Studies Towards the Total Synthesis of Tagetitoxin

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For the Degree of
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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

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ABBREVIATIONS

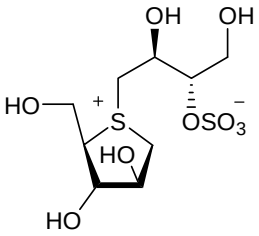
Ac	acetyl
acac	acetylacetonate
aq.	aqueous
Arg	arginine
Asn	asparagine
Asp	aspartic acid
Bn	benzyl
Boc	*tert*-butoxycarbonyl
***t*-Bu**	*tert*-butyl
conc.	concentrated
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyanoquinone
DEPT	distortionless enhancement by polarisation transfer
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EI	electron impact ionisation
eq.	equivalent
ESI	electrospray ionisation
Et	ethyl
FAB	fast atom bombardment
Gln	glutamine
Glu	glutamic acid
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence
***i*-Pr**	*iso*-propyl
L	ligand
LDA	lithium diisopropylamide

M	metal
mCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMP	nucleoside monophosphate
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NTP	nucleoside triphosphate
PG	protecting group
Ph	phenyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PPi	pyrophosphate
RNA	ribonucleic acid
RNAP	ribonucleic acid polymerase
rt	room temperature
Ser	serine
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran-2-yl
Tr	trityl
Ts	*para*-toluenesulfonyl
UTP	uridine triphosphate

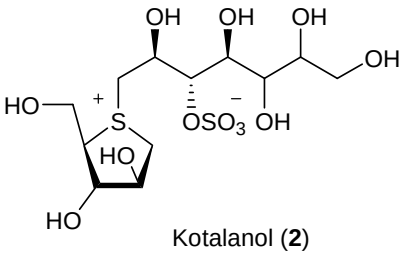
TABLE OF CONTENTS

1. INTRODUCTION

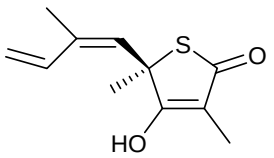
Thiosugars are sulfur-containing carbohydrate derivatives which commonly differ in biological activity from their non-sulfur-containing analogues; this is a consequence of thiosugars having different conformational and geometrical properties, as well as flexibility differences.[1] In addition, sulfides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



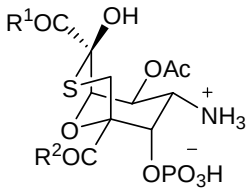
Salacinol (**1**)



Kotalanol (**2**)



Thiolactomycin (**3**)



4a $R^1 = NH_2$, $R^2 = OH$
4b $R^1 = OH$, $R^2 = NH_2$

Tagetitoxin (**4**)

Figure 1: Thiosugar based carbohydrates

Tagetitoxin (**4**) is a biologically active natural product, which inhibits RNA polymerase III in eukaryotic cells.[5] Some ambiguities over the structure of tagetitoxin still exist; however, spectroscopic data showed structure **4a** or **4b** to be most likely.[6] The positioning of the amide and carboxylic acid groups in tagetitoxin is ambiguous, with structure **4a** being narrowly favoured over the alternative structure **4b**. The absolute configuration of tagetitoxin is unknown.

The dense functionality in tagetitoxin (**4a**) 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 ^1H, ^{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 ^1H and ^{13}C NMR spectroscopic data allowed the eight membered ring structure **5** to be proposed by Mitchell and Hart **(Figure 2)**.[8]

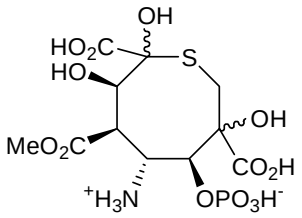


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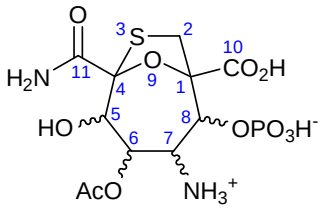
Figure 2: First proposed structure of tagetitoxin

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 $C_{11}H_{17}N_2O_{11}PS$. ^1H 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]



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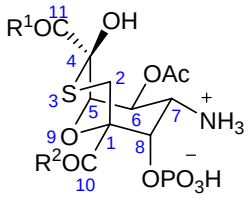


4a $R^1 = NH_2$, $R^2 = OH$
4b $R^1 = OH$, $R^2 = NH_2$

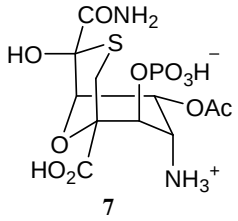
Figure 3: Revised structures for tagetitoxin

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 C*H*O and C*H*OAc protons, 12.4 Hz between the C*H*OAc and C*H*NH_3^+ and 6.0 between C*H*NH_3^+ and C*H*OPO_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 ^1H 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)**.



7

Figure 4: Tagetitoxin's structure bound to RNAP

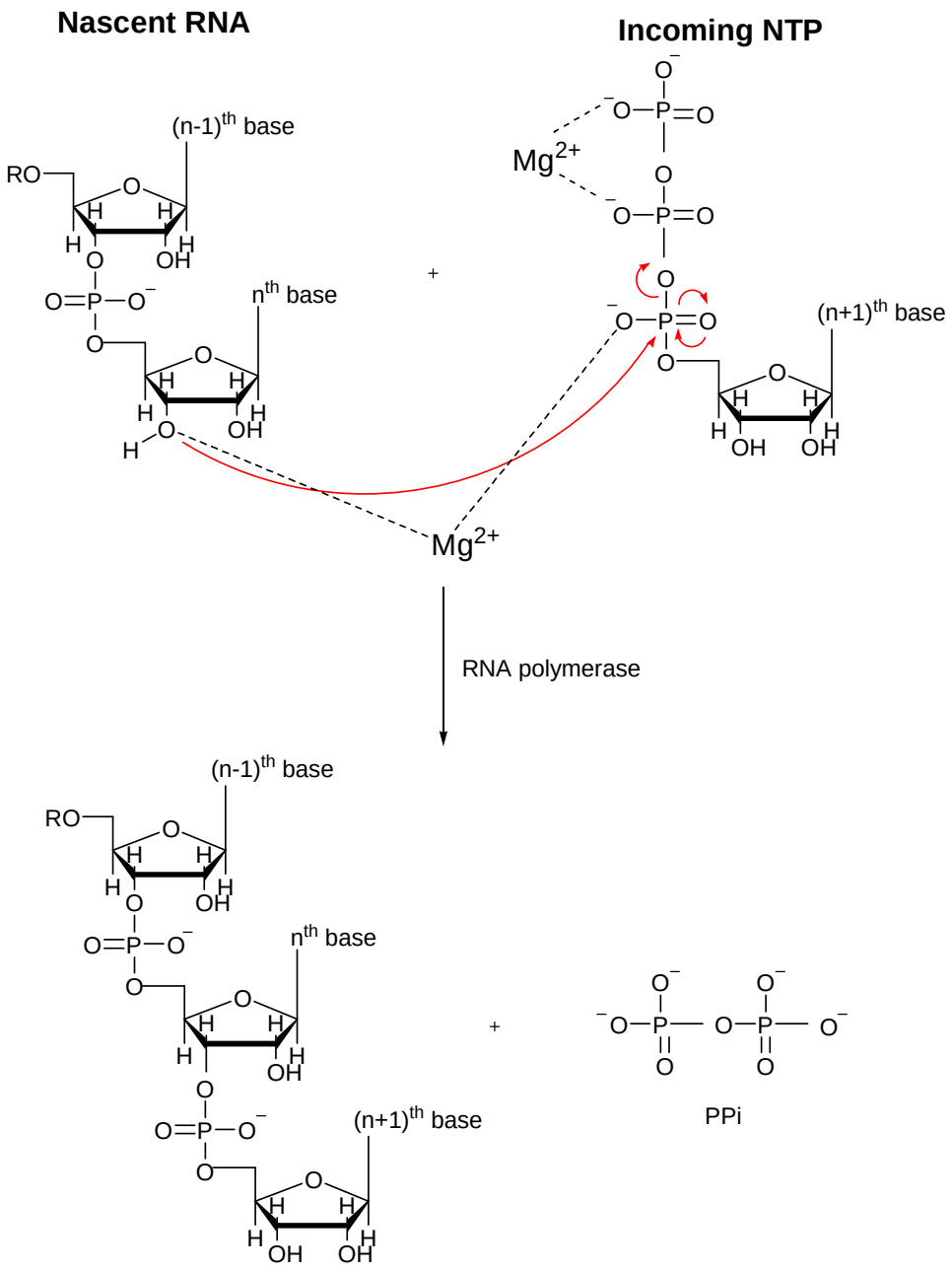
This structure is clearly inconsistent with the information reported in the NMR data.[6;8] A subsequent private communication from Vassylyev suggested that, due to the low resolution of the crystal structure, structure **4a** could not be ruled out, although structure **7** fits the experimental electron density map more closely than structure **4a**. This project will therefore concentrate on the synthesis of structure **4a** and analogues.

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*).[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.[5;11] Tagetitoxin was also shown to inhibit *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.[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) **(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.[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^{2+} ions (β′ Asp460, Asp462, Asp464 and β Asp814 in *E. coli* enzyme[14;15]).



Scheme 1: Synthesis of RNA using RNAP

RNAP can also be involved in two other types of hydrolysis reactions. Firstly, exonucleolytic hydrolysis,[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,[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:[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 [^{32}P] 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)**.

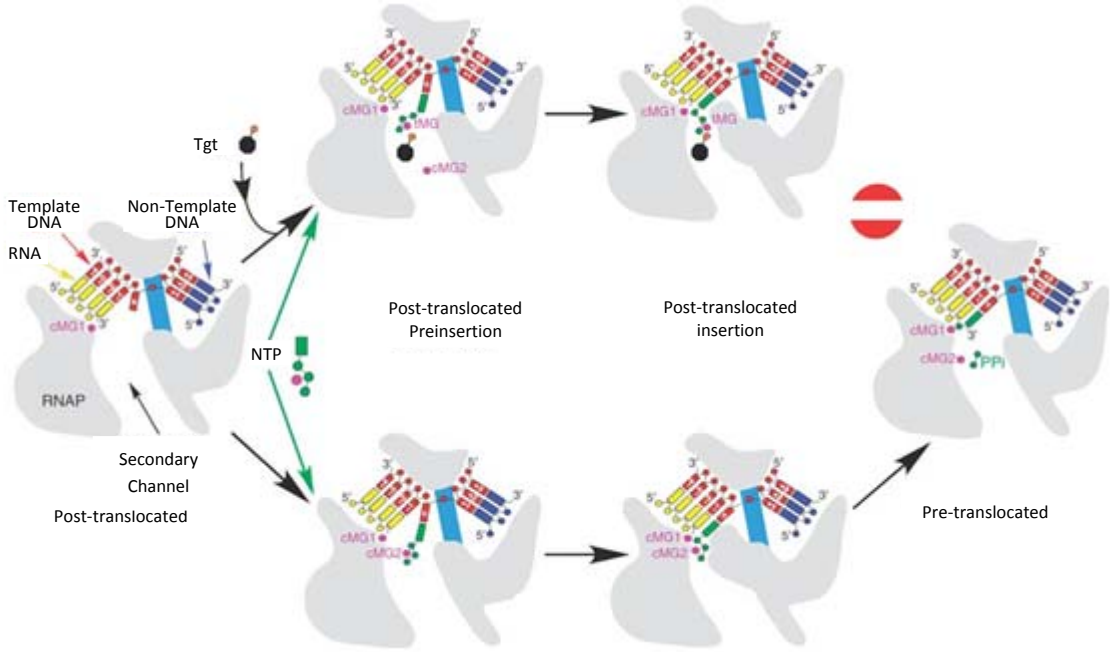


Figure 5: Tagetitoxin's mode of action [i]

Before 2005 it was known that tagetitoxin inhibits RNAP, however the mechanism was still not clear. Recently Vassylyev *et al*. published a crystal structure of (RNAP)-tagetitoxin complex at a resolution of 2.4 Å.[10] 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)**.

[i] Reproduced from *Nature Structural & Molecular Biology* **2005**, *12*, 1086-1093. Licence number: 2471900717131

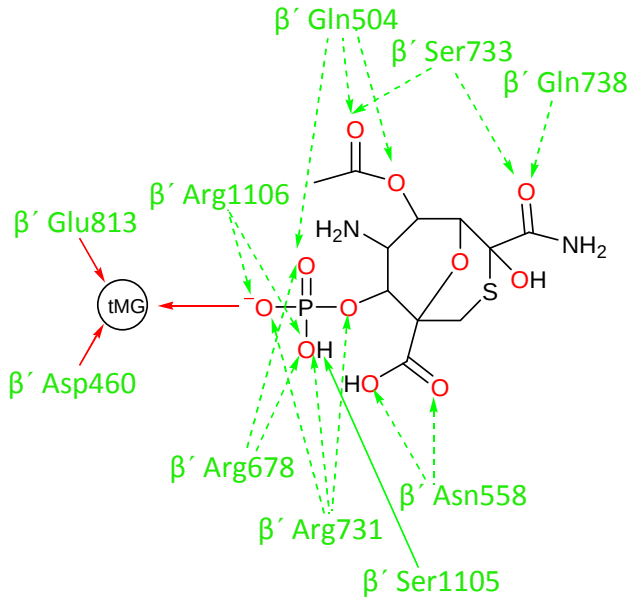


Figure 6: Tagetitoxin's binding to RNAP

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.

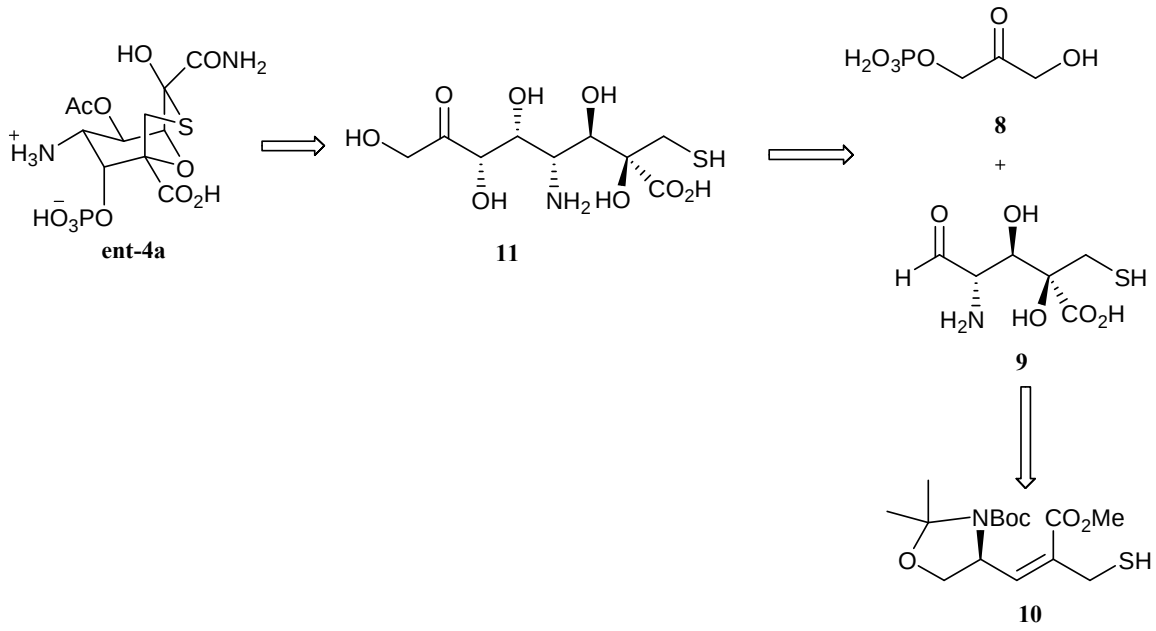
The authors suggested that the RNAP-tagetitoxin complex was strengthened by the well-fixed Mg^{2+} ion binding site that mediates RNAP interactions with tagetitoxin. It was shown that the phosphate group in tagetitoxin was also coordinated to the Mg^{2+} ion and two other active site residues, β´ Asp460 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*.,[21] who elected to synthesise tagetitoxin *via* a linear approach starting from a sulfur containing olefin. The second attempt was by Furneaux and co-workers,[22] 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

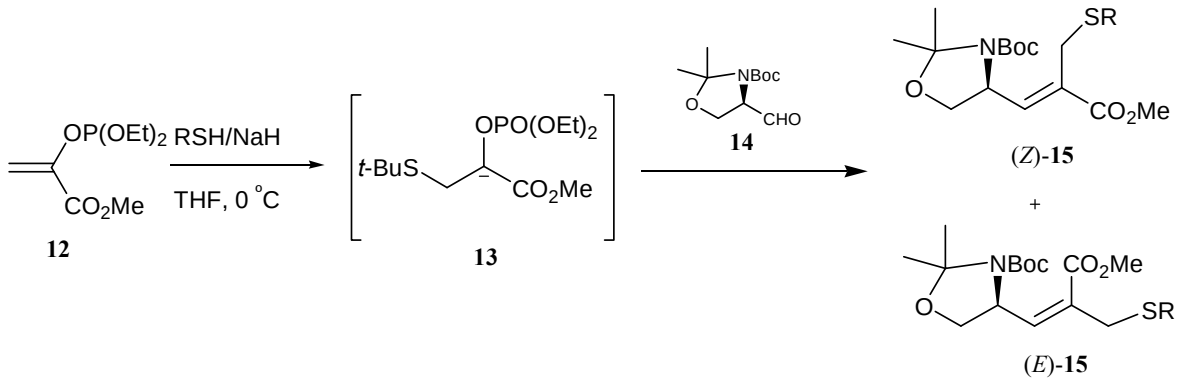
In 1996, Sammakia *et al*.[21] reported the dihydroxylation of sulfur-containing olefins as part of an approach to tagetitoxin. Sammakia envisaged a retrosynthetic analysis which included an enzymatic coupling of dihydroxyacetone phosphate **8** with aldehyde **9**, which itself could be prepared from fully protected oxazolidine olefin **10**, to form the pentaol intermediate **11**. Following this, an intramolecular cyclisation and functionalisation of the product should give the enantiomer of tagetitoxin (**ent-4a**) **(Scheme 2)**.



Scheme 2: Sammakia's approach to the synthesis of the enantiomer of tagetitoxin (**ent-4a**)[ii]

The synthesis began by treating methyl ester **12** with various sulfur nucleophiles to generate phosphonate intermediate **13** *in situ*. Subsequent quenching with oxazolidine aldehyde **14** gave different ratios of *Z*:*E* alkenes **15 (Scheme 3)**.[23;24]

[ii] 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.



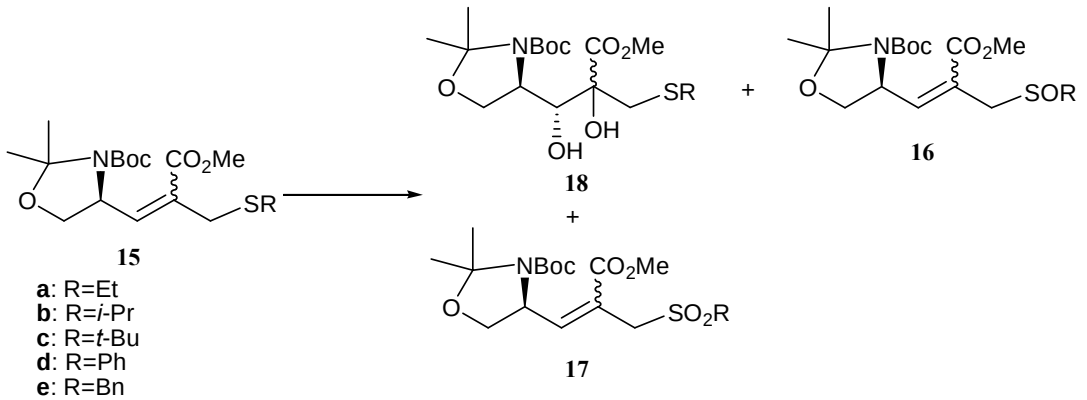
Scheme 3: Synthesis of olefin **15**

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)**.

R	Et	*i*-Pr	*t*-Bu	Ph	Bn
(*Z*)**-15**:(*E*)**-15**	40:60	30:70	0:100	80:20	70:30

Table 1: Ratios of *Z*:*E* isomers of olefin **15**

The dihydroxylation of **15** was then attempted. Initial dihydroxylation using conventional methods such as addition of stoichiometric or catalytic amounts of OsO_4 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.[25-27] 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)**.[28]



Scheme 4: Dihydroxylation of olefin **15**

When $K_3Fe(CN)_6$ 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.[29-33] Oxidation of phenyl sulfide **15d** also gave the sulfone as the major product.[34;35] However, *t*-butyl sulfide containing compound **15c** was the only substrate susceptible to dihydroxylation with $OsO_4/K_3Fe(CN)_6$ in preference to sulfur oxidation. **Table 2** summarises Sammakia's dihydroxylation results for five electron deficient olefins.

R	Oxidant	Recovered SM (%)	Yield 18 (%)	Yield 16 (%)	Yield 17 (%)
Et (**15a**)	AD-mix-β	54	-	46	-
	OsO_4, $K_3Fe(CN)_6$	30	-	70	-
i-Pr (**15b**)	AD-mix-β	56	6	28	-
	OsO_4, $K_3Fe(CN)_6$	39	15	44	-
t-Bu (**15c**)	AD-mix-β	86	14	-	-
	OsO_4, $K_3Fe(CN)_6$	32	55	11	-
Ph (**15d**)	AD-mix-β	99	-	<1	-
	OsO_4, $K_3Fe(CN)_6$	34	27	-	39
Bn (**15e**)	AD-mix-β	82	-	10	-
	OsO_4, $K_3Fe(CN)_6$	22	6	72	-

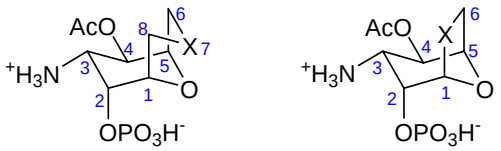
Table 2: Yield produced from the dihydroxylation of olefin **15**

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.*[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)**.



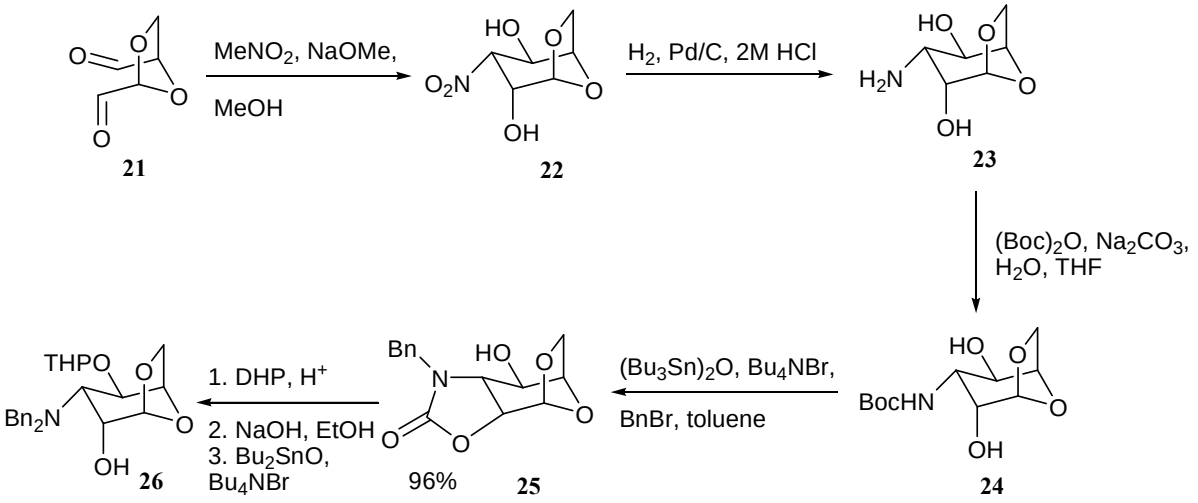
19 **20**

X=O, S

Figure 7: Analogues of tagetitoxin

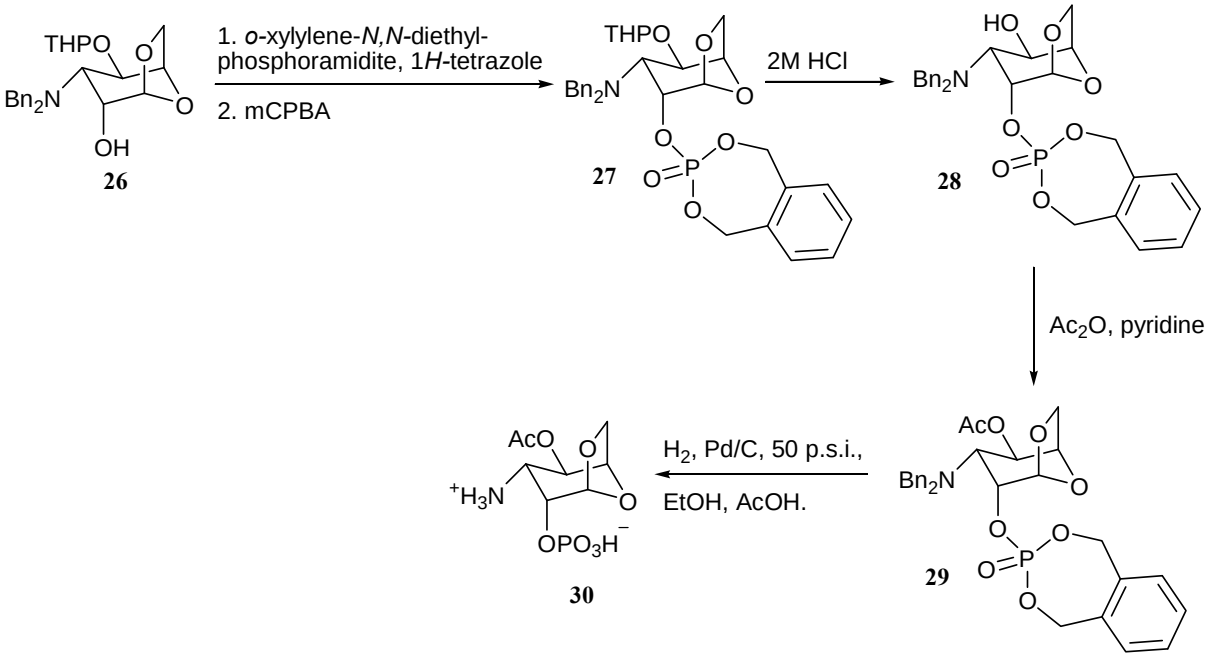
Starting from readily available D-sugars, 1,6-anhydro-D-hexoses could be synthetically derived. These compounds possess close similarities to tagetitoxin (**4a**).

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;[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.[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.[37] The presence of the benzyl group on the amine moiety was supported by the ^{13}C chemical shift of the benzylic carbon at δ = 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)**.



Scheme 5: Synthesis of analogue **26**

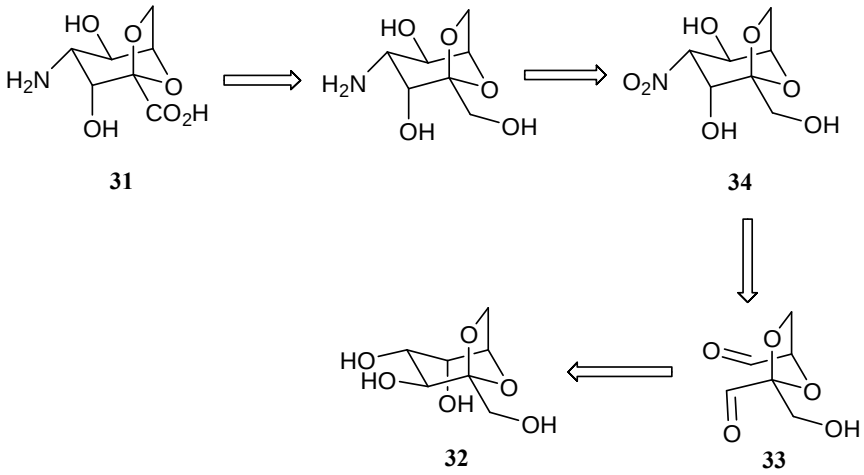
Further incorporation of the phosphate group using *o*-xylylene *N,N*-diethylphosphoramidite in the presence of 1*H*-tetrazole, followed by mCPBA oxidation successfully led to the formation of phosphate **27**.[38] Acidic removal of the THP protecting group gave alcohol **28** in a good yield. Subsequent acetylation at O-4 afforded compound **29** which when subjected to hydrogenolysis gave compound **30** in quantitative yield **(Scheme 6)**.



Scheme 6: Synthesis of compound **30**

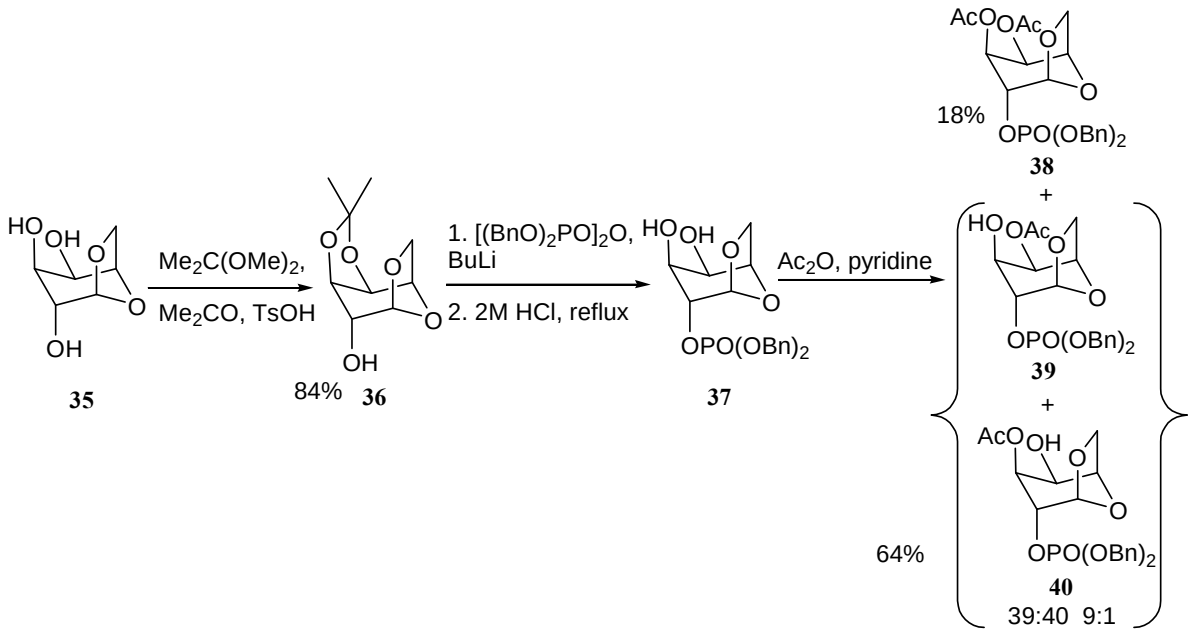
Unfortunately, *in vivo* biological testing of **30** gave no positive signs of biological activity against pre or post-emergent agriculturally important weeds such as *Avena fatua* (wild oat), *Setaria viridis* (green foxtail), *Amaranthus retroflexus* (redroot pigweed) or *Chenopodium album* (fat hen).

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-anhydrosedoheptulose (**32**) to give dialdehyde **33**; quenching with nitromethane would then give 4-deoxy-4-nitro-D-*gulo*-anhydride (**34**) **(Scheme 7)**.[39;40] This proposed synthesis was not carried out.



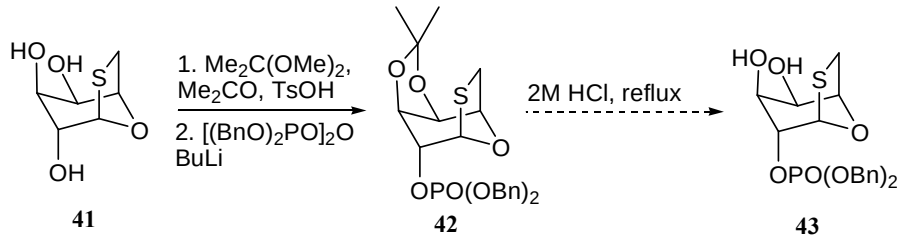
Scheme 7: Proposed retrosynthetic route to carboxylic acid **31**

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.[41] 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)**.



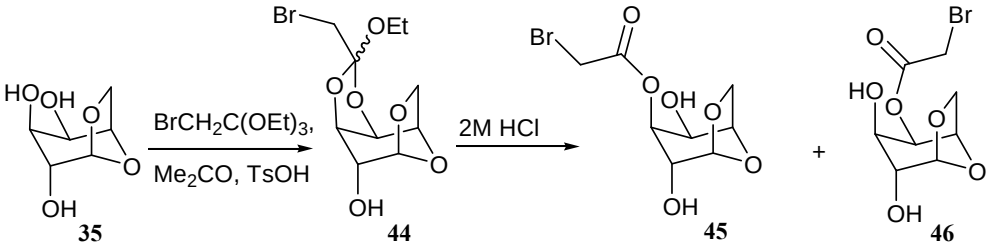
Scheme 8: Attempted selective acetylation of compound **37** at O-3

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)**.



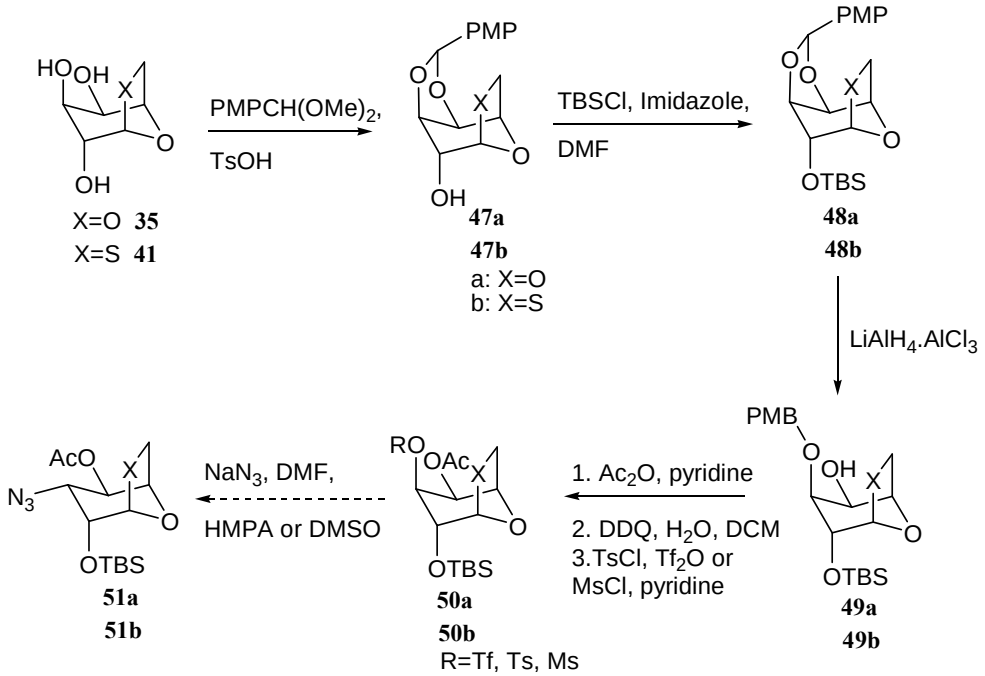
Scheme 9: Attempted hydrolysis of acetonide **42**

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**

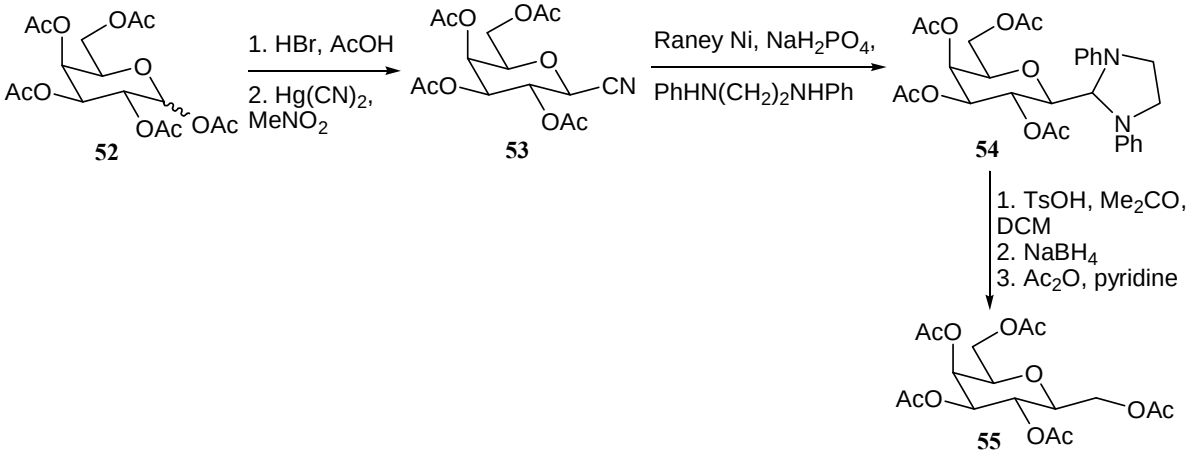
Alternatively, 4-methoxybenzylidene protection of triols **35** and **41** exclusively gave the *endo*-isomer of benzylidene acetals **47a** and **47b**. Subsequent silylation at O-2 using *tert*-butyl dimethylsilyl chloride and imidazole furnished compounds **48a** and **48b**, reduction gave the O-3 PMB protected ethers **49a** and **49b**. Acetylation at O-4, DDQ mediated debenzylation 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 azide**s 51a** and **51b**

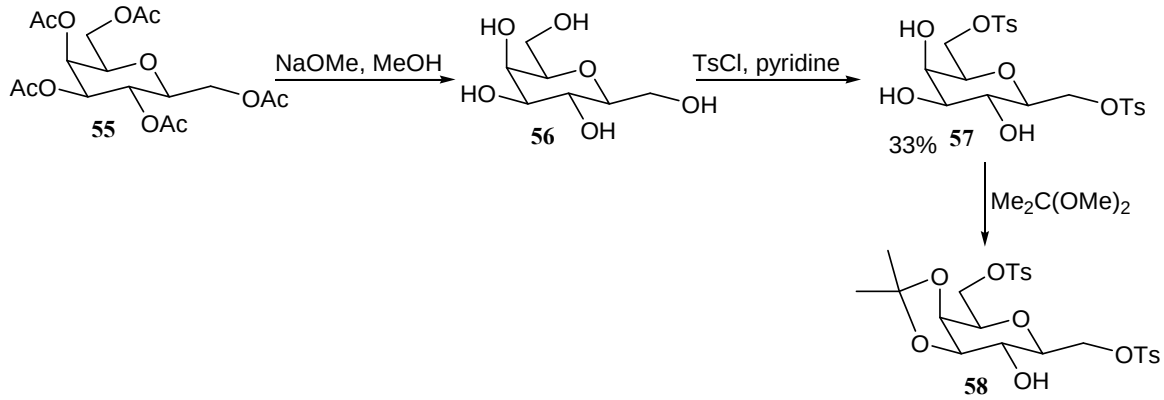
In a different route, the authors envisaged that compounds analogous to tagetitoxin (**4a**) could be made from readily available D-galactopyranose *via* initial addition of one extra carbon atom at C-1. To this end, pentaacetate **52** was brominated with HBr and acetic acid and then the product treated 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**.[44;45] Regeneration of the aldehyde followed by reduction and acetylation afforded pentaacetate **55 (Scheme 12)**.[46]



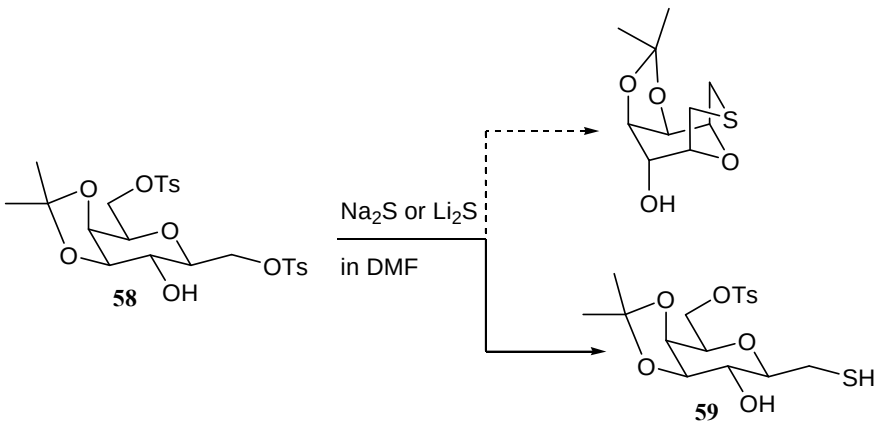
Scheme 12: Synthesis of pentaacetate **55**

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)**.



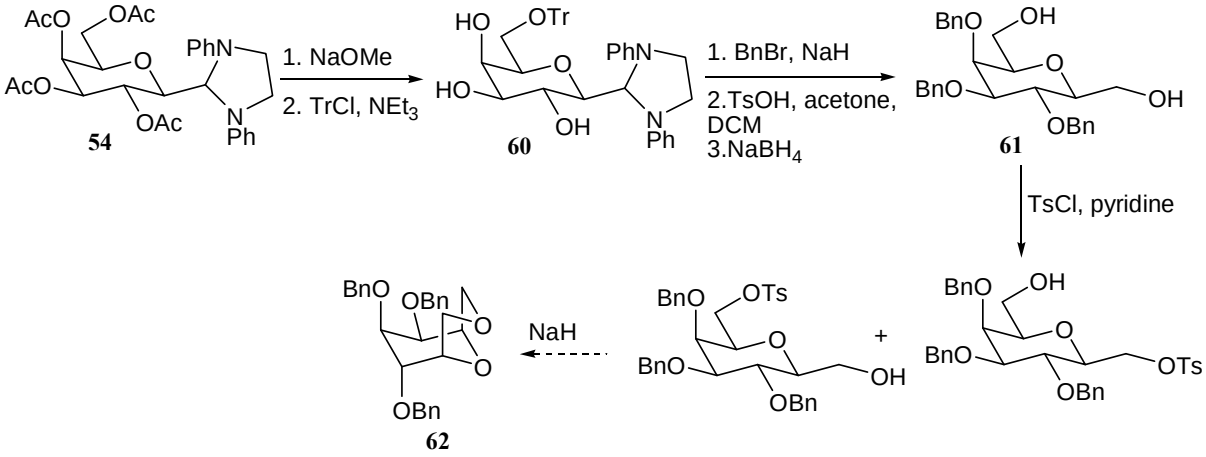
Scheme 13: Synthesis of acetonide **58**

Unfortunately, attempts to displace both tosyl groups with a divalent sulfur nucleophile failed; instead compound **59** was isolated **(Scheme 14)**.



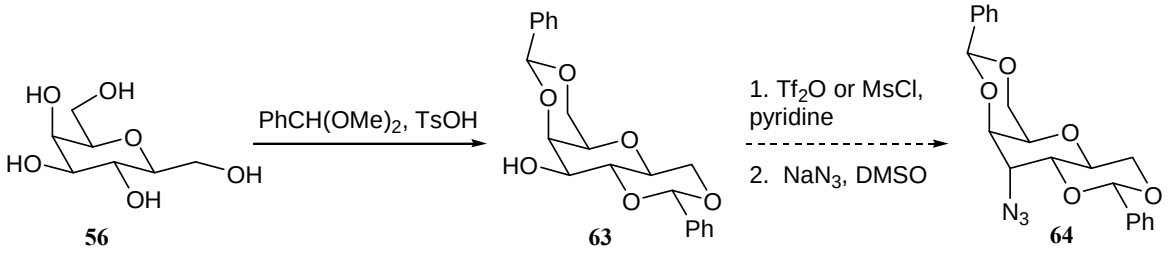
Scheme 14: Formation of compound **59**

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**; benzylation 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)**.



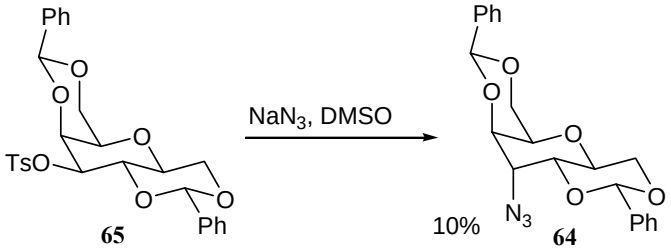
Scheme 15: Attempted synthesis of **62**

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**.[47] Unfortunately, displacement of various sulfonate derivatives of **63** by sodium azide or tetrabutylammonium cyanide failed to give desired axial azide **64 (Scheme 16)**.



Scheme 16: Attempted azide displacement at C-4

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)**.



Scheme 17: Synthesis of azide **64**

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)**.

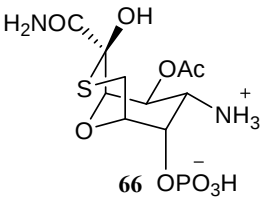
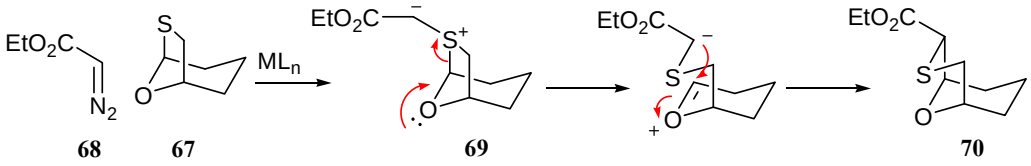


Figure 8: Decarboxytagetitoxin (**66**)

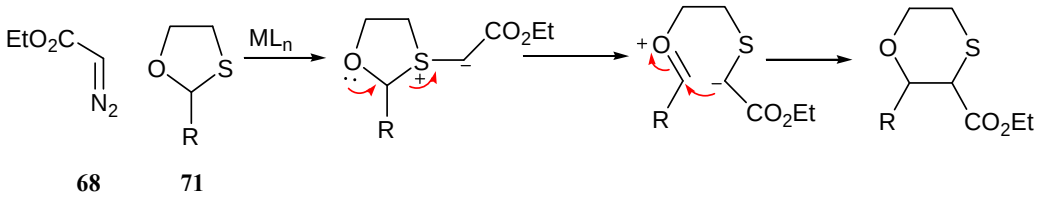
1.3.3.1 Ring expansion reaction of 1,3-oxathiolanes

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)**.[48;49]



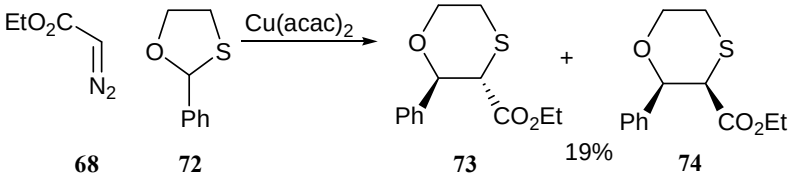
Scheme 18: Ring expansion strategy of 1,3-oxathiolanes

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)**.[48]



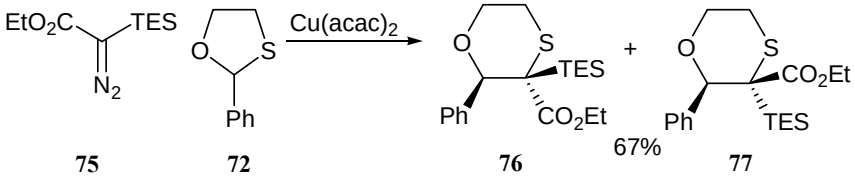
Scheme 19: Attempted ring expansion of monocyclic 1,3-oxathiolane **71**

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)**.[48;50]



Scheme 20: Ring expansion of 2-phenyl-1,3-oxathiolane (**72**)

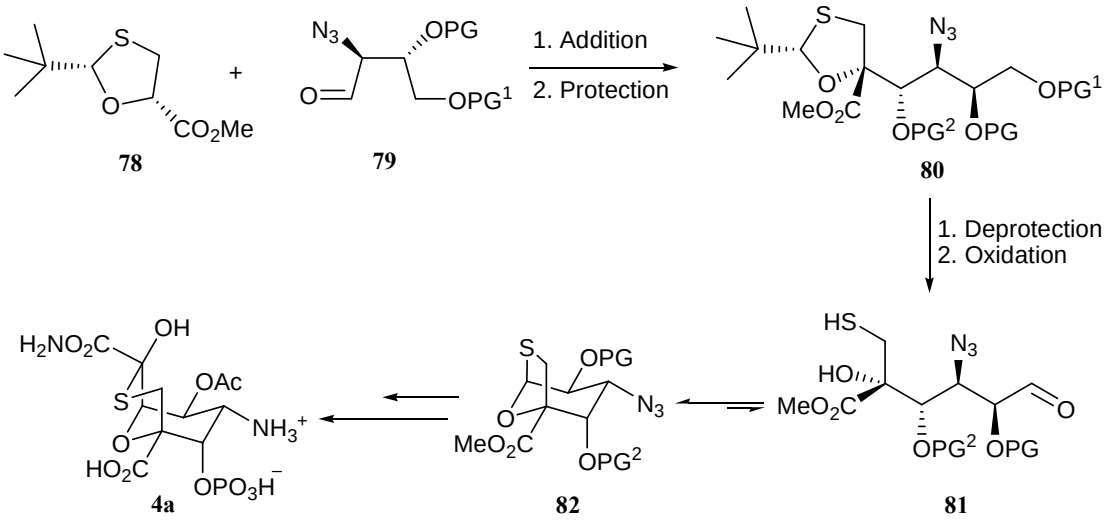
It was considered that the low yield obtained in this reaction might be due to the lack of differentiation of the metal carbene between the sulfur atom of the starting material and that of the product. To surmount this problem, ethyl (triethylsilyl)diazoacetate (**75**) was used instead of ethyl diazoacetate (**68**).[51] 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)**.[48;52;53]



Scheme 21: Ring expansion of 2-phenyl-1,3-oxathiolane (**72**) using **75**

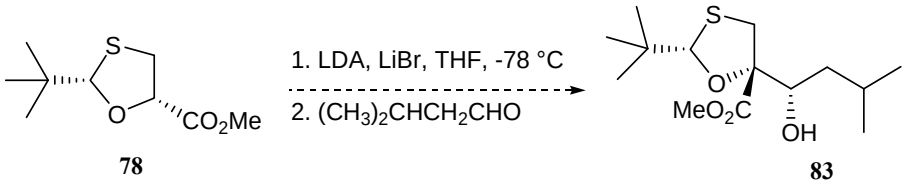
The success of this reaction prompted our group to attempt the synthesis of a bicyclic 1,3-oxathiolane intermediate, which could be used for the ring expansion process and subsequently form tagetitoxin. Hence, it was envisaged that starting from 1,3-oxathiolane **78**, diastereoselective addition to 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)**.[54]



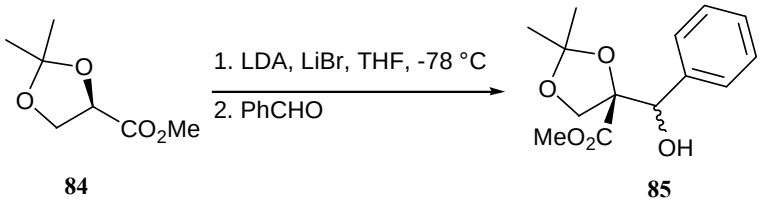
Scheme 22: Proposed synthesis of tagetitoxin (**4a**) *via* ring expansion strategy

Compound **78** was synthesised from commercially available L-serine in five steps.[54] 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**).[54]



Scheme 23: Attempted asymmetric synthesis of alcohol **83**

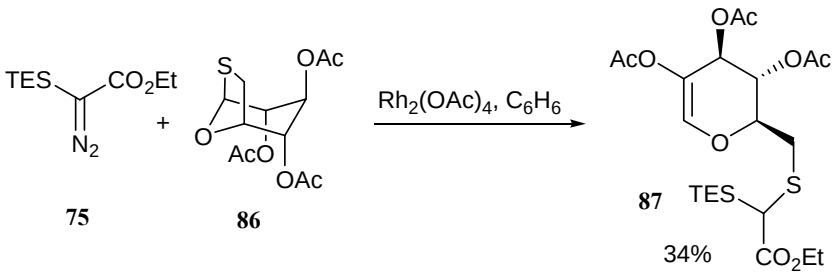
It was thought that the substrate decomposition was perhaps due to the elimination of the thioether. To test this hypothesis, the reaction was attempted with analogous dioxolane ester **84**; exposure of methyl ester **84** to a mixture of LDA and LiBr in THF followed by quenching with benzaldehyde gave the desired alcohol **85** in low yield **(Scheme 24)**.[54]



Scheme 24: Synthesis of alcohol **85**

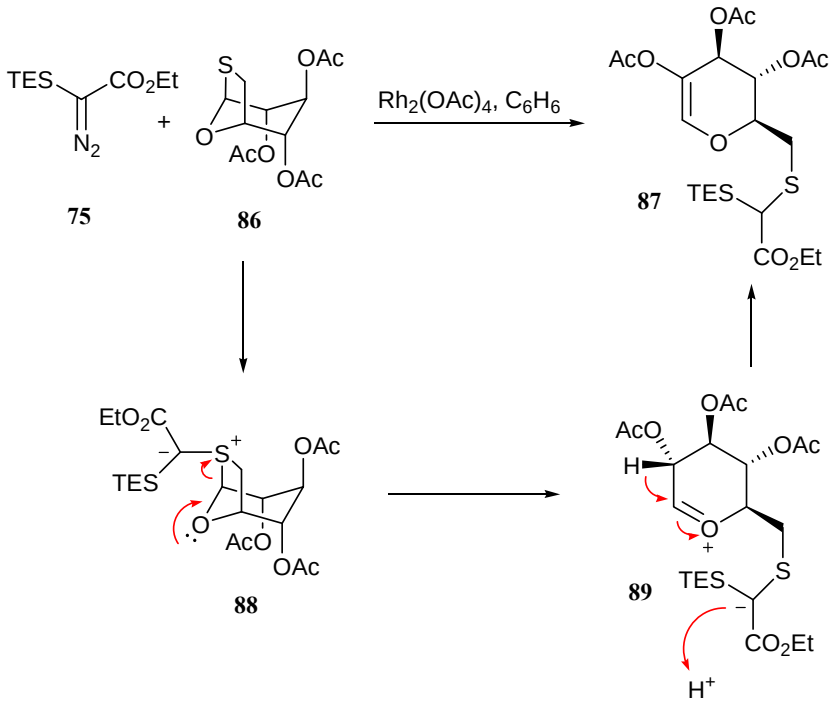
Although compound **85** was obtained in low yield, this result supports the explanation for the failure of the 1,3-oxathiolane reaction. This synthetic route was therefore abandoned.

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.[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)**.[58]



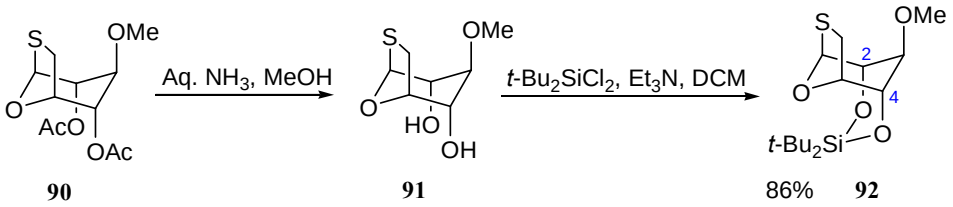
Scheme 25: Formation of compound **87**

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)**.[58]



Scheme 26: Proposed mechanism for the formation of compound **87**

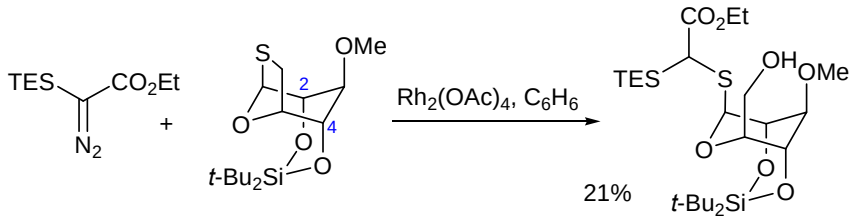
A bridging silyl protecting group was installed between O-2 and O-4 to provide a conformational constraint, and thus prevent the elimination process from occurring. To this end, compound **90** was deacetylated using aqueous ammonia and methanol, followed by silylation of the resulting diol **91** at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



90 **91** **92**

Scheme 27: Synthesis of tricyclic intermediate **92**

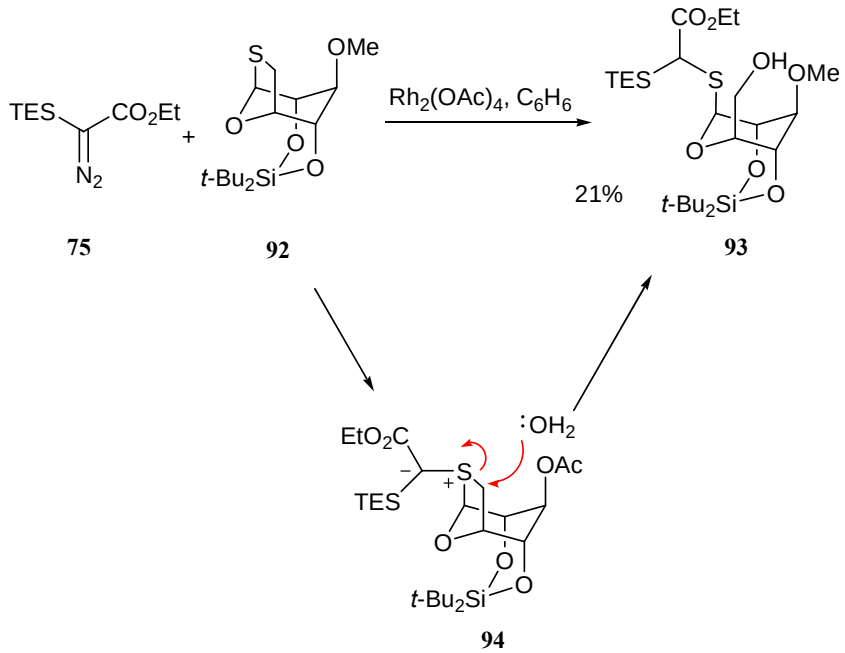
Unfortunately, when compound **92** was reacted with ethyl diazo(triethylsilyl)acetate in the presence of a catalytic amount of rhodium acetate, alcohol **93** was formed in 21% yield **(Scheme 28)**.[58]



75 **92** **93**

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)**.[58]

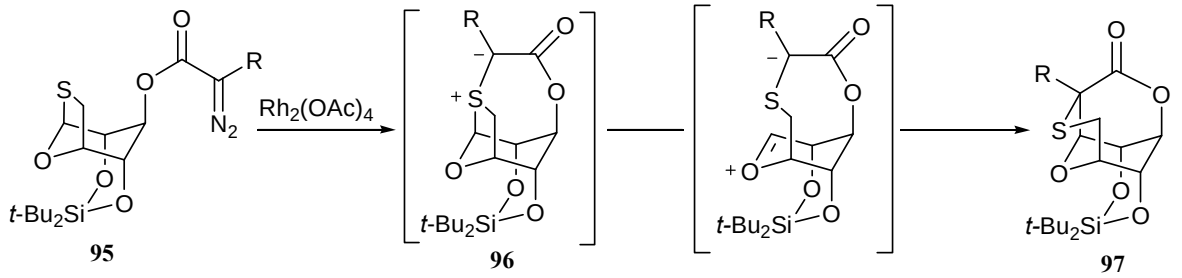


75 **92** **93** **94**

Scheme 29: Proposed mechanism for the formation of compound **93**

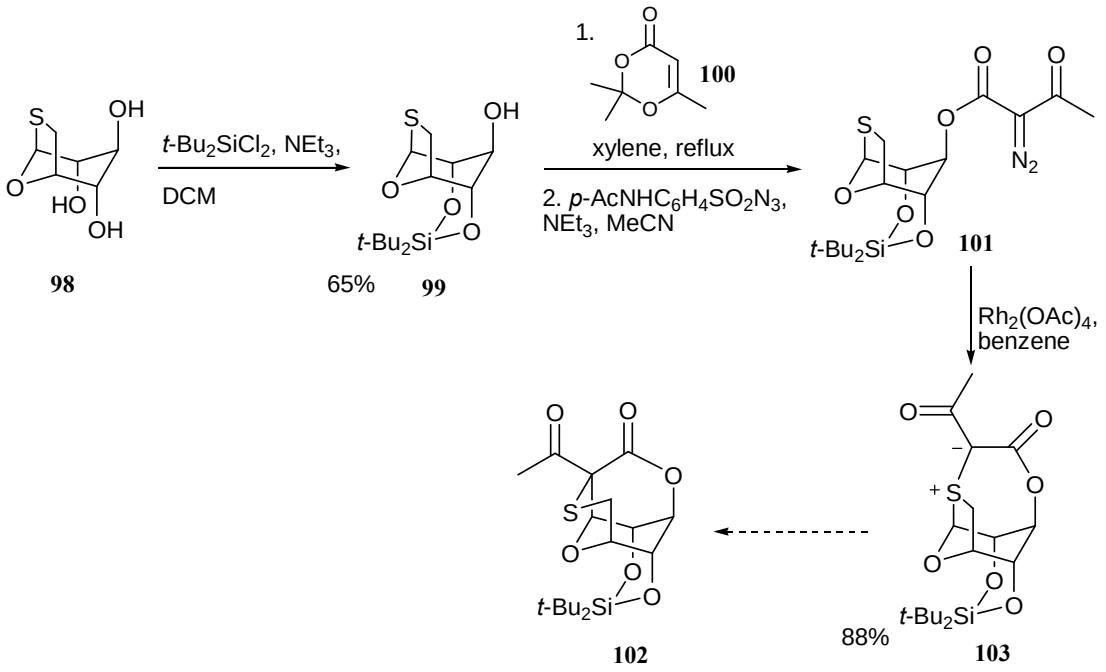
1.3.3.2 Synthesis of the Tagetitoxin core *via* Photo-Stevens Rearrangement

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]

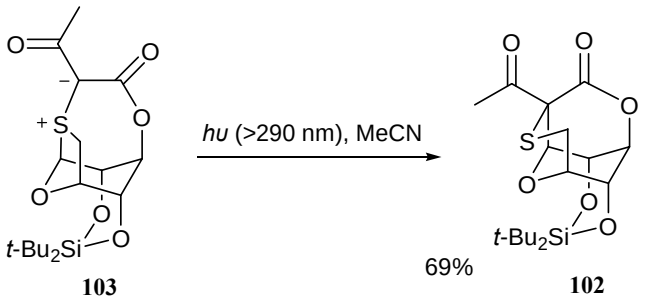


Scheme 31: Attempted synthesis of tagetitoxin core **102**

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.[60] 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**.[60]

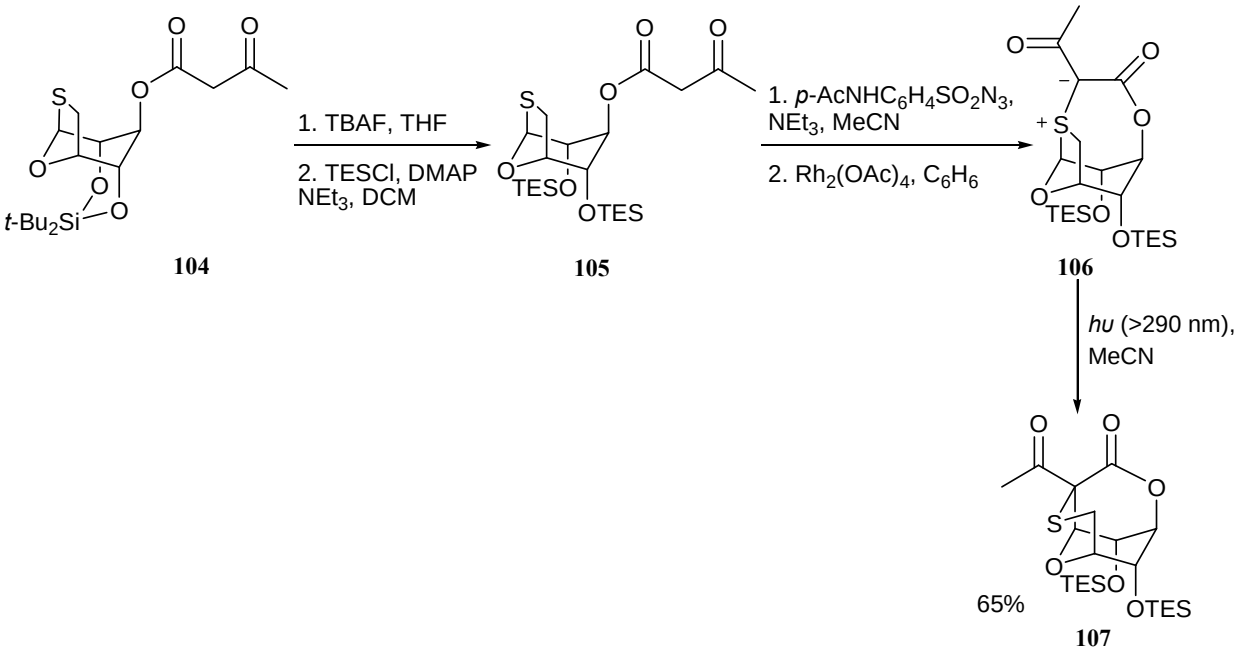
As a final attempt, rearrangement of ylide **103** was tested under photochemical conditions, *i.e.* a photochemical Stevens rearrangement.[67] Therefore, ylide **103** was subjected to ultraviolet irradiation (λ> 290 nm) in acetonitrile. After 2 hours, conversion to the tetracyclic tagetitoxin core **102** occured **(Scheme 32)**.[60]



103 **102**

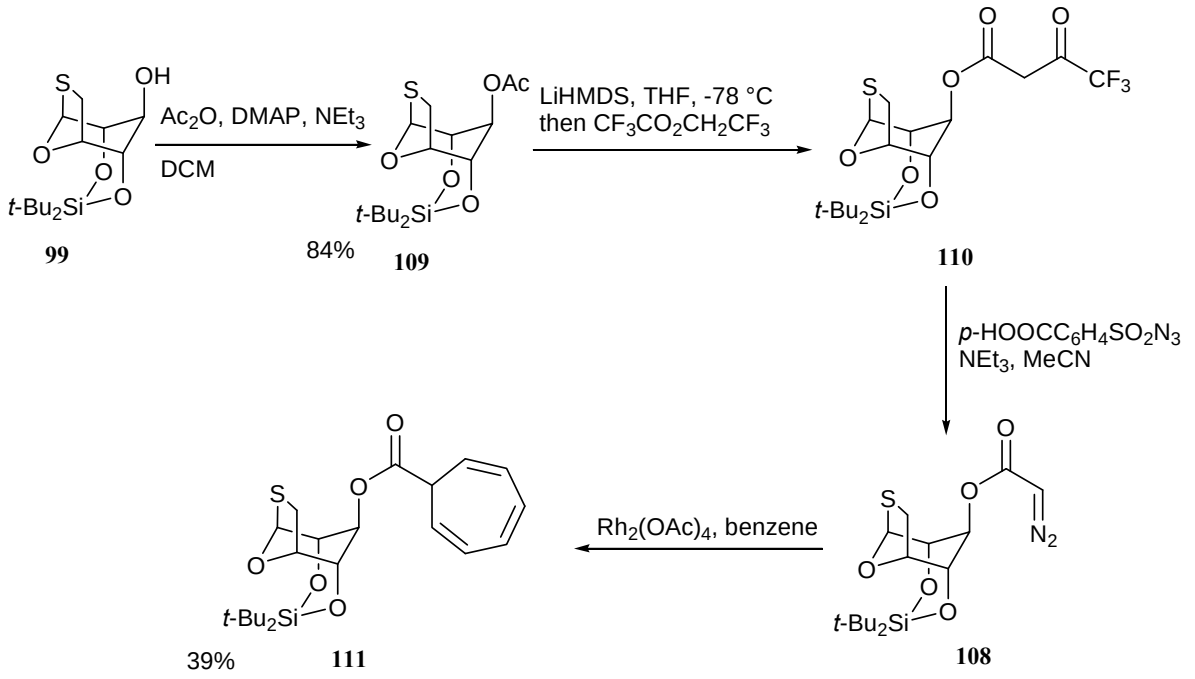
Scheme 32: Ring expansion of ylide **103** *via* photochemical Stevens rearrangement

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)**.[60]



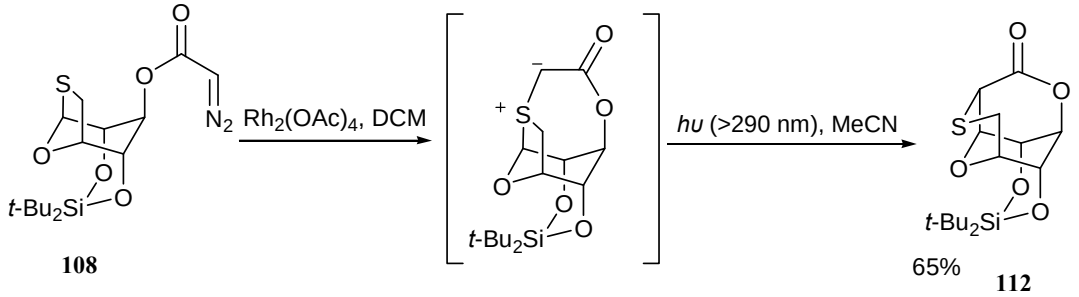
Scheme 33: Synthesis of tagetitoxin core **107**

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**

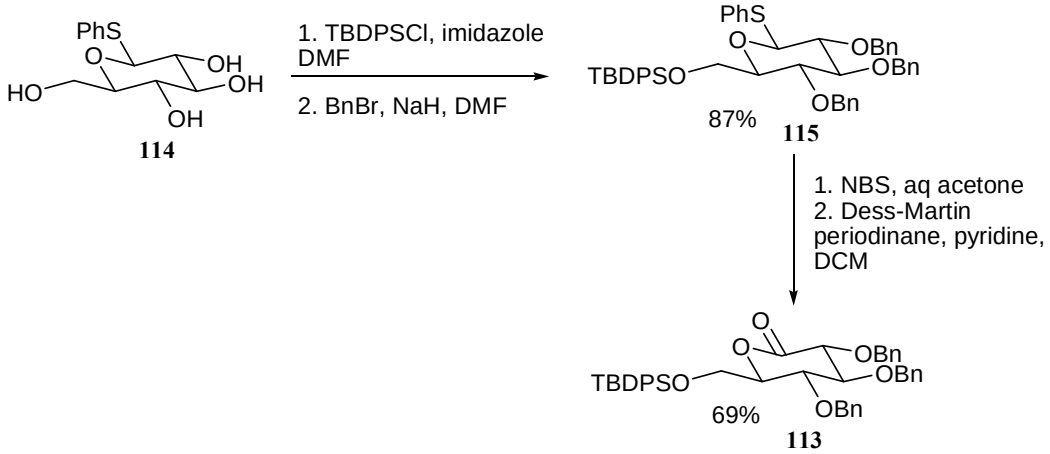
However, when benzene was replaced by dichloromethane in the final step, the reaction proceeded smoothly to give the target compound **112** in 65% yield **(Scheme 35)**.[60]



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

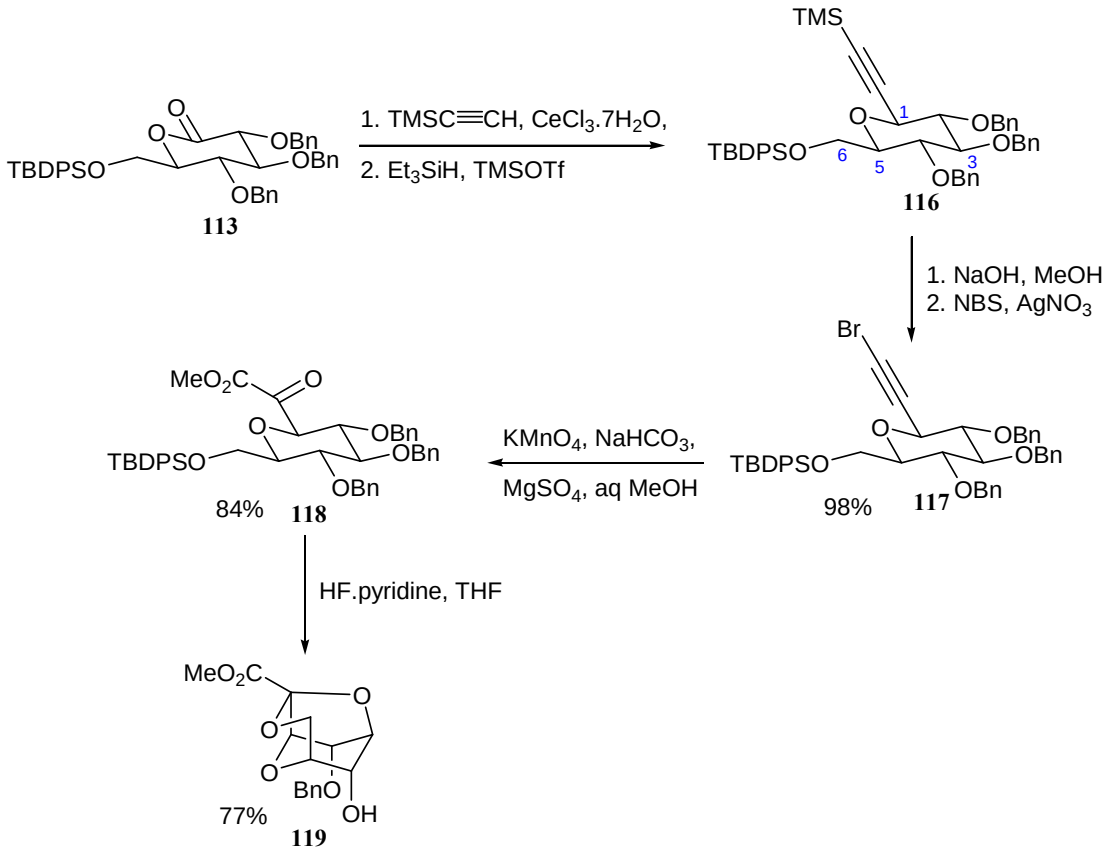
In an alternative strategy by our group, it was envisaged that the synthesis of the tagetitoxin core could be achieved *via* cyclisation of a thiol onto an α-ketoester to form the hemithioacetal moiety of the natural product. The feasibility of such a cyclisation was first tested on a simple model system. 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.[71] *N*-Bromosuccinimide promoted hydrolysis[72] and oxidation using Dess-Martin periodinane gave the desired lactone **113** in 69% yield **(Scheme 36)**.[58;73]



Scheme 36: Synthesis of lactone **113**

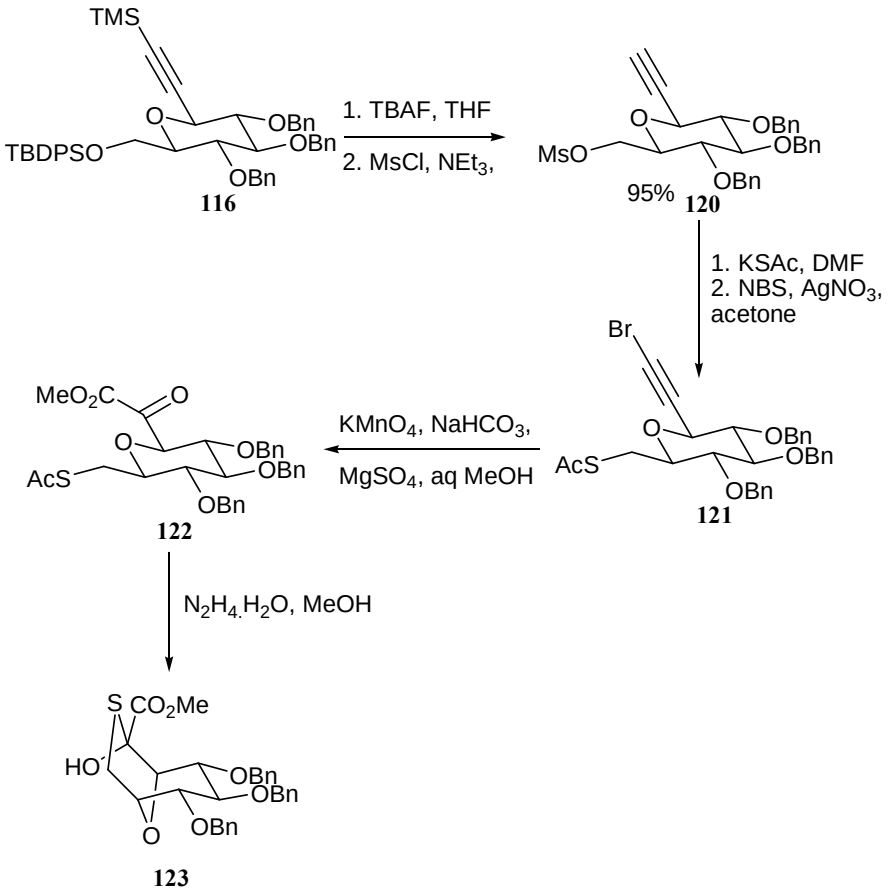
Cerium-mediated acetylene incorporation at C-1 of **113** followed by reduction with triethylsilane in the presence of TMSOTf resulted in compound **116** in 74% yield.[74] Selective TMS removal using sodium hydroxide in methanol followed by bromination yielded the desired bromoalkyne **117** in 98% yield.[75] Potassium permanganate mediated oxidation in methanol then afforded α-keto ester **118** in 84% yield.[76] Unexpectedly, exposure

of ester **118** to a solution of hydrogen fluoride in pyridine furnished tricyclic compound **119** in 77% yield **(Scheme 37)**.[58]



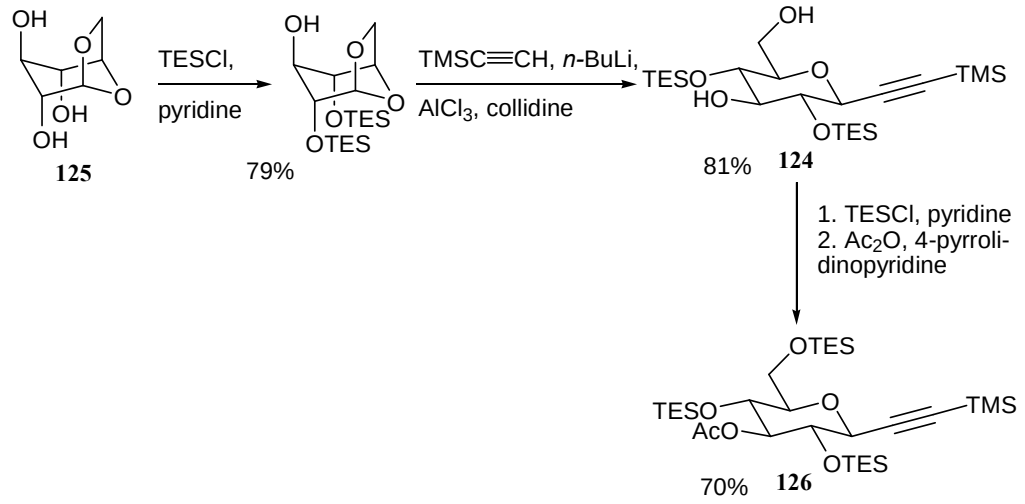
Scheme 37: Formation of compound **119**

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**.[75] Further oxidation using potassium permanganate in methanol afforded the targeted α-keto ester **122**.[76] Deacetylation and concomitant intramolecular cyclisation pleasingly provided tagetitoxin core **123 (Scheme 38)**.[58]



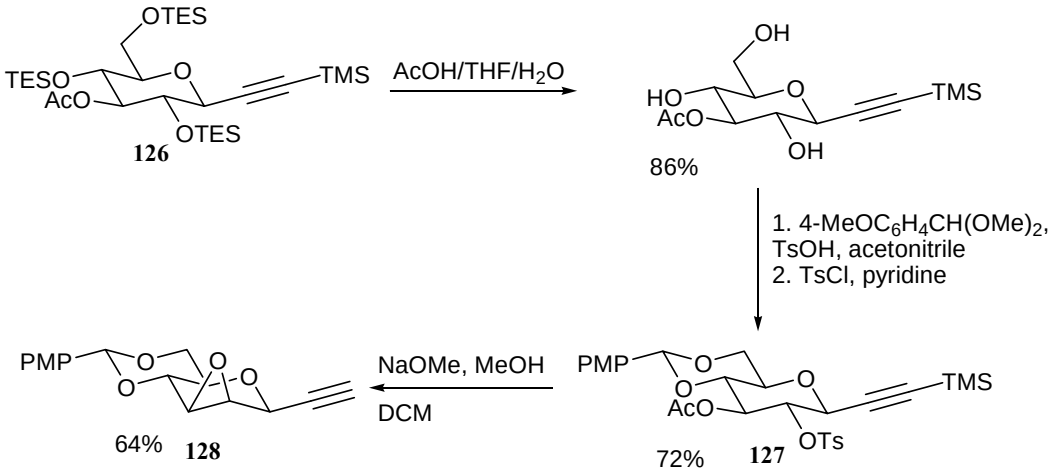
Scheme 38: Synthesis of tagetitoxin core **123**

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 trimethysilylacetylide in the presence of $AlCl_3$.[77] 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)**.[78;79]



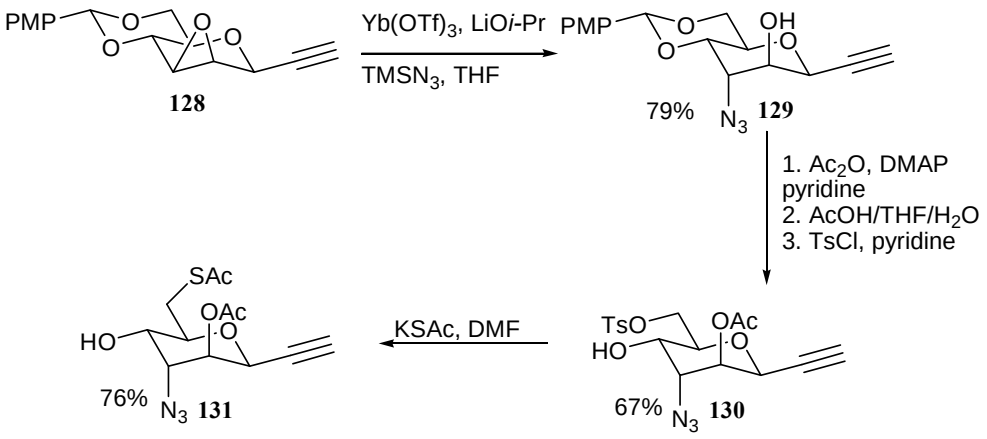
Scheme 39: Synthesis of acetate **126**

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]



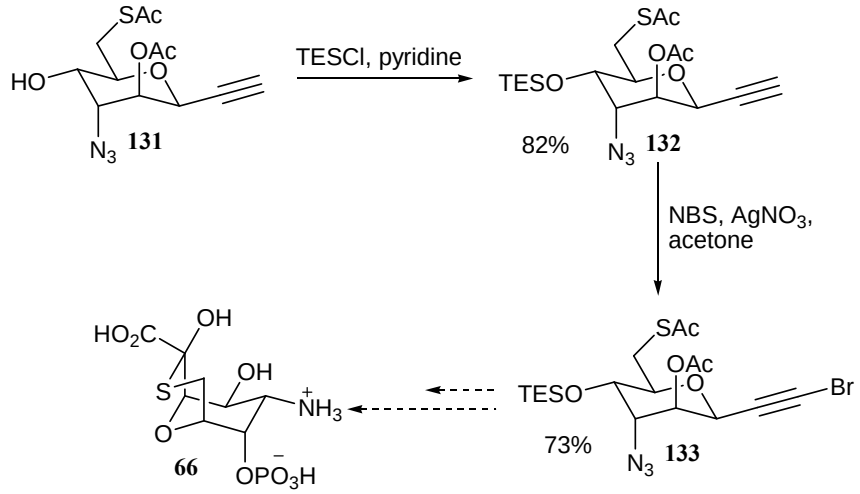
Scheme 40: Synthesis of epoxide **128**

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]



Scheme 41: Synthesis of thioacetate **131**

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.[78]

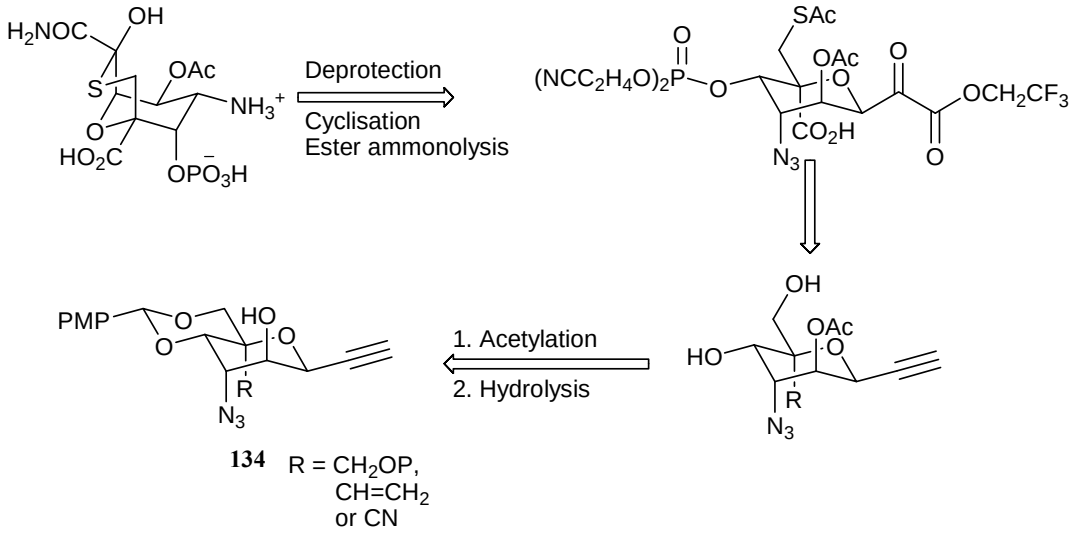


Scheme 42: Synthesis of azide **133**

1.4 Project objective

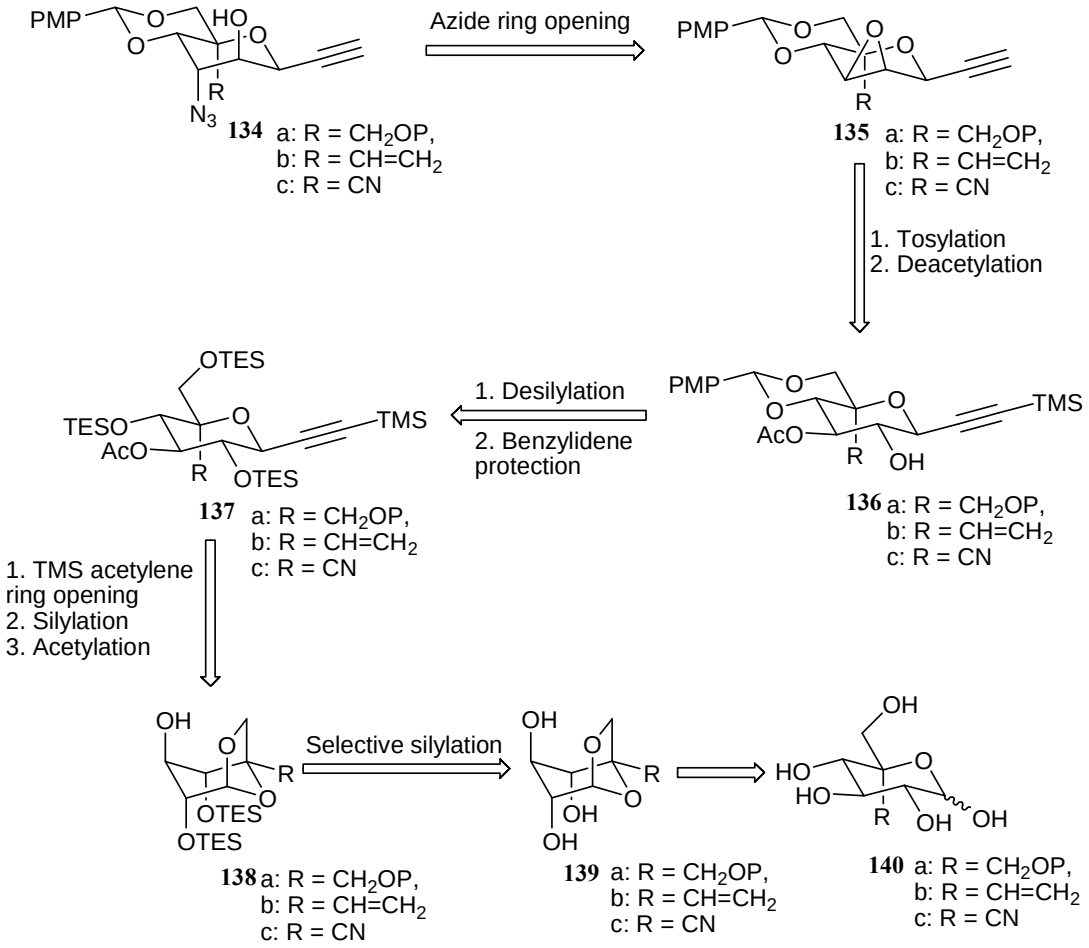
The objective of this work was to develop a new synthetic route towards tagetitoxin (**4a**), which would incorporate both stereochemical control and selective functionalisation of the sugar based starting material.

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)**.



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)**.

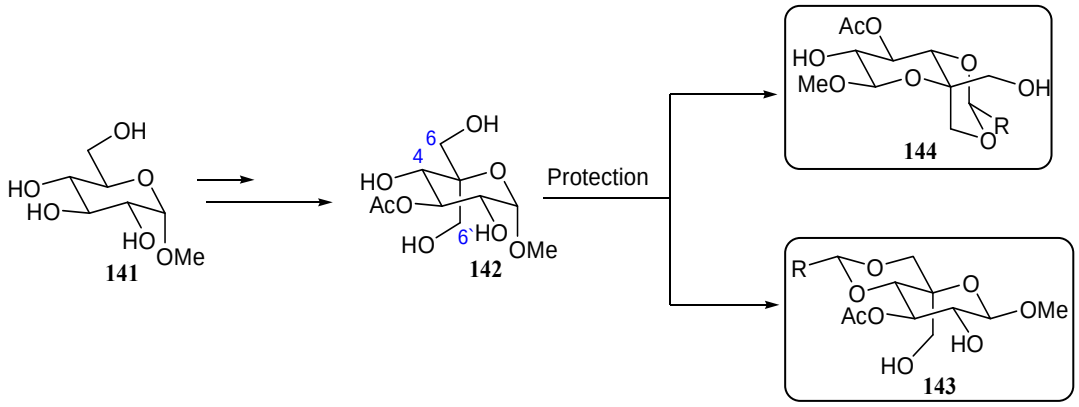


Scheme 44: Retrosynthetic analysis of azide **134**

2. RESULTS & DISCUSSION

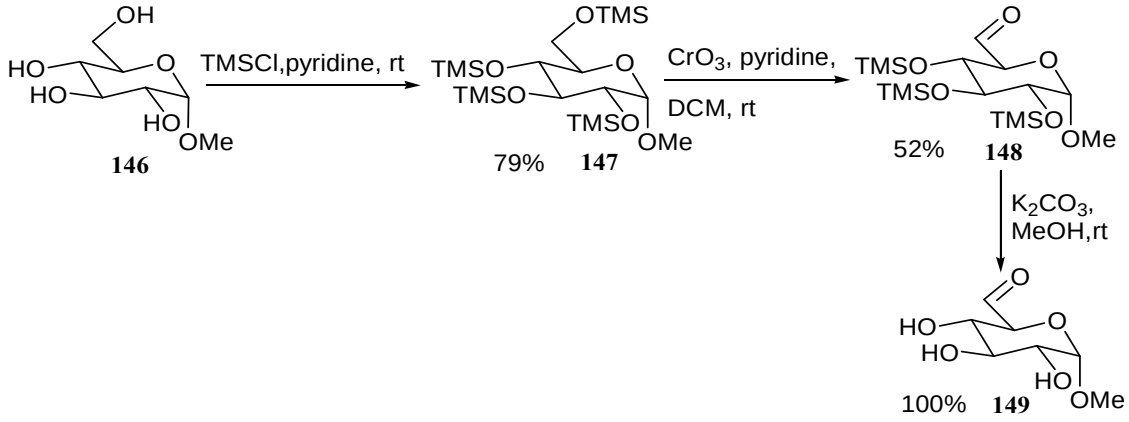
2.1 Synthetic approach *via* 1,6-anhydro-5-*C*-hydroxymethyl-D-glucose

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]



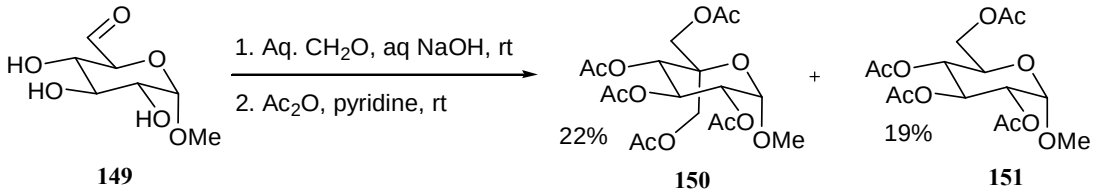
Scheme 45: Selective protection of tetraol **142**

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]



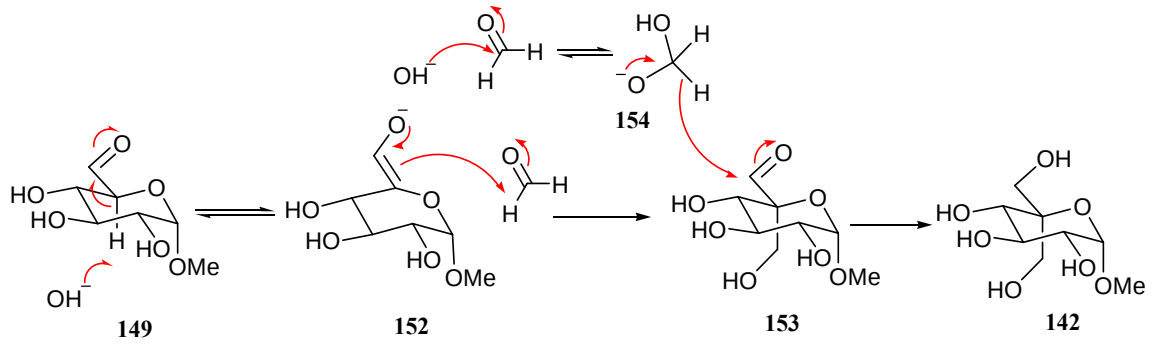
Scheme 46: Synthesis of aldehyde **149**

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]



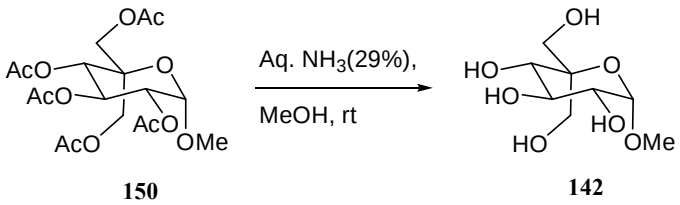
Scheme 47: Conversion of aldehyde **149** to pentaacetate **150**

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)**.



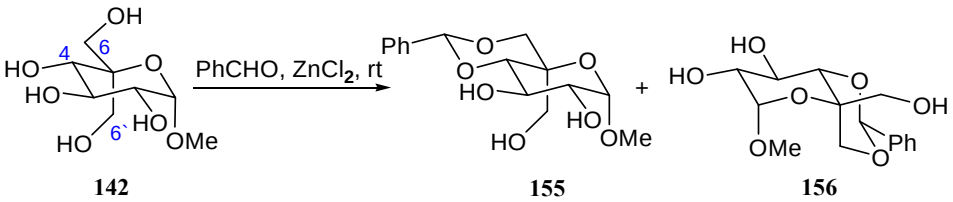
Scheme 48: Proposed mechanism for the formation of alcohol **142**

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)**.



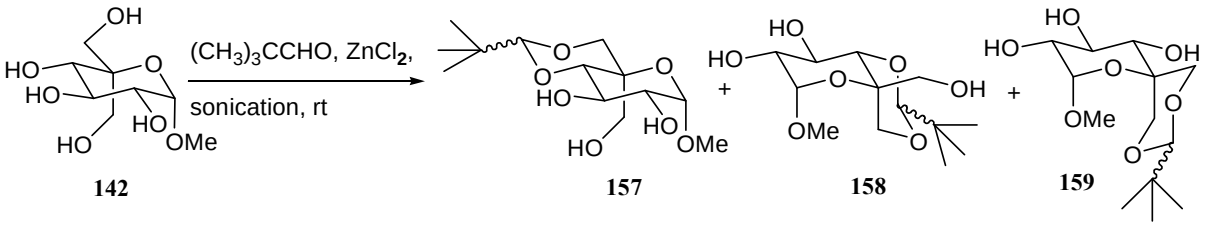
Scheme 49: Deacetylation of pentaacetate **150**

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)**.



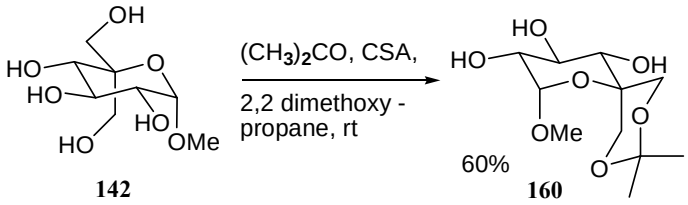
Scheme 50: Attempted selective protection of alcohol **142** using benzaldehyde

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)**.



Scheme 51: Attempted selective protection of alcohol **142** using pivalaldehyde

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)**.



Scheme 52 Attempted selective protection of alcohol **142** using 2,2-dimethoxy propane

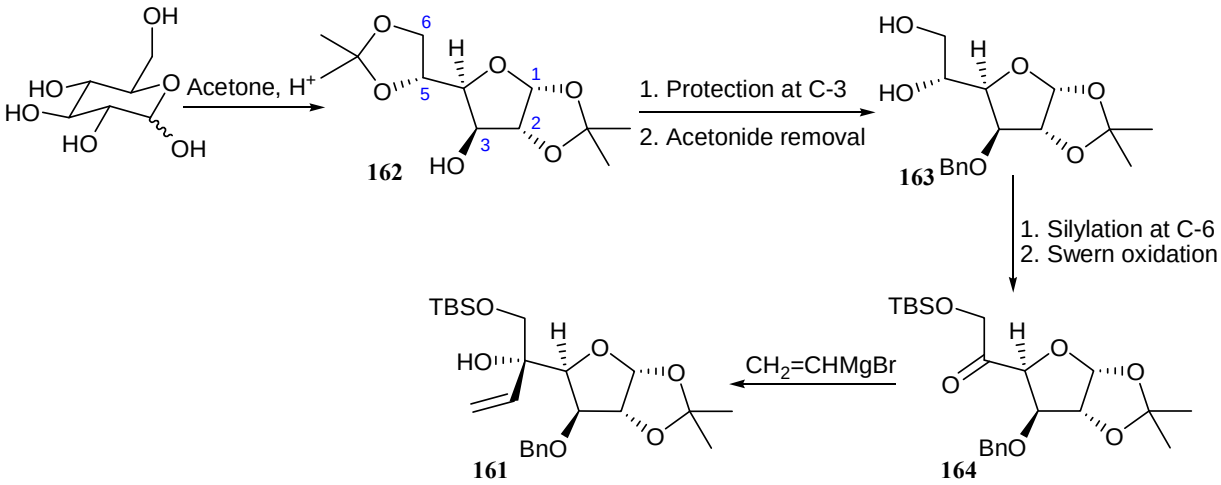
Unfortunately acetonide **160** was of no use to us as the primary alcohols had not been differentiated. In light of these results, we decided to abandon this strategy.

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

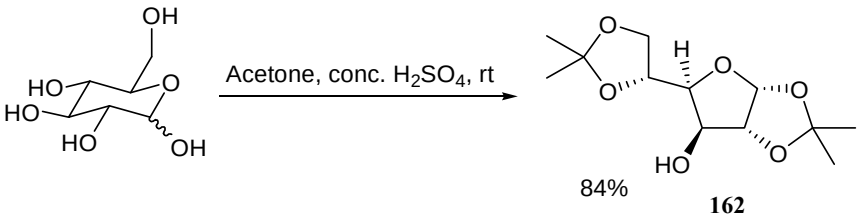
In 1993, Rama Rao and co-workers successfully synthesised glucofuranoside **161** in six steps starting from readily available D-glucose.[84] Conversion of D-glucose to glucofuranoside **162** followed by benzylation of the hydroxyl group at C-3 provided compound **163**. Selective acetonide removal 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)**.



Scheme 53: Rama Rao's synthesis of tertiary alcohol **161**

Our proposed route to synthesise 1,6-anhydro-5-*C*-vinyl-D-glucose (**139b**) follows the sequence devised by Rama Rao.[84] We chose to modify this route by the use of a more acid labile protecting group at C-3.

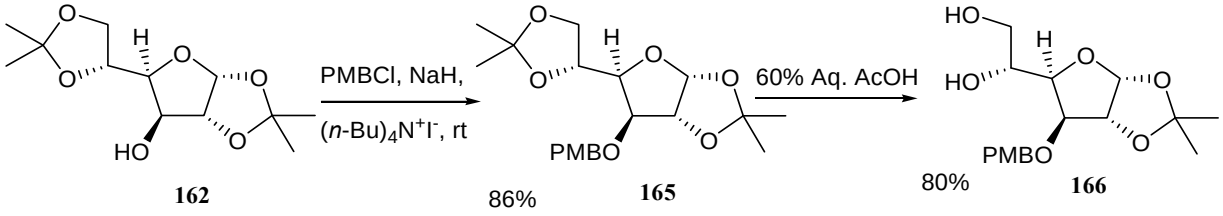
The treatment of D-glucose with acetone in the presence of concentrated H_2SO_4 afforded glucofuranoside **162** in 20% yield.[85] The low yield produced from this reaction was probably due to the loss of product during the basic aqueous work-up and so we used an alternative work-up procedure. After completion of the reaction, ammonia gas was bubbled through the reaction mixture and a white precipitate of ammonium sulphate was formed.[85] Filtration, followed by evaporation and subsequent recrystallisation from boiling petroleum spirit, afforded glucofuranoside **162** in 84% yield **(Scheme 54)**.[85]



Scheme 54: Synthesis of glucofuranoside **162**

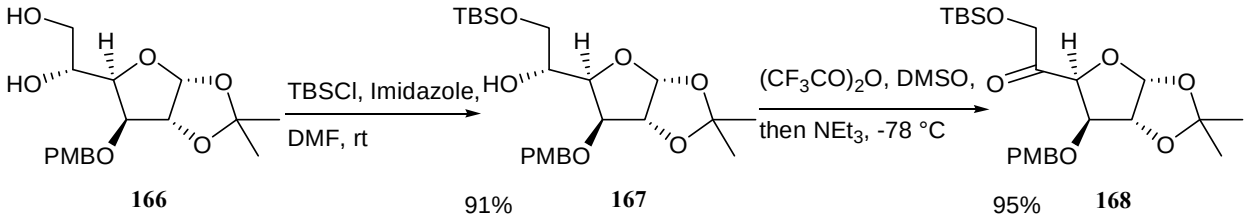
With glucofuranoside **162** in hand, we attempted the protection of the hydroxyl moiety at C-3. For this we decided to use 4-methoxybenzyl as a suitable protecting group.

Treatment of glucopyranoside **162** with 4-methoxybenzyl chloride[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)**.[86]



Scheme 55: Synthesis of diol **166**

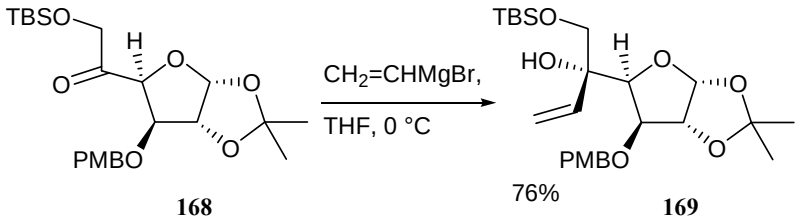
Silylation of diol **166** using one equivalent of TBSCl and imidazole gave alcohol **167** in 91% yield.[84] Swern oxidation of alcohol **167** using trifluoroacetic anhydride and dimethylsulfoxide,[87] successfully furnished ketone **168** in 95% yield **(Scheme 56)**.[88]



Scheme 56: Synthesis of ketone **168**

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.

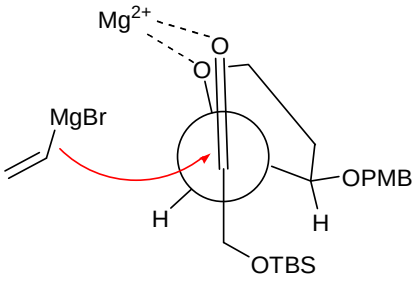
[iii] Prepared from 4-methoxybenzyl alcohol by treatment with sulfonyl chloride.



168 **169**

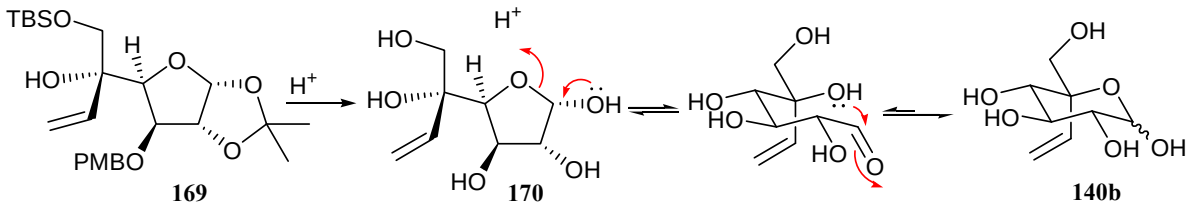
Scheme 57: Synthesis of alcohol **169**

The formation of a single stereoisomer of compound **169** can be rationalised by the Anti-Felkin approach depicted in **Scheme 58**.



Scheme 58: Anti-Felkin addition of vinylmagnesium bromide to ketone **168**

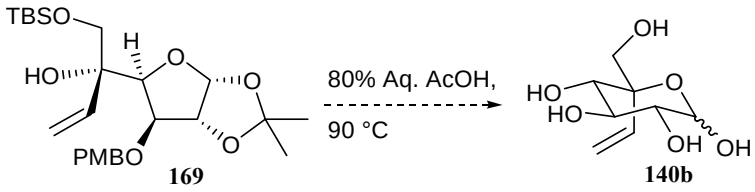
With compound **169** in hand, we turned our attention towards removal of the acetonide, *tert*-butyldimethylsilyl and 4-methoxybenzyl groups. Global deprotection of glucofuranoside **169** under acidic conditions would initially result in the furanose intermediate **170**. Subsequent ring opening of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



169 **170** **140b**

Scheme 59: Proposed mechanism for the formation of **140b**

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)**.

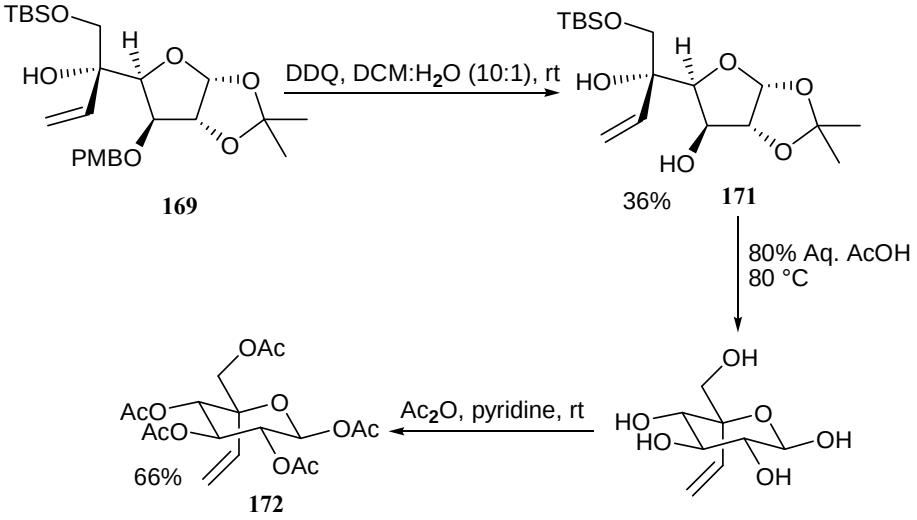


169 **140b**

Scheme 60: Attempted conversion of **169** to **140b**

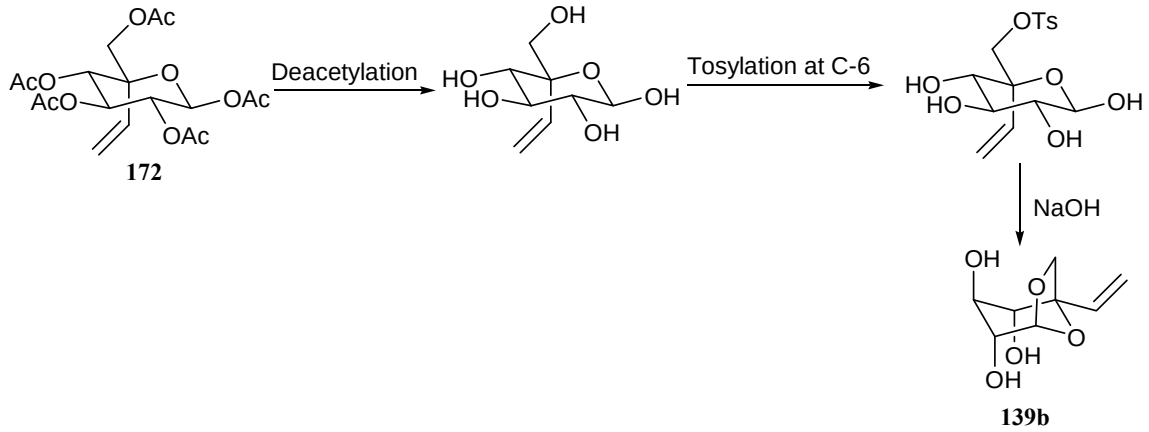
It was possible that the failure of this experiment was due to the inefficient deprotection of the 4-methoxybenzyl ether moiety at C-3. It was envisaged that instead, selective cleavage of

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 **140b**. Deprotection at C-3 was achieved *via* reaction of tertiary alcohol **169** with DDQ in a mixture of dichloromethane and water. Following purification, the desired diol **171** was obtained in 36% yield.[89] Unfortuantely, variation in temperature, concentration or reaction time failed to give higher yields of **171**. Diol **171** was then heated in 80% aqueous acetic acid. Acetylation of the crude mixture pleasingly furnished the desired pentaacetate **172** in 66% yield **(Scheme 61)**.



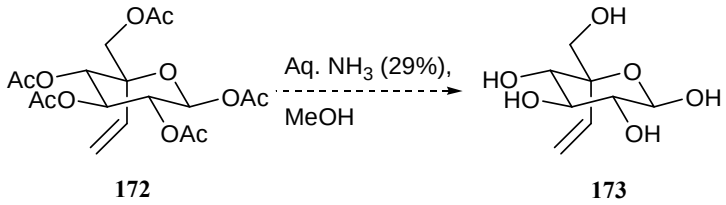
Scheme 61: Synthesis of pentaacetate **172**

With pentaacetate **172** in hand, we attempted conversion to the desired intermediate 1,6-anhydro-5-*C*-vinyl-D-glucopyranose (**139b**) using the Fraser-Reid method.[90] Thus, deacetylation of compound **172** followed by tosylation at O-6 and subsequent treatment with sodium hydroxide would afford the desired 1,6-anhydroglucose **139b (Scheme 62)**.[90]



Scheme 62: Fraser-Reid's approach to **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)**.



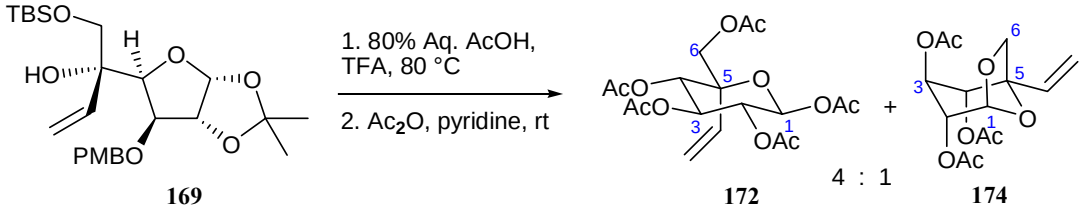
172 **173**

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)**.



169 **172** **174**

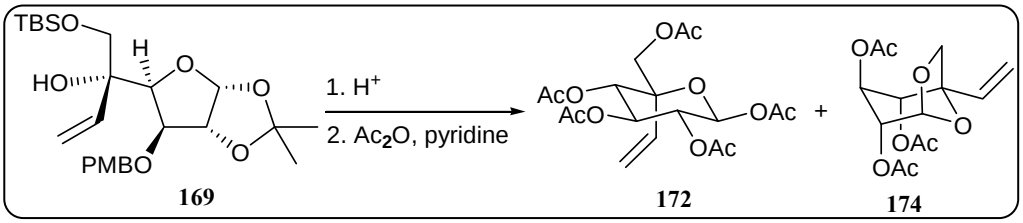
Scheme 64: Synthesis of **172** and **174**

^{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.



169 **172** **174**

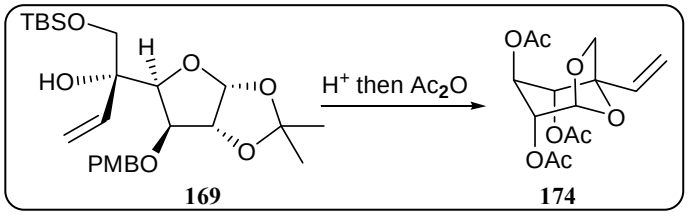
Entry	Reagents	Solvent, T	Time (h)	Composition of Crude	Yield[iv] 174 (%)
1	*p*-TsOH.H_2O (0.1 eq.)	Toluene, reflux	4	Predominantly **174**	21
2	TFA (1%)	AcOH, reflux	16	2 : 1 of **172** : **174**	Low
3	TFA	TFA, reflux	12	Predominantly **174**	14
4	*p*-TsOH.H_2O (0.1 eq.)	AcOH, 110 °C	16	Predominantly **174**	47
5	4 M HCl (in EtOAc)	EtOAc, reflux	16	Unidentified compounds	–
6	*p*-TsOH.H_2O (0.1 eq.)	EtOAc, reflux	16	Unidentified compounds	–
7	H_2SO_4 (0.1%)	AcOH, 100 °C	2.5	Predominantly **174**	32

[iv] Yield calculated over two steps

Table 3: Attempted conversion of **169** to **174**

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**.

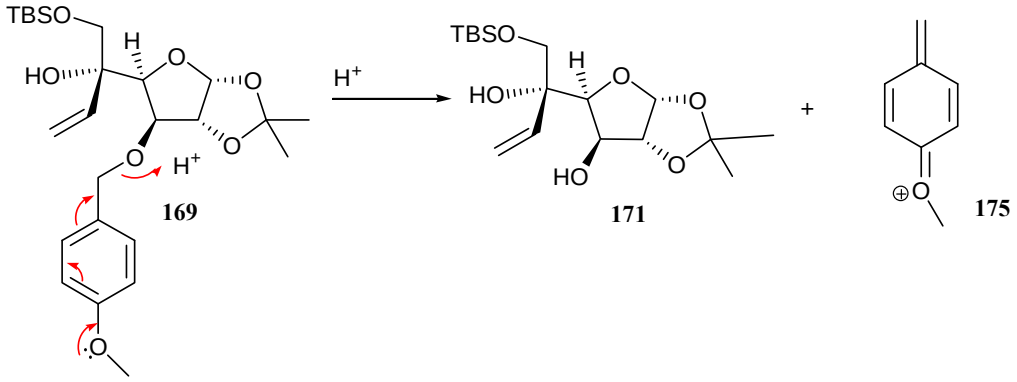


169 174

Entry	Reagents	Solvent, T (°C)	Time (h)	Composition of Crude	Yield 174 (%)
1	*p*-TsOH.H_2O (0.1 eq.), then Ac_2O	AcOH, 110	5	Predominantly **174**	41
2	1% H_2SO_4 in AcOH then Ac_2O	AcOH, 110	5	Complex mixture	---
3	0.01% H_2SO_4 in AcOH then Ac_2O	AcOH, 110	2.5	Predominantly **174**	32
4	0.01% H_2SO_4 in AcOH then Ac_2O	AcOH, 140	8	Predominantly **174**	40
5	0.05% H_2SO_4 in AcOH then Ac_2O	AcOH, 120	36	Predominantly **174**	40

Table 4: Attempted one pot conversion of **169** to **174**

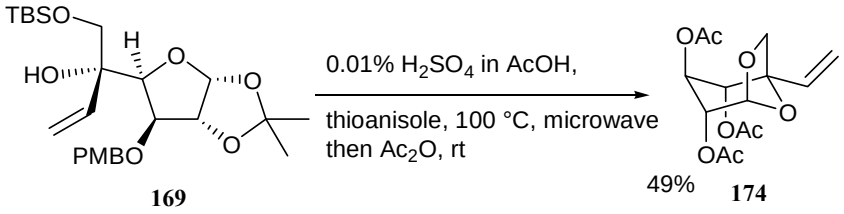
Although the one pot deprotection & acetylation reaction was successful, the yields obtained were still moderate. It was considered that the low yields obtained from the above reaction may be due to the presence of oxonium ion **175** in the reaction mixture causing unidentified side reactions **(Scheme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



Scheme 65: Formation of oxonium ion **175**

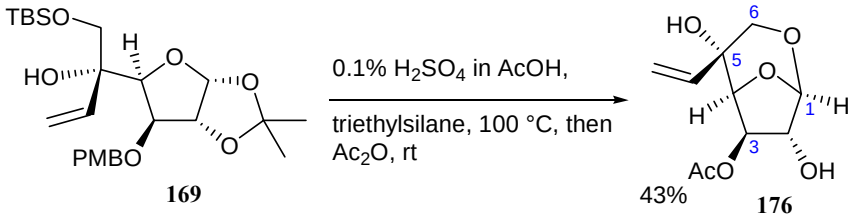
This prompted us to investigate the use of thioanisole or triethylsilane as nucleophilic scavengers. We also envisaged that microwave irradiation could enhance the deprotection and rearrangement of compound **169**. Thus, thioanisole was added to a solution of alcohol **169** in 0.01% H_2SO_4 in AcOH. 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)**.



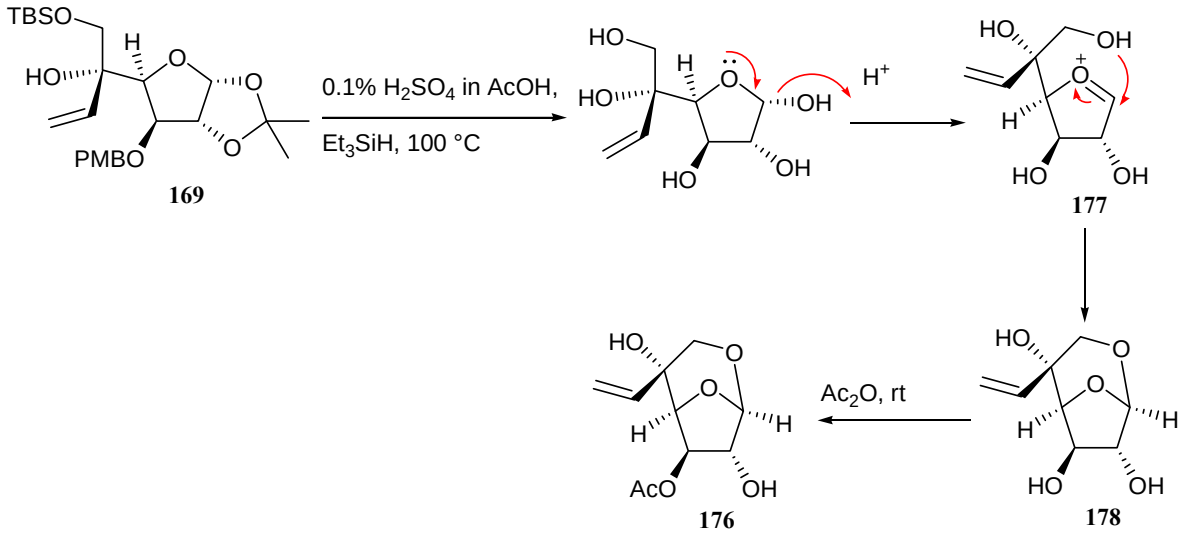
Scheme 66: Synthesis of compound **174**

Another method attempted was the addition of triethylsilane to a solution of compound **169** in the presence of H_2SO_4. Following treatment with acetic anhydride, a previously unobserved product was obtained, which was tentatively assigned as diol **176 (Scheme 67)**.[91]



Scheme 67: Formation of compound **176**

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*-butyldimethylsilyl 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)**.

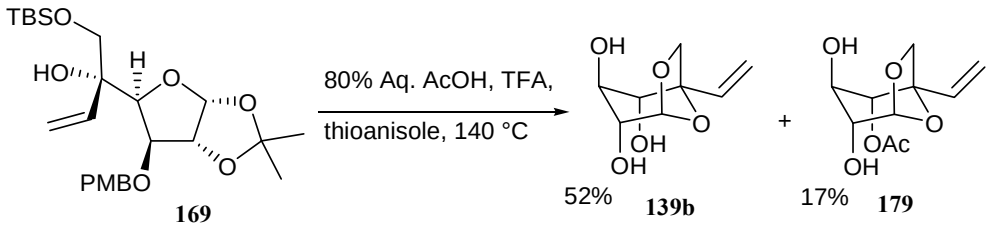


Scheme 68: Proposed mechanism for the formation of compound **176**

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.

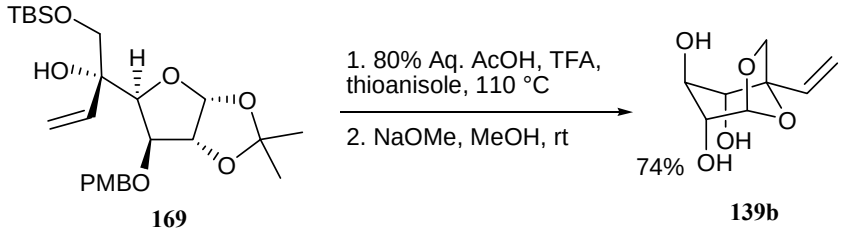
Gratifyingly, initial exposure of glucofuranoside **169** to TFA and thioanisole in 80% aq. AcOH, followed by purification, furnished our desired triol **139b** in 52% yield and diol **179** in 17% yield **(Scheme 69)**.



Scheme 69: Attempted isolation of triol **139b**

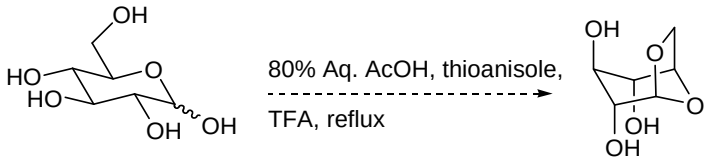
Although the yield of triol **139b** was good for such a complex transformation, the formation of diol **179** was not expected. Diol **179** presumably arises through a Fischer esterification process. To circumvent this problem, the crude reaction mixture was subjected to deacetylation using sodium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

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.[90] 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)**.



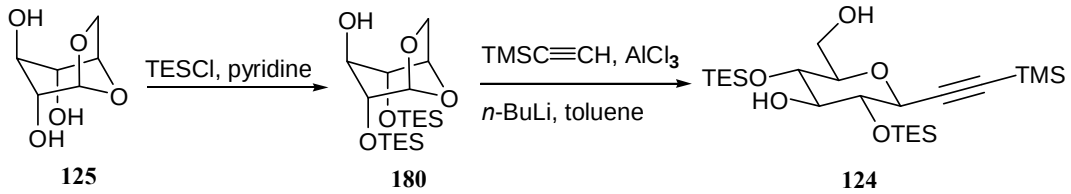
125

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

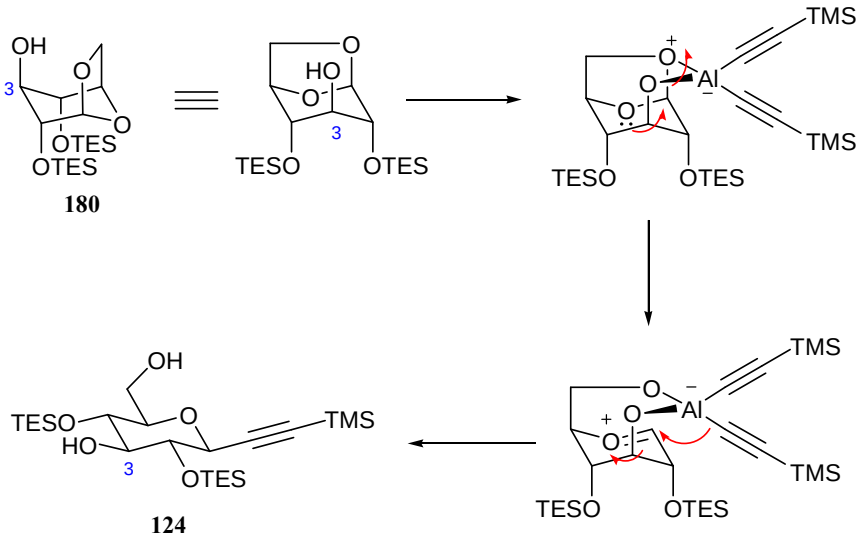
With 1,6-anhydro-5-*C*-vinyl-D-glucose (**139b**) in hand, we then proceeded to functionalise our sugar unit. In 2001, Vasella and co-workers reported that treatment of bis-silyl ether **180** (prepared by disilylation of 1,6-anhydroglucose **125**) with lithium (trimethylsilyl)acetylide in the presence of aluminium trichloride furnished diol **124 (Scheme 72)**.[77;92]



125 **180** **124**

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)**.



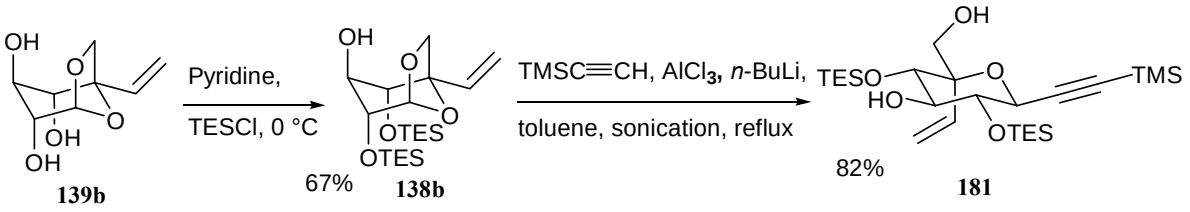
180 **124**

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.[58]

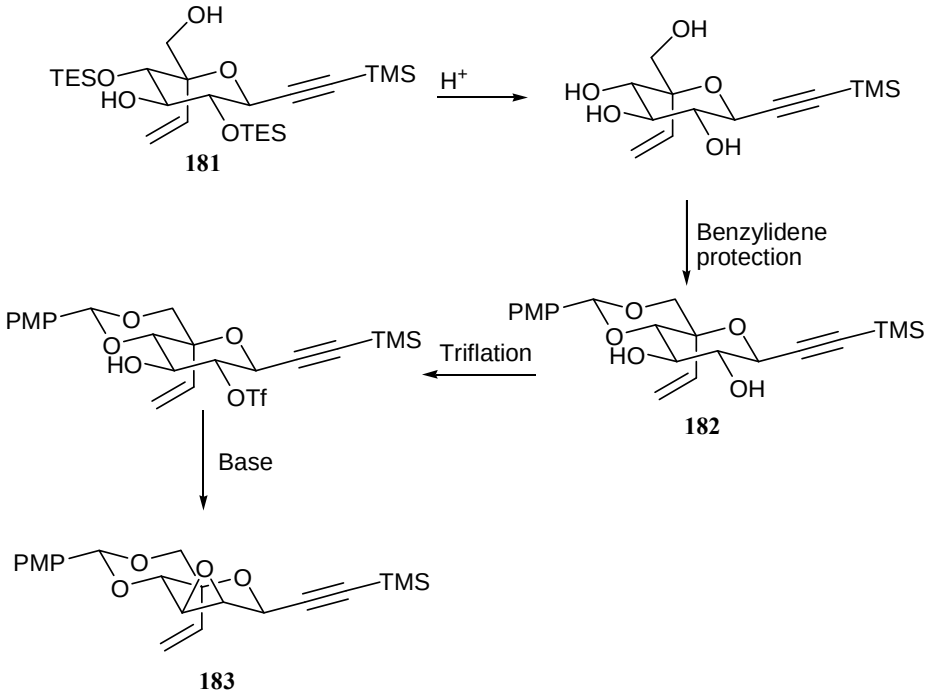
Similar treatment of compound **139b** with two equivalents of triethylsilyl chloride in pyridine successfully furnished the desired bis-silyl ether **138b** in 67% yield. Further treatment of

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]



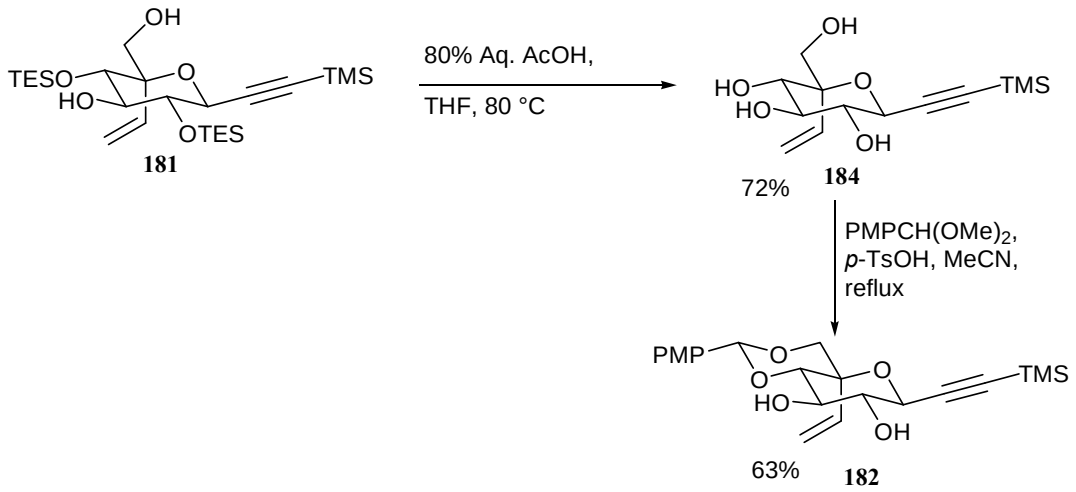
Scheme 74: Synthesis of glucoside **181**

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)**.



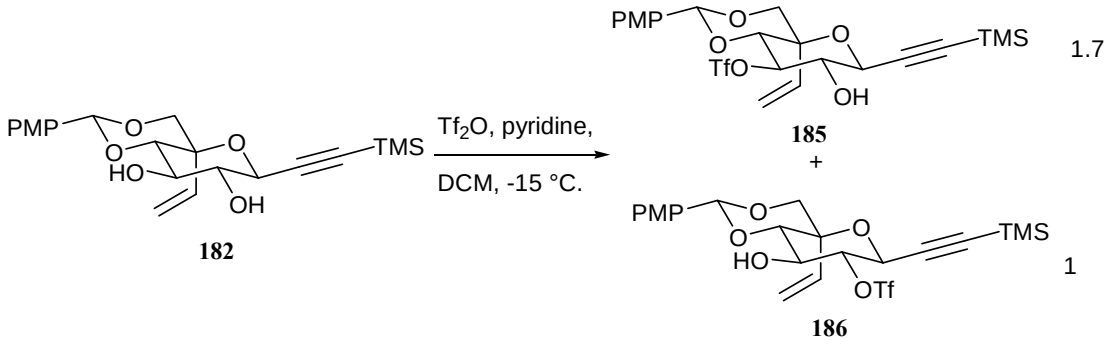
Scheme 75: Synthetic plan for the formation of epoxide **183**

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**

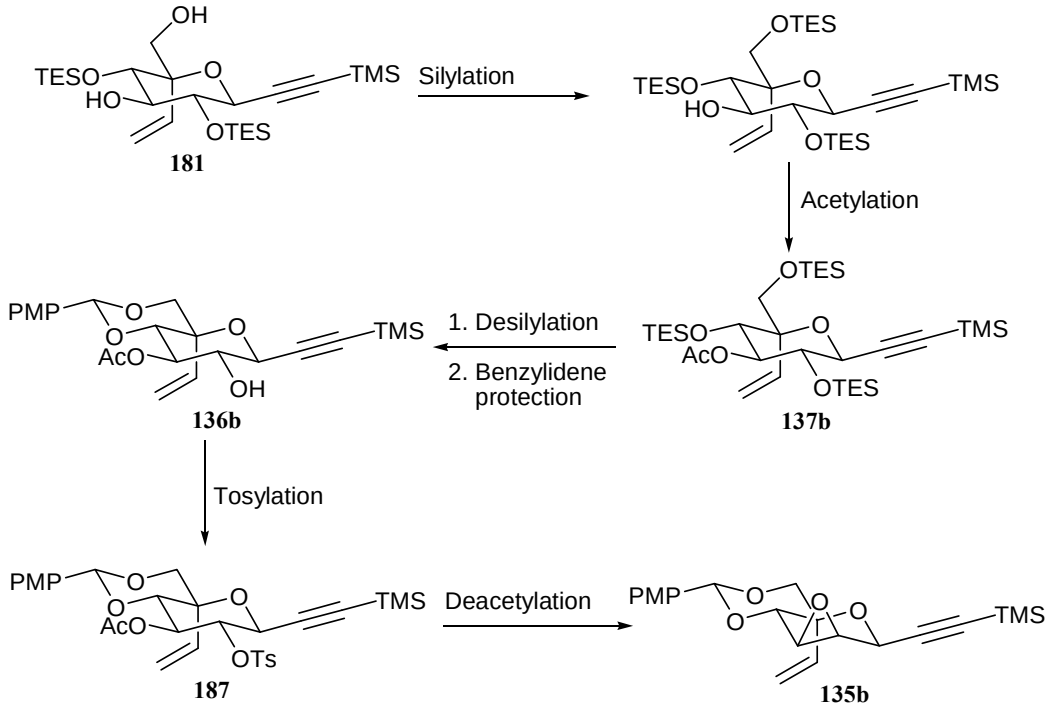
Triflation of benzylidene acetal **182** using triflic anhydride and pyridine, furnished a mixture of compounds **185** and **186** in a ratio of 1.7:1 in favour of the undesired triflate **185 (Scheme 77)**.



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

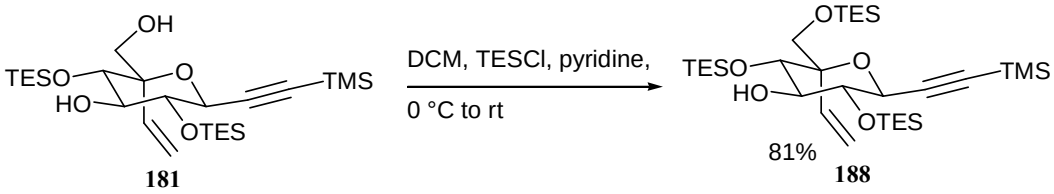
Unfortunately, due to the instability of these triflates, we were unable to obtain a complete set of characterisation data for either compound **185** or **186**. The preponderance of the undesired triflate **185** indicated that the yield of the subsequent epoxide formation would be low. This led us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



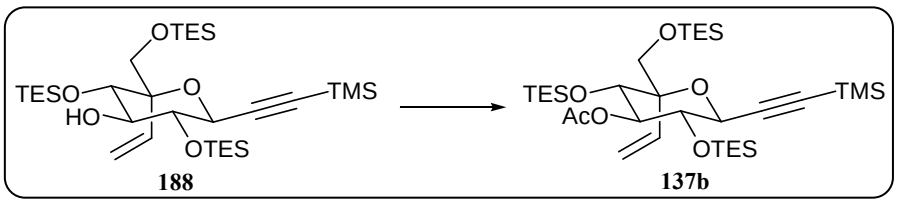
Scheme 78: Synthetic plan for the formation of epoxide **135b**

Initial treatment of diol **181** with triethylsilyl chloride and pyridine successfully furnished compound **188** in 81% yield (**Scheme 79**).



Scheme 79: Synthesis of **188**

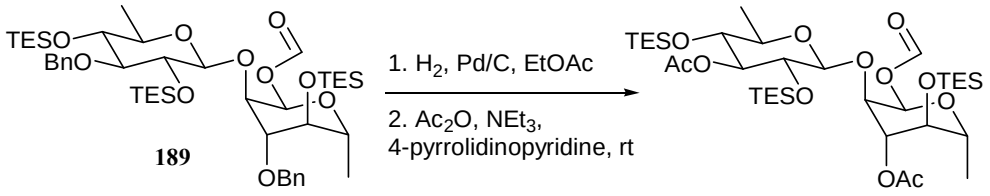
Unfortunately, attempted acetylation of the hydroxyl moiety at C-3 was non-trivial. The use of standard acetylation conditions such as acetic anhydride in pyridine or triethylamine failed to convert compound **188** to acetate **137b**. The failure of this transformation was perhaps due to the steric 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.



Entry	Reagents	Solvent	Time (h)	Temp	Results
1	Ac_2O (4 eq.)	Pyridine	14	rt	No reaction
2	Ac_2O (4 eq.)	NEt_3	14	rt	No reaction
3	Ac_2O (4 eq.), 4-pyrrolidinopyridine (0.25 eq.)	NEt_3	12	rt	No reaction
4	Ac_2O (4 eq.), 4-pyrrolidinopyridine (0.25 eq.)	NEt_3	2	80 °C	23%
5	Pentafluorophenyl acetate (2 eq.)	NEt_3	2	rt to 80 °C	No reaction
6	Ac_2O (2 eq.), TMSOTf (0.1 eq.)	DCM	0.25	rt	Decomposition
7	Ac_2O (2 eq.), TMSOTf (0.1 eq.)	DCM	0.25	−10 °C	Decomposition
8	AcCl (3 eq.)	NEt_3	2	rt	No reaction
9	AcCl (3 eq.), NaH (1.5 eq.)	THF	12	0 °C to rt	No Reaction
10	Isopropenyl acetate (3 eq.), I_2 (0.05 eq.)	Neat	0.3	80 °C	57%
11	Vinyl acetate (3 eq.), I_2 (0.05 eq)	Neat	2	rt to 80 °C	No reaction

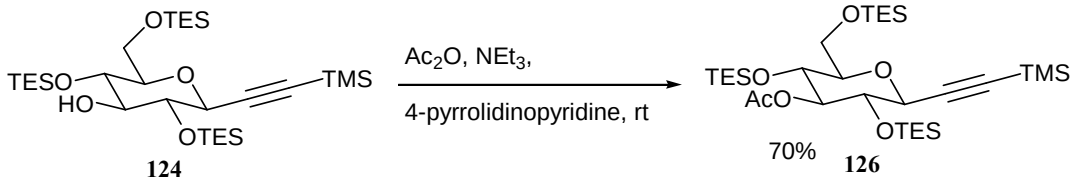
Table 5: Attempted conversion of alcohol **188** to acetate **137b**

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]



Scheme 80: Deprotection and acetylation of **189**

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)**.[78]

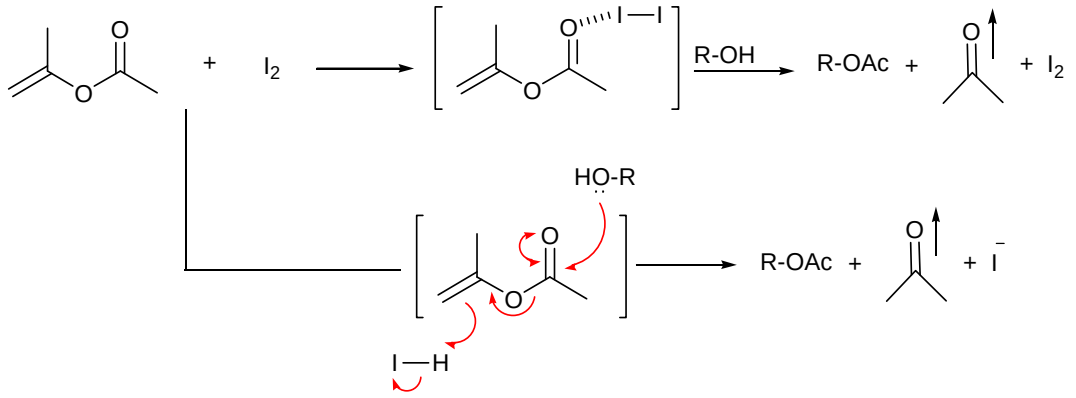


Scheme 81: Acetylation of **124**

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;[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**.

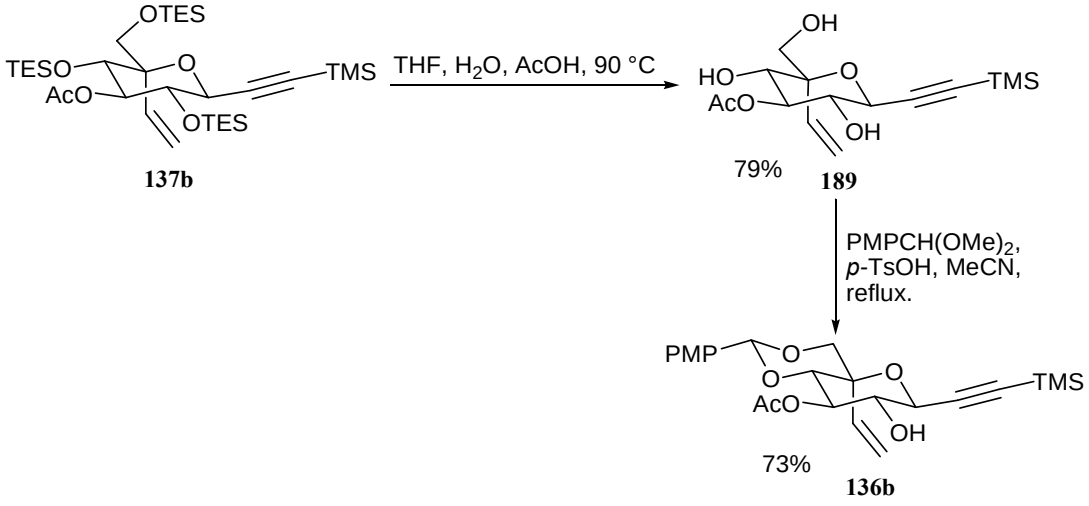
Fortunately, the use of isopropenyl acetate and iodine successfully furnished the desired acetate **137b** in a moderate yield (Table **5**, entry **10**). This method, described by Lier and co-workers in 2006, successfully utilised transesterification conditions to convert various free alcohols to their 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)**.[97]



Scheme 82: Acetylation mechanism of alcohols in the presence of I_2

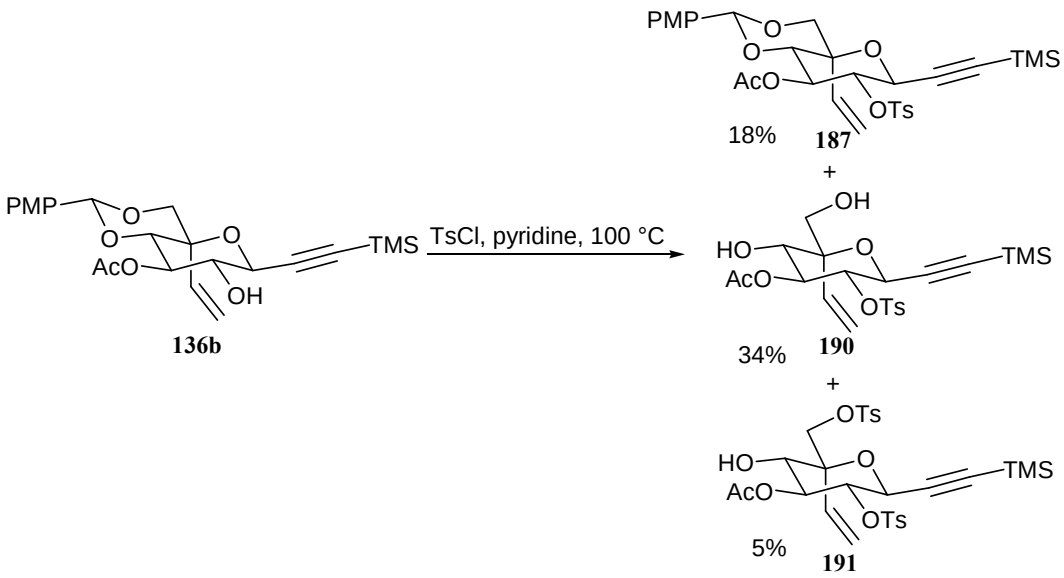
In 2006 Saikia *et al*. showed that acetylation of alcohols could also be achieved using vinyl acetate in the presence of molecular iodine. [98] Thus we hoped to utilise Saikia's method to increase the yield of our acetylation reaction. Unfortunately when isopropenyl acetate was replaced with vinyl acetate (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**).



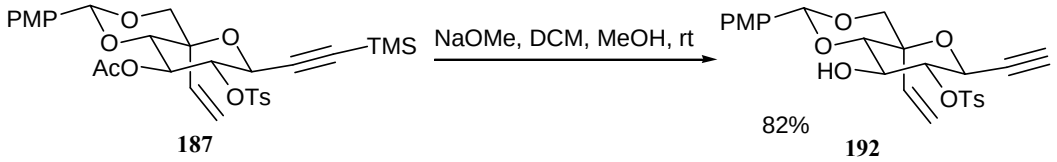
Scheme 83: Synthesis of benzylidene acetal **136b**

The attempted tosylation of compound **136b** using tosyl choride 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)**.



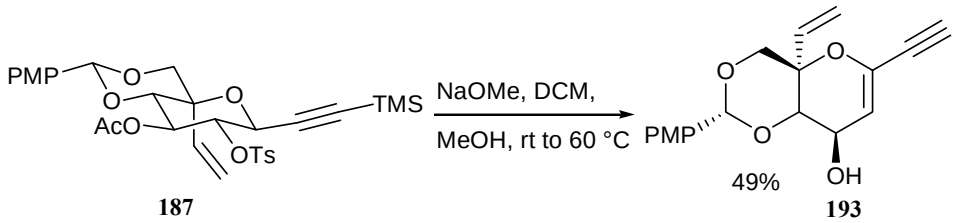
Scheme 84: Attempted tosylation of compound **136b**

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)**.



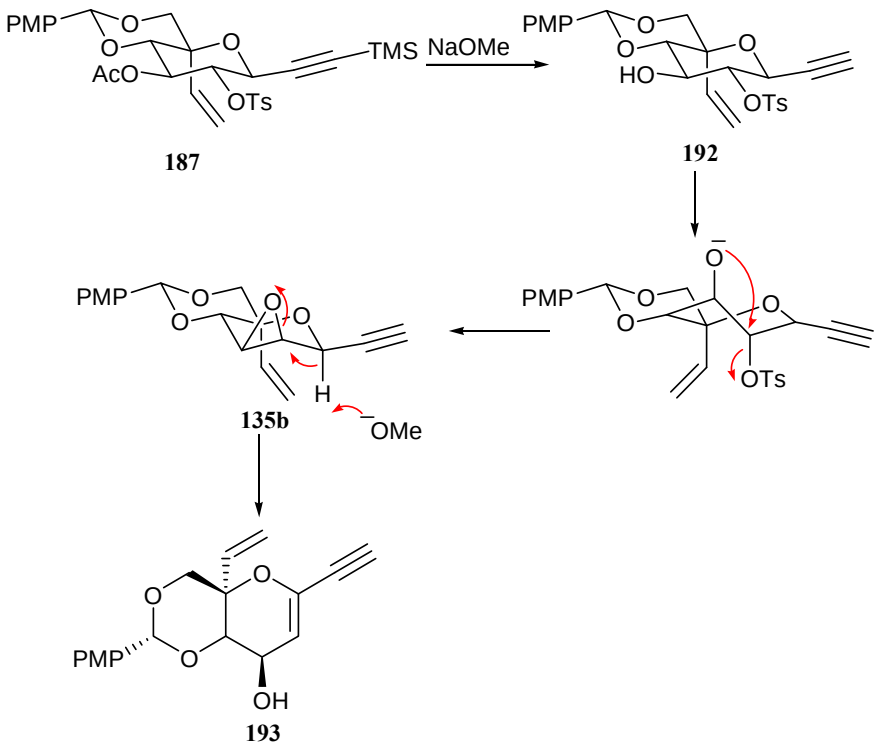
Scheme 85: Formation of alcohol **192**

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)**.



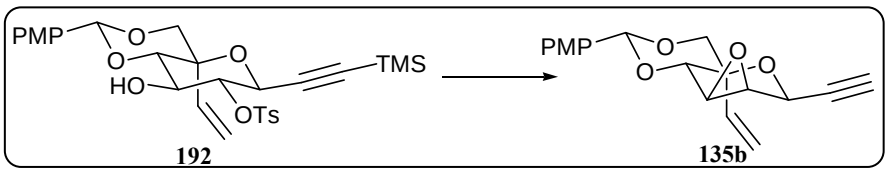
Scheme 86: Formation of enyne **193**

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**

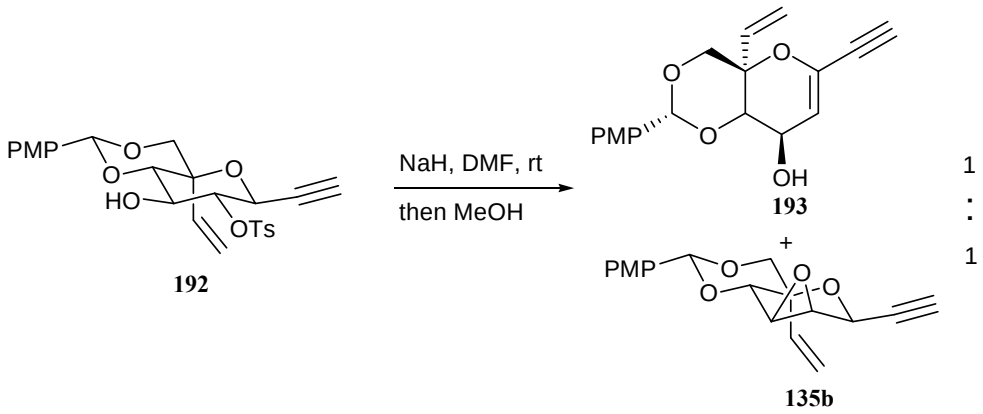
We investigated treatment of alcohol **192** with various combinations of base, solvent and temperature in the hope of finding conditions under which epoxide **135b** was formed but did not undergo elimination to enyne **193**. **Table 6** shows the different reaction conditions utilised to effect the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



Entry	Reagents	Temp	Results
1	Cs_2CO_3, MeOH	Rt	SM recovered
2	Cs_2CO_3, MeOH	60 °C	Enyne formation
3	NaH, DMF	Rt	Enyne formation
4	NaH, DMF	0 °C	SM recovered
5	*t*-BuOK, DMF	Rt	Enyne formation
6	*t*-BuOK, DMF	0 °C	SM recovered

Table 6: Attempted conversion of alcohol **192** to epoxide **135b**

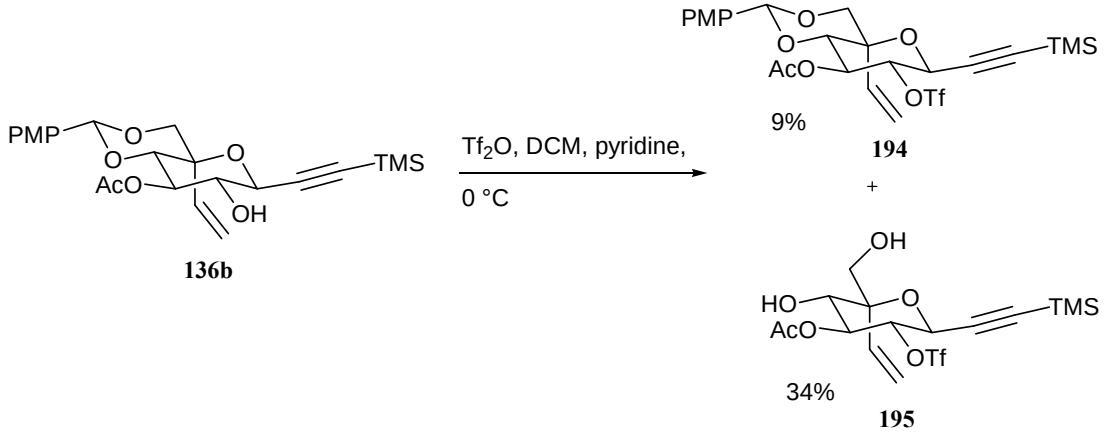
It appeared from the above results that the rate of E2 elimination of the epoxide was comparable to its rate of formation. Indeed, when the reaction of **192** with sodium hydride in DMF at room temperature was quenched with methanol after 1 min, a 1:1 mixture of **135b**:**192** was formed together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



Scheme 88: Formation of enyne **193** and epoxide **135b**

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**.

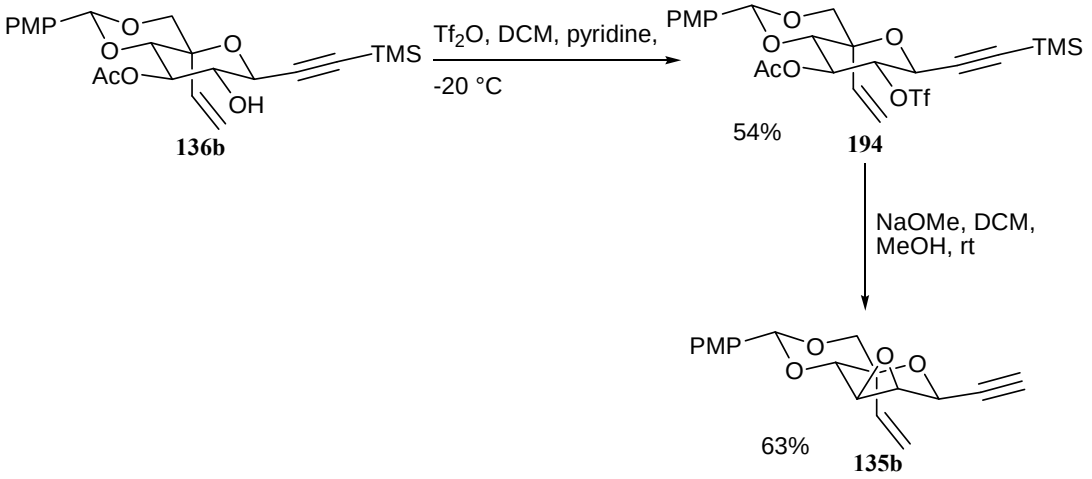
Initial exposure of compound **136b** to triflic anhydride and pyridine furnished a mixture of triflate **194** and diol **195** in 9% and 34% respectively **(Scheme 89)**.



Scheme 89: Attempted triflation of compound **136b**

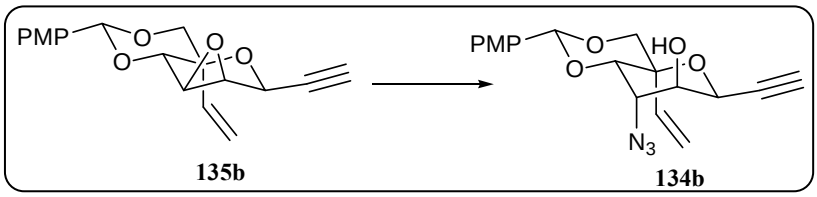
The formation of diol **195** was due to the hydrolysis of the 4-methoxybenzylidene acetal protecting group. Repeating the triflation experiment at −20 °C pleasingly furnished triflate

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)**.

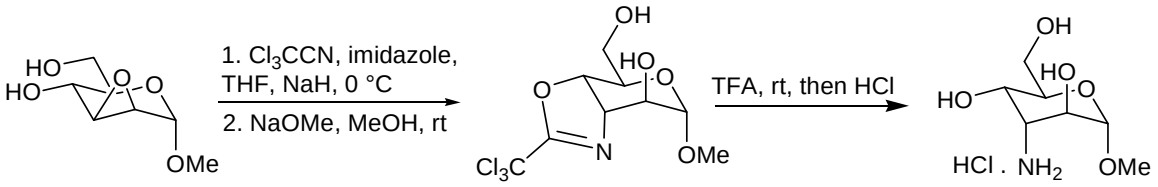


Entry	Reagents	Temp	Results
1	NaN_3, H_2O, NH_4Cl, 2-methoxyethanol	80 °C	Acetal deprotection
2	$LiClO_4$, NaN_3, MeCN	rt-80 °C	Acetal deprotection
3	$Yb(OTf)_3$, LiO*i*-Pr, Me_3SiN_3, THF	65 °C	No reaction
4	$Yb(OTf)_3$, LiO*i*-Pr, NaN_3, THF	65 °C	No reaction

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

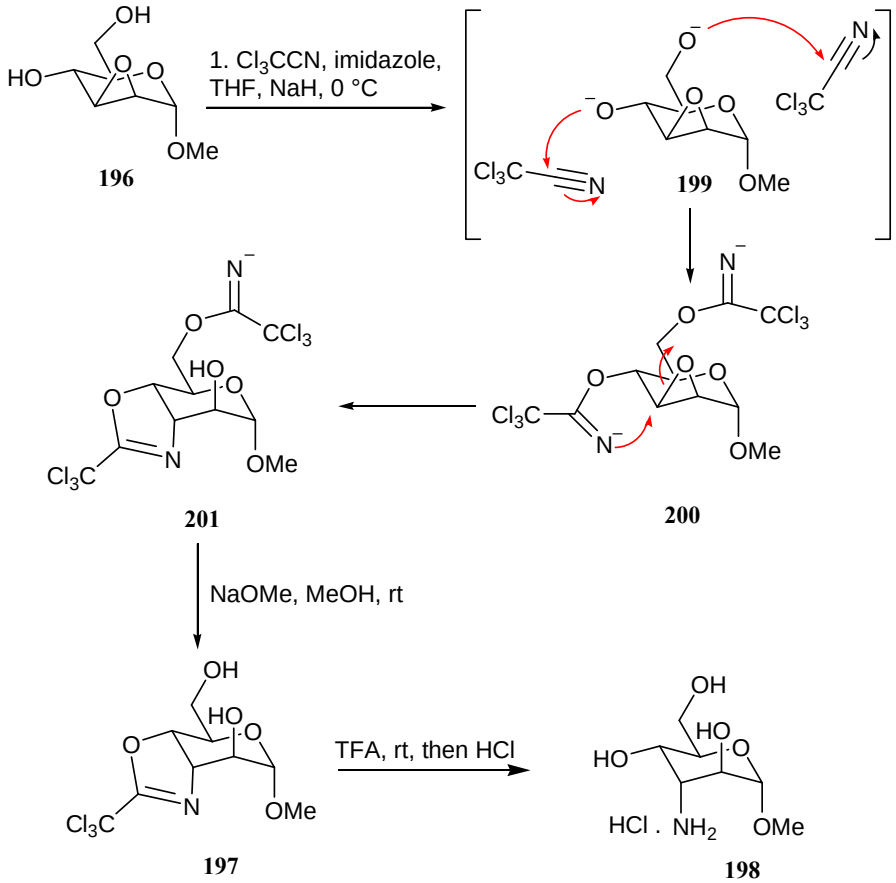
Treatment of epoxide **135b** with sodium azide and aqueous ammonium chloride in 2-methoxyethanol(Table **7**, entry **1**),[95] with lithium perchlorate and sodium azide in acetonitrile, (Table **7**, entry **2**),[99] or with ytterbium isopropoxide and either sodium azide and TMS azide (Table **7**, 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.[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)**.[101]



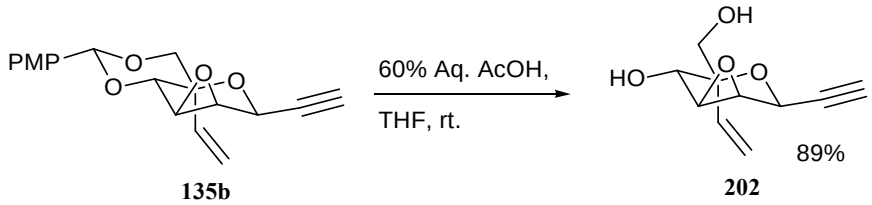
Scheme 91: Jacobsen's synthesis of aminosugar **198**

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)**.[101]



Scheme 92: Proposed mechanism for the formation of aminosugar **198**

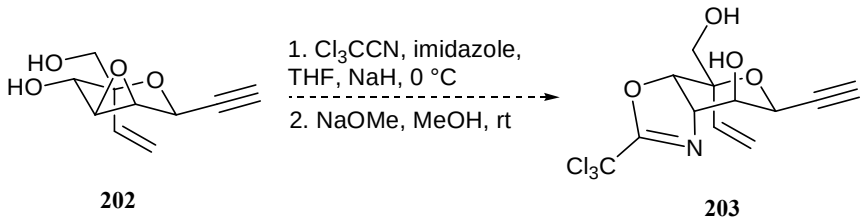
Therefore, the acetal group of epoxide **135b** was hydrolysed using 60% aqueous acetic acid in THF. After 5 hours, diol **202** was obtained in 89% yield **(Scheme 93)**



135b **202**

Scheme 93: Synthesis of diol **202**

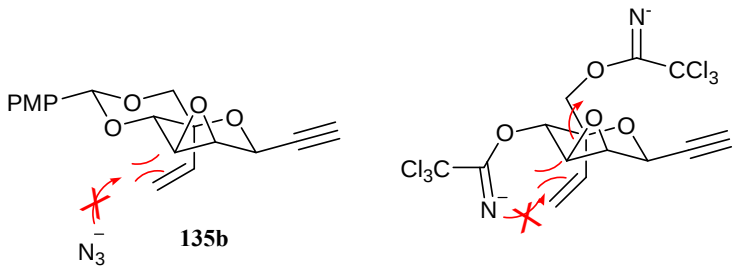
Diol **202** was dissolved in THF and treated with trichloroacetonitrile and imidazole in the presence of sodium hydride. After 1 hour, methanol was added followed by NaOMe (1M). Following neutralisation and evaporation, we were unable to obtain the desired oxazoline **203 (Scheme 94)**.



202 **203**

Scheme 94: Attempted conversion of diol **202** to oxazoline **203**

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)**.

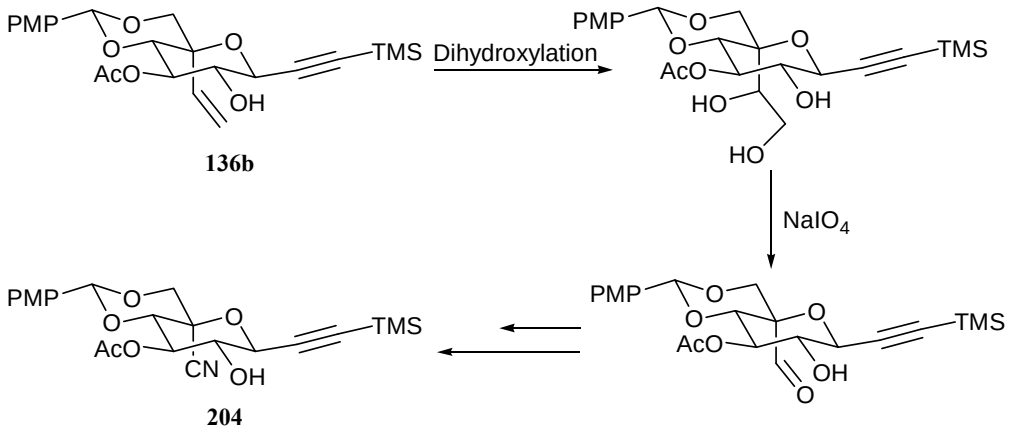


Scheme 95: Failure of epoxide ring opening

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.

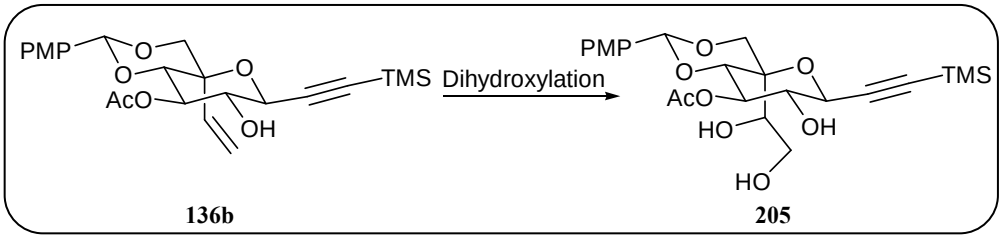
2.3 Synthesis *via* 1,6-anhydro-5-*C*-cyano-D-glucose

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**

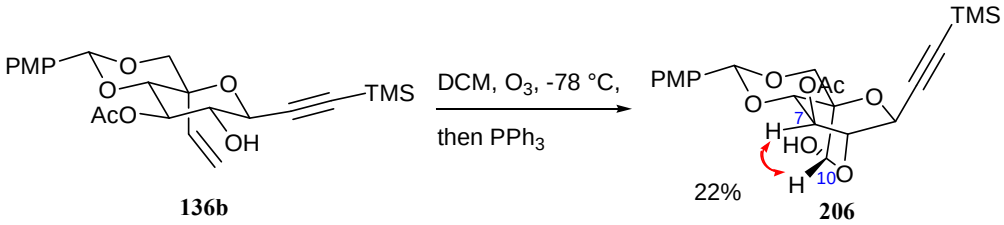
Unfortunately, attempted dihydroxylation of the terminal alkene failed to give the desired triol **205**. **Table 8** shows the various reaction conditions attempted to effect the transformation.



Entry	Reagents	Temp	Result
1	$K_2OsO_4.2H_2O$, NMO, acetone	Rt	No reaction
2	$K_2OsO_4.2H_2O$, NMO, citric acid, *t*-BuOH/H_2O	rt to 80 °C	No reaction
4	$RuCl_3$, H_2SO_4, $NaIO_4$, EtOAc/H_2O/MeCN	Rt	No reaction
5	AD-mix-α, *t*-BuOH/H_2O	Rt	No reaction

Table 8: Attempted dihydroxylation of **136b**

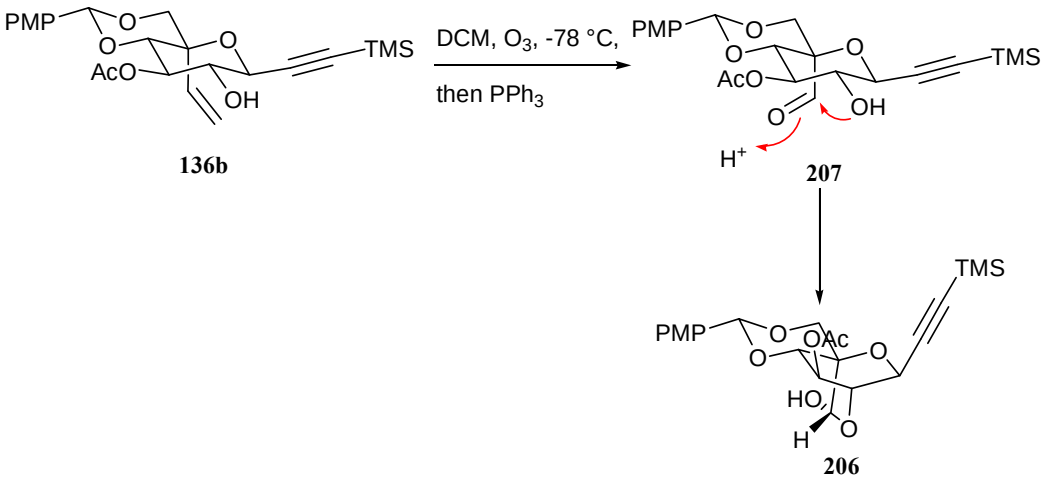
The failure of the dihydroxylation experiment led us to utilise ozonolysis as an alternative way to obtain our desired aldehyde. Therefore, ozone was bubbled through a solution of compound **136b** in dichloromethane. Treatment of the resulting solution with PPh_3 did not give the desired aldehyde and instead furnished hemiacetal **206** in 22% yield **(Scheme 97)**.



Scheme 97: Formation of hemiacetal **206**

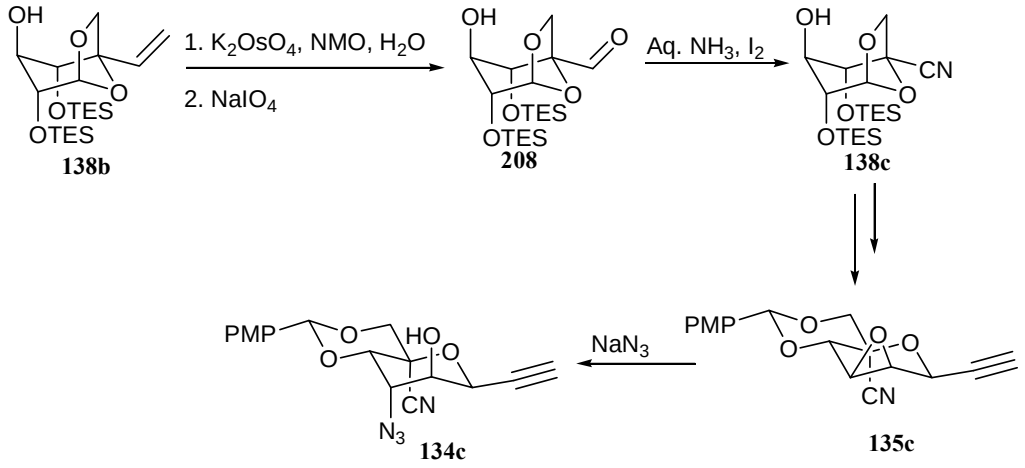
NOE studies positively revealed the stereochemistry of the hemiacetal chiral centre by indicating the presence of a long range interaction between the proton at C-7 and that of C-10.

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



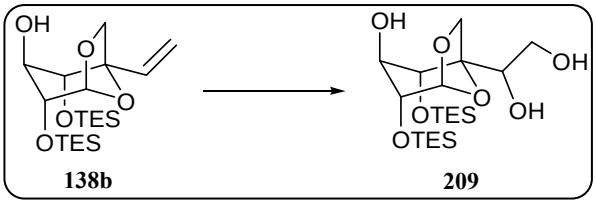
Scheme 98: Proposed mechanism for the formation of hemiacetal **206**

The unsuccessful attempt to isolate aldehyde **207** and the low yield of **206** prompted us to incorporate the nitrile moiety several steps backwards starting from bis-silyl ether **138b**. We envisaged that initial oxidative cleavage of the vinyl moiety followed by treatment with aqueous ammonia and iodine should furnish the desired nitrile **138c**.[102] Compound **138c** would be converted to epoxide **135c** using previously successful procedures. Epoxide **135c** would be subjected to treatment with sodium azide to form the desired diaxial azidoalcohol **134c (Scheme 99)**.



Scheme 99: Proposed synthesis of azidoalcohol **134c**

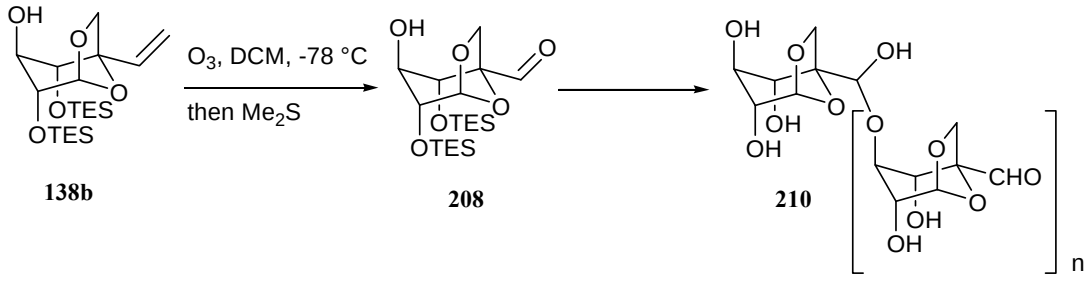
Conversion of alkene **138b** to aldehyde **208** was initially attempted *via* dihydroxylation. **Table 9** shows the various reaction conditions utilised to effect the transformation.



Entry	Reagents	Temp	Result
1	$K_2OsO_4.2H_2O$, NMO, acetone	Rt	No reaction
2	$K_2OsO_4.2H_2O$, NMO, citric acid, *t*-BuOH/H_2O	rt to 80 °C	No reaction
4	$RuCl_3$, H_2SO_4, $NaIO_4$, EtOAc/H_2O/MeCN	Rt	No reaction
5	AD-mix-α, *t*-BuOH/H_2O	Rt	No reaction

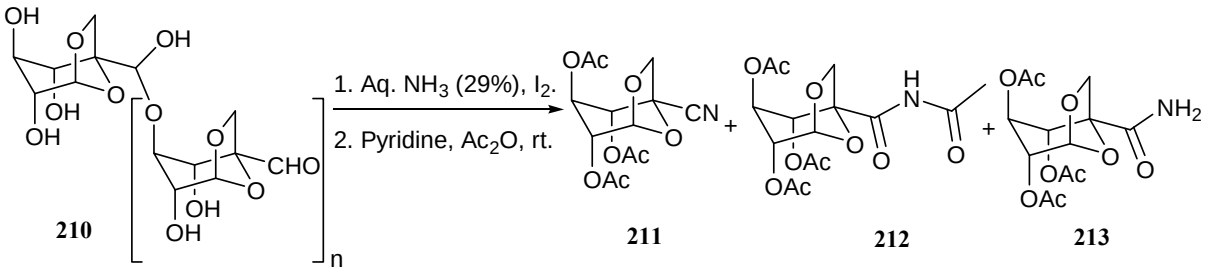
Table 9: Attempted dihydroxylation of alkene **138b**

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 Me_2S 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)**.



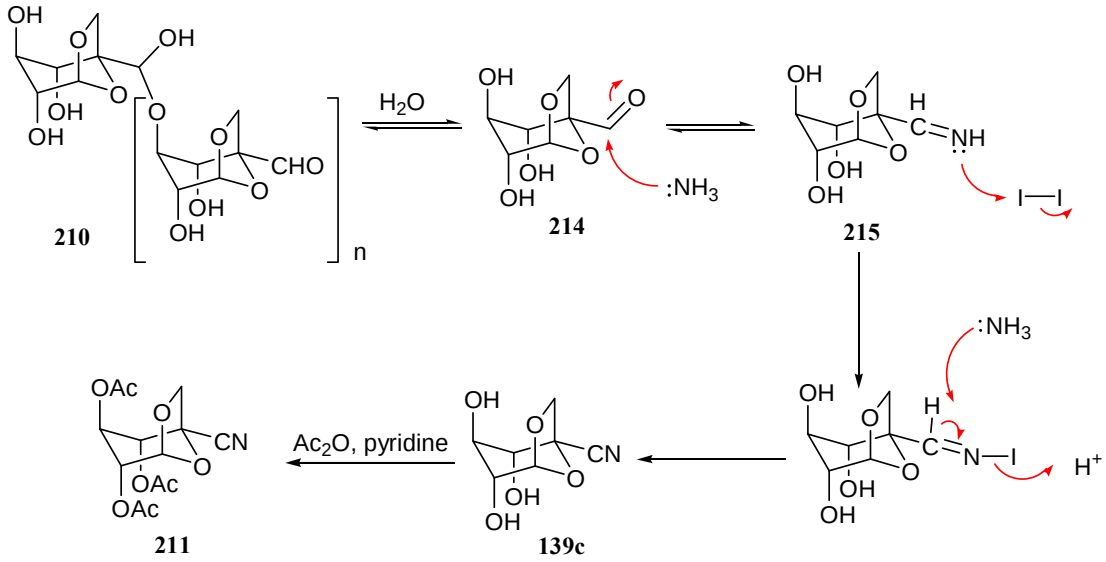
Scheme 100: Formation of polymer **210**

Subjection of polymer **210** to aqueous ammonia and iodine followed by acetylation resulted in the formation of compounds **211**, **212** and **213 (Scheme 101)**.[103]



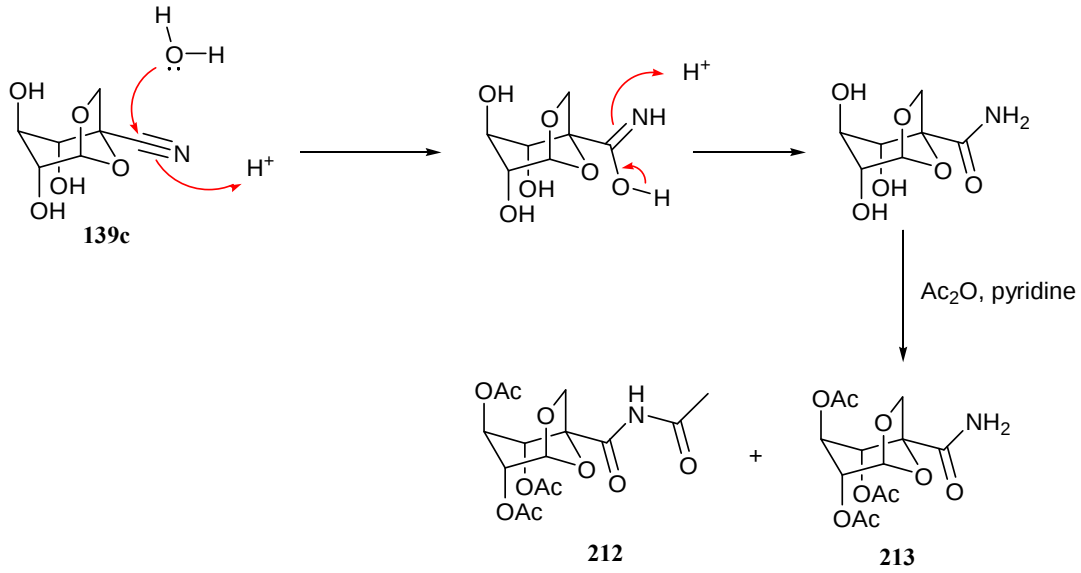
Scheme 101: Conversion of polymer **210** to **211**, **212** and **213**

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)**.



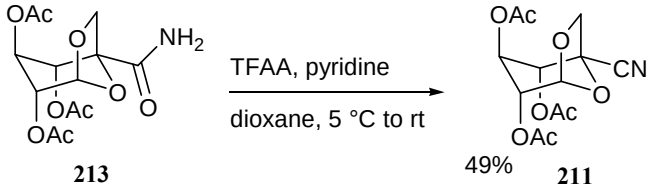
Scheme 102: Proposed mechanism for the formation of nitrile **211**

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)**.



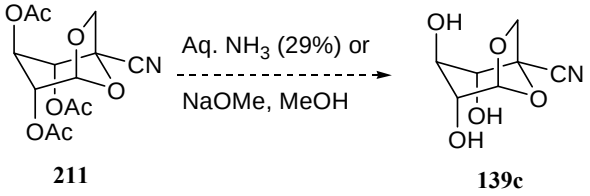
Scheme 103: Proposed mechanism for the formation of amide **213** and imide **212**

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**.[104] 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)**.[105]



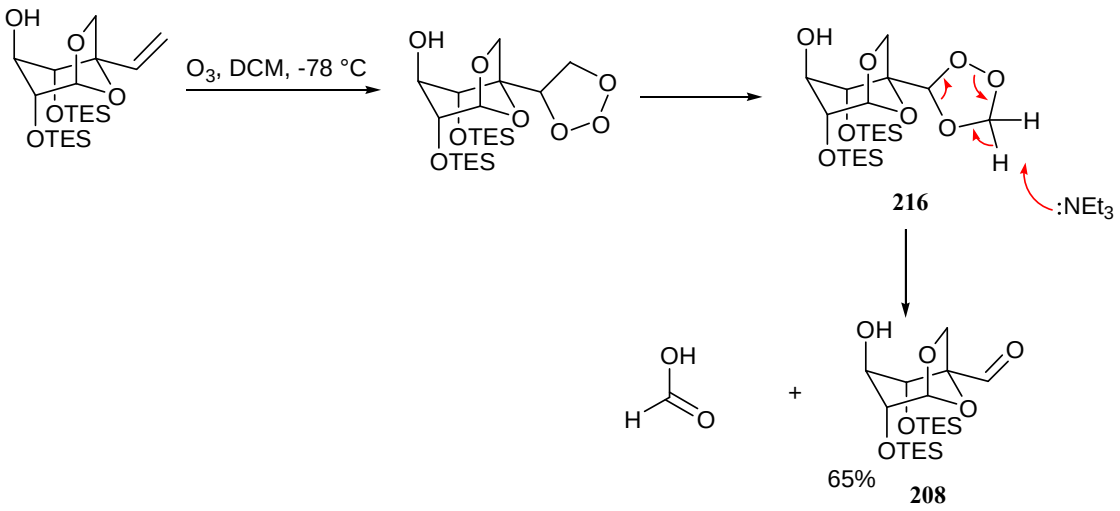
Scheme 104: Conversion of amide **213** to nitrile **211**

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



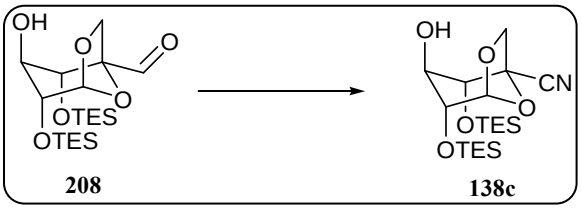
Scheme 105: Attempted deacetylation of nitrile **211**

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)**.[106]



Scheme 106: Proposed mechanism for the cleavage of trioxolane **216** in the presence of NEt_3

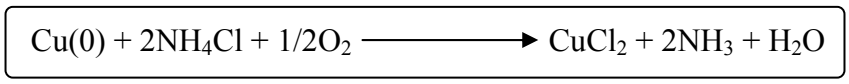
Table 10 illustrates the various attempted procedures for the conversion of aldehyde **208** to nitrile **138c**.



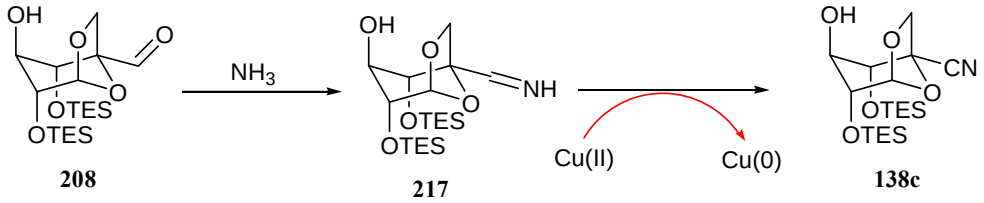
Entry	Reagents	Temp	Yield 138c (%)
1	NBS, aq NH_3	0 °C	No reaction
2	$NH_2OH.HCl$, NaI, MeCN	80 °C	No reaction
3	$NH_2OH.HCl$, $EtOPOCl_2$, DBU, DCM	Rt	No reaction
4	Cu(0), NH_4Cl, pyridine, O_2	Rt	42

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).

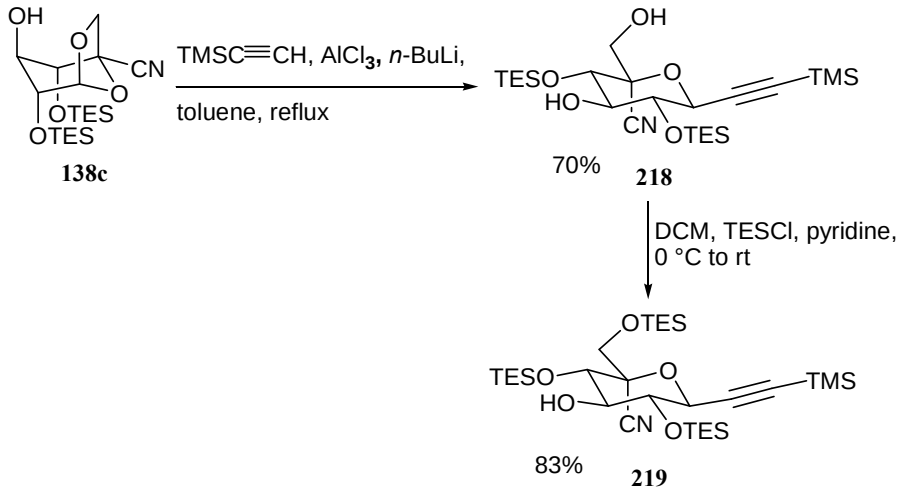


Ammonia will undergo a condensation reaction with aldehyde **208** to generate aldimine **217**, which can be oxidised to the desired nitrile **138c (Scheme 113)**.[110]



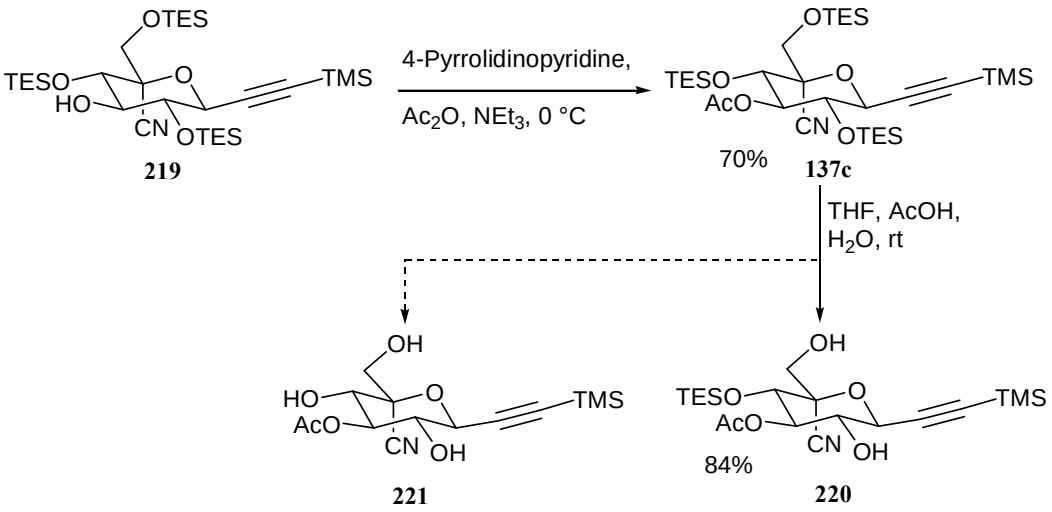
Scheme 107: Proposed mechanism for the formation of nitrile **138c**

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]



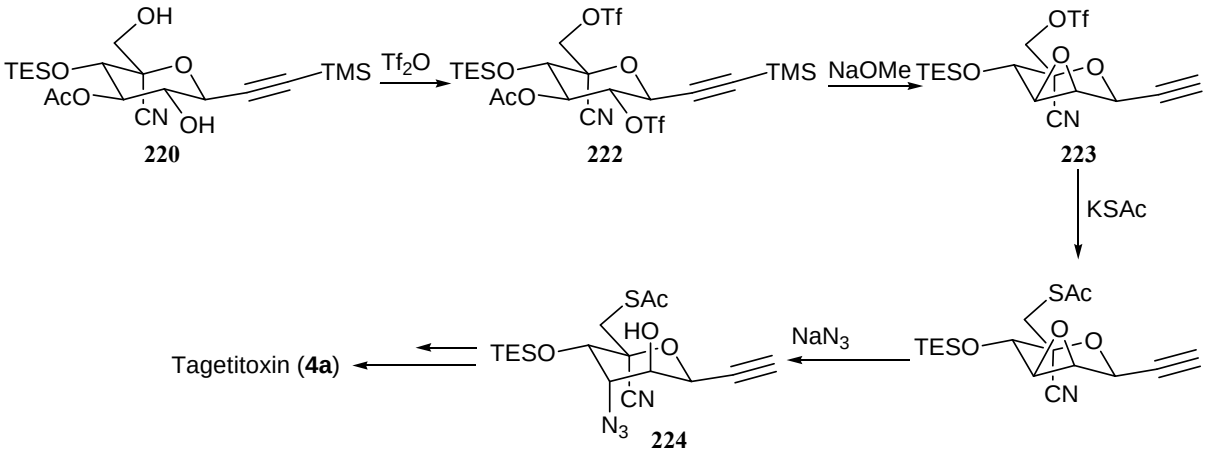
Scheme 108: Synthesis of tris-silyl ether **219**

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)**.



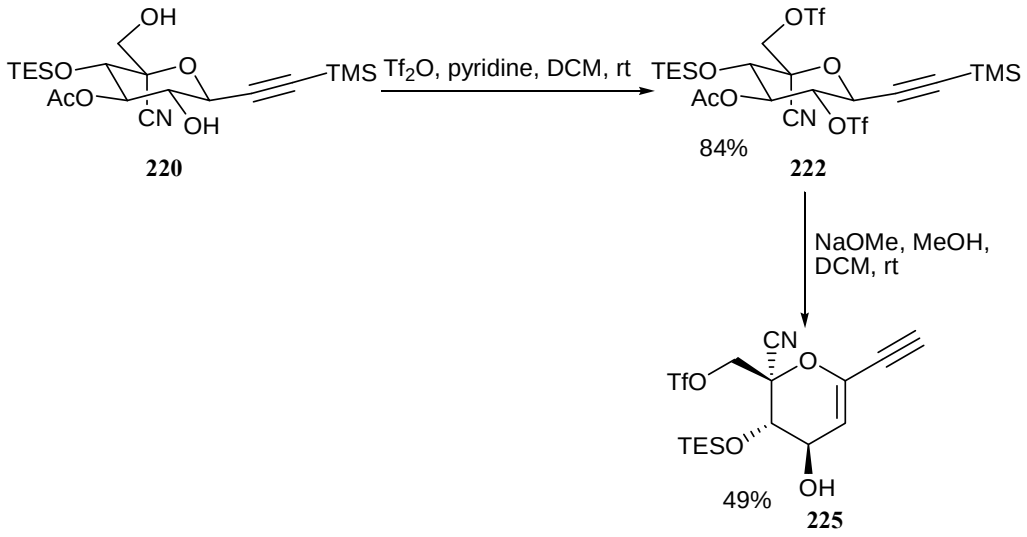
Scheme 109: Attempted synthesis of triol **221**

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)**.



Scheme 110: Proposed synthesis of azido intermediate **224**

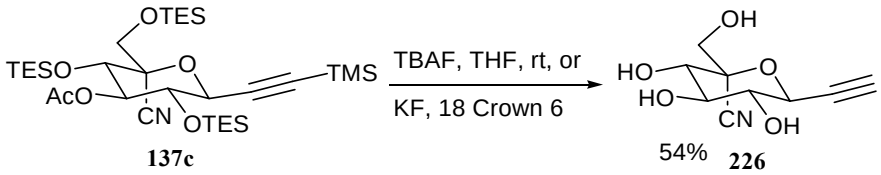
Starting from diol **220**, initial treatment with triflic anhydride and pyridine successfully furnished ditriflate **222** in excellent yield. Unfortunately, when compound **222** was subjected to treatment with sodium methoxide in methanol, no epoxide formation was observed and instead, enyne **225** was isolated in 49% yield **(Scheme 111)**.



Scheme 111: Synthesis of enyne **225**

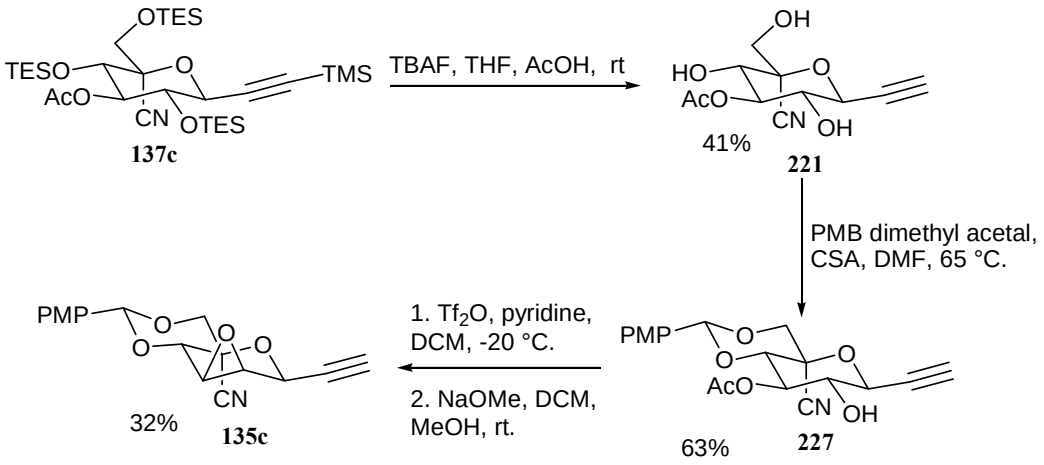
To overcome this problem, we decided to try other milder conditions. Unfortunately the same enyne product was formed when ditriflate **222** was treated with K_2CO_3, Cs_2CO_3 or aq. NH_3.

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)**.



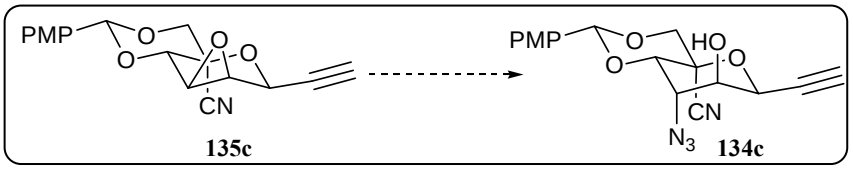
Scheme 112: Synthesis of compound **226**

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)**.



Scheme 113: Synthesis of epoxide **135c**

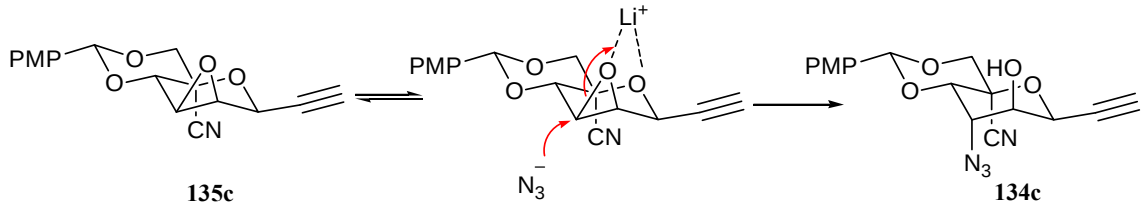
With epoxide **135c** in hand, we investigated its azide ring opening at C-3. **Table** (**11**) shows the various reaction conditions used to convert epoxide **135c** to azide **134c**.[95;99;100]



Entry	Reagents	Temp (°C)	Yield 134c (%)
1	$Yb(OTf)_3$, LiO*i*-Pr, NaN_3, THF	65	No reaction
2	NaN_3, MeOH, NH_4Cl	80	No reaction
3	DMF, NaN_3	65	No reaction
4	$LiClO_4$, NaN_3, MeCN	80	35

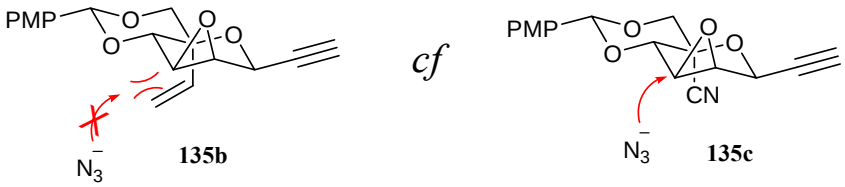
Table 11: Attempted conversion of epoxide **135c** to azide **134c**

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.[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 $LiClO_4$-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**

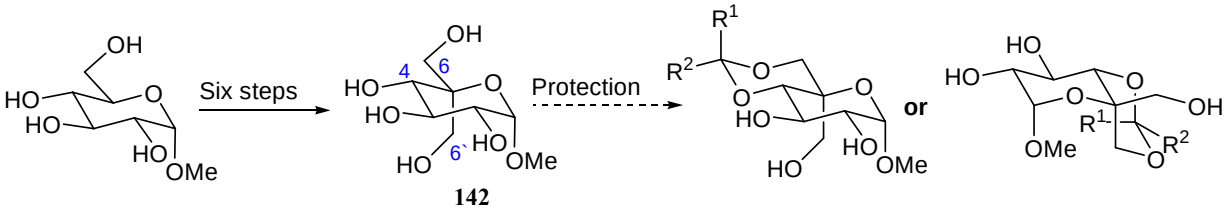
The formation of azide **135c** is encouraging for the completion of the synthesis of tagetitoxin. Unfortunately, time constraints prevented us from progressing further on this route.

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.

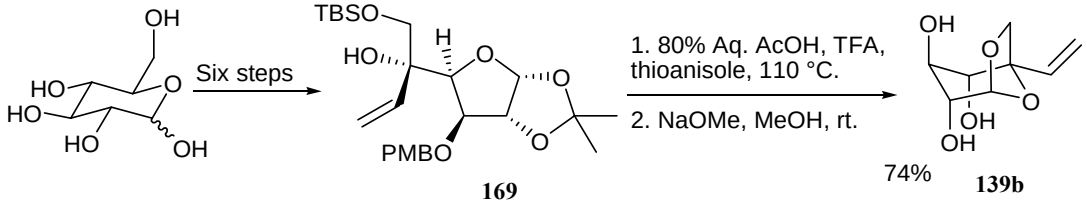
The aim of this project was to apply the thiol cyclisation methodology to a synthesis of tagetitoxin itself; as a first step, this necessitated the incorporation of the incorporation of a hydroxymethyl, vinyl or nitrile group into the C-5 position of D-glucose.

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)**.



Scheme 116: Attempted selective protection of pentaol **142**

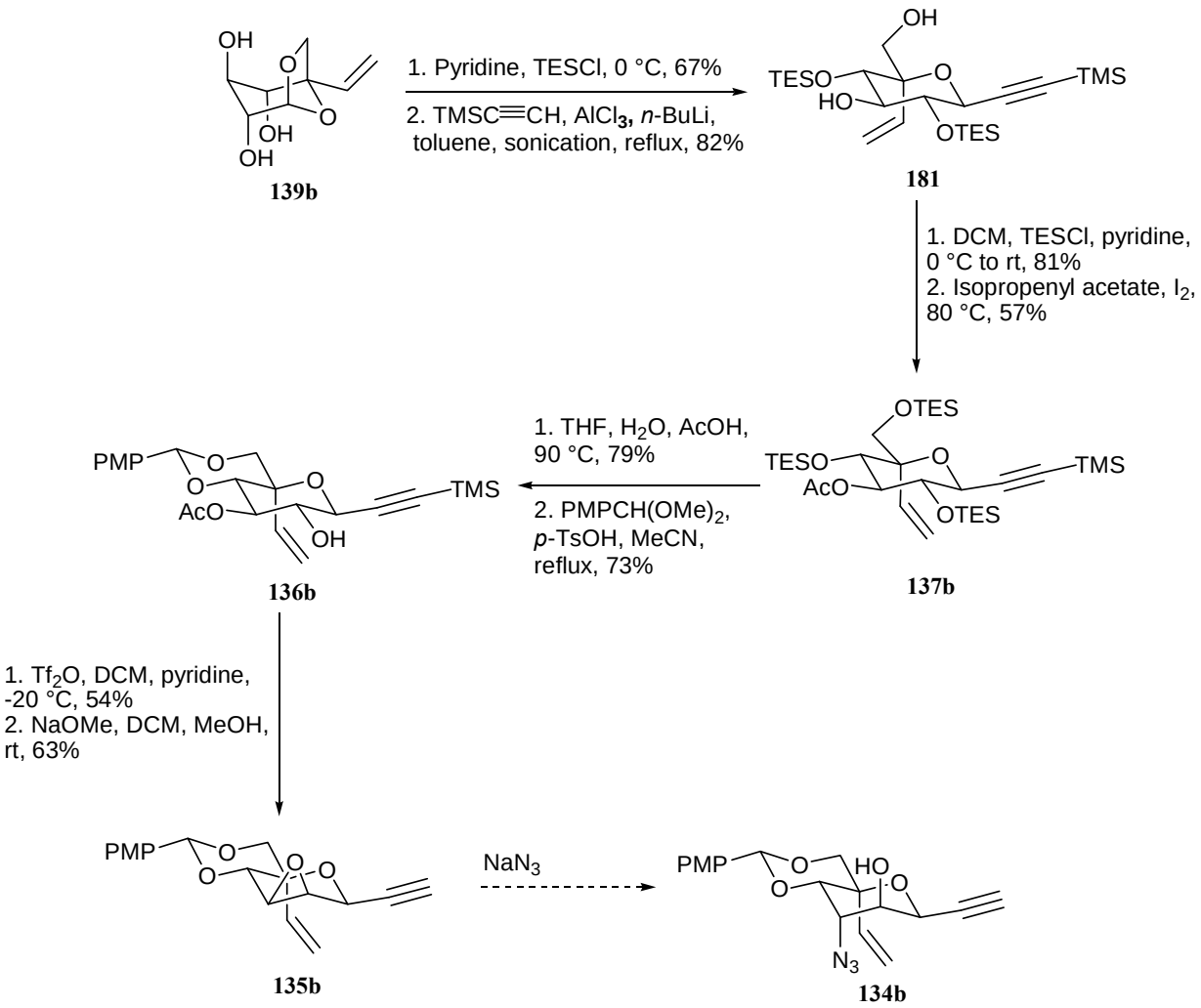
In an alternative approach, introduction of a vinyl group at C-5 of D-glucose was successfully achieved using a method described by Rama Rao *et al*. D-Glucose was converted to glucofuranoside **169** in six steps. After much optimisation, glucofuranoside **169** was successfully converted to the desired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



Scheme 117: Synthesis of 1,6-anhydro-5-*C*-vinylglucose (**139b**)

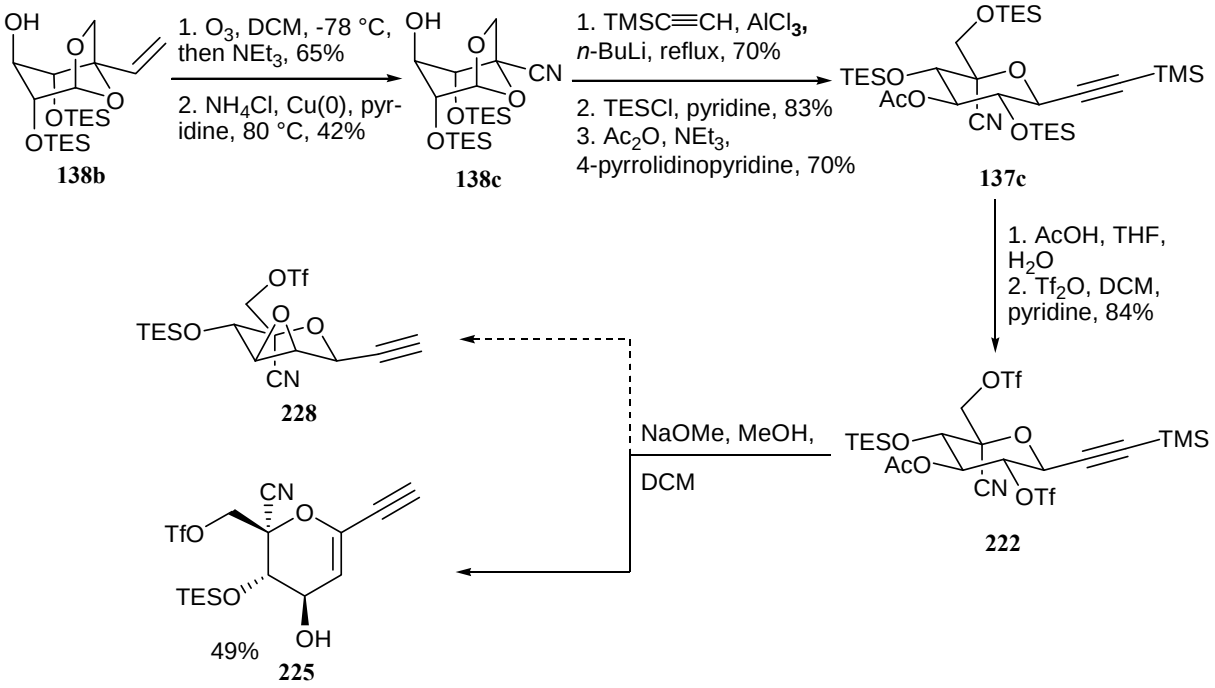
Selective silylation at O-2 and O-4 and ring opening with TMS acetylene gave the targeted diol **181** in good yields. Further TES protection at O-6 followed by acetylation using isopropenyl acetate and iodine, furnished the fully protected sugar **137b**. Desilylation and subsequent benzylidene protection 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)**.



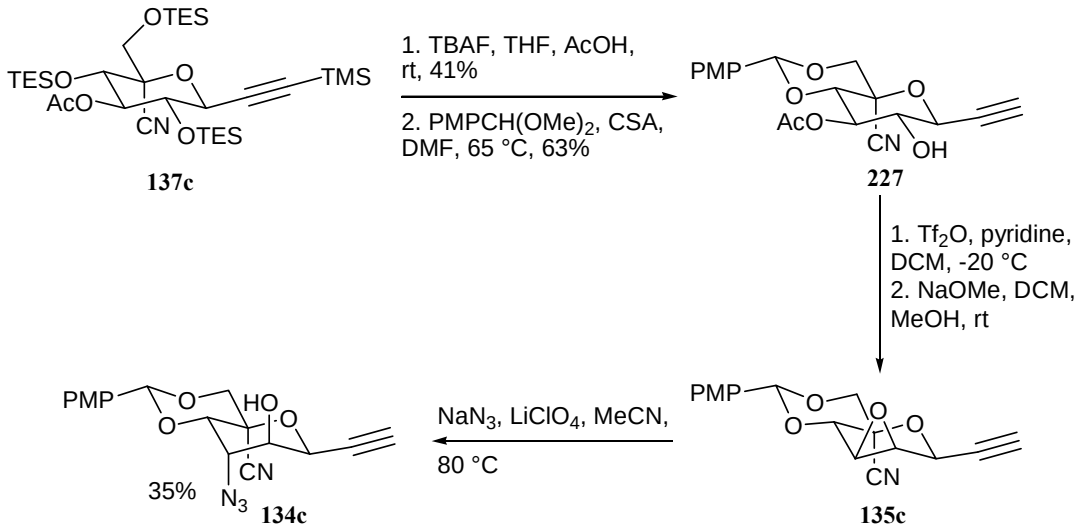
Scheme 118: Attempted synthesis of azido alcohol **134b**

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)**.



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

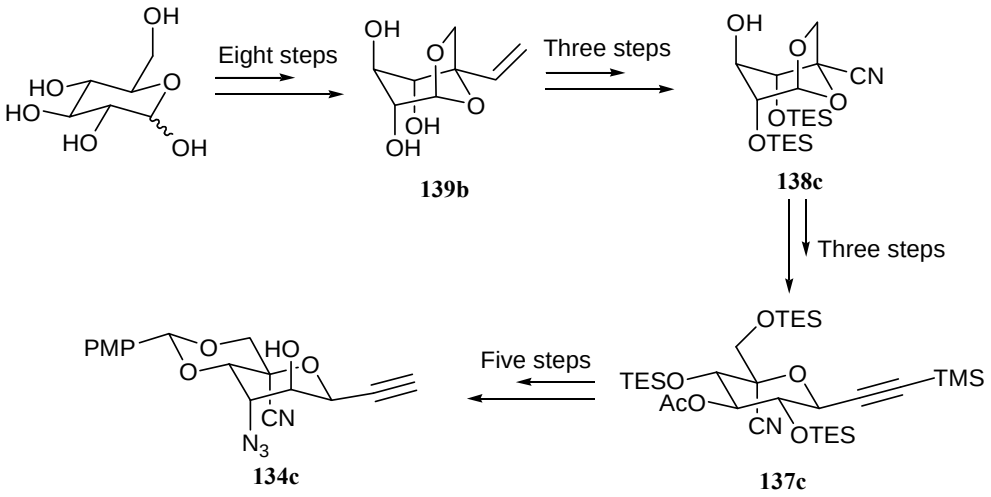
As we were unable to convert ditriflate **222** to epoxide **228**, we reverted to our original plan to obtain triol **221 (Scheme 109)**. Starting from tri-TES compound **137c**, desilylation followed by benzylidene protection led to the formation of benzylidene acetal **227**. Further triflation at 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 120: Synthesis of azide **134c**

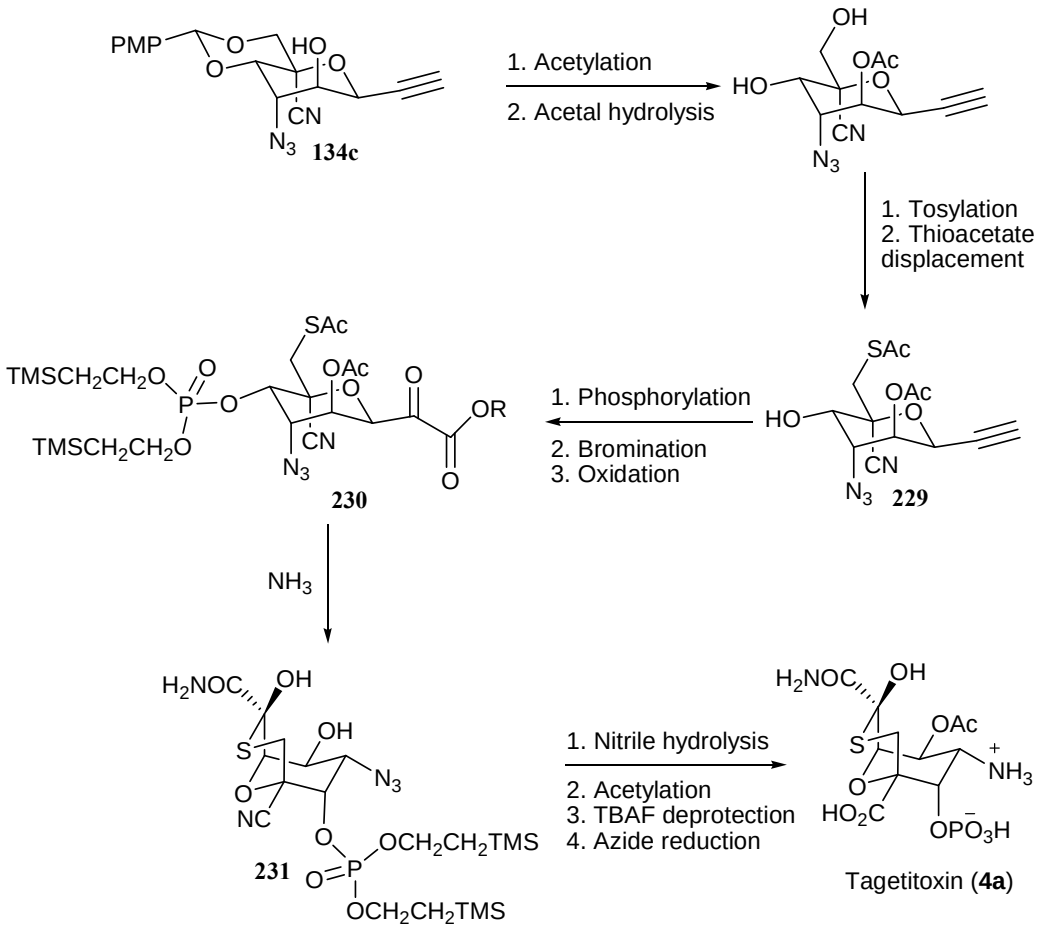
3.1 Future work

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**).



Scheme 121: Synthesis of azide **134c** from D-glucose

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, Et_2O, 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 P_2O_5. 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 F_{254}) 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.

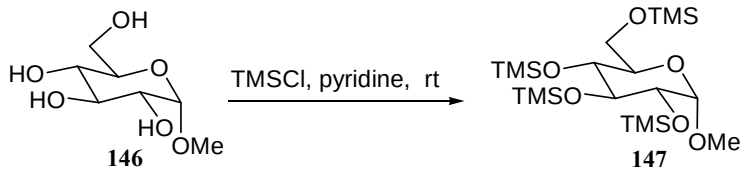
^{1}H NMR spectra were recorded on Bruker AMX-400, AVANCE 500 and AVANCE DRX600 MHz spectrometers. The signals are assigned as s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, tt = triplet of triplets. td = triplet of doublets, ddt = doublet of doublets of triplets, q = quartet, dq = doublet of quartets, m = multiplet. ^{13}C 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_2O 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 $[\propto]_{\mathbf{D}}^{\mathbf{t}}$ 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*-(trimethylsilanyl)-α-D-glucopyranoside (147)[82]



146 **147**

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 ($MgSO_4$) 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 tetrasilyl ether **147** as a colourless viscous oil (19.55 g, 79%).

R_f 0.67 (15:85, EtOAc-petroleum spirit).

$[\propto]_D^{25}$ = +84.5 (*c* 1.7, $CHCl_3$). [Lit $[\propto]_D^{22}$ = +85.7 (*c* 1.6, $CHCl_3$)][26].

δ_H (600 MHz; $CDCl_3$) 4.63 (1H, d, *J* 3.7, *H*-C1), 3.78-3.75 (2H, m, *H*-C6, *H*-C3), 3.68 (1H, dd, *J* 11.3, 5.4, *H*-C6), 3.52 (1H, ddd, *J* 9.7, 5.4, 1.9, *H*-C5), 3.48 (1H, dd, *J* 9.1, 3.7, *H*-C2), 3.44 (1H, dd, *J* 9.7, 8.4, *H*-C4), 3.35 (3H, s, CH_3O), 0.18 (9H, s, Si(CH_3)$_3$), 0.17 (9H, s, Si(CH_3)$_3$), 0.16 (9H, s, Si(CH_3)$_3$), 0.13 (9H, s, Si(CH_3)$_3$).

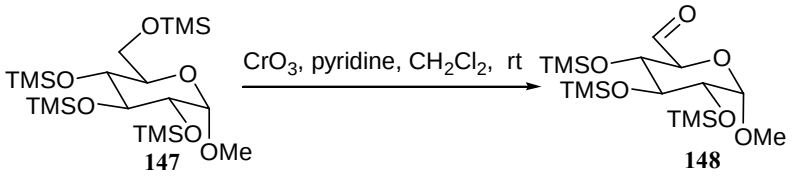
δ_C (150 MHz; $CDCl_3$) 99.6 (*C*-1), 75.3 (*C*-3), 73.9 (*C*-2), 72.2 (*C*-5), 72.0 (*C*-4), 62.2 (*C*-6), 54.5 (*C*H$_3$O), 1.4 (Si(*C*H$_3$)), 0.9 (Si(*C*H$_3$)), 0.6 (Si(*C*H$_3$)), –0.24 (Si(*C*H$_3$)).

ν_{max} ($CHCl_3$ cast)/cm^{-1}: 2956 (C-H).

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

HRMS: calculated for $C_{19}H_{46}O_6Si_4Na$: 505.2254, found 505.2269. Error 3.0 ppm.

Methyl 2,3,4-tris-*O*-(trimethylsilanyl)-α-D-*gluco*-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 tetrasilylether **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%).

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

$[\propto]_D^{25}$ = +100.8 (*c* 1.2, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 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, CH_3O), 0.17 (9H, s, Si(CH_3)$_3$), 0.17 (9H, s, Si(CH_3)$_3$), 0.14 (9H, s, Si(CH_3)$_3$).

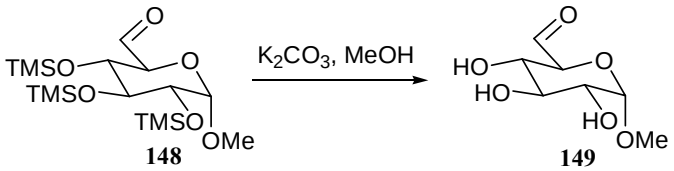
δ_C (150 MHz, CD_3OD) 198.6 (*C*-6), 100.2 (*C*-1), 75.6 (*C*-5), 74.7 (*C*-3), 73.2 (*C*-4), 72.8 (*C*-2), 55.5 (*C*H$_3$O), 1.2, 0.8, 0.4 (Si(*C*H$_3$)$_3$).

ν_{max} ($CHCl_3$ 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 $C_{16}H_{37}O_6Si_3^+$: 409.1920, found 409.1898. Error 5.4 ppm.

Methyl α-D-*gluco*-hexodialdo-1,5-pyranoside (149)[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%).

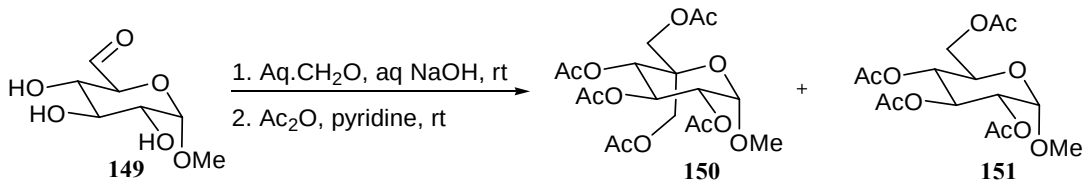
δ_H (600 MHz; D_2O) 5.13 (1H, s, *H*-C6 [hydrated]), 4.66 (1H, d, *J* 3.8, *H*-C1), 3.53 (1H, t, *J* 9.6, *H*-C3), 3.47-3.38 (2H, m, *H*-C2 & *H*-C5), 3.33 (1H, t, *J* 9.6, *H*-C4), 3.29 (3H, s,CH_3O).

δ_C (150 MHz; D_2O) 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 (*C*H_3O).

ν_{max} neat/cm^{-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)[83]



Using literature procedure[81]. 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).

$[\propto]_D^{22}$ = +71.7 (*c* 0.5, $CHCl_3$).

m.p. (EtOAc) 65-67 °C.

δ_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_2OAc), 4.39 (1H, d, *J* 12.2, CH_2OAc), 4.16 (1H, d, *J* 12.1, CH_2OAc), 4.07 (1H, d, *J* 12.1, CH_2OAc), 3.49 (3H, s, CH_3O), 2.13 (3H, s, CH_3CO), 2.12 (3H, s, CH_3CO), 2.10 (3H, s, CH_3CO), 2.05 (3H, s, CH_3CO), 2.03 (3H, s, CH_3CO).

δ_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 (*C*H_2OAc), 63.9 (*C*H_2OAc), 57.2 (*C*H_3O), 20.8, 20.8, 20.7, 20.6, 20.6 (5 × *C*H_3CO).

ν_{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).

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

δ_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_3O), 2.10 (3H, s, CH_3CO), 2.08 (3H, s, CH_3CO), 2.02 (3H, s, CH_3CO), 2.01 (3H, s, CH_3CO).

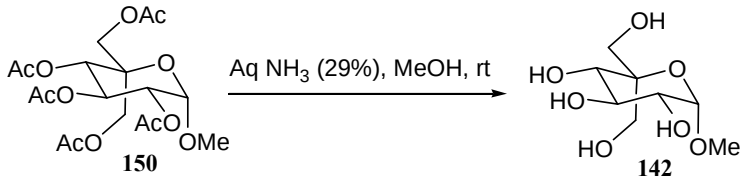
δ_C (150 MHz; $CDCl_3$) 170.7 (*C*=O), 170.2 (*C*=O), 170.1 (*C*=O), 169.6 (*C*=O), 96.7 (*C*-1), 70.7 (*C*-2), 70.1 (*C*-3), 68.4 (*C*-4), 67.1 (*C*-5), 61.9 (*C*-6), 55.5 (*C*H_3O), 20.8, 20.7, 20.6, 20.6 (4 × *C*H_3CO).

ν_{max} ($CHCl_3$ cast)/cm^{-1}: 2945 (C-H), 1741 (C=O).

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

HRMS: calculated for $C_{15}H_{22}O_{10}Na^+$: 385.1129, found 385.1111. Error 4.7 ppm.

Methyl 5-*C*-hydroxymethyl-α-D-glucopyranoside (142)



150 **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.

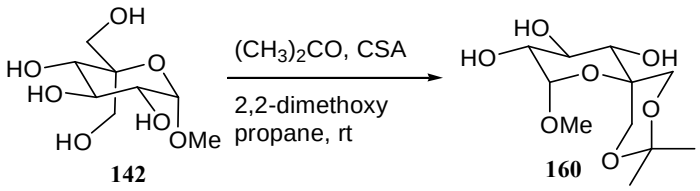
δ_H (600 MHz; CD_3OD) 4.57 (1H, d, *J* 4.1, *H*-C1), 3.96 (1H, d, *J* 11.6, C*H*$_2$OH), 3.85 (1H, t, *J* 9.8, *H*-C3), 3.81 (1H, d, *J* 11.6, C*H*$_2$OH), 3.77 (1H, d, *J* 11.6, C*H*$_2$OH), 3.72 (1H, d, *J* 9.8, *H*-C4), 3.68 (1H, d, *J* 11.6, C*H*$_2$OH), 3.52 (3H, s, CH_3O), 3.41 (1H, dd, *J* 9.8, 4.1, *H*-C2).

δ_C (150 MHz; CD_3OD) 101.5 (*C*-1), 79.9 (*C*-5), 72.0 (*C*-2), 71.8 (*C*-4), 69.9 (*C*-3), 63.4 (*C*H$_2$OAc), 62.8 (*C*H$_2$OAc), 56.0 (*C*H$_3$O).

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

HRMS: calculated for $C_8H_{15}O_7$: 223.0818, found 223.0809. Error 4.0 ppm.

(2*S*,3*R*,4*S*,5*S*)-2-Methoxy-9,9-dimethyl-1,8,10-trioxaspiro[5.5]undecane-3,4,5-triol (160)



142 **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%).

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

$[\propto]_{\mathbf{D}}^{\mathbf{25}}$ = +97.6 (*c* 0.1, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 4.84 (1H, d, *J* 4.1, *H*-C1), 4.23 (1H, d, *J* 12.6, CCH_2O), 4.13 (1H, d, *J* 12.2, CCH_2O), 4.03 (1H, d, *J* 12.6, CCH_2O)), 3.79 (1H, t, *J* 9.7, *H*-C3), 3.58 (3H, s, CH_3O), 3.55 (1H, d, *J* 12.2, CCH_2O), 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_3C), 1.429 (3H, s, CH_3C).

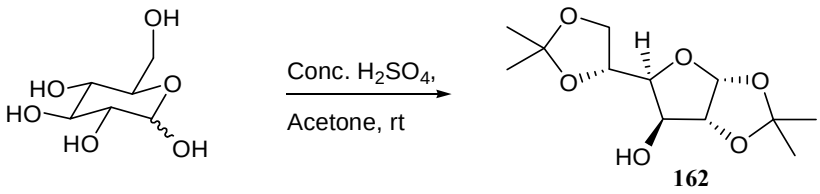
δ_C (150 MHz; $CDCl_3$) 100.4 (*C*-1), 98.7 (*C*$(CH_3)_2$), 73.9 (*C*-5), 73.6 (*C*-4), 72.1 (*C*-2), 70.3 (*C*-3), 66.9 (*C*-6), 62.6 (*C*-7), 56.6 (*C*H_3O), 26.7, 20.5 (2 × *C*H_3-*C*);

ν_{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-α-D-glucofuranose (162)



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 *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.

R_f 0.35 (40:60, EtOAc-petroleum spirit).

$[\propto]_D^{20}$ = –11.2 (*c* 5.0, EtOH). [Lit $[\propto]_D^{21}$ = –16.9 (*c* 2.4, H_2O)][85].

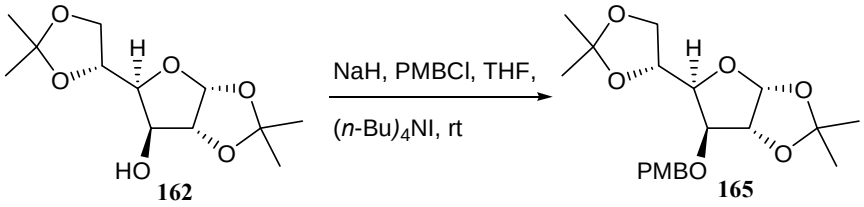
m.p. (petroleum spirit) 107-110 °C. Lit. **m.p.** (petroleum spirit) 107-110 °C.

δ_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, O*H*), 1.47 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.31 (3H, s, CH_3).

δ_C (75 MHz; $CDCl_3$) 111.8 ($(CH_3)_2C$), 109.6 ($(CH_3)_2C$), 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).

ν_{max} ($CHCl_3$ cast)/cm^{-1}: 3448 (O-H), 3055 (C-H).

3-*O*-(*p*-Methoxybenzyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (165)



162 **165**

Using literature procedure[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_2SO_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).

$[\propto]_D^{20}$ = –16.9 (*c* 0.9, $CHCl_3$). [Lit $[\propto]_D^{20}$ = –17 (*c* 1, $CHCl_3$)][86].

δ_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, C$H_a$$H_b$-Ar), 4.57 (1H, d, *J* 3.7, *H*-C2), 4.57 (1H, d, *J* 11.4, C$H_a$$H_b$-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_3O), 1.50 (3H, s, CH_3C), 1.44 (3H, s, CH_3C), 1.39 (3H, s, CH_3C), 1.32 (3H, s, CH_3C).

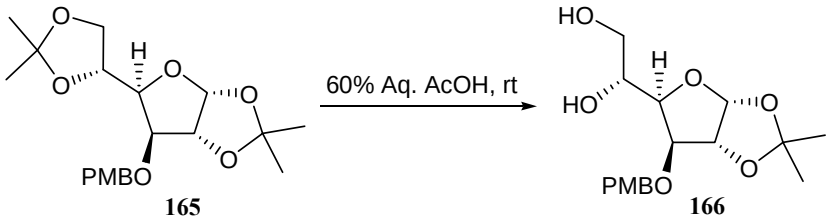
δ_C (150 MHz; $CDCl_3$) 159.3 (arom. *C*), 129.7 (arom. *C*), 129.4 (arom. *C*H), 113.8 (arom. *C*H), 111.8 ((CH$_3$)$_2$*C*), 108.9 ((CH$_3$)$_2$*C*), 105.3 (*C*-1), 82.7 (*C*-2), 81.3 (*C*-3 & *C*-5), 72.6 (*C*-4), 72.1 (*C*H$_2$-Ar), 67.3 (*C*-6), 55.3 (*C*H$_3$O), 26.8 (*C*H$_3$C), 26.8 (*C*H$_3$C), 26.2 (*C*H$_3$C), 25.5 (*C*H$_3$C).

ν_{max} ($CHCl_3$ cast)/cm^{-1}: 2987 (C-H), 1613 (C=C), 1514 (C=C), 1457 (C=C).

***m/z* (ES+):** 403 (MNa^+, 100%), 363 (40), 221 (10), 207 (10), 193 (10).

HRMS: calculated for $C_{20}H_{28}O_7Na^+$: 403.1714, found: 403.1733. Error 4.7 ppm.

1,2-*O*-Isopropylidene-3-*O*-(*p*-methoxybenzyl)-α-D-glucofuranose (166)



165 **166**

Using literature procedure[86]. 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 $NaHCO_3$ (3 × 150 mL). The organic layer was dried (Na_2SO_4), 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.

R_f 0.28 (50:50, EtOAc-petroleum spirit).

$[\alpha]_D^{21}$ = –39.1 (*c* 0.5, $CHCl_3$). [Lit $[\alpha]_D^{20}$ = –20 (*c* 1.0, $CHCl_3$)].[86]

δ_H (600 MHz; $CDCl_3$) 7.29 (2H, d, *J* 8.6, *H*-Ar), 6.91 (2H, d, *J* 8.6, *H*-Ar), 5.95 (1H, d, *J* 3.8, *H*-C1), 4.69 (1H, d, *J* 11.3, C*H*$_a$H$_b$-Ar), 4.63 (1H, d, *J* 3.8, *H*-C2), 4.47 (1H, d, *J* 11.5, CH$_a$*H*$_b$-Ar), 4.12 (1H, dd, *J* 7.7, 3.8, *H*-C4), 4.09 (1H, d, *J* 3.8, *H*-C3), 4.02 (1H, ddd, *J* 7.7, 5.7, 3.5, *H*-C5), 3.82 (3H, s, C*H*$_3$O), 3.81 (1H, dd, *J* 11.4, 3.5, *H*-C6), 3.69 (1H, dd, *J* 11.4, 5.7, *H*-C6), 1.50 (3H, s, C*H*$_3$C(O)$_2$), 1.34 (3H, s, C*H*$_3$C(O)$_2$).

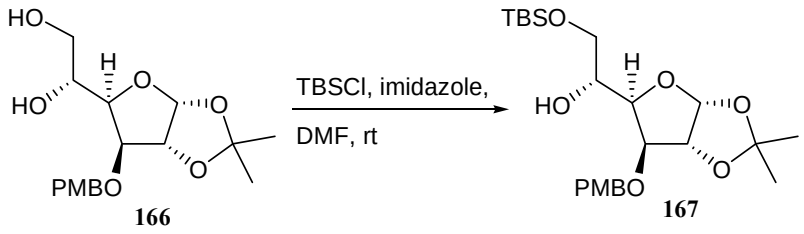
δ_C (150 MHz; $CDCl_3$) 159.7 (arom. *C*), 129.7 (arom. *C*H), 129.0 (arom. *C*), 114.2 (arom. *C*H), 111.8 ((CH$_3$)$_2$*C*), 105.1 (*C*-1), 83.1 (*C*-2), 82.1 (*C*-3), 79.9 (*C*-4), 71.7 (*C*H$_2$-Ar), 69.4 (*C*-5), 64.4 (*C*-6), 55.3 (*C*H$_3$O), 26.7 (*C*H$_3$C), 26.2 (*C*H$_3$C).

ν_{max} ($CHCl_3$ cast)/cm^{-1}: 3417 (O-H), 2936 (C-H), 1612 (C=C), 1514 (C=C), 1458 (C=C).

***m/z* (ES+):** 368 (MNa$^+$, 100%).

HRMS: calculated for $C_{17}H_{24}O_7Na^+$: 363.1418, found: 363.1420. Error 0.6 ppm.

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



Using literature procedure[84]. 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 ($MgSO_4$) 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_f 0.34 (15:85, EtOAc-petroleum spirit).

$[\propto]_D^{24}$ = –28.5 (*c* 0.4, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 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, C$H_a$$H_b$-Ar), 4.58-4.60 (2H, m, C$H_a$$H_b$-Ar & *H*-C2), 4.13 (1H, dd, *J* 8.4, 3.0, *H*-C4), 4.09 (1H, d, *J* 3.0, *H*-C3), 4.00 (1H, quin, *J* 4.3, *H*-C5), 3.82 (3H, s, CH_3O), 3.80 (1H, dd, *J* 10.2, 3.8, *H*-C6), 3.75 (1H, dd, *J* 10.2, 4.3, *H*-C6), 1.48 (3H, s, CH_3C(O)$_2$), 1.32 (3H, s, CH_3C(O)$_2$), 0.91 (9H, s, (CH_3)$_3$C), 0.09 (3H, s, CH_3-Si), 0.08 (3H, s, CH_3-Si).

δ_C (150 MHz; $CDCl_3$) 159.4 (arom. *C*), 129.6 (arom. *C*), 129.5 (arom. *C*H), 113.9 (arom. *C*H), 111.6 ((CH$_3$)$_2$*C*), 105.1 (*C*-1), 82.5 (*C*-2), 81.5 (*C*-3), 79.4 (*C*-4), 72.1 (*C*H$_2$-Ar), 68.6 (*C*-5), 64.5 (*C*-6), 55.3 (*C*H$_3$O), 26.7 (*C*H$_3$C), 26.3 (*C*H$_3$C), 25.9 ((*C*H$_3$)$_3$-C), 18.3 ((CH$_3$)$_3$*C*), –5.38 (*C*H$_3$-Si), –5.40 (*C*H$_3$-Si).

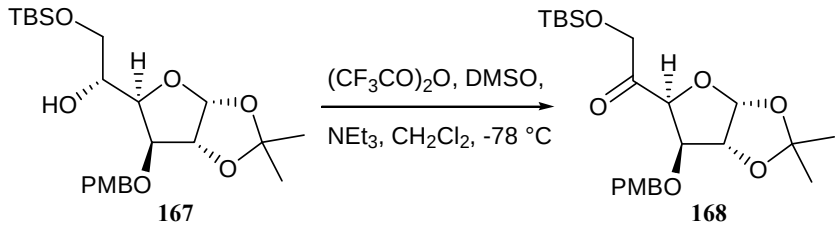
ν_{max} ($CHCl_3$ cast)/cm^{-1}: 3545 (O-H), 2953 (C-H), 1613 (C=C), 1514 (C=C).

***m/z* (ES+):** 477 (MNa$^+$, 100%).

HRMS: calculated for $C_{23}H_{38}O_7SiNa^+$: 475.2270, found: 477.2285. Error 3.1 ppm.

Elemental analysis: $C_{23}H_{38}O_7Si$ requires: C 60.8, H 8.4; found C 60.6, 8.5%.

6-*O*-(*tert*-Butyldimethylsilyl)-1,2-*O*-isopropylidene-3-*O*-(*p*-methoxybenzyl)-α-D-*xylo*-hexofuranose-5-ulose (168)



167 **168**

Using literature procedure[88]. To a stirred solution of dimethyl sulfoxide (5.1 mL, 76.2 mmol) in anhydrous dichloromethane (100 mL) at −78 °C was added trifluoroacetic 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 $NaHCO_3$ (300 mL), water (300 mL), brine (300 mL), dried (Na_2SO_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 ketone **168** (7.60 g, 95%) as a colourless viscous oil.

R_f 0.34 (15:85, EtOAc-petroleum spirit).

$[\propto]_{\mathbf{D}}^{\mathbf{22}}$ = –50.4 (*c* 0.5, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 7.19 (2H, d, *J* 8.6, *H*-Ar), 6.87 (2H, d, *J* 8.6, *H*-Ar), 6.05 (1H, d, *J* 3.7, *H*-C1), 4.88 (1H, d, *J* 3.7, *H*-C4), 4.58 (1H, d, *J* 3.7, *H*-C2), 4.54-4.49 (2H, m, C$H_a$$H_b$-Ar & *H*-C6), 4.44 (2H, m, CH$_a$$H_b$-Ar & *H*-C6), 4.36 (1H, d, *J* 3.7, *H*-C3), 3.81 (3H, s, CH_3O), 1.48 (3H, s, CH_3C(O)$_2$), 1.33 (3H, s, CH_3C(O)$_2$), 0.91 (9H, s, (CH_3)$_3$C), 0.06 (3H, s, CH_3-Si), 0.05 (3H, s, CH_3-Si).

δ_C (150 MHz; $CDCl_3$) 205.3 (*C*-5), 159.5 (arom. *C*), 129.5 (arom. *C*H), 128.9 (arom. *C*), 113.9 (arom. *C*H), 112.3 ((CH$_3$)$_2$*C*), 105.7 (*C*-1), 84.6 (*C*-4), 83.0 (*C*-3), 81.8 (*C*-2), 72.1 (*C*H$_2$-Ar), 68.8 (*C*-6), 55.3 (*C*H$_3$O), 26.9 (*C*H$_3$C), 26.3 (*C*H$_3$C), 25.8 ((*C*H$_3$)$_3$-C), 18.4 ((CH$_3$)$_3$*C*), −5.4 (*C*H$_3$-Si), −5.5 (*C*H$_3$-Si).

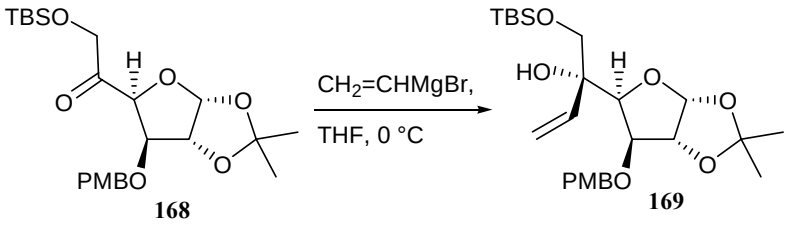
ν_{max} ($CHCl_3$ cast)/cm^{-1}: 2952 (C-H), 1739 (C=O), 1613 (C=C), 1514 (C=C).

***m/z* (ES+):** 475 (MNa^+, 100%), 180 (10).

HRMS: calculated for $C_{23}H_{36}O_7SiNa^+$: 475.2138, found: 475.2128. Error 2.1 ppm.

Elemental analysis: $C_{23}H_{36}O_7Si$ requires: C 61.0, H 8.0; found C 60.9, 8.1%.

6-*O*-(*tert*-Butyldimethylsilyl)-1,2-*O*-isopropylidene-3-*O*-(*p*-methoxybenzyl)-5-*C*-vinyl-α-D-glucofuranose (169)



Using literature procedure[84]. 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_2SO_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).

$[\propto]_D^{23}$ = –36.5 (*c* 0.9, chloroform).

δ_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, C*H*=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_aH_b), 4.65 (1H, d, *J* 11.4, CH_aH_b-Ar), 4.62 (1H, d, *J* 3.9, *H*-C2), 4.43 (1H, d, *J* 11.4, CH_aH_b-Ar), 4.32 (1H, d, *J* 3.9, *H*-C3), 4.14 (1H, d, *J* 3.9, *H*-C4), 3.99 (1H, br s, O*H*), 3.82 (3H, s, CH_3O), 3.55 (1H, d, *J* 9.5, *H*-C6), 3.41 (1H, d, *J* 9.5, *H*-C6), 1.48 (3H, s, CH_3C(O)$_2$), 1.34 (3H, s, CH_3C(O)$_2$), 0.86 (9H, s, (CH_3)$_3$C), 0.01 (3H, s, CH_3-Si), –0.03 (3H, s, CH_3-Si).

δ_C (150 MHz; $CDCl_3$) 159.7 (arom. *C*), 138.8 (*C*H=CH_2), 130.0 (arom. *C*H), 128.4 (arom. *C*), 114.3 (CH=*C*H_2), 114.0 (arom. *C*H), 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 (*C*H_2-Ar), 68.7 (*C*-6), 55.8 (*C*H_3O), 26.6 (*C*H_3C), 26.3 (*C*H_3C), 25.8 ((*C*H_3)$_3$-C), 18.1 ((CH$_3$)$_3$*C*), –5.5 (*C*H_3-Si), –5.6 (*C*H_3-Si).

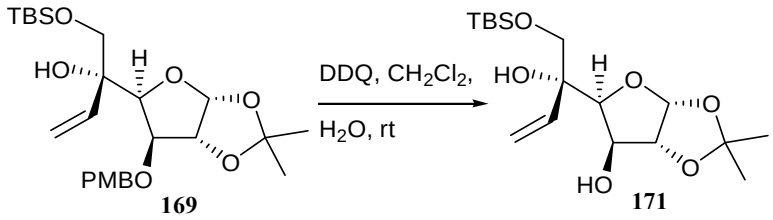
ν_{max} ($CHCl_3$ cast)/cm^{-1}: 3493 (O-H), 2953 (C-H), 1612 (C=C), 1514 (C=C).

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

HRMS: calculated for $C_{25}H_{40}O_7SiNa^+$: 503.2451, found: 503.2441. Error 2.0 ppm.

Elemental analysis: $C_{25}H_{40}O_7Si$ 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)



169 **171**

Using literature procedure[89]. 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.$NaHCO_3$ (3 mL), brine (3 mL), dried ($MgSO_4$) 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.

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

$[\propto]_{\mathbf{D}}^{\mathbf{23}}$ = –11.3 (*c* 0.5, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 5.99 (1H, dd, *J* 18.8, 12.4, C*H*=CH_2), 5.98 (1H, d, *J* 3.5, *H*-C1), 5.48 (1H, dd, *J* 18.8, 1.2, CH=CH_aH_b), 5.30 (1H, dd, *J* 12.4, 1.2, CH=CH_aH_b), 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, d, *J* 10.2, *H*-C6), 2.96 (1H, bs, O*H*), 1.50 (3H, s, $CH_3C(O)_2$), 1.33 (3H, s, $CH_3C(O)_2$), 0.92 (9H, s, $(CH_3)_3C$), 0.11 (3H, s, CH_3-Si), 0.10 (3H, s, CH_3-Si).

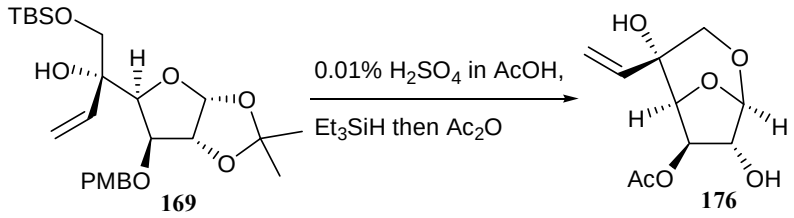
δ_C (150 MHz; $CDCl_3$) 139.2 (*C*H=CH_2), 115.6 (CH=*C*H_2), 111.5 ($(CH_3)_2C$), 104.6 (*C*-1), 84.9 (*C*-2), 81.4 (*C*-4), 76.1 (*C*-5), 76.0 (*C*-3), 67.2 (*C*-6), 26.8 (CH_3C), 26.2 (CH_3C), 25.8 ($(CH_3)_3$-C), 18.3 ($(CH_3)_3C$), – 5.55 (CH_3-Si), – 5.56 (CH_3-Si).

ν_{max} ($CHCl_3$ 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).

HRMS: calculated for $C_{17}H_{32}O_6SiNa^+$: 383.1880, found: 383.1866. Error 3.7 ppm.

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_2SO_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).

$[\propto]_D^{23}$ = –58.3 (*c* 0.3, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 6.12 (1H, dd, *J* 17.3, 11.0, C*H*=CH_2), 5.64 (1H, dd, *J* 17.3, 1.9, CH=C$H_a$$H_b$), 5.32 (1H, s, *H*-C1), 5.29 (1H, dd, *J* 11.0, 1.9, CH=C$H_a$$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_3CO).

δ_C (150 MHz; $CDCl_3$) 172.6 (**C**=O), 134.6 (*C*H=CH_2), 117.2 (CH=*C*H_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 (*C*H_3CO).

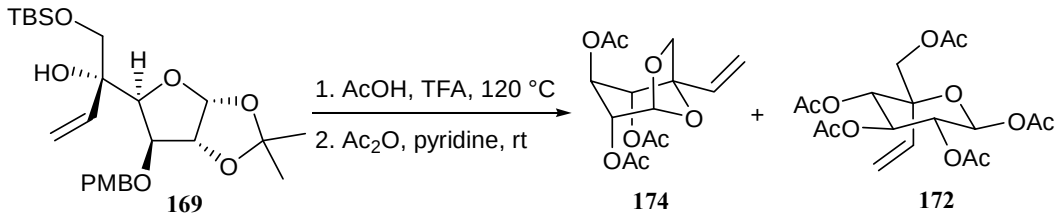
ν_{max} ($CHCl_3$ cast)/cm^{-1}: 3467 (O-H), 2974 (C-H), 1732 (C=O).

***m/z* (CI+, CH_4):** 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)



169 **174** **172**

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.

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

$[\propto]_D^{22}$ = –74.7 (*c* 0.8, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 6.00 (1H, dd, *J* 17.7, 10.4, C*H*=CH_2), 5.96-5.93 (2H, m, *H*-(C1) & CH=CH_aH_b), 5.69 (1H, dd, *J* 10.4, 1.2, CH=CH_aH_b), 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, CH_3-CO), 2.11 (3H, s, CH_3-CO), 2.05 (3H, s, CH_3-CO), 2.02 (3H, s, CH_3-CO), 2.01 (3H, s, CH_3-CO).

δ_C (150 MHz; $CDCl_3$) 170.6, 170.1 (2 × *C*=O), 169.7, 169.1 (2 × *C*=O), 129.2 (*C*H=CH_2), 122.7 (CH=*C*H_2), 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 (*C*H_3-CO), 20.8 (*C*H_3-CO), 20.6 (*C*H_3-CO), 20.58 (*C*H_3-CO), 20.57 (*C*H_3-CO).

ν_{max} ($CHCl_3$ cast)/cm^{-1}: 2923 (C-H), 1747 (C=O), 1640 (C=C).

***m/z* (FAB+, CH_4):** 439 (MNa^+, 100%), 379 (8), 329 (67), 177 (38).

HRMS: calculated for $C_{18}H_{24}O_{11}Na^+$: 439.1216, found: 439.1224. Error 1.8 ppm.

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%).

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

$[\propto]_D^{23}$ = –51.9 (*c* 0.60, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 5.87 (1H, dd, *J* 17.5, 11.2, C*H*=CH_2), 5.60 (1H, t, *J* 1.7, *H*-C1), 5.46 (1H, dd, *J* 17.5, 0.6, CH=CH_aH_b), 5.32 (1H, dd, *J* 11.2, 0.6, CH=CH_aH_b), 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_3-CO), 2.15 (3H, s, CH_3-CO), 2.13 (3H, s, CH_3-CO).

δ_C (150 MHz; $CDCl_3$) 169.7, 168.9 (2 × *C*=O), 132.3 (*C*H=CH_2), 117.4 (CH=*C*H_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 (*C*H_3-CO), 20.9 (*C*H_3-CO), 20.8 (*C*H_3-CO).

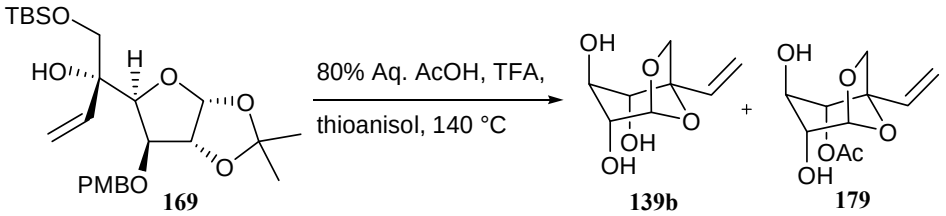
ν_{max} ($CHCl_3$ cast)/cm^{-1}: 2970 (C-H), 1737 (C=O), 1648 (C=C).

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

HRMS: calculated for $C_{14}H_{18}O_8Na^+$: 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)



169 **139b** **179**

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 CH_2Cl_2) gave diol **179** (20 mg, 17%) as a yellow viscous oil.

R_f 0.47 (10:90, MeOH- CH_2Cl_2)

$[\propto]_D^{22}$ = –70.4 (*c* 0.5, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 5.85 (1H, dd, *J* 17.6, 11.2, C*H*=CH_2), 5.63 (1H, t, *J* 1.9, *H*-C1), 5.44 (1H, dd, *J* 17.6, 0.8, CH=CH_aH_b), 5.32 (1H, dd, *J* 11.2, 0.8, CH=CH_aH_b), 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, CH_3CO).

δ_C (150 MHz; $CDCl_3$) 169.8 (*C*=O), 132.4 (*C*H=CH_2), 117.4 (CH=*C*H_2), 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 (*C*H_3CO).

ν_{max} ($CHCl_3$ cast)/ cm^{-1}: 3425 (O-H), 2958 (C-H), 1721 (C=O), 1647 (C=C).

***m/z* (CI+, CH_4)**: 231 (MH^+, 68%), 213 (100), 195 (10), 171 (33), 153 (56), 135 (17), 125 (25), 111 (14).

HRMS: calculated for $C_{10}H_{15}O_6^+$: 231.0869, found: 231.0875. Error 2.8 ppm

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

R_f 0.30 (10:90, MeOH-CH_2Cl_2)

$[\propto]_D^{20}$ = –73.1 (*c* 1.0, EtOH)

δ_H (600 MHz; CD_3OD) 6.05 (1H, dd, *J* 17.6, 11.2, C*H*=CH_2), 5.44 (1H, dd, *J* 17.6, 1.3, CH=CH_aH_b), 5.44 (1H, br t, *J* 1.6, *H*-C1), 5.31 (1H, dd, *J* 11.2, 1.3, CH=CH_aH_b), 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).

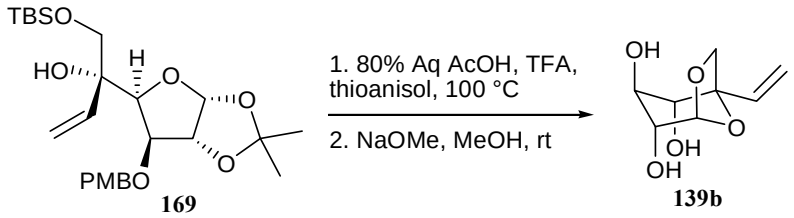
δ_C (150 MHz; CD_3OD) 135.0 (*C*H=CH_2), 115.1 (CH=*C*H_2), 103.1 (*C*-1), 82.6 (*C*-5), 74.1 (*C*-3), 72.6 (*C*-4), 69.6 (*C*-2), 69.4 (*C*-6).

ν_{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 $C_8H_{13}O_5^+$: 189.0763, found: 189.0765. Error 1.1 ppm.

1,6-Anhydro-5-*C*-vinyl-β-D-glucopyranose (139b)



169 **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 μL, 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 × 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→10:90, MeOH in CH_2Cl_2) to give anhydrosugar **139b** (0.86 g, 74%) as a brown viscous oil.

R_f 0.30 (10:90, MeOH-CH_2Cl_2).

$[\propto]_D^{20}$ = –73.1 (*c* 1.0, EtOH)

δ_H (600 MHz; CD_3OD) 6.05 (1H, dd, *J* 17.6, 11.2, C*H*=CH_2), 5.44 (1H, dd, *J* 17.6, 1.3, CH=CH_aH_b), 5.44 (1H, br t, *J* 1.6, *H*-C1), 5.31 (1H, dd, *J* 11.2, 1.3, CH=CH_aH_b), 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).

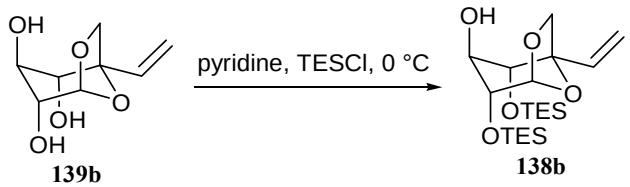
δ_C (150 MHz; CD_3OD) 135.0 (*C*H=CH_2), 115.1 (CH=*C*H_2), 103.1 (*C*-1), 82.6 (*C*-5), 74.1 (*C*-3), 72.6 (*C*-4), 69.6 (*C*-2), 69.4 (*C*-6).

ν_{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 $C_8H_{13}O_5^+$: 189.0763, found: 189.0765. Error 1.1 ppm

1,6-Anhydro-2,4-bis-*O*-triethylsilyl-5-*C*-vinyl-β-D-glucose (138b)



139b **138b**

Using literature procedure[92]. 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 ($MgSO_4$) 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.

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

$[\propto]_D^{20} = -18.4$ (*c* 1.5, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 6.16 (1H, dd, *J* 17.8, 11.2, C*H*=CH_2), 5.44 (1H, t, *J* 1.6, *H*-C1), 5.31 (1H, dd, *J* 17.8, 0.8, CH=CH_aH_b), 5.28 (1H, dd, *J* 11.2, 0.8, CH=CH_aH_b), 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, O*H*), 0.98 (18H, m, 2 × $Si(CH_2CH_3)_3$), 0.65 (12H, m, 2 × $Si(CH_2CH_3)_3$).

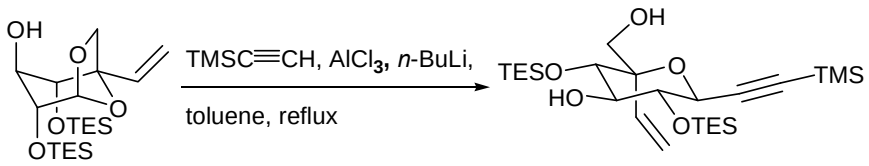
δ_C (150 MHz; $CDCl_3$) 135.1 (*C*H=CH_2), 116.1 (C=*C*H_2), 103.5 (*C*-1), 83.0 (*C*-5), 76.3 (*C*-3), 75.0 (*C*-4), 71.5 (*C*-2), 69.7 (*C*-6), 6.9 (CH_2-*C*H_3), 6.8 (CH_2-*C*H_3), 4.8 (CH_3-*C*H_2), 4.6 (CH_3-*C*H_2).

ν_{max} (CH_2Cl_2 cast)/cm^{-1}: 3460 (O-H), 2954 (C-H), 1648 (C=C).

***m/z* (ES+):** 439 (100, M^+).

HRMS: calculated for $C_{20}H_{40}O_5NaSi_2^+$: 439.2312, found: 439.2310. Error 0.5 ppm

1-(2,4-Bis-*O*-(triethylsilanyl)-5-*C*-vinyl-β-D-glucopyranosyl)-2-trimethylsilanylethyne (181)



138b **181**

Using literature procedure[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 *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.

m.p. (EtOAc) 55-57 °C.

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

$[\propto]_D^{22}$ = –65.9 (*c* 0.7, $CHCl_3$).

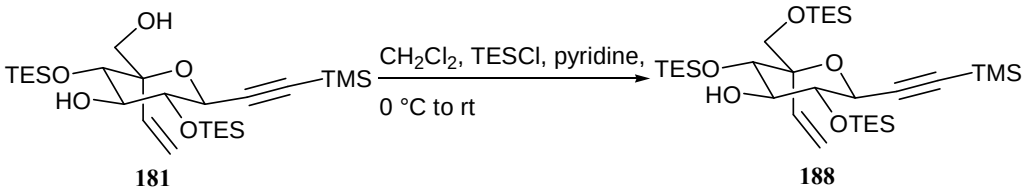
δ_H (600 MHz; $CDCl_3$) 6.00 (1H, dd, *J* 18.0, 11.3, C*H*=CH_2), 5.45 (1H, dd, *J* 18.0, 1.4, CH=CH_aH_b), 5.43 (1H, dd, *J* 11.3, 1.4, CH=CH_aH_b), 4.21 (1H, d, *J* 9.5, *H*-C1), 3.83 (1H, d, *J* 9.8, *H*-C4), 3.56 (1H, dd, *J* 11.7, 10.9, *H*-C6), 3.48 (1H, dd, *J* 9.5, 8.7, *H*-C2), 3.39 (1H, dd, *J* 11.7, 2.9, *H*-C6), 3.36 (1H, ddd, *J* 9.8, 8.7, 2.8, *H*-C3), 2.19 (1H, dd, *J* 10.9, 2.9, CH_2OH), 2.08 (1H, d, *J* 2.8, CHO*H*), 0.99 (18H, m, 2 × $Si(CH_2CH_3)_3$), 0.71 (12H, m, 2 × $Si(CH_2CH_3)_3$), 0.2 (9H, s, $Si(CH_3)_3$).

δ_C (150 MHz; $CDCl_3$) 132.5 (*C*H=CH_2), 119.2 (CH=*C*H_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-*C*H_3), 5.2 (CH_2-*C*H_3), 5.3 (CH_3-*C*H_2), 5.1 (CH_3-*C*H_2), – 0.2 ((*C*H_3)$_3$Si)

ν_{max} ($CHCl_3$ cast)/cm^{-1}: 3565 (O-H), 2182 (*C*≡C),1729 (C=C).

***m/z* (CI+, CH_4)** 515 (MH^+, 23%), 467 (10), 399 (30), 353 (35), 335 (22), 255 (100), 229 (45).
HRMS calculated for $C_{25}H_{50}O_5Si_3^+$: 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)



181 **188**

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 ($MgSO_4$) and concentrated *in vacuo* to give an oily residue, which was purified by column chromatography (4:96, EtOAc in CH_2Cl_2) to give tris-silyl ether **188** (0.7 g, 81%) as a colourless viscous oil,

R_f 0.95 (20:80, EtOAc-petroleum spirit).

$[\propto]_D^{20}$ = –55.9 (*c* 1.3, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 5.97 (1H, dd, *J* 18.0, 11.2, C*H*=CH_2), 5.41 (1H, dd, *J* 18.0, 1.8, CH=CH_a*H*$_b$), 5.35 (1H, dd, *J* 11.2, 1.8, CH=C*H*$_a$H$_b$), 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, O*H*), 0.98 (27H, m, 3 × Si(CH_2CH_3)$_3$), 0.65 (18H, m, 3 × Si(CH_2CH_3)$_3$), 0.17 (9H, s, Si(CH_3)$_3$).

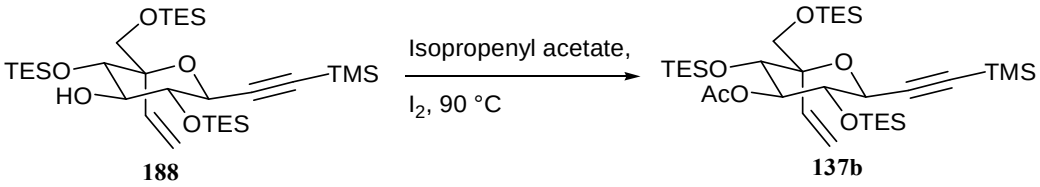
δ_C (150 MHz; $CDCl_3$) 133.0 (*C*H=CH_2), 118.4 (CH=*C*H$_2$), 104.1 (*C*≡CTMS), 88.9 (C≡*C*TMS), 81.7 (*C*-5), 75.9 (*C*-3), 75.9 (*C*-2), 70.7 (*C*-4), 66.7 (*C*-6), 65.7 (*C*-1), 6.9 (CH_2-*C*H$_3$), 5.2 (CH_3-*C*H$_2$), 5.0 (CH_3-*C*H$_2$), 4.8 (CH_3-*C*H$_2$), –0.4 ((*C*H$_3$)$_3$Si).

ν_{max} (CH_2Cl_2 cast)/cm^{-1}: 3619 (O-H), 2954 (C-H), 2182 (C≡C), 1759 (C=C).

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

HRMS: calculated for $C_{31}H_{64}O_5NaSi_4^+$: 651.3729, found: 651.3735. Error 0.9 ppm.

1-(3-*O*-Acetyl-2,4,6-tris-*O*-(triethylsilanyl)-5-*C*-vinyl-β-D-glucopyranosyl)-2-trimethylsilanylethyne (137b)



188 **137b**

Using literature procedure[97]. 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 ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude viscous oil which was purified by column chromatography (50:50, CH_2Cl_2 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).

$[\propto]_D^{20}$ = –71.0 (*c* 1.0, $CHCl_3$).

δ_H (400 MHz; $CDCl_3$) 6.02 (1H, dd, *J* 18.0, 11.1, C*H*=CH_2), 5.48-5.40 (2H, m, CH=CH_2), 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, CH_3CO), 0.97 (27H, m, 3 × Si(CH_2CH_3)$_3$), 0.66 (18H, m, 3 × Si(C$H_2$$CH_3$)$_3$), 0.18 (9H, s, Si(C$H_3$)$_3$).

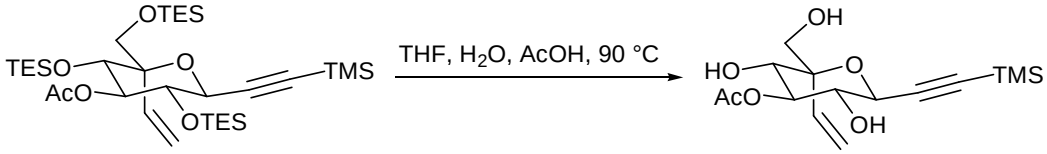
δ_C (125 MHz; $CDCl_3$) 169.7 (*C*=O), 132.7 (*C*H=CH_2), 119.2 (CH=*C*H_2), 103.8 (*C*≡CTMS), 89.5 (C≡*C*TMS), 82.0 (*C*-5), 76.5 (*C*-3), 74.4 (*C*-2), 69.1 (*C*-4), 66.7 (*C*-6), 66.2 (*C*-1), 21.8 (*C*H_3CO), 6.9 (*C*$H_3$$CH_2$), 5.4 ($CH_3$*C*$H_2$), 5.11 ($CH_3$*C*$H_2$), 4.8 ($CH_3$*C*$H_2$), –0.2 (Si(*C*$H_3$)$_3$).

***ν_{max}* (CH_2Cl_2 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 $C_{33}H_{66}O_6NaSi_4^+$: 693.3834, found: 693.3865. Error 4.5 ppm.

1-(3-*O*-Acetyl-5-*C*-vinyl-β-D-glucopyranosyl)-2-trimethylsilanylethyne (189)



137b **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, CH_3OH in CH_2Cl_2) to afford triol **189** (152 mg, 79%) as a colourless oil.

R_f 0.70 (10:90, CH_3OH in CH_2Cl_2)

$[\propto]_D^{20}$ = –119.5 (*c* 0.4, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 6.05 (1H, dd, *J* 18.3, 10.9, C*H*=CH_2), 5.57-5.54 (2H, m, CH=CH_2), 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, O*H*-C4), 2.52 (1H, br d, *J* 2.6, O*H*-C2), 2.31 (1H, br d, *J* 9.8, O*H*-C6), 2.18 (3H, s, CH_3CO), 0.21 (9H, s, Si(CH_3)$_3$).

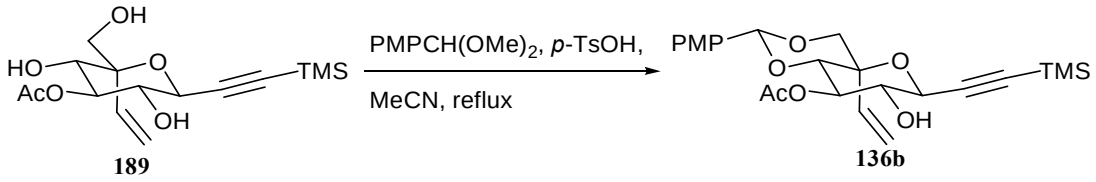
δ_C (150 MHz; $CDCl_3$) 172.5 (*C*=O), 131.3 (*C*H=CH_2), 120.6 (CH=*C*H_2), 101.1 (*C*≡CTMS), 91.9 (C≡*C*TMS), 81.4 (*C*-5), 76.3 (*C*-3), 73.2 (*C*-2), 68.8 (*C*-4), 66.8 (*C*-6), 65.9 (*C*-1), 21.1 (*C*H_3O), –0.2 (Si(*C*H_3)$_3$).

ν_{max} ($CHCl_3$ cast)/cm^{-1}: 3422 (O-H), 2178 (C≡C), 1721 (C=C).

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

HRMS: calculated for $C_{15}H_{24}O_6NaSi^+$: 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*-toluenesulfonic 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 CH_2Cl_2, 0.5% NEt_3 then 1:99→5:95, MeOH in CH_2Cl_2, 0.5% NEt_3) to give acetal **136b** (140 mg, 73%) as a colourless viscous oil.

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

$[\propto]_D^{23}$ = –41.2 (*c* 0.6, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 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, C*H*=CH_2), 5.72 (1H, dd, *J* 18.0, 1.1, CH=CH_aH_b), 5.63 (1H, dd, *J* 11.3, 1.1, CH=CH_aH_b), 5.55 (1H, s, C*H*$(O)_2$), 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, CH_3O), 3.76 (1H, d, *J* 10.6, *H*-C4), 3.75 (1H, br t, *J* 9.7, *H*-C2), 2.13 (3H, s, CH_3CO), 0.22 (9H, s, Si(CH_3)$_3$).

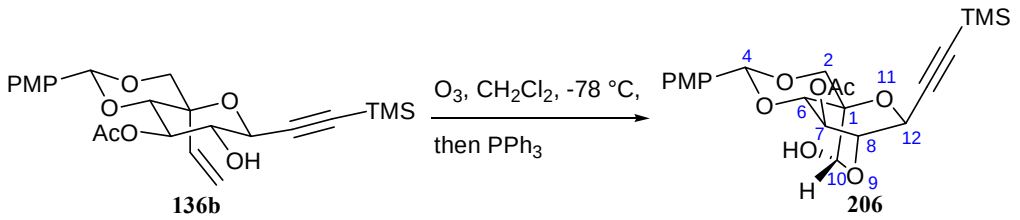
δ_C (150 MHz; $CDCl_3$) 171.3 (*C*=O), 160.2 (arom. *C*), 134.6 (*C*H=CH_2), 129.3 (arom. *C*), 127.6 (arom. *C*), 120.2 (CH=*C*H_2), 113.6 (arom. *C*), 102.6 (*C*H$(O)_2$), 100.9 (*C*≡CTMS), 92.1 (C≡*C*TMS), 80.3 (*C*-4), 77.0 (*C*-6), 74.6 (*C*-2), 72.3 (C-5), 71.9 (*C*-3), 66.8 (*C*-1), 55.6 (*C*H_3O), 21.0 (*C*H_3CO), –0.2 (Si(*C*H_3)$_3$).

ν_{max} ($CHCl_3$ 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 $C_{23}H_{31}O_7Si^+$: 447.1836, found: 447.1839. Error 0.7 ppm.

(1*R*,4*R*,6*S*,7*R*,8*S*,10*S*,12*S*)-7-Acetoxy-4-(4-methoxyphenyl)-12-(trimethylsilanylethynyl)-3,5,9,11-tetraoxatricyclo[6.2.2.0^{1,6}]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 triphenylphosphine (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.

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

$[\propto]_D^{23}$ = –67.6 (*c* 0.2, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 7.41 (2H, d, *J* 8.7, *H*-Ar), 6.91 (2H, d, *J* 8.7, *H*-Ar), 5.66 (1H, br s, OC*H*OH), 5.58 (1H, s, Ar-C*H*$(O)_2$), 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, CH_3O), 3.80 (1H, d, *J* 11.3, *H*-C2), 2.12 (3H, s, CH_3CO), 0.21 (9H, s, $(CH_3)_3$).

δ_C (150 MHz; $CDCl_3$) 170.1 (*C*=O), 160.4 (arom. *C*), 128.9 (arom. *C*), 127.5 (arom. *C*), 113.7 (arom. *C*), 101.9 (Ar*C*H$(O)_2$), 99.3 (*C*≡CTMS), 93.5 (C≡*C*TMS), 91.0 (O*C*HOH), 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 (CH_3O), 21.2 (CH_3CO). –0.14 (Si(CH_3)$_3$).

ν_{max} ($CHCl_3$ cast)/cm^{-1}: 3411 (O-H), 2962 (C-H), 2189 (C≡C), 1747 (C=O), 1615 (C=C), 1518 (C=C).

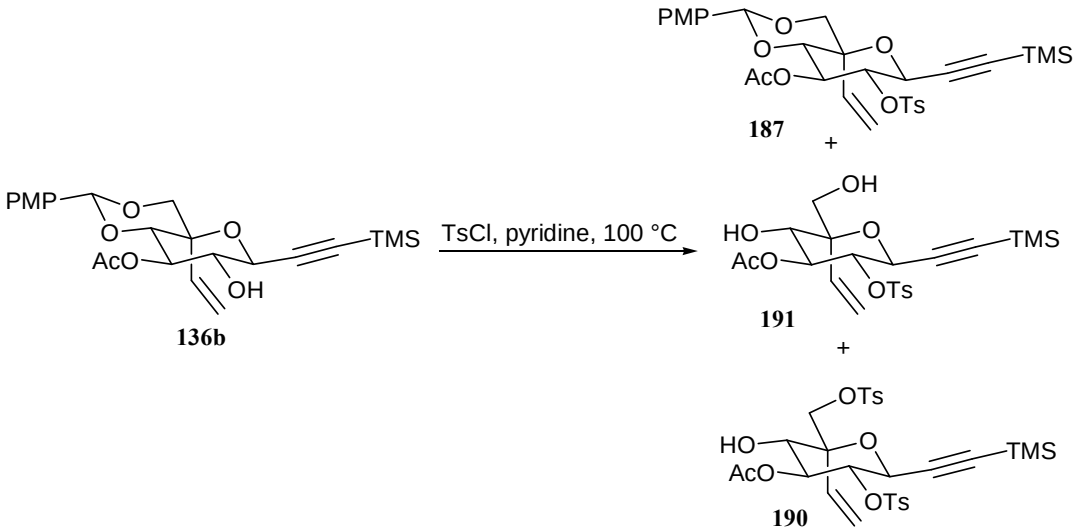
***m/z* (EI):** 448 (M^+, 100%), 279 (14).

HRMS: calculated for $C_{22}H_{28}O_8Si$: 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-trimethylsilanylethyne (187)

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

1-(3-*O*-Acetyl-2-*O*-(4-toluenesulfonyl)-5-*C*-vinyl)-β-D-glucopyranosyl)-2-trimethylsilanylethyne (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 ($MgSO_4$) 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%).

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

$[\propto]_D^{22}$ = –44.5 (*c* 0.3, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 7.82 (2H, d, *J* 8.6, *H*-Ar_{OTs}), 7.34 (2H, d, *J* 8.8, *H*-Ar), 7.32 (2H, d, *J* 8.6, *H*-Ar_{OTs}), 6.88 (1H, d, *J* 8.8, *H*-Ar), 6.22 (1H, dd, *J* 18.0, 11.4, C*H*=CH_2), 5.71 (1H, d, *J* 18.0, CH=CH_aH_b), 5.62 (1H, d, *J* 11.4, CH=CH_aH_b), 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, CH_3O), 3.73 (1H, d, *J* 9.7, *H*-C4), 2.44 (3H, s, CH_3-Ar), 1.88 (3H, s, CH_3CO), 0.24 (9H, s, $Si(CH_3)_3$).

δ_C (150 MHz; $CDCl_3$) 169.9 (*C*=O), 160.2 (arom. *C*), 144.8 (arom. C_{OTs}), 134.4 (arom. C_{OTs}), 134.1 (*C*H=CH_2), 129.1 (arom. *C*), 129.6 (arom. CH_{Ts}), 127.8 (arom. *C*H), 127.5

(arom. *C*H$_{Ts}$), 120.6 (CH=*C*H$_2$), 113.6 (arom. *C*H), 102.6 (*C*HO$_2$), 99.2 (*C*≡CTMS), 93.2 (C≡*C*TMS), 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 (*C*H$_3$O), 21.6 (*C*H$_3$-Ar), 20.7 (*C*H$_3$CO), –0.3 (Si(*C*H$_3$)$_3$).

ν_{max} (CHCl$_3$ cast)/cm^{-1}: 2957 (C-H), 2011.4 (C≡C), 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 $C_{30}H_{36}O_9NaSiS^+$: 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).

$[\alpha]_D^{20}$ = –10.0 (*c* 0.1, CHCl$_3$).

δ_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, C*H*=CH$_2$), 5.58 (1H, d, *J* 11.2, CH=C*H*$_a$H$_b$), 5.56 (1H, d, *J* 17.8, CH=CH$_a$*H*$_b$), 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, C*H*$_3$-Ar), 2.44 (3H, s, CH$_3$-Ar), 1.88 (3H, s, C*H*$_3$CO), 0.23 (9H, s, Si(C*H*$_3$)$_3$).

δ_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. *C*H), 129.6 (arom. *C*H), 129.3 (*C*H=CH$_2$), 128.0 (arom. *C*H), 127.8 (arom. *C*H), 122.5 (CH=*C*H$_2$), 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 (*C*H$_3$-Ar), 21.6 (*C*H$_3$-Ar), 20.7 (*C*H$_3$CO), –0.55 (Si(*C*H$_3$)$_3$).

ν_{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 $C_{29}H_{36}O_{10}NaSiS_2^+$: 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).

$[\alpha]_D^{20}$ = –87.8 (*c* 0.1, CHCl$_3$).

δ_H (600 MHz; $CDCl_3$) 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, C*H*=CH_2), 5.54 (1H, d, *J* 11.4, CH=CH_aH_b), 5.53 (1H, dd, *J* 17.8, 1.0, CH=CH_aH_b), 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_3-Ar), 1.91 (3H, s, CH_3CO), 0.22 (9H, s, Si(CH_3)$_3$).

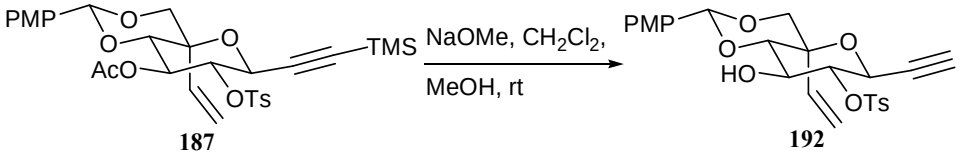
δ_C (150 MHz; $CDCl_3$) 171.2 (*C*=O), 144.7 (arom. *C*), 134.5 (arom. C_{Ts}), 131.0 (*C*H=CH_2), 129.6 (arom. *C*H), 127.8 (arom. *C*H), 120.9 (CH=*C*H_2), 99.5 (*C*≡C-TMS), 92.9 (C≡*C*-TMS), 81.6 (*C*-5), 78.6 (*C*-2), 72.7 (*C*-3), 68.8 (*C*-4), 66.5 (*C*-6), 63.5 (*C*-1), 21.6 (*C*H_3-Ar), 20.8 (*C*H_3CO), −0.36 (Si(*C*H_3)$_3$).

***ν_{max}* ($CHCl_3$ cast)/cm^{-1}:** 3444 (O-H), 2958 (C-H), 2174 (C≡C), 1749 (C=O), 1662 (C=C), 1597 (C=C).

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

HRMS: calculated for $C_{22}H_{30}O_8SiSNa^+$: 505.1353, found 505.1328. Error 4.9 ppm.

(4,6-*O*-(4-Methoxybenzylidene)-2-*O*-(4-toluenesulfonyl)-5-*C*-vinyl)-β-D-glucopyranosyl)ethyne (192)



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. $NaHCO_3$ (2 mL). The organic layer was dried ($MgSO_4$) 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).

$[\propto]_D^{20}$ = –31.0 (*c* 0.1, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 7.87 (2H, d, *J* 8.3, *H*-Ar_{OTs}), 7.40 (2H, d, *J* 8.6, *H*-Ar), 7.34 (2H, d, *J* 8.3, *H*-Ar_{OTs}), 6.89 (2H, d, *J* 8.6, *H*-Ar), 6.22 (1H, dd, *J* 18.1, 11.3, C*H*=CH_2), 5.64-5.57 (3H, m, C*H*$(O)_2$ & 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, O*H*), 2.46 (3H, s, CH_3-Ar).

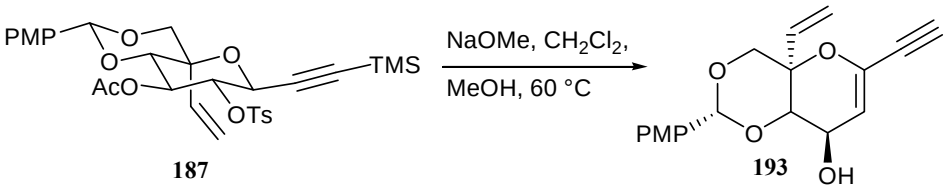
δ_C (150 MHz; $CDCl_3$) 160.4 (arom. *C*), 145.3 (arom. C_{OTs}), 134.2 (*C*H=CH_2), 133.3 (arom. *C*), 129.6 (arom. *C*H_{OTs}), 129.0 (arom. C_{OTs}), 128.5 (arom. *C*H_{OTs}), 127.7 (arom. *C*H), 119.9 (CH=*C*H_2), 113.7 (arom. *C*H), 103.1 (*C*H$(O)_2$), 82.9 (*C*-2), 81.9 (*C*-4), 75.0 (C≡*C*H), 77.0 (*C*≡CH), 76.8 (*C*-6), 71.9 (*C*-5), 69.3 (*C*-3), 63.1 (*C*-1), 55.3 (*C*H_3O), 21.7 (*C*H_3-Ar).

ν_{max} ($CHCl_3$ cast)/cm^{-1}: 3496 (O-H), 2925 (C-H), 1981 (C≡C), 1615 (C=C), 1518 (C=C_{Ar}).

***m/z* (ES+):** 487 (MH^+, 60%).

HRMS: calculated for $C_{25}H_{27}O_8S^+$: 487.1427, found 487.1446. Error 3.9 ppm.

(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.

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

$[\propto]_{\mathbf{D}}^{\mathbf{22}}$ = –2 (*c* 0.1, $CHCl_3$).

δ_H (600 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, C*H*=CH_2), 5.65 (1H, s, $CH(O)_2$), 5.47 (1H, dd, *J* 17.5, 0.8, CH=CH_aH_b), 5.39 (1H, d, *J* 11.1, CH=CH_aH_b), 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≡C*H*).

δ_C (150 MHz; $CDCl_3$) 160.4 (arom. *C*), 134.8 (*C*-1), 131.9 (*C*H=CH_2), 129.2 (arom. *C*), 127.6 (arom. *C*H), 116.5 (CH=*C*H_2), 113.8 (arom. *C*H), 110.6 (*C*-2), 102.8 (*C*H$(O)_2$), 81.9 (*C*-4), 77.2 (C≡*C*H), 74.9 (*C*-6), 73.9 (*C*-5), 64.9 (*C*-3), 55.3 (*C*H_3O).

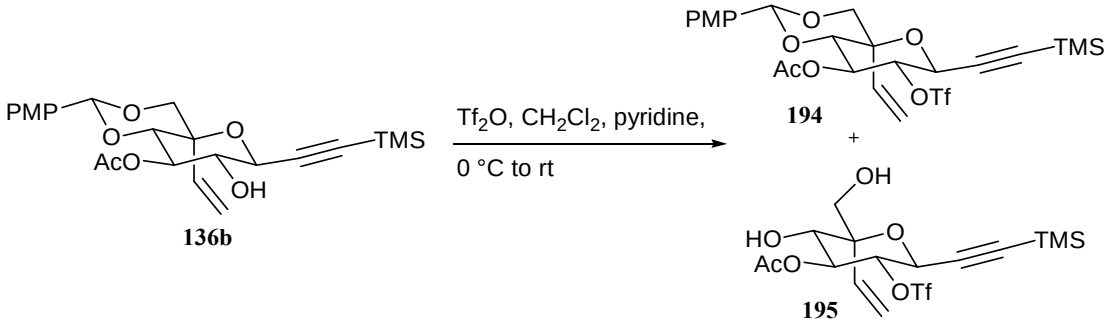
ν_{max} ($CHCl_3$ cast)/cm^{-1}: 3422 (O-H), 2922 (C-H), 2111 (C≡C), 1710 (C=C), 1615 (C=C), 1518 (C=C).

***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-β-D-glucopyranosyl)-2-trimethylsilanylethyne (194)

1-(3-*O*-Acetyl-2-*O*-(trifluoromethanesulfonyl)-5-*C*-vinyl-β-D-glucopyranosyl)-2-trimethylsilanylethyne (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 ($MgSO_4$) 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.

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

$[\propto]_D^{23}$ = –50.4 (*c* 0.2, $CHCl_3$)

δ_F (300 MHz; $CDCl_3$) –74.5.

δ_H (600 MHz; $CDCl_3$) 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, C*H*=CH_2), 5.77 (1H, d, *J* 18.1, CH=CH_aH_b), 5.70 (1H, d, *J* 11.4, CH=CH_aH_b), 5.53 (1H, s, C*H*$(O)_2$), 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, CH_3O), 3.74 (1H, d, *J* 10.7, *H*-C4), 2.11 (3H, s, CH_3CO), 0.22 (9H, s, Si$(CH_3)_3$).

δ_C (150 MHz; $CDCl_3$) 169.4 (*C*=O), 160.3 (arom. *C*), 133.6 (*C*H=CH_2), 128.8 (arom. *C*), 127.5 (arom. *C*H), 121.2 (CH=*C*H_2), 113.7 (arom. *C*H), 102.7 (*C*H$(O)_2$), 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 (*C*H_3O), 20.6 (*C*H_3CO), –0.6 (Si(*C*$H_3)_3$). N. B. The CF_3 was not observed.

***ν*$_{max}$ ($CHCl_3$ 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).

HRMS: calculated for $C_{24}H_{30}O_9F_3SiS^+$: 579.1321, found 579.1332. Error 1.9 ppm.

Further elution afforded diol **195** as a colourless oil (32 mg, 34%).

R_f 0.65 (65:35, EtOAc-petroleum spirit).

$[\propto]_D^{22}$ = –84.6 (*c* 0.4, $CHCl_3$).

δ_F (300 MHz; $CDCl_3$) –74.7.

δ_H (600 MHz; $CDCl_3$) 6.07 (1H, dd, *J* 17.8, 11.3 , C*H*=CH_2), 5.63 (1H, d, *J* 11.3, CH=CH_aH_b), 5.60 (1H, dd, *J* 17.8, 0.9, CH=CH_aH_b), 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_3CO), 0.21 (9H, s, Si(CH_3)$_3$).

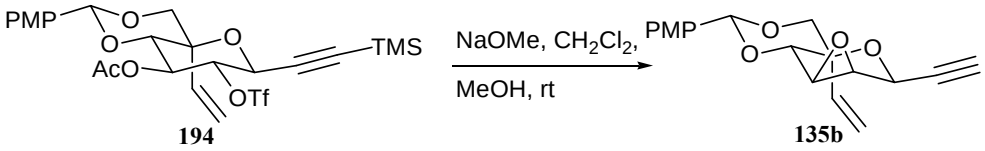
δ_C (150 MHz; $CDCl_3$) 171.0 (*C*=O), 130.5 (*C*H=CH_2), 121.4 (CH=*C*H_2), 118.3 (q, *J* 319.4, CF_3), 94.2 (*C*≡C-TMS), 94.7 (C≡*C*-TMS), 83.0 (*C*-2), 81.8 (*C*-5), 72.3 (*C*-3), 69.4 (*C*-4), 66.5 (*C*-6), 63.0 (*C*-1), 20.8 (*C*H_3CO), –0.6 (Si(*C*H_3)$_3$).

ν_{max} ($CHCl_3$ cast)/cm^{-1}: 3394 (O-H), 2924 (C-H), 2052 (C≡C), 1758 (C=O).

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

HRMS: calculated for $C_{16}H_{23}O_8F_3SiSNa^+$: 483.0733, found 483.0723. Error 2.01 ppm

(2,3-Anhydro-4,6-*O*-(4-methoxybenzylidene-5-*C*-vinyl)-β-D-mannopyranosyl)ethyne (135b)



To a stirred solution of compound **194** (25 mg, 40 μmol) in anhydrous DCM (0.1 mL) and methanol (50 μL) was added sodium methoxide (12 mg, 230 μmol). The mixture was stirred at room temperature for 12 h and then concentrated *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).

$[\propto]_{\mathbf{D}}^{\mathbf{25}}$ = + 41.0 (*c* 0.1, $CHCl_3$).

δ_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, C*H*=CH_2), 5.68 (1H, d, *J* 11.3, CH=CH_aH_b), 5.67 (1H, d, *J* 17.9, CH=CH_aH_b), 5.62 (1H, s, C*H*$(O)_2$), 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_3O), 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≡C*H*).

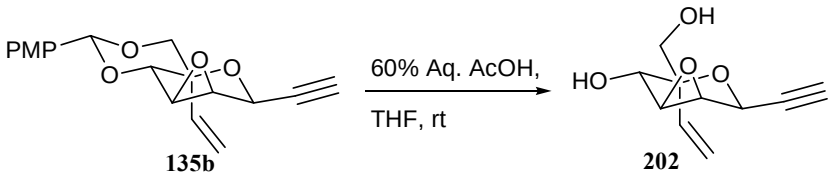
δ_C (150 MHz; $CDCl_3$) 160.3 (arom. *C*), 134.4 (*C*H=CH_2)), 129.4 (arom. *C*), 127.6 (arom. *C*H), 121.7 (CH=*C*H_2), 113.8 (arom. *C*H), 103.2 (*C*H$(O)_2$), 78.2 (*C*-4), 78.2 (*C*≡CH), 75.7 (*C*-6), 75.2 (C≡*C*H), 69.9 (*C*-5), 60.9 (*C*-1), 55.6 (*C*-4), 55.3 (*C*H_3O), 53.9 (*C*-3), 51.7 (*C*-2).

ν_{max} ($CHCl_3$ cast)/cm^{-1}: 3415 (O-H), 2126 (C≡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).

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)



135b **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.

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

$[\propto]_{\mathbf{D}}^{\mathbf{21}}$ = –31.0 (*c* 0.1, $CHCl_3$).

δ_H (400 MHz; $CDCl_3$) 5.98 (1H, dd, *J* 18.1, 11.3, C*H*=CH_2), 5.65 (1H, d, *J* 11.3, CH=C$H_a$$H_b$), 5.58 (1H, d, *J* 18.1, CH=C$H_a$$H_b$), 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≡C*H*).

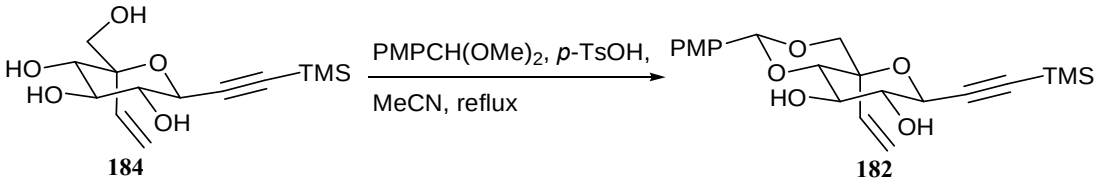
δ_C (150 MHz; $CDCl_3$) 133.7 (*C*H=CH_2), 118.3 (CH=*C*H_2), 79.6 (*C*≡CH), 77.8 (*C*-5), 74.2 (C≡*C*H), 68.2 (*C*-6), 66.5 (*C*-2), 62.3 (*C*-1), 55.0 (*C*-4), 52.2 (*C*-3).

ν_{max} ($CHCl_3$ cast)/cm^{-1}: 3390 (O-H), 3278 (O-H), 2149 (C≡C), 1722 (C=C).

***m/z* (CI, CH_4):** 197 (MH^+, 18%), 179 (14), 165 (100), 149 (20), 133 (20).

HRMS: calculated for $C_{10}H_{12}O_4^+$: 197.0808, found 197.0815. Error 3.4 ppm

1-(4,6-*O*-(4-Methoxybenzylidene)-5-*C*-vinyl-β-D-glucopyranosyl)-2-trimethylsilanylethy -ne (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.

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

$[\propto]_D^{25}$ = –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, C*H*=CH_2), 5.66 (1H, dd, *J* 18.0, 0.7, CH=CH_aH_b), 5.59 (1H, d, *J* 11.3, CH=CH_aH_b), 5.58 (1H, s, C*H*$(O)_2$), 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_3O), 3.69-3.64 (2H, m, *H*-C4 & *H*-C2), 0.22 (9H, s, Si(C$H_3)_3$).

δ_C (150 MHz; $CDCl_3$) 160.3 (arom. *C*), 134.9 (*C*H=CH_2), 129.3 (arom. *C*), 127.8 (arom. *C*H), 119.3 (CH=*C*H_2), 113.7 (arom. *C*H), 103.1 (*C*H$(O)_2$), 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 (*C*H_3O), 0.1 (Si(*C*$H_3)_3$).

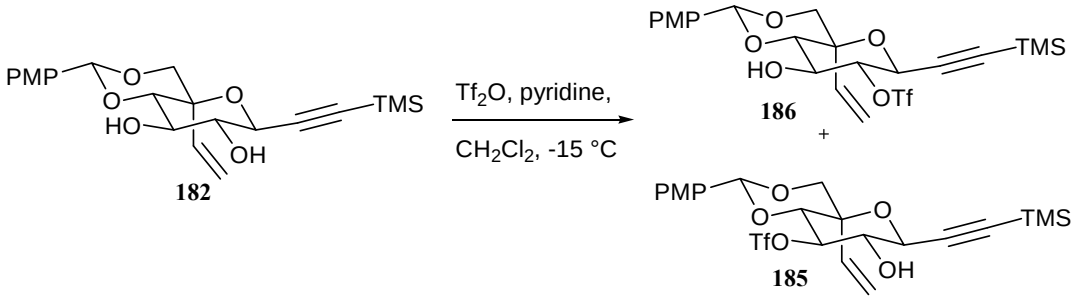
ν_{max} ($CHCl_3$ cast)/cm^{-1}: 3404 (O-H), 2179 (C≡C), 1615 (C=C), 1589 (C=C), 1518 (C=C).

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

HRMS: calculated for $C_{21}H_{29}O_6Si^+$: 405.1733, found 405.1748. Error 3.7 ppm.

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

1-(4,6-*O*-(4-Methoxybenzylidene)-3-*O*-(trifluoromethanesulfonyl)-5-*C*-vinyl-β-D-glucopyranosyl)-2-trimethylsilanylethyne (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% NEt_3) to give triflate **185** as a mixture with anisaldehyde.

R_f 0.80 (40:60, EtOAc-petroleum spirit).

δ_H (600 MHz; $CDCl_3$) 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, C*H*=CH_2), 5.69 (1H, dd, *J* 18.1, 0.8, CH=CH_aH_b), 5.65 (1H, d, *J* 11.3, CH=CH_aH_b), 5.58 (1H, s, C*H*$(O)_2$), 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, CH_3O), 3.66 (1H, d, *J* 9.8, *H*-C4), 2.75 (1H, br s, O*H*), 0.22 (9H, s, Si$(CH_3)_3$).

δ_C (150 MHz; $CDCl_3$) 160.5 (arom. *C*), 133.8 (*C*H=CH_2), 128.8 (arom. *C*), 127.7 (arom. *C*H), 120.3 (CH=*C*H_2), 113.8 (arom. *C*H), 103.2 (*C*H$(O)_2$), 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 (*C*H_3O), −0.58 (Si(*C*$H_3)_3$). N. B. The CF_3 was not observed.

Triflate **186** was also isolated as a colourless oil.

R_f 0.67 (40:60, EtOAc-petroleum spirit).

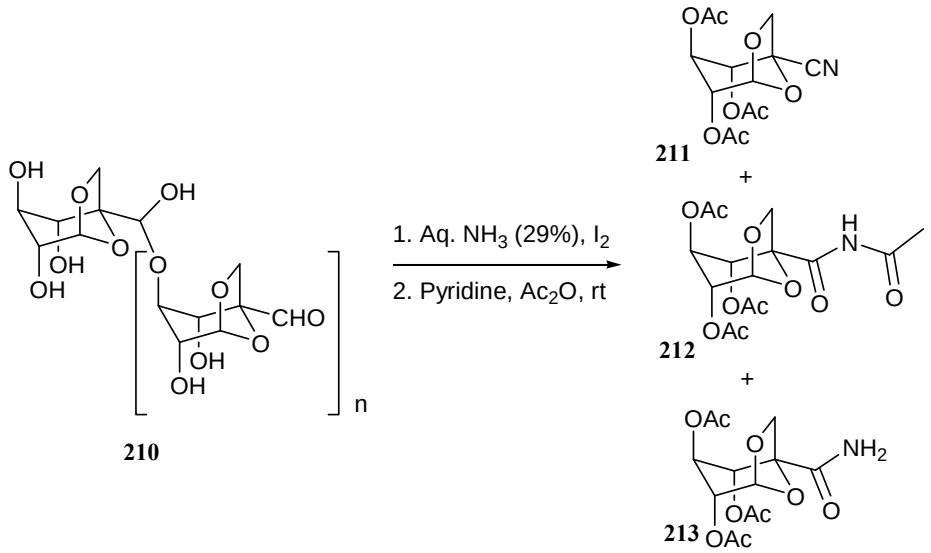
δ_H (600 MHz; $CDCl_3$) 7.42 (2H, d, *J* 8.8, *H*-Ar), 6.91 (2H, d, *J* 8.8, *H*-Ar), 6.17 (1H, dd, *J* 18.1, 11.4, C*H*=CH_2), 5.72 (1H, dd, *J* 18.1, 0.8, CH=CH_aH_b), 5.64 (1H, d, *J* 11.4, CH=CH_aH_b), 5.62 (1H, s, C*H*$(O)_2$), 4.94 (1H, dd, *J* 10.5, 8.9, *H*-C3), 4.52 (1H, d, *J* 9.6, *H*-C1), 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, CH_3O), 2.59 (1H, d, *J* 4.1, O*H*), 0.23 (9H, s, Si$(CH_3)_3$).

δ_C (150 MHz; $CDCl_3$) 160.2 (arom. *C*), 133.7 (*C*H=CH_2), 128.7 (arom. *C*), 127.3 (arom. *C*H), 121.1 (CH=*C*H_2), 113.6 (arom. *C*H), 102.4 (*C*H$(O)_2$), 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 (*C*H_3O), –0.28 (Si(*C*$H_3)_3$). 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[102]. To a stirred solution of polymer **210** (791 mg) in aq. 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 thiosulfite (1 mL), the mixture was concentrated *in vacuo* and co-evaporated with ethanol (3 × 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 ($MgSO_4$) and concentrated *in vacuo* to give a mixture of compounds which was purified by column chromatography using silica gel (1:99→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, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 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, C*H*$_3$CO), 2.174 (3H, s, C*H*$_3$CO), 2.167 (3H, s, C*H*$_3$CO).

δ_C (150 MHz; $CDCl_3$) 169.6 (CH_3CO), 169.3 (CH_3CO), 169.0 (CH_3CO), 113.5 (*C*≡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 × *C*H_3CO).

ν_{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).

$[\propto]_D^{20}$ = –33.2 (*c* 0.5, $CHCl_3$).

δ_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, C*H*$_3$CO), 2.16 (3H, s, C*H*$_3$CO), 2.15 (3H, s, C*H*$_3$CO), 2.11 (3H, s, C*H*$_3$CO).

δ_C (150 MHz; $CDCl_3$) 171.2 (*C*O), 169.4 (*C*O), 168.9 (*C*O), 168.5 (*C*O), 166.1 (*C*O), 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 × *C*H_3CO).

ν_{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).

$[\propto]_D^{25}$ = –14.4 (*c* 0.2, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 6.55 (1H, br s, CON*H*$_2$), 5.98 (1H, br s, CON*H*$_2$), 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, C*H*$_3$CO), 2.14 (3H, s, C*H*$_3$CO), 2.12 (3H, s, C*H*$_3$CO).

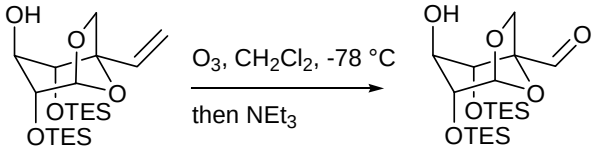
δ_C (150 MHz; $CDCl_3$) 169.4 (CH_3*C*O), 169.1 (*C*ONH_2), 169.0 (CH_3*C*O), 168.6 (*C*H_3CO), 100.7 (*C*-1), 81.7 (*C*-5), 69.8 (*C*-4), 69.1 (*C*-3), 68.2 (*C*-6), 67.9 (*C*-2), 20.9, 20.8, 20.7 (3 × *C*H_3CO).

ν_{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 $C_{13}H_{16}NO_9^+$: 330.0825, found 330.0839. Error 4.2 ppm

1,6-Anhydro-5-*C*-formyl-2,4-bis-*O*-triethylsilanyl-β-D-glucopyranose (208)



138b **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 O_2 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% NEt_3) to give aldehyde **208** as a colourless viscous oil (65 mg, 65%).

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

$[\propto]_D^{20}$ = –2.8 (*c* 1.2, chloroform).

δ_H (600 MHz; $CDCl_3$) 9.86 (1H, s, C*H*O), 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, O*H*), 1.00 (9H, t, *J* 8.0, $(CH_3CH_2)_3Si$), 0.96 (9H, t, *J* 8.0, $(CH_3CH_2)_3Si$), 0.68 (6H, q, *J* 8.0, $(CH_3CH_2)_3Si$), 0.63 (6H, q, *J* 8.0, $(CH_3CH_2)_3Si$).

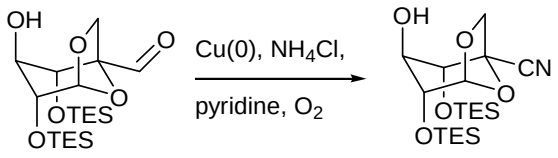
δ_C (150 MHz; $CDCl_3$) 199.8 (*C*=O), 104.0 (*C*-1), 86.5 (*C*-5), 76.3 (*C*-3), 73.7 (*C*-4), 71.9 (*C*-2), 65.7 (*C*-6), 6.8, 6.8 (2 × CH_3CH_2), 4.7, 4.6 (2 × CH_3-CH_2).

ν_{max} (CH_2Cl_2 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 $C_{19}H_{38}O_6Si_2Na^+$: 441.2104, found: 441.2088. Error 3.8 ppm.

1,6-Anhydro-5-*C*-cyano-2,4-bis-*O*-triethylsilanyl-β-D-glucose (138c)



208 **138c**

Using literature procedure[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 ($MgSO_4$), concentrated *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%).

m.p. (EtOAc) 43-45 °C.

R_f 0.70 (20:80, EtOAc-petroleum spirit).

$[\propto]_D^{20}$ = –15.4 (*c* 0.5, chloroform).

δ_H (400 MHz; $CDCl_3$) 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, O*H*), 1.04 (9H, t, *J* 7.9, $Si(CH_3CH_2)_3$), 0.98 (9H, t, *J* 7.9, $Si(CH_3CH_2)_3$), 0.74 (6H, q, *J* 7.9, 1.8, $Si(CH_3CH_2)_3$), 0.65 (6H, q, *J* 7.9, $Si(CH_3CH_2)_3$).

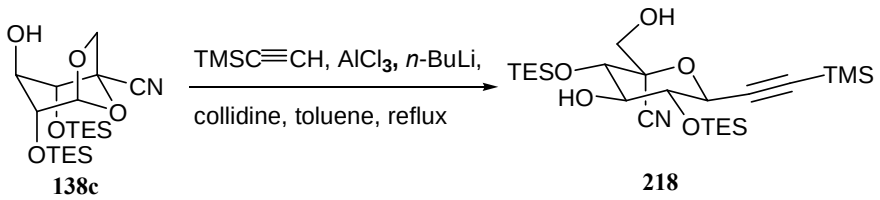
δ_C (100 MHz; $CDCl_3$) 115.4 (*C*≡N), 104.5 (*C*-1), 76.8 (*C*-5), 75.2 (*C*-3), 73.5 (*C*-4), 71.5 (*C*-2), 68.9 (*C*-6), 6.8, 6.7 (2 × CH_3-CH_2), 4.7, 4.6 (2 × CH_3-CH_2).

ν_{max} (CH_2Cl_2 cast)/cm^{-1}: 3473 (O-H), 2955 (C-H). N. B. (C≡N) stretch was not observed.

***m/z* (ES+):** 438 (40, MNa^+), 413 (10), 236 (10).

HRMS: calculated for $C_{19}H_{37}NO_5Si_2Na^+$: 438.2090, found: 438.2108. Error 4.1 ppm.

1-(5-*C*-Cyano-2,4-bis-*O*-(triethylsilanyl)-β-D-glucopyranosyl)-2-trimethylsilanylethyne (218)



138c **218**

Using literature procedure[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 μL, 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 × 50 mL) and the organic material was dried ($MgSO_4$) and concentrated *in vacuo* to give an oil which was purified by column chromatography using activated alumina (2:98→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).

$[\propto]_D^{20}$ = –27.9 (*c* 0.6, $CHCl_3$).

δ_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_2OH), 2.25 (1H, d, *J* 3.3, CHO*H*), 1.02 (9H, t, *J* 7.0, $Si(CH_3CH_2)_3$), 0.99 (9H, t, *J* 7.0, $Si(CH_3CH_2)_3$), 0.77-0.65 (12H, m, $2\times Si(CH_3CH_2)_3$), 0.21 (9H, s, $Si(CH_3)_3$).

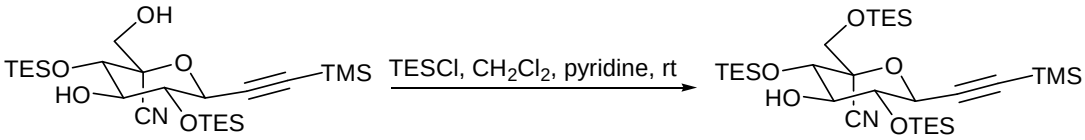
δ_C (150 MHz; $CDCl_3$) 115.6 (*C*≡N), 100.9 (*C*≡C-TMS), 92.5 (C≡*C*-TMS), 79.4 (*C*-5), 76.6 (*C*-3), 74.4 (*C*-2), 70.0 (*C*-4), 69.6 (*C*-1), 64.3 (*C*-6), 6.9 (CH_2-CH_3), 6.8 (CH_2-CH_3), 5.3 (CH_3-CH_2), 5.1 (CH_3-CH_2), –0.4 (CH_3).

ν_{max} ($CHCl_3$ cast)/cm^{-1}: 3526 (O-H), 1459 (C-H). N. B. (C≡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 $C_{24}H_{46}NO_5Si_3^+$: 512.2703, found 512.2684. Error 3.7 ppm

1-(5-*C*-Cyano-2,4,6-tris-*O*-(triethylsilanyl)-β-D-glucopyranosyl)-2-trimethylsilanyl-ethyne (219)



218 **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 ($MgSO_4$) 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%).

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

$[\propto]_D^{20}$ = –31.8 (*c* 0.4, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 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, O*H*), 1.05-0.95range (27H, m, 3×Si(CH_3CH$_2$)$_3$), 0.79-0.61 (18H, m, 3×Si(CH$_3$CH_2)$_3$), 0.18 (9H, s, Si(CH$_3$)$_3$).

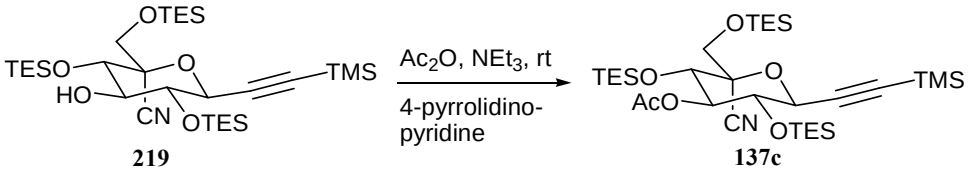
δ_C (150 MHz; $CDCl_3$) 115.9 (*C*≡N), 101.4 (*C*≡C-TMS), 91.7 (C≡*C*-TMS), 79.9 (*C*-5), 76.7 (*C*-3), 74.4 (*C*-2), 69.6 (*C*-4), 69.2 (*C*-1), 64.4 (*C*-6), 6.9, 6.8, 6.7 (3 × CH$_2$-*C*H$_3$), 5.3, 5.0, 4.5 (3 × CH$_3$-*C*H$_2$), 0.5 (*C*H$_3$).

ν_{max} ($CHCl_3$ 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 $C_{30}H_{60}NO_5Si_4^+$: 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)



219 **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-pyrrolidinopyridine (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 ($MgSO_4$) 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).

$[\propto]_D^{20}$ = –53.3 (*c* 0.8, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 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, CH_3CO), 1.05-0.96 (27H, m, 3×Si(CH_3CH_2)$_3$), 0.70-0.55 (18H, m, 3×Si(CH$_3$CH_2)$_3$), 0.19 (9H, s, Si(CH_3)$_3$).

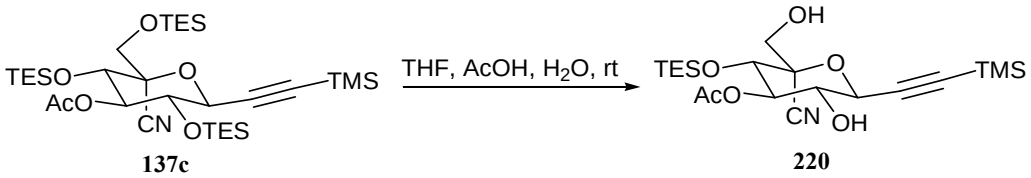
δ_C (150 MHz; $CDCl_3$) 169.0 (*C*=O), 115.5 (*C*≡N), 101.4 (*C*≡C-TMS), 92.2 (C≡*C*-TMS), 79.8 (*C*-5), 76.5 (*C*-3), 73.0 (*C*-2), 69.6 (*C*-1), 68.1 (*C*-4), 64.1 (*C*-6), 21.6 (*C*H$_3$CO), 6.8, 6.7 (2×Si(*C*H$_3$CH$_2$)$_3$), 5.3, 5.0, 4.5 (3×Si(CH$_3$*C*H$_2$)$_3$), –0.5 (Si(*C*H$_3$)$_3$).

ν_{max} ($CHCl_3$ 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 $C_{32}H_{64}NO_6Si_4^+$: 670.3842, found 670.3811. Error 4.6 ppm.

1-(3-*O*-Acetyl-5-*C*-cyano-4-*O*-(triethylsilanyl)-β-D-glucopyranosyl)-2-trimethylsilanyle-thyne (220)



137c **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%).

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

$[\propto]_D^{20} = -74.9$ (*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*H*), 2.24 (1H, dd, *J* 9.9, 5.4, CH_2OH), 2.19 (3H, s, CH_3CO), 0.98 (9H, t, *J* 7.8, $Si(CH_3CH_2)_3$), 0.65 (6H, q, *J* 7.8, $Si(CH_3CH_2)_3$), 0.21 (9H, s, $Si(CH_3)_3$).

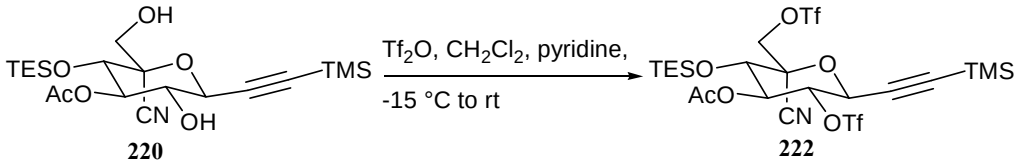
δ_C (100 MHz; $CDCl_3$) 171.4 (*C*=O), 115.0 (*C*≡N), 98.9 (*C*≡C-TMS), 93.9 (C≡*C*-TMS), 79.6 (*C*-5), 76.6 (*C*-3), 72.6 (*C*-2), 69.5 (*C*-1), 68.0 (*C*-4), 63.7 (*C*-6), 21.1 (CH_3CO), 6.6 ($Si(CH_3CH_2)_3$), 5.0 ($Si(CH_3CH_2)_3$), −0.3 ($(CH_3)_3Si$).

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 $C_{20}H_{34}NO_6Si_2$: 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 ($MgSO_4$) 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_f 0.70 (50:50, DCM-petroleum spirit).

$[\propto]_{\mathbf{D}}^{\mathbf{20}}$ = −50.0 (*c* 1.1, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 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, CH_3CO), 0.99 (9H, t, *J* 7.9, $Si(CH_3CH_2)_3$), 0.61-0.69 (6H, m, $Si(CH_3CH_2)_3$), 0.21 (9H, s, $Si(CH_3)_3$).

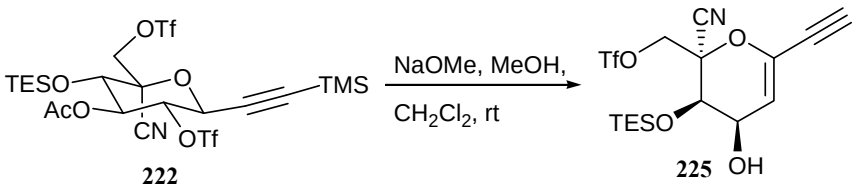
δ_C (150 MHz; $CDCl_3$) 168.8 (*C*=O), 119.3 (q, *J* 319.3, CF_3), 117.3 (q, *J* 319.3, CF_3), 112.0 (*C*≡N), 97.6 (*C*≡C-TMS), 94.4 (C≡*C*-TMS), 80.4 (*C*-2), 77.4 (*C*-5), 72.3 (*C*-6), 71.7 (*C*-3), 69.7 (*C*-4), 66.7 (*C*-1), 21.0 (CH_3CO), 6.5 ($Si(CH_3CH_2)_3$), 5.0 ($Si(CH_3CH_2)_3$), −0.9 ($Si(CH_3)_3$).

ν_{max} ($CHCl_3$ cast)/cm^{-1}: 2963 (C-H), 1755 (C=O). N. B. (C≡N) stretch was not observed.

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

HRMS: calculated for $C_{22}H_{34}O_{10}NS_2F_6Si_2$: 706.1067, found 706.1082. Error 2.2 ppm.

(5-*C*-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)

$[\propto]_{\mathbf{D}}^{\mathbf{20}}$ = +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≡C*H*), 1.01 (9H, t, *J* 8.0, $Si(CH_3CH_2)_3$), 0.71 (6H, m, $Si(CH_3CH_2)_3$).

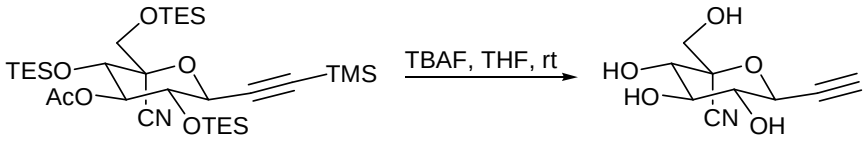
δ_C (150 MHz; $CDCl_3$) 137.7 (*C*-1), 115.4 (*C*≡N), 107.0 (*C*-2), 79.3 (*C*-5), 77.3 (*C*-6), 76.2 (*C*≡C-H), 76.1 (C≡*C*-H), 70.4 (*C*-3), 69.4 (*C*-4), 6.6 ($Si(CH_3CH_2)_3$), 4.7 ($Si(CH_3CH_2)_3$). N. B. CF3 does not appear.

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

HRMS: calculated for $C_{16}H_{23}O_6NSF_3Si$: 442.0967, found 442.0978. Error 2.4 ppm.

(5-*C*-cyano-β-D-glucopyranosyl)ethyne (226)



137c **226**

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

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

$[\propto]_D^{21}$ = –49.6 (*c* 0.9, EtOH).

δ_H (600 MHz; CD_3OD) 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*).

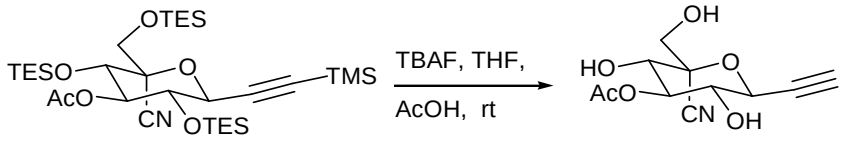
δ_C (150 MHz; CD_3OD) 115.9 (*C*≡N), 80.5 (*C*-5), 79.1 (*C*≡C-H), 75.1 (C≡*C*-H), 74.8 (*C*-3), 73.0 (*C*-2), 69.5 (*C*-4), 68.8 (*C*-1), 63.9 (*C*-6).

ν_{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 $C_9H_{10}NO_5$: 212.0564, found 212.0559. Error 2.4 ppm.

(3-*O*-Acetyl-5-*C*-cyano-β-D-glucopyranosyl)ethyne (221)



137c **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 ($MgSO_4$) 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%).

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

$[\propto]_D^{25}$ = –67.2 (*c* 0.1, EtOH).

δ_H (600 MHz; $CDCl_3$) 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, CH_3CO).

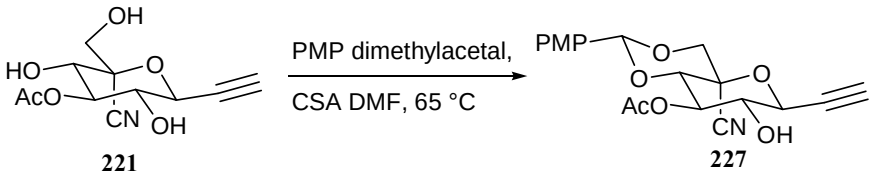
δ_C (150 MHz, CD_3OD) 173 (*C*=O), 114.9 (*C*≡N), 79.3 (*C*-5), 77.9 (*C*≡C-H), 77.2 (C≡*C*-H), 76.6 (*C*-3), 71.4 (*C*-2), 69.2 (*C*-4), 68.9 (*C*-1), 64.5 (*C*-6), 21.0 (*C*H_3CO).

ν_{max} (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 $C_{11}H_{12}NO_6$: 254.0678, found 254.0665. Error 5.1 ppm.

(3-*O*-Acetyl-5-*C*-cyano-4,6-*O*-(4-methoxybenzylidene)-β-D-glucopyranosyl)ethyne (227)



221 **227**

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 °C for 12 h. Concentration of the resulting solution *in vacuo* gave an oil which when purified by column chromatography (1:99, 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).

$[\propto]_D^{22}$ = –66.4 (*c* 0.1, $CHCl_3$).

δ_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, C*H*$(O)_2$), 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_3O), 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≡C-*H*), 2.14 (3H, s, CH_3CO).

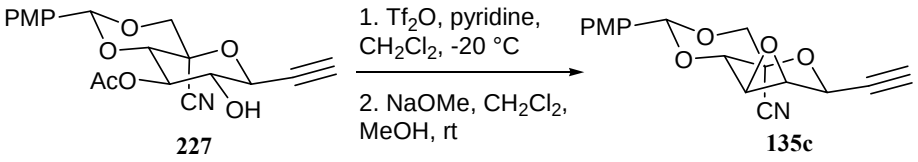
δ_C (150 MHz; $CDCl_3$) 171.3 (*C*=O), 160.7 (arom. *C*), 128.0 (arom. *C*H), 127.9 (arom. *C*), 115.4 (*C*≡N), 113.8 (arom. *C*H), 103.2 (*C*H$(O)_2$), 78.6 (*C*-4), 77.9 (*C*≡C-H), 76.3 (C≡*C*-H), 73.1 (*C*-2), 72.5 (*C*-3), 71.2 (*C*-6), 70.7 (*C*-5), 69.8 (*C*-1), 55.3 (*C*H_3O), 20.9 (*C*H_3CO).

ν_{max} ($CHCl_3$ cast)/cm^{-1}: 3396 (O-H), 2935 (C-H), 2131 (C≡C), 1749 (C=O), 1647 (C=C), 1615 (C=C), 1519 (C=C). N. B. (C≡N) stretch was not observed.

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

HRMS: calculated for $C_{19}H_{19}NO_7Na^+$: 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)



227 **135c**

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, NEt_3 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).

$[\propto]_D^{19}$ = +27.4 (*c* 0.1, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 7.48 (2H, d, *J* 8.7, *H*-Ar), 6.95 (2H, d, *J* 8.7, *H*-Ar), 5.60 (1H, s, C*H*$(O)_2$), 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, CH_3O), 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*).

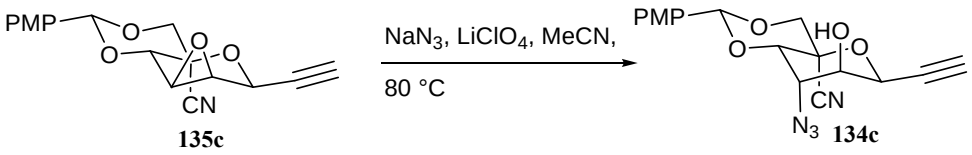
δ_C (150 MHz; $CDCl_3$) 160.7 (arom. *C*), 127.9 (arom. *C*), 127.9 (arom. *C*H), 115.7 (*C*≡N), 113.9 (arom. *C*H), 103.7 (*C*H$(O)_2$), 76.6 (*C*≡C-H), 76.3 (*C*-4), 76.0 (C≡*C*-H), 71.0 (*C*-6), 68.8 (*C*-5), 64.3 (*C*-1), 55.4 (*C*H_3O), 53.3 (*C*-3), 51.3 (*C*-2).

ν_{max} ($CHCl_3$ cast)/cm^{-1}: 2925 (C-H), 1615 (C=C), 1519 (C=C). N. B. (C≡N) stretch was not observed.

***m/z* (CI+, CH_4)** 337 (M+Na, 14%), 314 (M+H, 7), 204 (7), 136 (100).

HRMS: calculated for $C_{17}H_{16}NO_5$: 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[99]. 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 ($MgSO_4$) 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%).

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

$[\propto]_D^{19}$ = –93.3 (*c* 0.1, $CHCl_3$).

δ_H (600 MHz; $CDCl_3$) 7.47 (2H, d, *J* 8.7, *H*-Ar), 6.94 (2H, d, *J* 8.7, *H*-Ar), 5.63 (1H, s, C*H*$(O)_2$), 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, CH_3O), 2.71 (1H, d, *J* 2.2, C≡C-*H*), 2.52 (1H, d, *J* 2.7, O*H*).

δ_C (150 MHz; $CDCl_3$): 160.7 (arom. *C*), 128.1 (arom. *C*), 127.9 (arom. *C*H), 117.0 (*C*≡N), 113.9 (arom. *C*H), 104.0 (*C*H$(O)_2$), 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 (*C*H_3O).

***ν_{max}* ($CHCl_3$ cast)/cm^{-1}:** 3450 (O-H), 2920 (C-H), 2119 (N_3), 1615 (C=C), 1519 (C=C). N. B. (C≡N) stretch was not observed.

***m/z* (CI+, CH_4)** 357 (M+H, 53%), 338 (64), 329 (8), 295 (100), 136 (39).

HRMS: calculated for $C_{17}H_{17}N_4O_5$: 357.1199, found 357.1199.

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