Studies Towards the Total Synthesis of Tagetitoxin

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Partial Fulfilment of the Requirements
For the Degree of
Doctor of Philosophy

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I, Moussa Sehailia, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.
ABSTRACT

Tagetitoxin is a phytotoxin produced by the bacterium *Pseudomonas syringae pv. tagetis*. It is a selective inhibitor of RNA polymerase III in eukaryotic cells and RNA polymerase in bacteria. To date, no total synthesis of the proposed structure of tagetitoxin has been reported. While there is some ambiguity surrounding the structure of tagetitoxin, the most likely structure incorporates a unique 9-oxa-thiabicyclo[3.3.1]nonane core, with six stereogenic centres and a range of functional groups.

This thesis describes the development of a novel synthetic route towards tagetitoxin. The first task was the introduction, at C-5 of D-glucose, of a carbon substituent which could later be transformed to the carboxylic acid moiety of tagetitoxin. Initial studies showed that, while incorporation of a hydroxymethyl substituent was straightforward, problems arose in attempts to selectively functionalise one of the two primary hydroxyl groups in the resulting molecule.

Alternatively, incorporation of a vinyl moiety at C-5 of D-glucose was achieved using a procedure described by Rama Rao *et al*. This led to the formation of 1,6-anhydro-5-C-vinyl-D-glucose, which was successfully functionalised at C-1 via incorporation of a TMS acetylene group following a method described by Vasella and co-workers. The next task was to introduce a nitrogen substituent at C-3 of the sugar while inverting the configurations at both C-2 and C-3; for this purpose, conversion to a 2,3-β-epoxide was achieved in six steps. Unfortunately, attempted ring opening of the epoxide with various azide sources failed to give the desired product. A modified route was thus investigated in which the vinyl group at C-5 was converted to a less sterically demanding nitrile group. In this case, the 2,3-β-epoxide, when subjected to treatment with sodium azide in the presence of lithium perchlorate, furnished the desired azido compound with inversion of configuration at C-3.

While time constraints did not allow further progress to be made towards tagetitoxin, the remaining tasks are to further introduce a thiol group at C-6, a phosphate at O-4 and oxidation of the acetylene moiety to a methyl ketoester which upon cyclisation should give the desired tagetitoxin molecule.
“It is by logic we prove, it is by intuition that we invent.”

Jules Henri Poincaré
I would like to take this opportunity to thank Dr. Michael J. Porter for giving me the opportunity to work in one of his challenging synthetic chemistry projects within his group. I’m also thankful for the help and support I received from him throughout the course of my research period, I’m very grateful for his creative input in the project and I really believe that Michael is a very talented organic synthetic chemist that can make an immense contribution to the synthetic chemistry community during his academic career. I’m also thanking EPSRC for their financial support of the project.

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<table>
<thead>
<tr>
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<td>DEPT</td>
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<td>dimethylformamide</td>
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<td>NMR</td>
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<td>NOE</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>NTP</td>
<td>nucleoside triphosphate</td>
</tr>
<tr>
<td>PG</td>
<td>protecting group</td>
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<tr>
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<td>phenyl</td>
</tr>
<tr>
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</tr>
<tr>
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<td>para-methoxyphenyl</td>
</tr>
<tr>
<td>PPI</td>
<td>pyrophosphate</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>RNAP</td>
<td>ribonucleic acid polymerase</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>Ser</td>
<td>serine</td>
</tr>
<tr>
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<td>tetra-(n)-butylammonium fluoride</td>
</tr>
<tr>
<td>TBAI</td>
<td>tetra-(n)-butylammonium iodide</td>
</tr>
<tr>
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<td>tert-butyldiphenylsilyl</td>
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</tr>
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<tr>
<td>Tr</td>
<td>trityl</td>
</tr>
<tr>
<td>Ts</td>
<td>para-toluenesulfonyl</td>
</tr>
<tr>
<td>UTP</td>
<td>uridine triphosphate</td>
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</tbody>
</table>
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1. INTRODUCTION

Thiosugars are sulfur-containing carbohydrate derivatives which commonly differ in biological activity from their non-sulfur-containing analogues; this is a consequence of thiosugars having different conformational and geometrical properties, as well as flexibility differences.\textsuperscript{1} In addition, sulfides are less electronegative and more polarisable than ethers and hence possess different electronic properties.\textsuperscript{1} Among the examples of potential targets are salacinol (1), kotalanol (2), both potent inhibitors of intestinal $\alpha$-glucosidases, thiolactomycin (3), inhibitor of fatty acid synthase (FAS) and tagetitoxin (4), inhibitor of chloroplast RNA polymerase (Figure 1).\textsuperscript{2-4} A consequence of the biological activity of most thiosugars is that they are potential leads for the development of carbohydrate based therapeutics.

![Salacinol (1)](image1)

![Kotalanol (2)](image2)

![Thiolactomycin (3)](image3)

![Tagetitoxin (4)](image4)

**Figure 1:** Thiosugar based carbohydrates

Tagetitoxin (4) is a biologically active natural product, which inhibits RNA polymerase III in eukaryotic cells.\textsuperscript{5} Some ambiguities over the structure of tagetitoxin still exist; however, spectroscopic data showed structure 4\textsuperscript{a} or 4\textsuperscript{b} to be most likely.\textsuperscript{5} The positioning of the amide and carboxylic acid groups in tagetitoxin is ambiguous, with structure 4\textsuperscript{a} being narrowly favoured over the alternative structure 4\textsuperscript{b}. The absolute configuration of tagetitoxin is unknown.

The dense functionality in tagetitoxin (4\textsuperscript{a}) in conjunction with its complex bicyclic core prompted us to embark on a synthetic project to confirm its structure and to further study its
biological mode of action. This thesis will discuss recent synthetic strategies towards tagetitoxin (4a) and its analogues, including some previous and ongoing work by our group.

1.1 Origin and proposed structure of tagetitoxin

Tagetitoxin was first isolated by Mitchell and co-workers in 1981 from a plant pathogenic bacterium, *Pseudomonas syringae* pv. *tagetis*.\(^7\) It was originally isolated as a non-crystalline glassy residue following gel filtration, ion exchange and partition chromatography.

Initial mass spectroscopy measurements determined that tagetitoxin had a molecular weight of 435 for M\(^+\) which corresponded to a molecular formula of C\(_{11}\)H\(_{18}\)NO\(_{13}\)PS. Further tests using \(^1\)H, \(^13\)C and \(^{31}\)P NMR indicated the presence of carboxyl, hydroxyl and phosphate groups. Staining also showed the presence of nitrogen in an amine functional group and phosphorus in phosphate ester moiety; double labelling experiments following successful incorporation of \(^{32}\)P and \(^{35}\)S indicated the presence of one sulfur atom. Also, exposure of tagetitoxin to a very strong acid failed to liberate sulfate, which suggested that the presence of sulfur was either in the form of a thiol or a thioether. Further correlation of \(^1\)H and \(^13\)C NMR spectroscopic data allowed the eight membered ring structure 5 to be proposed by Mitchell and Hart (Figure 2).\(^8\)

In 1989, the same group revised their structures for tagetitoxin, proposing structures 4a and 6. This reassignment was made on the basis of new FAB mass spectrometry data. This gave MH\(^+\) of 417.0361, corresponding to a molecular formula of C\(_{11}\)H\(_{17}\)N\(_2\)O\(_{11}\)PS. \(^1\)H and \(^13\)C NMR analysis revealed that tagetitoxin contained: one amide, one acetyl, one phosphate, one carboxylic acid and two oxygens in either ether or hydroxyl groups (Figure 3).\(^6\)
These structures were also supported by the presence of a definite spatial proximity, using NOE experiments, between protons on C-5 & C-6 and C-2 & C-7. Although the data did not rule out the seven-membered ring present in structure 6, it was felt that particular coupling constants of 3.6 Hz between the $CHO$ and $CHOAc$ protons, 12.4 Hz between the $CHOAc$ and $CHNH_3^+$ and 6.0 between $CHNH_3^+$ and $CHOPO_3H^-$ protons were better assigned to the more rigid six-membered ring structure of 4a.6

The authors also observed a strong long range correlation between the carbon at 174.5 and the proton on C-8. Long range interactions were also observed between the carbon at 171.2 and the proton on C-5, which suggested the presence of a quaternary carbon at C-4. It was not clear from the data which position the amide moiety is placed, however the authors favoured the position at C-11 due to its smaller carbon chemical shift.

In 2005, Gronwald et al. published a paper casting doubt on Mitchell’s proposed structure of tagetitoxin.9 This paper recorded a molecular weight of 678 for tagetitoxin, despite reporting very similar $^1$H and $^{13}$C NMR data. The additional 262 mass units were accounted for, somewhat implausibly, “by the presence of atoms (oxygen, nitrogen, sulfur) and exchangeable protons that are not detected by 1D NMR”. As Gronwald was unable to provide a molecular formula, let alone a new structure for tagetitoxin, we continue to regard 4a as the most likely structure.6

In 2005, Vassylyev and co-workers, reported a crystal structure of tagetitoxin bound to the active site of RNA polymerase.10 Interestingly, this appeared to show the same relative configuration of tagetitoxin as in structure 4a, but with both phosphate and acetate bearing stereogenic centres inverted, as in structure 7 (Figure 4).
1.2 Biological properties of Tagetitoxin

Tagetitoxin, a bacterial phytotoxin, induces chlorosis and leaf spot in host species of the Asteraceae family of plants such as zinnia (Zinnia elegans Jacq) and sunflower (Helianthus annuus).\textsuperscript{11,12} Such chlorosis occurs through the translocation of toxin to the apical regions where it inhibits RNA Polymerase (RNAP) in chloroplasts, which in turn suppresses the chloroplast biogenesis.\textsuperscript{5,11} Tagetitoxin was also shown to inhibit \textit{in vitro} RNAPs of bacteria, insects and vertebrates at micromolar concentrations. In eukaryotic cells, RNAP III was inhibited by tagetitoxin while RNAPs I and II were resistant.\textsuperscript{10}

1.2.1 RNA polymerase

RNAP is an important cellular enzyme involved in gene expression during the transcription stage of protein synthesis. The principal enzymatic reaction of RNAP is nucleotide addition – the transfer of a nucleotidyl moiety from the incoming nucleotide triphosphate (NTP) substrate to the 3´-OH of the nascent RNA, followed by the release of pyrophosphate (PPi) and enzyme translocation by 1 nucleotide (nt) (\textbf{Scheme 1}). The polymerisation reaction can also be reversible, as in the presence of PPi, RNAP progressively degrades the nascent RNA, releasing nucleotidyl triphosphate from the 3´ end of the transcript.\textsuperscript{13} Most RNAP reactions are thought to happen in a single active site and conform to the general two metal-coordinated mechanism, whereby invariant aspartate residues coordinate to two catalytic Mg\textsuperscript{2+} ions (β´ Asp460, Asp462, Asp464 and β Asp814 in \textit{E. coli} enzyme\textsuperscript{14,15}).
RNAP can also be involved in two other types of hydrolysis reactions. Firstly, exonucleolytic
hydrolysis,\textsuperscript{16} which is a cleavage facilitated by the presence of noncognate substrates; this
reaction leads to the release of 3’ nucleotidyl monophosphate (NMPs). Secondly, endonucleolytic hydrolysis,\textsuperscript{17} which is a backward translocation that occurs when the nascent
RNA is threaded through the active site in the secondary channel of RNAP; this reaction is
also facilitated by other cellular cleavage factors and leads to the release of 3’ extruded RNA
segments. There are three different types of RNAPs.\textsuperscript{18}
1. **RNA polymerase I** – Consisting of 12 subunits and is responsible for 50-70% of all nuclear transcription. This type of RNAPs is mainly involved in the synthesis of large ribosomal RNAs.¹⁹

2. **RNA polymerase II** – Also consisting of 12 subunits and is responsible for the formation of messenger RNAs and most small nuclear RNAs.¹⁹

3. **RNA polymerase III** – Consisting of 17 subunits and is involved in about 10% of all nuclear transcription. It is responsible for the formation of small RNAs such as tRNA and 5S ribosomal RNA which are both required during protein synthesis.¹⁹

### 1.2.2 Inhibition of RNA polymerase by tagetitoxin

In 1990 Mathew et al. found that concentrations of just 0.3-3.0 µM of tagetitoxin were needed to inhibit RNAP III in *Xenopus leavis* oocytes, however RNAP II from wheatgerm required concentrations of more than 100 µM to produce the same effect.⁵ It was also established that tagetitoxin affects the incorporation of uridine into RNA in chloroplast; this was found when [³²P] UTP was inhibited from incorporation to RNA upon addition of tagetitoxin to a transcriptionally active chloroplast protein.²⁰

The simplest mechanism which can be envisaged for the inhibition of RNAP by tagetitoxin is a direct competition with the nucleotidyl triphosphate (NTP) substrate. However, this could be ruled out for two reasons: Firstly, kinetic data obtained shows tagetitoxin acting as an uncompetitive inhibitor,⁵ ²⁰ which suggests that tagetitoxin doesn’t prevent substrate binding. Secondly, it was shown that tagetitoxin inhibits catalytic reactions that use different substrates such as pyrophosphorolysis and exonucleic cleavages.

In 2005, Vassylyev and co-workers inspected the crystal structure of tagetitoxin-RNAP complex of bacterium *T. Thermophilus*, which argued against the competition between tagetitoxin and NTP substrate.¹⁰ Hence it was suggested that the mechanism by which tagetitoxin acted was by stabilising some inactive intermediate during the substrate loading into the active site.

Structural analysis also indicated that the intermediate could either be formed during the pre-insertion or insertion stage. The authors suggested that the intermediate was more likely to be formed in the pre-insertion stage, and then stabilised in the insertion step, suggesting a concerted two-step model (**Figure 5**).
It was reasoned that during the binding in the pre-insertion step and in the presence of tagetitoxin, the phosphate of the NTP substrate, which coordinates the Mg\(^{2+}\) in the cMG2 ion site, would probably switch interactions to a well-fixed Mg\(^{2+}\) in the tMG ion site. Thus, a subsequent loss of interaction with cMG2 occurs. This theory suggests that the resulting interaction of NTP with the Mg\(^{2+}\) binding site tMG would not be disturbed during the isomerisation; the more compact conformation of the active site in the insertion stage would result in a tighter binding of tMG-bound substrate to prevent both the dissociation of the substrate and the catalytic reaction, therefore irreversibly locking RNAP in a non-productive state (Figure 5).

![Figure 5: Tagetitoxin’s mode of action](image)

Before 2005 it was known that tagetitoxin inhibits RNAP, however the mechanism was still not clear. Recently Vassyljev et al. published a crystal structure of (RNAP)-tagetitoxin complex at a resolution of 2.4 Å. The bacterial *T. thermophilus* RNAP (ttRNAP)-tagetitoxin complex showed that the binding site of tagetitoxin is situated at the base of the RNAP secondary channel and not the enzyme’s active site. This binding was mediated exclusively by polar interactions, whereby 9 of the 11 tagetitoxin oxygen atoms form 18 hydrogen bonding interactions with the adjacent protein side chain (Figure 6).

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1 Reproduced from *Nature Structural & Molecular Biology* 2005, 12, 1086-1093. Licence number: 2471900717131
Figure 6: Tagetitoxin’s binding to RNAP

This extensive network, which is constituted by a set of basic and acidic side chains, forms a concerted mode of recognition that could be essential for the binding of tagetitoxin. The network is also highly unstable to smaller alterations in conformation or position of even one single residue.

Tagetitoxin also showed very strong interactions with three highly conserved RNAP basic residues (β Arg678, β Arg1106 and β’ Arg731). On the other hand it was suggested that β’ Asn458 was probably involved in substrate recognition. It was also noted that the binding sites of tagetitoxin and nucleotidyl triphosphate do not overlap, which suggested that competition with the substrate was not a major factor in tagetitoxin’s mode of action.

The authors suggested that the RNAP-tagetitoxin complex was strengthened by the well-fixed Mg$^{2+}$ ion binding site that mediates RNAP interactions with tagetitoxin. It was shown that the phosphate group in tagetitoxin was also coordinated to the Mg$^{2+}$ ion and two other active site residues, β’ Asp460 and β Glu813. Since RNAP contains more than one Mg$^{2+}$ binding site (e.g. cMG1, cMG2 and tMG), Vassylyev anticipated that the side chain of β’ Asp460 was better fixed in the complex by bridging the two Mg$^{2+}$ ions (cMG1 and tMG). Consequently, this would favour coordination and strengthen the binding of the catalytic cMG1. As a result tagetitoxin increases the RNAP affinity for the major catalytic Mg$^{2+}$ ion, cMG1.
1.3 Previous studies towards the synthesis of tagetitoxin

To date, there have been a number of published attempted syntheses of tagetitoxin and its analogues. The first piece of work in this area was done by Sammakia et al., who elected to synthesise tagetitoxin via a linear approach starting from a sulfur containing olefin. The second attempt was by Furneaux and co-workers, who chose to start from a cyclic hexose; the rest of the attempts towards tagetitoxin have been made by our group (Porter et al.).

1.3.1 Sammakia’s approach

In 1996, Sammakia et al. reported the dihydroxylation of sulfur-containing olefins as part of an approach to tagetitoxin. Sammakia envisaged a retrosynthetic analysis which included an enzymatic coupling of dihydroxyacetone phosphate with aldehyde, which itself could be prepared from fully protected oxazolidine olefin, to form the pentaol intermediate. Following this, an intramolecular cyclisation and functionalisation of the product should give the enantiomer of tagetitoxin (ent-4a) (Scheme 2).

\[ \text{ent-4a} \rightarrow \text{11} \]

\[ \text{11} \rightarrow \text{ent-4a} \]

**Scheme 2:** Sammakia’s approach to the synthesis of the enantiomer of tagetitoxin (ent-4a)\(^{ii}\)

The synthesis began by treating methyl ester with various sulfur nucleophiles to generate phosphonate intermediate in situ. Subsequent quenching with oxazolidine aldehyde gave different ratios of Z:E alkenes (Scheme 3).\(^{23,24}\)

\[^{ii}\text{Although the retrosynthesis in Sammakia’s paper is as depicted in Scheme 2, conversion of 11 to ent-4a will require inversion at the tertiary alcohol centre. This issue was not discussed in the paper.}\]
A series of compounds bearing different sulfur protecting groups was synthesised; the nature of the R group on sulfur influenced the ratio of (Z)-15:(E)-15 alkene in the products mixture (Table 1).

<table>
<thead>
<tr>
<th>R</th>
<th>Et</th>
<th>i-Pr</th>
<th>t-Bu</th>
<th>Ph</th>
<th>Bn</th>
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</thead>
<tbody>
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<td>(Z)-15:(E)-15</td>
<td>40:60</td>
<td>30:70</td>
<td>0:100</td>
<td>80:20</td>
<td>70:30</td>
</tr>
</tbody>
</table>

The dihydroxylation of 15 was then attempted. Initial dihydroxylation using conventional methods such as addition of stoichiometric or catalytic amounts of OsO₄ with amine N-oxides as stoichiometric co-oxidants gave products 16 and 17 in which the sulfur had been oxidised; alternative examination of different co-oxidants such as ferricyanide was largely unsuccessful. The authors suggested that this was probably due to the sterically demanding osmium-ligand complex which reacted very slowly with the electron deficient alkene (Scheme 4).

**Scheme 3:** Synthesis of olefin 15

**Scheme 4:** Dihydroxylation of olefin 15
When K$_3$Fe(CN)$_6$ was used as the stoichiometric co-oxidant, compounds 15b and 15e gave small amounts of the desired products, however over-oxidation to a sulfoxide was frequently observed. Oxidation of phenyl sulfide 15d also gave the sulfone as the major product. However, t-butyl sulfide containing compound 15c was the only substrate susceptible to dihydroxylation with OsO$_4$/K$_3$Fe(CN)$_6$ in preference to sulfur oxidation. Table 2 summarises Sammakia’s dihydroxylation results for five electron deficient olefins.

<table>
<thead>
<tr>
<th>R</th>
<th>Oxidant</th>
<th>Recovered SM (%)</th>
<th>Yield 18 (%)</th>
<th>Yield 16 (%)</th>
<th>Yield 17 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et (15a)</td>
<td>AD-mix-β</td>
<td>54</td>
<td>-</td>
<td>46</td>
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<td>30</td>
<td>-</td>
<td>70</td>
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<tr>
<td>i-Pr (15b)</td>
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<td>56</td>
<td>6</td>
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<td></td>
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<td>15</td>
<td>44</td>
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<tr>
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<td>14</td>
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<td></td>
<td>OsO$_4$, K$_3$Fe(CN)$_6$</td>
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<tr>
<td>Ph (15d)</td>
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<td></td>
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<td>-</td>
<td>10</td>
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<td>6</td>
<td>72</td>
<td>-</td>
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</table>

Table 2: Yield produced from the dihydroxylation of olefin 15

The best result obtained was that of compound 15c with OsO$_4$ using potassium ferricyanide as the co-oxidant. The resulting diastereomeric ratio was 25:1 with the major isomer being the desired one for the synthesis of tagetitoxin. The authors explained that the formation of the major isomer was in accordance with the distant approach of osmium from the Boc protecting group in the minimum energy conformation of the molecule.

This methodology was to be used to give unprotected aldehyde 9, which would lead to the synthesis of the enantiomer of tagetitoxin (ent-4a). Unfortunately, no subsequent work was reported after this point.
1.3.2 Furneaux’s approach

The intrinsic biological activity of tagetitoxin prompted Furneaux et al.\textsuperscript{22} to synthesise various related structures as potential herbicides and plant growth regulators. Furneaux’s work was designed to study the structure-activity relationships of tagetitoxin, while constructing the carbohydrate-based vicinal cis-amino phosphates. Hence bicyclic structures 19 and 20 were targeted. The authors envisaged that the presence of acetate, phosphate and amine moieties is important for the activity of tagetitoxin, while the sulfur bridge is important in determining the desired geometry of the pyranoid ring (Figure 7).

![Figure 7: Analogue of tagetitoxin](image)

Starting from readily available D-sugars, 1,6-anhydro-D-hexoses could be synthetically derived. These compounds possess close similarities to tagetitoxin (4a).

The initial approach to synthesise analogue 20 (where X=O) involved a cyclisation of dialdehyde 21 with nitromethane to form 1,6-anhydro-3-deoxy-3-nitro-D-gulose (22). Dialdehyde 21 was accessible from the periodate oxidation of levoglucosan;\textsuperscript{36} hydrogenation of nitro-D-gulose 22 gave amine 23. The configuration at C-3 and C-4 was confirmed by the large coupling constant $J_{3,4} = 9.9$ Hz and by the X-ray crystal structure of compound 23 in its hydrochloride salt form.\textsuperscript{22} The syn-configuration between C-2 and C-3 allowed the authors to selectively effect orthogonal protection of the hydroxyl moieties at C-2 and C-4. Therefore, initial N-Boc protection using Boc anhydride in THF gave derivative 24 and further treatment with bis(tributyltin) oxide and benzyl bromide in the presence of tetrabutylammonium bromide led to the desired tricyclic carbamate 25 in 96% yield.\textsuperscript{37} The presence of the benzyl group on the amine moiety was supported by the $^{13}$C chemical shift of the benzylic carbon at $\delta = 46.6$ ppm. THP protection at O-4 using dihydropyran under acidic conditions followed by ring opening of the cyclic carbamate and a subsequent second N-benzylation gave tertiary amine 26 (Scheme 5).
Further incorporation of the phosphate group using o-xyylene N,N-diethylphosphoramidite in the presence of 1H-tetrazole, followed by mCPBA oxidation successfully led to the formation of phosphate \( \text{27} \). Acidic removal of the THP protecting group gave alcohol \( \text{28} \) in a good yield. Subsequent acetylation at O-4 afforded compound \( \text{29} \) which when subjected to hydrogenolysis gave compound \( \text{30} \) in quantitative yield (Scheme 6).

Unfortunately, \textit{in vivo} biological testing of \( \text{30} \) gave no positive signs of biological activity against pre or post-emergent agriculturally important weeds such as \textit{Avena fatua} (wild oat), \textit{Setaria viridis} (green foxtail), \textit{Amaranthus retroflexus} (redroot pigweed) or \textit{Chenopodium album} (fat hen).
The authors also indicated that this route could be used to form analogues such as 31 containing a carboxylic acid group at C-1. This could be achieved via periodate oxidation of 2,7-anhydroseodeheptulose (32) to give dialdehyde 33; quenching with nitromethane would then give 4-deoxy-4-nitro-D-gulo-anhydride (34) (Scheme 7). This proposed synthesis was not carried out.

![Scheme 7](image)

**Scheme 7:** Proposed retrosynthetic route to carboxylic acid 31

In a different approach to synthesise compounds based on structure 20, Furneaux et al. decided to introduce a good leaving group at C-3 of anhydrosugar 35 which could then be displaced by a nitrogen nucleophile with inversion of configuration. Starting from anhydrosugar 35, selective acetonide protection using 2,2-dimethoxypropane and tosic acid in acetone gave acetonide 36 in 84% yield. Incorporation of a phosphate moiety at O-2 followed by acid hydrolysis under reflux gave diol 37. Unfortunately, the authors failed to establish selective acetylation at O-3 since treatment of diol 37 with acetic anhydride and pyridine gave diacetate 38 in 18% yield and an inseparable mixture of monoacetates 39 and 40 in 64% yield. However, 90% of the major acetate contained O-4 esters; this was due to the enhanced reactivity of the hydroxyl group occupying an equatorial position (Scheme 8).


**Scheme 8:** Attempted selective acetylation of compound 37 at O-3

By contrast, reactions containing a sulfur bridged anhydrosugar 41 successfully gave acetonide 42, however, further acid hydrolysis of this compound failed to give the corresponding diol 43. This failure was thought to be due to the sensitivity of the sulfur containing substrate to acid hydrolysis, possibly due to the involvement of the sulfur atom with the generated carbocation in the mixture (Scheme 9).

**Scheme 9:** Attempted hydrolysis of acetonide 42

Other attempted esterifications whereby the starting material was treated with dibutyltin oxide and pivaloyl chloride also led to undesired mixtures of monoesters. Furneaux envisaged that the possibility of ester migration could have played a part in reducing the selectivity of the esterification process. Incorporation of a brominated ortho-ester upon treatment with 1,1,1-triethoxy-2-bromoethane and tosic acid gave cyclic orthoacetate 44. Unfortunately, acid hydrolysis failed to give an O-3 ester and instead gave an inseparable mixture of bromoacetates 45 and 46 (Scheme 10).
Scheme 10: Attempted selective hydrolysis of compound 44

Alternatively, 4-methoxybenzylidene protection of triols 35 and 41 exclusively gave the endo-isomer of benzylidene acetals 47a and 47b. Subsequent silylation at O-2 using tert-butyl dimethylsilyl chloride and imidazole furnished compounds 48a and 48b, reduction gave the O-3 PMB protected ethers 49a and 49b. Acetylation at O-4, DDQ mediated debenzylaion at O-3 and sulfonylation furnished acetates 50a and 50b. Unexpectedly, attempts to convert either 50a or 50b into the corresponding azide 51a and 51b were all unsuccessful (Scheme 11).42

Scheme 11: Attempted synthesis of azides 51a and 51b

In a different route, the authors envisaged that compounds analogous to tagetitoxin (4a) could be made from readily available D-galactopyranose via initial addition of one extra carbon atom at C-1. To this end, pentaacetate 52 was brominated with HBr and acetic acid and then the product treated with mercury cyanide in nitromethane to give β-nitrile 53.43 Raney nickel reduction afforded an unstable aldehyde which when trapped with dianilinoethane gave
compound 54.\textsuperscript{44,45} Regeneration of the aldehyde followed by reduction and acetylation afforded pentaacetate 55 (Scheme 12).\textsuperscript{46}

\begin{align*}
\text{Scheme 12: Synthesis of pentaacetate 55}
\end{align*}

Compound 55 was deacetylated to afford pentaol 56 and further tosylation of the primary hydroxyl groups afforded ditosylate 57 in 33\% yield. Acetonide protection using 2,2-dimethoxypropane and tosic acid successfully furnished the desired acetonide 58 (Scheme 13).

\begin{align*}
\text{Scheme 13: Synthesis of acetonide 58}
\end{align*}

Unfortunately, attempts to displace both tosyl groups with a divalent sulfur nucleophile failed; instead compound 59 was isolated (Scheme 14).
To ease any steric constraints imposed by the isopropylidene group during the ring closure process, the authors replaced the acetonide protecting group with benzyl groups at O-3 and O-4. Following this, the formation of the anhydride precursor for compound 19 (X=O) was attempted. Thus, starting from tetraacetate 54, deacetylation and tritylation at O-6 afforded 60; benzylaion followed by acid hydrolysis and sodium borohydride reduction afforded diol 61. However, subsequent tosylation and treatment of the product with sodium hydride failed to give 62 (Scheme 15).

Furneaux also assessed the possibility of introducing a nitrogen group at C-4 prior to the ring closing process, thus eliminating any steric encumbrance related to the axial substituent at that position. Initial benzylidene protection of pentaol 56 using benzaldehyde dimethyl acetal successfully afforded acetal 63. Unfortunately, displacement of various sulfonate derivatives of 63 by sodium azide or tetrabutylammonium cyanide failed to give desired axial azide 64 (Scheme 16).
In an alternative attempt, the tosylate derivative 65 was made and treated with sodium azide in DMSO at reflux; this resulted in small amounts of azide 64 in 10% yield. Unfortunately the inefficiency of this reaction prevented the authors from proceeding any further with the synthesis (Scheme 17).

1.3.3 Previous work in the Porter group

Several attempts have been made by our group to synthesise both the core of tagetitoxin, and its full structure; we have also made progress towards the synthesis of decarboxytagetitoxin (66) (Figure 8).

1.3.3.1 Ring expansion reaction of 1,3-oxathiolanes

The initial strategy towards the tagetitoxin skeleton involved the ring expansion of bicyclic 1,3-oxathiolane 67. It was believed that subjection of compound 67 to a metal carbene generated from ethyl diazoacetate 68 would afford sulfur ylide 69. Ylide 69 would undergo a ring opening, followed by ring closure to afford the core structure 70, in which the five-membered ring of 67 has been expanded to a six-membered ring (Scheme 18).

---

**Scheme 16:** Attempted azide displacement at C-4

**Scheme 17:** Synthesis of azide 64

**Scheme 18:** Ring expansion strategy of 1,3-oxathiolanes

**Figure 8:** Decarboxytagetitoxin (66)
Before committing to the above sequence of reactions, the group decided to investigate the feasibility of the ring expansion strategy by using a simpler system such as monocyclic 1,3-oxathiolane 71 (Scheme 19).

![Scheme 19: Attempted ring expansion of monocyclic 1,3-oxathiolane 71](image)

Initial treatment of 2-phenyl-1,3-oxathiolane (72) with ethyl diazoacetate 68 in the presence of Cu(acac)₂ successfully gave a 2:1 inseparable mixture of 73:74 in 19% yield (Scheme 20).

![Scheme 20: Ring expansion of 2-phenyl-1,3-oxathiolane (72)](image)

It was considered that the low yield obtained in this reaction might be due to the lack of differentiation of the metal carbene between the sulfur atom of the starting material and that of the product. To surmount this problem, ethyl (triethylsilyl)diazoacetate (75) was used instead of ethyl diazoacetate (68). Addition of ethyl (triethylsilyl)diazoacetate (75) to compound 72 in the presence of Cu(acac)₂ furnished compounds 76 and 77 in an 8:1 ratio in 67% yield (Scheme 21).

![Scheme 21: Ring expansion of 2-phenyl-1,3-oxathiolane (72) using 75](image)

The success of this reaction prompted our group to attempt the synthesis of a bicyclic 1,3-oxathiolane intermediate, which could be used for the ring expansion process and subsequently form tagetitoxin. Hence, it was envisaged that starting from 1,3-oxathiolane 78, diastereoselective addition to aldehyde 79 and orthogonal protection of the resulting secondary alcohol was expected to give compound 80. Selective removal of the t-butyl acetal followed by deprotection of the primary alcohol and subsequent oxidation would then afford aldehyde 81. Intramolecular acetal formation should result in the bicyclic 1,3-oxathiolane.
intermediate 82 which upon ring expansion would afford the desired tagetitoxin structure (4a) (Scheme 22).

Scheme 22: Proposed synthesis of tagetitoxin (4a) via ring expansion strategy

Compound 78 was synthesised from commercially available L-serine in five steps. Unfortunately, model studies to test the validity of the asymmetric addition of 78 to 79 upon treatment of compound 78 with LDA in the presence of LiBr, followed by quenching with 3-methylbutanal failed to give the desired alcohol 83; instead, decomposition of the starting material was observed (Scheme 23).

Scheme 23: Attempted asymmetric synthesis of alcohol 83

It was thought that the substrate decomposition was perhaps due to the elimination of the thioether. To test this hypothesis, the reaction was attempted with analogous dioxolane ester 84; exposure of methyl ester 84 to a mixture of LDA and LiBr in THF followed by quenching with benzaldehyde gave the desired alcohol 85 in low yield (Scheme 24).

Scheme 24: Synthesis of alcohol 85

Although compound 85 was obtained in low yield, this result supports the explanation for the failure of the 1,3-oxathiolane reaction. This synthetic route was therefore abandoned.
Due to the difficulty in accessing a fully-functionalised precursor of tagetitoxin or decarboxytagetitoxin, a simpler bicyclic model system was tested in the ring expansion chemistry. Triacetate 86 was synthesised from D-glucose in four steps.\textsuperscript{55-57} When compound 86 was exposed to ethyl diazoacetate 75 in the presence of rhodium acetate, the elimination product 87 was isolated (Scheme 25).\textsuperscript{58}

\begin{equation}
\text{Scheme 25: Formation of compound 87}
\end{equation}

It was believed that compound 87 arose from initial formation of the sulfur ylide 88 followed by ring opening to form the zwitterion intermediate 89; proton transfer would then result in the formation of undesired derivative 87 (Scheme 26).\textsuperscript{58}

\begin{equation}
\text{Scheme 26: Proposed mechanism for the formation of compound 87}
\end{equation}

A bridging silyl protecting group was installed between O-2 and O-4 to provide a conformational constraint, and thus prevent the elimination process from occurring. To this end, compound 90 was deacetylated using aqueous ammonia and methanol, followed by silylation of the resulting diol 91 at O-2 and O-4 to give the desired tricyclic product 92 in 86% yield (Scheme 27).\textsuperscript{58}
Scheme 27: Synthesis of tricyclic intermediate 92

Unfortunately, when compound 92 was reacted with ethyl diazo(triethylsilyl)acetate in the presence of a catalytic amount of rhodium acetate, alcohol 93 was formed in 21% yield (Scheme 28).

Scheme 28: Formation of compound 93

Although no elimination had occurred on this occasion, formation of the undesired compound was a result of reaction of the ylide 94 (or the cation arising from its protonation) with water to afford bicyclic alcohol 93 (Scheme 29).

Scheme 29: Proposed mechanism for the formation of compound 93
1.3.3.2 Synthesis of the Tagetitoxin core via Photo-Stevens Rearrangement

The failure of the reactions in Schemes 25 and 28 to deliver ring-expanded products led to a modified strategy in which the ylide formation step was carried out intramolecularly. It was envisaged that exposure of a substrate such as 95 to catalytic rhodium acetate would result in the formation of intermediate ylide 96. Ylide 96 could then undergo [1,2] rearrangement to give the tetracyclic tagetitoxin core 97 (Scheme 30).59-61

Scheme 30: Intramolecular ring expansion strategy

Thus, starting from triol 98,62,63 protection at O-2 and O-4 using di-tert-butyl silyl dichloride in DMF gave the desired product 99.64 Acetoacetylation using commercially available acetonide 100,65 followed by a diazo transfer process,66 provided the desired diazo compound 101 in excellent yield. Further exposure of intermediate 101 to catalytic amounts of rhodium acetate in benzene failed to thermally proceed to the tetracyclic tagetitoxin core 102 and instead gave the stable ylide 103 in 88% yield (Scheme 31).60

Scheme 31: Attempted synthesis of tagetitoxin core 102

It was found that this ylide was stable even when heated in various solvents such as xylene, methanol and DMSO; in all cases starting material was recovered. Ylide 103 was also found
to be highly thermally stable with a melting point of 243-245 °C. Other attempts to form the core structure from ylide 103 were also made. For example addition of protic acids (TFA, TfOH) or Lewis acids (Cu(acac)₂) to ylide 103 (in the hope of increasing the polarisation of the C-S bond) failed to induce a thermal rearrangement to give the tetracyclic tagetitoxin core 102.

As a final attempt, rearrangement of ylide 103 was tested under photochemical conditions, i.e. a photochemical Stevens rearrangement. Therefore, ylide 103 was subjected to ultraviolet irradiation (λ> 290 nm) in acetonitrile. After 2 hours, conversion to the tetracyclic tagetitoxin core 102 occurred (Scheme 32).

Scheme 32: Ring expansion of ylide 103 via photochemical Stevens rearrangement

With this methodology in hand, further substrates were synthesised to identify which structural features were important for the ylide formation and the photo-Stevens rearrangement. Hence, starting from compound 104, desilylation using TBAF in THF followed by protection of the diol intermediate at O-2 and O-4, successfully furnished bis-triethylsilyl ether 105. Successful incorporation of the diazo moiety followed by exposure to rhodium acetate, gave ylide 106 in good yields. Subsequent photolysis of 106 smoothly afforded the desired core 107 in 65% yield (Scheme 33).
Scheme 33: Synthesis of tagetitoxin core 107

The [1,2] rearrangement was also tested on compound 108, which lacks the acetyl group of the previous structures. Starting from previously synthesised alcohol 99, acetylation using acetic anhydride in pyridine gave acetate 109 in 84% yield. Conversion of the acetate to trifluoroacetoacetate 110 followed by diazo transfer afforded diazoacetate 108 in good yield.\(^{68}\) Surprisingly, initial treatment of compound 108 with catalytic amounts of rhodium acetate in benzene gave cycloheptatriene 111 in 39% yield through reaction of the rhodium carbenoid with the solvent (Scheme 34).\(^{60,69,70}\)

Scheme 34: Formation of compound 111
However, when benzene was replaced by dichloromethane in the final step, the reaction proceeded smoothly to give the target compound 112 in 65% yield (Scheme 35).

**Scheme 35: Synthesis of tagetitoxin core 112**

### 1.3.3.3 Synthesis of the tagetitoxin core via cyclisation of a thiol onto an α-ketoester

In an alternative strategy by our group, it was envisaged that the synthesis of the tagetitoxin core could be achieved via cyclisation of a thiol onto an α-ketoester to form the hemithioacetal moiety of the natural product. The feasibility of such a cyclisation was first tested on a simple model system. Hence, lactone 113 was synthesised from commercially available phenyl 1-thio-β-D-glucopyranoside (114) in four steps. Selective silyl protection at O-6 followed by benzylation at O-2, O-3 and O-4, furnished fully protected glucopyranoside 115 in 87% yield. N-Bromosuccinimide promoted hydrolysis and oxidation using Dess-Martin periodinane gave the desired lactone 113 in 69% yield (Scheme 36).

**Scheme 36: Synthesis of lactone 113**

Cerium-mediated acetylene incorporation at C-1 of 113 followed by reduction with triethylsilane in the presence of TMSOTf resulted in compound 116 in 74% yield. Selective TMS removal using sodium hydroxide in methanol followed by bromination yielded the desired bromoalkyne 117 in 98% yield. Potassium permanganate mediated oxidation in methanol then afforded α-keto ester 118 in 84% yield. Unexpectedly, exposure
of ester 118 to a solution of hydrogen fluoride in pyridine furnished tricyclic compound 119 in 77% yield (Scheme 37).

**Scheme 37: Formation of compound 119**

Although formation of compound 119 was not anticipated, the intramolecular cyclisation of the hydroxyl moiety onto the α-keto ester suggested that a sulfur atom at C-6 would also cyclise successfully, leading to the bicyclic tagetitoxin core. Thus, starting from acetylene 116, initial treatment with TBAF in THF followed by mesylation at O-6 gave compound 120 in 95% yield. Displacement with potassium thioacetate and subsequent bromination using N-bromosuccinimide in the presence of silver nitrate resulted in bromoalkyne 121. Further oxidation using potassium permanganate in methanol afforded the targeted α-keto ester 122. Deacetylation and concomitant intramolecular cyclisation pleasingly provided tagetitoxin core 123 (Scheme 38).
Starting from glucose, a synthesis of decarboxytagetitoxin (66) would require inversion of both the C-2 and C-3 stereocentres, with introduction of a nitrogen moiety at C-3. These could be achieved by formation of a 2,3-β-configured epoxide and ring-opening at C-3. Alkyne 124 was synthesised by the procedure of Vasella and co-workers via initial treatment of triol 125 with two equivalents of TESCl in pyridine followed by incorporation of alkyne moiety at C-1 using lithium trimethylsilylacetylide in the presence of AlCl₃. Further TES protection at O-6 followed by acetylation at O-3 using acetic anhydride and 4-pyrrolidinopyridine furnished acetate 126 in 70% yield (Scheme 39).
**Scheme 39:** Synthesis of acetate 126

Removal of the silyl protecting groups, benzylidene protection and tosylation at O-2 using tosyl chloride in pyridine gave intermediate 127. Exposure of compound 127 to a solution of sodium methoxide in methanol gave epoxide 128 in 64% yield (Scheme 40).78

**Scheme 40:** Synthesis of epoxide 128

Ytterbium isopropoxide mediated azide ring opening at C-3 afforded azide derivative 129 in 79% yield.80 Further acetylation at O-2, acetal hydrolysis and subsequent tosylation at O-6 furnished the desired tosylate 130. Displacement of the tosylate moiety using potassium thioacetate in DMF produced the desired thioacetate 131 in 67% yield (Scheme 41).78
Subsequent silylation at O-4 using TESCl in pyridine gave pyranoside 132 which was then brominated at the terminal alkyne with a solution of N-bromosuccinimide and silver nitrate in acetone to give 133 (Scheme 42). Due to time constraints, further progress on this route was not achieved.\textsuperscript{78}

\textbf{Scheme 41:} Synthesis of thiaoacetate 131

\textbf{Scheme 42:} Synthesis of azide 133
1.4 Project objective

The objective of this work was to develop a new synthetic route towards tagetitoxin (4a), which would incorporate both stereochemical control and selective functionalisation of the sugar based starting material. The route was to be based on the thiol cyclisation route described in section 1.3.3.3. We envisaged that the carboxylate moiety of tagetitoxin could be derived from a hydroxymethyl, vinyl or cyano group in precursor 134 (Scheme 43).

\[
\begin{align*}
\text{H}_2\text{NOC} & \quad \text{OH} \\
\text{O} & \quad \text{OAc} \\
\text{O} & \quad \text{NH}_3^+ \\
\text{O}_2\text{C} & \quad \text{OPO}_3\text{H} \\
\text{S} & \quad \text{N}_3
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{NOC} & \quad \text{OH} \\
\text{O} & \quad \text{OAc} \\
\text{O} & \quad \text{NH}_3^+ \\
\text{O}_2\text{C} & \quad \text{OPO}_3\text{H} \\
\text{S} & \quad \text{N}_3
\end{align*}
\]

**Scheme 43:** Proposed retrosynthesis of tagetitoxin (4a)

Azide 134 would be synthesised from β-epoxide 135, which itself would be prepared by tosylation and subsequent deacetylation of benzylidene acetal 136. Benzylidene acetal 136 would be formed from tri-TES ether 137 upon desilylation and benzylidene protection. Formation of tri-TES ether 137 would be achieved from 1,6-anhydrosugar 138 following acetylenation at C-1, silylation at O-6 and acetylation at O-3. 1,6-Anhydrosugar 138 could then be formed from selective silylation at O-2 and O-4 of triol 139, which would be made from 5-substituted glucose 140 (Scheme 44).
Scheme 44: Retrosynthetic analysis of azide 134
2. RESULTS & DISCUSSION

2.1 Synthetic approach via 1,6-anhydro-5-C-hydroxymethyl-D-glucose

Our initial strategy was to synthesise tagetitoxin (4a) via incorporating a hydroxymethyl moiety at the C-5 position of methyl α-D-glucopyranoside (141). This approach would require a selective protection of one of the two primary alcohols in 142 either as 4,6-acetal 143 or 4,6′ acetal 144 (Scheme 45).81

Scheme 45: Selective protection of tetraol 142

Compound 142 was synthesised from commercially available methyl α-D-glucopyranoside (146) in six steps. The hydroxyl groups were protected using trimethylsilyl chloride in pyridine to give compound 147 in 79% yield. Oxidation of compound 147 gave aldehyde 148 which when desilylated under basic conditions afforded triol 149 (Scheme 46).82

Scheme 46: Synthesis of aldehyde 149

Compound 149 was subjected to aldol/Cannizzaro reaction using aqueous sodium hydroxide and formaldehyde (37%); upon acetylation, pentaacetate 150 was obtained in 22% yield together with tetraacetate 151 in 19% yield (Scheme 47).81,83
A proposed mechanism for the aldol/Cannizzaro reaction proceeds via enolate 152 which reacts with formaldehyde to afford aldehyde intermediate 153. Aldehyde 153 is then reduced to alcohol 142 by hydride transfer from adduct 154 (Scheme 48).

Competitive reduction of starting aldehyde 149 before the formaldehyde addition step also occurred forming the undesired tetraol which upon acetylation gave acetate 151 (Scheme 47). Deacetylation of compound 150 gave the desired methyl 5-C-hydroxymethyl-α-D-xylo-hexopyranoside (142) in quantitative yield (Scheme 49).

With compound 142 in hand, we turned our attention to the selective protection of either of the primary alcohols at C-6 or C-6’ with the hydroxyl moiety at C-4. We initially decided to implement a standard protocol which would give a benzylidene protected sugar. Compound 142 was treated with benzaldehyde and zinc chloride at room temperature, but a mixture containing compounds 155 and 156 was isolated (Scheme 50).
As we were unable to obtain a single regioisomer of either triol 155 or 156, we decided to introduce a bulkier protecting group instead; for this we selected pivalaldehyde as a suitable protecting reagent. Unfortunately, sonication of glucopyranoside 142 with pivalaldehyde and zinc chloride at 50 °C produced an inseparable mixture of compounds 157, 158 and 159 (Scheme 51).

Finally we investigated the installation of an acetonide. Treatment of compound 142 with 2,2-dimethoxy propane and CSA in acetone, selectively afforded compound 160 in 60% yield (Scheme 52).

Unfortunately acetonide 160 was of no use to us as the primary alcohols had not been differentiated. In light of these results, we decided to abandon this strategy.
2.2 Synthesis via 1,6-anhydro-5-C-vinyl-D-glucose

As earlier model studies failed to show the feasibility of incorporating a hydroxymethyl moiety at C-5 of D-glucose, we opted to incorporate a vinyl moiety instead.

2.2.1 Synthesis of 1,6-anhydro-5-C-vinyl-D-glucose

In 1993, Rama Rao and co-workers successfully synthesised glucofuranoside 161 in six steps starting from readily available D-glucose. Conversion of D-glucose to glucofuranoside 162 followed by benzylation of the hydroxyl group at C-3 provided compound 163. Selective acetonide removal at O-5 and O-6 followed by silyl protection of the primary alcohol then oxidation resulted in aldehyde 164. Vinylmagnesium bromide addition stereoselectively gave the tertiary alcohol 161 (Scheme 53).

Our proposed route to synthesise 1,6-anhydro-5-C-vinyl-D-glucose (139b) follows the sequence devised by Rama Rao. We chose to modify this route by the use of a more acid labile protecting group at C-3.

The treatment of D-glucose with acetone in the presence of concentrated H₂SO₄ afforded glucofuranoside 162 in 20% yield. The low yield produced from this reaction was probably due to the loss of product during the basic aqueous work-up and so we used an alternative work-up procedure. After completion of the reaction, ammonia gas was bubbled through the reaction mixture and a white precipitate of ammonium sulphate was formed. Filtration, followed by evaporation and subsequent recrystallisation from boiling petroleum spirit, afforded glucofuranoside 162 in 84% yield (Scheme 54).
With glucofuranoside 162 in hand, we attempted the protection of the hydroxyl moiety at C-3. For this we decided to use 4-methoxybenzyl as a suitable protecting group. Treatment of glucopyranoside 162 with 4-methoxybenzyl chloride\textsuperscript{iii} in the presence of sodium hydride and TBAI resulted in the desired PMB ether 165 in 86% yield. Selective acetonide removal using 60% aqueous acetic acid furnished the desired diol 166 in 80% yield (Scheme 55).\textsuperscript{86}

Silylation of diol 166 using one equivalent of TBSCl and imidazole gave alcohol 167 in 91% yield.\textsuperscript{84} Swern oxidation of alcohol 167 using trifluoroacetic anhydride and dimethylsulfoxide,\textsuperscript{87} successfully furnished ketone 168 in 95% yield (Scheme 56).\textsuperscript{88}

Subsequent treatment of ketone 168 with vinylmagnesium bromide furnished tertiary alcohol 169 as a single stereoisomer in 76% yield (Scheme 57). The stereoisomer was assigned by analogy with Rama Rao’s work and confirmed by subsequent reactions.

\textsuperscript{iii} Prepared from 4-methoxybenzyl alcohol by treatment with sulfonoyl chloride.
The formation of a single stereoisomer of compound 169 can be rationalised by the Anti-Felkin approach depicted in Scheme 58.

With compound 169 in hand, we turned our attention towards removal of the acetonide, tert-butyldimethylsilyl and 4-methoxybenzyl groups. Global deprotection of glucofuranoside 169 under acidic conditions would initially result in the furanose intermediate 170. Subsequent ring opening of intermediate 170 followed by 6-exo-trig ring closure should afford vinyl glucose 140b in its pyranose form (Scheme 59).

Initial exposure of compound 169 to 80% aqueous acetic acid failed to form the desired vinyl glucose 140b. Unfortunately, the product formed from this reaction couldn’t be identified (Scheme 60).

It was possible that the failure of this experiment was due to the inefficient deprotection of the 4-methoxybenzyl ether moiety at C-3. It was envisaged that instead, selective cleavage of
the 4-methoxybenzyl group using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) could result in the formation of a diol which when treated with 80% aqueous acetic acid would lead to the formation of pentaol \textit{140b}. Deprotection at C-3 was achieved \textit{via} reaction of tertiary alcohol \textit{169} with DDQ in a mixture of dichloromethane and water. Following purification, the desired diol \textit{171} was obtained in 36% yield. Unfortunately, variation in temperature, concentration or reaction time failed to give higher yields of \textit{171}. Diol \textit{171} was then heated in 80% aqueous acetic acid. Acetylation of the crude mixture pleasingly furnished the desired pentaacetate \textit{172} in 66% yield (Scheme 61).

With pentaacetate \textit{172} in hand, we attempted conversion to the desired intermediate 1,6-anhydro-5-C-vinyl-D-glucopyranose (\textit{139b}) using the Fraser-Reid method. Thus, deacetylation of compound \textit{172} followed by tosylation at O-6 and subsequent treatment with sodium hydroxide would afford the desired 1,6-anhydroglucose \textit{139b} (Scheme 62).

\underline{Scheme 61:} Synthesis of pentaacetate \textit{172}

\underline{Scheme 62:} Fraser-Reid’s approach to \textit{139b}
Unfortunately, initial attempts to deacetylate compound 172 using aqueous ammonia solution (29%) failed to give compound 173 as the sole product and instead gave a mixture of unidentified compounds (Scheme 63).

Scheme 63: Attempted deacetylation of compound 172

Although the formation of pentacetate 172 was successful, the removal of the 4-methoxybenzyl moiety from glucofuranoside 169 was not as efficient as we expected at such an early stage of the synthesis. Therefore we decided to re-investigate the original strategy of global deprotection.

It was considered that treatment of glucofuranoside 169 with a stronger acid such as trifluoroacetic acid could lead to the removal of all protecting groups including the 4-methoxybenzyl ether. Such a process could enhance both the yield of the reaction and the rearrangement process to form vinyl glucose 173.

To our delight, addition of trifluoroacetic acid (0.1%) to a solution of tertiary alcohol 169 in 80% aqueous acetic acid, followed by acetylation using acetic anhydride in pyridine, furnished a mixture of pentacetate 172 and the unexpected anhydrosugar 174 in a 4 : 1 ratio (Scheme 64).

Scheme 64: Synthesis of 172 and 174

$^1$H-NMR analysis also showed that the geminal coupling constant of the protons at C-6 of the 1,6-anhydroglucose 174 was about 7.6 Hz whereas that of the uncyclised vinyl glucose 172 was about 12.6 Hz. This variation in the coupling constants was used to distinguish between 1,6-anhydroglucose 174 and pentaacetate 172 in the crude mixtures.

The formation of compound 174 during the deprotection step had not been expected, since 1,6-anhydrosugars are generally not readily accessible from glucofuranoside type structures under aqueous acidic conditions. It seems likely that the incorporation of a vinyl moiety at
C-5 of glucofuranoside 169 played a vital role in the formation of anhydrosugar 174 by biasing the conformation towards that required for cyclisation.

Since 1,6-anhydrosugar 174 had been our next target, we decided to abandon the Fraser-Reid method and focus on optimising the deprotection condition for the formation of this product. Table 3 summarises the different reagents and reaction conditions investigated in the global deprotection reaction.

Table 3:

The above results indicated that acetic acid was a suitable solvent to use for the global deprotection, while a stronger acid such as sulfuric acid or p-toluenesulfonic acid was required to enhance the formation of the desired anhydrosugar 174.

It was also anticipated that carrying out the acetylation in one pot, rather than in pyridine in a separate step, under acidic conditions, could improve the yield of the 1,6-anhydroglucose 174. Thus compound 169 was subjected to a one pot global deprotection and acetylation protocol under various conditions. The results are summarised in Table 4.
RESULTS & DISCUSSION

Table 4: Attempted one pot conversion of 169 to 174

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent, T (°C)</th>
<th>Time (h)</th>
<th>Composition of Crude</th>
<th>Yield 174 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( p)-TsOH.H2O (0.1 eq.), then Ac2O</td>
<td>AcOH, 110</td>
<td>5</td>
<td>Predominantly 174</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>1% H2SO4 in AcOH then Ac2O</td>
<td>AcOH, 110</td>
<td>5</td>
<td>Complex mixture</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>0.01% H2SO4 in AcOH then Ac2O</td>
<td>AcOH, 110</td>
<td>2.5</td>
<td>Predominantly 174</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>0.01% H2SO4 in AcOH then Ac2O</td>
<td>AcOH, 140</td>
<td>8</td>
<td>Predominantly 174</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>0.05% H2SO4 in AcOH then Ac2O</td>
<td>AcOH, 120</td>
<td>36</td>
<td>Predominantly 174</td>
<td>40</td>
</tr>
</tbody>
</table>

Although the one pot deprotection & acetylation reaction was successful, the yields obtained were still moderate. It was considered that the low yields obtained from the above reaction may be due to the presence of oxonium ion 175 in the reaction mixture causing unidentified side reactions (Scheme 65).

Scheme 65: Formation of oxonium ion 175

This prompted us to investigate the use of thioanisole or triethylsilane as nucleophilic scavengers. We also envisaged that microwave irradiation could enhance the deprotection and rearrangement of compound 169. Thus, thioanisole was added to a solution of alcohol 169 in 0.01% H2SO4 in AcOH. The mixture was stirred under microwave irradiation for 1
hour then acetic anhydride was added. After a further 12 hours the desired product 174 was obtained in 49% yield (Scheme 66).

Another method attempted was the addition of triethylsilane to a solution of compound 169 in the presence of H₂SO₄. Following treatment with acetic anhydride, a previously unobserved product was obtained, which was tentatively assigned as diol 176 (Scheme 67).<sup>91</sup>

Structure 176 was indicated by the presence of a long range interaction between the protons at C-6 and the anomeric carbon (C-1) in the HMBC spectrum. It was possible that the formation of diol 176 was due to initial deprotection of the acetonide, tert-butyldimethysilyl and 4-methoxybenzyl groups followed by dehydration at C-1 to give intermediate 177. Intramolecular 6-endo-trig cyclisation afforded triol 178. Addition of acetic anhydride resulted in selective acetylation at O-3 and afforded diol 176 in 43% yield (Scheme 68).

---

**Scheme 66:** Synthesis of compound 174

**Scheme 67:** Formation of compound 176

**Scheme 68:** Proposed mechanism for the formation of compound 176
Although the addition of thioanisole to the reaction mixture did not enhance the yield of the reaction, it was clear that its presence played a positive role in scavenging the oxonium ion since the product isolated was much cleaner when compared to previous isolations. Therefore we decided to continue using thioanisole in future reactions.

We next considered that extending the time of the global deprotection reaction of 169 in the presence of thioanisole may result in good quantities of the more thermodynamically stable product 139b. Also, attempted purification of the crude mixture without acetylation may enhance the yield of the reaction.

Gratifyingly, initial exposure of glucofuranoside 169 to TFA and thioanisole in 80% aq. AcOH, followed by purification, furnished our desired triol 139b in 52% yield and diol 179 in 17% yield (Scheme 69).

![Scheme 69: Attempted isolation of triol 139b](image_url)

Although the yield of triol 139b was good for such a complex transformation, the formation of diol 179 was not expected. Diol 179 presumably arises through a Fischer esterification process. To circumvent this problem, the crude reaction mixture was subjected to deacetylation using sodium methoxide in methanol prior to purification.

Therefore, in an alternative attempt, a solution of glucofuranoside 169, TFA and thioanisole in 80% aq. AcOH was heated for four days. Concentration, followed by treatment with sodium methoxide in methanol afforded a mixture, which when purified, furnished the desired 1,6-anhydro-5-C-vinyl-D-glucose (139b) in 74% yield (Scheme 70).

![Scheme 70: Synthesis of triol 139b](image_url)
We also decided to test these conditions on commercial D-glucose, as the conversion of D-glucose to 1,6-anhydro-D-glucose (125) had not been previously reported in one step. Unfortunately treatment of D-glucose with TFA in 80% aq. AcOH under reflux, failed to furnish the desired 1,6-anhydro-D-glucose (125) (Scheme 71).

Scheme 71: Attempted conversion of D-glucose to 1,6-anhydro-D-glucose (125)
The failure of the above experiment emphasised the importance of the vinyl moiety at C-5 in the conversion to 1,6-anhydro-5-C-vinyl-D-glucose (139b).
2.2.2 Functionalisation of 1,6-anhydro-5-C-vinyl-D-glucose

With 1,6-anhydro-5-C-vinyl-D-glucose (139b) in hand, we then proceeded to functionalise our sugar unit. In 2001, Vasella and co-workers reported that treatment of bis-silyl ether 180 (prepared by disilylation of 1,6-anhydroglucose 125) with lithium (trimethylsilyl)acetylide in the presence of aluminium trichloride furnished diol 124 (Scheme 72).

**Scheme 72:** Vassella’s approach to 124

Vasella proposed that the β-orientation of the alkyne substituent in 124 was due to the strong chelation effect of the aluminate species to both the hydroxyl group at C-3 and the bridging oxygen, thus facilitating opening of the five-membered ring and subsequently enhancing the delivery of the TMS-acetylide moiety from the top face (Scheme 73).

**Scheme 73:** Proposed mechanism for the formation of 124

Previous work in our group, in which 124 was synthesised using the Vasella protocol, had shown that sonication during the reaction of aluminium trichloride with lithium acetylide was necessary for the displacement of chloride by TMS acetylide group. Our group also found that freshly sublimed aluminium trichloride was essential for the reaction to succeed. Similar treatment of compound 139b with two equivalents of triethylsilyl chloride in pyridine successfully furnished the desired bis-silyl ether 138b in 67% yield. Further treatment of
138b with lithium (trimethylsilyl)acetylide in the presence of aluminium trichloride, resulted exclusively in the desired 5-C-vinyl-C-glucoside 181 (Scheme 74).\(^93\)

![Scheme 74: Synthesis of glucoside 181](image1)

Our next objective was to invert the stereocentres at C-2 and C-3, with introduction of a nitrogen nucleophile at C-3. We envisaged that selective removal of the silyl groups at O-2 and O-4 under acidic conditions followed by protection of the hydroxyl moieties at C-6 and C-4 would lead to the formation of benzylidene acetal 182. Although literature methods for the formation of 2,3-β-epoxides from glucosides rely on the selective tosylation of the 2-hydroxyl group,\(^94;95\) there is nothing in literature to suggest whether this differential reactivity would extend to C-glucosides. However we were hopeful and decided to try the sulfonylation reaction as it would be the most direct route. Therefore, triflation of 182 and subsequent treatment with base should result in the desired β-epoxide 183 (Scheme 75).

![Scheme 75: Synthetic plan for the formation of epoxide 183](image2)

The initial removal of both silyl groups at C-2 and C-4 was successfully accomplished using 80% aq. AcOH. The resulting tetraol 184 was treated with 4-methoxybenzaldehyde dimethyl acetal under acidic conditions to furnish the desired benzylidene acetal 182 in 63% yield (Scheme 76).
**Scheme 76:** Synthesis of benzylidene acetal 182

Triflation of benzylidene acetal 182 using triflic anhydride and pyridine, furnished a mixture of compounds 185 and 186 in a ratio of 1.7:1 in favour of the undesired triflate 185 (Scheme 77).

**Scheme 77:** Attempted selective triflation of benzylidene acetal 182

Unfortunately, due to the instability of these triflates, we were unable to obtain a complete set of characterisation data for either compound 185 or 186. The preponderance of the undesired triflate 185 indicated that the yield of the subsequent epoxide formation would be low. This led us to conclude the impracticality of this route.

To ensure differentiation between the hydroxyl moieties at C-2 and C-3, we envisaged that further triethylsilyl protection of the hydroxyl moiety at C-6 of compound 181 followed by acetylation at O-3 should result in the fully protected sugar 137b. Desilylation, followed by 4-methoxybenzylidene protection would give compound 136b. Tosylation instead of triflation at O-2 should result in the more stable 2-tosylate 187. Deacetylation of compound 187 under basic conditions should then result in the formation of β-epoxide 135b (Scheme 78).
Initial treatment of diol 181 with triethylsilyl chloride and pyridine successfully furnished compound 188 in 81% yield (Scheme 79).

Unfortunately, attempted acetylation of the hydroxyl moiety at C-3 was non-trivial. The use of standard acetylation conditions such as acetic anhydride in pyridine or triethylamine failed to convert compound 188 to acetate 137b. The failure of this transformation was perhaps due to the steric encumbrance of both silyl groups at O-2 and O-4 around the hydroxyl moiety at C-3, thus preventing it from reacting with the acylating species. Table 5 shows the various reagents and reaction conditions attempted to effect the transformation.
Table 5: Attempted conversion of alcohol 188 to acetate 137b

In 1987 Smith and co-workers showed that acetylation of a sterically hindered hydroxyl moiety in compound 189 could be achieved using acetic anhydride in the presence of 4-pyrrolidinopyridine as a catalyst (Scheme 80).79
Similarly, previous work in our group had shown that 4-pyrrolidinopyridine could catalyse the acetylation reaction of sterically encumbered O-3 in compound 124 (Scheme 81).\textsuperscript{78}

However when this catalyst was tried on our substrate (Table 5, entry 3 & 4), we were unable to obtain good yields of acetate 137b.

TMSOTf has also been shown to catalyse the acetylation of alcohols in the presence of acetic anhydride;\textsuperscript{96} however, only decomposition was observed when these conditions were applied to alcohol 188 (Table 5, entry 6). This is possibly due to the lability of the triethylsilyl protecting groups under acidic conditions. The generation of triflic acid as a byproduct in the solution could have led to the removal of these protecting groups and subsequently acetylation of the resulting free alcohols. This reaction was also attempted at low temperature (Table 5, entry 7); unfortunately this also failed and resulted in the formation of a complex mixture. Treatment of compound 188 with the more reactive acetyl chloride (Table 5, entry 8 & 9) also failed to yield the desired acetate 137b.

Fortunately, the use of isopropenyl acetate and iodine successfully furnished the desired acetate 137b in a moderate yield (Table 5, entry 10). This method, described by Lier and co-workers in 2006, successfully utilised transesterification conditions to convert various free alcohols to their acetate counterparts. Lier postulated that the iodine acted as a strong Lewis acid catalyst, facilitating the acetylation of the alcohol. It is also possible that the above reaction could be catalysed by the presence of small amounts of HI in the solution mixture. This would protonate the isopropenyl species which upon nucleophilic attack by the alcohol can result in the desired acetate (Scheme 82).\textsuperscript{97}
In 2006 Saikia et al. showed that acetylation of alcohols could also be achieved using vinyl acetate in the presence of molecular iodine.\(^\text{98}\) Thus we hoped to utilise Saikia’s method to increase the yield of our acetylation reaction. Unfortunately when isopropenyl acetate was replaced with vinyl acetate (Table 5, entry 11), we were unable to observe any product formation.

The successful acetylation of the hydroxyl moiety at C-3, although only in moderate yield, allowed us to continue with the synthetic route. Treatment of compound 137b with 80% aq. AcOH in THF successfully resulted in the formation of triol 189 in 79% yield. Protection of triol 189 using 4-methoxybenzaldehyde dimethyl acetal in the presence of p-toluenesulfonic acid, furnished the desired benzylidene acetal 136b in 73% yield (Scheme 83).

The attempted tosylation of compound 136b using tosyl chloride and pyridine failed to solely produce compound 187, and instead gave a mixture of compound 187, compound 190 and compound 191 in 18%, 34% and 5% yield respectively (Scheme 84).
**Scheme 84: Attempted tosylation of compound 136b**

The formation of compounds 190 and 191 was likely due to the instability of the PMB acetal to pyridinium chloride. Although the yield of tosylate 187 was low, we decided to utilise it in subsequent steps to further validate our route. Unfortunately, initial treatment of tosylate 187 with sodium methoxide in methanol failed to form epoxide 135b, and instead resulted in the generation of alcohol 192 (Scheme 85).

**Scheme 85: Formation of alcohol 192**

The failure of the above experiment was probably due to the high activation energy required to form epoxide 138b. To surmount this, we decided to slowly elevate the temperature of the reaction to 60 °C. Unexpectedly, enyne 193 was formed in 49% yield (Scheme 86).

**Scheme 86: Formation of enyne 193**

As an E2 elimination of the tosylate from 192 is stereoelectronically less favourable, it seems likely that enyne 193 is formed via E2 elimination of the desired epoxide 135b (Scheme 87).95
Scheme 87: Proposed mechanism for the formation of enyne 193

We investigated treatment of alcohol 192 with various combinations of base, solvent and temperature in the hope of finding conditions under which epoxide 135b was formed but did not undergo elimination to enyne 193. **Table 6** shows the different reaction conditions utilised to effect the transformation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Temp</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cs₂CO₃, MeOH</td>
<td>Rt</td>
<td>SM recovered</td>
</tr>
<tr>
<td>2</td>
<td>Cs₂CO₃, MeOH</td>
<td>60 °C</td>
<td>Enyne formation</td>
</tr>
<tr>
<td>3</td>
<td>NaH, DMF</td>
<td>Rt</td>
<td>Enyne formation</td>
</tr>
<tr>
<td>4</td>
<td>NaH, DMF</td>
<td>0 °C</td>
<td>SM recovered</td>
</tr>
<tr>
<td>5</td>
<td>t-BuOK, DMF</td>
<td>Rt</td>
<td>Enyne formation</td>
</tr>
<tr>
<td>6</td>
<td>t-BuOK, DMF</td>
<td>0 °C</td>
<td>SM recovered</td>
</tr>
</tbody>
</table>

**Table 6**: Attempted conversion of alcohol 192 to epoxide 135b
It appeared from the above results that the rate of E2 elimination of the epoxide was comparable to its rate of formation. Indeed, when the reaction of 192 with sodium hydride in DMF at room temperature was quenched with methanol after 1 min, a 1:1 mixture of 135b:192 was formed together with recovered starting material, which constituted 20% of the reaction mixture (Scheme 88).

The fast formation of enyne 193 indicated a small difference in transition state energies for the reaction leading from alcohol 192 to epoxide 135b, and from epoxide 135b to enyne 193. Therefore we envisaged that incorporation of a triflate moiety rather than a tosylate at O-2 may lower the energy barrier required for the epoxide formation and increase the difference in energies between the two transition states, thus preventing the formation of enyne 193.

Initial exposure of compound 136b to triflic anhydride and pyridine furnished a mixture of triflate 194 and diol 195 in 9% and 34% respectively (Scheme 89).

The formation of diol 195 was due to the hydrolysis of the 4-methoxybenzylidene acetal protecting group. Repeating the triflation experiment at $-20 \, ^\circ\text{C}$ pleasingly furnished triflate
194 in 54% yield. Treatment of triflate 194 with sodium methoxide and methanol at room temperature, furnished the desired epoxide 135b in 63% yield (Scheme 90).

Scheme 90: Synthesis of epoxide 135b

Epoxide 135b was treated with various azide sources in an attempt to form compound 134b (Table 7).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Temp</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaN3, H2O, NH4Cl, 2-methoxyethanol</td>
<td>80 °C</td>
<td>Acetal deprotection</td>
</tr>
<tr>
<td>2</td>
<td>LiClO4, NaN3, MeCN</td>
<td>rt-80 °C</td>
<td>Acetal deprotection</td>
</tr>
<tr>
<td>3</td>
<td>Yb(OTf)3, LiOi-Pr, Me3SiN3, THF</td>
<td>65 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>Yb(OTf)3, LiOi-Pr, NaN3, THF</td>
<td>65 °C</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Table 7: Attempted conversion of epoxide 135b to compound 134b

Treatment of epoxide 135b with sodium azide and aqueous ammonium chloride in 2-methoxyethanol (Table 7, entry 1),95 with lithium perchlorate and sodium azide in acetonitrile, (Table 7, entry 2),99 or with ytterbium isopropoxide and either sodium azide and TMS azide (Table 7, entry 3 & 4)100 failed to produce the desired azide 134b. Unfortunately, after several attempts, we were unable to obtain azide 134b. This failure prompted us to consider an alternative strategy for the introduction of a nitrogen substituent at C-3.
In 1988 Jacobsen et al. used trichloroacetonitrile to successfully introduce amine moieties at C-3 of various glucopyranosides.\textsuperscript{101} Treatment of epoxide 196 with sodium hydride and trichloroacetonitrile at 0 °C followed by addition of sodium methoxide in methanol furnished the cyclic acetimidate 197. Addition of TFA gave the desired aminosugar 198 in good yields (Scheme 91).\textsuperscript{101}

\textbf{Scheme 91:} Jacobsen’s synthesis of aminosugar 198

It was postulated that the reaction proceeded via initial deprotonation of the hydroxyl groups at C-4 and C-6 to give bis-alkoxide 199. Subsequent nucleophilic attack on trichloroacetonitrile generated bis-imidate 200. Intramolecular nucleophilic attack of the imidate moiety at C-4 resulted in the bicyclic imidate 201. Further addition of sodium methoxide in methanol gave diol 197. Hydrolysis under acidic conditions generated the desired amine salt 198 (Scheme 92).\textsuperscript{101}

\textbf{Scheme 92:} Proposed mechanism for the formation of aminosugar 198
Therefore, the acetal group of epoxide 135b was hydrolysed using 60% aqueous acetic acid in THF. After 5 hours, diol 202 was obtained in 89% yield (Scheme 93)

![Scheme 93: Synthesis of diol 202](image)

Diol 202 was dissolved in THF and treated with trichloroacetonitrile and imidazole in the presence of sodium hydride. After 1 hour, methanol was added followed by NaOMe (1M). Following neutralisation and evaporation, we were unable to obtain the desired oxazoline 203 (Scheme 94).

![Scheme 94: Attempted conversion of diol 202 to oxazoline 203](image)

Given the similarity between 202 and Jacobsen’s substrate 196, it seemed likely that the failure of the epoxide ring opening experiment was due to the presence of the vinyl moiety at C-5. This would induce enough steric encumbrance around the epoxide’s bottom face and prevent the imidate nucleophiles from reaching the epoxide at C-3. The same steric encumbrance could potentially account for the failure of the azidolysis reactions in Table 7 (Scheme 95).

![Scheme 95: Failure of epoxide ring opening](image)

Due to the bulkiness of the vinyl moiety around the epoxide’s bottom face, we anticipated that incorporation of a smaller functional group at C-5 such as a nitrile may facilitate the epoxide ring opening process.
2.3 Synthesis via 1,6-anhydro-5-C-cyano-D-glucose

The initial step in preparing a nitrile derivative was oxidative cleavage of the C=C double bond prior to the epoxide formation. Thus, dihydroxylation followed by treatment with sodium periodate and subsequent nitrile formation should result in the desired compound 204 (Scheme 96).

Scheme 96: Proposed synthesis of compound 204

Unfortunately, attempted dihydroxylation of the terminal alkene failed to give the desired triol 205. Table 8 shows the various reaction conditions attempted to effect the transformation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Temp</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂OsO₄₂H₂O, NMO, acetone</td>
<td>Rt</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>K₂OsO₄₂H₂O, NMO, citric acid, ( t )-BuOH/H₂O</td>
<td>rt to 80 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>RuCl₃, H₂SO₄, NaIO₄, EtOAc/H₂O/MeCN</td>
<td>Rt</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>AD-mix-α, ( t )-BuOH/H₂O</td>
<td>Rt</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Table 8: Attempted dihydroxylation of 136b
The failure of the dihydroxylation experiment led us to utilise ozonolysis as an alternative way to obtain our desired aldehyde. Therefore, ozone was bubbled through a solution of compound \textit{136b} in dichloromethane. Treatment of the resulting solution with PPh$_3$ did not give the desired aldehyde and instead furnished hemiacetal \textit{206} in 22\% yield (Scheme 97).

\[ \text{DCM, O}_3, -78 \, ^\circ\text{C}, \text{then PPh}_3 \]

\textbf{Scheme 97:} Formation of hemiacetal \textit{206}

NOE studies positively revealed the stereochemistry of the hemiacetal chiral centre by indicating the presence of a long range interaction between the proton at C-7 and that of C-10.

The formation of compound \textit{206} was a result of initial conversion of alkene \textit{136b} to aldehyde intermediate \textit{207} followed by an \textit{in situ} intramolecular 6-exo-trig cyclisation (Scheme 98).

\[ \text{DCM, O}_3, -78 \, ^\circ\text{C}, \text{then PPh}_3 \]

\textbf{Scheme 98:} Proposed mechanism for the formation of hemiacetal \textit{206}

The unsuccessful attempt to isolate aldehyde \textit{207} and the low yield of \textit{206} prompted us to incorporate the nitrile moiety several steps backwards starting from bis-silyl ether \textit{138b}. We envisaged that initial oxidative cleavage of the vinyl moiety followed by treatment with aqueous ammonia and iodine should furnish the desired nitrile \textit{138c}. Compound \textit{138c} would be converted to epoxide \textit{135c} using previously successful procedures. Epoxide \textit{135c} would be subjected to treatment with sodium azide to form the desired diaxial azidoalcohol \textit{134c} (Scheme 99).
Conversion of alkene 138b to aldehyde 208 was initially attempted via dihydroxylation. Table 9 shows the various reaction conditions utilised to effect the transformation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Temp</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂OsO₄·2H₂O, NMO, acetone</td>
<td>Rt</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>K₂OsO₄·2H₂O, NMO, citric acid, t-BuOH/H₂O</td>
<td>rt to 80 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>RuCl₃, H₂SO₄, NaIO₄, EtOAc/H₂O/MeCN</td>
<td>Rt</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>AD-mix-α, t-BuOH/H₂O</td>
<td>Rt</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Unfortunately as with alkene 139b, we were unable to obtain the desired diol 209. It was envisaged that ozonolysis of the vinyl moiety could result in aldehyde 208. Treatment of alkene 138b with ozone at −78 °C, followed by reductive work-up with Me₂S furnished the desired aldehyde 208. Unfortunately this compound was rapidly polymerised; we were unable to confirm the structure of the polymer formed due to insufficient analytical data, however it was likely that the structure of the polymer may well resemble that of structure 210. We were also unable to determine which hydroxyl group was involved in the formation of the hemiacetal functionality (Scheme 100).
Subjection of polymer 210 to aqueous ammonia and iodine followed by acetylation resulted in the formation of compounds 211, 212 and 213 (Scheme 101). Subjection of polymer 210 to aqueous ammonia and iodine followed by acetylation resulted in the formation of compounds 211, 212 and 213 (Scheme 101).  

Subjection of polymer 210 to aqueous ammonia and iodine followed by acetylation resulted in the formation of compounds 211, 212 and 213 (Scheme 101).  

The mechanism of nitrile formation may proceed via initial transformation of aldehyde 214 to aldimine 215. Elimination of HI afforded the nitrile product 139c which upon acetylation gave acetate 211 (Scheme 102).  

Unfortunately, the acid byproduct in the reaction mixture also prompted the hydrolysis of nitrile 139c, hence the formation of amide 213. Upon further acetylation, amide 213 was converted to imide 212 (Scheme 103).
To minimise the amount of wasted material, we envisaged that amide 213 could be dehydrated to give nitrile 211. Initial treatment of amide 213 with oxalyl chloride and dimethyl sulfoxide in the presence of triethyl amine failed to furnish nitrile 211. However, exposure of amide 213 to a solution of trifluoroacetic anhydride and pyridine as described by Casini et al., successfully furnished nitrile 211 in 49% yield (Scheme 104).

Unfortunately, attempted deacetylation of nitrile 211 using aqueous ammonia (29%) or sodium methoxide in methanol failed to give the desired triol 139c (Scheme 105).

A reinvestigation of the ozonolysis step showed that addition of triethylamine instead of dimethyl sulfide upon ozonolysis, successfully cleaved the trioxolane intermediate 216 and prevented the molecule from polymerising (Scheme 106).
Scheme 106: Proposed mechanism for the cleavage of trioxolane 216 in the presence of NEt$_3$

Table 10 illustrates the various attempted procedures for the conversion of aldehyde 208 to nitrile 138c.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Temp</th>
<th>Yield 138c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NBS, aq NH$_3$</td>
<td>0 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>NH$_2$OH.HCl, NaI, MeCN</td>
<td>80 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>NH$_2$OH.HCl, EtOPOCl$_2$, DBU, DCM</td>
<td>Rt</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>Cu(0), NH$_4$Cl, pyridine, O$_2$</td>
<td>Rt</td>
<td>42</td>
</tr>
</tbody>
</table>

Table 10: Attempted conversion of aldehyde 208 to nitrile 138c

Treatment of aldehyde 208 with NBS and aqueous ammonia (Table 10, entry 1),$_{107}$ with hydroxylamine hydrochloride and sodium iodide (Table 10, entry 2)$_{108}$ or with hydroxylamine hydrochloride, ethyl dichlorophosphate and DBU (Table 10, entry 3)$_{109}$ failed to yield the desired nitrile. We were pleased to find that the use of copper and ammonium chloride under an O$_2$ atmosphere was successful in producing moderate yields of nitrile 138c (Table 10, entry 4). This procedure was reported by Maumy and co-workers in 1989.$^{110}$ It was envisaged that in the presence of oxygen and ammonium chloride, copper (0) is oxidised to copper (II).
Ammonia will undergo a condensation reaction with aldehyde 208 to generate aldimine 217, which can be oxidised to the desired nitrile 138c (Scheme 113).[^110]

Scheme 107: Proposed mechanism for the formation of nitrile 138c

Compound 138c was subjected to aluminium trichloride assisted ring opening with a lithium acetylide to furnish alkyne 218 in 70% yield. Silylation of compound 218 using one equivalent of triethylsilyl chloride and pyridine gave the tris-silyl ether 219 in 83% yield (Scheme 108).[^92]

Scheme 108: Synthesis of tris-silyl ether 219

Unfortunately, when compound 219 was subjected to acetylation using isopropenyl acetate and iodine, starting material was recovered.[^97] However, when 219 was treated with acetic anhydride and triethylamine in the presence of a catalytic amount of 4-pyrrolidinopyridine, the reaction proceeded smoothly to give acetate 137c in 70% yield. Compound 137c was subjected to desilylation using 80% aq. AcOH in THF. Surprisingly, diol 220 was isolated in 84% yield instead of triol 221 (Scheme 109).
While the selective removal of only two of the silyl groups was unexpected, we were hopeful that it could be turned to our advantage. Triflation of diol 220 should give ditriflate 222; exposure of this compound to sodium methoxide could then lead to epoxide 223, with the primary triflate intact. Potassium thioacetate displacement of the primary triflate followed by azide ring opening at C-3 should furnish the azido intermediate 224. Further manipulation of intermediate 224 would lead to tagetitoxin (4a) (Scheme 110).

Starting from diol 220, initial treatment with triflic anhydride and pyridine successfully furnished ditriflate 222 in excellent yield. Unfortunately, when compound 222 was subjected to treatment with sodium methoxide in methanol, no epoxide formation was observed and instead, enyne 225 was isolated in 49% yield (Scheme 111).
To overcome this problem, we decided to try other milder conditions. Unfortunately the same enyne product was formed when ditriflate 222 was treated with K₂CO₃, Cs₂CO₃ or aq. NH₃.

As we were unable to convert ditriflate 222 to the epoxide, we reverted to our original plan to obtain triol 221. Treatment of compound 137c with 80% aq. AcOH in THF under reflux did not result in triol 221. Addition of TBAF to a solution of compound 137c in THF effected deacetylation as well as desilylation and furnished tetraol 226 in 54% yield. Other reagents such as KF in the presence of 18-crown-6 also gave compound 226 (Scheme 112).

The formation of tetraol 226 was perhaps due the presence of tetrabutyl ammonium hydroxide and potassium hydroxide in the solution mixture. To our delight, addition of acetic acid to a solution of compound 137c in THF followed by TBAF (1M in THF), furnished the desired triol 221 in 41% yield. Treatment of triol 221 with 4-methoxybenzaldehyde dimethyl acetal in DMF successfully resulted in benzylidene acetal 227 in 63% yield. Furthermore, triflation of acetal 227 followed by treatment with sodium methoxide in methanol, furnished epoxide 135c in 32% yield over two steps (Scheme 113).
With epoxide 135c in hand, we investigated its azide ring opening at C-3. Table (11) shows the various reaction conditions used to convert epoxide 135c to azide 134c.\textsuperscript{95,99,100}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Temp (°C)</th>
<th>Yield 134c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yb(OTf)_3, LiO-i-Pr, NaN_3, THF</td>
<td>65</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>NaN_3, MeOH, NH_4Cl</td>
<td>80</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>DMF, NaN_3</td>
<td>65</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>LiClO_4, NaN_3, MeCN</td>
<td>80</td>
<td>35</td>
</tr>
</tbody>
</table>

Table 11: Attempted conversion of epoxide 135c to azide 134c

We were pleased to find that treatment of epoxide 135c with LiClO_4 and NaN_3 in acetonitrile, successfully furnished the desired azide 134c in 35% yield.\textsuperscript{99} The success of this reaction can be attributed to two factors. The first is the strong chelation effect induced between the lithium ion, the oxirane oxygen and the oxygen at C-5 which facilitated the axial nucleophilic attack at C-3 (Scheme 114).
Scheme 114: Proposed mechanism for the formation of azide 134c

Another possible factor is the lower steric encumbrance to nucleophilic attack, this is because the linear cyano group is smaller than the vinyl group, however, as the LiClO₄-catalysed azidolysis was not attempted with 135b, we could not be certain of the real factors affecting the ring opening process (Scheme 115).

Scheme 115: Azide ring opening of epoxide 135b Vs 135c

The formation of azide 135c is encouraging for the completion of the synthesis of tagetitoxin. Unfortunately, time constraints prevented us from progressing further on this route.
3. CONCLUSION

In 2006, our group succeeded in developing a novel approach towards the synthesis of the bicyclic core of tagetitoxin (4a). In this approach the 9-oxa-3-thiabicyclo[3.3.1]nonane ring system, which constitutes the core of RNA polymerase inhibitor was synthesised through cyclisation of a thiol onto an electrophilic ketone.

The aim of this project was to apply the thiol cyclisation methodology to a synthesis of tagetitoxin itself; as a first step, this necessitated the incorporation of the incorporation of a hydroxymethyl, vinyl or nitrile group into the C-5 position of D-glucose.

Initial studies used literature methods to incorporate a hydroxymethyl group to give pentaol 142. However, problems in effecting selective protection of this compound led us to abandon this route (Scheme 116).

In an alternative approach, introduction of a vinyl group at C-5 of D-glucose was successfully achieved using a method described by Rama Rao et al. D-Glucose was converted to glucofuranoside 169 in six steps. After much optimisation, glucofuranoside 169 was successfully converted to the desired 1,6-anhydro-5-C-vinylglucose (139b) in 74% yield (Scheme 117).

Selective silylation at O-2 and O-4 and ring opening with TMS acetylene gave the targeted diol 181 in good yields. Further TES protection at O-6 followed by acetylation using isopropenyl acetate and iodine, furnished the fully protected sugar 137b. Desilylation and subsequent benzylidene protection resulted in benzylidene acetal 136b in moderate yields. As expected, triflation at O-2 followed by treatment with sodium methoxide in methanol
afforded the desired β-epoxide 135b. Unfortunately, attempted ring opening of epoxide 135b with various azide sources failed to furnish azide 134b (Scheme 118).

Scheme 118: Attempted synthesis of azido alcohol 134b

To overcome the failure of the epoxide ring opening step, it was envisaged that conversion of the vinyl group at C-5 to a nitrile moiety may facilitate the ring opening process by relieving steric encumbrance around the molecule’s lower face. Thus, ozonolysis of di-TES compound 138b and subsequent treatment with ammonium chloride and copper (0) in the presence of pyridine gave the desired nitrile 138c in moderate yield. TMS-acetylene ring opening followed by silylation at O-6 and acetylation at O-3 gave the fully protected compound 137c. Treatment of 137c with aqueous acetic acid and triflation at O-2 and O-6 resulted in di-triflate 222. Unexpectedly, subjection of 222 to a solution of sodium methoxide in methanol failed to furnish the desired epoxide 228 and instead gave enyne 225 (Scheme 119).
As we were unable to convert ditriflate 222 to epoxide 228, we reverted to our original plan to obtain triol 221 (Scheme 109). Starting from tri-TES compound 137c, desilylation followed by benzylidene protection led to the formation of benzylidene acetal 227. Further triflation at O-2, deacetylation and concomitant epoxide formation successfully gave the desired epoxide 135c. Gratifyingly, treatment of epoxide 135c with sodium azide in the presence of lithium perchlorate furnished the targeted azide 134c in 35% yield (Scheme 120).

Scheme 119: Attempted conversion of compound 138b to epoxide 228

Scheme 120: Synthesis of azide 134c
3.1 Future work

Initial introduction of a vinyl moiety at C-5 of D-glucose succeeded in producing 1,6-anhydro-5-C-vinylglucose (139b) in good yields. This served as a good synthetic precursor towards tagetitoxin (4a). So far, we have been successful in appropriately functionalising the glucose unit at C-1, C-2, C-3 and C-5 to give intermediate azide 134c in 19 steps (Scheme 121).

We anticipate that further acetylation at O-2, acetal hydrolysis, tosylation at O-6 and thioacetate displacement would afford pyranoside 229. Phosphorylation at O-4, bromination of the terminal alkyne and oxidation could give the desired ketoester 230 which when treated with ammonia should result in the fully-functionalised tagetitoxin core 231. Nitrile hydrolysis, followed by selective acetylation at O-2, TBAF deprotection and azide reduction would furnish tagetitoxin (4a) (Scheme 122).
Scheme 122: Proposed route for the completion of the synthesis of tagetitoxin (4a)
4. EXPERIMENTAL

All reactions were carried out in anhydrous conditions unless stated otherwise, all glassware was flame-dried prior to use and allowed to cool to rt in vacuo. The reactions were then carried out under an argon atmosphere. THF, DCM, Et₂O, toluene, hexane, and MeCN for reactions were obtained from the UCL Chemistry anhydrous solvent system, whereby solvents are dried by passing through alumina columns under nitrogen. Anhydrous methanol and DMF from Romil, and anhydrous isopropanol from Acros were used as supplied. DMSO, pyridine, triethylamine were distilled from calcium hydride. Acetone was distilled from molecular sieves. Ethanol was dried by stirring with magnesium turnings and iodide, heating to reflux, then distillation.

*p*-Toluenesulfonyl chloride was recrystallised from toluene and petroleum spirit (bp: 40-60 °C) prior to use. NBS was recrystallised from boiling water and dried over P₂O₅. Lithium isopropoxide was prepared by dropwise addition of *n*-BuLi (1.6 M in hexane, 5 mmol) to anhydrous isopropanol (5 mmol) in hexane (0.5 mL), cooled in an ice-bath. The solution was stirred at rt for 35 min then concentrated in vacuo. The resulting white solid was dried under high vacuum then stored under argon.

Other chemicals were purchased from Lancaster, Sigma-Aldrich, Acros, Alfa Aesar and Avocado and were used without further purification.

For column chromatography, BDH silica gel (40-63 µm) was used. TLC was carried out on aluminium plates pre-coated with Merck silica gel (60 F₂₅₄) which were visualised using UV at 254 nm or by staining with vanillin or potassium permanganate. Solvents were removed using a Buchi rotary evaporator. Petroleum ether refers to the fraction with boiling point 40-60 °C throughout.

¹H NMR spectra were recorded on Bruker AMX-400, AVANCE 500 and AVANCE DRX600 MHz spectrometers. The signals are assigned as s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, tt = triplet of triplets, td = triplet of doublets, ddt = doublet of triplets of triplets, q = quartet, dq = doublet of quartets, m = multiplet. ¹³C NMR spectra were recorded at 100 MHz, 125 MHz and 150 MHz on a Bruker AMX 400, AVANCE 500 and AVANCE DRX600 spectrometers, respectively. ¹H COSY, ¹³C DEPT, HMQC, HMBC and NOE experiments were used to aid peak assignments and determine structures when required. Chemical shifts (δ), in parts per
million, are referenced to the residual solvent peak, except for spectra in D$_2$O which are referenced to internal 1,4-dioxane.

IR spectra were recorded on a Perkin Elmer Precisely Spectrum 100 FT-IR spectrometer with ATR. Mass spectra and high resolution mass spectra were recorded by Mr John Hill and Dr Lisa Harris on Micromass 70-SE and MAT 900XP instruments.

Melting points were measured using Reichert-Jung Thermovar instrument. Optical rotations were measured on a Perkin Elmer Model 343 Polarimeter (using the sodium D-line, 529 nm) and $[\alpha]_D^\text{obs}$ values are given in $10^1$ deg cm$^2$ g$^{-1}$, concentration ($c$) in g per 100 mL. Elemental analyses were carried out by Mrs Jill Maxwell.
Methyl 2,3,4,6-tetrakis-O-(trimethylsilyl)-α-D-glucopyranoside (147)\textsuperscript{82}

\[
\begin{array}{c}
\text{HO} \quad \text{HO} \\
\text{HO} \quad \text{OH}
\end{array}
\xrightarrow{\text{TMSCl, pyridine, rt}}
\begin{array}{c}
\text{TMSO} \quad \text{TMSO} \\
\text{TMSO} \quad \text{OTMS}
\end{array}
\]

To a stirred solution of methyl α-D-glucopyranoside (146) (10.00 g, 51.5 mmol) in pyridine (52 mL) at 0 °C was added trimethylsilyl chloride (31.6 mL, 247 mmol) dropwise and the mixture allowed to warm to room temperature and stirred for 2 h. Water (20 mL) was added, and the organic material extracted with diethyl ether (3 × 80 mL). The organic layer was dried (MgSO\textsubscript{4}) and concentrated in vacuo to give a colourless crude product which was purified by column chromatography (5:95 → 10:90, EtOAc in petroleum spirit) to give tetrasislyl ether 147 as a colourless viscous oil (19.55 g, 79%).

R\textsubscript{f} 0.67 (15:85, EtOAc-petroleum spirit).

\([\alpha]_D^{25} = +84.5 (c 1.7, \text{CHCl}_3)\). [Lit \([\alpha]_D^{25} = +85.7 (c 1.6, \text{CHCl}_3)\)]\textsuperscript{26}.

\(\begin{array}{c}
\delta_\text{H (600 MHz; CDCl}_3) \\
4.63 (1\text{H, d, } J 3.7, H-C1), 3.78-3.75 (2\text{H, m, } H-C6, H-C3), 3.68 (1\text{H, dd, } J 11.3, 5.4, H-C6), 3.52 (1\text{H, ddd, } J 9.7, 5.4, 1.9, H-C5), 3.48 (1\text{H, dd, } J 9.1, 3.7, H-C2), 3.44 (1\text{H, dd, } J 9.7, 8.4, H-C4), 3.35 (3\text{H, s, CH}_3\text{O}), 0.18 (9\text{H, s, Si(CH}_3)_3), 0.17 (9\text{H, s, Si(CH}_3)_3), 0.16 (9\text{H, s, Si(CH}_3)_3), 0.13 (9\text{H, s, Si(CH}_3)_3). \\
\delta_\text{C (150 MHz; CDCl}_3) \\
99.6 (C-1), 75.3 (C-3), 73.9 (C-2), 72.2 (C-5), 72.0 (C-4), 62.2 (C-6), 54.5 (CH}_3\text{O), 1.4 (Si(CH}_3)_3), 0.9 (Si(CH}_3)), 0.6 (Si(CH}_3)), −0.24 (Si(CH}_3)).
\end{array}\)

\(\nu_{\text{max}} (\text{CHCl}_3 \text{ cast}/\text{cm}^{-1}): 2956 (\text{C-H}).\)

\(m/z (\text{ES}^+) 505 (\text{MNa}^+, 100%), 361 (23), 331 (12), 271 (12), 243 (16).\)

\(\text{HRMS}:\) calculated for C\textsubscript{19}H\textsubscript{46}O\textsubscript{6}Si\textsubscript{4}Na: 505.2254, found 505.2269. Error 3.0 ppm.
Methyl 2,3,4-tris-O-(trimethylsilyl)-α-D-glucal-hexodialdo-1,5-pyranoside (148)82

To a stirred suspension of chromium (VI) oxide (23.67 g, 236.8 mmol) in DCM (790 mL) at 0 °C was added pyridine (37.53 mL) dropwise over the course of 10 min. The mixture was allowed to warm to room temperature and stirred for 30 min. A solution of tetrakisylether 147 in dichloromethane (54 mL) was then added and the mixture stirred for another 1 h. The crude material was passed through a short plug of silica using dichloromethane as the eluent, then concentrated in vacuo. This material was then purified by column chromatography (5:95→10:90, EtOAc in petroleum spirit) to afford aldehyde 148 as a colourless viscous oil (8.36 g, 52%).

Rf 0.32 (15:85, EtOAc-petroleum spirit).

[α]D25 = +100.8 (c 1.2, CHCl3).

δH (600 MHz; CDCl3) 9.74 (1H, d, J 1.3, H-C6), 4.71 (1H, d, J 3.5, H-C1), 4.15 (1H, dd, J 10.0, 1.3, H-C5), 3.86 (1H, t, J 8.7, H-C3), 3.58 (1H, dd, J 10.0, 8.7, H-C4), 3.51 (1H, dd, J 8.7, 3.5, H-C2), 3.37 (3H, s, CH3O), 0.17 (9H, s, Si(CH3)3), 0.17 (9H, s, Si(CH3)3), 0.14 (9H, s, Si(CH3)3).

δC (150 MHz, CD3OD) 198.6 (C-6), 100.2 (C-1), 75.6 (C-5), 74.7 (C-3), 73.2 (C-4), 72.8 (C-2), 55.5 (CH3O), 1.2, 0.8, 0.4 (Si(CH3)3).

νmax (CHCl3 cast)/cm⁻¹: 2956 (C-H), 1744 (C=O).

m/z (ES+): 409 (MH+, 100%), 394 (18), 376 (28), 257 (30), 253 (20), 222 (20).

HRMS: calculated for C16H37O6Si3+: 409.1920, found 409.1898. Error 5.4 ppm.
Methyl α-D-gluco-hexodialdo-1,5-pyranoside (149)\textsuperscript{82}

A solution of aldehyde 148 (6.84 g, 1.7 mmol) and potassium carbonate (137 mg) in methanol (137 mL) was stirred at room temperature for 12 h. The mixture was then concentrated in vacuo to afford compound 149 as colourless oil (3.26 g, 100%).

δ\textsubscript{H} (600 MHz; D\textsubscript{2}O) 5.13 (1H, s, H\textsubscript{-C6} [hydrated]), 4.66 (1H, d, J 3.8, H-C1), 3.53 (1H, t, J 9.6, H-C3), 3.47-3.38 (2H, m, H-C2 & H-C5), 3.33 (1H, t, J 9.6, H-C4), 3.29 (3H, s,CH\textsubscript{3}O).

δ\textsubscript{C} (150 MHz; D\textsubscript{2}O) 99.2 (C-1), 87.8 (C-6 [hydrated]), 72.8 (C-3), 72.3 (C-5), 71.0 (C-2), 70.2 (C-4), 55.0 (CH\textsubscript{3}O).

ν\textsubscript{max} neat/cm\textsuperscript{-1}: 3225 (O-H), 2917 (C-H).
Methyl 5-C-acetoxymethyl-2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside (150)

Methyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside (151)

Using literature procedure. To a stirred solution of aldehyde 149 (3.26 g, 16.9 mmol) in aqueous formaldehyde (37%, 65.2 mL, 0.80 mol) at 0 °C was added aqueous sodium hydroxide (50%, 24.7 mL, 0.30 mol) dropwise and the mixture was allowed to warm to room temperature and stirred for 16 h. The solution was slowly passed through a base exchange resin (Amberlite 120 (H\(^+\))) column and then concentrated in vacuo and co-evaporated with ethanol (3 × 100 mL). The crude material was dissolved in pyridine (20 mL) and acetic anhydride (18.0 mL, 0.19 mol) was added. The mixture was stirred for a further 12 h and then quenched with methanol (10 mL) and co-evaporated with toluene (3 × 50 mL). The resulting crude was dissolved in ethyl acetate (50 mL), and the organic material washed with water (2 × 20 mL), dried (MgSO\(_4\)) and concentrated in vacuo to give a viscous oil which was purified using flash chromatography (10:90 → 40:60, EtOAc in petroleum spirit) to afford pentaacetate 150 as a white solid (1.60 g, 22%).

R\(_f\) 0.29 (40:60, EtOAc-petroleum spirit).

\([\alpha]_D^{22} = +71.7 \ (c \ 0.5, \ \text{CHCl}_3)\).

m.p. (EtOAc) 65-67 °C.

\(\delta_H\) (600 MHz; CDCl\(_3\)) 5.16 (1H, t, J 10.3, H-C3), 5.41 (1H, d, J 10.3, H-C4), 5.06 (1H, d, J 4.2, H-C1), 4.93 (1H, dd, J 10.3, 4.2, H-C2), 4.63 (1H, d, J 12.2, CH\(_2\)OAc), 4.39 (1H, d, J 12.2, CH\(_2\)OAc), 4.16 (1H, d, J 12.1, CH\(_2\)OAc), 4.07 (1H, d, J 12.1, CH\(_2\)OAc), 3.49 (3H, s, CH\(_3\)O), 2.13 (3H, s, CH\(_3\)CO), 2.12 (3H, s, CH\(_3\)CO), 2.10 (3H, s, CH\(_3\)CO), 2.05 (3H, s, CH\(_3\)CO), 2.03 (3H, s, CH\(_3\)CO).

\(\delta_C\) (150 MHz; CDCl\(_3\)) 170.5 (C=O), 170.4 (C=O), 170.2 (C=O), 169.7 (C=O), 169.2 (C=O), 98.5 (C-1), 76.8 (C-5), 70.7 (C-2), 69.3 (C-4), 66.9 (C-3), 64.2 (CH\(_2\)OAc), 63.9 (CH\(_2\)OAc), 57.2 (CH\(_3\)O), 20.8, 20.8, 20.7, 20.6, 20.6 (5 × CH\(_3\)CO).

\(v_{\text{max}}\) (CHCl\(_3\) cast)/cm\(^{-1}\): 2943 (C-H), 1744 (C=O).

m/z (FAB+): 457 (MNa\(^+\), 30%), 403 (10), 376 (50), 329 (28), 307 (20), 289 (10), 241 (27), 176 (100), 154 (72).

HRMS: calculated for C\(_{18}\)H\(_{26}\)O\(_{12}\)Na\(^+\): 457.1322, found 457.1330. Error 2.0 ppm.
Further elution gave tetraacetate 151 as a colourless oil (1.20 g, 19%).

$R_f$ 0.26 (40:60, EtOAc-petroleum spirit).

$[\alpha]_D^{20} = +127.0 \ (c \ 0.5, \ CHCl_3)$.  [Lit $[\alpha]_D^{25} = +117.1 \ (c \ 9.1, \ CHCl_3)$]83.

$\delta_H$ (600 MHz; CDCl$_3$) 5.47 (1H, t, $J \ 9.8$, $H$-C3), 5.06 (1H, t, $J \ 9.8$, $H$-C4), 4.95 (1H, d, $J \ 3.7$, $H$-C1), 4.90 (1H, dd, $J \ 9.8$, 3.7, $H$-C2), 4.26 (1H, dd, $J \ 12.3$, 4.5, $H$-C6), 4.10 (1H, dd, $J \ 9.8$, 2.6, $H$-C6), 3.98 (1H, ddd, $J \ 9.8$, 4.5, 2.6, $H$-C5), 3.41 (3H, s, $CH_3$O), 2.10 (3H, s, $CH_3$CO), 2.08 (3H, s, $CH_3$CO), 2.02 (3H, s, $CH_3$CO), 2.01 (3H, s, $CH_3$CO).

$\delta_C$ (150 MHz; CDCl$_3$) 170.7 ($C$=O), 170.2 ($C$=O), 170.1 ($C$=O), 169.6 ($C$=O), 96.7 ($C$-1), 70.7 ($C$-2), 70.1 ($C$-3), 68.4 ($C$-4), 67.1 ($C$-5), 61.9 ($C$-6), 55.5 ($CH_3$O), 20.8, 20.7, 20.6, 20.6 (4 $\times$ $CH_3$CO).

$\nu_{\text{max}}$ (CHCl$_3$ cast)/cm$^{-1}$: 2945 (C-H), 1741 (C=O).

$m/z$ (ES$^+$) 385 (MNa$^+$, 100%), 171 (12).

HRMS: calculated for C$_{13}$H$_{22}$O$_{10}$Na$^+$: 385.1129, found 385.1111. Error 4.7 ppm.
Methyl 5-C-hydroxymethyl-α-D-glucopyranoside (142)

To a stirred solution of pyranoside 150 (1.60 g, 3.7 mmol) in methanol (20 mL) was added aqueous ammonia (29%, 15 mL) and the mixture stirred for 12 h. The solution was concentrated in vacuo and co-evaporated with ethanol (3 × 50 mL) to afford pentaol 142 as a brown viscous oil.

$\delta_H$ (600 MHz; CD$_3$OD) 4.57 (1H, d, $J$ 4.1, H-C1), 3.96 (1H, d, $J$ 11.6, CH$_2$OH), 3.85 (1H, t, $J$ 9.8, H-C3), 3.81 (1H, d, $J$ 11.6, CH$_2$OH), 3.77 (1H, d, $J$ 11.6, CH$_2$OH), 3.72 (1H, d, $J$ 9.8, H-C4), 3.68 (1H, d, $J$ 11.6, CH$_2$OH), 3.52 (3H, s, CH$_3$O), 3.41 (1H, dd, $J$ 9.8, 4.1, H-C2).

$\delta_C$ (150 MHz; CD$_3$OD) 101.5 (C-1), 79.9 (C-5), 72.0 (C-2), 71.8 (C-4), 69.9 (C-3), 63.4 (CH$_2$OAc), 62.8 (CH$_2$OAc), 56.0 (CH$_3$O).

$m/z$ (ES-) 223 (M-H, 100%).

HRMS: calculated for C$_8$H$_{15}$O$_7$: 223.0818, found 223.0809. Error 4.0 ppm.
(2S,3R,4S,5S)-2-Methoxy-9,9-dimethyl-1,8,10-trioxaspiro[5.5]undecane-3,4,5-triol (160)

To a stirred solution of pentaol 142 (160 mg, 0.7 mmol) in acetone (1.1 mL) was added camphorsulfonic acid (16 mg) followed by 2,2-dimethoxypropane (894 mg, 1.1 mL, 7.8 mmol) and the mixture sonicated for 1 h then stirred for further 12 h and concentrated in vacuo. The crude material was purified by column chromatography (5:95-10:90, MeOH in DCM) to afford compound 160 as a colourless viscous oil (112 mg, 60%).

Rf 0.20 (10:90, MeOH-DCM).

$\left[\alpha\right]_{D}^{25} = +97.6 \; (c \; 0.1, \; CHCl_3)$.

$\delta_H$ (600 MHz; CDCl$_3$) 4.84 (1H, d, $J$ 4.1, $H$-C1), 4.23 (1H, d, $J$ 12.6, CCH$_2$O), 4.13 (1H, d, $J$ 12.2, CCH$_2$O), 4.03 (1H, d, $J$ 12.6, CCH$_2$O), 3.79 (1H, t, $J$ 9.7, H-C3), 3.58 (3H, s, CH$_3$O), 3.55 (1H, d, $J$ 12.2, CCH$_2$O), 3.51 (1H, dd, $J$ 9.7, 4.1, H-C2), 3.25 (1H, d, $J$ 9.7, H-C4), 1.434 (3H, s, CH$_3$C), 1.429 (3H, s, CH$_3$C).

$\delta_C$ (150 MHz; CDCl$_3$) 100.4 ($\text{C}$-1), 98.7 ($\text{C}$(CH$_3$)$_2$), 73.9 ($\text{C}$-5), 73.6 ($\text{C}$-4), 72.1 ($\text{C}$-2), 70.3 ($\text{C}$-3), 66.9 ($\text{C}$-6), 62.6 ($\text{C}$-7), 56.6 (CH$_3$O), 26.7, 20.5 ($2 \times \text{CH}_3$-C);

$\nu_{\text{max}}$ (CHCl$_3$ cast)/cm$^{-1}$: 3388 (O-H), 2936 (C-H).

$m/z$ (CI+, CH$_4$) 265 (MH$^+$, 5%), 249 (34), 233 (100), 215 (10), 185 (10), 175 (30), 157 (95), 139 (30), 127 (35), 115 (23), 100 (30), 85 (40).

HRMS: calculated for C$_{11}$H$_{21}$O$_7$: 265.1287, found 265.1289. Error 0.9 ppm.
1,2:5,6-Di-O-isopropylidene-\(\alpha\)-D-glucofuranose (162)

Using literature procedure\(^{85}\). To a stirred solution of finely powdered anhydrous D-glucose (5.00 g, 27.8 mmol) in acetone (150 mL) at 0 °C was added concentrated sulfuric acid (5.1 mL, 97.1 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The solution was cooled to 0 °C and ammonia gas was bubbled through until complete neutralisation. The resulting ammonium sulfate mixture was filtered and the filtrate was concentrated \textit{in vacuo}. The residue was dissolved in hot petroleum spirit (60-80 °C) and upon refrigeration the extract deposited crystals of the crude product. Recrystallisation from petroleum spirit gave the desired alcohol 162 (6.05 g, 84%) as a white solid.

\(\text{Rf} 0.35\) (40:60, EtOAc-petroleum spirit).

\([\alpha]_D^{20} = -11.2\) (c 5.0, EtOH). [Lit \([\alpha]_D^{21} = -16.9\) (c 2.4, H\(_2\)O)]\(^{85}\).

\textbf{m.p.} (petroleum spirit) 107-110 °C. Lit. \textbf{m.p.} (petroleum spirit) 107-110 °C.

\(\delta_H\) (400 MHz; CDCl\(_3\)) 5.91 (1H, d, J 3.8, H-C1), 4.49 (1H, d, J 3.8, H-C2), 4.30 (1H, ddd, J 8.0, 6.2, 5.4, H-C5), 4.27 (1H, dd, J 8.0, 7.8, H-C4), 4.12 (1H, dd, J 8.8, 6.2, H-C6), 4.01 (1H, dd, J 7.8, 3.8, H-C3), 3.96 (1H, dd, J 8.8, 5.4, H-C6), 2.91 (1H, br s, OH), 1.47 (3H, s, CH\(_3\)), 1.42 (3H, s, CH\(_3\)), 1.36 (3H, s, CH\(_3\)), 1.31 (3H, s, CH\(_3\)).

\(\delta_C\) (75 MHz; CDCl\(_3\)) 111.8 (2CH\(_3\)), 109.6 (2CH\(_3\)), 105.2 (C-1), 85.1 (C-2), 81.2 (C-3), 75.0 (C-4), 73.2 (C-5), 67.6 (C-6), 26.8 (CH\(_3\)), 26.7 (CH\(_3\)), 26.2 (CH\(_3\)), 25.2 (CH\(_3\)).

\(\nu_{\text{max}}\) (CHCl\(_3\) cast)/cm\(^{-1}\): 3448 (O-H), 3055 (C-H).
3-\(O-(p\text{-Methoxybenzyl})-1,2:5,6\text{-di-}\text{-O-isopropylidene-}\alpha\text{-D-glucofuranose (165)}\)

Using literature procedure\textsuperscript{86}. To a suspension of sodium hydride (60% in mineral oil) (1.54 g, 46.1 mmol) in dry tetrahydrofuran (30 mL) at 0 °C was added a solution of glucofuranoside 162 (10.00 g, 38.4 mmol) in dry tetrahydrofuran (20 mL) dropwise over 30 min. The mixture was stirred for a further 45 min and 4-methoxybenzyl chloride (6.3 mL, 46.1 mmol) was added slowly followed by tetrabutyl ammonium iodide (4.26 g, 11.5 mmol). The mixture was stirred at room temperature for 72 h, cooled to 0 °C and quenched with water (30 mL). The product was extracted with ethyl acetate (3 × 150 mL), washed with brine (200 mL), dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo to give a viscous oil which was purified by flash chromatography (5:95→20:80, EtOAc in petroleum spirit) to give PMB ether 165 (12.64 g, 86%) as a colourless viscous oil.

\(R_f\) 0.33 (15:85, EtOAc-petroleum spirit).

\([\alpha]_D^{20} = -16.9 \ (c\ 0.9, \ CHCl_3)\). [Lit \([\alpha]_D^{20} = -17 \ (c\ 1, \ CHCl_3)\)]\textsuperscript{86}.

\(\delta_H\) (600 MHz; CDCl\(_3\)) 7.28 (2H, d, J 8.6, H-Ar), 6.89 (2H, d, J 8.6, H-Ar), 5.90 (1H, d, J 3.7, H-C1), 4.62 (1H, d, J 11.4, CH\(_3\)H\(_3\)-Ar), 4.57 (1H, d, J 3.7, H-C2), 4.57 (1H, d, J 11.4, CH\(_3\)H\(_3\)-Ar), 4.35 (1H, dt, J 7.6, 6.1, H-C4), 4.15 (1H, dd, J 7.6, 3.7, H-C3), 4.11 (1H, dd, J 8.5, 6.3, H-C6), 3.99-4.02 (2H, m, H-C6 & H-C5), 3.82 (3H, s, CH\(_3\)O), 1.50 (3H, s, CH\(_3\)C), 1.44 (3H, s, CH\(_3\)C), 1.39 (3H, s, CH\(_3\)C), 1.32 (3H, s, CH\(_3\)C).

\(\delta_C\) (150 MHz; CDCl\(_3\)) 159.3 (arom. C), 129.7 (arom. C), 129.4 (arom. CH), 113.8 (arom. CH), 111.8 ((CH\(_3\))\(_2\))C, 108.9 ((CH\(_3\))\(_2\))C, 105.3 (C-1), 82.7 (C-2), 81.3 (C-3 & C-5), 72.6 (C-4), 72.1 (CH\(_2\)-Ar), 67.3 (C-6), 55.3 (CH\(_3\)O), 26.8 (CH\(_3\)C), 26.8 (CH\(_3\)C), 26.2 (CH\(_3\)C), 25.5 (CH\(_3\)C).

\(v_{\text{max}}\) (CHCl\(_3\) cast)/cm\(^{-1}\): 2987 (C-H), 1613 (C=C), 1514 (C=C), 1457 (C=C).

\(m/z\) (ES\(^+\)): 403 (M\(^{+}\), 100%), 363 (40), 221 (10), 207 (10), 193 (10).

HRMS: calculated for C\(_{20}\)H\(_{28}\)O\(_7\)Na\(^+\): 403.1714, found: 403.1733. Error 4.7 ppm.
1,2-<i>O</i>-Isopropylidene-3-<i>O</i>-(<i>p</i>-methoxybenzyl)<i>α</i>-D-glucofuranose (166)

Using literature procedure<sup>86</sup>. A solution of glucofuranoside 165 (11.62 g, 30.6 mmol) in 60% aqueous acetic acid (70 mL) was stirred at room temperature for 12 h. Petroleum spirit (50 mL) was added and the aqueous layer was separated then concentrated in vacuo, co-evaporated with ethanol (3 × 40 mL) and toluene (3 × 40 mL) to give a viscous oil. The crude material was dissolved in dichloromethane (200 mL) and washed with saturated NaHCO<sub>3</sub> (3 × 150 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo to give a residue which was purified by flash chromatography (20:80→50:50, EtOAc-petroleum spirit) to give diol 166 (8.37 g, 80%) as a colourless viscous oil. 

<sup>R</sup><sub>f</sub> 0.28 (50:50, EtOAc-petroleum spirit).

[<i>α</i>]<sub>D</sub><sup>21</sup> = −39.1 (c 0.5, CHCl<sub>3</sub>). [Lit [<i>α</i>]<sub>D</sub><sup>20</sup> = −20 (c 1.0, CHCl<sub>3</sub>).]<sup>86</sup>

<i>δ</i><sub>H</sub> (600 MHz; CDCl<sub>3</sub>)  7.29 (2H, d, <i>J</i> 8.6, H-Ar), 6.91 (2H, d, <i>J</i> 8.6, H-Ar), 5.95 (1H, d, <i>J</i> 3.8, H-C1), 4.69 (1H, d, J 11.3, CH<sub>3</sub>H<sub>5</sub>-Ar), 4.63 (1H, d, <i>J</i> 3.8, H-C2), 4.47 (1H, d, <i>J</i> 11.5, CH<sub>3</sub>H<sub>5</sub>-Ar), 4.12 (1H, dd, <i>J</i> 7.7, 3.8, H-C4), 4.09 (1H, d, <i>J</i> 3.8, H-C3), 4.02 (1H, ddd, <i>J</i> 7.7, 5.7, 3.5, H-C5), 3.82 (3H, s, CH<sub>3</sub>O), 3.81 (1H, dd, <i>J</i> 11.4, 3.5, H-C6), 3.69 (1H, dd, <i>J</i> 11.4, 5.7, H-C6), 1.50 (3H, s, CH<sub>3</sub>C(O)O), 1.34 (3H, s, CH<sub>3</sub>C(O)O).

<i>δ</i><sub>C</sub> (150 MHz; CDCl<sub>3</sub>)  159.7 (arom. C), 129.7 (arom. CH), 129.0 (arom. C), 114.2 (arom. CH), 111.8 ((CH<sub>3</sub>)<sub>2</sub>C), 105.1 (C-1), 83.1 (C-2), 82.1 (C-3), 79.9 (C-4), 71.7 (CH<sub>2</sub>-Ar), 69.4 (C-5), 64.4 (C-6), 55.3 (CH<sub>3</sub>O), 26.7 (CH<sub>3</sub>C), 26.2 (CH<sub>3</sub>C).

<i>ν</i><sub>max</sub> (CHCl<sub>3</sub> cast)/cm<sup>−1</sup>: 3417 (O-H), 2936 (C-H), 1612 (C=C), 1514 (C=C), 1458 (C=C).

<i>m</i>/<i>z</i> (ES<sup>+</sup>): 368 (MNa<sup>+</sup>, 100%).

HRMS: calculated for C<sub>17</sub>H<sub>24</sub>O<sub>7</sub>Na<sup>+</sup>: 363.1418, found: 363.1420. Error 0.6 ppm.
CHAPTER 4 EXPERIMENTAL

6-O-(tert-Butyldimethylsilyl)-1,2-O-isopropylidene-3-O-(p-methoxybenzyl)-α-D-glucofuranose (167)

Using literature procedure. To a stirred solution of diol 166 (9.97 g, 29.3 mmol) and imidazole (2.20 g, 32.2 mmol) in dry DMF (80 mL) was added tert-butyldimethylsilyl chloride (4.86 g, 32.2 mmol) at room temperature. The mixture was stirred for 4 h and then diethyl ether (200 mL) was added. The mixture was washed with water (5 × 300 mL) and the resulting organic extract was dried (MgSO₄) and concentrated in vacuo to give a yellow viscous oil which was purified by flash chromatography (5:95 → 20:80, EtOAc in petroleum spirit) to give silyl ether 167 (12.2 g, 91%) as a white solid.

m.p. (EtOAc) 53-55 °C.

R<sub>f</sub> 0.34 (15:85, EtOAc-petroleum spirit).

[α]<sup>24</sup> <sub>D</sub> = −28.5 (c 0.4, CHCl₃).

δ<sub>H</sub> (600 MHz; CDCl₃) 7.30 (2H, d, J 8.6, H-Ar), 6.90 (2H, d, J 8.6, H-Ar), 5.92 (1H, d, J 3.7, H-C1), 4.65 (1H, d, J 11.5, CH₂H₅-Ar), 4.58-4.60 (2H, m, CH₂H₅-Ar & H-C2), 4.13 (1H, dd, J 8.4, 3.0, H-C4), 4.09 (1H, d, J 3.0, H-C3), 4.00 (1H, quin, J 4.3, H-C5), 3.82 (3H, s, CH₃O), 3.80 (1H, dd, J 10.2, 3.8, H-C6), 3.75 (1H, dd, J 10.2, 4.3, H-C6), 1.48 (3H, s, CH₃C(O)₂), 1.32 (3H, s, CH₃C(O)₂), 0.91 (9H, s, (CH₃)₃C), 0.09 (3H, s, CH₃-Si), 0.08 (3H, s, CH₃-Si).

δ<sub>C</sub> (150 MHz; CDCl₃) 159.4 (arom. C), 129.6 (arom. C), 129.5 (arom. CH), 113.9 (arom. CH), 111.6 ((CH₃)₂C), 105.1 (C-1), 82.5 (C-2), 81.5 (C-3), 79.4 (C-4), 72.1 (CH₂-Ar), 68.6 (C-5), 64.5 (C-6), 55.3 (CH₃O), 26.7 (CH₃C), 26.3 (CH₃C), 25.9 ((CH₃)₂-C), 18.3 ((CH₃)₂-C), −5.38 (CH₃-Si), −5.40 (CH₃-Si).

ν<sub>max</sub> (CHCl₃ cast)/cm<sup>−1</sup>: 3545 (O-H), 2953 (C-H), 1613 (C=C), 1514 (C=C).

m/z (ES+): 477 (MNa<sup>+</sup>, 100%).

HRMS: calculated for C<sub>23</sub>H<sub>38</sub>O<sub>7</sub>SiNa<sup>+</sup>: 475.2270, found: 477.2285. Error 3.1 ppm.

Elemental analysis: C<sub>23</sub>H<sub>38</sub>O<sub>7</sub>Si requires: C 60.8, H 8.4; found C 60.6, 8.5%.
Using literature procedure\textsuperscript{88}. To a stirred solution of dimethyl sulfoxide (5.1 mL, 76.2 mmol) in anhydrous dichloromethane (100 mL) at \(-78^\circ\text{C}\) was added trifluorooacetic anhydride (7.4 mL, 53.2 mmol) dropwise. The mixture was stirred for 1 h and then a solution of alcohol 167 (8.06 g, 17.7 mmol) in dichloromethane (50 mL) was added dropwise over 45 min. After stirring for 1.5 h, triethylamine (19.9 mL, 141.8 mmol) was added and the solution allowed to warm to room temperature and stirred for a further 30 mins. The resulting solution was diluted with dichloromethane (300 mL), washed with sat NaHCO\textsubscript{3} (300 mL), water (300 mL), brine (300 mL), dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated \textit{in vacuo} to give a viscous oil which was purified by flash chromatography (5:95 \textrightarrow 20:80, EtOAc in petroleum spirit) to give ketone 168 (7.60 g, 95\%) as a colourless viscous oil. 

R\text{f} 0.34 (15:85, EtOAc-petroleum spirit).

\[ [\alpha]\text{D}\textsuperscript{22} = -50.4 \text{ (c 0.5, CHCl}_3) \text{].} \]

\( \delta_H \text{ (600 MHz; CDCl}_3 \) \text{:} 7.19 (2H, d, \textit{J} 8.6, H-Ar), 6.87 (2H, d, \textit{J} 8.6, H-Ar), 6.05 (1H, d, \textit{J} 3.7, H-C1), 4.88 (1H, d, \textit{J} 3.7, H-C4), 4.58 (1H, d, \textit{J} 3.7, H-C2), 4.54-4.49 (2H, m, CH\textsubscript{3}H\textsubscript{5}-Ar & H-C6), 4.44 (2H, m, CH\textsubscript{3}H\textsubscript{5}-Ar & H-C6), 4.36 (1H, d, \textit{J} 3.7, H-C3), 3.81 (3H, s, CH\textsubscript{3}O), 1.48 (3H, s, CH\textsubscript{3}C(O)\textsubscript{2}), 1.33 (3H, s, CH\textsubscript{3}C(O)\textsubscript{2}), 0.91 (9H, s, (CH\textsubscript{3})\textsubscript{3}C), 0.06 (3H, s, CH\textsubscript{3}-Si), 0.05 (3H, s, CH\textsubscript{3}-Si).

\( \delta_C \text{ (150 MHz; CDCl}_3 \) \text{:} 205.3 (C-5), 159.5 (arom. C), 129.5 (arom. CH), 128.9 (arom. C), 113.9 (arom. CH), 112.3 ((CH\textsubscript{3})\textsubscript{2}C), 105.7 (C-1), 84.6 (C-4), 83.0 (C-3), 81.8 (C-2), 72.1 (CH\textsubscript{2}-Ar), 68.8 (C-6), 55.3 (CH\textsubscript{3}O), 26.9 (CH\textsubscript{3}C), 26.3 (CH\textsubscript{3}C), 25.8 ((CH\textsubscript{3})\textsubscript{3}-C), 18.4 ((CH\textsubscript{3})\textsubscript{3}C), -5.4 (CH\textsubscript{3}-Si), -5.5 (CH\textsubscript{3}-Si).

\( \nu_{\text{max}} \text{ (CHCl}_3 \text{ cast)/cm}\textsuperscript{-1:} 2952 \text{ (C-H), 1739 \text{ (C-O), 1613 \text{ (C=C), 1514 \text{ (C=C).}}} \]

\textit{m/z} (ES+): 475 (MNa\textsuperscript{+}, 100\%), 180 (10).

HRMS: calculated for C\textsubscript{23}H\textsubscript{36}O\textsubscript{7}SiNa\textsuperscript{+}: 475.2138, found: 475.2128. Error 2.1 ppm.

Elemental analysis: C\textsubscript{23}H\textsubscript{36}O\textsubscript{7}Si requires: C 61.0, H 8.0; found C 60.9, 8.1\%. 

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6-\textit{O-(tert-Butyldimethylsilyl)-1,2-\textit{O-isopropylidene-3-\textit{O-(p-methoxybenzyl)-\alpha-D-xylo-hexofuranose-5-ulose (168)}}
6-O-(tert-Butyldimethylsilyl)-1,2-O-isopropylidene-3-O-(p-methoxybenzyl)-5-C-vinyl-\(\alpha\)-D-glucofuranose (169)

Using literature procedure. To a stirred solution of ketone 168 (23.41 g, 51.7 mmol) in anhydrous THF (260 mL) was added vinylmagnesium bromide (1 M in THF) (62 mL, 62 mmol) dropwise at 0 °C and the mixture stirred for 4 h. The reaction was quenched with saturated ammonium chloride (100 mL) and the organic material was extracted with ethyl acetate (3 × 300 mL). The organic layers were combined, dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo to give an oil which when recrystallised using hot petroleum spirit afforded tertiary alcohol 169 (17.40 g, 76 %) as a white solid.

**m.p.** (petroleum spirit) 90-92 °C.

**\(R_f\)** 0.38 (20 : 80, EtOAc-petroleum spirit).

\(\alpha\)^D\(_{23} = -36.5\) (c 0.9, chloroform).

**\(\delta_H\) (600 MHz; CDCl\(_3\))** 7.27 (2H, d, J 8.6, H-Ar), 6.90 (2H, d, J 8.6, H-Ar), 6.04 (1H, dd, J 17.3, 10.9, CH=CH\(_2\)), 6.01 (1H, d, J 3.9, H-C1), 5.47 (1H, dd, J 17.3, 1.8, CH=CH\(_2\)), 5.20 (1H, dd, J 10.9, 1.8, CH=CH\(_3\))H\(_6\)), 4.65 (1H, d, J 11.4, CH\(_3\)H\(_6\)-Ar), 4.62 (1H, d, J 3.9, H-C2), 4.43 (1H, d, J 11.4, CH\(_3\)H\(_6\)-Ar), 4.32 (1H, d, J 3.9, H-C3), 4.14 (1H, d, J 3.9, H-C4), 3.99 (1H, br s, OH), 3.82 (3H, s, CH\(_3\)). 3.55 (1H, d, J 9.5, H-C6), 3.41 (1H, d, J 9.5, H-C6), 1.48 (3H, s, CH\(_3\)C(O)\(_2\)), 1.34 (3H, s, CH\(_3\)C(O)\(_2\)), 0.86 (9H, s, (CH\(_3\))\(_3\)C), 0.01 (3H, s, CH\(_3\)-Si), −0.03 (3H, s, CH\(_3\)-Si).

**\(\delta_C\) (150 MHz; CDCl\(_3\))** 159.7 (arom. C), 138.8 (CH=CH\(_2\)), 130.0 (arom. CH), 128.4 (arom. C), 114.3 (CH=CH\(_2\)), 114.0 (arom. CH), 111.5 ((CH\(_3\))\(_2\)C), 104.6 (C-1), 82.5 (C-4), 81.7 (C-2), 80.0 (C-3), 75.0 (C-5), 71.5 (CH\(_3\)-Ar), 68.7 (C-6), 55.8 (CH\(_3\)O), 26.6 (CH\(_3\)C), 26.3 (CH\(_3\)C), 25.8 ((CH\(_3\))\(_2\)C), 18.1 ((CH\(_3\))\(_3\)C), −5.5 (CH\(_3\)-Si), −5.6 (CH\(_3\)-Si).

**\(v_{\max}\) (CHCl\(_3\) cast)/cm\(^{-1}\):** 3493 (O-H), 2953 (C-H), 1612 (C=C), 1514 (C=C).

**m/z (ES\(^{+}\))** 503 (MNa\(^{+}\), 100%), 194 (20), 180 (45), 171 (18).

**HRMS:** calculated for C\(_{25}\)H\(_{40}\)O\(_7\)SiNa\(^{+}\): 503.2451, found: 503.2441. Error 2.0 ppm.

**Elemental analysis:** C\(_{25}\)H\(_{40}\)O\(_7\)Si requires: C 62.5, H 8.4; found C 62.5, 8.5%.
6-O-(**tert**-Butyldimethylsilyl)-1,2-O-isopropylidene-5-C-vinyl-α-D-glucofuranose (171)

![Chemical Structure](image)

Using literature procedure. To a stirred solution of glucofuranoside 169 (150 mg, 0.31 mmol) in dichloromethane (2.0 mL) and water (0.2 mL) was added 2,3-dichloro-5,6-dicyanobenzoquinone (84 mg, 0.37 mmol). The mixture was stirred for 12 h and then diluted with dichloromethane (10 mL). The solution was washed with sat. NaHCO₃ (3 mL), brine (3 mL), dried (MgSO₄) and concentrated in vacuo to give an oil which was purified by flash chromatography (30:70, EtOAc in petroleum spirit) to give diol 171 (42 mg, 38%) as a colourless viscous oil.

Rf 0.32 (30:70, EtOAc-petroleum spirit).

[\xi]_{D}^{23} = −11.3 (c 0.5, CHCl₃).

δH (600 MHz; CDCl₃) 5.99 (1H, dd, J 18.8, 12.4, CH=CH₂), 5.98 (1H, d, J 3.5, H-C1), 5.48 (1H, dd, J 18.8, 1.2, CH=CH₂H₆), 5.30 (1H, dd, J 12.4, 1.2, CH=CH₂H₅), 4.53 (1H, d, J 3.5, H-C2), 4.39 (1H, d, J 2.6, H-C3), 4.14 (1H, d, J 2.6, H-C4), 3.69 (1H, d, J 10.2, H-C6), 3.64 (1H, J 10.2, H-C6), 2.96 (1H, bs, OH), 1.50 (3H, s, CH₃C(O)₂), 1.33 (3H, s, CH₃C(O)₂), 0.92 (9H, s, (CH₃)₃C), 0.11 (3H, s, CH₃-Si), 0.10 (3H, s, CH₃-Si).

δC (150 MHz; CDCl₃) 139.2 (CH=CH₂), 115.6 (CH=CH₂), 111.5 ((CH₃)₂C), 104.6 (C-1), 84.9 (C-2), 81.4 (C-4), 76.1 (C-5), 76.0 (C-3), 67.2 (C-6), 26.8 (CH₃C), 26.2 (CH₃C), 25.8 ((CH₃)₃-C), 18.3 ((CH₃)₃C), −5.55 (CH₃-Si), −5.56 (CH₃-Si).

νmax (CHCl₃ cast)/cm⁻¹: 3395 (O-H), 2930 (C-H), 1606 (C=C).

m/z (ES⁺): 383 (MNa⁺, 100%), 274 (15), 220 (20), 210 (50), 196 (52).

1,6-Anhydro-3-O-acetyl-5-C-vinyl-β-D-glucofuranose (176)

To a stirred solution of glucofuranoside 169 (100 mg, 0.20 mmol) in 0.01% H$_2$SO$_4$ in acetic acid (2.0 mL) was added triethylsilane (30 μL, 0.21 mmol). The mixture was stirred at reflux for 4 h then left to cool to room temperature. Acetic anhydride (1.0 mL, 10.60 mmol) was added and the solution was stirred for a further 16 h. The mixture was concentrated in vacuo and co-evaporated with toluene (3 × 5 mL), ethanol (3 × 5 mL) and purified by flash chromatography (30:70, EtOAc in petroleum spirit) to give anhydrosugar 176 (20 mg, 43%) as a yellow viscous oil.

R$_f$ 0.15 (40:60, EtOAc-petroleum spirit).

[α]$_D^{23}$ = −58.3 (c 0.3, CHCl$_3$).

δ$_H$ (600 MHz; CDCl$_3$) 6.12 (1H, dd, J 17.3, 11.0, CH=CH$_2$), 5.64 (1H, dd, J 17.3, 1.9, CH=CH$_2$H$_b$), 5.32 (1H, s, H-C1), 5.29 (1H, dd, J 11.0, 1.9, CH=CH$_2$H$_b$), 4.96 (1H, d, J 2.4, H-C3), 4.35 (1H, br d, J 6.4, H-C2), 4.17 (1H, d, J 12.0, H-C6), 4.17 (1H, dd, J 6.6, 2.4, H-C4), 3.67 (1H, dd, J 12.0, 2.0, H-C6), 3.15 (1H, s, H=O-C2), 2.18 (3H, s, CH$_3$CO).

δ$_C$ (150 MHz; CDCl$_3$) 172.6 (C=O), 134.6 (CH=CH$_2$), 117.2 (CH=CH$_2$), 100.9 (C-1), 84.7 (C-3), 83.4 (C-4), 78.5 (C-2), 70.7 (C-5), 70.1 (C-6), 20.8 (CH$_3$CO).

ν$_{max}$ (CHCl$_3$ cast)/cm$^{-1}$: 3467 (O-H), 2974 (C-H), 1732 (C=O).

m/z (Cl+, CH$_3$): 231 (MH$^+$, 20%), 213 (100), 195 (10), 171 (20), 162 (30), 153 (95), 135 (53), 125 (27), 107 (35), 95 (30).

HRMS: calculated for C$_{10}$H$_{15}$O$_6^+$: 231.0869, found: 231.0875. Error 2.8 ppm.
1,6-Anhydro-2,3,4-tri-O-acetyl-5-C-vinyl-β-D-glucopyranose (174)

Penta-O-acetyl-5-C-vinyl-β-D-glucopyranose (172)

![Chemical structure](image)

To a solution of glucofuranoside 169 (0.50 g, 1.04 mmol) in 80% aqueous acetic acid (8 mL) was added TFA (50 μL, 0.65 mmol) and the mixture stirred at 120 °C for 12 h. The reaction mixture was concentrated in vacuo and co-evaporated with ethanol (3 × 25 mL) to afford a dark brown gum. Pyridine (4 mL) and acetic anhydride (2 mL, 21.19 mmol) were then added and the solution stirred for a further 12 h at room temperature. Upon completion the reaction mixture was concentrated in vacuo. Purification by flash column chromatography (1:99→15:85, EtOAc in petroleum spirit) afforded pentaacetate 172 (126 mg, 29 %) as a colourless oil.

Rf 0.46 (15:85, EtOAc-Petroleum spirit).

[α]D 22 = −74.7 (c 0.8, CHCl3).

δH (600 MHz; CDCl3) 6.00 (1H, dd, J 17.7, 10.4, CH=CH2), 5.96-5.93 (2H, m, H-(C1) & CH=CH3), 5.69 (1H, dd, J 10.4, 1.2, CH=CH2Hb), 5.40 (1H, d, J 9.8, H-C4), 5.24 (1H, app t, J 9.8, H-C3), 5.19 (1H, dd, J 9.8, 8.2, H-C2), 4.18 (1H, d, J 12.6, H-C6), 3.71 (1H, d, J 12.6, H-C6), 2.12 (3H, s, CH3-CO), 2.11 (3H, s, CH3-CO), 2.05 (3H, s, CH3-CO), 2.02 (3H, s, CH3-CO), 2.01 (3H, s, CH3-CO).

δC (150 MHz; CDCl3) 170.6, 170.1 (2 × C=O), 169.7, 169.1 (2 × C=O), 129.2 (CH=CH2), 122.7 (CH=CH3), 88.4 (C-1), 78.4 (C-5), 71.0 (C-2), 70.7 (C-3), 67.9 (C-4), 64.9 (C-6), 20.9 (CH3-CO), 20.8 (CH3-CO), 20.6 (CH3-CO), 20.58 (CH3-CO), 20.57 (CH3-CO).

νmax (CHCl3 cast)/cm⁻¹: 2923 (C-H), 1747 (C=O), 1640 (C=C).

m/z (FAB+, CH4): 439 (MNa+, 100%), 379 (8), 329 (67), 177 (38).


Further elution gave triacetate 174 as a yellow oil which was crystallised using a mixture of petroleum spirit and diethyl ether (50:50) (64 mg, 20%).

Rf 0.46 (15:85, EtOAc-Petroleum spirit).

[α]D 23 = −51.9 (c 0.60, CHCl3).
δ\textsubscript{H} (\textbf{600 MHz; CDCl\textsubscript{3}}) 5.87 (1H, dd, J 17.5, 11.2, CH=CH\textsubscript{2}), 5.60 (1H, t, J 1.7, H-C1), 5.46 (1H, dd, J 17.5, 0.6, CH=CH\textsubscript{2}H\textsubscript{b}), 5.32 (1H, dd, J 11.2, 0.6, CH=CH\textsubscript{2}H\textsubscript{a}), 4.97 (1H, br s, H-C4), 4.83 (1H, br q, J 1.2, H-C3), 4.62 (1H, br q, J 1.2, H-C2), 4.26 (1H, d, J 7.7, H-C6), 3.56 (1H, d, J 7.7, H-C6), 2.16 (3H, s, CH\textsubscript{3}-CO), 2.15 (3H, s, CH\textsubscript{3}-CO), 2.13 (3H, s, CH\textsubscript{3}-CO).

δ\textsubscript{C} (\textbf{150 MHz; CDCl\textsubscript{3}}) 169.7, 168.9 (2 × C=O), 132.3 (CH=CH\textsubscript{2}), 117.4 (CH=CH\textsubscript{2}), 100.0 (C-1), 81.5 (C-5), 70.5 (C-3), 70.0 (C-6), 69.9 (C-4), 67.9 (C-2), 21.0 (CH\textsubscript{3}-CO), 20.9 (CH\textsubscript{3}-CO), 20.8 (CH\textsubscript{3}-CO).

v\textsubscript{max} (CHCl\textsubscript{3} cast)/cm\textsuperscript{-1}: 2970 (C-H), 1737 (C=O), 1648 (C=C).

m/z (ES\textsuperscript{+}) 337 (MNa\textsuperscript{+}, 100%), 315 (30), 255 (20), 223 (10), 222 (50), 213 (45), 197 (18), 135 (20).

HRMS: calculated for C\textsubscript{14}H\textsubscript{18}O\textsubscript{8}Na\textsuperscript{+}: 337.0909, found: 337.0899. Error 3.0 ppm.
1,6-Anhydro-5-C-vinyl-β-D-glucopyranose (139b)

1,6-Anhydro-4-O-acetyl-5-C-vinyl-β-D-glucopyranose (179)

![Chemical Structures](image)

Thioanisole (44 μL, 0.5 mmol) was added to a solution of glucofuranoside 169 (250 mg, 0.5 mmol) and 80% aqueous acetic acid (4 mL) at room temperature. TFA (6 μL, 52 μmol) was added and the mixture stirred at 140 °C for 24 h. The reaction mixture was concentrated in vacuo and co-evaporated with ethanol (3 × 20 mL). Purification by flash column chromatography (1:99→10:90, MeOH in CH₂Cl₂) gave diol 179 (20 mg, 17%) as a yellow viscous oil.

Rₜ 0.47 (10:90, MeOH-CH₂Cl₂)

[α]₂₀° = −70.4 (c 0.5, CHCl₃).

δH (600 MHz; CDCl₃) 5.85 (1H, dd, J 17.6, 11.2, CH=CH₂), 5.63 (1H, t, J 1.9, H-C1), 5.44 (1H, dd, J 17.6, 0.8, CH=CH₂Hₐ), 5.32 (1H, dd, J 11.2, 0.8, CH=CH₂Hₐ), 5.02 (1H, s, H-C4), 4.38 (1H, d, J 7.7, H-C6), 3.83 (1H, br q, J 1.9, H-C3), 3.61 (1H, br q, J 1.9, H-C2), 3.56 (1H, d, J 7.7, H-C6), 2.10 (3H, s, C₃H₃CO).

δC (150 MHz; CDCl₃) 169.8 (C=O), 132.4 (CH=CH₂), 117.4 (CH=CH₂), 102.9 (C-1), 82.0 (C-5), 72.8 (C-4), 71.8 (C-3), 70.2 (C-6), 68.9 (C-2), 20.9 (CH₃CO).

νmax (CHCl₃ cast)/cm⁻¹: 3425 (O-H), 2958 (C-H), 1721 (C=O), 1647 (C=C).

m/z (CI+, CH₄): 231 (MH⁺, 68%), 213 (100), 195 (10), 171 (33), 153 (56), 135 (17), 125 (25), 111 (14).

HRMS: calculated for C₁₀H₁₅O₆⁺: 231.0869, found: 231.0875. Error 2.8 ppm

Further elution gave triol 139b as a brown viscous oil (50 mg, 52%)

Rₜ 0.30 (10:90, MeOH-CH₂Cl₂)

[α]₂₀° = −73.1 (c 1.0, EtOH).

δH (600 MHz; CD₃OD) 6.05 (1H, dd, J 17.6, 11.2, CH=CH₂), 5.44 (1H, dd, J 17.6, 1.3, CH=CH₂Hₐ), 5.44 (1H, br t, J 1.6, H-C1), 5.31 (1H, dd, J 11.2, 1.3, CH=CH₂Hₐ), 4.32 (1H, d, J 7.0, H-C6), 3.82 (1H, br q, J 1.6, H-C3), 3.59 (1H, br s, H-C4), 3.45 (1H, br q, J 1.6, H-C2), 3.42 (1H, d, J 7.0, H-C6).
$\delta_C$ (150 MHz; CD$_3$OD) 135.0 (CH=CH$_2$), 115.1 (CH=CH$_2$), 103.1 (C-1), 82.6 (C-5), 74.1 (C-3), 72.6 (C-4), 69.6 (C-2), 69.4 (C-6).

$v_{\text{max}}$ (film)/cm$^{-1}$: 3368 (O-H), 1646 (C=C).

$m/z$ (CI+, CH$_4$): 189 (MH$^+$, 10%), 171 (45), 153 (96), 141 (25), 135 (68), 125 (100).

HRMS: calculated for C$_8$H$_{13}$O$_5$+: 189.0763, found: 189.0765. Error 1.1 ppm.
1,6-Anhydro-5-C-vinyl-\(\beta\)-D-glucopyranose (139b)

Thioanisole (0.52 mL, 6.2 mmol) was added to a stirred solution of glucofuranoside 169 (3.00 g, 6.2 mmol) and TFA (130 \(\mu\)L, 1.2 mmol) in 80\% aqueous acetic acid (62.5 mL) at room temperature. The mixture was stirred at 100 °C for 5 days and then concentrated in vacuo. Co-evaporation with heptane (3 \(\times\) 100 mL) afforded a brown oil which was triturated with MeOH (80 mL). NaOMe (0.70 g, 12.9 mmol) was added to the MeOH solution and the mixture was stirred for 3 h at room temperature. The solution was concentrated, and purified by flash column chromatography (1:99\(\rightarrow\)10:90, MeOH in CH\(_2\)Cl\(_2\)) to give anhydrosugar 139b (0.86 g, 74\%) as a brown viscous oil.

\[ R_f \] 0.30 (10:90, MeOH-CH\(_2\)Cl\(_2\)).

\[ \alpha \]\(^{20}\) = −73.1 (c 1.0, EtOH)

\(\delta_H\) (600 MHz; CD\(_3\)OD) 6.05 (1H, dd, \(J\) 17.6, 11.2, CH=CH\(_2\)), 5.44 (1H, dd, \(J\) 17.6, 1.3, CH=CH\(_2\)H\(_6\)), 5.44 (1H, br t, \(J\) 1.6, H-C1), 5.31 (1H, dd, \(J\) 11.2, 1.3, CH=CH\(_2\)H\(_6\)), 4.32 (1H, d, \(J\) 7.0, H-C6), 3.82 (1H, br q, \(J\) 1.6, H-C3), 3.59 (1H, br s, H-C4), 3.45 (1H, br q, \(J\) 1.6, H-C2), 3.42 (1H, d, \(J\) 7.0, H-C6).

\(\delta_C\) (150 MHz; CD\(_3\)OD) 135.0 (CH=CH\(_2\)), 115.1 (CH=CH\(_2\)), 103.1 (C-1), 82.6 (C-5), 74.1 (C-3), 72.6 (C-4), 69.6 (C-2), 69.4 (C-6).

\(v_{\text{max}}\) (film/cm\(^{-1}\)): 3368 (O-H), 1646 (C=C).

\(m/z\) (CI\(+\), CH\(_4\)): 189 (MH\(^+\), 10\%), 171 (45), 153 (96), 141 (25), 135 (68), 125 (100).

HRMS: calculated for C\(_8\)H\(_{13}\)O\(_5\)\(^+\): 189.0763, found: 189.0765. Error 1.1 ppm
1,6-Anhydro-2,4-bis-O-triethylsilyl-5-C-vinyl-β-D-glucose (138b)

Using literature procedure. Triethylsilyl chloride (1.2 mL, 7.5 mmol) was slowly added to a solution of anhydrosugar 139b (641 mg, 3.4 mmol) in pyridine (11 mL) at 0 °C and the mixture stirred for 3 h. The solution was diluted with petroleum spirit (30 mL), washed with water (10 mL), dried (MgSO₄) and concentrated in vacuo to afford the crude residue, which was purified by column chromatography (10:90-20:80, EtOAc in petroleum spirit) to give bis-silyl ether 138b (945 mg, 67%) as a colourless viscous oil.

Rₖ 0.40 (15:85, EtOAc-petroleum spirit).

[α]ₒ²⁰ = −18.4 (c 1.5, CHCl₃).

δₜ (600 MHz; CDCl₃) 6.16 (1H, dd, J 17.8, 11.2, CH=CH₂), 5.44 (1H, t, J 1.6, H-C1), 5.31 (1H, dd, J 17.8, 0.8, CH=CH₂H₂), 5.28 (1H, dd, J 11.2, 0.8, CH=CH₂H₂), 4.14 (1H, d, J 7.3, H-C6), 3.67 (1H, br d, J 1.6, H-C4), 3.63 (1H, dq, J 7.3, 1.6, H-C3), 3.53 (1H, d, J 7.3, H-C6), 3.51 (1H, td, J 1.6, 1.1, H-C2), 2.22 (1H, d, J 7.3, OH), 0.98 (18H, m, 2 × Si(CH₂CH₃)₃), 0.65 (12H, m, 2 × Si(CH₂CH₃)₃).

δₖ (150 MHz; CDCl₃) 135.1 (CH=CH₂), 116.1 (C=CH₂), 103.5 (C-1), 83.0 (C-5), 76.3 (C-3), 75.0 (C-4), 71.5 (C-2), 69.7 (C-6), 6.9 (CH₂-CH₃), 6.8 (CH₂-CH₃), 4.8 (CH₃-CH₂), 4.6 (CH₃-CH₂).

νₘₐₓ (CH₂Cl₂ cast)/cm⁻¹: 3460 (O-H), 2954 (C-H), 1648 (C=C).

m/z (ES⁺): 439 (100, M⁺).

HRMS: calculated for C₂₀H₄₀O₅Na₂Si₂⁺: 439.2312, found: 439.2310. Error 0.5 ppm
1-(2,4-Bis-O-(triethylsilanyl)-5-C-vinyl-β-D-glucopyranosyl)-2-trimethylsilanylyethyne (181)

Using literature procedure\textsuperscript{111}. Trimethylsilyl acetylene (2.7 mL, 9.7 mmol) was dissolved in anhydrous toluene (8.1 mL) and cooled to −20 °C. \(n\)-BuLi (1.5 M in hexane, 6.3 mL, 9.45 mmol) was added dropwise, and the solution stirred at room temperature for 30 min. Anhydrous THF (1.5 mL) was then added dropwise and the solution was added dropwise to a suspension of freshly sublimed AlCl\(_3\) (1.29 g, 9.7 mmol) in toluene (6.1 mL). The mixture was heated at 50 °C in an ultrasound bath for 2 h. Following this the solution was heated to 60 °C (without sonication) and a solution of anhydrosugar 138b (0.92 g, 2.2 mmol) and 2,4,6-trimethylpyridine (0.2 mL, 2.4 mmol) in dry toluene (1.4 mL) was added dropwise. The reaction mixture was heated at 120 °C for 5 days, cooled to 0 °C and poured into an ice-cold saturated aqueous ammonium chloride solution (5 mL). The organic compound was extracted with EtOAc (5 × 50 mL) and the organic layers were combined, dried (MgSO\(_4\)) and concentrated \textit{in vacuo} to give a yellow coloured oil which was purified by column chromatography (2:98-20:80, EtOAc in petroleum spirit) on activated alumina to afford diol 181 (930 mg, 82%) as a white solid.

\textbf{m.p.} (EtOAc) 55-57 °C.

\(R_f\) 0.75 (20:80, EtOAc-petroleum spirit)

\([\alpha]\)\textsubscript{D}\textsuperscript{22} = −65.9 (c 0.7, CHCl\(_3\)).

\(\delta_H\) (600 MHz; CDCl\(_3\)) 6.00 (1H, dd, J 18.0, 11.3, CH=CH\(_2\)), 5.45 (1H, dd, J 18.0, 1.4, CH=CH\(_3\)H\(_6\)), 5.43 (1H, dd, J 11.3, 1.4, CH=CH\(_3\)H\(_6\)), 4.21 (1H, d, J 9.5, H-C1), 3.83 (1H, d, J 9.8, H-C4), 3.56 (1H, dd, J 11.7, 10.9, H-C6), 3.48 (1H, dd, J 9.5, 8.7, H-C2), 3.39 (1H, dd, J 11.7, 2.9, H-C6), 3.36 (1H, ddd, J 9.8, 8.7, 2.8, H-C3), 2.19 (1H, d, J 10.9, 2.9, CH\(_2\)OH), 2.08 (1H, d, J 2.8, CH\(_2\)OH), 0.99 (18H, m, 2 × Si(CH\(_2\)CH\(_3\))\(_3\)), 0.71 (12H, m, 2 × Si(CH\(_2\)CH\(_3\))\(_3\)), 0.2 (9H, s, Si(CH\(_3\))\(_3\)).

\(\delta_C\) (150 MHz; CDCl\(_3\)) 132.5 (CH=CH\(_2\)), 119.2 (CH=CH\(_2\)), 103.4 (C≡C-TMS), 89.9 (C≡C-TMS), 81.7 (C-5), 76.0 (C-3), 75.9 (C-2), 71.0 (C-4), 66.7 (C-1), 65.9 (C-6), 6.9 (CH\(_2\)-CH\(_3\)), 5.2 (CH\(_2\)-CH\(_3\)), 5.3 (CH\(_3\)-CH\(_2\)), 5.1 (CH\(_3\)-CH\(_2\)), −0.2 ((CH\(_3\))\(_3\)Si).

\(\nu_{\max}\) (CHCl\(_3\) cast)/cm\(^{-1}\): 3565 (O-H), 2182 (C≡C), 1729 (C=C).
m/z (Cl+, CH₄) 515 (MH⁺, 23%), 467 (10), 399 (30), 353 (35), 335 (22), 255 (100), 229 (45).

HRMS calculated for C₂₅H₅₀O₅Si₃⁺: 515.3044, found: 515.3050. Error 1.1 ppm
1-trimethylsilanyl-2-(2,4,6-Tris-O-(triethylsilanyl)-5-C-vinyl-β-D-glucopyranosyl)ethyne (188)

![Chemical structure](image)

To a stirred solution of diol 181 (710 mg, 1.4 mmol) in anhydrous dichloromethane (1.38 mL) and pyridine (0.34 mL, 4.1 mmol) was added chlorotriethylsilane (230 μL, 1.4 mmol) at 0 °C. The mixture was left to warm to room temperature and stirred for a further 2 h. Water (5 mL) was added to the resulting solution, and the organic material was extracted with dichloromethane (3 × 25 mL), dried (MgSO₄) and concentrated *in vacuo* to give an oily residue, which was purified by column chromatography (4:96, EtOAc in CH₂Cl₂) to give tris-silyl ether 188 (0.7 g, 81%) as a colourless viscous oil, \( R_f \) 0.95 (20:80, EtOAc-petroleum spirit).

\[ [\alpha]_D^{20} = -55.9 \ (c \ 1.3, \ CHCl_3) \]

\( \delta_H \ (600 \text{ MHz; } CDCl_3) \) 5.97 (1H, dd, \( J \) 18.0, 11.2, CH=CH₂), 5.41 (1H, dd, \( J \) 18.0, 1.8, CH=CH₂H₆), 5.35 (1H, dd, \( J \) 11.2, 1.8, CH=CH₂H₆), 4.10 (1H, d, \( J \) 9.5, H-C₁), 3.90 (1H, d, \( J \) 9.8, H-C₄), 3.60 (1H, d, \( J \) 11.6, H-C₆), 3.45 (1H, dd, \( J \) 9.5, 9.8, H-C₂), 3.31 (1H, ddd, \( J \) 9.7, 9.8, 2.8, H-C₃), 3.29 (1H, d, \( J \) 11.6, H-C₆), 2.06 (1H, d, \( J \) 2.8, OH), 0.98 (27H, m, 3 × Si(CH₂CH₃)₃), 0.65 (18H, m, 3 × Si(CH₂CH₃)₃), 0.17 (9H, s, Si(CH₃)₃).

\( \delta_C \ (150 \text{ MHz; } CDCl_3) \) 133.0 (CH=CH₂), 118.4 (CH=CH₂), 104.1 (C≡CTMS), 88.9 (C≡CTMS), 81.7 (C-5), 75.9 (C-3), 75.9 (C-2), 70.7 (C-4), 66.7 (C-6), 65.7 (C-1), 6.9 (CH₂CH₂), 5.2 (CH₃CH₂), 5.0 (CH₃CH₂), 4.8 (CH₃CH₂), −0.4 ((CH₃)₃Si).

\( \nu_{\text{max}} \ (\text{CH}_2\text{Cl}_2 \text{ cast})/\text{cm}^{-1}: \) 3619 (O-H), 2954 (C-H), 2182 (C≡C), 1759 (C=C).

\( m/z \ (\text{ES}^+): \) 651 (M⁺, 100%), 611 (10), 537 (28), 479 (20), 454 (15).

**HRMS:** calculated for C₃₁H₆₄O₅NaSi₄⁺: 651.3729, found: 651.3735. Error 0.9 ppm.
1-(3-O-Acetyl-2,4,6-tris-O-(triethylsilyl)-5-C-vinyl-β-D-glucopyranosyl)-2-
trimethylsilylene (137b)

Using literature procedure. To a stirred mixture of alcohol 188 (2.79 g, 4.4 mmol) and dry isopropenyl acetate (740 μL, 6.6 mmol) at 90 °C was added iodine (28 mg, 0.2 mmol). The mixture was stirred at the same temperature under an inert atmosphere for 10 min. Further isopropenyl acetate (740 μL, 6.6 mmol) was added and the mixture was stirred for an additional 10 min. The solution was quenched with saturated aqueous sodium thiosulfate (0.5 mL), diluted with dichloromethane (60 mL) and the organic material was washed with water (10 mL). The organic layer was dried (MgSO₄), filtered and concentrated in vacuo to give the crude viscous oil which was purified by column chromatography (50:50, CH₂Cl₂ in petroleum spirit) to give acetate 137b (1.70 g, 57%) as a colourless viscous oil. \[ R_f 0.68 \] (50:50, DCM-petroleum spirit).

\[ \alpha \]D = −71.0 (c 1.0, CHCl₃).

\( \delta_H \) (400 MHz; CDCl₃) 6.02 (1H, dd, J 18.0, 11.1, CH=CH₂), 5.48-5.40 (2H, m, CH=CH₂), 4.94 (1H, dd, J 10.1, 9.5, H-C3), 4.16 (1H, d, J 9.5, H-C1), 4.05 (1H, d, J 10.1, H-C4), 3.58 (1H, t, J 9.5, H-C2), 3.58 (1H, d, J 11.8, H-C6), 3.30 (1H, d, J 11.8, H-C6), 2.14 (3H, s, CH₃CO), 0.97 (27H, m, 3 × Si(CH₂CH₃)₃), 0.66 (18H, m, 3 × Si(CH₂CH₃)₃), 0.18 (9H, s, Si(CH₃)₃).

\( \delta_C \) (125 MHz; CDCl₃) 169.7 (C=O), 132.7 (CH=CH₂), 119.2 (CH=CH₂), 103.8 (C≡CTMS), 89.5 (C≡CTMS), 82.0 (C-5), 76.5 (C-3), 74.4 (C-2), 69.1 (C-4), 66.7 (C-6), 66.2 (C-1), 21.8 (CH₃CO), 6.9 (CH₃CH₂), 5.4 (CH₃CH₂), 5.11 (CH₃CH₂), 4.8 (CH₃CH₂), −0.2 (Si(CH₃)₃).

\( v_{\text{max}} \) (CH₂Cl₂ cast)/cm⁻¹: 2955 (C-H), 2182 (C≡C), 1757 (C=O).

m/z (ES⁺): 693 (MNa⁺, 100%), 686 (30), 651 (50), 611 (30), 539 (15), 479 (20), 463 (15).

HRMS: calculated for C₃₃H₆₆O₆NaSi₄⁺: 693.3834, found: 693.3865. Error 4.5 ppm.
1-(3-O-Acetyl-5-C-vinyl-β-D-glucopyranosyl)-2-trimethylsilanylethyne (189)

To a stirred solution of acetate 137b (393 mg, 0.6 mmol) in THF (2.0 mL) at room temperature were added acetic acid (17.7 mL) and water (6 mL). The mixture was heated to 90 °C and stirred overnight. The reaction mixture was concentrated in vacuo and the crude material purified by column chromatography (5:95, CH₃OH in CH₂Cl₂) to afford triol 189 (152 mg, 79%) as a colourless oil.

Rₙ 0.70 (10:90, CH₃OH in CH₂Cl₂)

[α]₂⁰° = −119.5 (c 0.4, CHCl₃).

δH (600 MHz; CDCl₃) 6.05 (1H, dd, J 18.3, 10.9, CH=CH₂), 5.57-5.54 (2H, m, CH=CH₂), 4.90 (1H, dd, J 10.1, 9.8, H-C3), 4.35 (1H, d, J 9.8, H-C1), 4.04 (1H, dd, J 10.1, 3.6, H-C4), 3.69 (1H, dd, J 12.0, 9.8, H-C6), 3.61 (1H, td, J 9.8, 2.6, H-C2), 3.50 (1H, d, J 12.0, H-C6), 2.91 (1H, br d, J 3.6, OH-C4), 2.52 (1H, br d, J 2.6, OH-C2), 2.31 (1H, br d, J 9.8, OH-C6), 2.18 (3H, s, CH₃CO), 0.21 (9H, s, Si(CH₃)₃).

δC (150 MHz; CDCl₃) 172.5 (C=O), 131.3 (CH=CH₂), 120.6 (CH=CH₂), 101.1 (C≡CTMS), 91.9 (C≡CTMS), 81.4 (C-5), 76.3 (C-3), 73.2 (C-2), 68.8 (C-4), 66.8 (C-6), 65.9 (C-1), 21.1 (CH₃O), −0.2 (Si(CH₃)₃).

νmax (CHCl₃ cast)/cm⁻¹: 3422 (O-H), 2178 (C≡C), 1721 (C=C).

m/z (ES+): 351 (MNa⁺, 100%), 331 (10).

HRMS: calculated for C₁₅H₂₄O₆NaSi⁺: 351.1240, found: 351.1255. Error 4.3 ppm
1-(3-O-Acetyl-4,6-O-(4-methoxybenzylidene)-5-C-vinyl-β-D-glucopyranosyl)-2-trimethylsilanylethyne (136b)

To a stirred solution of triol 189 (142 mg, 0.4 mmol) and p-toluene sulfonic acid (8 mg, 43 µmol) in anhydrous acetonitrile (2.15 mL) was added p-anisaldehyde dimethyl acetal (18 µL, 0.10 µmol). The mixture was stirred at reflux under an inert atmosphere for 12 h. The solution was quenched with triethylamine (50 µL) and concentrated in vacuo to give an oil which was purified by column chromatography (50:50, toluene in CH₂Cl₂, 0.5% NEt₃ then 1:99→5:95, MeOH in CH₂Cl₂, 0.5% NEt₃) to give acetal 136b (140 mg, 73%) as a colourless viscous oil.

Rf 0.60 (20:80, EtOAc-petroleum spirit).

[α]⁺23 = −41.2 (c 0.6, CHCl₃).

δ_H (600 MHz; CDCl₃) 7.38 (2H, d, J 8.7, H-Ar), 6.90 (2H, d, J 8.7, H-Ar), 6.26 (1H, dd, J 18.0, 11.3, CH=CH₂), 5.72 (1H, dd, J 18.0, 1.1, CH=CH₂H₆), 5.63 (1H, dd, J 11.3, 1.1, CH=CH₂H₆), 5.55 (1H, s, CH(O)₂), 5.19 (1H, dd, J 10.6, 9.7, H-C3), 4.51 (1H, d, J 9.7, H-C1), 4.05 (1H, d, J 9.8, H-C6), 3.88 (1H, d, J 9.8, H-C6), 3.82 (3H, s, CH₃O), 3.76 (1H, d, J 10.6, H-C4), 3.75 (1H, br t, J 9.7, H-C2), 2.13 (3H, s, CH₃CO), 0.22 (9H, s, Si(CH₃)₃).

δ_c (150 MHz; CDCl₃) 171.3 (C=O), 160.2 (arom. C), 134.6 (CH=CH₂), 129.3 (arom. C), 127.6 (arom. C), 120.2 (CH=CH₂), 113.6 (arom. C), 102.6 (CH(O)₂), 100.9 (C≡CTMS), 92.1 (C≡CTMS), 80.3 (C-4), 77.0 (C-6), 74.6 (C-2), 72.3 (C-5), 71.9 (C-3), 66.8 (C-1), 55.6 (CH₃O), 21.0 (CH₃CO), −0.2 (Si(CH₃)₃).

ν_max (CHCl₃ cast)/cm⁻¹: 3450 (O-H), 2960 (C-H), 2184 (C≡C), 1749 (C=O), 1679 (C=C), 1615 (C=C), 1518 (C=C).

m/z (ES⁺): 469 (MNa⁺, 30%), 447 (MH⁺, 100), 440 (18), 399 (29), 251 (22), 141 (29).

HRMS: calculated for C₂₃H₃₁O₇Si⁺: 447.1836, found: 447.1839. Error 0.7 ppm.
(1R,4R,6S,7R,8S,10S,12S)-7-Acetoxy-4-(4-methoxyphenyl)-12-(trimethylsilanylethynyl)-3,5,9,11-tetraoxatricyclo[6.2.2.01,6]dodecan-10-ol (206)

Ozone was bubbled through a solution of alcohol 136b (35 mg, 80 μmol) in anhydrous dichloromethane (2.0 mL) for 6 min at −78 °C. The mixture was allowed to warm to room temperature and triphenylphosphi ne (55 mg) was added. The mixture was stirred for a further 1 h and the solution was concentrated in vacuo. The crude material was purified by preparative TLC (40:60, EtOAc in petroleum ether) to afford hemiacetal 206 (8 mg, 22%) as a colourless oil.

Rf 0.42 (40:60, EtOAc-petroleum spirit).

[α]D23 = −67.6 (c 0.2, CHCl3).

δH (600 MHz; CDCl3) 7.41 (2H, d, J 8.7, H-Ar), 6.91 (2H, d, J 8.7, H-Ar), 5.66 (1H, br s, OCH(OH)), 5.58 (1H, s, Ar-CH(O)2), 5.11 (1H, dd, J 2.3, 1.4, H-C12), 4.99 (1H, td, J 3.6, 1.3, H-C7), 4.40 (1H, d, J 3.6, H-C6), 4.32 (1H, dd, J 3.6, 2.3, H-C8), 4.30 (1H, d, J 11.3, H-C2), 3.82 (3H, s, CH3O), 3.80 (1H, d, J 11.3, H-C2), 2.12 (3H, s, CH3CO), 0.21 (9H, s, (CH3)3).

δC (150 MHz; CDCl3) 170.1 (C=O), 160.4 (arom. C), 128.9 (arom. C), 127.5 (arom. C), 113.7 (arom. C), 101.9 (ArCH(O)2), 99.3 (C≡CTMS), 93.5 (C≡CTMS), 91.0 (OCHOH), 79.2 (C-4), 72.4 (C-3), 68.5 (C-2), 68.5 (C-6), 66.5 (C-5), 65.9 (C-1), 55.4 (CH3O), 21.2 (CH3CO). −0.14 (Si(CH3)3).

νmax (CHCl3 cast)/cm−1: 3411 (O-H), 2962 (C-H), 2189 (C≡C), 1747 (C=O), 1615 (C=C), 1518 (C=C).

m/z (EI): 448 (M+, 100%), 279 (14).

HRMS: calculated for C22H28O8Si: 448.1548, found: 448.1537. Error 2.5 ppm
1-(3-O-Acetyl-4,6-O-(4-methoxybenzylidene)-2-O-(4-toluenesulfonyl)-5-C-vinyl)-β-D-glucopyranosyl)-2-trimethylsilanylene (187)

1-(3-O-Acetyl-2,6-O-(4-toluenesulfonyl)-5-C-vinyl-β-D-glucopyranosyl)-2-trimethylsilanylene (190)

1-(3-O-Acetyl-2-O-(4-toluenesulfonyl)-5-C-vinyl)-β-D-glucopyranosyl)-2-trimethylsilanylene (191)

To a stirred solution of alcohol 136b (144 mg, 0.3 mmol) in anhydrous pyridine (0.8 mL) was added p-toluenesulfonyl chloride (152 mg, 0.8 mmol) and the mixture stirred at 100 °C overnight. After allowing the solution to cool to room temperature, the mixture was diluted with ethyl acetate (8 mL) and the organic material washed with water (2 mL). The organic layer was dried (MgSO4) and concentrated in vacuo to afford dark brown oil. Purification by column chromatography (5:95→10:90, EtOAc in petroleum spirit) gave tosylate 187 as a yellow oil, (36 mg, 18%).

Rf 0.70 (20:80, EtOAc in petroleum spirit).

[α]D 22 = −44.5 (c 0.3, CHCl3).

δH (600 MHz; CDCl3) 7.82 (2H, d, J 8.6, H-ArOTs), 7.34 (2H, d, J 8.8, H-Ar), 7.32 (2H, d, J 8.6, H-ArOTs), 6.88 (1H, d, J 8.8, H-Ar), 6.22 (1H, dd, J 18.0, 11.4, CH=CH2), 5.71 (1H, d, J 18.0, CH=CH2Hb), 5.62 (1H, d, J 11.4, CH=CH2Hb), 5.52 (1H, s, CH(O)2), 5.39 (1H, dd, J 10.7, 9.7, H-C3), 4.92 (1H, t, J 9.7, H-C2), 4.65 (1H, d, J 9.7, H-C1), 4.05 (1H, d, J 9.9, H-C6), 3.88 (1H, d, J 9.9, H-C6), 3.81 (3H, s, CH3O), 3.73 (1H, d, J 9.7, H-C4), 2.44 (3H, s, CH3-Ar), 1.88 (3H, s, CH3CO), 0.24 (9H, s, Si(CH3)3).

δC (150 MHz; CDCl3) 169.9 (C=O), 160.2 (arom. C), 144.8 (arom. COTs), 134.4 (arom. COTs), 134.1 (CH=CH2), 129.1 (arom. C), 129.6 (arom. CHTs), 127.8 (arom. CH), 127.5
(arom. CH$_3$), 120.6 (CH=CH$_2$), 113.6 (arom. CH), 102.6 (CHO$_2$), 99.2 (C≡CTMS), 93.2 (C≡CTMS), 80.4 (C-4), 79.3 (C-2), 76.6 (C-6), 72.3 (C-5), 68.8 (C-3), 64.5 (C-1), 55.3 (CH$_3$O), 21.6 (CH$_3$-Ar), 20.7 (CH$_3$CO), −0.3 (Si(CH$_3$)$_3$).

$\nu_{\text{max}}$ (CHCl$_3$ cast)/cm$^{-1}$: 2957 (C-H), 2011.4 (C=CH$_2$), 1756 (C=O), 1702 (C=C), 1615 (C=C), 1518 (C=C).

$m/z$ (ES+): 623 (MNa$^+$, 100), 544 (10), 451 (20).

HRMS: calculated for C$_{30}$H$_{36}$O$_9$NaSiS$^+$: 623.1747, found 623.1738. Error 1.4 ppm.

Further elution with (10:90→20:80, EtOAc in petroleum spirit) gave ditosylate 191 (10 mg, 5%) as colourless oil.

R$_f$ 0.35 (20:80, EtOAc-petroleum spirit).

$\lbrack \alpha \rbrack^2_D = -10.0 (c 0.1, CHCl$_3$).

$\delta_H$ (600 MHz; CDCl$_3$) 7.83 (2H, d, J 8.3, H-Ar), 7.80 (2H, d, J 8.3, H-Ar), 7.38 (2H, d, J 8.0, H-Ar), 7.31 (2H, d, J 8.0, H-Ar), 5.97 (1H, dd, J 17.8, 11.2, CH=CH$_2$), 5.58 (1H, d, J 11.2, CH=CH$_2$H$_2$), 5.56 (1H, d, J 17.8, CH=CH$_2$H$_2$), 5.06 (1H, t, J 9.8, H-C3), 4.75 (1H, t, J 9.8, H-C2), 4.44 (1H, d, J 9.8, H-C1), 4.20 (1H, d, J 11.5, H-C6), 3.97 (1H, dd, J 9.8, 5.5, H-C4), 3.77 (1H, d, J 11.5, H-C6), 3.09 (1H, d, J 5.5, O-H), 2.48 (3H, s, CH$_3$-Ar), 2.44 (3H, s, CH$_3$-Ar), 1.88 (3H, s, CH$_3$CO), 0.23 (9H, s, Si(CH$_3$)$_3$).

$\delta_C$ (150 MHz; CDCl$_3$) 171.0 (C=O), 145.3 (arom. C), 144.7 (arom. C), 144.5 (arom. C), 132.5 (arom. C), 130.0 (arom. CH), 129.6 (arom. CH), 129.3 (CH=CH$_2$), 128.0 (arom. CH), 127.8 (arom. CH), 122.5 (CH=CH$_2$), 98.9 (C≡C-TMS), 93.1 (C≡C-TMS), 80.1 (C-5), 78.4 (C-2), 71.9 (C-3), 70.6 (C-6), 68.7 (C-4), 63.7 (C-1), 21.7 (CH$_3$-Ar), 21.6 (CH$_3$-Ar), 20.7 (CH$_3$CO), −0.55 (Si(CH$_3$)$_3$).

$\nu_{\text{max}}$ (CHCl$_3$ cast)/cm$^{-1}$: 3370 (O-H), 2923 (C-H), 2155 (C≡C), 1755 (C=O), 1661 (C=C), 1599 (C=C).

$m/z$ (ES+): 661 (25), 660 (40), 659 (MNa$^+$, 100), 654 (15), 488 (15), 487 (50), 399 (40).

HRMS: calculated for C$_{29}$H$_{36}$O$_{10}$NaSiS$^+$: 659.1417, found 659.1382. Error 5.3 ppm.

Further elution with (40:60→70:30, EtOAc in petroleum spirit) gave diol 190 as colourless oil (53 mg, 34%).

R$_f$ 0.39 (65:35, EtOAc-petroleum spirit).

$\lbrack \alpha \rbrack^2_D = -87.8 (c 0.1, CHCl$_3$).
δ<sub>H</sub> (600 MHz; CDCl<sub>3</sub>) 7.80 (2H, d, J 8.3, H-Ar), 7.31 (2H, d, J 8.3, H-Ar), 6.01 (1H, dd, J 17.8, 11.4, CH=CH<sub>2</sub>), 5.54 (1H, d, J 11.4, CH=CH<sub>2</sub>H<sub>3</sub>), 5.53 (1H, dd, J 17.8, 1.0, CH=CH<sub>2</sub>H<sub>3</sub>), 5.09 (1H, t, J 9.8, H-C3), 4.78 (1H, t, J 9.8, H-C2), 4.51 (1H, d, J 9.8, H-C1), 4.03 (1H, d, J 9.8, H-C4), 3.66 (1H, d, J 12.2, H-C6), 3.49 (1H, d, J 12.2, H-C6), 2.43 (3H, s, CH<sub>3</sub>-Ar), 1.91 (3H, s, CH<sub>3</sub>CO), 0.22 (9H, s, Si(CH<sub>3</sub>)<sub>3</sub>).

δ<sub>C</sub> (150 MHz; CDCl<sub>3</sub>) 171.2 (C=O), 144.7 (arom. C), 134.5 (arom. C<sub>Ts</sub>), 131.0 (CH=CH<sub>2</sub>), 129.6 (arom. CH), 127.8 (arom. CH), 120.9 (CH=CH<sub>2</sub>), 99.5 (C≡C-TMS), 92.9 (C≡C-TMS), 81.6 (C-5), 78.6 (C-2), 72.7 (C-3), 68.8 (C-4), 66.5 (C-6), 63.5 (C-1), 21.6 (CH<sub>3</sub>-Ar), 20.8 (CH<sub>3</sub>CO), −0.36 (Si(CH<sub>3</sub>)<sub>3</sub>).

ν<sub>max</sub> (CHCl<sub>3</sub> cast)/cm<sup>−1</sup>: 3444 (O-H), 2958 (C-H), 2174 (C≡C), 1749 (C=O), 1662 (C=C), 1597 (C=C).

m/z (ES<sup>+</sup>): 505 (MNa<sup>+</sup> + 100), 471 (28), 374 (20), 343 (22), 333 (30), 301 (18), 214 (18), 180 (30).

HRMS: calculated for C<sub>22</sub>H<sub>30</sub>O<sub>8</sub>SiNa<sup>+</sup>: 505.1353, found 505.1328. Error 4.9 ppm.
(4,6-\(O\)-(4-Methoxybenzylidene)-2-\(O\)-(4-toluenesulfonyl)-5-\(C\)-vinyl)-\(\beta\)-D-glucopyranosyl)ethyne (192)

![Chemical Structure](image)

To a stirred solution of acetate 187 (65 mg, 0.1 mmol) in dry dichloromethane (0.8 mL) and methanol (0.3 mL) was added sodium methoxide (22 mg, 0.4 mmol) and the mixture stirred at room temperature under an inert atmosphere for 18 h. The solution was concentrated in vacuo, dissolved in ethyl acetate (10 mL) and washed with sat. aq. NaHCO₃ (2 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo to give a yellow oil which was purified by column chromatography (5:95→20:80, EtOAc in petroleum spirit) to afford alcohol 192 (40 mg, 82%) as a colourless viscous oil.

\(R_f\) 0.35 (20:80, EtOAc-petroleum spirit).

\([\alpha]_D^{20} = -31.0 \ (c \ 0.1, \ CHCl_3)\).

\(\delta_H (600 \text{ MHz; } CDCl_3)\) 7.87 (2H, d, \(J\ 8.3, \ H-\text{ArOTs}\)), 7.40 (2H, d, \(J\ 8.6, \ H-\text{Ar}\)), 7.34 (2H, d, \(J\ 8.3, \ H-\text{ArOTs}\)), 6.89 (2H, d, \(J\ 8.6, \ H-\text{Ar}\)), 6.22 (1H, dd, \(J\ 18.1, 11.3, \ CH=CH_2\)), 5.64-5.57 (3H, m, \(CH(O)_2\) & \(CH=CH_2\)), 4.66 (1H, dd, \(J\ 9.8, 8.5, \ H-C2\)), 4.57 (1H, d, \(J\ 9.8, \ H-C1\)), 4.03 (1H, d, \(J\ 9.8, \ H-C6\)), 3.98 (1H, ddd, \(J\ 10.4, 8.5, 2.2, \ H-C3\)), 3.85 (1H, d, \(J\ 9.8, \ H-C6\)), 3.81 (3H, s, \(CH_3O\)), 3.69 (1H, d, \(J\ 10.4, \ H-C4\)), 2.98 (1H, d, \(J\ 2.2, \ OH\)), 2.46 (3H, s, \(CH_3-Ar\)).

\(\delta_C (150 \text{ MHz; } CDCl_3)\) 160.4 (arom. C), 145.3 (arom. COTs), 134.2 (CH=CH₂), 133.3 (arom. C), 129.6 (arom. CHOTs), 129.0 (arom. COTs), 128.5 (arom. CHOTs), 127.7 (arom. CH), 119.9 (CH=CH₂), 113.7 (arom. CH), 103.1 (CH(O)₂), 82.9 (C-2), 81.9 (C-4), 75.0 (C≡CH), 77.0 (C≡CH), 76.8 (C-6), 71.9 (C-5), 69.3 (C-3), 63.1 (C-1), 55.3 (CH₃O), 21.7 (CH₃-Ar).

\(\nu_{\max} (\text{CHCl}_3 \text{ cast})/\text{cm}^{-1}\): 3496 (O-H), 2925 (C-H), 2981 (C≡C), 1615 (C=C), 1518 (C=CAr).

\(m/z \ (ES^+): \) 487 (MH⁺, 60%).

(1,2-Dideoxy-4,6-O-(4-methoxybenzylidene)-5-C-vinyl-D-arabino-hex-1-enopyranosyl)ethyne (193)

To a stirred solution of tosylate 187 (27 mg, 40 μmol) in anhydrous DCM (0.1 mL) and methanol (0.1 mL) was added sodium methoxide (12 mg, 230 μmol) and the mixture stirred at 60 °C overnight. Concentration of the solution in vacuo followed by purification using preparative TLC (20:80, EtOAc in petroleum spirit) afforded enyne 193 (6.2 mg, 49%) as a colourless oil.

Rf 0.42 (20:80, EtOAc-petroleum spirit).

$\delta_\text{D} = -2 (c 0.1, \text{CHCl}_3)$.

$\delta_\text{H} (600 \text{ MHz; CDCl}_3)$ 7.46 (2H, d, $J$ 8.7, $H$-Ar), 6.93 (2H, d, $J$ 8.7, $H$-Ar), 6.34 (1H, dd, $J$ 17.5, 11.1, $CH=CH_2$), 5.65 (1H, s, CH(O)$_2$), 5.47 (1H, dd, $J$ 17.5, 0.8, CH=CH$_2$H$_6$), 5.39 (1H, d, $J$ 11.1, CH=CH$_2$H$_6$), 5.27 (1H, d, $J$ 2.2, $H$-C2), 4.23 (1H, dd, $J$ 8.6, 2.2, $H$-C3), 4.09 (1H, d, $J$ 10.1, $H$-C6), 3.97 (1H, d, $J$ 10.1, $H$-C6), 3.90 (1H, d, $J$ 8.6, $H$-C4), 3.83 (3H, s, OCH$_3$), 2.99 (1H, s, $C\rightleftarrows C\rightleftarrows H$).

$\delta_\text{C} (150 \text{ MHz; CDCl}_3)$ 160.4 (arom. $C$), 134.8 (C-1), 131.9 (CH=CH$_2$), 129.2 (arom. $C$), 127.6 (arom. CH), 116.5 (CH=CH$_2$), 113.8 (arom. CH), 110.6 (C-2), 102.8 (CH(O)$_2$), 81.9 (C-4), 77.2 (C≡CH), 74.9 (C-6), 73.9 (C-5), 64.9 (C-3), 55.3 (CH$_3$O).

$v_{\text{max}}$ (CHCl$_3$ cast)/cm$^{-1}$: 3422 (O-H), 2922 (C-H), 2111 (C≡C), 1710 (C≡C), 1615 (C≡C), 1518 (C≡C).

$m/z$ (EI): 314 (M$^+$, 30%), 281 (24), 270 (10), 218 (18).

**HRMS:** calculated for C$_{18}$H$_{18}$O$_5$: 314.1149, found 314.1142. Error 2.13 ppm
1-(3-O-Acetyl-4,6-O-(4-methoxybenzylidene)-2-O-(trifluoromethanesulfonyl)-5-C-vinyl-\(\beta\)-D-glucopyranosyl)-2-trimethylsilanylethyn (194)

1-(3-O-Acetyl-2-O-(trifluoromethanesulfonyl)-5-C-vinyl-\(\beta\)-D-glucopyranosyl)-2-trimethylsilanylethyn (195)

To a stirred solution of alcohol 136b (89 mg, 0.2 mmol) in anhydrous dichloromethane (0.7 mL) and pyridine (32 μL, 0.4 mmol) at 0 °C was added triflic anhydride (38 μL, 230 μmol). The mixture was allowed to warm to room temperature and then stirred for 12 h. The mixture was diluted with dichloromethane (3 mL) and the organic material washed with water (1 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo to give the crude material which was purified by column chromatography (5:95 → 30:70, EtOAc in petroleum spirit) to afford triflate 194 (20 mg, 9%) as a colourless oil.

Rf 0.60 (20:80, EtOAc-petroleum spirit)

[\(\alpha\)]\text{D}^{23} = −50.4 (c 0.2, CHCl₃)

\(\delta\)F (300 MHz; CDCl₃) −74.5.

\(\delta\)H (600 MHz; CDCI₃) 7.35 (2H, d, J 8.8, H-Ar), 6.90 (2H, d, J 8.8, H-Ar), 6.25 (1H, dd, J 18.1, 11.4, CH=CH₂), 5.77 (1H, d, J 18.1, CH=CH₃H₂b), 5.70 (1H, d, J 11.4, CH=CH₃H₂b), 5.53 (1H, s, CH(O)₂), 5.52 (1H, dd, J 10.7, 9.8, H-C3), 4.92 (1H, t, J 9.8, H-C2), 4.77 (1H, d, J 9.8, H-C1), 4.08 (1H, d, J 9.9, H-C6), 3.88 (1H, d, J 9.9, H-C6), 3.82 (3H, s, CH₃O), 3.74 (1H, d, J 10.7, H-C4), 2.11 (3H, s, CH₃CO), 0.22 (9H, s, Si(CH₃)₃).

\(\delta\)C (150 MHz; CDCl₃) 169.4 (C=O), 160.3 (arom. C), 133.6 (CH=CH₂), 128.8 (arom. C), 127.5 (arom. CH), 121.2 (CH=CH₂), 113.7 (arom. CH), 102.7 (CH(O)₂), 97.2 (C≡C-TMS), 95.1 (C≡C-TMS), 83.7 (C-2), 80.4 (C-4), 76.4 (C-6), 72.5 (C-5), 68.2 (C-3), 64.0 (C-1), 55.3 (CH₃O), 20.6 (CH₃CO), −0.6 (Si(CH₃)₃). N. B. The CF₃ was not observed.

\(\nu\)max (CHCl₃ cast)/cm⁻¹: 2962 (C-H), 2187 (C=C), 1759 (C=O), 1615 (C=C), 1518 (C=C).

m/z (ES⁺): 579 (MH⁺, 65%), 338 (10), 282 (20), 243 (19), 242 (100).


Further elution afforded diol 195 as a colourless oil (32 mg, 34%).
$R_f$ 0.65 (65:35, EtOAc-petroleum spirit).

$[\alpha]_D^{22} = -84.6$ (c 0.4, CHCl$_3$).

$\delta_F$ (300 MHz; CDCl$_3$) –74.7.

$\delta_H$ (600 MHz; CDCl$_3$) 6.07 (1H, dd, $J$ 17.8, 11.3 , CH=CH$_2$), 5.63 (1H, d, $J$ 11.3, CH=CH$_2$H$_3$), 5.60 (1H, dd, $J$ 17.8, 0.9, CH=CH$_2$H$_0$), 5.21 (1H, t, $J$ 9.8, H-C3), 4.80 (1H, t, $J$ 9.8, H-C2), 4.63 (1H, d, $J$ 9.8, H-C1), 4.10 (1H, d, $J$ 9.8, H-C4), 3.69 (1H, d, $J$ 12.4, H-C6), 3.54 (1H, d, $J$ 12.4, H-C6), 2.18 (3H, s, CH$_3$CO), 0.21 (9H, s, Si(CH$_3$)$_3$).

$\delta_C$ (150 MHz; CDCl$_3$) 171.0 (C=O), 130.5 (CH=CH$_2$), 121.4 (CH=CH$_2$), 118.3 (q, $J$ 319.4, CF$_3$), 94.2 (C≡C-TMS), 94.7 (C≡C-TMS), 83.0 (C-2), 81.8 (C-5), 72.3 (C-3), 69.4 (C-4), 66.5 (C-6), 63.0 (C-1), 20.8 (CH$_3$CO), –0.6 (Si(CH$_3$)$_3$).

$v_{\text{max}}$ (CHCl$_3$ cast)/cm$^{-1}$: 3394 (O-H), 2924 (C-H), 2052 (C≡C), 1758 (C=O).

$m/z$ (FAB+) 483 (M$^+$/Na, 20%), 360 (25), 333 (49), 304 (18), 205 (14), 176 (100).

HRMS: calculated for $C_{16}H_{23}O_8F_3SiSn^+: 483.0733$, found 483.0723. Error 2.01 ppm.
(2,3-Anhydro-4,6-O-(4-methoxybenzylidene-5-C-vinyl)-\(\beta\)-D-mannopyranosyl)ethyne (135b)

To a stirred solution of compound 194 (25 mg, 40 \(\mu\)mol) in anhydrous DCM (0.1 mL) and methanol (50 \(\mu\)L) was added sodium methoxide (12 mg, 230 \(\mu\)mol). The mixture was stirred at room temperature for 12 h and then concentrated \textit{in vacuo}. The crude material was purified using preparative TLC (20:80, EtOAc in petroleum spirit) to give epoxide 135b (8 mg, 63\%) as a colourless oil.

\(R_f\) 0.5 (20:80, EtOAc-petroleum spirit).

\([\alpha]^{25}_{D} = +41.0\) (c 0.1, CHCl\(_3\)).

\(\delta_H\) (600 MHz; CDCl\(_3\)) 7.43 (2H, d, \(J\) 8.7, H-Ar), 6.92 (2H, d, \(J\) 8.7, H-Ar), 6.08 (1H, dd, \(J\) 17.9, 11.3, \(CH=CH_2\)), 5.68 (1H, d, \(J\) 11.3, \(CH=CH_2H_b\)), 5.67 (1H, d, \(J\) 17.9, \(CH=CH_2H_b\)), 5.62 (1H, s, \(CH(O)2\)), 4.98 (1H, t, \(J\) 2.2, H-C1), 4.06 (1H, d, \(J\) 10.1, H-C6), 3.91 (1H, s, H-C4), 3.85 (1H, d, \(J\) 10.1, H-C6), 3.83 (3H, s, CH\(_3\)O), 3.54 (1H, d, \(J\) 3.9, H-C3), 3.34 (1H, dd, \(J\) 3.9, 2.2, H-C2), 2.62 (1H, d, \(J\) 2.2, C\(\equiv\)CH).

\(\delta_C\) (150 MHz; CDCl\(_3\)) 160.3 (arom. C), 134.4 (CH=CH\(_2\)), 129.4 (arom. C), 127.6 (arom. CH), 121.7 (CH=CH\(_2\)), 113.8 (arom. CH), 103.2 (CH(O)\(_2\)), 78.2 (C-4), 78.2 (C\(\equiv\)CH), 75.7 (C-6), 75.2 (C\(\equiv\)CH), 69.9 (C-5), 60.9 (C-1), 55.6 (C-4), 55.3 (CH\(_3\)O), 53.9 (C-3), 51.7 (C-2).

\(\nu_{max}\) (CHCl\(_3\) cast)/cm\(^{-1}\): 3415 (O-H), 2126 (C\(\equiv\)C), 1712 (C=C), 1615 (C=C), 1518 (C=C).

\(m/z\) (EI): 314 (M\(^+\), 80\%), 293 (13), 279 (35), 205 (68), 167 (39), 149 (47), 94 (100).

\textbf{HRMS:} calculated for C\(_{18}\)H\(_{18}\)O\(_5\)\(^+\): 314.1149, found 314.1155. Error 1.9 ppm.
(2,3-Anhydro-5-C-vinyl-β-D-mannopyranosyl)ethyne (202)

To a stirred solution of compound 135b (10 mg, 30 μmol) in THF (50 μL) was added 60% aqueous acetic acid (0.1 mL) and the mixture stirred at room temperature for 5 h. Concentration in vacuo followed by purification using flash chromatography (1:99→5:99, MeOH in DCM) afforded diol 202 (5 mg, 89%) as a colourless oil.

Rf 0.3 (5:95, MeOH in DCM).

[α] D 21 = −31.0 (c 0.1, CHCl3).

δH (400 MHz; CDCl3)  5.98 (1H, dd, J 18.1, 11.3, CH=CH2), 5.65 (1H, d, J 11.3, CH=CH2Hb), 5.58 (1H, d, J 18.1, CH=CH2Hb), 4.87 (1H, br s, H-C1), 4.25 (1H, br s, H-C2), 3.70 (1H, d, J 11.7, H-C6), 3.62 (1H, d, J 11.7, H-C6), 3.41 (1H, d, J 3.8, H-C3), 3.27 (1H, dd, J 3.8, 1.1, H-C4), 2.56 (1H, d, J 1.9, C≡CH).

δC (150 MHz; CDCl3)  133.7 (CH=CH2), 118.3 (CH=CH2), 79.6 (C≡CH), 77.8 (C-5), 74.2 (C≡CH), 68.2 (C-6), 66.5 (C-2), 62.3 (C-1), 55.0 (C-4), 52.2 (C-3).

νmax (CHCl3 cast)/cm⁻¹: 3390 (O-H), 3278 (O-H), 2149 (C≡C), 1722 (C=C).

m/z (CI, CH₄): 197 (MH⁺, 18%), 179 (14), 165 (100), 149 (20), 133 (20).

HRMS: calculated for C10H12O4⁺: 197.0808, found 197.0815. Error 3.4 ppm
1-(4,6-O-(4-Methoxybenzylidene)-5-vinyl-β-D-glucopyranosyl)-2-trimethylsilanylene (182)

To a stirred solution of tetraol 184 (126 mg, 440 μmol) in anhydrous acetonitrile (2.2 mL) and 4 Å molecular sieves (25 mg) was added p-toluenesulfonic acid (8 mg, 40 μmol) followed by p-anisaldehyde dimethyl acetal (0.2 mL, 1.1 mmol). The mixture was stirred at reflux under an inert atmosphere overnight. The solution was quenched with triethylamine (0.1 mL) and concentrated in vacuo to give a viscous oil which was purified by column chromatography (5:95→20:80, EtOAc in petroleum spirit, 0.5% NEt$_3$) to give p-methoxybenzylidene acetal 182 (113 mg, 63%) as a colourless oil.

Rf 0.40 (20:80, EtOAc-petroleum spirit)

[α]$_D^{25}$ = −11.6 (c 0.2, CHCl$_3$).

δ$_H$ (600 MHz; CDCl$_3$)  7.43 (2H, d, J 8.7, H-Ar), 6.91 (2H, d, J 8.7, H-Ar), 6.27 (1H, dd, J 18.0, 11.3, CH=CH$_2$), 5.66 (1H, dd, J 18.0, 0.7, CH=CH$_2$H$_b$), 5.59 (1H, d, J 11.3, CH=CH$_2$H$_a$), 5.58 (1H, s, CH(O)$_2$), 4.44 (1H, d, J 9.7, H-C1), 4.04 (1H, d, J 9.8, H-C6), 3.87 (1H, d, J 9.8, H-C6), 3.82 (1H, t, J 9.4, H-C3), 3.82 (3H, s, CH$_3$O), 3.69-3.64 (2H, m, H-C4 & H-C2), 0.22 (9H, s, Si(CH$_3$)$_3$).

δ$_C$ (150 MHz; CDCl$_3$)  160.3 (arom. C), 134.9 (CH=CH$_2$), 129.3 (arom. C), 127.8 (arom. CH), 119.3 (CH=CH$_2$), 113.7 (arom. CH), 103.1 (CH(O)$_2$), 101.2 (C≡C-TMS), 91.9 (C≡C-TMS), 82.5 (C-4), 77.2 (C-6), 75.8 (C-2), 72.1 (C-5), 70.7 (C-3), 66.2 (C-1), 55.3 (CH$_3$O), 0.1 (Si(CH$_3$)$_3$).

ν$_{max}$ (CHCl$_3$ cast)/cm$^{-1}$: 3404 (O-H), 2179 (C≡C), 1615 (C≡C), 1589 (C≡C), 1518 (C≡C).

m/z (ES$^+$)  427 (MNa$^+$, 100), 406 (20), 405 (MH$^+$, 60), 318 (28), 277 (10), 260 (10), 194 (55).

HRMS: calculated for C$_{21}$H$_{29}$O$_6$Si+: 405.1733, found 405.1748. Error 3.7 ppm.

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1-(4,6-O-(4-Methoxybenzylidene)-2-O-(trifluoromethanesulfonyl)-5-C-vinyl-β-D-glucopyranosyl)-2-trimethylsilany ethyne (186)

1-(4,6-O-(4-Methoxybenzylidene)-3-O-(trifluoromethanesulfonyl)-5-C-vinyl-β-D-glucopyranosyl)-2-trimethylsilany ethyne (185)

To a stirred solution of diol 182 (97 mg, 240 μmol) in anhydrous dichloromethane (0.80 mL) and pyridine (780 μL, 960 μmol) at -15 °C was added triflic anhydride (47 μL, 280 μmol) and the mixture stirred under an inert atmosphere for 1 h. The solution was concentrated in vacuo to give a viscous oil which was purified by preparative TLC (40:60, EtOAc in petroleum spirit, 0.5% NEt₃) to give triflate 185 as a mixture with anisaldehyde. Rₐ 0.80 (40:60, EtOAc-petroleum spirit).

δ_H (600 MHz; CDCl₃) 7.41 (2H, d, J 8.8, H-Ar), 6.92 (2H, d, J 8.8, H-Ar), 6.23 (1H, dd, J 18.1, 11.3, CH=CH₂), 5.69 (1H, dd, J 18.1, 0.8, CH=CH₂H₃b), 5.65 (1H, d, J 11.3, CH=CH₂H₃b), 5.58 (1H, s, CH(O)₂), 4.81 (1H, dd, J 9.8, 9.8, H-C₂), 4.71 (1H, d, J 9.8, H-C₁), 4.08 (1H, d, J 9.9, H-C₆), 4.05 (1H, br t, J 9.8, H-C₃), 3.87 (1H, d, J 9.9, H-C₆), 3.83 (3H, s, CH₃O), 3.66 (1H, d, J 9.8, H-C₄), 2.75 (1H, br s, OH), 0.22 (9H, s, Si(CH₃)₃).

δ_C (150 MHz; CDCl₃) 160.5 (arom. C), 133.8 (CH=CH₂), 128.8 (arom. C), 127.7 (arom. CH), 120.3 (CH=CH₂), 113.8 (arom. CH), 103.2 (CH(O)₂), 97.7 (C≡C-TMS), 94.5 (C≡C-TMS), 86.4 (C-2), 82.2 (C-4), 77.0 (C-6), 72.1 (C-5), 68.7 (C-3), 63.5 (C-1), 55.3 (CH₃O), −0.58 (Si(CH₃)₃). N. B. The CF₃ was not observed.

Triflate 186 was also isolated as a colourless oil. Rₐ 0.67 (40:60, EtOAc-petroleum spirit).

δ_H (600 MHz; CDCl₃) 7.42 (2H, d, J 8.8, H-Ar), 6.91 (2H, d, J 8.8, H-Ar), 6.17 (1H, dd, J 18.1, 11.4, CH=CH₂), 5.72 (1H, dd, J 18.1, 0.8, CH=CH₂H₃b), 5.64 (1H, d, J 11.4, CH=CH₂H₃b), 5.62 (1H, s, CH(O)₂), 4.94 (1H, dd, J 10.5, 8.9, H-C₃), 4.52 (1H, d, J 9.6, H-C₁), 4.08 (1H, d, J 10.0, H-C₆), 3.95-3.88 (3H, m, H-C₂, H-C₄ & H-C₆), 3.83 (3H, s, CH₃O), 2.59 (1H, d, J 4.1, OH), 0.23 (9H, s, Si(CH₃)₃).
$\delta_C$ (150 MHz; CDCl$_3$) 160.2 (arom. C), 133.7 (CH=CH$_2$), 128.7 (arom. C), 127.3 (arom. CH), 121.1 (CH=CH$_2$), 113.6 (arom. CH), 102.4 (CH(O)$_2$), 99.6 (C≡C-TMS), 93.5 (C≡C-TMS), 84.6 (C-3), 79.5 (C-4), 76.5 (C-6), 73.4 (C-2), 72.8 (C-5), 67.0 (C-1), 55.3 (CH$_3$O), −0.28 (Si(CH$_3$)$_3$). N. B. The CF$_3$ was not observed.
2,3,4-Tri-\(O\)-acetyl-1,6-anhydro-5-C-cyano-D-glucose (211)

2,3,4-Tri-\(O\)-acetyl-N-acetyl-5-C-aminocarbonyl-1,6-anhydro-D-glucose (212)

2,3,4-Tri-\(O\)-acetyl-5-C-aminocarbonyl-1,6-anhydro-D-glucose (213)

Using literature procedure\textsuperscript{102}. To a stirred solution of polymer 210 (791 mg) in aq. \(\text{NH}_3\) (25.2 mL, 7.3 mmol, 29\%) and THF (1.9 mL), was added iodine (360 mg, 1.42 mmol) and the mixture was stirred at room temperature for 12 h. After quenching with sat. aq. sodium thiosulphite (1 mL), the mixture was concentrated \textit{in vacuo} and co-evaporated with ethanol (3 \(\times\) 50 mL) to give the crude material. The crude material was dissolved in anhydrous pyridine (4 mL) at room temperature and acetic anhydride (1 mL, 10.6 mmol) was then added. The mixture was stirred for a further 12 h then diluted with EtOAc (20 mL). The organic material was washed with water (4 mL), dried (\(\text{MgSO}_4\)) and concentrated \textit{in vacuo} to give a mixture of compounds which was purified by column chromatography using silica gel (1:99 \(\rightarrow\) 40:60, EtOAc in petroleum spirit) to give nitrile 211 as a yellow coloured solid (95 mg).

**m.p.** (EtOAc) 142-145 °C.

**\(R_f\)** 0.77 (65:35, EtOAc-petroleum spirit).

\([\alpha]_D^{22} = -18.4 (c 0.6, \text{CHCl}_3)\).

\(\delta_h\) (600 MHz; \(\text{CDCl}_3\)) 5.66 (1H, br s, \(H\)-C1), 5.06 (1H, br s, \(H\)-C4), 4.86 (1H, br s, \(H\)-C3), 4.61 (1H, br s, \(H\)-C2), 4.46 (1H, d, \(J 7.9\), \(H\)-C6), 4.09 (1H, d, \(J 7.9\), \(H\)-C6), 2.28 (3H, s, \(\text{CH}_3\text{CO}\)), 2.174 (3H, s, \(\text{CH}_3\text{CO}\)), 2.167 (3H, s, \(\text{CH}_3\text{CO}\)).

\(\delta_c\) (150 MHz; \(\text{CDCl}_3\)) 169.6 (\(\text{CH}_3\text{CO}\)), 169.3 (\(\text{CH}_3\text{CO}\)), 169.0 (\(\text{CH}_3\text{CO}\)), 113.5 (\(\text{C} \equiv \text{N}\)), 100.8 (C-1), 74.0 (C-5), 69.2 (C-4), 69.1 (C-3), 68.7 (C-6), 67.2 (C-2), 20.8, 20.7, 20.6 (3 \(\times\) \(\text{CH}_3\text{CO}\)).
$\nu_{\text{max}}$ (CHCl$_3$ cast)/cm$^{-1}$: 1739 (C=O). N. B. (C≡N) stretch was not observed.

$m/z$ (CI+, CH$_4$): 314 (14%, MH$^+$), 272 (23), 254 (100), 212 (30), 152 (13), 103 (19).

HRMS: calculated for C$_{13}$H$_{16}$NO$_8$: 314.0876, found 314.0881. Error 1.7 ppm.

Further elution gave imide 212 as a brown viscous oil (54 mg).

$R_f$ 0.35 (65:35, EtOAc-petroleum spirit).

$[\alpha]_D^{20} = -33.2$ (c 0.5, CHCl$_3$).

$\delta$H (600 MHz; CDCl$_3$) 5.67 (1H, br s, H-C1), 5.24 (1H, s, H-C4), 4.88 (1H, br q, J 1.13, H-C3), 4.59 (1H, br s, H-C2), 4.43 (1H, d, J 8.3, H-C6), 3.78 (1H, d, J 8.3, H-C6), 2.47 (3H, s, CH$_3$CO), 2.16 (3H, s, CH$_3$CO), 2.15 (3H, s, CH$_3$CO), 2.11 (3H, s, CH$_3$CO).

$\delta$C (150 MHz; CDCl$_3$) 171.2 (CO), 169.4 (CO), 168.9 (CO), 168.5 (CO), 166.1 (CO), 100.9 (C-1), 81.9 (C-5), 69.5 (C-4), 69.2 (C-3), 67.9 (C-6), 67.6 (C-2), 25.4, 20.8, 20.8, 20.6 (4 × CH$_3$CO).

$v_{\text{max}}$ (CHCl$_3$ cast)/cm$^{-1}$: 3326 (N-H), 1739 (C=O), 1713 (C=O).

$m/z$ (ES$^+$) 396 (100%, MNa$^+$), 196 (12).

HRMS: calculated for C$_{15}$H$_{19}$NO$_{10}$Na$: 396.0912, found 396.0907. Error 1.3 ppm.

Further elution gave amide 213 as a brown viscous oil (162 mg).

$R_f$ 0.25 (65:35, EtOAc-petroleum spirit).

$[\alpha]_D^{25} = -14.4$ (c 0.2, CHCl$_3$).

$\delta$H (600 MHz; CDCl$_3$) 6.55 (1H, br s, H-C1), 5.98 (1H, br s, CONH$_2$), 5.64 (1H, s, H-C1), 5.28 (1H, s, H-C4), 4.88 (1H, s, H-C3), 4.59 (1H, s, H-C2), 4.42 (1H, d, J 8.2, H-C6), 3.77 (1H, d, J 8.2, H-C6), 2.15 (3H, s, CH$_3$CO), 2.14 (3H, s, CH$_3$CO), 2.12 (3H, s, CH$_3$CO).

$\delta$C (150 MHz; CDCl$_3$) 169.4 (CH$_3$CO), 169.1 (CONH$_2$), 169.0 (CH$_3$CO), 168.6 (CH$_3$CO), 100.7 (C-1), 81.7 (C-5), 69.8 (C-4), 69.1 (C-3), 68.2 (C-6), 67.9 (C-2), 20.9, 20.8, 20.7 (3 × CH$_3$CO).

$v_{\text{max}}$ (CHCl$_3$ cast)/cm$^{-1}$: 3371 (O-H), 1745 (C=O), 1693 (C=O), 1667 (C=O).

$m/z$ (ES$^-$) 330 (100, M$^-$), 288 (20), 276 (13), 270 (30).

HRMS: calculated for C$_{15}$H$_{19}$NO$_9$: 330.0825, found 330.0839. Error 4.2 ppm.
1,6-Anhydro-5-C-formyl-2,4-bis-O-triethylsilyl-β-D-glucopyranose (208)

Ozone was bubbled through a solution of alkene 138b (100 mg, 240 μmol) in dichloromethane (2.4 mL) at −78 °C for 5 min. Then O₂ was bubbled through the solution to remove excess ozone. The mixture was left to warm to room temperature and triethylamine (2 mL) was added. The mixture was stirred for a further 1 h and concentrated in vacuo to give a residue, which was purified by column chromatography (10:90→20:80, EtOAc in petroleum spirit & 1% NEt₃) to give aldehyde 208 as a colourless viscous oil (65 mg, 65%).

Rᵣ 0.37 (20:80, EtOAc-petroleum spirit).

[α]D²⁰ = −2.8 (c 1.2, chloroform).

δH (600 MHz; CDCl₃) 9.86 (1H, s, CHO), 5.51 (1H, br s, H-C1), 4.10 (1H, d, J 7.9, H-C6), 4.06 (1H, br s, H-C4), 3.68 (1H, qd, J 6.1, 1.7, H-C3), 3.52-3.54 (2H, m, H-C6 & H-C2), 2.03 (1H, d, J 7.9, OH), 1.00 (9H, t, J 8.0, (CH₃CH₂)₃Si), 0.96 (9H, t, J 8.0, (CH₃CH₂)₃Si), 0.68 (6H, q, J 8.0, (CH₃CH₂)₃Si), 0.63 (6H, q, J 8.0, (CH₃CH₂)₃Si).

δC (150 MHz; CDCl₃) 199.8 (C=O), 104.0 (C-1), 86.5 (C-5), 76.3 (C-3), 73.7 (C-4), 71.9 (C-2), 65.7 (C-6), 6.8, 6.8 (2 × CH₃CH₂), 4.7, 4.6 (2 × CH₃-CH₂).

νmax (CH₂Cl₂ cast)/cm⁻¹: 3454 (O-H), 2955 (C-H), 1738 (C=O).

m/z (FAB+): 441 (58, MNa⁺), 369 (19), 323 (22), 301 (15), 173 (100).

HRMS: calculated for C₁₉H₃₈O₆Si₂Na⁺: 441.2104, found: 441.2088. Error 3.8 ppm.
1,6-Anhydro-5-C-cyano-2,4-bis-O-triethylsilyl-β-D-glucose (138c)

Using literature procedure\textsuperscript{110}. To a stirred solution of aldehyde 208 (217 mg, 520 μmol) and copper (49 mg, 0.8 mmol) in pyridine (0.5 mL) was added ammonium chloride (55 mg, 1 mmol) and the mixture stirred under oxygen at room temperature overnight. Sodium hydroxide (1M, 2 mL) was added and the mixture stirred for a further 30 min. The mixture was filtered through Celite and the filtrate was diluted with ethyl acetate (30 mL) and washed with water (10 mL). The organic material was dried (MgSO\textsubscript{4}), concentrated \textit{in vacuo}, and purified by column chromatography using activated neutral alumina (10:90→20:80, EtOAc in petroleum spirit) to afford the desired nitrile 138c as a white solid (91 mg, 42%).

\textbf{m.p.} (EtOAc) 43-45 °C.

$\alpha$\textsuperscript{20} D = −15.4 (c 0.5, chloroform).

$\delta$\textsubscript{H} (400 MHz; CDCl\textsubscript{3}) 5.44 (1H, t, J 1.5, H-C1), 4.29 (1H, d, J 7.5, H-C6), 3.93 (1H, d, J 7.5, H-C6), 3.81 (1H, td, J 2.4, 0.7, H-C4), 3.67 (1H, br s, H-C3), 3.48 (1H, ddd, J 2.2, 1.5, 1.0, H-C2), 2.08 (1H, br d, J 5.5, OH), 1.04 (9H, t, J 7.9, Si(CH\textsubscript{3}CH\textsubscript{2})\textsubscript{3}), 0.98 (9H, t, J 7.9, Si(CH\textsubscript{3}CH\textsubscript{2})\textsubscript{3}), 0.74 (6H, q, J 7.9, 1.8, Si(CH\textsubscript{3}CH\textsubscript{2})\textsubscript{3}), 0.65 (6H, q, J 7.9, Si(CH\textsubscript{3}CH\textsubscript{2})\textsubscript{3}).

$\delta$\textsubscript{C} (100 MHz; CDCl\textsubscript{3}) 115.4 (C=N), 104.5 (C-1), 76.8 (C-5), 75.2 (C-3), 73.5 (C-4), 71.5 (C-2), 68.9 (C-6), 6.8, 6.7 (2 × CH\textsubscript{3}-CH\textsubscript{2}), 4.7, 4.6 (2 × CH\textsubscript{3}-CH\textsubscript{2}).

$\nu$\textsubscript{max} (CH\textsubscript{2}Cl\textsubscript{2} cast)/cm\textsuperscript{−1}: 3473 (O-H), 2955 (C-H). N. B. (C≡N) stretch was not observed.

$\textit{m/z}$ (ES\textsuperscript{+}): 438 (40, MNa\textsuperscript{+}), 413 (10), 236 (10).

\textbf{HRMS}: calculated for C\textsubscript{19}H\textsubscript{37}NO\textsubscript{5}Si\textsubscript{2}Na\textsuperscript{+}: 438.2090, found: 438.2108. Error 4.1 ppm.
Using literature procedure\textsuperscript{111}. Trimethylsilylacetylene (1.60 mL, 5.6 mmol) was dissolved in toluene (4.6 mL) and the mixture cooled to \(-20\) °C. \(n\)-BuLi (2.5 M in hexane, 2.24 mL, 5.6 mmol) was then added dropwise. Stirring was continued at room temperature for 45 min. THF (1 mL) was added dropwise and the resulting solution was added dropwise to a suspension of freshly sublimed AlCl\(_3\) (744 mg, 5.6 mmol) in toluene (3.49 mL). The mixture was heated at 50 °C in an ultrasound bath for 2 h, followed by heating at 60 °C. A solution of 138c (385 mg, 0.9 mmol) and 2,4,6-trimethylpyridine (80 \(\mu\)L, 1 mmol) in toluene (0.56 mL) was then added dropwise to this heated mixture. The reaction mixture was then heated at 120 °C for 7 days, cooled to 0 °C and poured into ice-cold water (5 mL). The organic compound was extracted with EtOAc (5 \(\times\) 50 mL) and the organic material was dried (MgSO\(_4\)) and concentrated \textit{in vacuo} to give an oil which was purified by column chromatography using activated alumina (2:98 \(\rightarrow\) 20:80, EtOAc in petroleum spirit) to give alkyne 218 as a colourless viscous oil (334 mg, 70%).

\(R_f\) 0.75 (20:80, EtOAc-petroleum spirit).

\([\alpha]_D^{20}\) = \(-27.9\) (c 0.6, CHCl\(_3\)).

\(\delta_H\) (600 MHz; CDCl\(_3\)) 4.39 (1H, d, J 9.5, H-C1), 3.98 (1H, dd, J 12.0, 6.0, H-C6), 3.83 (1H, dd, J 12.0, 9.0, H-C6), 3.69 (1H, d, J 8.5, H-C4), 3.63 (1H, td, J 8.5, 3.3, H-C3), 3.49 (1H, dd, J 9.5, 8.5, H-C2), 2.23 (1H, dd, J 9.0, 6.0, CH\(_2\)OH), 2.25 (1H, d, J 3.3, CHO\(_H\)), 1.02 (9H, t, J 7.0, Si(CH\(_3\)CH\(_2\))\(_3\)), 0.99 (9H, t, J 7.0, Si(CH\(_3\)CH\(_2\))\(_3\)), 0.77-0.65 (12H, m, 2\(\times\)Si(CH\(_3\)CH\(_2\))\(_3\)), 0.21 (9H, s, Si(CH\(_3\))\(_3\)).

\(\delta_C\) (150 MHz; CDCl\(_3\)) 115.6 (C\(\equiv\)N), 100.9 (C\(\equiv\)C-TMS), 92.5 (C\(\equiv\)C-TMS), 79.4 (C-5), 76.6 (C-3), 74.4 (C-2), 70.0 (C-4), 69.6 (C-1), 64.3 (C-6), 6.9 (CH\(_2\)-CH\(_3\)), 6.8 (CH\(_2\)-CH\(_3\)), 5.3 (CH\(_3\)-CH\(_2\)), 5.1 (CH\(_3\)-CH\(_2\)), –0.4 (CH\(_3\)).

\(\nu_{max}\) (CHCl\(_3\) cast)/cm\(^{-1}\): 3526 (O-H), 1459 (C-H). N. B. (C\(\equiv\)N) stretch was not observed.

\(m/z\) (ES) 513 (50), 512 (MH\(^+\), 100), 398 (20), 309 (10), 255 (20), 241 (10), 215 (20).

HRMS: calculated for C\(_{24}\)H\(_{46}\)NO\(_5\)Si\(_3\)\(^+\): 512.2703, found 512.2684. Error 3.7 ppm
1-(5-Cyano-2,4,6-tris-O-(triethylsilanyl)-β-D-glucopyranosyl)-2-trimethylsilanylethynyl (219)

To a stirred solution of diol 218 (285 mg, 550 μmol) in DCM (1.1 mL) at 0 °C under argon was added pyridine (130 μL, 1.6 mmol) followed by TESCl (0.1 mL, 550 μmol). The mixture was warmed to room temperature and left stirring for 2 h. After reaction completion, the mixture was diluted with DCM (10 mL) and the organic material washed with water (1 × 2 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo to give the crude product which was purified by column chromatography using activated alumina (1:99→10:90, EtOAc in petroleum spirit) to give tris-silyl ether 219 as a colourless viscous oil (287 mg, 83%).

Rₜ 0.82 (20:80, EtOAc-petroleum spirit).

[α]D²⁰ = −31.8 (c 0.4, CHCl₃).

δH (600 MHz; CDCl₃) 4.31 (1H, d, J 9.5, H-C1), 3.93 (2H, s, H-C6), 3.75 (1H, d, J 9.4, H-C4), 3.61 (1H, ddd, J 9.4, 8.6, 3.3, H-C3), 3.46 (1H, dd, J 9.5, 8.6, H-C2), 2.22 (1H, d, J 3.3, OH), 1.05-0.95 range (27H, m, 3×Si(CH₃CH₂)₃), 0.79-0.61 (18H, m, 3×Si(CH₃CH₃)₃), 0.18 (9H, s, Si(CH₃)₃).

δC (150 MHz; CDCl₃) 115.9 (C=N), 101.4 (C≡C-TMS), 91.7 (C≡C-TMS), 79.9 (C-5), 76.7 (C-3), 74.4 (C-2), 69.6 (C-4), 69.2 (C-1), 64.4 (C-6), 6.9, 6.8, 6.7 (3×CH₂-CH₃), 5.3, 5.0, 4.5 (3×CH₂-CH₂), 0.5 (CH₃).

νmax (CHCl₃ cast)/cm⁻¹: 3516 (O-H), 1459 (C-H). N. B. (C≡N) stretch was not observed.

m/z (ES−): 628 (30), 627 (55), 626 (M-H, 100), 513 (10), 512 (30), 309 (15).

HRMS: calculated for C₃₀H₆₀NO₅Si₄⁺: 626.3549, found 626.3521. Error 4.5 ppm.
1-(3-O-Acetyl-5-C-cyano-2,4,6-tris-O-(triethylsilanyl-β-D-glucopyranosyl))-2-trimethylsilanylethyne (137c)

To a stirred solution of alcohol 219 (237 mg, 0.4 mmol) in anhydrous triethylamine (760 μL) at 0 °C under argon was added 4-pyrroldinopyridine (28 mg, 0.2 mmol) followed by acetic anhydride (0.21 mL, 2.3 mmol). The mixture was warmed to room temperature and left stirring for 3 h. The mixture was diluted with DCM (4 mL) and the organic material washed with water (1 × 2 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo to give an oil which was purified by column chromatography using activated alumina (5:95→50:50, DCM in petroleum spirit) to give acetate 137c as a colourless viscous oil (180 mg, 70%).

R_f 0.54 (50:50, DCM-petroleum spirit).

[α]_D²⁰ = −53.3 (c 0.8, CHCl₃).

δ_H (600 MHz; CDCl₃) 5.19 (1H, t, J 9.5, H-C3), 4.38 (1H, d, J 9.5, H-C1), 3.96-3.92 (3H, m, H-C4 & H-C6), 3.59 (1H, t, J 9.5, H-C2), 2.16 (3H, s, CH₃CO), 1.05-0.96 (27H, m, 3×Si(CH₃CH₂)₃), 0.70-0.55 (18H, m, 3×Si(CH₃CH₂)₃), 0.19 (9H, s, Si(CH₃)₃).

δ_C (150 MHz; CDCl₃) 169.0 (C=O), 115.5 (C≡N), 101.4 (C≡C-TMS), 92.2 (C≡C-TMS), 79.8 (C-5), 76.5 (C-3), 73.0 (C-2), 69.6 (C-1), 68.1 (C-4), 64.1 (C-6), 21.6 (CH₃CO), 6.8, 6.7 (2×Si(CH₃CH₂)₃), 5.3, 5.0, 4.5 (3×Si(CH₃CH₂)₃), −0.5 (Si(CH₃)₃).

ν_max (CHCl₃ cast)/cm⁻¹: 2955 (C-H), 1761 (C=O). N. B. (C≡N) stretch was not observed.

m/z (ES⁺): 670 (MH⁺,100%), 611 (15), 539 (18), 478 (20), 448 (20).

HRMS: calculated for C₃₂H₆₄NO₆Si₄⁺: 670.3842, found 670.3811. Error 4.6 ppm.
1-(3-0-Acetyl-5-C-cyano-4-0-(triethylsilanyl)-β-D-glucopyranosyl)-2-trimethylsilanylethyne (220)

To a stirred solution of tris-silyl ether 137c (302 mg, 450 μmol) in tetrahydrofuran (1.5 mL) at room temperature was added water (4.5 mL) followed by acetic acid (13.5 mL) and the mixture was stirred for 12 h. The mixture was concentrated in vacuo to give an oil which was purified by column chromatography (1:99→10:90, MeOH in DCM) to afford diol 220 as a colourless oil (166 mg, 84%).

Rf 0.42 (20:80, EtOAc-petroleum spirit)

[α]$_D^{20}$ = −74.9 (c 0.5, CHCl$_3$).

δ$_H$ (400 MHz; CDCl$_3$) 5.12 (1H, t, $J$ 9.8, H-C3), 4.52 (1H, d, $J$ 9.8, H-C1), 4.04-3.97 (2H, m, H-C6 & H-C4), 3.85 (1H, dd, $J$ 12.2, 9.9, H-C6), 3.54 (1H, td, $J$ 9.8, 5.1, H-C2), 2.67 (1H, d, $J$ 5.1, CHO), 2.24 (1H, dd, $J$ 9.9, 5.4, CH$_3$OH), 2.19 (3H, s, CH$_3$CO), 0.98 (9H, t, $J$ 7.8, Si(CH$_3$CH$_2$)$_3$), 0.65 (6H, q, $J$ 7.8, Si(CH$_3$CH$_2$)$_3$), 0.21 (9H, s, Si(CH$_3$)$_3$).

δ$_C$ (100 MHz; CDCl$_3$) 171.4 (C=O), 115.0 (C≡N), 98.9 (C≡C-TMS), 93.9 (C≡C-TMS), 79.6 (C-5), 76.6 (C-3), 72.6 (C-2), 69.5 (C-1), 68.0 (C-4), 63.7 (C-6), 21.1 (CH$_3$CO), 6.6 (Si(CH$_3$CH$_2$)$_3$), 5.0 (Si(CH$_3$CH$_2$)$_3$), −0.3 ((CH$_3$)$_3$Si).

ν$_{max}$ (CHCl$_3$ cast)/cm$^{-1}$: 3478 (O-H), 2958 (C-H), 1755 (C=O). N. B. (C≡N) stretch was not observed.

m/z (ES-) 440 (M-H, 100%), 434 (20), 398 (50), 326 (28), 286 (20).

HRMS: calculated for C$_{20}$H$_{34}$NO$_6$Si$_2$: 440.1934, found 440.1925. Error 2.0 ppm.
1-(3-O-Acetyl-5-C-cyano-4-O-(triethylsilanyl)-2,6-O-trifluoromethanesulfonyl-β-D-glucopyranosyl)-2-trimethylsilanylethyne (222)

To a stirred solution of diol 220 (108 mg, 250 μmol) in DCM (0.8 mL) at −15 °C was added pyridine (80 μL, 750 μmol) followed by trifluoromethanesulfonic anhydride (130 μL, 750 μmol). The mixture was allowed to warm to room temperature and stirred for 12 h. The mixture was diluted with dichloromethane (5 mL) and the organic material washed with water (2 mL). The organic material was dried (MgSO₄) and concentrated in vacuo to give the crude product which was purified by column chromatography (10:90→50:50, DCM in petroleum spirit) to afford ditriflate 222 as a colourless viscous oil, (147 mg, 83%).

R<sub>f</sub> 0.70 (50:50, DCM-petroleum spirit).

[α]<sub>B</sub><sup>20</sup> = −50.0 (c 1.1, CHCl₃).

δ<sub>H</sub> (600 MHz; CDCl₃) 5.49 (1H, ddd, J 9.3, 7.8, 1.5, H-C3), 4.80-4.73 (3H, m, H-C1 & H-C2 & H-C6), 4.58 (1H, d, J 11.0, H-C6), 3.93 (1H, d, J 9.3, H-C4), 2.20 (3H, s, CH₃CO), 0.99 (9H, t, J 7.9, Si(CH₃CH₂)₃), 0.61-0.69 (6H, m, Si(CH₃CH₂)₃), 0.21 (9H, s, Si(CH₃)₃).

δ<sub>C</sub> (150 MHz; CDCl₃) 168.8 (C=O), 119.3 (q, J 319.3, CF₃), 117.3 (q, J 319.3, CF₃), 112.0 (C=N), 97.6 (C≡C-TMS), 94.4 (C≡C-TMS), 80.4 (C-2), 77.4 (C-5), 72.3 (C-6), 71.7 (C-3), 69.7 (C-4), 66.7 (C-1), 21.0 (CH₃CO), 6.5 (Si(CH₃CH₂)₃), 5.0 (Si(CH₃CH₂)₃), −0.9 (Si(CH₃)₃).

ν<sub>max</sub> (CHCl₃ cast)/cm<sup>−1</sup>: 2963 (C-H), 1755 (C=O). N. B. (C≡N) stretch was not observed.

m/z (FAB<sup>+</sup>): 706 (MH<sup>+</sup>, 12%), 676 (22), 556 (20), 468 (13), 337 (10), 289 (19), 256 (23), 227 (26), 176 (83).

HRMS: calculated for C<sub>22</sub>H<sub>34</sub>O<sub>10</sub>N<sub>2</sub>F<sub>6</sub>Si<sub>2</sub>: 706.1067, found 706.1082. Error 2.2 ppm.
(5-Cyano-1,2-dideoxy-4-O-triethylsilyl-6-O-trifluoromethanesulfonyl-D-arabino-hex-1-enopyranosyl)ethyne (225)

To a stirred solution of ditriflate 222 (7 mg, 10 μmol) in DCM (30 μL) at room temperature was added methanol (10 μL) followed by sodium methoxide (3 mg, 40 μmol) and the mixture was stirred for 12 h. The reaction mixture was concentrated in vacuo and purified by column chromatography (5:95→20:80, EtOAc in petroleum spirit) to afford enyne 225 as a colourless oil (2 mg, 41%).

R_f 0.49 (20:80, EtOAc-petroleum spirit)

[α]_D^20 = +22.6 (c 0.1, CHCl_3)

δ_H (600 MHz; CDCl_3)  5.46 (1H, br d, J 6.1, H-C2), 4.48 (1H, d, J 11.3, H-C6), 4.42 (1H, d, J 4.6, 1.2, H-C4), 4.38 (1H, d, J 11.3, H-C6), 4.11 (1H, dd, J 6.1, 4.6, H-C3), 3.08 (1H, s, C≡CH), 1.01 (9H, t, J 8.0, Si(CH_3CH_2)_3), 0.71 (6H, m, Si(CH_3CH_2)_3).

δ_C (150 MHz; CDCl_3) 137.7 (C-1), 115.4 (C≡N), 107.0 (C-2), 79.3 (C-5), 77.3 (C-6), 76.2 (C≡C-H), 76.1 (C≡C-H), 70.4 (C-3), 69.4 (C-4), 6.6 (Si(CH_3CH_2)_3), 4.7 (Si(CH_3CH_2)_3). N. B. CF_3 does not appear.

ν_max (CHCl_3 cast)/cm^{-1}: 3299 (O-H), 2852 (C-H), 1625 (C=C). N. B. (C≡N) stretch was not observed.

m/z (Cl^+, CH_4): 442 (MH^+, 5%), 391 (25), 338 (20), 282 (100), 262 (53), 225 (40), 196 (61), 172 (38).

HRMS: calculated for C_{16}H_{23}O_{6}NSF_3Si: 442.0967, found 442.0978. Error 2.4 ppm.
(5-C-cyano-\(\beta\)-D-glucopyranosyl)ethyne (226)

![Reaction Scheme]

To a stirred solution of tris-silyl ether 137c (35 mg, 50 \(\mu\)mol) in tetrahydrofuran (0.2 mL) was added tetrabutylammonium fluoride (1M solution in THF, 310 \(\mu\)L, 310 \(\mu\)mol) at room temperature. The mixture was stirred overnight and concentrated in \textit{vacuo} to give a brownish oil which was purified by column chromatography (1:99 \(\rightarrow\) 10:90, MeOH in DCM) to give tetraol 226 as a colourless oil, (6 mg, 54%).

\(R_f\) 0.10 (10:90, MeOH-DCM).

\([\alpha]_{D}^{21} = -49.6\) (c 0.9, EtOH).

\(\delta_H\) (600 MHz; CD\(_3\)OD) 4.21 (1H, dd, \(J\) 9.4, 2.2, \(H\)-C1), 3.89 (1H, d, \(J\) 12.2, \(H\)-C6), 3.73 (1H, d, \(J\) 12.2, \(H\)-C6), 3.48 (1H, t, \(J\) 9.4, \(H\)-C3), 3.42 (1H, d, \(J\) 9.4, \(H\)-C4), 3.31 (1H, t, \(J\) 9.4, \(H\)-C2), 2.97 (1H, d, \(J\) 2.2, C\(\&\)C-H).

\(\delta_C\) (150 MHz; CD\(_3\)OD) 115.9 (C\(\&\)N), 80.5 (C-5), 79.1 (C\(\&\)C-H), 75.1 (C\(\&\)C-H), 74.8 (C-3), 73.0 (C-2), 69.5 (C-4), 68.8 (C-1), 63.9 (C-6).

\(\nu_{max}\) (film)/cm\(^{-1}\): 3280 (O-H), 2928 (C-H), 2129 (C\(\&\)C). N. B. (C\(\&\)N) stretch was not observed.

\(m/z\) (ES-): 212 (M-H, 15%), 188 (25), 156 (100).

**HRMS:** calculated for C\(_9\)H\(_{10}\)NO\(_5\): 212.0564, found 212.0559. Error 2.4 ppm.
(3-O-Acetyl-5-C-cyano-β-D-glucopyranosyl)ethyne (221)

To a stirred solution of tris-silyl ether 137c (380 mg, 0.6 mmol) in tetrahydrofuran (1.9 mL) at room temperature was added acetic acid (3 mL) followed by tetrabutylammonium fluoride (1M solution in THF, 6.8 mL, 6.8 mmol) and the mixture stirred for 12 h. The resulting solution was concentrated in vacuo to give the crude material. The crude material was dissolved in ethyl acetate (20 mL), washed with 1M HCl (1 × 5 mL), dried (MgSO₄) and concentrated in vacuo to give a viscous oil which was purified by column chromatography (1:99→10:90, MeOH in DCM) to give triol 221 as a colourless oil, (60 mg, 41%).

Rf 0.34 (10:90, MeOH-DCM).

[α]D²⁵ = −67.2 (c 0.1, EtOH).

δH (600 MHz; CDCl₃)  5.09 (1H, t, J 9.8, H-C3), 4.54 (1H, dd, J 9.8, 2.2, H-C1), 4.06 (1H, d, J 12.1, H-C6), 3.99 (1H, d, J 12.1, H-C6), 3.86 (1H, d, J 9.8, H-C4), 3.72 (1H, t, J 9.8, H-C2), 2.68 (1H, d, J 2.2, C≡C-H), 2.14 (3H, s, CH₃CO).

δC (150 MHz, CD₃OD)  173 (C=O), 114.9 (C≡N), 79.3 (C-5), 77.9 (C≡C-H), 77.2 (C≡C-H), 76.6 (C-3), 71.4 (C-2), 69.2 (C-4), 68.9 (C-1), 64.5 (C-6), 21.0 (CH₃CO).

νmax (film)/cm⁻¹: 3387 (O-H), 3282 (O-H), 2943 (C-H), 2130 (C≡C), 1720 (C=O). N. B. (C≡N) stretch was not observed.

m/z (ES−): 254 (M–H, 33%), 212 (35), 171 (100).

HRMS: calculated for C₁₁H₁₂NO₆: 254.0678, found 254.0665. Error 5.1 ppm.
To a stirred solution of triol 221 (150 mg, 0.6 mmol) in dimethylformamide (2.9 mL) was added \( p \)-methoxybenzaldehyde dimethylacetal (214 mg, 1.2 mmol) followed by camphorsulfonic acid (20 mg, 0.2 mmol) and the mixture was stirred at 65 \( ^\circ \)C for 12 h. Concentration of the resulting solution \textit{in vacuo} gave an oil which when purified by column chromatography (1:99, \( \text{NEt}_3 \) in petroleum ether then 100\% toluene, then 100\% dichloromethane, then 1:99→5:95, MeOH in DCM) gave acetate 227 as a colourless oil (140 mg, 63\%).

R\(_f\) 0.63 (10:90, MeOH-DCM).

\([\alpha]_D^{22} = -66.4\) (c 0.1, CHCl\(_3\)).

\(\delta_H\) (600 MHz; CDCl\(_3\)) 7.43 (2H, d, J 8.7, H-Ar), 6.92 (2H, d, J 8.7, H-Ar), 5.53 (1H, s, CH(O)\(_2\)), 5.34 (1H, dd, J 10.2, 9.7, H-C3), 4.69 (1H, dd, J 9.7, 2.1, H-C1), 4.50 (1H, d, J 10.8, H-C6), 3.90 (1H, d, J 10.8, H-C6), 3.83 (3H, s, CH\(_3\)O), 3.80 (1H, t, J 9.7, H-C2), 3.77 (1H, d, J 10.2, H-C4), 2.69 (1H, d, J 2.1, C\(\equiv\)C-H), 2.14 (3H, s, CH\(_3\)CO).

\(\delta_C\) (150 MHz; CDCl\(_3\)) 171.3 (C=O), 160.7 (arom. C), 128.0 (arom. CH), 127.9 (arom. C), 115.4 (C\(\equiv\)N), 113.8 (arom. CH), 103.2 (CH(O)\(_2\)), 78.6 (C-4), 77.9 (C\(\equiv\)C-H), 76.3 (C\(\equiv\)C-H), 73.1 (C-2), 72.5 (C-3), 71.2 (C-6), 70.7 (C-5), 69.8 (C-1), 55.3 (CH\(_3\)O), 20.9 (CH\(_3\)CO).

\(v_{\max}\) (CHCl\(_3\) cast)/cm\(^{-1}\): 3396 (O-H), 2935 (C-H), 2131 (C\(\equiv\)C), 1749 (C=O), 1647 (C=C), 1615 (C=C), 1519 (C=C). N. B. (C\(\equiv\)N) stretch was not observed.

\(m/z\) (ES\(^+\)): 396 (M+Na, 80\%), 374 (M+H, 100), 349 (18), 224 (19), 213 (29).

\textbf{HRMS:} calculated for C\(_{19}\)H\(_{19}\)NO\(_7\)Na\(^+\): 396.1043, found 396.1059. Error 2.6 ppm.
(2,3-Anhydro-5-C-cyano-4,6-O-(4-methoxybenzylidene)-β-D-mannopyranosyl)ethyne (135c)

\[
\begin{align*}
&\text{PMP} \quad \text{O} \quad \text{O} \quad \text{PMP} \\
&\text{O} \quad \text{C} \quad \text{OH} \\
&\text{AcO} \\
&\text{CN} \\
&\text{OH} \\
&227 \\
\end{align*}
\]

To a stirred solution of alcohol 227 (220 mg, 0.6 mmol) in anhydrous dichloromethane (5.8 mL) and pyridine (0.4 mL, 4.6 mmol) at -20 °C was added trifluoromethanesulfonic anhydride (0.2 mL, 1.2 mmol) and the mixture stirred for a further 1 h at the same temperature. Concentration of the resulting mixture gave the crude material which was re-dissolved in diethyl ether and filtered through celite. The filtrate was concentrated in vacuo and the resultant viscous oil (210 mg) was dissolved in a mixture of DCM:MeOH (3:1, 4 mL), treated with sodium methoxide (100 mg, 1.8 mmol) and stirred at room temperature for a further 10 h. The mixture was concentrated in vacuo and purified by column chromatography (1:99, NEt₃ in petroleum ether then 2:98→15:95, EtOAc in petroleum ether) to give epoxide 135c as a colourless oil (57 mg, 32% over two steps). \( R_f 0.22 \) (20:80, EtOAc-petroleum ether). 

\( [\alpha]_D^{19} = +27.4 \) (c 0.1, CHCl₃).

\( \delta_H \) (600 MHz; CDCl₃) 7.48 (2H, d, J 8.7, H-Ar), 6.95 (2H, d, J 8.7, H-Ar), 5.60 (1H, s, CH(O)₂), 5.21 (1H, t, J 2.1, H-C1), 4.44 (1H, d, J 10.9, H-C6), 3.89 (1H, d, J 10.9, H-C6), 3.86 (1H, s, H-C4), 3.84 (3H, s, CH₃O), 3.64 (1H, d, J 3.8, H-C3), 3.58 (1H, dd, J 3.8, 2.1, H-C2), 2.72 (1H, d, J 2.3, C≡C-H).

\( \delta_C \) (150 MHz; CDCl₃) 160.7 (arom. C), 127.9 (arom. C), 127.9 (arom. CH), 115.7 (C≡N), 113.9 (arom. CH), 103.7 (CH(O)₂), 76.6 (C≡C-H), 76.3 (C-4), 76.0 (C≡C-H), 71.0 (C-6), 68.8 (C-5), 64.3 (C-1), 55.4 (CH₃O), 53.3 (C-3), 51.3 (C-2).

\( \nu_{\text{max}} \) (CHCl₃ cast)/cm⁻¹: 2925 (C-H), 1615 (C=C), 1519 (C=C). N. B. (C≡N) stretch was not observed.

\( m/z \) (CI⁺, CH₄) 337 (M+Na, 14%), 314 (M+H, 7), 204 (7), 136 (100).

HRMS: calculated for C₁₇H₁₆NO₅: 314.1028, found 314.1032. Error 1.2 ppm.
(3-Azido-3-deoxy-5-C-cyano-4,6-O-(4-methoxybenzylidene)-β-D-altropyranosyl)ethyne (134c)

Using literature procedure. To a stirred solution of epoxide 135c (5 mg, 15 μmol) in acetonitrile (0.4 mL) and lithium perchlorate (64 mg, 0.6 mmol) at room temperature was added sodium azide (78 mg, 1.2 mmol). The mixture was stirred at 80 °C for 3 days. During this period, the solvent had fully evaporated and the remaining solid was re-dissolved in ethyl acetate (5 mL) and the organic material washed with water (2 mL). The organic layer was dried (MgSO4) and concentrated in vacuo to give an oil which was purified by preparative TLC (5:95, MeOH in DCM) to give epoxide 134c as a colourless oil (2 mg, 35%).

Rf 0.49 (5:95, MeOH-DCM).

[α]D19 = −93.3 (c 0.1, CHCl3).

δH (600 MHz; CDCl3) 7.47 (2H, d, J 8.7, H-Ar), 6.94 (2H, d, J 8.7, H-Ar), 5.63 (1H, s, CH(O)2), 5.07 (1H, t, J 2.1, H-C1), 4.44 (1H, d, J 10.5, H-C6), 4.33 (1H, d, J 3.3, H-C4), 4.31 (1H, t, J 3.3, H-C3), 3.96 (1H, d, J 10.5, H-C6), 3.92 (1H, m, H-C2), 3.83 (1H, s, CH3O), 2.71 (1H, d, J 2.2, C≡C-H), 2.52 (1H, d, J 2.7, OH).

δC (150 MHz; CDCl3): 160.7 (arom. C), 128.1 (arom. C), 127.9 (arom. CH), 117.0 (C≡N), 113.9 (arom. CH), 104.0 (CH(O)2), 77.5 (C≡C-H), 76.8 (C-4), 76.6 (C≡C-H), 72.5 (C-6), 70.5 (C-2), 68.3 (C-5), 66.0 (C-1), 57.6 (C-3), 55.3 (CH3O).

νmax (CHCl3 cast)/cm⁻¹: 3450 (O-H), 2920 (C-H), 2119 (N3), 1615 (C=C), 1519 (C=C). N. B. (C≡N) stretch was not observed.

m/z (CI+, CH4) 357 (M+H, 53%), 338 (64), 329 (8), 295 (100), 136 (39).

HRMS: calculated for C17H17N4O5: 357.1199, found 357.1199.
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