.98 (dd, $J = 8.8$, 3.7 Hz, 1H, H-C-7), 4.05 (dd, $J = 8.9$, 5.9 Hz, 1H, H'-C-7), 4.22 (ddd, $J = 8.8$, 5.9, 3.7 Hz, 1H, H-C-6), 4.32 (d, $J = 2.7$ Hz, 1H, H-C-2), 4.38 (d, $J = 10.5$ Hz, 1H, 1H of CH$_2$OTf), 4.40 (dd, $J = 7.9$, 1.9 Hz, 1H, H-C-4), 4.52 (d, $J = 10.5$ Hz, 1H, 1H of CH$_2$OTf), 4.69 (dd, $J = 7.9$, 2.7 Hz, 1H, H-C-3); $^{13}$C NMR (101 MHz, CDCl₃) $\delta$ 24.3 (1C, CH$_3$ Isopropylidene), 25.3 (1C, CH$_3$ Isopropylidene), 25.4 (1C, CH$_3$ Isopropylidene), 25.8 (1C, CH$_3$ Isopropylidene), 26.7 (1C, CH$_3$ Isopropylidene), 27.3 (1C, CH$_3$ Isopropylidene), 67.1 (1C, C-7), 70.1 (1C, C-5), 70.5 (1C, C-4), 70.6 (2C, C-2, C-3), 73.3 (1C, C-6), 74.1 (1C, CH$_2$OTf), 100.6 (1C, C-1), 109.7 (1C, C$_q$Isopropylidene), 109.8 (1C, C$_q$Isopropylidene), 110.3 (1C, C$_q$Isopropylidene); $^{19}$F NMR (376
MHz, CDCl₃) δ -74.41; HRMS (ESI-TOF) \( m/z \) found for [M+Na]⁺: 515.1175; 
[C₁₈H₂₇O₁₀F₃S+Na]⁺ requires 515.1174.
S-(((3aS,5R,5aS,8aS,8bR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,7,7-
tetramethyltetrahydro-3aH-bis([1,3]dioxolo[4,5-b:4',5'-d]pyran-3-yl)methyl)
ethanethioate (386)

Potassium thioacetate (0.658 g, 5.76 mmol, 4.4 equiv.) was added to a stirred solution of 385
(0.645 g, 1.31 mmol) in dry MeCN (87 ml), which formed a brown coloured solution. The
mixture was heated under reflux for 16 h, then cooled to rt after which the solvent was removed
in vacuo. The residue was treated with water (ca. 30 ml) and EtOAc (ca. 30 ml), and the layers
were separated. The aqueous layer was then extracted with EtOAc two times. The combined
organic extracts were washed with water, brine, and dried over anhydrous MgSO₄. Filtration and
removal of the solvent under reduced pressure gave a crude brown oil. The crude product was
purified by flash column chromatography on silica gel (petrol:EtOAc, 6:1) to furnish 386 as a
pure yellow oil (0.548 g, quant.); [α]_D^25 = -24.4 (c 0.87 in CHCl₃); IR ν_max (film)/cm⁻¹: 2994,
2937, 1697, 1210, 1070; ¹H NMR (500 MHz, Chloroform-d) δ 1.36 (s, 6H, 2 X CH₃ Isopropylidene),
1.40 (s, 3H, CH₃ Isopropylidene), 1.41 (s, 3H, CH₃ Isopropylidene), 1.49 (s, 3H, CH₃ Isopropylidene), 1.50 (s,
3H, CH₃ Isopropylidene), 2.35 (s, 3H, CH₃ Thioacetate), 3.33 (d, J = 13.8 Hz, 1H, 1H of CH₂SAC), 3.39
(d, J = 13.8 Hz, 1H, 1H of CH₂SAC), 3.68 (dd, J = 8.5, 1.9 Hz, 1H, H-C₅), 3.98 (dd, J = 8.8, 4.0
Hz, 1H, H-C₇), 4.06 (dd, J = 8.8, 6.1 Hz, 1H, H'-C₇), 4.21 (d, J = 2.6 Hz, 1H, H-C₂), 4.24 (ddd,
J = 8.5, 6.1, 4.0 Hz, 1H, H-C₆), 4.36 (dd, J = 7.9, 1.9 Hz, 1H H-C₄), 4.62 (dd, J = 7.9, 2.6 Hz,
1H, H-C₃); ¹³C NMR (101 MHz, CDCl₃) δ 24.5 (1C, CH₃ Isopropylidene), 25.3 (1C, CH₃ Isopropylidene),
25.5 (1C, CH₃ Isopropylidene), 25.9 (1C, CH₃ Isopropylidene), 26.6 (1C, CH₃ Isopropylidene), 27.3 (1C, CH₃
Isopropylidene), 30.6 (1C, CH₃ Thioacetate), 37.3 (1C, CH₂SAC), 67.2 (1C, C₇), 69.9 (1C, C₅), 70.6 (1C,
C₄), 71.2 (1C, C₃), 73.2 (1C, C₂), 73.5 (1C, C₆), 103.1 (1C, C₁), 108.9 (1C, C_q Isopropylidene),
109.5 (1C, C_q Isopropylidene), 109.7 (1C, C_q Isopropylidene), 194.8 (1C, C_q Thioacetate); HRMS (ESI-TOF)
m/z found for [M+Na]⁺: 441.1571; [C₁₉H₃₀O₈S+Na]⁺ requires 441.1559.
S-(((3aS,5R,5aS,8aS,8bR)-5-((R)-1,2-dihydroxyethyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl) ethanethioate (387)

Compound 386 (0.532 g, 1.27 mmol), was dissolved in 90% Acetic acid (54 ml). The stirred reaction mixture was left at 40 °C for 24 hours. The mixture was then concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 3:2) to afford the title compound as a pure colourless solid (0.387 g, 80%); mp 82-85 °C; [α]D25 = -27.1 (c 1.05 in CHCl3); IR νmax (film)/cm⁻¹: 3434, 2989, 2937, 1697, 1210, 1071; ¹H NMR (400 MHz, Chloroform-d) δ 1.35 (s, 3H, CH₃ Isopropyldene), 1.39 (s, 3H, CH₃ Isopropyldene), 1.49 (s, 6H, 2 X CH₃ Isopropyldene), 2.35 (s, 3H), 3.34 (d, J = 13.7 Hz, 1H, 1H of CH₂SAc), 3.38 (d, J = 13.7 Hz, 1H, 1H of CH₂SAc), 3.73 – 3.83 (m, 3H, H-C₅, H'-C₅, H-C₆), 3.88 (ddd, J = 8.2, 4.7, 3.4 Hz, 1H, H-C₆), 4.21 (d, J = 2.6 Hz, 1H, H-C₂), 4.42 (dd, J = 7.9, 1.9 Hz, 1H, H-C₄), 4.64 (dd, J = 7.9, 2.6 Hz, 1H, H-C₃); ¹³C NMR (101 MHz, CDCl₃) δ 24.4 (1C, CH₃ Isopropyldene), 25.0 (1C, CH₃ Isopropyldene), 25.8 (1C, CH₃ Isopropyldene), 26.3 (1C, CH₃ Isopropyldene), 30.4 (1C, CH₃ Thioacetate), 37.4 (1C, CH₂SAc), 64.1 (1C, C-7), 69.1 (1C, C-₅), 70.0 (1C, C-₆), 70.6 (1C, C-₄), 71.2 (1C, C-₃), 73.0 (1C, C-₂), 102.9 (1C, C-₁), 108.8 (1C, C₉ Isopropyldene), 109.6 (1C, C₉ Isopropyldene), 194.6 (1C, C₉ Thioacetate); HRMS (ESI-TOF) m/z found for [M+Na]+: 401.1237; [C₁₆H₂₆OₘS+Na]+ requires 401.1246.
S-((3aS,5R,5aS,8aS,8bR)-5-((R)-2-((tert-butyldimethylsilyl)oxy)-1-hydroxyethyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3-yl)methyl ethanethioate (388)

TBSCl (0.065 g, 0.43 mmol) was added to a stirred solution of 387 (0.136 g, 0.36 mmol) and imidazole (0.060 g, 0.90 mmol, 2.5 equiv.) in dry DCM (3.6 mL) at 0 °C. The resultant mixture was stirred overnight at rt. The reaction mixture was then quenched with saturated aqueous NH₄Cl and extracted with DCM three times. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO₄. Filtration and removal of the solvent under reduced pressure gave a crude yellow oil. The crude oil was purified by flash column chromatography on silica gel (petrol:EtOAc, 5:1) to furnish the title compound as a pure colourless oil (0.112 g, 63%); [α]D25 = -14.3 (c 1.15 in CHCl₃); IR νmax (film)/cm⁻¹: 3530, 2934, 2857, 1698, 1382, 1210, 1073; ¹H NMR (500 MHz, Chloroform-d) δ 0.08 (s, 3H, CH₃ (TBS)), 0.09 (s, 3H, CH₃ (TBS)), 0.90 (s, 9H, 3 X CH₃ tBu (TBS)), 1.36 (s, 3H, CH₃ Isopropylidene), 1.39 (s, 3H, CH₃ Isopropylidene), 1.48 (s, 3H, CH₃ Isopropylidene), 1.50 (s, 3H, CH₃ Isopropylidene), 2.35 (s, 3H, CH₃ Thioacetate), 3.34 (d, J = 13.7 Hz, 1H, 1H of CH₂SAc), 3.38 (d, J = 13.7 Hz, 1H, 1H of CH₂SAc), 3.61 – 3.67 (m, 1H, H-C-7), 3.68 – 3.73 (m, 1H, H-C-5), 3.79 – 3.87 (m, 2H, H-C-6, H’-C-7), 4.19 (d, J = 2.5 Hz, 1H, H-C-2), 4.45 (dd, J = 8.9, 1.9 Hz, 1H, H-C-4), 4.62 (dd, J = 8.0, 2.5 Hz, 1H, H-C-3); ¹³C NMR (101 MHz, CDCl₃) δ -5.3 (1C, CH₃Me (TBS)), -5.2 (1C, CH₃Me (TBS)), 18.4 (1C, Cq tBu (TBS)), 24.5 (1C, CH₃ Isopropylidene), 25.2 (1C, CH₃ Isopropylidene), 25.9 (3C, 3 X CH₃ tBu (TBS)), 26.1 (1C, CH₃ Isopropylidene), 26.7 (1C, CH₃ Isopropylidene), 30.5 (1C, CH₃ Thioacetate), 37.6 (1C, CH₂SAc), 64.1 (1C, C-7), 68.5 (1C, C-5), 69.7 (1C, C-6), 70.7 (1C, C-4), 71.3 (1C, C-3), 73.1 (1C, C-2), 103.0 (1C, C-1), 108.7 (1C, Cq Isopropylidene), 109.5 (1C, Cq Isopropylidene), 194.9 (1C, Cq Thioacetate); HRMS (NSI-FTMS) m/z found for [M+NH₄]⁺: 510.2536; [C₂₂H₄₀O₈SSi+NH₄]⁺ requires 510.2551.
S-(((3aS,5S,5aR,8aS,8bR)-5-(2-((tert-butyldimethylsilyl)oxy)acetyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl)ethanethioate (389)

DMSO (0.13 ml, 1.92 mmol, 3.5 equiv.) was added dropwise to a stirred solution of oxalyl chloride (0.07 ml, 0.82 mmol, 1.5 equiv.) in DCM (4 ml) at -78 °C. The resultant stirred mixture was left for 30 minutes at this temperature. Then a solution of compound 388 (0.271 g, 0.55 mmol) dissolved in DCM was added dropwise to the reaction mixture at -78 °C. The reaction mixture was stirred for 1 hour at this temperature. To this mixture was then added Et₃N (0.37 ml, 2.74 mmol, 5.0 equiv.) and was stirred at -78 °C for 10 minutes before being warmed slowly to rt. The mixture was then stirred at rt until the reaction was complete (monitored by TLC). Once complete, the reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with DCM three times. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO₄. Filtration and removal of the solvent under vacuo furnished 389 as a pure colourless oil (0.232 g, 86%); [α]D²⁵ = -64.7 (c 1.10 in CHCl₃); IR νmax (film)/cm⁻¹: 2990, 2932, 2857, 1742, 1699, 1384, 1211, 1071; ¹H NMR (500 MHz, Chloroform-d) δ 0.07 (s, 3H, CH₃ Me (TBS)), 0.10 (s, 3H, CH₃ Me (TBS)), 0.92 (s, 9H, 3 X CH₃ tBu (TBS)), 1.29 (s, 3H, CH₃ Isopropylidene), 1.40 (s, 3H, CH₃ Isopropylidene), 1.47 (s, 3H, CH₃ Isopropylidene), 1.50 (s, 3H, CH₃ Isopropylidene), 2.38 (s, 3H, CH₃ Thioacetate), 3.31 (d, J = 13.8 Hz, 1H, 1H of CH₂SAc), 3.53 (d, J = 13.8 Hz, 1H, 1H of CH₂SAc), 4.23 (d, J = 2.6 Hz, 1H, H-C-2), 4.37 (d, J = 2.2 Hz, 1H, H-C-3), 4.49 (d, J = 19.6 Hz, 1H, H-C-7), 4.56 (dd, J = 7.8, 2.2 Hz, 1H, H-C-4), 4.60 (d, J = 19.6 Hz, 1H, H'-C-7), 4.61 – 4.64 (m, 1H, H-C-3); ¹³C NMR (126 MHz, CDCl₃) δ -5.4 (1C, CH₃ Me (TBS)), -5.1 (1C, CH₃ Me (TBS)), 18.6 (1C, C₁tBu (TBS)), 24.1 (1C, CH₃ Isopropylidene), 25.0 (1C, CH₃ Isopropylidene), 25.7 (1C, CH₃ Isopropylidene), 26.0 (3C, 3 X CH₃ tBu (TBS)), 26.5 (1C, CH₃ Isopropylidene), 30.5 (1C, CH₃ Isopropylidene), 37.6 (1C, CH₂SAc), 68.9 (1C, C-7), 71.1 (1C, C-3), 72.0 (1C, C-4), 73.1 (1C, C-2), 74.8
(1C, C-5), 102.9 (1C, C-1), 109.2 (1C, C_q Isopropylidene), 109.9 (1C, C_q Isopropylidene), 194.4 (1C, C_q Thioacetate), 205.8 (1C, C-6 Ketone); HRMS (NSI-FTMS) m/z found for [M+NH_4]^+: 508.2382; [C_{22}H_{38}O_8S_i+NH_4]^+ requires 508.2395.
To a stirred solution of \( \text{387} \) (0.425 g, 1.12 mmol) in dry DCM (11 mL) at 0 °C, was added imidazole (0.191 g, 2.808 mmol, 2.5 equiv.) and DMAP (0.027 g, 0.225 mmol, 0.2 equiv.). TIPSCl (0.29 mL, 1.348 mmol, 1.2 equiv.) was then added dropwise to this suspension. The resultant mixture was stirred overnight at rt. The reaction mixture was then quenched with saturated aqueous NH\(_4\)Cl and extracted with DCM three times. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO\(_4\). After filtration, the solvent was removed in vacuo. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 6:1) to furnish the title compound as a pure colourless oil (0.538 g, 90%); \([\alpha]_D^{25} = -25.7 \) (c 0.56 in CHCl\(_3\)); IR \( \nu_{\text{max}} \) (film)/cm\(^{-1}\): 3548, 2941, 2867, 1698, 1382, 1210, 1072; \(^1\)H NMR (500 MHz, Chloroform-\(d\)) \( \delta \): 1.04 – 1.08 (m, 18H, 6 X CH\(_3\)TIPS), 1.09 – 1.17 (m, 3H, 3 X H-CMe\(_2\)TIPS), 1.37 (s, 3H, CH\(_3\)Isopropylidene), 1.39 (s, 3H, CH\(_3\)Isopropylidene), 1.48 (s, 3H, CH\(_3\)Isopropylidene), 1.50 (s, 3H, CH\(_3\)Isopropylidene), 2.34 (s, 3H, CH\(_3\)Thiaoacetate), 3.33 (d, \( J = 13.6 \) Hz, 1H, 1H of CH\(_2\)SAc), 3.38 (d, \( J = 13.6 \) Hz, 1H, 1H of CH\(_2\)SAc), 3.68 – 3.74 (m, 2H, H-C\(_7\)), 3.88 (ddd, \( J = 8.4, 5.9, 3.8 \) Hz, 1H, H-C\(_6\)), 3.92 (dd, \( J = 9.6, 3.8 \) Hz, 1H, H\(^{-}\)C\(_7\)), 4.19 (d, \( J = 2.5 \) Hz, 1H, H-C\(_2\)), 4.46 (dd, \( J = 7.9, 1.9 \) Hz, 1H, H-C\(_4\)), 4.62 (dd, \( J = 7.9, 2.5 \) Hz, 1H, H-C\(_3\)); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \): 12.1 (6C, 6 X CH\(_3\)TIPS), 18.1 (3C, 3 X CHMe\(_2\)TIPS), 24.5 (1C, CH\(_3\)Isopropylidene), 25.2 (1C, CH\(_3\)Isopropylidene), 25.9 (1C, CH\(_3\)Isopropylidene), 26.7 (1C, CH\(_3\)Isopropylidene), 30.5 (1C, CH\(_3\)Thiaoacetate), 37.7 (1C, CH\(_2\)SAc), 64.6 (1C, C\(_7\)), 68.6 (1C, C\(_5\)), 69.8 (1C, C\(_6\)), 70.8 (1C, C\(_4\)), 71.3 (1C, C\(_3\)), 73.2 (1C, C\(_2\)), 102.9 (1C, C\(_1\)), 108.7 (1C, C\(_q\)Isopropylidene), 109.5 (1C, C\(_q\)Isopropylidene), 194.9 (1C, C\(_q\)Thiaoacetate); HRMS (NSI-FTMS) \( m/z \) found for [M+NH\(_4\)]\(^+\): 552.3015; [C\(_{25}\)H\(_{46}\)O\(_8\)SSi+NH\(_4\)]\(^+\) requires 552.3021.
S-(((3aS,5S,5aR,8aS,8bR)-2,2,7,7-tetramethyl-5-((triisopropylsilyl)oxy)acetyl)tetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl) ethanethioate (394)

To a stirred solution of oxalyl chloride (0.08 ml, 1.01 mmol, 1.5 equiv.) in DCM (4 ml) at -78 °C, was added dropwise DMSO (0.16 ml, 2.34 mmol, 3.5 equiv.). The reaction mixture was stirred for 30 minutes at this temperature. Then a solution of compound 392 (0.359 g, 0.67 mmol) dissolved in DCM was added dropwise to the reaction mixture. The reaction mixture was stirred for a further hour at this temperature. To this mixture was then added Et$_3$N (0.45 ml, 3.36 mmol, 5.0 equiv.) and was stirred at -78 °C for 10 minutes before being warmed slowly to rt. The mixture was stirred at rt until the reaction was complete (monitored by TLC). Once complete, the reaction mixture was quenched with saturated aqueous NH$_4$Cl and extracted with DCM three times. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO$_4$. Filtration and evaporation of the solvent under reduced pressure afforded the title compound as a pure colourless oil (0.322 g, 91%); [α]$_D^{25}$ = -68.2 (c 0.98 in CHCl$_3$); IR $\nu_{\text{max}}$(film)/cm$^{-1}$: 2942, 2894, 2867, 1743, 1699, 1256, 1130, 1071; $^1$H NMR (500 MHz, Chloroform-d) $\delta$: 1.04 – 1.08 (m, 18H, 6 X CH$_3$ TIPS), 1.09 – 1.17 (m, 3H, 3 X HMMe$_2$ TIPS), 1.28 (s, 3H, CH$_3$ Isopropylidene), 1.39 (s, 3H, CH$_3$ Isopropylidene), 1.46 (s, 3H, CH$_3$ Isopropylidene), 1.47 (s, 3H, CH$_3$ Isopropylidene), 2.37 (s, 3H, CH$_3$ Thioacetate), 3.32 (d, $J$ = 13.8 Hz, 1H, 1H of CH$_2$SAc), 3.52 (d, $J$ = 13.8 Hz, 1H, 1H of CH$_2$SAc), 4.22 (d, $J$ = 2.2 Hz, 1H, H-C$_2$), 4.41 (d, $J$ = 1.7 Hz, 1H, H-C$_3$), 4.55 (d, $J$ = 19.3 Hz, 1H, H-C$_7$), 4.59 – 4.63 (m, 2H, H-C$_4$, H-C$_3$), 4.65 (d, $J$ = 19.3 Hz, 1H, H’-C$_7$); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 12.1 (3C, 3 X CHMe$_2$ TIPS), 18.0 (3C, 3 X CH$_3$ TIPS), 24.2 (1C, CH$_3$ Isopropylidene), 25.0 (1C, CH$_3$ Isopropylidene), 25.7 (1C, CH$_3$ Isopropylidene), 26.5 (1C, CH$_3$ Isopropylidene), 30.5 (1C, CH$_3$ Thioacetate), 37.6 (1C, CH$_2$SAc), 68.9 (1C, C$_7$), 71.1 (1C, C$_3$), 72.0 (1C, C$_4$), 73.2 (1C, C$_2$), 74.7 (1C, C$_5$), 102.9 (1C, C$_1$), 109.2 (1C, C$_q$
Isopropyldene, 109.9 (1C, C₆ Isopropyldene), 194.4 (1C, C₆ Thioacetate), 205.2 (1C, C₆ Ketone); HRMS (ASAP-OTF) m/z found for [M+H]⁺: 533.2606; [C₂₅H₄₆O₈SSi+H]⁺ requires 533.2604.
S-((3aS,5R,5aS,8aS,8bR)-5-((tert-butyldiphenylsilyl)oxy)-1-hydroxyethyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl ethanethioate (393)

To a stirred solution of 387 (0.173 g, 0.46 mmol) in dry DCM (5 ml) at 0 °C, was added imidazole (0.094 g, 1.38 mmol, 3.0 equiv.) and DMAP (11 mg, 0.0916 mmol, 0.2 equiv.). TBDPSCI (0.14 mL, 0.55 mmol, 1.2 equiv.), was then added dropwise to this suspension. The resultant mixture was stirred at rt for 24 hours. The reaction mixture was then quenched with saturated aqueous NH₄Cl and extracted with DCM three times. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO₄. After filtration, the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 5:1) to furnish the title compound as a pure colourless oil (0.209 g, 74%); [α]D²⁵ = -20.2 (c 0.98 in CHCl₃); IR ν max (film)/cm⁻¹: 3072, 3049, 2890, 2934, 2858, 1742, 1699, 1428, 1211, 1113, 1071; ¹H NMR (500 MHz, Chloroform-d) δ 1.06 (s, 9H, 3 X CH₃ tBu (TBDPS)), 1.35 (s, 3H, CH₃ Isopropylidene), 1.38 (s, 3H, CH₃ Isopropylidene), 1.41 (s, 3H, CH₃ Isopropylidene), 1.47 (s, 3H, CH₃ Isopropylidene), 1.48 (s, 3H, CH₃ Isopropylidene), 1.47 (s, 3H, CH₃ Isopropylidene), 2.30 (s, 3H, CH₃ Thioacetate), 3.34 (s, 2H, CH₂SAc), 3.78 – 3.87 (m, 3H, H-C-5, H-C-7, H'-C-7), 3.92 (ddd, J = 8.7, 5.2, 3.9 Hz, 1H, H-C-6), 4.19 (d, J = 2.5 Hz, 1H, H-C-2), 4.45 (dd, J = 7.9, 2.0 Hz, 1H, H-C-4), 4.62 (dd, J = 7.9, 2.5 Hz, 1H, H-C-3), 7.34 – 7.46 (m, 6H, 6 X H-AR), 7.66 – 7.72 (m, 4H, 4 X H-AR); ¹³C NMR (126 MHz, CDCl₃) δ 19.4 (1C, Cq tBu (TBDPS)), 24.5 (1C, CH₃ Isopropylidene), 25.1 (1C, CH₃ Isopropylidene), 25.9 (1C, CH₃ Isopropylidene), 26.7 (1C, CH₃ Isopropylidene), 27.1 (3C, 3 X CH₃ tBu (TBDPS)), 30.5 (1C, CH₃ Thioacetate), 37.7 (1C, CH₂SAc), 64.7 (1C, C-7), 68.3 (1C, C-5), 70.0 (1C, C-6), 70.8 (1C, C-4), 71.3 (1C, C-3), 73.1 (1C, C-2), 103.0 (1C, C-1), 108.7 (1C, Cq Isopropylidene), 109.5 (1C, Cq Isopropylidene), 127.87 (2C, 2 X C-AR), 127.93 (2C, 2 X C-AR), 129.82 (1C, C-AR), 129.95 (1C, C-AR), 133.07 (1C, CqAR), 133.24 (1C, Cq AR), 135.81 (2C, 2 X C-AR), 135.83 (2C, 2 X C-AR), 195.0 (1C,
Cq Thioacetate; HRMS (NSI-FTMS) m/z found for [M+NH₄]⁺: 634.2855; [C₃₂H₄₄O₈SSi+NH₄]⁺ requires 634.2864.
DMSO (0.08 ml, 1.10 mmol, 3.5 equiv.) was added dropwise to a stirred solution of oxalyl chloride (0.04 ml, 0.47 mmol, 1.5 equiv.) in DCM (4 ml) at -78 °C and was left stirring for 30 minutes. Then a solution of alcohol 393 (0.193 g, 0.31 mmol) dissolved in DCM was added dropwise to the reaction mixture at -78 °C. The reaction mixture was stirred for a further hour at this temperature. To this mixture was then added dropwise Et$_3$N (0.21 ml, 1.56 mmol, 5.0 equiv.) and was stirred at -78 °C for 10 minutes before being warmed slowly to rt. The mixture was stirred at rt until the reaction was complete (monitored by TLC). Once complete, the reaction mixture was quenched with saturated aqueous NH$_4$Cl and extracted with DCM three times. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO$_4$. Filtration and evaporation of the solvent under reduced pressure afforded the title compound as a pure colourless oil (0.160 g, 83%); [α]$_D$ $^{24}$ = -59.3 (c 1.09 in CHCl$_3$); IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3552, 2989, 2934, 1695, 1473, 1428, 1210, 1072; $^1$H NMR (500 MHz, Chlorofo$^8$rm-$d$) δ 1.09 (s, 9H, 3 X CH$_3$ tBu (TBDPS)), 1.25 (s, 3H, CH$_3$ Isopropylidene), 1.25 (s, 3H, CH$_3$ Isopropylidene), 1.37 (s, 3H, CH$_3$ Isopropylidene), 1.44 (s, 3H, CH$_3$ Isopropylidene), 2.22 (s, 3H, CH$_3$ Thioacetate), 3.23 (d, J = 13.8 Hz, 1H, 1H of CH$_2$SAc), 3.30 (d, J = 13.8 Hz, 1H, 1H of CH$_2$SAc), 4.18 (d, J = 2.2 Hz, 1H, H-C$_2$), 4.36 (d, J = 1.8 Hz, 1H, H-C$_5$), 4.49 (d, J = 19.3 Hz, 1H, H-C$_7$), 4.55 – 4.61 (m, 2H, H-C$_3$, H-C$_4$), 4.67 (d, J = 19.3 Hz, 1H, H'-C$_7$), 7.34 – 7.42 (m, 6H, 6 X H-C$_{AR}$), 7.65 – 7.70 (m, 4H, 4 X H-C$_{AR}$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 19.5 (1C, C$_q$ tBu (TBDPS)), 24.2 (1C, CH$_3$ Isopropylidene), 25.0 (1C, CH$_3$ Isopropylidene), 25.5 (1C, CH$_3$ Isopropylidene), 26.4 (1C, CH$_3$ Isopropylidene), 26.9 (3C, 3 X CH$_3$ tBu (TBDPS)), 30.3 (1C, CH$_3$ Thioacetate), 37.4 (1C, CH$_2$SAc), 69.1 (1C, C$_7$), 71.0 (1C, C$_3$), 72.0 (1C, C$_4$), 73.1 (1C, C$_2$), 74.8 (1C, C$_5$), 102.9 (1C, C$_1$), 109.1 (1C, C$_q$ Isopropylidene), 110.0 (1C, C$_q$ Isopropylidene), 127.8 (2C, 2 X C$_{AR}$), 127.9 (2C, 2 X C$_{AR}$), 129.8 (1C, C$_{AR}$), 129.8 (1C, C$_{AR}$), 133.1
(1C, C₄₈AR), 133.4 (1C, C₄₈AR), 135.7 (2C, 2 X C₄₈AR), 135.8 (2C, 2 X C₄₈AR), 194.3 (1C, C₄₈
Thioacetate), 204.8 (1C, C₆ Ketone); HRMS (ASAP-OTF) m/z found for [M+NH₄]⁺: 632.2711;
[C₃₂H₄₂O₈SSi+NH₄]⁺ requires 632.2714.
Trifluoromethanesulfonic anhydride (0.035 ml, 0.21 mmol, 1.0 Equiv.) was added dropwise over 15 minutes to a stirred solution of 388 (0.102 g, 0.21 mmol) and pyridine (0.025 ml, 0.31 mmol, 1.5 equiv.) in dry DCM (2 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes then allowed to warm up to rt and monitored by TLC until full consumption of the starting material was observed. The mixture was diluted with DCM and was treated with ice-cold water (ca. 15 ml), and the layers were separated. The aqueous layer was extracted with DCM twice. The combined organic extracts were then washed with water and dried over anhydrous MgSO₄. Filtration and removal of the solvent under reduced pressure gave the title compound as a pure yellow oil (0.124 g, 96%); [α]D²⁴ = -15.0 (c 0.99 in CHCl₃); IR νmax (film)/cm⁻¹: 2992, 2935, 2859, 1699, 1385, 1211, 1146, 1072, 837; ¹H NMR (500 MHz, Chloroform-d) δ 0.08 (s, 6H, 2 X CH₃ Me (TBS)), 0.90 (s, 9H, 3 X CH₃ tBu (TBS)), 1.32 (s, 3H, CH₃ Isopropylidene), 1.38 (s, 3H, CH₃ Isopropylidene), 1.48 (s, 3H, CH₃ Isopropylidene), 1.49 (s, 3H, CH₃ Isopropylidene), 2.34 (s, 3H, CH₃ Thioacetate), 3.29 (d, J = 13.8 Hz, 1H, 1H of CH₂SAc), 3.40 (d, J = 13.8 Hz, 1H, 1H of CH₂SAc), 3.88 (dd, J = 12.3, 5.3 Hz, 1H, H-C₇), 4.07 (dd, J = 12.3, 2.4 Hz, 1H, H'-C₇), 4.15 (dd, J = 7.2, 1.9 Hz, 1H, H-C₅), 4.20 (d, J = 2.6 Hz, 1H, H-C₂), 4.28 (dd, J = 7.9, 1.9 Hz, 1H, H-C₄), 4.63 (dd, J = 7.9, 2.6 Hz, 1H, H-C₅), 5.04 (dddd, J = 7.2, 5.3, 2.4 Hz, 1H, H-C₆); ¹³C NMR (126 MHz, CDCl₃) δ -5.5 (1C, CH₃ Me (TBS)), -5.4 (1C, CH₃ Me (TBS)), 18.5 (1C, CH₃ Isopropylidene), 24.0 (1C, CH₃ Isopropylidene), 25.1 (1C, CH₃ Isopropylidene), 25.7 (1C, CH₃ Isopropylidene), 26.0 (3C, 3 X CH₃ tBu (TBS)), 26.7 (1C, CH₃ Isopropylidene), 30.5 (1C, CH₃ Thioacetate), 37.3 (1C, CH₂SAc), 61.5 (1C, C-7), 67.1 (1C, C-5), 69.8 (1C, C₄), 71.3 (1C, C-3), 73.0 (1C, C-2), 87.3 (1C, C-6), 103.0 (1C, C-1), 109.1 (1C, CH₃ Isopropylidene),
110.0 (1C, $C_q$ Isopropylidene), 119.9 (1C, $C_q$ CF$_3$ (OTf)), 194.6 (1C, $C_q$ Thioacetate); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -75.09; HRMS (ASAP-TOF) $m/z$ found for [M+H]$^+$: 625.1786; [C$_{23}$H$_{39}$F$_3$O$_{10}$S$_2$Si+H]$^+$ requires 625.1784.
S-(((3aS,5S,5aR,8aS,8bR)-2,2,7,7-tetramethyl-5-((R)-1-((methylsulfonyl)oxy)-2-(tert-butyldimethylsilyloxy)ethyl)tetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl) ethanethioate

(404)

MsCl (0.058 ml, 0.75 mmol, 2 equiv.), was added dropwise to a stirred solution of 388 (0.185 g, 0.38 mmol) and Et3N (0.26 ml, 1.87 mmol, 5 equiv.) in dry DCM (3.8 ml) at 0°C. The orange mixture was stirred at rt for 3 hours. The reaction mixture was then quenched with brine and extracted with DCM three times. The combined organic extracts were washed with saturated aqueous NH4Cl solution, water, brine, and dried over anhydrous MgSO4. Filtration and removal of the solvent under reduced pressure furnished a crude yellow oil. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 5:1) to afford 404 as a pure colourless oil (0.142 g, 66%); [α]25D = -21.6 (c 0.96 in CHCl3); IR νmax (film)/cm⁻¹: 2989, 2935, 2857, 1698, 1360, 1072, 835; 1H NMR (500 MHz, Chloroform-d) δ 0.09 (s, 6H, 2 X CH₃ Me (TBS)), 0.91 (s, 9H, 3 X CH₃ tBu (TBS)), 1.33 (s, 3H, CH₃ Isopropylidene), 1.38 (s, 3H, CH₃ Isopropylidene), 1.49 (s, 3H, CH₃ Isopropylidene), 1.50 (s, 3H, CH₃ Isopropylidene), 2.35 (s, 3H, CH₃ Thioacetate), 3.09 (s, 3H, CH₃ OMs), 3.31 (d, J = 13.7 Hz, 1H, 1H Of CH₂SAc), 3.40 (d, J = 13.7 Hz, 1H, 1H of CH₂SAc), 3.87 (dd, J = 11.9, 4.8 Hz, 1H, H-C7), 4.05 – 4.09 (m, 1H, H’C7), 4.13 (dd, J = 7.5, 1.9 Hz, 1H, H-C5), 4.19 (d, J = 2.6 Hz, 1H, H-C2), 4.33 (dd, J = 7.9, 1.9 Hz, 1H, H-C4), 4.63 (dd, J = 7.9, 2.6 Hz, 1H, H-C3), 4.71 (ddd, J = 7.5, 4.8, 2.4 Hz, 1H, H-C6); 13C NMR (126 MHz, CDCl3) δ -5.3 (1C, CH₃ Me (TBS)), -5.2 (1C, CH₃ Me (TBS)), 18.6 (3C, 3 X CH₃ tBu (TBS)), 24.4 (1C, CH₃ Isopropylidene), 25.2 (1C, CH₃ Isopropylidene), 25.9 (1C, CH₃ Isopropylidene), 26.2 (3C, 3 X CH₃ tBu (TBS)), 26.7 (1C, CH₃ Isopropylidene), 30.5 (1C, CH₃ Thioacetate), 37.4 (1C, CH₂SAc), 38.6 (1C, CH₃ OMs), 62.3 (1C, C7), 67.0 (1C, C5), 70.2 (1C, C4), 71.4 (1C, C3), 73.0 (1C, C2), 81.6 (1C, C6), 103.0 (1C, C1), 109.1 (1C, Cq Isopropylidene), 109.7 (1C, Cq Isopropylidene), 194.7 (1C, Cq Thioacetate);
HRMS (NSI-FTMS) m/z found for [M+NH\textsubscript{4}]\textsuperscript{+}: 588.2319; [C\textsubscript{23}H\textsubscript{42}O\textsubscript{10}S\textsubscript{2}Si+NH\textsubscript{4}]\textsuperscript{+} requires 588.2327.
(S-((S,S,5S,5aR,8aS,8bR)-2,2,7,7-tetramethyl-5-((R)-1-(((trifluoromethyl)sulfonyl)oxy)-2-(triisopropylsilyloxy)ethyl)tetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl) ethanethioate

(405)

Trifluoromethanesulfonic anhydride (0.035 ml, 0.21 mmol, 1.0 Equiv.) was added dropwise over 15 minutes to a stirred solution of 392 (0.111 g, 0.21 mmol) and pyridine (0.025 ml, 0.31 mmol, 1.5 equiv.) in dry DCM (2 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes then allowed to warm up to rt and monitored by TLC until full consumption of the starting material was observed. The mixture was diluted with DCM and was treated with ice-cold water (ca. 15 ml), and the layers were separated. The aqueous layer was extracted with DCM twice. The combined organic extracts were then washed with water and dried over anhydrous MgSO₄. Filtration and evaporation of the solvent in vacuo gave 405 as a pure yellow oil (0.135 g, 98%); [α]D²⁴ = -14.6 (c 0.85 in CHCl₃); IR νmax (film)/cm⁻¹: 2943, 2896, 2869, 1699, 1385, 1211, 1146, 1071, 908; ¹H NMR (400 MHz, Chloroform-d) δ 1.03–1.14 (m, 21H, 6 X CH₃ TIPS, 3 X H-CMe₂ TIPS), 1.31 (s, 3H, CH₃ Isoproplidene), 1.38 (s, 3H, CH₃ Isopropyldiene), 1.47 (s, 3H, CH₃ Isopropyldiene), 1.48 (s, 3H, CH₃ Isopropyldiene), 2.34 (s, 3H, CH₃ Thioacetate), 3.28 (d, J = 13.8 Hz, 1H, 1H of CH₂SAc), 3.40 (d, J = 13.8 Hz, 1H, 1H of CH₂SAc), 3.96 (dd, J = 12.4, 6.2 Hz, 1H, H-C-7), 4.13 (dd, J = 6.2, 2.0 Hz, 1H, H-C-5), 4.19 (d, J = 2.6 Hz, 1H, H-C-2) 4.20 (dd, J = 12.4, 2.4 Hz, 1H, H',C-7), 4.28 (dd, J = 7.9, 2.0 Hz, 1H, H-C-4), 4.62 (dd, J = 7.9, 2.6 Hz, 1H, H-C-3), 5.09 (td, J = 6.2, 2.4 Hz, 1H, H-C-6); ¹³C NMR (101 MHz, CDCl₃) δ 12.1 (3C, 3 X CHMe₂ TIPS), 18.0 (3C, 3 X CH₃ TIPS), 18.0 (3C, 3 X CH₃ TIPS), 24.0 (1C, CH₃ Isopropyldiene), 25.0 (1C, CH₃ Isopropyldiene), 25.7 (1C, CH₃ Isopropyldiene), 26.5 (1C, CH₃ Isopropyldiene), 30.5 (1C, CH₃ Thioacetate), 37.4 (1C, CH₂SAc), 62.1 (1C, C-7), 67.9 (1C, C-5), 70.1 (1C, C-4), 71.3 (1C, C-3), 73.0 (1C, C-2), 88.4 (1C, C-6), 103.0 (1C, C-1), 109.1 (1C, C₉ Isopropyldiene), 110.0 (1C, C₉ Isopropyldiene), 194.6 (1C, C₉ Thioacetate); ¹⁹F NMR
(376 MHz, CDCl\textsubscript{3}) δ -75.02; HRMS (ASAP-TOF) m/z found for [M+H]\textsuperscript{+}: 667.2260; [C\textsubscript{26}H\textsubscript{45}F\textsubscript{3}O\textsubscript{10}S\textsubscript{2}Si+H]\textsuperscript{+} requires 667.2254.
S-(((3aS,5S,5aR,8aS,8bR)-2,2,7,7-tetramethyl-5-((R)-1-((methylsulfonyl)oxy)-2-(triisopropylsilyloxy)ethyl)tetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-y1)methyl) ethanethioate (406)

MsCl (0.039 ml, 0.51 mmol, 2 equiv.), was added dropwise to a stirred solution of 392 (0.136 g, 0.25 mmol) and Et3N (0.18 ml, 1.27 mmol, 5 equiv.) in dry DCM (2.6 ml) at 0 °C. The mixture was stirred at rt until TLC showed complete consumption of starting material. The reaction mixture was then quenched with brine and extracted with DCM three times. The combined organic extracts were washed with saturated aqueous NH₄Cl solution, water, brine, and dried over anhydrous MgSO₄. Filtration and removal of the solvent in vacuo furnished a crude residue. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 5:1) to afford the title compound as a pure colourless oil (0.099 g, 64%); [α]D²⁴ = -17.0 (c 0.99 in CHCl₃); IR νmax (film)/cm⁻¹: 2942, 2894, 2867, 1698, 1360, 1175, 1071, 907; ¹H NMR (500 MHz, Chloroform-d) δ 1.05 – 1.16 (m, 21H, 6 X CH₃ TIPS, 3 X H-CMe₂ TIPS), 1.33 (s, 3H, CH₃ Isopropylidene), 1.38 (s, 3H, CH₃ Isopropylidene), 1.49 (s, 6H, 2 X CH₃ Isopropylidene), 2.34 (s, 3H, CH₃ Thioacetate), 3.09 (s, 3H, CH₃ OMs), 3.30 (d, J = 13.7 Hz, 1H, 1H of CH₂SAc), 3.39 (d, J = 13.7 Hz, 1H, 1H of CH₂SAc), 3.92 (dd, J = 11.8, 5.8 Hz, 1H, H-C-7), 4.12 (dd, J = 6.7, 1.9 Hz, 1H, H-C-5), 4.16 (dd, J = 11.8, 2.4 Hz, 1H, H'-C-7), 4.18 (d, J = 2.6 Hz, 1H, H-C-2), 4.35 (dd, J = 7.9, 1.9 Hz, 1H, H-C-4), 4.63 (dd, J = 7.9, 2.6 Hz, 1H, H-C-3), 4.78 (ddd, J = 6.7, 5.8, 2.4 Hz, 1H, H-C-6); ¹³C NMR (126 MHz, CDCl₃) δ 12.1 (3C, 3 X CHME₂ TIPS), 18.1 (3C, 3 X CH₂ TIPS), 18.1 (3C, 3 X CH₂ TIPS), 24.3 (1C, CH₃ Isopropylidene), 25.1 (1C, CH₃ Isopropylidene), 25.8 (1C, CH₃ Isopropylidene), 26.6 (1C, CH₃ Isopropylidene), 30.5 (1C, CH₃ Thioacetate), 37.5 (1C, CH₂SAc), 38.5 (1C, CH₃ OMs), 62.6 (1C, C-7), 67.7 (1C, C-5), 70.4 (1C, C-4), 71.4 (1C, C-3), 73.1 (1C, C-2), 82.3 (1C, C-6), 103.0 (1C, C-1),

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109.1 (1C, C₉ Isopropylidene), 109.7 (1C, C₉ Isopropylidene), 194.7 (1C, C₉ Thioacetate); HRMS (ASAP-TOF) m/z found for [M+H]+: 613.2537; [C₂₆H₄₈O₁₀S₂Si+H]+ requires 613.2537.
((3aR,5R,5aS,8aS,8bR)-5-((R)-1,2-dihydroxyethyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4′,5′-d]pyran-3a-yl)methyl acetate (411)

Compound 383 (2.705 g, 6.72 mmol), was dissolved in 80% Acetic acid (67 ml). The stirred reaction mixture was heated at 50 °C until TLC showed complete consumption of starting material was observed, after which the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 1:1) to afford 411 as a pure colourless white solid (2.202 g, 90%); mp 118−119 °C; [α]D 22 = -2.1 (c 0.95 in CHCl3); IR νmax (film)/cm⁻¹: 3449, 2991, 2939, 1750, 1208, 1071; ¹H NMR (400 MHz, Chloroform-d) δ 1.35 (s, 3H, CH₃ Isopropylidene), 1.38 (s, 3H, CH₃ Isopropylidene), 1.44 (s, 3H, CH₃ Isopropylidene), 1.53 (s, 3H, CH₃), 2.09 (s, 3H, CH₃ Acetate), 3.71–3.84 (m, 2H, H-C₇, H'-C₇), 3.84–3.90 (m, 2H, H-C₅, H-C₆), 3.96 (d, J = 11.7 Hz, 1H, 1H of CH₂OAc), 4.33 (d, J = 2.7 Hz, 1H, H-C₂), 4.43 (d, J = 11.7 Hz, 1H, 1H of CH₂OAc), 4.43–4.47 (m, 1H, H-C₄), 4.67 (dd, J = 7.9, 2.7 Hz, 1H, H-C₃); ¹³C NMR (101 MHz, CDCl₃) δ 21.0 (1C, CH₃ Acetate), 24.5 (1C, CH₃ Isopropylidene), 25.3 (1C, CH₃ Isopropylidene), 26.0 (1C, CH₃ Isopropylidene), 26.6 (1C, CH₃ Isopropylidene), 63.9 (1C, C-7), 64.9 (1C, CH₂OAc), 68.5 (1C, C-5), 70.2 (1C, C-6), 70.7 (1C, C-2), 70.9 (1C, C-4), 71.1 (1C, C-3), 102.3 (1C, C-1), 109.3 (1C, Cq Isopropylidene), 109.7 (1C, Cq Isopropylidene), 170.2 (1C, Cq Acetate); HRMS (ESI-TOF) m/z found for [M+Na]⁺: 385.1467; [C₁₆H₂₆O₉+Na]⁺ requires 385.1469;

Compound 412 was also isolated as a colourless oil (0.095 g, 3%); [α]D 26 = +5.7 (c 0.84 in CHCl₃); IR νmax (film)/cm⁻¹: 3448, 2990, 2940, 1745, 1250, 1072; ¹H NMR (500 MHz, Chloroform-d) δ 1.36 (s, 3H, CH₃ Isopropylidene), 1.39 (s, 3H, CH₃ Isopropylidene), 1.45 (s, 3H, CH₃ Isopropylidene), 1.53 (s, 3H, CH₃ Isopropylidene), 2.09 (s, 3H, CH₃ Acetate), 2.09 (s, 3H, CH₃ Acetate), 3.86 (dd, J = 8.9, 2.0 Hz, 1H, H-C₅), 3.96 (d, J = 11.7 Hz, 1H, 1H of CH₂OAc), 4.04 (dd, J = 8.9, 5.4, 2.6 Hz, 1H, H-C₆), 4.19 (dd, J = 11.8, 5.4 Hz, 1H, H-C₇), 4.35 (d, J = 2.7 Hz, 1H, H-C₂),
4.41 (dd, J = 11.8, 2.6, H'–C·7), 4.43 (d, J = 11.7 Hz, 1H, 1H of CH₂OAc), 4.47 (dd, J = 7.9, 2.0 Hz, 1H, H-C·4), 4.68 (dd, J = 7.9, 2.7 Hz, 1H, H-C·3); \(^{13}\)C NMR (126 MHz, CDCl₃) δ 21.0 (2C, 2 X CH₃ Acetate), 24.5 (1C, CH₃ Isopropylidene), 25.3 (1C, CH₃ Isopropylidene), 26.0 (1C, CH₃ Isopropylidene), 26.6 (1C, CH₃ Isopropylidene), 64.9 (1C, CH₂OAc), 66.1 (1C, C·7), 67.9 (1C, C·5), 68.8 (1C, C·6), 70.7 (2C, C·4, C·2), 71.1 (1C, C·3), 102.3 (1C, C·1), 109.1 (1C, Cq Isopropylidene), 109.8 (1C, Cq Isopropylidene), 170.2 (1C, Cq Acetate), 171.6 (1C, Cq Acetate); HRMS (NSI-FTMS) \(m/z\) found for [M+NH₄]⁺: 422.2014; [C₁₈H₂₈O₁₀+NH₄]⁺ requires 422.2021;
Et$_3$N (0.10 ml, 0.74 mmol, 2 equiv.) was added to a stirred solution of 411 (0.134 g, 0.37 mmol) in dry DCM (2.2 ml). After cooling the resultant solution to 0 °C, trityl chloride (0.124 g, 0.44 mmol, 1.2 equiv.) was added in one portion. The mixture was stirred at rt overnight. The solvent was then removed under reduced pressure. The residue was treated with water and EtOAc. The layers were separated. The aqueous layer was then extracted with EtOAc twice. The combined organic extracts were dried over anhydrous MgSO$_4$. Filtration and removal of the solvent under reduced pressure gave a crude residue. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 4:1) to yield the title compound as a pure colourless solid (0.199 g, 89%); mp 64–67 °C; [α]$_D^{26}$ = +4.9 (c 0.97 in CHCl$_3$); IR ν$_{max}$ (film)/cm$^{-1}$: 3473, 3059, 3025, 2890, 2936, 1750, 1491, 1448, 1208, 1072; $^1$H NMR (500 MHz, Chloroform-$d$) δ 1.33 (s, 3H, CH$_3$ Isopropylidene), 1.37 (s, 3H, CH$_3$ Isopropylidene), 1.40 (s, 3H, CH$_3$ Isopropylidene), 1.41 (s, 3H, CH$_3$ Isopropylidene), 2.08 (s, 3H, CH$_3$ Acetate), 2.65 (d, $J$ = 6.6 Hz, 1H, OH), 3.32 (dd, $J$ = 9.6, 4.0 Hz, 1H, H'-C$_7$), 3.88–3.97 (m, 2H, H$_2$OAc, H-C$_6$), 4.32 (d, $J$ = 2.6 Hz, 1H, H-C$_2$), 4.39–4.44 (m, 2H, H-C$_4$, 1H of CH$_2$OAc), 4.63 (dd, $J$ = 7.9, 2.6 Hz, 1H, H-C$_3$), 7.20–7.25 (m, 3H, 3 X H-C$_{AR}$), 7.43–7.47 (m, 6H, 6 X H-C$_{AR}$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 21.1 (1C, CH$_3$ Acetate), 24.4 (1C, CH$_3$ Isopropylidene), 25.3 (1C, CH$_3$ Isopropylidene), 26.0 (1C, CH$_3$ Isopropylidene), 26.6 (1C, CH$_3$ Isopropylidene), 65.0 (1C, C$_7$), 68.0 (1C, CH$_2$OAc), 69.6 (1C, C$_5$), 70.7 (1C, C$_6$), 71.1 (1C, C$_2$), 71.1 (2C, C$_3$, C$_4$), 86.9 (1C, C$_q$ Trityl), 102.3 (1C, C$_1$), 109.0 (1C, C$_q$ Isopropylidene), 109.5 (1C, C$_q$ Isopropylidene), 127.2 (3C, 3 X C$_{AR}$), 128.0 (6C, 6 X C$_{AR}$), 128.9 (6C, 6 X C$_{AR}$), 143.9 (3C, 3 X C$_q$AR), 170.2 (1C, C$_q$ Acetate); HRMS (NSI-FTMS) $m/z$ found for [M+NH$_4$]$^+$: 622.3007; [C$_{35}$H$_{40}$O$_9$+NH$_4$]$^+$ requires 622.3011.
A methanolic solution of sodium methoxide (1.68 ml, 3.37 mmol, 2M in methanol, 3 equiv.) was added slowly to a stirred solution of 413 (0.678 g, 1.12 mmol) in dry methanol (11.2 ml). The mixture was stirred at rt until TLC showed complete consumption of starting material. The solvent was then removed in vacuo. The residue was treated with water (ca. 10 ml) and Et₂O (ca. 10 ml), and the layers were separated. The aqueous layer was extracted with Et₂O two times. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO₄. Filtration and removal of the solvent under reduced pressure gave a crude residue. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 3:1) to yield the title compound as a pure colourless solid (0.591 g, 94%); mp 70–72 °C; [α]D²⁶ = +3.8 (c 1.36 in CHCl₃); IR νmax (film)/cm⁻¹: 3476, 3059, 3033, 2989, 2936, 1491, 1449, 1213, 1072; ¹H NMR (400 MHz, Chloroform-d) δ 1.32 (s, 3H, CH₃ Isopropylidene), 1.35 (s, 3H, CH₃ Isopropylidene), 1.40 (s, 3H, CH₃ Isopropylidene), 1.42 (s, 3H, CH₃ Isopropylidene), 1.98 – 2.00 (m, 1H, OH), 2.69 (d, J = 6.5 Hz, 1H, OH), 3.32 (dd, J = 9.6, 4.1 Hz, 1H, H-C₇), 3.39 (dd, J = 9.6, 4.2 Hz, 1H, H'-C₇), 3.54 – 3.70 (m, 2H, 2H of CH₂OH), 3.87 – 4.00 (m, 2H, H-C₆, H-C₅), 4.32 (d, J = 2.6 Hz, 1H, H-C₂), 4.39 (dd, J = 7.9, 1.8 Hz, 1H, H-C₄), 4.62 (dd, J = 7.9, 2.6 Hz, 1H, H-C₃), 7.19 – 7.31 (m, 9H, 9 X H-AR), 7.42 – 7.47 (m, 6H, 6 X H-AR); ¹³C NMR (101 MHz, CDCl₃) δ 24.3 (1C, CH₃ Isopropylidene), 25.5 (1C, CH₃ Isopropylidene), 25.8 (1C, CH₃ Isopropylidene), 26.6 (1C, CH₃ Isopropylidene), 64.0 (1C, C-7), 65.7 (1C, CH₂OH), 68.0 (1C, C-6), 69.7 (1C, C-5), 71.0 (1C, C-3), 71.1 (1C, C-4), 71.4 (1C, C-2), 86.9 (1C, Cq Trityl), 103.8 (1C, C-1), 108.8 (1C, Cq Isopropylidene), 109.4 (1C, Cq Isopropylidene), 127.2 (3C, 3 X C-AR), 128.0 (6C, 6 X C-AR), 129.0 (6C, 6 X C-AR), 143.9 (3C, 3 X Cq AR); HRMS (NSI-FTMS) m/z found for [M+NH₄]+: 580.2901; [C₃₃H₃₈O₈+NH₄]⁺ requires 580.2905.
MsCl (0.036 ml, 0.47 mmol, 2.5 equiv.) was added dropwise to a stirred solution of \textbf{414} (0.106 g, 0.19 mmol) and Et$_3$N (0.09 ml, 0.66 mmol, 3.5 equiv.) in dry DCM (1.9 ml) at 0 °C. The mixture was stirred at rt for 2 hours. Saturated aqueous NaHCO$_3$ was then added and the mixture was extracted three times with DCM. The combined organic extracts were washed with water twice, brine, and dried over anhydrous MgSO$_4$. Filtration and removal of the solvent under reduced pressure gave a crude yellow oil. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 3:1) to yield the title compound as a pure colourless solid (0.133g, 70%); mp 75–79 °C; [α]$_D$ = +7.2 (c 0.67 in CHCl$_3$); IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3026, 2925, 2854, 1491, 1450, 1360, 1176, 1073, 969; $^1$H NMR (500 MHz, Chloroform-d) δ 1.31 (s, 6H, 2 X CH$_3$ Isopropylidene), 1.32 (s, 3H, CH$_3$ Isopropylidene), 1.34 (s, 3H, CH$_3$ Isopropylidene), 2.96 (s, 3H, CH$_3$ OMs), 3.00 (s, 3H, CH$_3$ OMs), 3.25 (dd, $J = 11.2$, 3.8 Hz, 1H, H-C$_7$), 3.68 (dd, $J = 11.2$, 2.3 Hz, 1H, H'-C$_7$), 4.05 (d, $J = 10.9$ Hz, 1H, 1H of CH$_2$OMs), 4.17 (d, $J = 10.9$ Hz, 1H, 1H of CH$_2$OMs), 4.30 (d, $J = 2.7$ Hz, 1H, H-C$_2$), 4.37 – 4.40 (m, 2H, H-C$_4$, H-C$_5$), 4.66 – 4.70 (m, 1H, H-C$_3$), 4.85 (ddd, $J = 7.3$, 3.8, 2.3 Hz, 1H, H-C$_6$), 7.20 – 7.25 (m, 3H, 3 x H-C$_{AR}$), 7.27 – 7.32 (m, 6H, 6 x H-C$_{AR}$), 7.45 – 7.49 (m, 6H, 6 x H-C$_{AR}$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 24.2 (1C, CH$_3$ Isopropylidene), 25.3 (1C, CH$_3$ Isopropylidene), 25.9 (1C, CH$_3$ Isopropylidene), 26.5 (1C, CH$_3$ Isopropylidene), 37.8 (1C, CH$_3$ OMs), 38.8 (1C, CH$_3$ OMs), 61.9 (1C, C$_7$), 67.0 (1C, C$_4$), 69.1 (1C, CH$_2$OMs), 70.1 (1C, C$_5$), 70.4 (1C, C$_2$), 80.0 (1C, C$_3$), 79.9 (1C, C$_6$), 87.1 (1C, C$_{q Trityl}$), 101.4 (1C, C$_1$), 109.8 (1C, C$_{q Isopropylidene}$), 110.0 (1C, C$_{q Isopropylidene}$), 127.2 (3C, 3 x C$_{AR}$), 127.9 (6C, 6 X C$_{AR}$), 129.0 (6C, 6 X C$_{AR}$), 143.6 (3C, 3 x C$_{q AR}$); HRMS (ASAP-TOF) $m/z$ found for [M+NH$_4$]$: 736.2462; [C$_{35}$H$_{42}$O$_{12}$S$_2$+NH$_4$]$^+$ requires 736.2465.
(R)-1-(((3aR,5S,5aR,8aS,8bR)-2,2,7,7-tetramethyl-3a-
(((trifluoromethyl)sulfonyloxy)methyl)tetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-
d]pyran-5-yl)-2-(trityloxy)ethyl trifluoromethanesulfonate (417)

Trifluoromethanesulfonic anhydride (0.071 ml, 0.43 mmol, 2.4 equiv.) was added dropwise over
15 minutes to a stirred solution of pyridine (0.057 ml, 0.71 mmol, 4 equiv.) and 417 (0.100 g,
0.18 mmol) in dry DCM (1.8 ml) at 0 °C. The reaction mixture was stirred at 0 °C and monitored
by TLC until full consumption of the starting material was observed. The mixture was diluted
with DCM and was treated with ice-cold water (ca. 10 ml), and the layers were separated. The
aqueous layer was then extracted with DCM twice. The combined organic extracts were washed
with water, saturated aqueous copper sulfate solution and dried over anhydrous MgSO₄.
Filtration and removal of the solvent in vacuo afforded a pure yellow oil (0.128 g, 87%); [α]D₂²²
= +4.9 (c 0.89 in CHCl₃); IR νmax (film)/cm⁻¹: 3000, 2925, 2853, 1491, 1450, 1417, 1385, 1210,
1074, 983; ¹H NMR (500 MHz, Chloroform-d) δ 1.29 (s, 3H, CH₃ Isopropylidene), 1.31 (s, 3H, CH₃ Isopropylidene), 1.33 (s, 3H, CH₃ Isopropylidene), 1.35 (s, 3H, CH₃ Isopropylidene), 3.43 (dd, J = 11.8, 3.5 Hz,
1H, H-C-7), 3.62 (dd, J = 11.8, 2.3 Hz, 1H, H'-C-7), 4.25 (d, J = 10.5 Hz, 1H, 1H of CH₂OTf),
4.31 (d, J = 2.7 Hz, 1H, H-C-2), 4.37 (dd, J = 7.8, 2.1 Hz, 1H, H-C-4), 4.39 (d, J = 10.5 Hz, 1H,
1H of CH₂OTf), 4.50 (dd, J = 7.7, 2.1 Hz, 1H, H-C-5), 4.71 (dd, J = 7.8, 2.7 Hz, 1H, H-C-3), 5.11
(ddd, J = 7.7, 3.5, 2.3 Hz, 1H, H-C-6), 7.22 – 7.27 (m, 3H, 3 X H-CAR), 7.27 – 7.33 (m, 6H, 6 X
H-CAR), 7.44 – 7.48 (m, 6H, 6 X H-CAR); ¹³C NMR (126 MHz, CDCl₃) δ 23.7 (1C, CH₃ Isopropylidene), 25.0 (1C, CH₃ Isopropylidene), 25.6 (1C, CH₃ Isopropylidene), 26.5 (1C, CH₃ Isopropylidene), 61.2 (1C, C-7), 66.8 (1C, C-5), 69.5 (1C, C-4), 70.3 (1C, C-2), 70.6 (1C, C-3), 73.5 (1C, CH₂OTf), 85.3 (1C, C-6), 87.3 (1C, Cq Trityl), 100.6 (1C, C-1), 110.0 (1C, Cq Isopropylidene), 110.7 (1C, Cq Isopropylidene), 127.4 (3C, 3 X CqAR), 128.0 (6C, 6 X CqAR), 129.0 (6C, 6 X CqAR), 143.2 (3C, 3 X Cq AR); ¹⁹F NMR
(471 MHz, CDCl₃) δ -74.40, -75.08; HRMS (ASAP-TOF) m/z found for [M]⁺: 826.1537; [C₃₅H₃₆F₆O₁₂S₂]⁺ requires 826.1552.
To a stirred solution of 411 (0.753 g, 2.08 mmol) in dry DCM at 0 °C, was added imidazole (0.353 g, 5.19 mmol, 2.5 equiv.) and DMAP (0.051 g, 0.42 mmol, 0.2 equiv.). TIPSCl (0.53 ml, 2.49 mmol, 1.2 equiv.), was then added dropwise to this suspension. The resultant mixture was stirred at rt for 24hr. The reaction mixture was then quenched with saturated aqueous NH₄Cl and extracted with DCM three times. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO₄. After filtration, the solvent was removed in vacuo. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 11:2) to furnish the title compound as a pure colourless oil (0.961 g, 89%); [α]D²² = +2.6 (c 0.91 in CHCl₃); IR νmax (film)/cm⁻¹: 3543, 2990, 2943, 2895, 2867, 1753, 1230, 1073; ¹H NMR (500 MHz, Chloroform-d) δ 1.04 – 1.08 (m, 18H, 6 X CH₃ TIPS), 1.08 – 1.16 (m, 3H, 3 X H-CMe₂ TIPS), 1.36 (s, 3H, CH₃ Isopropylidene), 1.39 (s, 3H, CH₃ Isopropylidene), 1.45 (s, 3H, CH₃ Isopropylidene), 1.51 (s, 3H, CH₃ Isopropylidene), 2.09 (s, 3H, CH₃ Acetate), 2.80 (d, J = 5.3 Hz, 1H, OH), 3.72 (dd, J = 9.6, 5.4 Hz, 1H, H-C₇), 3.80 (dd, J = 8.4, 1.9 Hz, 1H, H-C₅), 3.84 – 3.89 (m, 1H, H-C₆), 3.91 (dd, J = 9.6, 3.8 Hz, 1H, H'-C₇), 3.96 (d, J = 11.6 Hz, 1H, 1H of CH₂OAc), 4.33 (d, J = 2.6 Hz, 1H, H-C₂), 4.42 (d, J = 11.6 Hz, 1H, 1H of CH₂OAc), 4.49 (dd, J = 7.9, 1.9 Hz, 1H, H-C₄), 4.66 (dd, J = 7.9, 2.6 Hz, 1H, H-C₃); ¹³C NMR (126 MHz, CDCl₃) δ 12.0 (3C, 3 X CHMe₂ TIPS), 18.1 (3C, 3 X CH₃ TIPS), 21.0 (1C, CH₃ Isopropylidene), 24.4 (1C, CH₃ Isopropylidene), 25.3 (1C, CH₃ Isopropylidene), 26.0 (1C, CH₃ Isopropylidene), 26.8 (1C, CH₃ Acetate), 64.4 (1C, C-7), 65.0 (1C, CH₂OAc), 68.3 (1C, C₅), 69.6 (1C, C₆), 70.7 (1C, C₂), 71.0 (1C, C₄), 71.0 (1C, C₂), 102.2 (1C, C-1), 109.0 (1C, C₉ Isopropylidene), 109.5 (1C, C₉ Isopropylidene), 170.2 (1C, C₉ Acetate); HRMS (ESI-TOF) m/z found for [M+Na]⁺: 541.2821; [C₂₅H₄₆O₉Si+Na]⁺ requires 541.2809.
(R)-1-((3aR,5R,5aS,8aS,8bR)-3a-(hydroxymethyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)-2-((triisopropylsilyl)oxy)ethanol (419)

Anhydrous K$_2$CO$_3$ (0.156 g, 1.13 mmol, 1.21 equiv.) was added to a stirred solution of 418 (0.485 g, 0.93 mmol) in dry methanol (9.4 ml). The mixture was stirred at rt until TLC showed complete consumption of starting material. The solvent was then removed under reduced pressure. The residue was treated with water and Et$_2$O, and the layers were separated. The aqueous layer was then extracted with Et$_2$O two times. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO$_4$. Filtration and removal of the solvent under reduced pressure gave a crude oil. The crude product was purified by flash column chromatography (petrol:EtOAc, 4:1) to yield the title compound as a pure colourless oil (0.344 g, 77%); [α]$_D^{22}$ = -14.2 (c 0.73 in CHCl$_3$); IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3503, 2942, 2894, 2867, 1101, 1072; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$1.02 – 1.17 (m, 21H, 6X CH$_3$ TIPS, 3X H-CMe$_2$ TIPS), 1.38 (s, 6H, 2X CH$_3$ Isopropylidene), 1.46 (s, 3H, CH$_3$ Isopropylidene), 1.52 (s, 3H, CH$_3$ Isopropylidene), 2.81 (br, 1H, OH), 3.63 (d, $J$ = 11.6 Hz, 1H, 1H of CH$_2$OH), 3.69 (d, $J$ = 11.6 Hz, 1H, 1H of CH$_2$OH), 3.73 – 3.79 (m, 1H, H-C$_7$), 3.83 (dd, $J$ = 8.4, 1.8 Hz, 1H, H-C$_5$), 3.85 – 3.94 (m, 2H, H-C$_6$, H'-C$_7$), 4.35 (d, $J$ = 2.6 Hz, 1H, H-C$_2$), 4.51 (dd, $J$ = 7.9, 1.8 Hz, 1H, H-C$_4$), 4.67 (dd, $J$ = 7.9, 2.6 Hz, 1H, H-C$_3$); $^{13}$C NMR (101 MHz, CDC$_3$) $\delta$ 12.0 (3C, 3X CHMe$_2$ TIPS), 18.1 (6C, 6X CH$_3$ TIPS), 24.3 (1C, CH$_3$ Isopropylidene), 25.5 (1C, CH$_3$ Isopropylidene), 25.8 (1C, CH$_3$ Isopropylidene), 26.7 (1C, CH$_3$ Isopropylidene), 64.3 (1C, C-$\gamma$), 65.6 (1C, CH$_2$OH), 68.3 (1C, C$_5$), 69.9 (1C, C$_6$), 70.9 (1C, C$_4$), 71.0 (1C, C$_3$), 71.5 (1C, C$_2$), 103.8 (1C, C$_1$), 108.8 (1C, C$_q$ Isopropylidene), 109.4 (1C, C$_q$ Isopropylidene); HRMS (ASAP-TOF) $m/z$ found for [M+H]$^+$: 472.2888; [C$_{23}$H$_{44}$O$_8$Si+H]$^+$ requires 477.2884.
MsCl (0.039 ml, 0.50 mmol, 2.5 equiv.) was added dropwise to a stirred solution of 419 (0.095 g, 0.20 mmol) and Et$_3$N (0.084 ml, 0.60 mmol, 3 equiv.) in dry DCM (2 ml) at 0 °C. The mixture was stirred at rt for 2 hours. Saturated aqueous NaHCO$_3$ was then added and the mixture was extracted three times with DCM. The combined organic extracts were washed with water twice, brine, and dried over anhydrous MgSO$_4$. Filtration and removal of the solvent under reduced pressure gave a crude yellow oil. The crude product was purified by flash column chromatography (petrol:EtOAc, 5:2) to yield 420 as a pure colourless oil (0.107 g, 85%); $[\alpha]_D^{26} = -12.4$ (c 0.97 in CHCl$_3$); IR $\nu_{\max}$ (film)/cm$^{-1}$: 2942, 2867, 1359, 1210, 1177, 1070, 969; $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 1.05 – 1.09 (m, 18H, 6 X CH$_3$TIPS), 1.09 – 1.16 (m, 3H, 3 X H-CMe$_2$TIPS), 1.33 (s, 3H, CH$_3$Isopropylidene), 1.40 (s, 3H, CH$_3$Isopropylidene), 1.44 (s, 3H, CH$_3$Isopropylidene), 1.55 (s, 3H, CH$_3$Isopropylidene), 3.05 (s, 3H, CH$_3$OMs), 3.09 (s, 3H, CH$_3$OMs), 3.92 (dd, $J = 11.8, 5.5$ Hz, 1H, H-C$_7$), 4.16 – 4.22 (m, 2H, H'-C$_7$, 1H of CH$_2$OMs), 4.25 (dd, $J = 6.5, 1.8$ Hz, 1H, H-C$_3$), 4.27 (d, $J = 10.9$ Hz, 1H of CH$_2$OMs), 4.33 (d, $J = 2.6$ Hz, 1H, H-C$_2$), 4.38 (dd, $J = 7.9, 1.8$ Hz, 1H, H-C$_4$), 4.68 (dd, $J = 7.9, 2.6$ Hz, 1H, H-C$_3$), 4.75 (ddd, $J = 6.4, 5.5, 2.3$ Hz, 1H, H-C$_6$); $^{13}$C NMR (126 MHz, CDCI$_3$) $\delta$ 12.1 (3C, 3 X CHMe$_2$TIPS), 18.1 (3C, 3 X CH$_3$TIPS), 24.1 (1C, CH$_3$Isopropylidene), 25.4 (1C, CH$_3$Isopropylidene), 25.9 (1C, CH$_3$Isopropylidene), 26.8 (1C, CH$_3$Isopropylidene), 37.7 (1C, CH$_3$OMs), 38.5 (1C, CH$_3$OMs), 62.4 (1C, C$_7$), 67.9 (1C, C$_3$), 69.1 (1C, CH$_2$OMs), 70.4 (2C, C$_2$, C$_4$), 71.0 (1C, C$_3$), 82.2 (1C, C$_6$), 101.4 (1C, C$_1$), 109.8 (1C, C$_q$Isopropylidene), 110.0 (1C, C$_q$Isopropylidene); HRMS (ASAP-TOF) m/z found for [M+H]$^+$: 633.2449; [C$_{25}$H$_{48}$O$_{12}$S$_2$Si+H]$^+$ requires 633.2435.
Trifluoromethanesulfonic anhydride (0.075 ml, 0.45 mmol, 2.4 equiv.) was added dropwise over 15 minutes to a stirred solution of 419 (0.089 g, 0.19 mmol) and pyridine (0.06 ml, 0.75 mmol, 4 equiv.) in dry DCM (1.9 ml) at 0 °C. The reaction mixture was stirred at 0 °C and monitored by TLC until full consumption of the starting material was observed. The mixture was diluted with DCM and was treated with ice-cold water (ca. 10 ml), and the layers were separated. The aqueous layer was extracted with DCM twice. The combined organic extracts were washed with water, saturated aqueous copper sulfate solution, and dried over anhydrous MgSO₄. Filtration and removal of the solvent in vacuo afforded the title compound as a pure yellow oil (0.131 g, 99%); [α]D²⁶ = -6.5 (c 0.93 in CHCl₃); IR νmax (film)/cm⁻¹: 2945, 2869, 1416, 1385, 1210, 1145, 1071, 920; 1H NMR (500 MHz, Chloroform-d) δ 1.05 – 1.09 (m, 18H, 6 X CH₃ TIPS), 1.09 – 1.16 (m, 3H, 3 X H-CMe₂ TIPS), 1.34 (s, 3H, CH₃ Isopropylidene), 1.39 (s, 3H, CH₃ Isopropylidene), 1.43 (s, 3H, CH₃ Isopropylidene), 1.54 (s, 3H, CH₃ Isopropylidene), 4.00 (dd, J = 12.2, 5.7 Hz, 1H, H-C-7), 4.20 (dd, J = 12.2, 2.5 Hz, 1H, H'-C-7), 4.28 (dd, J = 5.7, 1.9 Hz, 1H, H-C-5), 4.31 (d, J = 2.7 Hz, 1H, H-C-2), 4.34 (dd, J = 7.9, 1.9 Hz, 1H, H-C-4), 4.37 (d, J = 10.6 Hz, 1H, 1H of CH2OTf), 4.50 (d, J = 10.6 Hz, 1H, 1H of CH2OTf), 4.70 (dd, J = 7.9, 2.7 Hz, 1H, H-C-3), 5.07 (td, J = 5.7, 2.5 Hz, 1H, H-C-6); 13C NMR (101 MHz, CDCl₃) δ 12.1 (3C, 3 X CHMe₂ TIPS), 18.0 (3C, 3 X CH₃ TIPS), 18.0 (3C, 3 X CH₃ TIPS), 23.7 (1C, CH₃ Isopropylidene), 25.0 (1C, CH₃ Isopropylidene), 25.6 (1C, CH₃ Isopropylidene), 26.7 (1C, CH₃ Isopropylidene), 61.8 (1C, C-7), 67.8 (1C, C-5), 69.9 (1C, C-4), 70.5 (1C, C-2), 70.6 (1C, C-3), 74.1 (1C, CH2OTf), 87.6 (1C, C-6), 100.6 (1C, C-1), 110.1 (1C, Cq Isopropylidene), 110.5 (1C, Cq Isopropylidene); 19F
NMR (471 MHz, CDCl3) δ -74.38, -74.93; HRMS (ASAP-TOF) m/z found for [M+H]+: 741.1870; [C25H42O12F6S2Si+H]+ requires 741.1870.
S-(((3αS,5S,5αR,8αS,8βR)-5-(2-hydroxyacetyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl) ethanethioate (427)

Compound 394 (0.084 g, 0.16 mmol), was dissolved in 80% Acetic acid (0.20 ml). The stirred reaction mixture was heated at 70 °C for 72 hours, after which the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 1:1) to afford the title compound as a colourless oil (0.039 g, 66%); [α]_D^{25} = -80.3 (c 1.17 in CHCl₃); IR ν_{max} (film)/cm⁻¹: 3496, 2890, 2937, 1731, 1698, 1211, 1070; ^1H NMR (400 MHz, Chloroform-d) δ 1.30 (s, 3H, CH₃ Isopropylidene), 1.40 (s, 3H, CH₃ Isopropylidene), 1.47 (s, 3H, CH₃ Isopropylidene), 1.50 (s, 3H, CH₃ Isopropylidene), 2.39 (s, 3H, CH₃ Thioacetate), 3.31 (d, J = 13.8 Hz, 1H, CH₂SAc), 3.52 (d, J = 13.8 Hz, 1H, CH₂SAc), 4.25 (d, J = 2.7 Hz, 1H, H-C₂), 4.36 (d, J = 20.5 Hz, 1H, H-C₇), 4.41 (d, J = 2.2 Hz, 1H, H-C₅), 4.55 (dd, J = 7.8, 2.2 Hz, 1H, H′-C₄), 4.56 (d, J = 20.5 Hz, 1H, H′-C₇), 4.65 (dd, J = 7.8, 2.7 Hz, 1H, H-C₃); ^13C NMR (101 MHz, CDCl₃) δ 24.1 (1C, CH₃ Isopropylidene), 24.9 (1C, CH₃ Isopropylidene), 25.7 (1C, CH₃ Isopropylidene), 26.5 (1C, CH₃ Isopropylidene), 30.5 (1C, CH₃ Thioacetate), 37.5 (1C, CH₂SAc), 68.0 (1C, C₇), 71.1 (1C, C₃), 72.1 (1C, C₄), 73.2 (1C, C₂), 74.6 (1C, C₅), 103.0 (1C, C₁), 109.3 (1C, Cq Isopropylidene), 110.2 (1C, Cq Isopropylidene), 194.3 (1C, Cq Thioacetate), 208.7 (1C, C₆ Ketone); HRMS (NSI-FTMS) m/z found for [M+NH₄]⁺: 394.1528; [C₁₆H₂₆O₈S+NH₄]⁺ requires 394.1530.
Sodium acetate (2.0 g, 24.4 mmol, 1.09 equiv.) was added to acetic anhydride (40 ml) at rt. The mixture was then heated to 120 °C and stirred for 30 minutes. Then D-galactose 433 (4.0 g, 22.2 mmol) was added portion wise to the stirred solution. The reaction mixture was stirred at 120 °C for 3 hours. The mixture was then cooled and poured into ice-cold water (ca. 40 ml), then neutralized with saturated aqueous NaHCO₃. The mixture was then extracted with DCM (ca. 200 X 3). The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO₄. Filtration and removal of the solvent under reduced pressure gave a crude colourless residue. Recrystallization from hexane/ethyl acetate (2:1) afforded the title compound as a colourless solid (5.563 g, 64%); mp 140 – 143 °C [lit. 143-144 °C], [8] [lit. 139-142 °C]9; [α]D²² = +22.7 (c 1.04 in CHCl₃) [lit. [α]D²⁰ = +22 (c 1 in CHCl₃)]10 [lit. [α]D²₃.₅ = +27.1 (c 1.03 in CHCl₃)]¹¹; IR νmax (film)/cm⁻¹: 2984, 2941, 1752, 1223, 1067; ¹H NMR (400 MHz, Chloroform-d) δ 1.99 (s, 3H, CH₃ Acetate), 2.04 (s, 6H, 2 X CH₃ Acetate), 2.12 (s, 3H, CH₃ Acetate), 2.16 (s, 3H, CH₃ Acetate), 4.05 (ddd, J = 7.1, 6.1, 1.2 Hz, 1H, H-C₅), 4.09-4.18 (m, 2H, H-C₇, H’-C₇), 5.07 (dd, J = 10.4, 3.4 Hz, 1H, H-C₃), 5.33 (dd, J = 10.4, 8.3 Hz, 1H, H-C₂), 5.42 (dd, J = 3.4, 1.2 Hz, 1H, H-C₄), 5.70 (d, J = 8.3 Hz, 1H, H-C₁); ¹³C NMR (101 MHz, CDCl₃) δ 20.6 (1C, CH₃ Acetate), 20.7 (1C, CH₃ Acetate), 20.7 (2C, 2 X CH₃ Acetate), 20.9 (1C, CH₃ Acetate), 61.1 (1C, C₆), 66.9 (1C, C₄), 67.9 (1C, C₂), 70.9 (1C, C₃), 71.8 (1C, C₅), 92.2 (1C, C₈), 169.1 (1C, C₉ Acetate), 169.5 (1C, C₉ Acetate), 170.0 (1C, C₉ Acetate), 170.2 (1C, C₉ Acetate), 170.4 (1C, C₉ Acetate).

Data is in agreement with the literature references.⁸–¹¹
(TMSCN (9.6 ml, 76.7 mmol, 3 equiv.) was added dropwise to a stirred solution of compound β-63 (10.0 g, 25.6 mmol) in anhydrous nitromethane (42 ml), which formed a brown solution. After heating the solution to 35-37 °C, BF₃.OEt₂ (3.5 ml, 28.4 mmol, 1.1 equiv.) was added dropwise. The dark brown solution was stirred at 35-37 °C for 2 hours. The mixture was then concentrated in vacuo. The brown residue was dissolved in DCM and washed with water, then saturated aqueous NaHCO₃ three times, water, brine, and dried over anhydrous MgSO₄. Filtration and evaporation of the solvent in vacuo gave a crude brown residue. Recrystallization from methanol furnished 64 as yellow crystals (6.166 g, 67%); mp 166-168 °C [lit. 169-170 °C]¹²,¹³; [α]D²² = +36.0 (c 1.10 in CHCl₃) [lit. [α]D¹⁸ = +34.1 (c 1.33 in CHCl₃)]¹² [lit. [α]D²⁵ = +35.7 (c 3.74 in CHCl₃)]¹³; IR νmax (film)/cm⁻¹: 2984, 2941, 1752, 1223, 1067; ¹H NMR (400 MHz, CDCl₃) δ 2.00 (s, 3H, CH₃ Acetate), 2.06 (s, 3H, CH₃ Acetate), 2.12 (s, 3H, CH₃ Acetate), 2.18 (s, 3H, CH₃ Acetate), 3.91 – 3.97 (m, H-C₅), 4.12 (d, J = 6.4 Hz, 2H, H-C₆, H'-C₆), 4.28 (d, J = 10.2 Hz, 1H, H-C₁), 5.00 (dd, J = 10.2, 3.2 Hz, 1H, H-C₃), 5.40-5.45 (m, 1H, H-C₄), 5.53 (t, J = 10.2 Hz, 1H, H-C₂). ¹³C NMR (101 MHz, CDCl₃) δ 20.6 (2C, 2 X CH₃ Acetate), 20.7 (1C, CH₃ Acetate), 20.8 (1C, CH₃ Acetate), 61.4 (1C, C₆), 66.2 (1C, C₂), 66.9 (1C, C₄), 67.0 (1C, C₁), 71.0 (1C, C₃), 75.6 (1C, C₅), 114.5 (1C, C₉ Nitrile), 168.9 (1C, C₉ Acetate), 170.0 (1C, C₉ Acetate), 170.1 (1C, C₉ Acetate), 170.5 (1C, C₉ Acetate); HRMS (NSI-FTMS) m/z found for [M+NH₄]⁺: 375.1398; [C₁₅H₁₉NO₉+NH₄]⁺ requires 375.1398.

Data is in agreement with the literature references.¹²,¹³
(2S,3R,4R,5R,6R)-3,4,5-trihydroxy-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-carbonitrile (436b)

A solution of methanolic sodium methoxide (69 ml, 0.1 M in MeOH, 6.9 mmol) was added dropwise to a stirred solution of 64 (13.970 g, 39.1 mmol) in dry methanol (30 ml). The mixture was stirred at rt for 2 h. The mixture was then concentrated in vacuo affording 435 (7.394 g) in an unpurified state, which was then used directly in the next step without any purification.

Crude 435 (7.394 g) was then dissolved in dry DMF (143 ml) and cooled to 0 °C. To this stirred solution was added imidazole (2.66 g, 156.4 mmol, 4 equiv.) and TIPSCl (16.7 ml, 78.2 mmol, 2 equiv.). The mixture was stirred for 72 hours at rt and was then concentrated in vacuo. The residue was then treated with water and DCM, and the layers were then separated. The aqueous layer was extracted with DCM twice. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO₄. Filtration and evaporation of the solvent under reduced pressure furnished a colourless crude residue. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 1:1) to yield 436b as a pure colourless oil (5.677 g, 42%); [α]D₂⁴ = +28.1 (c 1.01 in CHCl₃); IR νmax (film)/cm⁻¹: 3391, 2942, 2892, 2867, 1463, 1142, 1073; ¹H NMR (400 MHz, CDCl₃) δ 1.09 – 1.03 (m, 18H, 6 X CH₃TIPS), 1.17 – 1.09 (m, 3H, H-CMe₂TIPS), 2.93 (br, 3H, 3 X OH), 3.44 – 3.49 (m, 1H, H-C₅), 3.52 (dd, J = 8.6, 3.1 Hz, 1H, H-C₁), 3.52 (dd, J = 8.6, 3.1 Hz, 1H, H-C₁), 3.52 (dd, J = 8.6, 3.1 Hz, 1H, H-C₁), 3.52 (dd, J = 8.6, 3.1 Hz, 1H, H-C₁), 4.11 – 3.96 (m, 4H, H-C₆, H'-C₆, H-C₁, H-C₂), 4.19 (m, 4.16 – 4.21, 1H, H-C₄). ¹³C NMR (101 MHz, CDCl₃) δ 11.9 (3C, 3 X CHMe₂TIPS), 17.9 (3C, 3 X CH₃TIPS), 18.0 (3C, 3 X CH₃TIPS), 63.9 (1C, C₆), 69.0 (C₂), 69.5 (C₁), 69.7 (C₄), 74.6 (C₃), 78.3 (C₅), 116.6 (1C, CQ Nitrile); HRMS (NSI-FTMS) m/z found for [M+H]+: 346.2045; [C₁₆H₃₁NO₅Si+H]^+ requires 346.2044.
Sodium hydride (0.045 g, 1.86 mmol, 3.7 equiv.) was added in one portion to a stirred solution of 436b (0.174 g, 0.50 mmol) in dry DMF (2 ml) at 0 °C. The mixture was then stirred at 0 °C for a further 30 minutes. Then benzyl bromide (0.27 ml, 2.27 mmol, 4.5 equiv.), was added dropwise to the mixture. The mixture was then stirred for 72 hours at rt, then quenched cautiously with methanol. The mixture was then concentrated under reduced pressure. The residue was treated with water (ca. 10 ml) and EtOAc (ca. 10 ml), and the layers were separated. The aqueous layer was then extracted with EtOAc twice. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO₄. After filtration, the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (petrol:EtOAc, 12:1) afforded the title compound 437 as a pure colourless oil (0.140 g, 45%); [α]D₂₃ = +21.0 (c 0.99 in CHCl₃); IR νmax (film)/cm⁻¹: 3066, 3032, 2942, 2866, 1497, 1455, 1110; ¹H NMR (400 MHz, Chloroform-d) δ 1.01 – 1.06 (m, 18H, 6 X CH₃TIPS), 1.07 – 1.18 (m, 3H, H-CMe₂TIPS), 3.39 (td, J = 6.7 1.1 Hz, 1H, H-C₅), 3.51 (dd, J = 9.6, 2.8 Hz, 1H, H-C₃), 3.74-3.83 (m, 2H, H-C₆), 3.98 (dd, J = 2.8, 1.1 Hz, 1H, H-C₄), 4.03 (d, J = 9.6 Hz, 1H, H-C₁), 4.19 (t, J = 9.6 Hz, 1H, H-C₂), 4.66 (d, J = 11.3 Hz, 1H, 1H of CH₂PhBn), 4.73 (d, J = 11.9 Hz, 1H, 1H of CH₂PhBn), 4.77 (d, J = 11.9 Hz, 1H, 1H of CH₂PhBn), 4.98 – 5.00 (m, 3H, 3H of CH₂PhBn), 7.27 – 7.41 (m, 15H, 15 X H-C₅Ar). ¹³C NMR (101 MHz, CDCl₃) δ 12.0 (3C, 3 X CHMe₂TIPS), 18.1 (3C, 3 X CH₃TIPS), 18.1 (3C, 3 X CH₃TIPS), 61.5 (1C, C₆), 68.1 (1C, C₁), 72.9 (1C, CH₂Bn), 73.4 (1C, C₄), 75.1 (1C, CH₂Bn), 76.1 (1C, CH₂Bn), 76.5 (1C, C₂), 80.1 (1C, C₅), 83.2 (1C, C₃), 117.0 (1C, C₅Nitrile), 127.8 (2C, 2 X C₅Ar), 127.8 (1C, C₅Ar), 128.0 (1C, C₅Ar),
Further elution (petrol:EtOAc, 7:1) gave compound 438 as a pure colourless oil (0.017 g, 6%); \([\alpha]_D^{23} = +29.5\) (c 0.84 in CHCl₃); IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 3501, 3096, 3073, 3033, 2943, 2866, 1497, 1456, 1210, 1108; \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 1.03 – 1.08 (m, 18H, \(6 \times \text{CH}_3\) TIPS), 1.09 – 1.17 (m, \(3 \text{H}, \text{H-CMe}_2\) TIPS), 3.45 – 3.51 (m, \(1 \text{H}, \text{H-C}_5\)), 3.60 (dd, \(J = 9.1, 3.0 \text{ Hz,} \ 1 \text{H}\)), 3.81 – 3.90 (m, \(3 \text{H}, \text{H}_2\text{-C}_6, \text{H-C}_2\)), 3.96 – 4.01 (m, \(2 \text{H}, \text{H-C}_1, \text{H-C}_4\)), 4.73 (d, \(J = 11.5 \text{ Hz,} \ 1 \text{H}, \text{H of CH}_2\text{PhBa}\)), 4.81 (d, \(J = 11.5 \text{ Hz,} \ 1 \text{H}, \text{H of CH}_2\text{PhBa}\)), 4.84 (d, \(J = 10.8 \text{ Hz,} \ 1 \text{H, H of CH}_2\text{PhBa}\)), 4.92 (d, \(J = 10.8 \text{ Hz,} \ 1 \text{H, H of CH}_2\text{PhBa}\)), 7.43 – 7.29 (m, 10H, 10 X H-CAR). \(^{13}\)C NMR (101 MHz, CDCl₃) \(\delta\) 12.0 (3C, 3 X CHMe₂ TIPS), 18.1 (3C, 3 X CH₃ TIPS), 61.2 (1C, C₆), 67.7 (1C, C₁ or C₄), 74.9 (1C, C₃), 75.6 (1C, CH₂Ba), 75.6 (1C, CH₂Ba), 75.79 (1C, C₄ or C₁), 77.5 (1C, C₂) 79.9 (1C, C₅), 117.0 (1C, C₉ Nitile), 128.1 (1C, 2 X CAR), 128.3 (1C, CAR), 128.5 (1C, CAR), 128.7 (2C, 2 X CAR), 128.8 (2C, 2 X CAR), 137.3 (1C, Cq AR), 138.2 (1C, Cq AR); HRMS (ASAP-TOF) \(m/z\) found for \([\text{M+H}]^+\): 526.2990; \([\text{C}_{30}\text{H}_{43}\text{NO}_5\text{Si}+\text{H}]^+\) requires 526.2989.

439 was also isolated as a pure colourless oil (0.009 g, 3%); \([\alpha]_D^{23} = +7.5\) (c 1.01 in CHCl₃); IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 3480, 3090, 3065, 3032, 2943, 2866, 1463, 1455, 1211, 1105; \(^1\)H NMR (500 MHz, Chloroform-d) \(\delta\) 1.02 – 1.08 (m, 18H, \(6 \times \text{CH}_3\) TIPS), 1.09 – 1.16 (m, \(3 \text{H}, \text{H-CMe}_2\) TIPS), 2.97 (br, \(1 \text{H, OH}\)), 3.37 (ddd, \(J = 6.0, 4.7, 1.1 \text{ Hz,} \ 1 \text{H, H-C}_5\)), 3.47 (dd, \(J = 8.9, 3.0 \text{ Hz,} \ 1 \text{H, H-C}_3\)), 3.91 (dd, \(J = 10.3, 4.7 \text{ Hz,} \ 1 \text{H, H-C}_6\)), 3.99 (dd, \(J = 10.4, 6.0, 1 \text{H, H’-C}_6\)), 4.02 (d, \(J = 10.1 \text{ Hz,} \ 1 \text{H, H-C}_1\)), 4.10 (dd, \(J = 10.1, 8.9 \text{ Hz,} \ 1 \text{H, H-C}_2\)), 4.13 – 4.15 (m, \(1 \text{H, H-C}_4\)), 4.75 (s, \(2 \text{H, CH}_2\text{PhBa}\)), 4.90 (s, \(2 \text{H, CH}_2\text{PhBa}\)), 7.29 – 7.41 (m, 10H, 10 X H-CAR). \(^{13}\)C NMR (126 MHz, CDCl₃) \(\delta\) 12.0 (3C, 3 X CHMe₂ TIPS), 18.0 (3C, 3 X CH₃ TIPS), 62.9 (1C, C₆), 66.8 (1C, C₄), 68.0 (1C, C₁), 72.3 (1C, CH₂Ba), 75.9 (1C, C₂), 76.2 (1C, CH₂Ba), 78.8 (1C, C₅), 81.6 (1C, C₃), 116.9 (1C, C₉ Nitile), 128.0 (2C, 2 X CAR), 128.3 (1C, CAR), 128.7 (4C, 4 X CAR), 128.8 (2C, 2 X CAR), 137.3 (1C, Cq AR), 137.6 (1C, Cq AR); HRMS (ASAP-TOF) \(m/z\) found for \([\text{M+H}]^+\): 526.2991; \([\text{C}_{30}\text{H}_{43}\text{NO}_5\text{Si}+\text{H}]^+\) requires 526.2989.
Further elution (petrol:EtOAc, 3:1) gave compound 440 as a pure colourless solid (0.005 g, 2%); $[\alpha]_D^{23} = +18.6 \, (c \, 0.99 \, \text{in CHCl}_3)$; IR $\nu_{\text{max}} \, (\text{film})/\text{cm}^{-1}$: 3432, 3065, 3033, 2943, 2890, 2867, 1498, 1463, 1367, 1212, 1108; $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 1.04 – 1.09 (m, 18H, 6 X CH$_3$TIPS), 1.09 – 1.17 (m, 3H, H-CMe$_2$TIPS), 3.40 – 3.43 (m, 1H, H-C$_5$), 3.53 (br, 1H, OH), 3.57 (dd, $J = 8.8, 3.2 \, \text{Hz}$, 1H, H-C$_3$), 3.91 – 3.95 (m, 1H, H-C$_2$), 3.99 (dd, $J = 10.8, 4.3 \, \text{Hz}$, 1H, H-C$_6$), 4.01 (d, $J = 10.0 \, \text{Hz}$, 1H, H-C$_1$), 4.05 (dd, $J = 10.8, 5.1 \, \text{Hz}$, 1H, H$'$-C$_6$), 4.15 (dd, $J = 3.2, 1.0 \, \text{Hz}$, 1H, H-C$_4$), 4.88 (d, $J = 10.9 \, \text{Hz}$, 1H, 1H of CH$_2$Ph$_{Bn}$), 4.95 (d, $J = 10.9 \, \text{Hz}$, 1H, 1H of CH$_2$Ph$_{Bn}$), 7.31 – 7.35 (m, 1H, H-C$_{AR}$), 7.36 – 7.40 (m, 2H, 2 X H-C$_{AR}$), 7.41 – 7.44 (m, 2H, 2 X H-C$_{AR}$). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 11.9 (3C, 3 X CH$_3$TIPS), 18.0 (3C, 3 X CH$_3$TIPS), 18.0 (3C, 3 X CH$_3$TIPS), 63.9 (1C, C$_6$), 67.6 (1C, C$_1$), 69.8 (1C, C$_4$), 74.7 (1C, C$_3$), 75.7 (1C, C$_2$), 77.1 (1C, C$_2$), 78.1 (1C, C$_5$), 117.0 (1C, C$_q$Nitrile), 128.5 (1C, C$_{AR}$) 128.6 (2C, 2 X C$_{AR}$), 128.8 (2C, 2 X C$_{AR}$), 137.4 (1C, C$_q$AR); HRMS (ASAP-TOF) $m/z$ found for [M+H]$^+$: 436.2518; [C$_{23}$H$_{37}$NO$_5$Si+H]$^+$ requires 436.2519.

441 was also isolated as a pure colourless solid (0.009 g, 4%); $[\alpha]_D^{23} = +13.9 \, (c \, 0.66 \, \text{in CHCl}_3)$; IR $\nu_{\text{max}} \, (\text{film})/\text{cm}^{-1}$: 3450, 3070, 3032, 2943, 2895, 2866, 1497, 1463, 1367, 1100; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.01 – 1.08 (m, 18H, 6 X CH$_3$TIPS), 1.09 – 1.15 (m, 3H, H-CMe$_2$TIPS), 2.65 (br, 1H, OH), 2.90 (br, 1H, OH), 3.34 (dd, $J = 9.0, 3.0 \, \text{Hz}$, 1H, H-C$_3$), 3.39 – 3.43 (m, 1H, H-C$_5$), 3.91 (dd, $J = 10.3, 4.7 \, \text{Hz}$, 1H, H-C$_6$), 3.96 – 4.04 (m, 2H, H$'$-C$_6$, H-C$_1$), 4.14 – 4.21 (m, 2H, H-C$_4$, H-C$_2$), 4.69 (d, $J = 11.9 \, \text{Hz}$, 1H, 1H of CH$_2$Ph$_{Bn}$), 4.78 (d, $J = 11.9 \, \text{Hz}$, 1H, 1H of CH$_2$Ph$_{Bn}$), 7.30 – 7.41 (m, 5H, 5 X H-C$_{AR}$). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$12.0 (3C, 3 X CH-Me$_2$TIPS), 18.0 (3C, 3 X CH$_3$TIPS), 18.0 (3C, 3 X CH$_3$TIPS), 62.9 (1C, C$_6$), 66.3 (1C, C$_4$), 68.3 (1C, C$_2$), 69.1 (1C, C$_1$), 72.2 (1C, CH$_2$Bn), 79.0 (1C, C$_5$), 81.4 (1C, C$_3$), 116.4 (1C, C$_q$Nitrile), 128.1 (2C, 2 X C$_{AR}$), 128.5 (1C, C$_{AR}$), 128.9 (2C, 2 X C$_{AR}$), 137.5 (1C, C$_q$AR); HRMS (ASAP-TOF) $m/z$ found for [M+H]$^+$: 436.2521; [C$_{23}$H$_{37}$NO$_5$Si+H]$^+$ requires 436.2519.
(2S,3R,4R,5R,6R)-3,4,5-trihydroxy-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-carbonitrile (437)

Sodium hydride (0.377 g, 15.69 mmol, 4.95 equiv.) in one portion was added to a stirred solution of 436b (1.096 g, 3.17 mmol) in dry THF (12.7 ml) at 0 °C. The mixture was then stirred at 0 °C for a further 30 minutes. Then, after the dropwise addition of benzyl bromide (1.7 ml, 14.30 mmol, 4.5 equiv.), TBAI (0.094 g, 0.25 mmol, 0.08 equiv.) was added. The mixture was then stirred for 72 hours at rt, then quenched cautiously with methanol. The mixture was then concentrated in vacuo. The residue was treated with water (ca. 50 ml) and EtOAc (ca. 50 ml). The layers were separated. The aqueous layer was then extracted with EtOAc twice. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO₄. After Filtration, the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 12:1) to furnish 437 as a pure colourless oil (1.358 g, 70%).
Sodium (2R,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-carboxylate (448)\(^\text{14}\)

![Chemical Structures]

A solution of methanolic sodium methoxide (7.3 ml, 0.73 mmol, 0.1 M in methanol, 0.18 equiv.) was added dropwise to a stirred solution of 64 (1.449 g, 4.06 mmol) in dry methanol (3.1 ml). The mixture was stirred at rt for 2 h. The mixture was then concentrated \textit{in vacuo} affording crude 435 (0.764 g), which was then used directly in the next step without any purification.

Crude 435 (0.764 g) was then dissolved in 12.5% aqueous NaOH (18 ml). The stirred solution was refluxed for 3 hours. After the brown reaction mixture was cooled to rt, water (60 ml) was added. The solution was then acidified with Amberlite IR-120 (H\(^+\)-form) and filtered. The filtrate was evaporated under reduced pressure to furnish 448 as a colourless solid (0.969 g, 60% over two steps); \([\alpha]_D^{22} = +75.8 \text{ (c 0.95 in H}_2\text{O)} \) \([\text{lit. } [\alpha]_D^{25} = +51.8 \text{ (c 1.03 in H}_2\text{O)}])\(^\text{14}\); IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 3391, 2918, 1725, 1091; \(^1\text{H NMR (500 MHz, D}_2\text{O)} \delta 3.64 – 3.84 \text{(m, 6H, } H-\text{C}_1, H-\text{C}_2, H-\text{C}_3, H-\text{C}_5, H-\text{C}_6, H'-\text{C}_6), 3.95 \text{(bd, } J = 3.3 \text{ Hz, } H-\text{C}_4). \) \(^{13}\text{C NMR (126 MHz, D}_2\text{O; internal standard, methanol)} \delta 61.9 \text{(1C, C}_6), 69.7 \text{(1C, C}_2), 69.7 \text{(1C, C}_4), 74.5 \text{(1C, C}_3), 79.0 \text{(1C, C}_5), 80.1 \text{(1C, C}_1), 177.0 \text{(1C, C}_q \text{ carboxylate); HRMS (NSI-FTMS) } m/z \text{ found for [M-Na]}^{+}: 207.0510; [\text{C}_7\text{H}_2\text{O}_7\text{-Na}^{+}] \text{ requires 207.0510.}

Data is in agreement with the literature reference.\(^\text{14}\)
Acetyl chloride (1.24 ml, 17.4 mmol, 7.15 equiv.) was added dropwise over 10 minutes to dry methanol (7.5 ml) in a 3-neck round bottom flask fitted with a condenser at 0 °C and was stirred for 5 minutes. Compound 448 (0.969 g, 2.43 mmol) was added in one portion to the stirred solution. The solution was then heated under reflux for 72 hours. The mixture was then concentrated in vacuo furnishing a crude brown solid. The crude residue was purified by trituration with EtOAc affording the title compound as a pure brown solid (0.537 g, quant.); mp 121 – 122 °C [lit. 121 – 123 °C]15; [α]D22 = -33.8 (c 1.30 in H2O) [lit. [α]D20 = -32 (c 0.12 in H2O)]15; IR νmax (film)/cm⁻¹: 3347, 2924, 2854, 1722, 1251, 1089; ¹H NMR (400 MHz, Deuterium Oxide) δ 3.70 – 3.86 (m, 5H, H-C-3, H-C-4, H-C-5, H-C-6, H'-C-6), 3.87 (s, 3H, CH₃ Ester), 3.97 – 4.05 (m, 2H, H-C-2, H-C-1); ¹³C NMR (101 MHz, D₂O; internal standard, methanol) δ 53.6 (1C, CH₃ Ester), 61.7 (1C, C-6), 69.0 (1C, C-2), 69.3 (1C, C-4), 74.1 (1C, C-3), 79.1 (1C, C-1), 79.6 (1C, C-5), 172.1 (1C, C_q Ester); HRMS (NSI-FTMS) m/z found for [M+H]+: 223.0814; [C₈H₁₄O₇+H]⁺ requires 223.0812.

Data is in agreement with the literature references.15,16
To a solution of 446 (0.338 g, 1.52 mmol) in dry DMF (5.6 ml) at 0 °C, was added imidazole (0.414 g, 6.08 mmol, 4 equiv.), then TIPSCl (0.65 ml, 3.04 mmol, 2 equiv.) dropwise. The mixture was stirred for 72 hours at rt and then concentrated in vacuo. The residue was then treated with water and DCM, and the layers were then separated. The aqueous layer was then extracted with DCM twice. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO₄. Filtration and removal of the solvent in vacuo furnished a colourless crude residue. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 1:2) to yield 449 as a pure colourless oil (0.141 g, 24%); [α]D²³ = +16.3 (c 0.81 in CHCl₃); IR νmax (film)/cm⁻¹: 3390, 2944, 2891, 2867, 1739, 1244, 1105, 1071; ¹H NMR (400 MHz, CDCl₃) δ 1.07 – 1.03 (m, 18H, 6 X CH₃TIPS), 1.16 – 1.08 (m, 3H, H-CMe₂TIPS), 3.16 (br, 2H, 2 X OH), 3.41 (br, 1H, OH), 3.54 (ddd, J = 6.6, 4.8, 1.2 Hz, 1H, H-C₅), 3.61 (dd, J = 9.2, 3.3 Hz, 1H, H-C₃), 3.78 – 3.82 (m, 4H, CH₃Ester, H-C₁), 3.95 (dd, J = 10.2, 4.8 Hz, 1H, H-C₆), 4.05 – 3.98 (m, 2H, H-C₆, H-C₂), 4.16 (dd, J = 3.3, 1.2 Hz, 1H, H-C₄). ¹³C NMR (101 MHz, CDCl₃) δ 12.0 (3C, 3 X CH₃TIPS), 18.0 (3C, 3 X CH₃TIPS), 18.0 (3C, 3 X CH₃TIPS), 52.8 (1C, CH₃Ester), 62.9 (1C, C₆), 68.8 (1C, C₄), 69.6 (1C, C₂), 74.8 (1C, C₃), 78.1 (1C, C₁), 78.4 (1C, C₅), 170.7 (1C, CqEster); HRMS (NSI-FTMS) m/z found for [M+H]⁺: 379.2150; [C₁₇H₃₄O₇Si+H]⁺ requires 371.2147.
Methyl ester 449 (0.190 g, 0.50 mmol) was dissolved in dry DMF (2 ml). After cooling the stirred solution to 0 °C, sodium hydride (0.060 g, 2.48 mmol, 4.95 equiv.) was added in one portion. The mixture was stirred at 0 °C for a further 30 minutes. Then, after the dropwise addition of benzyl bromide (1.7 ml, 14.30 mmol, 4.5 equiv.), TBAI (0.094 g, 0.25 mmol, 0.08 equiv.) was added. The mixture was then stirred for 72 hours at rt, then quenched cautiously with methanol. The mixture was then concentrated under reduced pressure. The residue was treated with water (ca. 20 ml) and EtOAc (ca. 20 ml), and the layers were separated. The aqueous layer was then extracted with EtOAc twice. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO₄. After filtration, the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petrol:EtOAc, 10:1) to furnish glycal 451 as a pure colourless oil (0.160 g, 59%); \( [\alpha]_D^{23} = +46.8 \) (c 0.88 in CHCl₃); IR \( \nu_{\text{max}} \) (film)/cm⁻¹: 3089, 3064, 3031, 2943, 2890, 2866, 1737, 1651, 1497, 1455, 1285, 1103, 1063; \(^1\)H NMR (400 MHz, Chloroform-d) \( \delta \) 1.04 – 1.10 (m, 18H, 6 X CH₃TIPS), 1.11 – 1.19 (m, 3H, H-CMe₂TIPS), 3.81 (s, 3H, CH₃Ester), 4.00 – 4.12 (m, 3H, H-C₆, H'-C₆, H-C₅), 4.13 – 4.18 (m, 1H, H-C₃), 4.38 – 4.42 (m, 1H, H-C₄), 4.67 (d, \( J = 12.1 \) Hz, 1H, 1H of CH₂PhBn), 4.74 (d, \( J = 12.1 \) Hz, 1H, 1H of CH₂PhBn), 4.76 (d, \( J = 11.6 \) Hz, 1H, 1H of CH₂PhBn), 5.01 (d, \( J = 11.6 \) Hz, 1H, 1H of CH₂PhBn), 6.15 (t, \( J = 2.1 \) Hz, 1H, H-C₂), 7.25 – 7.43 (m, 10H, 10 X H-C₅AR). \(^{13}\)C NMR (101 MHz, CDCl₃) \( \delta \) 12.0 (3C, 3 X CHMe₂TIPS), 18.1 (3C, 3 X CH₃TIPS), 52.4 (1C, CH₃Ester), 61.1 (1C, C₆), 69.3 (1C, C₅), 71.1 (1C, CH₂Bn), 72.9 (1C, C₄), 74.6 (1C, CH₂Bn), 78.5 (1C, C₅), 109.7 (1C, C₂), 127.6 (2C, 2 X C₅AR), 127.6 (1C, C₅AR), 127.9 (1C C₅AR), 128.0 (2C, 2 X C₅AR), 128.3 (2C, 2 X C₅AR), 128.6 (2C, 2 X C₅AR), 138.1 (1C, C₄AR), 138.7 (1C, C₄AR), 143.9 (1C, C₁), 162.8 (1C, C₃Ester); HRMS (NSI-FTMS) m/z found for [M+NH₄]⁺: 558.3242; \([C₃H₄₄O₆Si+NH₄]⁺\) requires 558.3245.
Red-Al® (52 μl, 3.5 M in toluene, 0.18 mmol, 1 equiv.) was added dropwise to a stirred solution of 437 (0.111 g, 0.18 mmol) in dry toluene (1.8 ml) at -78 °C. The stirred reaction mixture was then warmed slowly to 0 °C over 30 minutes. After 90 minutes at 0 °C, 1M aqueous tartaric acid (ca. 1 ml) was added. After warming to rt, the suspension was poured into Et₂O (ca. 10 ml) and the layers were then separated. The aqueous layer was extracted with Et₂O (2 X 10 ml). The combined organic layers were washed with water, brine, and dried over anhydrous MgSO₄. Filtration and the removal of the solvent under reduced pressure furnished a crude residue. The crude residue was purified by flash column chromatography on silica gel (DCM:methanol, 20:1) to afford 458 as a pure colourless oil (0.005 g, 4%); [α]D²³ = +34.5 (c 0.73 in CHCl₃); IR νmax (film)/cm⁻¹: 3088, 3064, 3031, 2942, 2865, 1497, 1454, 1364, 1108, 1069; ¹H NMR (400 MHz, Chloroform-d) δ 1.05 – 1.11 (m, 18H, 6 X CH₃ TIPS), 1.11 – 1.20 (m, 3H, H-CMe₂ TIPS), 1.95 – 2.19 (br, 2H, 2 X OH), 2.81 (br, 1H, 1H of CH₂NH₂), 3.07 (s, 1H br, 1H, 1H of CH₂NH₂), 3.20 – 3.31 (m, 1H, H-C₁), 3.42 – 3.48 (m, 1H, H-C₅), 3.67 (dd, J = 9.4, 2.8 Hz, 1H, H-C₁⁻³), 3.73 – 3.87 (m, 3H, H-C₆, H'-C₆, H-C₂), 4.04 – 4.09 (m, 1H, H-C₄), 4.63 – 4.83 (m, 5H, 5 X CH₂Ph Bn), 4.98 (d, J = 11.6 Hz, 1H , 1H of CH₂Ph Bn), 5.01 (d, J = 11.6 Hz, 1H , 1H of CH₂Ph Bn), 7.45 – 7.27 (m, 15H, 15 X H-CAR). ¹³C NMR (101 MHz, CDCl₃) δ 12.0 (3C, 3 X CHMe₂ TIPS), 18.1 (3C, 3 X CH₃ TIPS), 18.2 (3C, 3 X CH₃ TIPS), 43.1 (1C, CH₂NH₂), 62.1 (1C, C₆), 72.4 (1C, CH₂ Bn), 73.9 (1C, C₄), 74.8 (1C, CH₂ Bn), 75.3 (1C, CH₂ Bn), 76.5 (1C, C₂), 78.9 (1C, C₅), 80.9 (1C, C₁), 85.1 (1C, C₃), 127.6 (1C, C₁AR), 127.7 (2C, 2 X C₁AR), 127.8 (1C, C₁AR), 127.9 (1C, C₁AR), 128.1 (2C, 2 X C₁AR), 128.3 (2C, 2 X C₁AR), 128.4 (2C, 2 X C₁AR), 128.6 (4C, 4 X C₁AR), 138.4 (1C, Cq AR), 138.5 (1C, Cq AR), 139.1 (1C, Cq AR); HRMS (ESI-TOF) m/z found for [M+H]+: 620.3776; [C₃₇H₅₃NO₅Si+H]+ requires 620.3771.
Further elution (DCM:methanol, 10:1) gave compound 457 as a pure colourless solid (0.065 g, 78%); mp 122 – 144 °C; $[\alpha]_D^{23} = +60.3$ (c 0.69 in CHCl$_3$); IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3367, 3309, 3088, 3063, 3030, 2917, 2863, 1469, 1454, 1102, 1027; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 2.44 (br, 2H, 2 X OH), 2.78 (d, $J = 12.7$ Hz, 1H, 1H of CH$_2$NH$_2$), 3.06 (d, $J = 13.7$ Hz, 1H, 1H of CH$_2$NH$_2$), 3.20 – 3.29 (m, 1H, H-C$_1$), 3.38 – 3.49 (m, 2H, H-C$_5$, H-C$_6$), 3.64 (dd, $J = 9.4$, 2.7 Hz, 1H, H-C$_3$), 3.68 – 3.81 (m, 2H, H-C$_2$, H’-C$_6$), 3.85 – 3.90 (m, 1H, H-C$_4$), 4.64 (d, $J = 10.6$ Hz, 1H, 1H of CH$_2$Ph$_{Bn}$), 4.67 (d, $J = 11.3$ Hz, 1H, 1H of CH$_2$Ph$_{Bn}$), 4.73 (d, $J = 11.7$ Hz, 1H, 1H of CH$_2$Ph$_{Bn}$), 4.79 (d, $J = 11.7$ Hz, 1H, 1H of CH$_2$Ph$_{Bn}$), 4.82 (d, $J = 10.6$ Hz, 1H, 1H of CH$_2$Ph$_{Bn}$), 4.83 (d, $J = 11.3$ Hz, 1H, 1H of CH$_2$Ph$_{Bn}$), 7.24 – 7.43 (m, 15H, 15 X H-C$_{AR}$). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 43.1 (1C, CH$_2$NH$_2$), 62.5 (1C, C$_6$), 72.6 (1C, CH$_2$Bn), 73.8 (1C, C$_4$), 74.4 (1C, CH$_2$Bn), 75.4 (1C, CH$_2$Bn), 76.4 (1C, C$_2$), 79.1 (1C, C$_5$), 80.6 (1C, C$_3$), 85.1 (1C, C$_3$), 127.7 (2C, 2 X C$_{AR}$), 127.9 (1C, C$_{AR}$), 128.0 (1C, C$_{AR}$), 128.0 (1C, C$_{AR}$), 128.3 (2C, 2 X C$_{AR}$), 128.5 (2C, 2 X C$_{AR}$), 128.6 (2C, 2 X C$_{AR}$), 128.6 (2C, 2 X C$_{AR}$), 128.7 (2C, 2 X C$_{AR}$), 138.28 (1C, C$_{q AR}$), 138.29 (1C, C$_{q AR}$), 138.42 (1C, C$_{q AR}$); HRMS (ESI-TOF) $m/z$ found for [M+H]$^+$: 464.2438; [C$_{28}$H$_{33}$NO$_5$Si+H]$^+$ requires 464.2438.
Raney nickel grade 2800 (ca. 12.6 g from an aqueous suspension) was added to a stirred solution of pyridine (47.8 ml), acetic acid (28.6 ml) and water (28.6 ml). To the heterogogenous mixture was then added sodium hypophosphite monohydrate (7.48 g, 70.5 mmol, 8.4 equiv.), tosylhydrazide (2.64 g, 14.3 mmol, 1.7 equiv.) and compound 64 (3.0 g, 8.40 mmol). After leaving the reaction for 24 hours, the mixture was filtered through a pad of celite and washed with DCM. The layers of the filtrate were then separated. The aqueous layer was extracted with DCM twice. The combined organic layers were washed with 10% aqueous HCl (ca. 2 X 30 ml), saturated aqueous NaHCO₃ solution (ca. 2 X 30 ml), water (ca. 30 ml), brine (ca. 30 ml), and dried over anhydrous MgSO₄. Filtration and removal of the solvent in vacuo gave a crude residue. The crude residue was purified by flash column chromatography on silica gel (hexane:EtOAc, 3:2) to furnish 465 as a pure colourless solid (3.682 g, 83%); mp 68-70 °C; [α]D²⁰ = +10.1 (c 1.27 in CHCl₃) [lit. [α]D = +6 (c 0.97 in CHCl₃)]¹⁷; IR νmax (film)/cm⁻¹: 3620, 3198, 2970, 1751, 1371, 1225, 1166, 1056; ¹H NMR (500 MHz, DMSO-d₆) δ 1.66 (s, 3H, CH₃ Acetate), 1.90 (s, 3H, CH₃ Acetate), 1.98 (s, 3H, CH₃ Acetate), 2.10 (s, 3H, CH₃ Acetate), 2.37 (s, 3H, CH₃ Tosylate), 3.94 (dd, J = 11.5, 7.2 Hz, 1H, H-C₁), 3.98 – 4.01 (m, 1H, H'-C₆), 4.14 (dd, J = 10.0, 6.7 Hz, 1H, H-C₁), 4.22 (ddd, J = 7.2, 5.2, 1.3 Hz, 1H, H-C₅), 4.95 (t, J = 10.0 Hz, 1H, H-C₂), 5.22 (dd, J = 10.0, 3.5 Hz, 1H, H-C₃), 5.29 (dd, J = 3.5, 1.3 Hz, 1H, H-C₄), 7.00 (d, J = 6.7 Hz, 1H, HC=N hydrazone), 7.39 – 7.43 (m, 2H, 2 X H-C₆AR Tosylate), 7.65 – 7.69 (m, 2H, 2 X H-C₆AR Tosylate), 11.61 (s, 1H, NH). ¹³C NMR (126 MHz, CDCl₃) δ 20.4 (1C, CH₃ Acetate), 20.7 (1C, CH₃ Acetate), 20.8 (1C, CH₃ Acetate), 20.8 (1C, CH₃ Acetate), 21.7 (1C, CH₃ Tosylate), 61.8 (1C, C₆), 67.0 (1C, C₂), 67.6 (1C, C₄), 71.0 (1C, C₃), 74.6 (1C, C₅), 78.4 (1C, C₁), 128.3 (2C, 2 X C₁AR), 129.9 (2C, 2 X C₁AR), 135.4 (1C, C₆ AR), 144.3 (1C, C₆ AR), 144.5 (1C, C₁), 170.1 (1C, C₆ Acetate), 170.2 (1C, C₆ Acetate), 170.6 (1C, C₆ Acetate), 170.7 (1C, C₆ Acetate). Data is in agreement with the literature references.¹⁷
(2R,3S,4S,5R)-2-(acetoxy methyl)-6-methylene tetrahydro-2H-pyran-3,4,5-triy triacetate (466)\(^\text{17}\)

![Chemical Structure](image)

A stirred suspension of sodium hydride (0.582 g, 24.3 mmol, 10 equiv.) in dry 1,4-dioxane (61 ml) was heated under reflux. A solution of compound 465 (1.282 g, 2.43 mmol) in dry 1,4-dioxane (61 ml) was added to this mixture. The suspension was then refluxed for 30 minutes and then cooled to rt. The mixture was then filtered through a pad of celite and washed with DCM. The filtrate was evaporated under reduce pressure to give a crude residue. The crude residue was purified by flash column chromatography on silica gel (hexane:EtOAc, 3:1) to furnish 466 as a pure colourless solid (0.605 g, 72%); \([\alpha]_D^{26} = +67.6\) (c 0.84 in CHCl\(_3\)) [lit. \([\alpha]_D = +74\) (c 1.45 in CHCl\(_3\))]\(^1\); IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 2942, 1751, 1666, 1374, 1219, 1085; \(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 2.00 (s, 3H, CH\(_3\) Acetate), 2.06 (s, 3H, CH\(_3\) Acetate), 2.13 (s, 3H, CH\(_3\) Acetate), 2.16 (s, 3H, CH\(_3\) Acetate), 4.01 (td, \(J = 6.5, 1.5\) Hz, 1H, H-C\(_5\)), 4.11 – 4.23 (m, 2H, H-C\(_6\), H'-C\(_6\)), 4.50 (t, \(J = 1.9\) Hz, 1H, H-C= C Alkene), 4.81 (t, \(J = 1.9\) Hz, 1H, H'-C= C Alkene), 5.05 (dd, \(J = 10.4, 3.1\) Hz, 1H, H-C\(_3\)), 5.51 (dd, \(J = 3.1, 1.5\) Hz, 1H, H-C\(_4\)), 5.68 (dt, \(J = 10.4, 1.9\) Hz, 1H H-C\(_2\)). \(^{13}\)C NMR (126 MHz, CDC\(_3\)) \(\delta\) 20.8 (2C, 2 X CH\(_3\) Acetate), 20.8 (1C, CH\(_3\) Acetate), 20.9 (1C, CH\(_3\) Acetate), 61.7 (1C, C\(_6\)), 67.0 (1C, C\(_2\)), 67.7 (1C, C\(_4\)), 71.4 (1C, C\(_3\)), 75.7 (1C, C\(_5\)), 96.1 (1C, H\(_2\)C=C Alkene), 154.1 (1C, C\(_1\)), 169.6 (1C, C\(_q\) Acetate), 170.1 (1C, C\(_q\) Acetate), 170.2 (1C, C\(_q\) Acetate), 170.5 (1C, C\(_q\) Acetate).

Data is in agreement with the literature references.\(^\text{17}\)
A solution of methanolic sodium methoxide (9.7 ml, 0.1 M in methanol, 0.97 mmol, 0.18 equiv.) was added dropwise to a stirred solution of 466 (1.850 g, 5.37 mmol) in dry methanol (4 ml). The mixture was stirred at rt and monitored by TLC until full consumption of 466 was observed. The mixture was then concentrated in vacuo affording 467 as a colourless solid (0.945 g, quant.); [α]_D^{25} = +86.4 (c 1.06 in H_2O); IR ν_{max} (film)/cm^{-1}: 3480, 3291, 3185, 2910, 1653, 1069; \^1H NMR (500 MHz, DMSO-\textit{d}_6) δ 3.27 (dd, \textit{J} = 9.6, 3.3 Hz, 1H, H-\textit{C}-3), 3.42 (td, \textit{J} = 6.0, 1.3 Hz, 1H, H-\textit{C}-5), 3.54 (d, \textit{J} = 6.0 Hz, 2H, H-\textit{C}-6, H'-\textit{C}-6), 3.78 (dd, \textit{J} = 3.3, 1.3 Hz, 1H, H-\textit{C}-4), 3.97 (dt, \textit{J} = 9.6, 2.0 Hz, 1H, H-\textit{C}-2), 4.38 (d, \textit{J} = 2.0 Hz, 1H, H-C=C_{Alkene}), 4.49 (d, \textit{J} = 2.0 Hz, 1H, H'-C=C_{Alkene}), 4.69 (br, 1H, OH). \^13C NMR (126 MHz, DMSO) δ 60.9 (1C, C-\textit{o}), 68.3 (1C, C-2), 68.8 (1C, C-4), 74.1 (1C, C-3), 80.4 (1C, C-5), 90.9 (1C, H_2C=C_{Alkene}), 162.4 (1C, C-1); HRMS (NSI-FTMS) \textit{m}/\textit{z} found for [M+H]^+: 177.0756; [C_{7}H_{12}O_{5}+H]^+ requires 177.0757.
Compound 467 (0.424 g, 2.41 mmol) was dissolved in dry DMF (8.8 ml) and the solution was then cooled to 0 °C. To this stirred solution was added imidazole (0.656 g, 9.63 mmol, 4 equiv.), then TIPSCl (1.03 ml, 4.82 mmol, 2 equiv.) dropwise. The reaction mixture was stirred at rt for 48 hours. The mixture was then concentrated in vacuo. The residue was treated with water (ca. 20 ml) and EtOAc (ca. 20 ml), and the layers were then separated. The aqueous layer was extracted with EtOAc (2 X 20 ml). The combined organic extracts were then washed with water, brine, and dried over anhydrous MgSO₄. Filtration and removal of the solvent under reduced pressure gave a crude residue. The crude residue was purified by flash column chromatography (petrol:EtOAc, 1:2) to afford 469 as a pure colourless oil (0.571 g, 43%); mp 118-119 °C; [α]D²⁶ = +40.0 (c 0.96 in CHCl₃); IR νmax (film)/cm⁻¹: 3155, 2943, 2867, 1464, 1101, 1073; ¹H NMR (500 MHz, Chloroform-d) δ 1.03 – 1.17 (m, 42H, 6 X H-CMe₂TIPS, 12 X CH₃TIPS,), 1.73 (s, 3H, CH₃), 2.64 (br, 1H, OH), 3.23 (br, 1H, OH), 3.45 (td, J = 5.9, 1.3 Hz, 1H, H-C₅), 3.88 – 4.00 (m, 4H, H-C₆, H'-C₆, H-C₃, H-C₄), 4.18 (d, J = 9.8 Hz, 1H, H-C₂), 7.06 (br, 1H, H-C₉AR), 7.35 (br, 1H, H-C₉AR), 8.12 (br, 1H, H-CAR). ¹³C NMR (126 MHz, CDCl₃) δ 12.0 (3C, 3 X CHMe₂TIPS), 12.5 (3C, 3 X CHMe₂TIPS), 18.0 (6C, 6 X CH₃TIPS), 18.1 (3C, 3 X CH₃TIPS), 18.1 (3C, 3 X CH₃TIPS), 29.4 (1C, CH₃), 62.9 (1C, C₆), 69.7 (1C, C₄), 72.1 (1C, C₃), 73.1 (1C, C₅), 74.4 (1C, C₂), 89.8 (1C, C₁), 117.4 (1C, CAR). 128.4 (1C, CAR), 136.2 (1C, CAR); HRMS (NSI-FTMS) m/z found for [M+H]⁺: 557.3795; [C₂₈H₅₆N₂O₅Si₂+H]⁺ requires 557.3811.
Further elution (petrol:EtOAc, 1:3) gave compound **470** as a pure colourless solid (0.249 g, 19%); \([\alpha]_D^{26} = +4.2\) (c 1.04 in CHCl₃); IR \(\nu_{\text{max}}\) (film)/cm⁻¹: 3569, 3141, 2943, 2892, 2867, 1464, 1383, 1235, 1103, 1071; ¹H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 1.03 – 1.07 (m, 18H, 6 X CH₃TIPS), 1.07 – 1.22 (m, 24H, 6 X CH₃TIPS, 6 X H-CMe₂TIPS), 1.72 (s, 3H, CH₃), 3.78 (d, \(J = 9.4\) Hz, H-C₂), 3.80 – 3.83 (m, 1H, H-C₅), 3.87 – 3.92 (m, 2H, H-C₆, H-C₃), 4.04 – 4.09 (m, 2H, H'-C₆, H-C₄), 6.77 (br, 1H, H-C₁₉), 7.15 (br, 1H, H-C₁₉), 7.57 (br, 1H, H-C₁₉). ¹³C NMR (126 MHz, CDCl₃) \(\delta\) 12.1 (3C, 3 X CHMe₂TIPS), 12.6 (3C, 3 X CHMe₂TIPS), 18.0 (6C, 3 X CH₃TIPS), 18.1 (6C, 3 X CH₃TIPS), 18.2 (6C, 6 X CH₃TIPS), 62.5 (1C, C₆), 69.2 (C₄), 73.6 (C₅), 73.6 (C₃), 74.2 (C₂), 90.6 (1C, C₁), 116.3 (1C, C₁₉), 127.8 (1C, C₁₉), 134.5 (1C, C₁₉); HRMS (ASAP-TOF) \(m/z\) found for [M+H]⁺: 557.3806; [C₂₈H₅₆N₂O₅Si₂+H]⁺ requires 557.3811.

Further elution (DCM:Methanol, 10:1) gave compound **471** as a pure colourless solid (0.110 g, 11%); mp 144-145 °C; \([\alpha]_D^{26} = +42.4\) (c 1.00 in MeOH); IR \(\nu_{\text{max}}\) (film)/cm⁻¹: 3376, 2942, 2866, 1464, 1376, 1219, 10921235, 1103, 1071; ¹H NMR (500 MHz, DMSO-\(d₆\)) \(\delta\) 0.99 – 1.11 (m, 21H, 6 X CH₃TIPS, 3 X H-CMe₂TIPS), 1.56 (s, 3H, CH₃), 3.18 – 3.22 (m, 1H, H-C₅), 3.44 – 3.51 (m, 1H, H-C₃), 3.68 (ddd, \(J = 4.4, 3.2, 1.2\) Hz, 1H, H-C₄), 3.71 – 3.79 (m, 2H, H-C₆, H'-C₆), 3.87 (dd, \(J = 10.4, 5.5\) Hz, 1H, H-C₂), 4.69 (d, \(J = 4.4\) Hz, 1H, OH), 5.03 (d, \(J = 5.1\) Hz, 1H, OH, OH), 6.02 (d, \(J = 5.5\) Hz, 1H, OH), 6.87 (t, \(J = 1.1\) Hz, 1H, H-C₁₉), 7.34 (t, \(J = 1.1\) Hz, 1H, H-C₁₉), 7.98 (t, \(J = 1.1\) Hz, 1H, H-C₁₉). ¹³C NMR (126 MHz, DMSO) \(\delta\) 11.4 (3C, 3 X CHMe₂TIPS), 17.8 (3C, 3 X CH₃TIPS), 17.8 (3C, 3 X CH₃TIPS), 29.2 (1C, CH₃), 63.1 (1C, C₆), 68.5 (1C, C₄), 69.4 (1C, C₃), 72.6 (1C, C₂), 74.1 (1C, C₅), 89.6 (1C, C₁), 117.3 (1C, C₁₉), 127.4 (1C, C₁₉), 135.9 (1C, C₁₉); HRMS (NSI-FTMS) \(m/z\) found for [M+H]⁺: 401.2465; [C₁₉H₆₆N₂O₅Si₂+H]⁺ requires 401.2472.
(3R,4S,5R,6R)-2-methylene-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2H-pyran-3,4,5-triol (468)

To a solution of compound 467 (0.304 g, 1.73 mmol) in dry DMF (6.3 ml) at 0 °C was added imidazole (0.258 g, 3.80 mmol, 2.2 equiv.) then TIPSCl (0.41 ml, 1.90 mmol, 1.1 equiv.) dropwise. After 48 hours at rt, the mixture was then concentrated in vacuo. The residue was treated with water (ca. 15 ml) and EtOAc (ca. 15 ml), and the layers were then separated. The aqueous layer was extracted with EtOAc (2 X 15 ml). The combined organic extracts were then washed with water, brine, and dried over anhydrous MgSO₄. Filtration and evaporation of the solvent under reduced pressure gave a crude residue. The crude residue was purified by flash column chromatography (DCM:Methanol, 12:1) to furnish 471 as a pure colourless solid (0.439 g, 64%).

The title compound 468 was also isolated as pure colourless gum (0.114 g, 11%); [α]D²⁶ = +49.9 (c 0.77 in MeOH); IR ν_max (film)/cm⁻¹: 3369, 2942, 2866, 1660, 1463, 1092, 681; ¹H NMR (500 MHz, DMSO-d₆) δ 1.00 – 1.05 (m, 18H, 6 X CH₃TIPS), 1.06 – 1.12 (m, 3H, 3 X H-CMe₂ TIPS), 3.28 – 3.33 (m, 1H, H-C₃), 3.47 – 3.51 (m, 1H, H-C₅), 3.74 – 3.86 (m, 3H, H-C₆, H'-C₆, H-C₄), 4.00 (ddt, J = 9.7, 5.7, 2.2 Hz, 1H, H-C₂), 4.39 (d, J = 2.2 Hz, 1H, H-C=C алкена), 4.52 (d, J = 2.2 Hz, 1H, H'-C=C алкена), 4.67 (d, J = 4.6, 1H, OH), 4.95 (d, J = 5.2 Hz, 1H, OH), 5.15 (d, J = 5.7 Hz, 1H, OH). ¹³C NMR (126 MHz, DMSO) δ 11.4 (3C, 3 X CHMe₂ TIPS), 17.8 (6C, 6 X CH₃ TIPS), 62.9 (1C, C₆), 68.1 (1C, C₂), 68.6 (1C, C₄), 73.9 (1C, C₃), 80.4 (1C, C₅), 91.3 (1C, H₅C=C алкена), 162.2 (1C, C₁); HRMS (ASAP-TOF) m/z found for [M+H]⁺: 333.2090; [C₁₆H₃₂O₅Si+H]⁺ requires 333.2097.
(2S,3R,4S,5R,6R)-2-methyl-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2H-pyran-2,3,4,5-tetraol (472)

To a stirred solution of compound 467 (0.349 g, 1.98 mmol) in dry DMF (26 ml) at 0°C was added 2,6-lutidine (0.46 ml, 3.96 mmol, 2 equiv.) followed by the dropwise addition of TIPSOTf (0.59 ml, 2.18 mmol, 1.1 equiv.). The reaction mixture was stirred at 0°C for 15 minutes then at rt for 24 hours. The reaction mixture was then quenched with water (10 ml) and saturated aqueous NaHCO₃ solution (10 ml). The solvents were evaporated under reduced pressure. The residue was treated with EtOAc and water, and the layers were then separated. The aqueous layer was then extracted with EtOAc twice. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO₄. Filtration and removal of the solvent in vacuo gave a crude residue. The crude residue was purified by flash column chromatography on silica gel (petrol:EtOAc, 2:1) to yield 472 as a pure colourless oil (0.021 g, 3%); [α]D²₂ = +14.4 (c 0.73 in CHCl₃); IR ν_max (film)/cm⁻¹: 3385, 2942, 2867, 2973, 1749, 1382, 1247, 1089; ¹H NMR (500 MHz, DMSO-d₆) δ 0.99 – 1.11 (m, 21H, 6 × CH₃ TIPS, 3 × H-CMe₂ TIPS), 1.37 (s, 3H, CH₃), 3.40 – 3.41 (m, 1H, H-C₆), 3.42 – 3.43 (m, 1H, H-C₆), 3.46 – 3.51 (m, 2H, H’-C₆, H-C₄), 3.60 – 3.64 (m, 1H, H-C₃), 4.16 (m, 1H, H-C₅), 4.97 (d, J = 7.8 Hz, 1H, OH), 5.26 (d, J = 4.4 Hz, 1H, OH); ¹³C NMR (126 MHz, DMSO) δ 11.3 (3C, 3 × CHMe₂ TIPS), 15.9 (1C, CH₃), 17.8 (6C, 6 × CH₃ TIPS), 63.5 (1C, C₆), 76.1 (1C, C₃), 78.0 (1C, C₄), 83.2 (1C, C₅), 85.2 (1C, C₂), 107.1 (1C, C₁); HRMS (NSI-FTMS) m/z found for [M+Na]⁺: 373.2018; [C₁₆H₃₄O₆Si+Na]⁺ requires 373.2017.
An aqueous solution of NaHCO$_3$ (0.62 ml, 0.6 M, 1.03 mmol, 3.62 equiv.) was added to a solution of 466 (0.099 g, 0.29 mmol) in DCM (4.3 ml). mCPBA (0.059 g, 0.34 mmol, 1.3 equiv.) was added to the mixture at 0 °C. The reaction mixture was stirred at rt overnight. A saturated aqueous solution of NaHCO$_3$ was added and the layers were separated. The aqueous layer was extracted with DCM twice. The combined organic extracts were washed with a saturated aqueous solution of NaHCO$_3$, water, brine, and dried over anhydrous MgSO$_4$. Filtration and removal of the solvent under reduced pressure at ambient temperature gave a pure colourless solid (0.103 g, 98%); mp 93-95 °C; [α]$_D^{22}$ = +53.3 (c 0.96 in CHCl$_3$); IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2973, 1749, 1373, 1215, 1079; $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 2.00 (s, 3H, CH$_3$ Acetate), 2.04 (s, 3H, CH$_3$ Acetate), 2.05 (s, 3H, CH$_3$ Acetate), 2.18 (s, 3H, CH$_3$ Acetate), 2.74 (d, $J$ = 4.0 Hz, 1H of CH$_2$ Epoxide), 3.07 (d, $J$ = 4.0 Hz, 1H of CH$_2$ Epoxide), 4.07 (dd, $J$ = 11.4, 6.6 Hz, 1H, H-C$_6$), 4.13 (dd, $J$ = 11.4, 6.6 Hz, 1H, H'-C$_6$), 4.29 (tt, $J$ = 6.6, 1.3 Hz, 1H, H-C$_5$), 5.31 (dd, $J$ = 10.8, 3.3 Hz, 1H, H-C$_3$), 5.57 (dd, $J$ = 3.3, 1.3 Hz, 1H, H-C$_4$), 5.76 (d, $J$ = 10.8 Hz, 1H, H-C$_2$). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 20.7 (2C, 2 X CH$_3$ Acetate), 20.8 (1C, CH$_3$ Acetate), 20.8 (1C, CH$_3$ Acetate), 50.4 (1C, CH$_2$ Epoxide), 61.3 (1C, C$_6$), 64.0 (1C, C$_2$), 68.0 (1C, C$_4$), 70.0 (1C, C$_3$), 72.0 (1C, C$_5$), 82.0 (1C, C$_1$), 170.0 (1C, C$_q$ Acetate), 170.1 (1C, C$_q$ Acetate), 170.2 (1C, C$_q$ Acetate), 170.5 (1C, C$_q$ Acetate).

HRMS (ASAP-TOF) $m/z$ found for [M+H]$^+$: 361.1133; [C$_{15}$H$_{20}$O$_{10}$+H]$^+$ requires 361.1135.
To a stirred solution of epoxide $\alpha$-473 (0.201 g, 0.56 mmol) in toluene (6 ml) and hexane (3 ml) at 0 °C, was added iodine (0.283 g, 1.12 mmol, 2 equiv.) then TMSCN (0.35 ml, 2.79 mmol, 5 equiv.) dropwise. The mixture was stirred at 0 °C until TLC showed complete consumption of starting material. Once complete, a saturated aqueous solution of Na$_2$SO$_3$ (ca. 10 ml) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 X 10 ml). The combined organic extracts were washed with water (ca. 30 ml), brine (ca. 30 ml), and dried over anhydrous MgSO$_4$. After filtration, the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane:EtOAc, 3:1) to furnish 479 as a pure colourless oil (0.0094 g, 4%); $[\alpha]_D^{22} = -71.0$ (c 0.49 in CHCl$_3$); IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2960, 1755, 1371, 1215, 1060; $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 0.21 (s, 9H, 3 X CH$_3$ TMS), 1.99 (s, 3H, CH$_3$ Acetate), 2.06 (s, 3H, CH$_3$ Acetate), 2.12 (s, 3H, CH$_3$ Acetate), 2.19 (s, 3H, CH$_3$ Acetate), 4.08 (d, $J = 11.5$ Hz, 1H of CH$_2$OTMS), 4.12 (d, $J = 6.5$ Hz, 2H, H-C$_6$, H'-C$_6$), 4.19 (d, $J = 11.5$ Hz, 1H, 1H of CH$_2$OTMS), 4.59 (td, $J = 6.5$, 1.7 Hz, 1H, H-C$_5$), 5.41 (dd, $J = 3.5$, 1.7 Hz, 1H, H-C$_4$), 5.58 (dd, $J = 10.3$, 3.5 Hz, 1H, H-C$_3$), 5.79 (d, $J = 10.3$ Hz, 1H, H-C$_2$). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ -0.7 (3C, 3 X CH$_3$ TMS), 20.7 (1C, CH$_3$ Acetate), 20.7 (1C, CH$_3$ Acetate), 20.8 (1C, CH$_3$ Acetate), 20.8 (1C, CH$_3$ Acetate), 61.9 (1C, CH$_2$ of CH$_2$OTMS), 64.5 (1C, C$_6$), 67.4 (1C, C$_4$), 67.6 (1C, C$_2$), 68.4 (1C, C$_3$), 71.8 (1C, C$_5$), 75.7 (1C, C$_1$), 116.8 (1C, C$_q$ Nitrile), 168.8 (1C, C$_q$ Acetate), 170.0 (1C, C$_q$ Acetate), 170.3 (1C, C$_q$ Acetate), 170.5 (1C, C$_q$ Acetate); HRMS (ASAP-TOF) $m/z$ found for [M+H]$^+$: 460.1639; [C$_{19}$H$_{29}$NO$_{10}$Si+H]$^+$ requires 460.1639.
A solution of 9-BBN in THF (0.63 ml, 0.5 M in THF, 0.32 mmol, 1 equiv.) was added dropwise to a stirred solution of compound 466 (0.109 g, 0.32 mmol) in dry THF (2.5 ml) at 0 °C. The mixture was gradually warmed to rt and stirred until the starting material was fully consumed (monitored by TLC). Once complete, the reaction mixture was cooled to 0 °C and treated with 1:1 EtOH-THF (0.6 ml), pH 7 0.1 M potassium phosphate buffer (0.6 ml) and 30% aqueous H$_2$O$_2$ (0.97 ml). After being left for 5 hours stirring at rt, the reaction mixture was poured into a mixture of EtOAc (10 ml) and 30% aqueous NaHSO$_3$ (10 ml), and the layers were then separated. The aqueous layer was extracted with EtOAc twice. The combined organic extracts were washed with saturated aqueous Na$_2$SO$_3$, saturated aqueous NaHCO$_3$, water, brine, and dried over anhydrous MgSO$_4$. Filtration and removal of the solvent in vacuo gave a crude oil.

Purification by flash column chromatography on silica gel (hexane:EtOAc 2:1 → 1:1) furnished an inseparable mixture (481:unknown compound, 7:1) of 481 and an unknown compound (0.013 g, 11%)*; IR $\nu_{\text{max}}$(film)/cm$^{-1}$: 3482, 2926, 2857, 1745, 1228, 1050; $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 1.99 (s, 3H, CH$_3$ Acetate), 2.05 s, 3H, CH$_3$ Acetate), 2.07 (s, 3H, CH$_3$ Acetate), 2.15 (s, 3H, CH$_3$ Acetate), 3.48 (dd, $J = 10.0, 4.8, 2.3$ Hz, 1H, H-C$_1$), 3.61 (dd, $J = 12.6, 4.8$ Hz, 1H, 1H of CH$_2$OH), 3.73 (dd, $J = 12.6, 2.3$ Hz, 1H, 1H of CH$_2$OH), 3.90 – 3.95 (m, 1H, H-C$_5$), 4.07-4.17 (m, 2H, H-C$_6$, H’-C$_6$), 5.10 (dd, $J = 10.0, 3.5$ Hz, 1H, H-C$_3$), 5.21 (t, $J = 10.0$ Hz, 1H, H-C$_2$), 5.44 (dd, $J = 3.5, 1.1$ Hz, 1H, H-C$_4$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 20.8 (1C, CH$_3$ Acetate), 20.8 (1C, CH$_3$ Acetate), 20.9 (1C, CH$_3$ Acetate), 20.9 (1C, CH$_3$ Acetate), 61.7 (1C, CH$_2$OH), 61.9 (1C, C$_6$), 66.4 (1C, C$_2$), 67.8 (1C, C$_4$), 72.0 (1C, C$_3$), 74.5 (1C, C$_5$), 78.7(1C, C$_1$), 170.3 (1C, C$_q$ Acetate), 170.4 (1C, C$_q$ Acetate), 170.6 (1C, C$_q$ Acetate), 170.7 (1C, C$_q$ Acetate); HRMS (NSI-FTMS) $m/z$ found for [M+Na]$^+$: 385.1099; [C$_{15}$H$_{22}$O$_{10}$+Na]$^+$ requires 385.1105.

*Assuming the unknown compound is an isomer of the title compound 481, the number of moles of the title compound 481 in the inseparable mixture were calculated from molar ratios seen in
the $^1$H NMR spectrum. Since the yield of 481 is based on the number of moles of 481 in the inseparable mixture, the yield of the 481 derives from the aforementioned molar ratios seen in the $^1$H NMR spectrum of the inseparable mixture.
References for Experimental Section


