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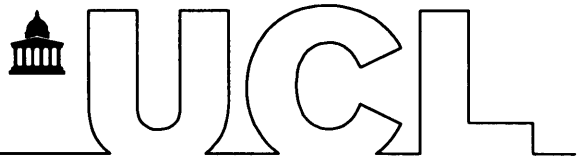

Studies towards the synthesis of Tagetitoxin

A Thesis Presented to the University of London
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Abstract

Tagetitoxin is a phytotoxin which was first isolated in 1981 from a strain of *Pseudomonas syringae* pv. *tagetis*. It is viewed as a challenging synthetic target for a variety of reasons:

- The molecule shows a unique biological activity as a specific inhibitor of RNA polymerase III. It has found some use within the biological community in the study of transcription.

- Its structure is assigned upon spectroscopic and chemical analysis of biological extracts, and has some ambiguities.

- Its probable structure contains a unique bicyclic ring system which has never been synthesised before.

- The natural product itself has never been synthesised.

In this thesis, we report an efficient, high-yielding and short synthetic route to the core structure of tagetitoxin from simple carbohydrate starting materials.

The initial research focused on the ring expansion of a bicyclic 1,3-oxathiolane to the corresponding 1,4-oxathiane using metallocarbene chemistry *via* Stevens rearrangement. This reaction proved not to be feasible on the studied precursors; possible reasons for this failure are discussed herein.

The second route investigated involved the intramolecular cyclisation of a thiol onto an electron-deficient ketone. Initial studies on unfunctionalised substrates proved unsuccessful, however, the use of a carbohydrate as starting material was more efficient and the core structure of tagetitoxin was synthesised from D-glucose in 32% yield over 15 steps.

Studies towards a more complex substrate were carried out and key intermediates were successfully synthesised. Future plans towards the total synthesis of tagetitoxin are laid out based on the findings of this thesis.

A mes parents

Acknowledgments

I would like to express my most sincere gratitude to Mike Porter for giving me the opportunity to spend these past four years in his group. He provided me with a thriving total synthesis project and has always been sharing my highs and understanding my lows in the lab. I am profoundly thankful for his guidance and support; the years spent in the Porter group have clearly been the highlight of my education and this was only possible thanks to Mike.

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Abbreviations

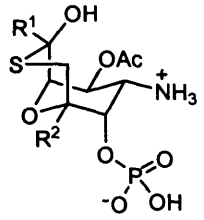
Ac	acetyl
acac	acetylacetonate
Ar	aryl
B^-	base
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
n-Bu	*n*-butyl
t-Bu	*t*-butyl
Bz	benzoyl
CI	chemical ionisation
m-CPBA	*meta*-Chloroperbenzoic acid
CSA	camphorsulfonic acid
d	doublet
dd	doublet of doublet
ddd	doublet of doublet of doublet
dt	doublet of triplet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dr	diastereoisomeric ratio
E^+	electrophile
ee	enantiomeric excess
eq	equivalent
ESI	electrospray ionisation
Et	ethyl
FAB	fast atomic bombardment
hfacac	hexafluoro acetylacetonate

HMBC	heteronuclear multiple bond connectivity
HMQC	heteronuclear multiple quantum coherence
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infra red
J	coupling constant
L	ligand
m	*meta*
m/z	mass to charge ratio
Me	methyl
mM	milimolar
Ms	methylsulfonyl
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Nu^-	Nucleophile
o	*ortho*
p	*para*
PG	protecting group
Ph	phenyl
PMB	*para*-methoxybenzyl
PPTS	pyridinium *para*-toluenesulfonate
i-Pr	isopropyl
pyr	pyridine
R	alkyl
RT	room temperature
s	singlet
SM	starting material
t	triplet
TBAF	tetra *n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid

THF	tetrahydrofuran
THP	tetrahydropyran-2-yl
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF	time of flight
Ts	*p*-toluenesulfonyl

1 Introduction

This thesis describes attempts to synthesise the structurally unique RNA polymerase inhibitor tagetitoxin **1** (Figure 1).



1a: R^1=$CONH_2$, R^2=COOH
1b: R^1=COOH, R^2=$CONH_2$

Figure 1: Tagetitoxin structure

In this introduction, the mode of action of tagetitoxin will be reviewed, along with its characterisation and attempted total synthesis. In order to understand the mechanism of action of tagetitoxin, it is necessary to fully appreciate the process of RNA transcription, which is carried out by RNA polymerases.

1.1 Genetic information

Life relies on the ability of cells to store, retrieve and translate the genetic instructions to make and maintain a living organism. This hereditary information is passed to daughter cells at cell division, and from generation to generation of organisms through reproductive cells. These instructions are stored within every living cell in its genes and determine the characteristics of a particular individual. Essentially, genetic information consists of instructions for making proteins. The latter are of an enormous importance to the cell. Proteins enable cells to move and communicate with each other, are the precursors of enzymes which catalyse a cell's chemical reactions, and regulate gene expression.[1]

1.1.1 DNA structure and Gene expression

The genetic information is carried in DNA (deoxyribonucleic acid) whose structure is based on a double-stranded helix, each strand being a long polynucleotide chain. Nucleotides are composed of three different parts (Figure 2):

- a five carbon-sugar (2-deoxyribose in the case of DNA);
- a phosphate group;
- a base that can be either adenine (A), thymine (T), cytosine (C) or guanine (G).

The backbone of one strand of DNA is made up of alternating phosphate and sugar groups. All the bases are contained within the interior of the helix, and are bound together by hydrogen bonding whereas the sugar-phosphate backbones are on the outside. The bases pair in a strictly ordered manner: adenine only pairs up with thymine whereas cytosine only associates with guanine. Thus a purine always pairs up with a pyrimidine making the most favoured energetic arrangement in the DNA helix (Figure 2).

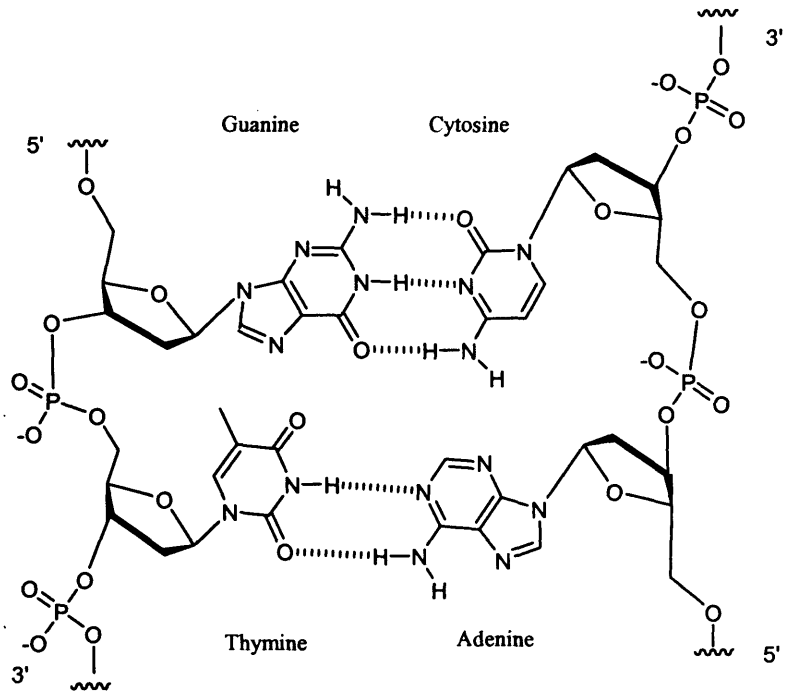


Figure 2: Base pairing in DNA

1.1.2 DNA transcription

Although DNA stores the genetic information, it does not actually direct protein synthesis itself.[2] When a particular protein is needed by the cell, the appropriate portion of the DNA is first copied into another type of nucleic acid called ribonucleic acid (RNA), which then induces protein synthesis in the cell. The mechanism of copying the information of the DNA into RNA is called transcription, whereas the process where RNA is used to produce proteins is called translation.

RNA molecules which serve as templates for protein synthesis are called messenger RNA (mRNA). Ribosomal RNA (rRNA) forms part of the structure of the ribosomes, on which mRNA is translated into a protein and transfer RNA (tRNA) forms the adaptors that select amino acids and hold them in place on a ribosome for their incorporation into a protein.

RNA is very similar in structure to DNA. It is made of a five-carbon sugar (ribose rather than deoxyribose in DNA), a phosphate group and one of the four following bases: adenine, guanine, cytosine and uracil (U) (instead of thymine in DNA) (Figure 3). Complementary base-pairing applies in the same ways as for DNA, the difference being that base pairing occurs between A and U whereas it is between A and T in DNA.

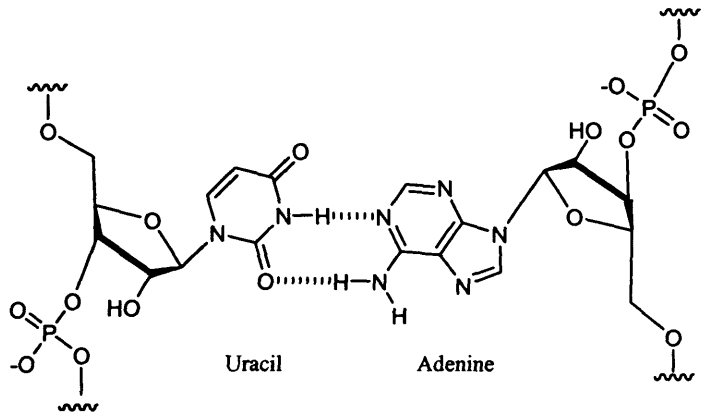


Figure 3: Base pairing in RNA

Despite these relatively small chemical differences, DNA and RNA differ quite dramatically in overall structure. DNA always occurs in cells as a double-stranded helix, whereas RNA exists as single-stranded chains and can therefore fold up into a variety of shapes.

Transcription begins with the opening and unwinding of a small portion of the DNA double helix so that the bases on each strand are exposed.[3] One strand of the DNA then acts as a template for the synthesis of an RNA molecule. The nucleotides then add sequentially to the growing RNA chain through complementary base-pairing with the DNA template. Each incoming nucleotide is covalently bound to the RNA chain in an enzymatically catalysed reaction, and the resulting sequence is called the transcript. The RNA strand does not remain hydrogen-bonded to the DNA template;

as soon as a nucleotide has been transcribed, the RNA molecule is released as a single strand.

The enzymes that carry out transcription are called RNA polymerases. Their role is to catalyse the formation of the phosphodiester bonds that link the nucleotides together and form the sugar-phosphate backbone of the RNAchain.[3] The enzymes move stepwise along the DNA, unwinding the DNA helix just ahead of the active site for polymerisation, so exposing a new region of the template strand for complementary base-pairing. The growing RNA chain is therefore extended one nucleotide at a time. In both prokaryotes and eukaryotes, RNA polymerase binds tightly to the DNA strand when it encounters a promoter, which is the sequence of nucleotides that indicates the starting point of RNA synthesis.[4-6] When the RNA polymerase encounters a sequence of nucleotides that indicate the termination of the RNA synthesis (a terminator), the polymerase halts and releases both the DNA template and the newly made RNA chain.[3] During transcription, non-coding nucleotide sequences called introns are removed, and coding nucleotides called exons are joined together; this phenomenon is known as splicing.

There are major differences between prokaryotic and eukaryotic RNA polymerases. In prokaryotes, only a single type of RNA polymerase is found, whereas three different kinds of RNA polymerase are found in eukaryotes. Bacterial RNA polymerase is made of four subunits and an additional fifth subunit called the sigma factor; the latter is responsible for the recognition of a promoter and therefore initiation of transcription.[7]

The three eukaryotic RNA polymerases (RNA pol I, RNA pol II, RNA pol III) are responsible for transcribing different kind of genes.[8,9] They consist of large multi-subunit enzymes that have several common subunits.

- RNA pol I is in charge of the transcription of most ribosomal RNA.
- RNA pol II deals with messenger RNA.
- RNA pol III is responsible for transfer RNA as well as some small structural RNAs, including the 5S ribosomal RNA subunit.

RNA polymerases themselves are not responsible for recognizing the DNA sequences that control gene transcription. Initiation of transcription is triggered by proteins known as transcription factors. Most of these factors contain domains that can bind specifically to short regions of DNA that have a particular base sequence. They in turn recruit RNA polymerases to the appropriate sites, in order that transcription can begin.

1.1.2.1 RNA polymerases I and II

RNA pol I is responsible for the transcription of most genes encoding ribosomal RNA. Although accounting for the synthesis of only one product, RNA pol I is responsible for 70% of all nuclear transcription. The promoter DNA sequence is located within the 50 bases immediately upstream of the start site.

In vertebrates, at sequences around –50, the first protein transcription factor involved is known as UBF (Upstream Binding Factor), a modular polypeptide.[10] Another regulatory protein, SL1, is then recruited via protein-protein interaction with UBF forming a complex. RNA pol I can only enter the complex at this moment and thus initiates transcription.[11] Termination occurs when a termination factor known as TTF-I is recruited.[12-14]

RNA pol II transcribes the majority of genes, generating messenger RNA which is in turn translated to produce proteins. Therefore, the wide variety of RNA

pol II templates is reflected in a diversity of promoter structure. Generally, these sites are found within a few hundred base pairs upstream of the transcription start site and can contain binding sites for various transcription factors. Two general motifs can be seen in a large proportion of cases;[15] firstly, the region immediately upstream of the transcriptional start site of genes transcribed by RNA pol II is made of a sequence of bases rich in A and T nucleotides, the so-called TATA box;[16,17] the second common feature is the initiator which is centred at the transcription start site. The commonality between these initiators is the presence of a large number of pyrimidine bases, their sequence varying between each gene. Binding to the promoter and transcription initiation requires a large family of transcription factors.

Elongation factors that can facilitate transcript synthesis have also been identified. Their main role is to suppress pausing in the transcription. Termination occurs in most cases upon encountering the sequence AAUAAA.

This complex system is well understood due to the contributions of Kornberg *et al.*, who developed an *in vitro* yeast transcription system based on *Saccharomyces cerevisiae*.[18,19] Structural elucidation of RNA pol II complexed with the template DNA and product RNA were achieved by Kornberg *et al.* using a combination of electron microscopy and X-ray crystallography.[20,21] It showed the binding site of the nucleic acid as a cleft bridged by an α-helix passing through the active site for RNA chain elongation.

Kornberg's remarkable contribution provided molecular understanding of the initiation,[20-22] the DNA-RNA hybrid translocation[20,22] and the separation of the RNA strand from the DNA template.[23] This contribution was recognised through the award of the 2006 Nobel Prize in Chemistry to Kornberg, "for his studies of the molecular basis of eukaryotic transcription".

1.1.2.2 RNA polymerase III

RNA polymerase III is responsible for the production of transfer RNA and some other small structural RNA molecules. In RNA pol III, a specific transcription factor is involved to recruit both the polymerase and other specific factors, as is the case for RNA pol I.[24,25]

The essential promoter DNA sequences, which are recognised by the transcription factors that recruit the RNA pol III, can be located either upstream or downstream of the transcribed region. Downstream promoters, specific to RNA pol III, have been characterised on the basis of studies focusing on the genes encoding the ribosomal 5S RNA.[26] It has been demonstrated that the entire upstream region of this particular gene could be deleted without drastic effect on the gene expression until it crosses a boundary of 40 bases within the transcribed region. This means that the promoter for this gene was located entirely in the transcribed region.

This particular region was shown to bind first to the transcription factor TFIIIA.[27] Subsequently another factor called TFIIIC binds to the DNA next to TFIIIA; this in turn recruits TFIIIB to form a stable transcription complex. It is this particular complex, stable through many cell divisions, that promotes the binding of RNA pol III and consequently, transcription is not dependent on the precise sequence of the DNA to which it binds.

After formation of a closed complex consisting of the transcription factors, RNA pol III and the DNA, the DNA helix around the initiation site is broken down, resulting in an open-strand complex which allows the enzyme to move along the gene. Nonetheless, elongation does not proceed at a uniform rate, due to pausing of the transcription complex at internal sites. The rate of extension at individual nucleotides can vary 31 fold. No elongation factors have been identified for RNA pol III.

During elongation, the enormous factor TFIIIC (one of the largest and most complex transcription factors that have been studied) is located in the transcribed region and it is not clear how a small class III gene can be expressed in its presence. The voluntary removal of TFIIIC does not make any significant difference to the rate of RNA elongation. It is thought that RNA pol III displaces a given factor from its binding site after transcription of a particular region but this factor still remains stable through protein-protein interaction with other factors bound to the DNA template.

Whereas RNA pol I and RNA pol II require additional factors to terminate transcription, RNA pol III recognises clusters of at least four T residues as termination signals. After an initial round of transcription, the polymerase can be recycled without being released from the template, due to the stability of the pre-initiation complex. Multiple transcriptions are therefore possible, and occur at a greater rate, allowing for the efficient production of RNA transcripts necessary to the further processing of the genetic information.

1.2 Tagetitoxin

Tagetitoxin is a phytotoxin isolated from the bacterium *Pseudomonas syringae* pv. *tagetis*, which induces chlorosis (the yellowing or whitening of normally green plant tissue because of a decreased amount of chlorophyll) in host plants.[28] This is due to the inhibition of transcription in chloroplasts. Tagetitoxin has also been shown to specifically inhibit *Escherichia coli* RNA polymerase as well as RNA pol III from yeast, insects and vertebrates at micromolar levels *in vitro*. Its isolation and chemical structure have been the source of much debate and its final characterisation is still tentative.

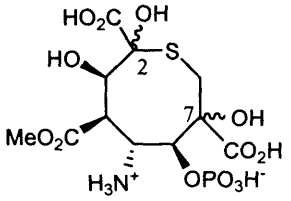
The production of tagetitoxin from a selected strain of *Pseudomonas syringae* pv. *tagetis* and its use as a plant-growth regulator have been patented.[29] Furthermore, tagetitoxin has been an object of growing interest to the biological community for its use in the study of DNA transcription, with a particular emphasis on the discovery and characterisation of new promoters. While tagetitoxin is commercially available (cost: £300 for 30 μg, August 2007),[30] a synthetic route to tagetitoxin would provide larger quantities of the compound and would also give access to analogues, which could be tested as potential herbicides[31] or antibacterial agents.[32]

In the next section, the methods used to isolate a purified fraction of tagetitoxin and the interpretation of spectroscopic data for the characterisation of tagetitoxin will be discussed. Finally, the biological activity of tagetitoxin will be reviewed.

1.2.1 Isolation and characterisation

The natural product tagetitoxin was first isolated, purified and partially characterised by Mitchell and Durbin in 1981 from liquid cultures of the plant-pathogenic bacterium *Pseudomonas syringae* pv. *tagetis* by a sequence of precipitation, solvent extraction and chromatography steps. The purified toxin was unreactive towards treatment with strong acid but dilute acids generated a new inactive component.

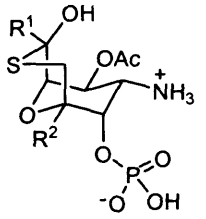
The initial interpretation of chemical and spectroscopic data led to the proposed 8-membered ring structure **2** (Figure 4).[33] Mass spectrometry gave a molecular mass of 435 which was consistent with the molecular formula $C_{11}H_{18}NO_{13}PS$.



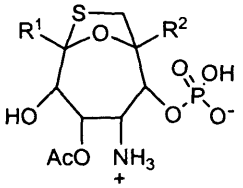
2

Figure 4: Initially proposed tagetitoxin structure

In 1989, the same group of researchers conducted further analysis using FAB mass spectrometry that gave a high resolution molecular ion (MH^+) peak at 417.0361. This result ruled out the original structure **2** but was in accordance with a molecular formula of $C_{11}H_{17}N_2O_{11}PS$. This data, in conjunction with ^1H, ^{13}C and ^{31}P NMR studies led to four new postulated structures **1a**, **1b**, **3a** and **3b** (Figure 4).[34] The absolute configuration was not assigned.



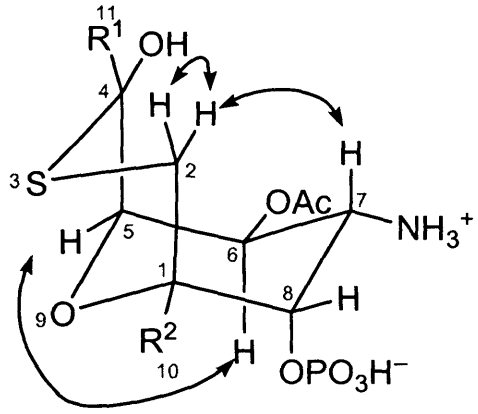
1a: R^1=$CONH_2$, R^2=COOH
1b: R^1=COOH, R^2=$CONH_2$



3a: R^1=$CONH_2$, R^2=COOH
3b: R^1=COOH, R^2=$CONH_2$

Figure 5: Revised structures of tagetitoxin

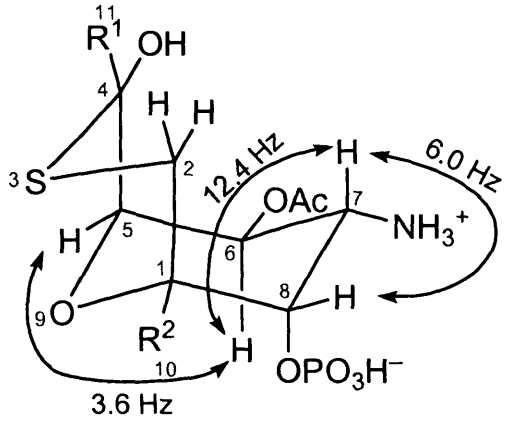
Strong nuclear Overhauser enhancements were observed between the vicinal protons at H-5 and H-6, and also between one of the protons at H-2 and H-7, hence showing a spatial proximity between these two positions which are far from each other in the bonding framework (Figure 6). This, together with the large vicinal coupling constant between H-6 and H-7 led the authors to favour structure **1a** or **1b** over **3a** or **3b**.



1a: R^1=$CONH_2$, R^2=COOH
1b: R^1=COOH, R^2=$CONH_2$

Figure 6: NOE interactions

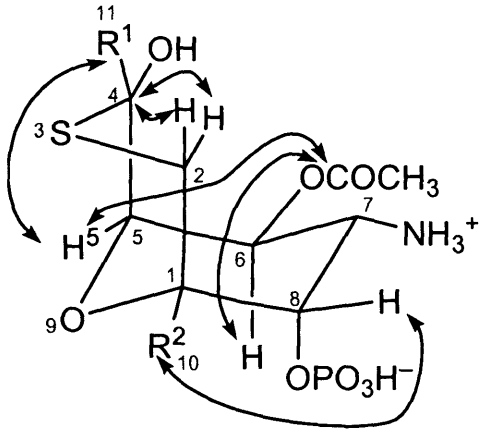
The assignment of the conformation of the oxathiane ring and the orientation of its substituents was based on vicinal ^1H–^1H coupling constants along the carbon framework. Coupling between H-6 and H-7 (^3J = 12.4 Hz) suggests that these two protons are in a diaxial relationship, while couplings between H-5 and H-6 (^3J = 3.6 Hz) and between H-7 and H-8 (^3J = 6.0 Hz) show axial-equatorial arrangements (Figure 7).



1a: R^1=$CONH_2$, R^2=COOH
1b: R^1=COOH, R^2=$CONH_2$

Figure 7: Three-bond coupling constants

Long range ^{13}C-^{1}H shift correlation experiments were run in order to deduce the connectivity through multiple bonds (Figure 8). There was a very strong correlation between the quaternary carbon C-4 at 85.7 ppm and both protons of the SCH_2 group, indicating a thioacetal or hemithioacetal. The acetate carbonyl signal at 174.1 ppm, had strong correlations with H-5 and H-6, the carbonyl at 174.5 ppm correlated strongly with H-8, and that at 171.2 ppm correlated with H^5. Hence, the quaternary centres at C-1 and C-4 must bear a carboxylic acid and an amide. The assignment of these functional groups is not definitive; the authors speculate that the amide is more likely to be attached at C-4 on the basis of the lower chemical shift of the carbonyl carbon, but the small difference between the two chemical shifts means that this assignment should be viewed as tentative.



1a: R^1=$CONH_2$, R^2=COOH
1b: R^1=COOH, R^2=$CONH_2$

Figure 8: ^{13}C-^{1}H shift correlation

In 2005, Gronwald *et al.* carried out a different purification protocol to isolate tagetitoxin.[35] The initial methanol precipitation and organic solvent partitioning steps used by Mitchell and Durbin were substituted by anion exchange chromatography (QAE-Sepharose). The remaining purification steps were unaltered. These authors

concluded, on the basis of TLC staining, that tagetitoxin contains a phosphate ester but lacks a primary amine.

Positive ion electrospray ionisation (ESI) mass spectrometry was applied to the purified sample. It showed a molecular weight of 678 (MH^+, m/z = 679.5216). MS-MS experiments suggested that the species at m/z = 417 observed by Mitchell and Durbin (and interpreted as the molecular ion of tagetitoxin) is in fact a fragmentation product of an ion with m/z = 453. This species in turn arises from fragmentation of the ion at m/z = 679. A commercially available preparation of tagetitoxin was subjected to similar analysis; the only biologically active component gave the same spectrometric results.

Additional high resolution experiments showed that a fragment ion at m/z = 417.3316 was generated from the ion at m/z = 679.5216 but that the ion with m/z = 417.0361 reported by Mitchell *et al.* was not. The latter ion was only ever observed in partially purified tagetitoxin fractions as a fragmentation product of ions at m/z = 531.9 and 647.5. Therefore, Gronwald *et al.* deduced that the ion interpreted by Mitchell and Durbin as the molecular ion of tagetitoxin was due to contaminants.

Gronwald *et al.* also carried out 1D and 2D NMR studies. The NMR spectra were very similar to those from Mitchell and Durbin, although the absence of any reported coupling constants makes a direct comparison difficult. One discrepancy was the presence of additional singlets at δ = 1.75 and 2.53 ppm in the ^1H NMR and signals at δ = 23.2 and 181.5 ppm in the ^{13}C NMR. While these ^1H NMR signals are reported as "3H, s", the 1D NMR spectrum reproduced in the publication suggests that these peaks are much larger than those arising from tagetitoxin. Although Gronwald does not suggest this possibility, it seems likely that the extra ^{13}C signals

and the ^{1}H NMR signal at δ = 1.75 ppm are due to ammonium acetate, which was used as a chromatographic eluent.

Despite obtaining high resolution mass spectra, Gronwald *et al.* did not report a revised empirical formula for tagetitoxin, nor do they suggest a new structure. They suggest that the extra 244 mass units are "from atoms undetectable by NMR, *i.e.* N, O, S".

The reasons for the discrepancy between Gronwald's and Durbin's mass spectrometry results are not clear. The NMR data of both groups are consistent with the bicyclic structure **1** and, in the absence of an alternative structure, this compound will form our synthetic target. However, the controversy over the structure undoubtedly strengthens the case for structural confirmation by total synthesis.

Recently, the X-ray crystal structure of tagetitoxin bound to an enzyme active site has been published (see section 1.2.2.3).[36] However, the resolution of the structure is insufficient to clarify the structural ambiguity surrounding tagetitoxin.

1.2.2 Biological activity

In the next section, the biological studies carried out on tagetitoxin will be reviewed. Its inhibition of RNA synthesis and in particular, its specific inhibition of RNA pol III will be considered from a mechanistic viewpoint.

1.2.2.1 Inhibition of RNA synthesis

In 1990, Durbin and Mathews reported studies on the biological effects of tagetitoxin and its mechanism of action.[37]

In contrast to other chlorosis-inducing plant phytotoxins from *Pseudomonas* bacteria,[38] an interesting feature of tagetitoxin is that the chlorosis it causes is confined to the apex of the plant. Indeed, tagetitoxin treatment prevents new chlorophyll accumulation but does not reduce existing chlorophyll levels. It was shown that in tagetitoxin-treated plants, proplastids did not differentiate into chloroplasts and failed to develop. Plastid 70S ribosomes failed to accumulate and consequently plastid-encoded polypeptides usually translated on these ribosomes could not be detected. Moreover, the amount of both ribosomal chloroplasts and messenger RNAs were greatly reduced in leaves of toxin-treated plants.

The authors isolated intact chloroplasts and carried out *in organello* incorporation reactions in which they recorded the rate of incorporation of radiolabelled uridine, thymidine and methionine into nucleic acids. The rate of incorporation of thymidine into DNA decreased only by a small amount; in contrast, uridine incorporation into RNA was quickly reduced, and ceased completely at a tagetitoxin concentration of 1 mM.

Durbin and Mathews subsequently studied *in vitro* transcription in chloroplasts.[39] It was shown that the addition of tagetitoxin to *in vitro* transcription reactions resulted in a decreased rate of UTP incorporation into RNA, and such incorporation was negligible at a tagetitoxin concentration of 10 μM. From these results, it was clear that *in vitro* chloroplast transcription was more sensitive than *in organello* chloroplast transcription to inhibition by tagetitoxin, suggesting that the chloroplast envelope may present a partial barrier to tagetitoxin. It was also shown that tagetitoxin reduces UTP incorporation by inhibiting RNA synthesis rather than by enhancing RNA degradation in the chloroplast extracts.

1.2.2.2 Specific inhibition of RNA polymerase III

Experiments on the effect of tagetitoxin on RNA synthesis directed by eukaryotic RNA polymerase enzymes *in vitro* showed tagetitoxin potency to be dependent on the nature of the RNA polymerase.[40] Inhibition is specific for RNA polymerase III at levels similar to that required for the corresponding inhibition of *E. coli* RNA polymerase. The inhibition of promoter-directed RNA polymerase III by tagetitoxin occurs in a wide range of organisms (yeast, insects and vertebrates).

Differences were found in the extent of tagetitoxin inhibition in the transcription of different genes by RNA polymerase III. The nature of the promoter elements of these genes may therefore play a role in the mechanism of inhibition.

In conclusion, tagetitoxin is the first example of an RNA polymerase inhibitor that acts against bacterial RNA polymerases and is specific for one of the nuclear RNA polymerases.

1.2.2.3 Mechanism of inhibition

Tagetitoxin shows a unique profile of RNA polymerase inhibition and studies reveal that the toxin interacts with the enzymes at highly specific sites. RNA polymerase enzymes that are sensitive to tagetitoxin consist of multimeric enzymes found for example in archaebacteria, eubacteria, chloroplasts and the eukaryotic nucleus.

Steinberg and Burgess observed template-dependence in the inhibition of transcription by yeast nuclear extracts or purified polymerase III.[41] Transcription of tRNA genes resulted in the accumulation of full-length precursor tRNA along with low molecular weight RNAs resulting from transcription complex pausing or premature RNA release.

In order to establish which stage of the transcription cycle is affected by tagetitoxin, transcription experiments were limited to a single round by addition of heparin to prevent reinitiation. It was found that as more tagetitoxin was included in the reaction mixture, less full-length product accumulated, accompanied by an increase in smaller RNAs. The authors suggested that these low molecular weight RNAs arose from pausing or stalling of transcription complexes at particular sites rather than from premature release of nascent RNA.

It was indicated that the inhibitor binds most efficiently to the transcription complex when it is already paused, resulting in an increased stability of intrinsic pausing.

Mathews and Durbin investigated the tagetitoxin inhibition of *in vitro* RNA synthesis by *E. coli* RNA polymerase.[40] This inhibition could not be circumvented by increasing the DNA template concentration, thus indicating that the toxin interacts with RNA polymerase or the enzyme-template complex but not with the DNA template alone.

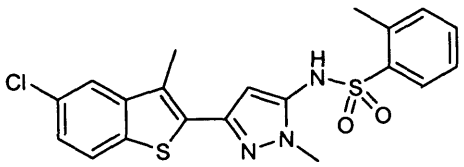
The inhibition of *E. coli* RNA polymerase during the elongation phase of RNA synthesis by tagetitoxin showed that the toxin can affect the ternary complex (enzyme, DNA template and nascent RNA chain). The toxin seems neither to compete with nucleotide substrates for binding to the polymerase nor to affect phosphodiester bond formation.[42] Other modes of action have been suggested such as interference with the binding of oligonucleotides to the enzyme-template complex. Binding enhancement of dinucleotide tetraphosphate and of longer oligonucleotides to the complex should slow the rate of product formation. On the other hand, tagetitoxin could interfere with translocation of the catalytic active centre with respect to the 5'-OH of the nascent oligonucleotide and substantially inhibit the nascent RNA chain elongation.

In 2005, Vassylyev *et al.* produced an X-ray crystal structure at a resolution of 2.4 Å of the complex between tagetitoxin and the RNA polymerase from *Thermus thermophilus*.[36] In the structure, the binding site for tagetitoxin is located at the base of the RNA polymerase secondary channel, adjacent to the enzyme's active site. The binding is mediated by polar interactions between 9 of the 11 oxygen atoms of tagetitoxin and the adjacent protein side chains. A Mg^{2+} ion coordinated to tagetitoxin's phosphate group and to two protein residues enhances the binding further. Tagetitoxin's binding site does not interfere with that of the natural substrate. However, the spatial proximity between the tagetitoxin binding site and the enzyme active site suggests how the toxin may act in inhibiting RNA synthesis and also other reactions catalysed by RNA polymerase (exonuclease activity, pyrophosphorolysis).

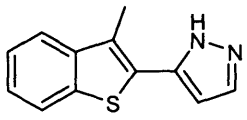
Vassylev *et al.* have proposed that three different sites are involved during nucleotide triphosphate loading onto the RNA polymerase. On a structural basis, all three of these sites are in the vicinity of the tagetitoxin binding site and hence, each of them could be a potential reason for the toxin's inhibition of the enzyme. Homology modelling experiments suggested that the activity of tagetitoxin is not due to competition between tagetitoxin and the substrate, but rather to the stabilisation of some inactive intermediate during substrate loading into the active site.

1.2.3 Other Polymerase III inhibitors

In 2003, McGovern *et al.* found that anti-fungal compounds ML-60218 **4** and UK-118005 **5** (Figure 9) inhibited RNA polymerase III in *S. cerevisiae*.[43] These are the first synthetic compounds found to specifically inhibit this enzyme.



ML-60218 **4**



UK-118005 **5**

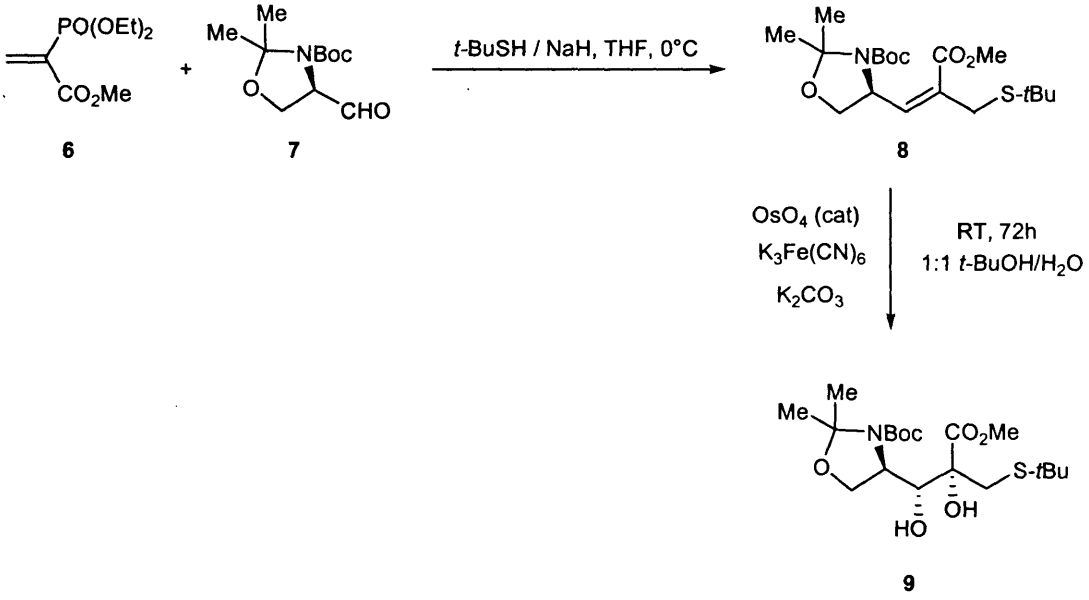
Figure 9: RNA pol III inhibitors ML-60218 **4** and UK-118005 **5**

1.2.4 Previous synthetic approaches to tagetitoxin

Prior to our group's research, only two research groups had published studies towards the synthesis of tagetitoxin. The earlier one involved the cyclisation of a fully functionalised linear precursor while a more recent approach centred on the use of carbohydrate starting materials.

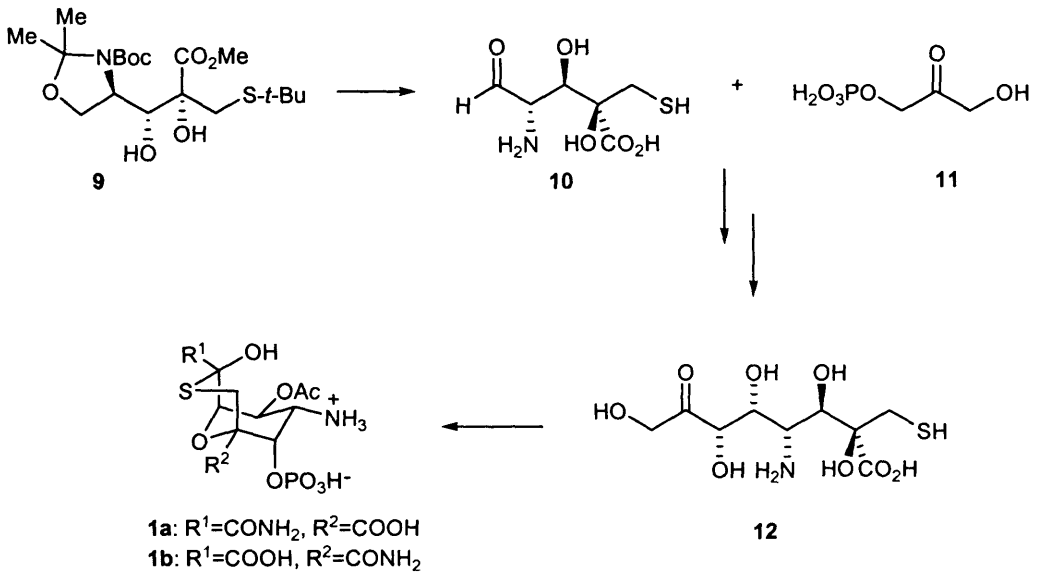
1.2.4.1 From a linear precursor

Sammakia *et al.* proposed an approach to tagetitoxin utilising olefin dihydroxylation and enzyme-catalysed aldol reaction as key steps.[44] Treatment of phosphonate **6** with sodium *tert*-butylthiolate in the presence of aldehyde **7**[45,46] afforded alkene **8** as a mixture of geometric isomers. Osmium-catalysed dihydroxylation of the alkene led to diol **9** with 25:1 dr (Scheme 1). The use of potassium ferricyanide as the stoichiometric co-oxidant in this reaction and the bulky *tert*-butyl protecting group were found to be essential in avoiding competitive oxidation of the sulfur.



Scheme 1 : Route to diol **9**

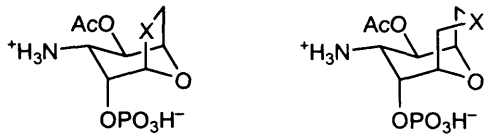
No further progress on this synthesis has been published; however the planned route involved conversion of diol **9** to aldehyde **10**, followed by enzymatic coupling with dihydroxyacetone phosphate **11** to afford ketone **12**. Cyclisation and functional group manipulation would lead to tagetitoxin (Scheme 2).



Scheme 2: Planned synthetic route to tagetitoxin from diol **9**

1.2.4.2 From carbohydrates

Furneaux *et al.* envisaged synthetic strategies to both the core structures of tagetitoxin and its oxo-analogue.[31] Their plan was to synthesise the two D-sugar derivatives **13** and **14** where X = O or S (Figure 10).

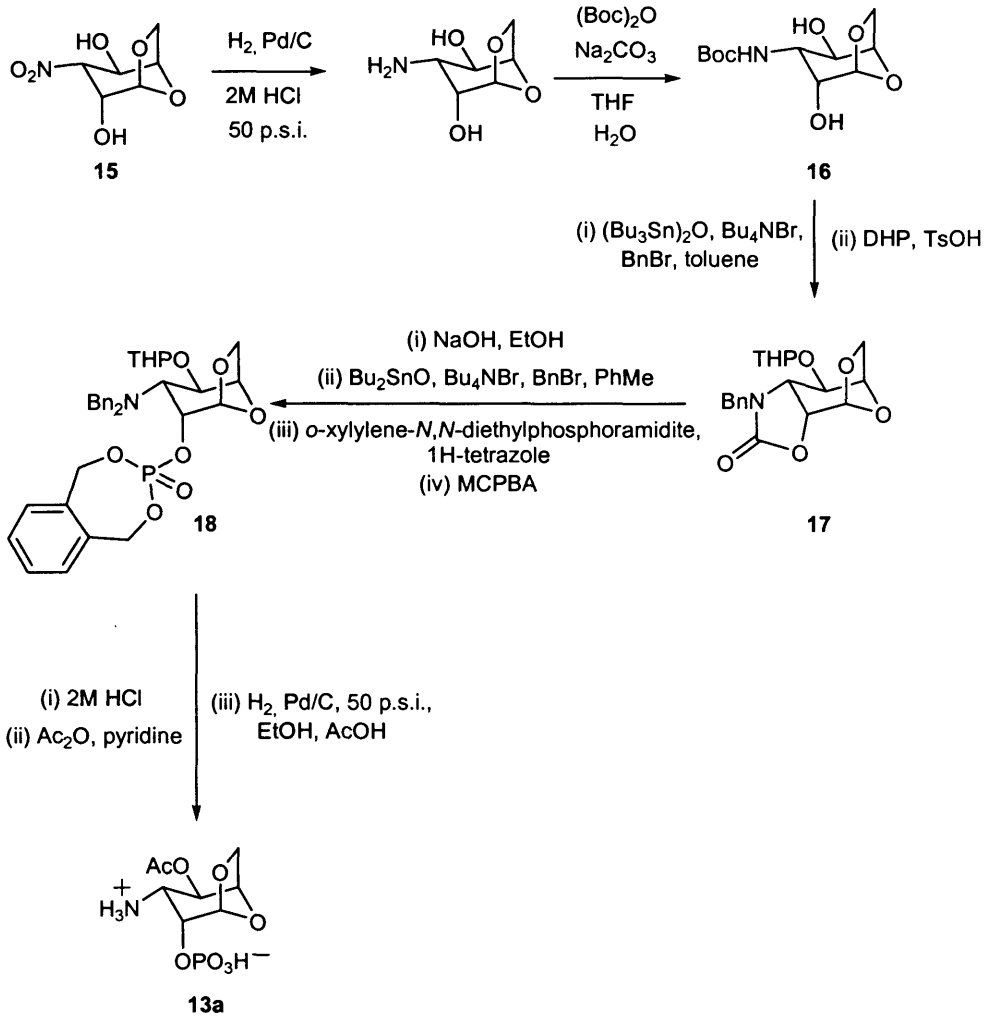


13a: X=O **13b: X=S** **14a: X=O** **14b: X=S**

Figure 10: Furneaux's targets

Starting from 1,6-anhydro-3-deoxy-3-nitro-D-gulose **15**, which bears the same configuration at C-2, C-3 and C-4 as tagetitoxin, reduction of the nitro group to an amine was followed by Boc protection, giving carbamate **16**. Protection of the amine and alcohol groups as an *N*-benzyloxazolidinone and subsequent THP-protection of the free alcohol gave advanced intermediate **17**. Alkaline cleavage of the carbamate, followed by *N*-benzylation offered the opportunity to functionalise the free alcohol at C-2 as a phosphate giving **18**. Finally, THP-deprotection at C-4 and subsequent acetylation at the same position followed by hydrogenolysis afforded **13a** (Scheme 3).

These compounds were tested for herbicidal activity against a range of agriculturally important weeds at 1000 g ha^{-1}. No herbicidal activity was observed.

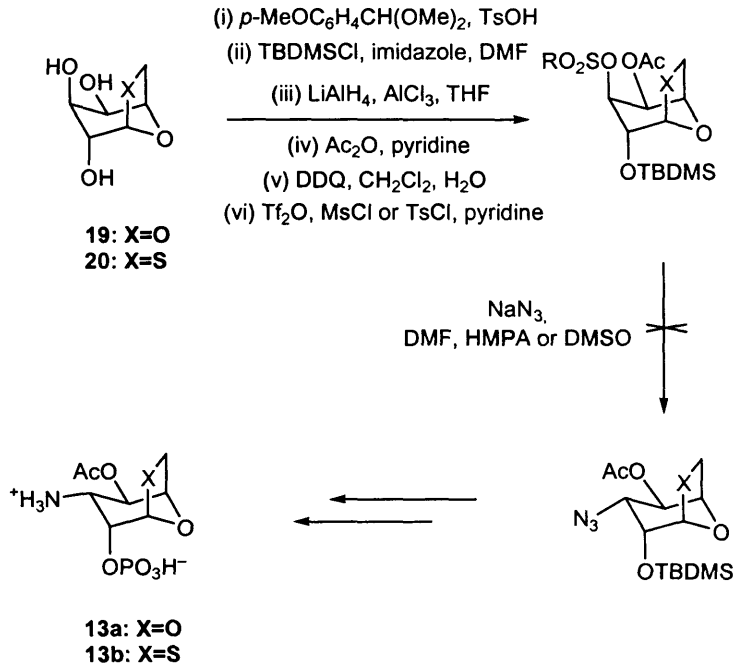


Scheme 3: Synthetic route to tagetitoxin analogue **13a**

In a second route to compounds of structure **13**, 1,6-anhydro-D-galactose (**19**, X = O) or 1,6-anhydro-6-thio-D-galactose (**20**, X = S) were used as the starting materials. This required differential functionalisation of O-2 and O-4 and installation of a good leaving group at C-3 that would allow the introduction of the amino function with inversion of configuration.

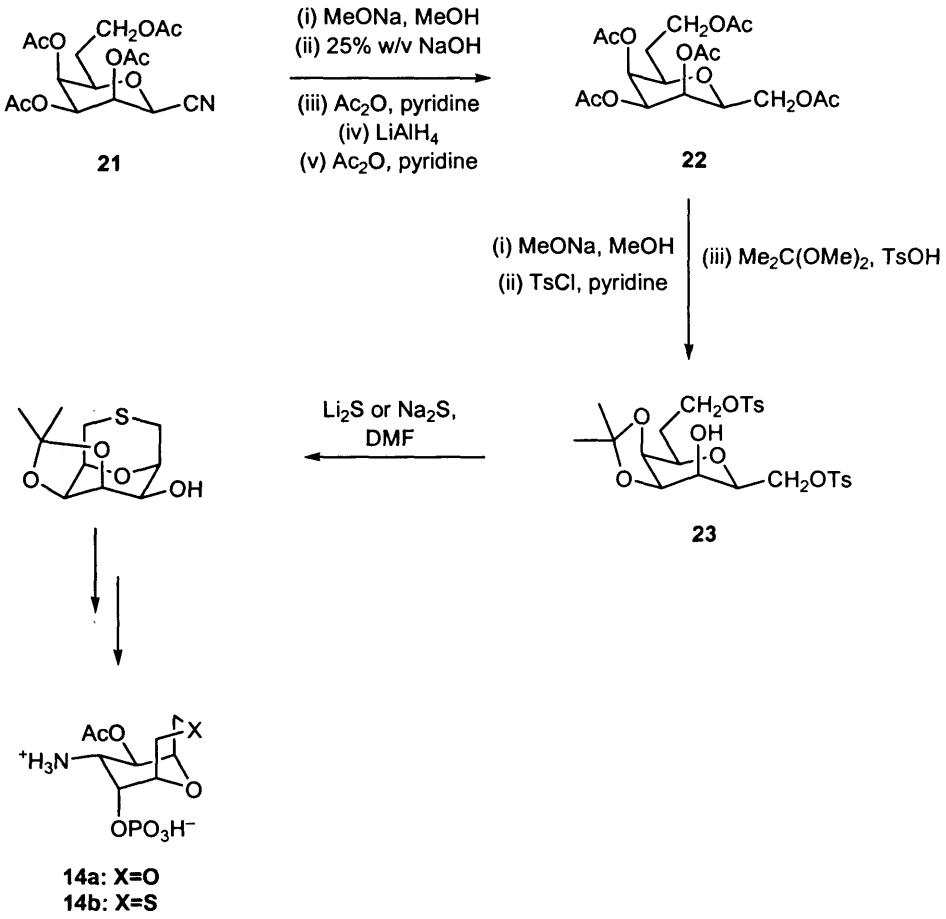
Thus in the first step, O-3 and O-4 were protected as an acetal, and this was followed by protection of O-2 by a *tert*-butyldimethylsilyl group (Scheme 4). Then, regioselective reductive cleavage of the acetal, followed by acetylation and cleavage of the PMB group, offered the opportunity to activate O-3 as a sulfonate. However,

azide substitution at C-3 was not possible, which was ascribed to the very bulky substituent at C-2 (Scheme 4).



Scheme 4: Second synthetic route to target structures **13a** and **13b**

Finally, the attempted synthesis of analogues of tagetitoxin of the closely related structure **14** was reported (Scheme 5). β-Cyano-D-galactopyranose tetraacetate **21** was synthesised in two steps from an anomeric mixture of D-galactopyranose pentaacetates. The nitrile was hydrolysed to give initially a δ-lactone, which, upon hydrolysis, reduction and peracetylation, afforded pentaacetate **22**. Following methanolysis, selective tosylation of both primary alcohols and protection of the secondary alcohols O-3 and O-4 as an acetal gave tetrahydropyran **23**. However, attempted sulfur installation and cyclisation using lithium or sodium sulfide was not successful. It was thought that steric hindrance due to the isopropylidene acetal was inhibiting the reaction.



Scheme 5: Synthetic route to target structures **14a** and **14b**

1.3 Aims of this research

The aim of this research is to establish a viable synthetic route to the postulated core structure of tagetitoxin. Tagetitoxin was viewed as an interesting target for several reasons:

- The molecule has unique biological activity.
- Its characterisation is based upon spectroscopic and chemical analysis of biological extracts, and is still somewhat ambiguous.
- Its probable structure consists of a challenging and unique 9-oxa-3-thiabicyclo[3.3.1]nonane ring system.
- It has never been synthesised.

These features make tagetitoxin a truly attractive and challenging synthetic target.

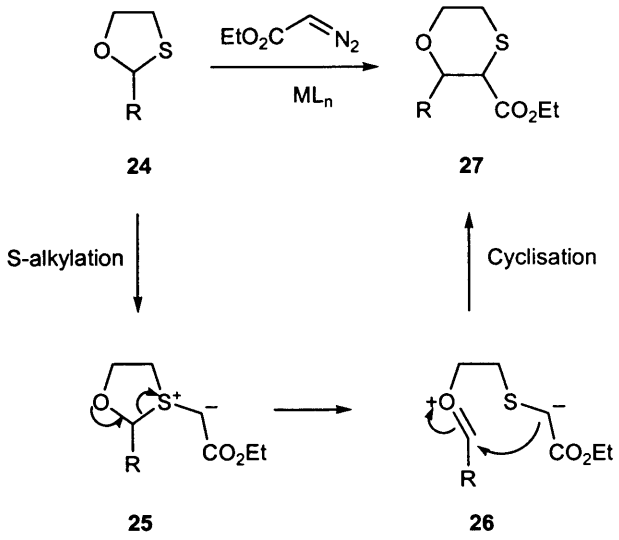
2 RESULTS AND DISCUSSION

2.1 Sulfur ylide approach

2.1.1 Ring expansion of 1,3-oxathiolanes

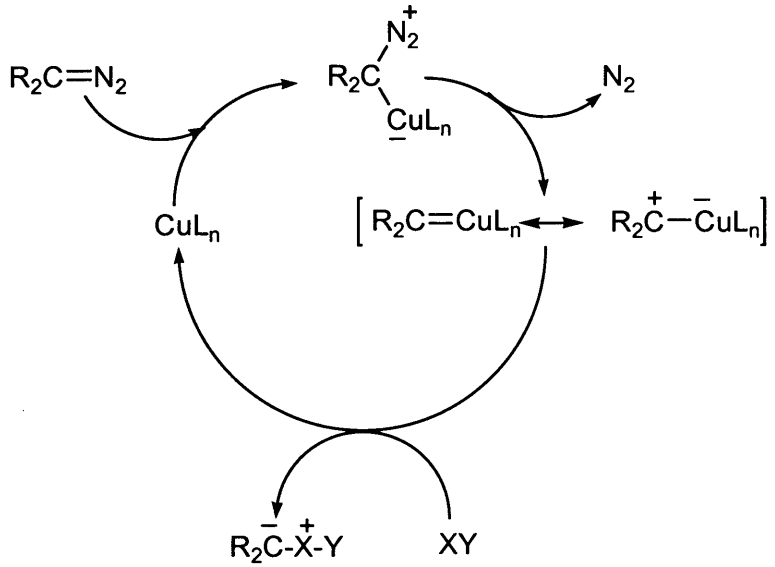
Generation of sulfur ylides through metal-catalysed reaction of diazo compounds with sulfides has been extensively reported in the literature.[47-52] These species readily undergo a variety of rearrangements including intramolecular [1,2]-,[53,54] intermolecular [1,2]-,[55-57] intramolecular [2,3]-,[58,59] intermolecular [2,3]-,[60] and [1,4]-shifts,[61-63] or react with carbonyls to form epoxides.[64] A variety of metal catalysts have been used but the most commonly employed ones are Rh(II), Cu(II) and Cu(I).

As part of the project on the synthesis of tagetitoxin, Porter *et al.* developed a metal-catalysed ring expansion reaction of 1,3-oxathiolanes with diazo compounds.[65,66] Porter *et al.* postulated that treatment of oxathiolane **24** with ethyl diazoacetate in the presence of an appropriate metal catalyst would lead to sulfur ylide **25** through sulfur alkylation. Electron donation from the oxygen into the C-O bond would break the C-S bond to give the oxonium ion **26**. Ring closure would then lead to 1,4-oxathiane **27** (Scheme 6). This [1,2]-rearrangement corresponds to an overall insertion of the $CH\text{-}CO_2Et$ moiety into a C-S bond, and hence a one-carbon ring expansion of the original 1,3-oxathiolane **24**.



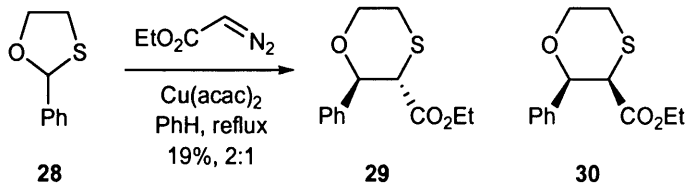
Scheme 6: Mechanism of the ring expansion of 1,3-oxathiolane **24**

Mechanistic studies into the generation of sulfur ylides by copper carbenoids have shown that the active catalyst is a Cu(I) species when copper (II) salts are used. The diazo compound is believed to act first as a reducing agent for the precatalyst; it is therefore used in slight excess. The copper (I) species acts as a Lewis acid and so can accept electron density from the diazo carbon at a vacant coordination site. Back-donation of electron density from the metal and nitrogen loss yields a stabilised transient metallocarbene intermediate, which can then accept electron density from a nucleophilic heteroatom to yield the desired ylide. Regeneration of the copper catalyst completes the catalytic cycle (Scheme 7).



Scheme 7: Catalytic cycle of the ring expansion reaction

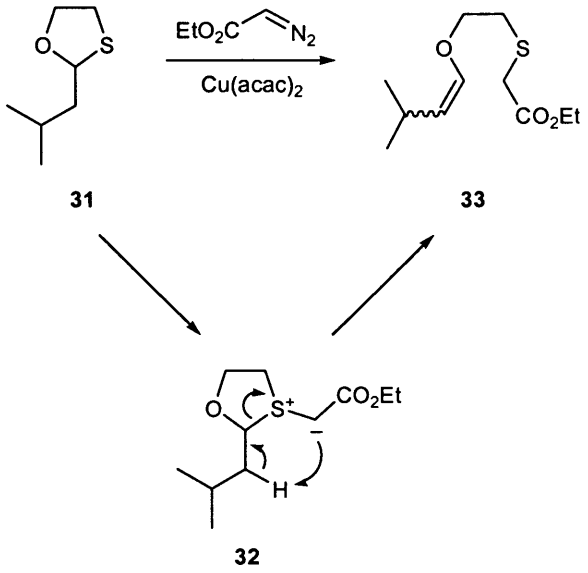
The initial investigations of Porter *et al.* were conducted using 2-phenyl-1,3-oxathiolane **28**, ethyl diazoacetate and copper(II) acetylacetonate in benzene at reflux: an isomeric mixture of ring expanded products **29** and **30** was obtained in 19 % combined yield (Scheme 8).[65]



Scheme 8: Ring expansion of 2-phenyl-1,3-oxathiolane **28**

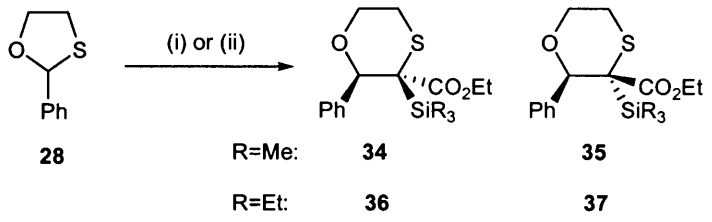
Under these conditions, substantial amounts of diethyl fumarate, diethyl maleate and unreacted 1,3-oxathiolane were also observed.[49] The addition of further diazo compound led to complex mixtures of unidentified products presumed to arise from reaction of 1,4-oxathianes **29** and **30** with further diazo compound. It was concluded firstly that ethyl diazoacetate tends to form alkene by-products, and secondly, that the metal carbene lacks discrimination between the sulfur atoms in

starting material and products. When a 2-alkyl-substituted 1,3-oxathiolane **31** was subjected to these conditions, a competitive elimination reaction of the sulfur ylide species **32** occurred in preference to ring expansion leading to a mixture of alkene geometric isomers **33** (Scheme 9).



Scheme 9: Elimination reaction of sulfur ylide species **32**

The use of silylated diazo compounds, as reported by Van Vranken[67] and Aggarwal,[68] overcame the problem of multiple addition because they have less tendency to form side-products and more importantly, the desired products do not react further. It was found that acceptable yields were obtained only when a silylated diazoester was used.

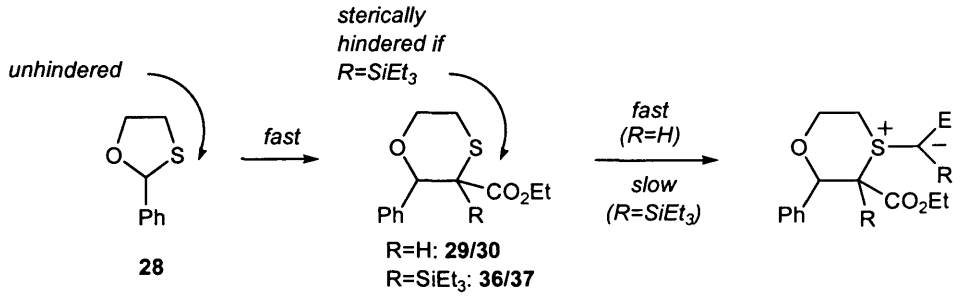


Reagents and conditions: (i) **R=Me:** ethyl diazo(TMS)acetate (1.04 eq), $Cu(acac)_2$ (2 mol%), PhH, reflux, 29 h, 46% **34**, 10% **35**; (ii) **R=Et:** ethyl diazo(Et_3Si)acetate (1.2 eq), $Cu(acac)_2$ (10 mol%), PhH, reflux, 22 h, 67% (**36**:**37** 8:1)

Scheme 10: Use of silylated diazo compounds

The relative stereochemistries of these compounds **34**, **35** and **36**, **37** were identified using ^{1}H NMR spectroscopy. It was found that the major stereoisomers (**34** and **36**) were those with the phenyl and trialkylsilyl groups in a *cis* disposition. Furthermore, the phenyl group occupied an axialposition and the silyl group an equatorial position.

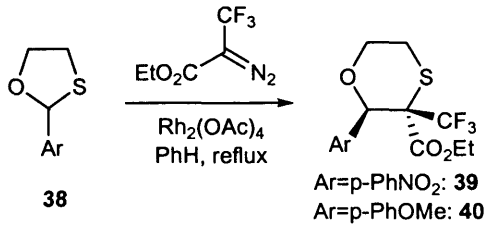
It is thought that the major improvement made to the reaction yield by using silylated diazoesters is due to their increased steric bulk. While the carbene derived from ethyl diazoacetate did not discriminate between the sulfur atom of the starting material and that of the products, the reaction of the bulkier silylated metal carbene with the more sterically hindered sulfur of 1,4-oxathiane **36** or **37** (R = $SiEt_3$) was markedly slower than its reaction with the starting material 1,3-oxathiolane **28** (Scheme 11).



Scheme 11: Rationalisation of the use of silylated diazo compounds

Varying the nature of the substituent at the 2-position, it was demonstrated that better yields were obtained with an aryl group than with an alkyl group. The authors attribute these results to the additional stabilisation of the oxonium ion intermediate provided by the aromatic ring.

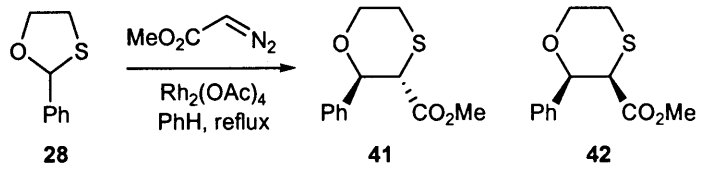
Zhu *et al.* have reported the stereoselective ring expansion reaction of various 2-aryl 1,3-oxathiolanes **38** with methyl 2-diazo-3,3,3-trifluoropropanoate (Scheme 12).[69] The mechanism of the reaction is believed to be the same as in Scheme 6.



Scheme 12: Use of silylated fluoro diazo compounds

The use of $Rh_2(OAc)_4$ as a catalyst in this system gave a better result than $Cu(acac)_2$, although yields were not published. ^1H NMR spectroscopic analysis and X-ray crystallography showed that the aromatic and the carbmethoxy groups were *trans* and equatorial in the major isomer. It was found that higher yields were obtained, but with a lower diasteromeric ratio for electron-deficient aromatic substituents. For example, the *p*-nitrophenyl substituted product **39** was obtained in 100 % yield as a 2:1 *trans/cis* ratio whereas the *p*-methoxyphenyl compound **40** was obtained as a 99:1 *trans/cis* ratio but in only 83% yield. It was speculated that the electronic repulsion between the nitrophenyl and the trifluoromethyl groups lead to a lower diastereomeric ratio. The ring expansion of a 2-spiro-1,3-oxathiolane using the same experimental conditions was also reported.

In contrast to Porter's result, Kostikov and co-workers demonstrated the ring expansion of 2-phenyl-1,3-oxathiolane **28** with methyl diazoacetate in the presence of $Rh_2(OAc)_4$ leading to the corresponding 1,4-oxathiane **41** and **42** in 48 % yield (Scheme 13) with the *trans*-isomer favoured in a 1.8:1 ratio.[70] The equivalent reaction of 2,2-diphenyl-1,3-oxathiolane with methyl diazoacetate afforded the corresponding oxathiane in 51 % yield.



Scheme 13: Use of methyl diazoacetate in a ring expansion reaction

2.1.2 Strategy and retrosynthesis

As discussed previously, this project has been directed towards the synthesis of the structure of tagetitoxin, **1a**, that best fitted the chemical and spectroscopic data.

The most significant challenge for the synthesis of tagetitoxin appeared to be the construction of the 9-oxa-3-thiabicyclo[3.3.1]nonane ring system. This bicyclic system can be viewed as a 1,4-oxathiane ring, bridged with a tetrahydropyran ring (Figure 11).

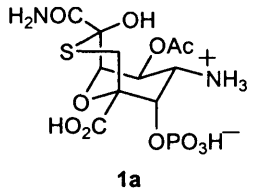
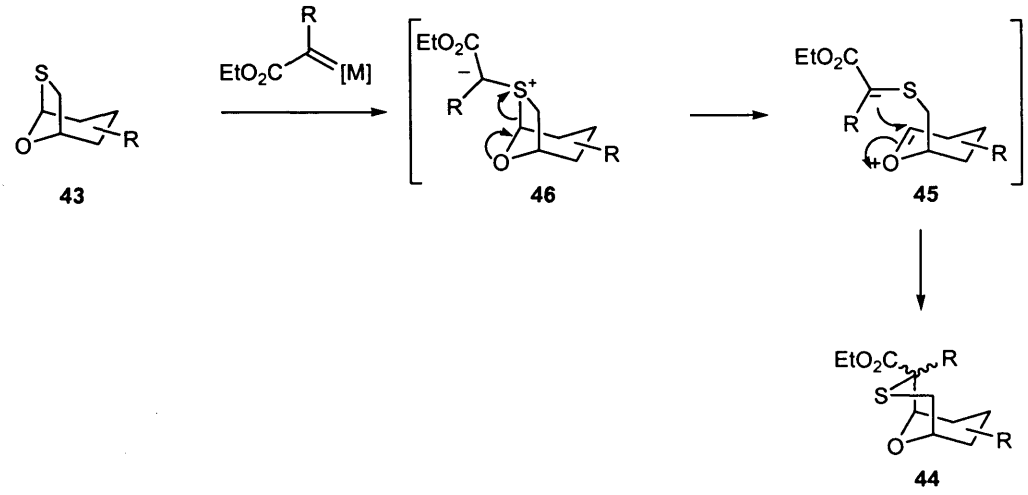


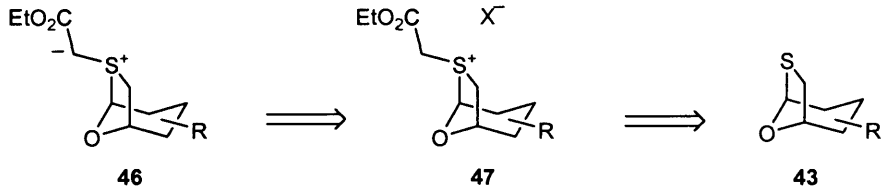
Figure 11: Target structure for tagetitoxin

Initial efforts were directed towards the synthesis of a model 9-oxa-3-thiabicyclo[3.3.1]nonane. It was postulated that a ring expansion reaction of a bicyclic 1,3-oxathiolane **43** would secure the corresponding 1,4-oxathiane **44** when the 1,3-oxathiolane **43** was treated with a metallocarbene formed from a diazoester. Following ylide formation, the neighbouring oxygen atom and the positive charge on the sulfur should induce cleavage of the C-S bond giving the oxonium ion **45** which can reclose to the corresponding 1,4-oxathiane **44** (Scheme 14).



Scheme 14: Mechanism for the formation of bicyclic 1,4-oxathiane **44**

Should the generation of sulfur ylide **46** (R = H) via a metallocarbene not be possible, it could be obtained through sulfur alkylation and α-deprotonation of the resulting sulfonium salt **47** (Scheme 15).



Scheme 15: Retrosynthesis of sulfur ylide **46**

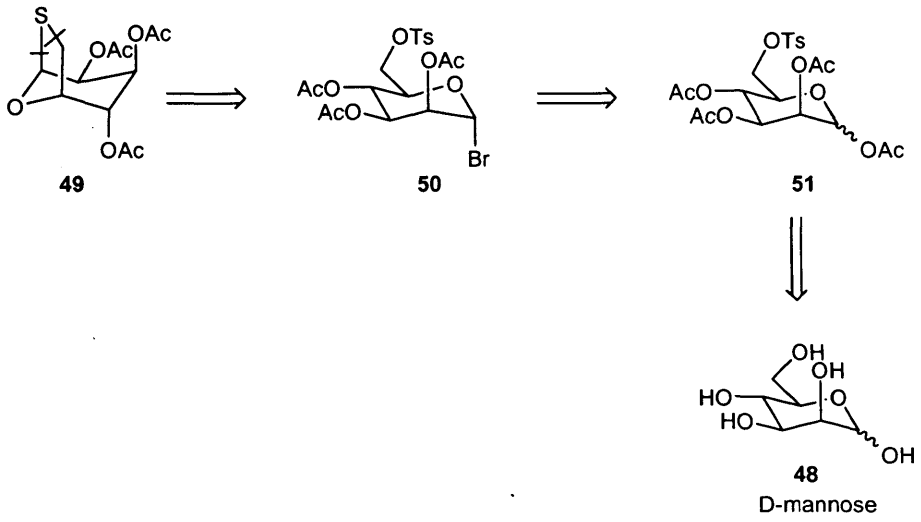
2.1.3 Results

2.1.3.1 Use of D-mannose as a starting material

2.1.3.1.1 Strategy and retrosynthesis

A cheap readily available starting material with suitable functionalities would be an aldohexose. We started our investigations with D-mannose **48** as its stereochemistry corresponds to that of tagetitoxin, and thus it was felt to be the best model system.

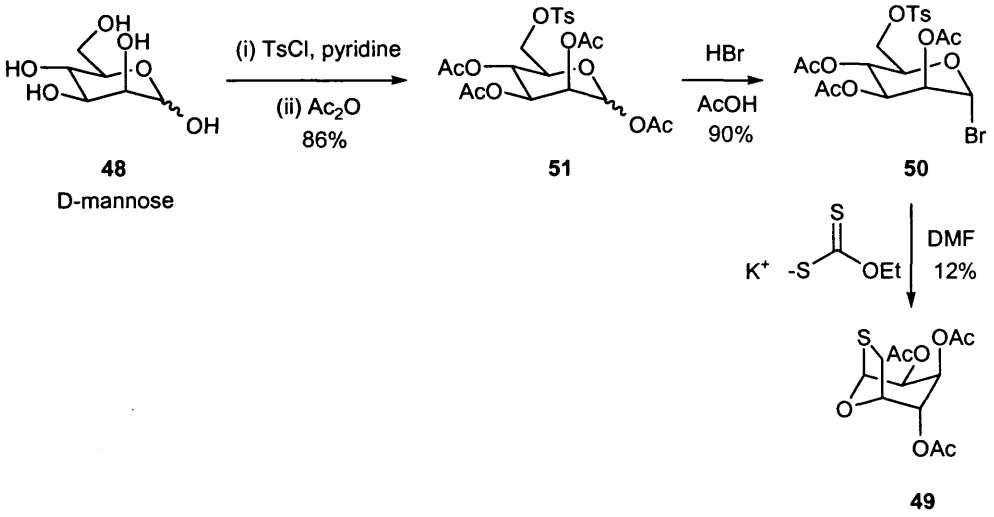
Excision of the sulfur atom in the target compound **49** gives anomeric bromide **50** and a sulfur nucleophile. This anomeric bromide could be obtained from the tetra-acetate **51** which can in turn be derived from D-mannose **48** (Scheme 16).[71]



Scheme 16: Retrosynthesis of 1,3-oxathiolane **49** from D-mannose **48**

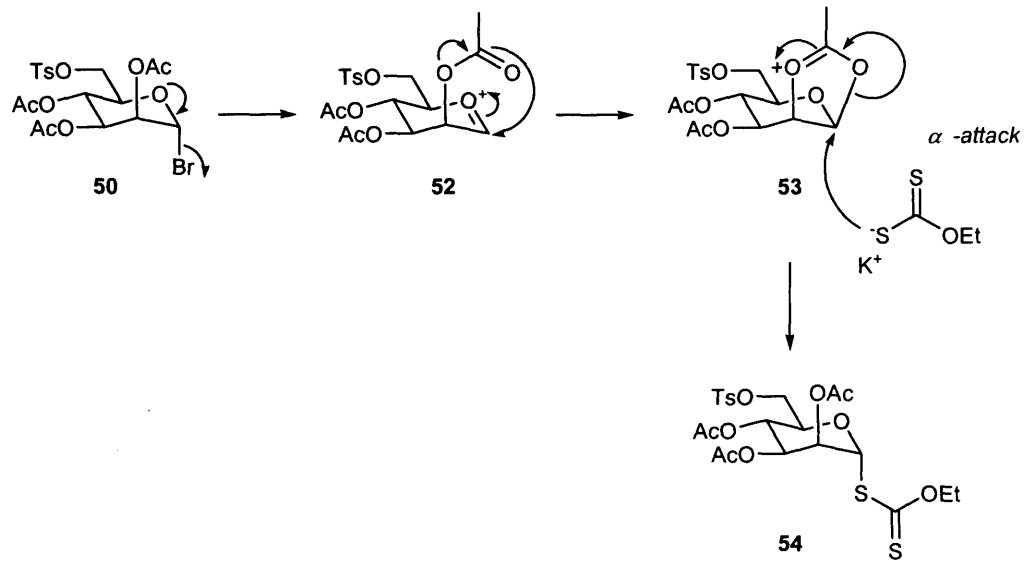
2.1.3.1.2 Results

The primary hydroxyl of commercially available D-mannose **48** was tosylated in pyridine, and addition of acetic anhydride yielded a mixture of anomeric acetates **51** in 86 % yield. The crude mixture was then treated with hydrogen bromide in acetic acid yielding 90 % of the α-anomeric bromide **50**. Presumably, rapid equilibration occurs under the acidic reaction conditions, leading to the formation of the thermodynamically favoured α-anomer **50**. Reaction with potassium ethyl xanthate afforded the bicyclic 1,3-oxathiolane **49** in very low yield (10-12 %) (Scheme 17).



Scheme 17: Synthesis of tri-acetate **49** from D-mannose **48**

In this reaction, the first step is presumed to be the loss of bromide leading to oxonium ion **52**. The participation of the acetate protecting group at C-2 leads to a lower energy cation **53**, in which the charge is delocalised over two oxygen atoms. The low yield of cyclised product can perhaps be explained by the fact that this cyclic oxonium ion **53** can then only be opened from the α-face by the xanthate ion, to give a xanthate **54** which is unable to cyclise onto C-6. However, none of this α-xanthate **54** was isolated from the reaction mixture (Scheme 18).



Scheme 18: Mechanism of the reaction between bromide **50** and potassium ethyl xanthate

The isolation of the 1,3-oxathiolane **49** in 12 % yield suggests that cyclisation can occur to some extent. Although neighbouring group participation from the acetate at C-2 favours nucleophilic attack of the xanthate from the α-face, it is possible that a small amount of the initial oxonium ion **52** is attacked by the xanthate to give the desired β-xanthate. An alternative explanation was that initial displacement of the tosylate at C-6 may occur.

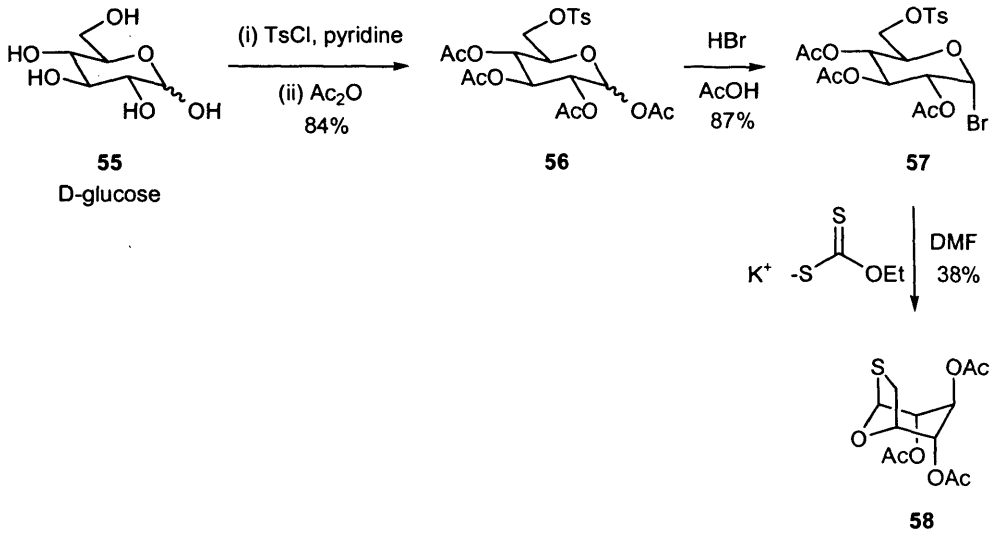
The mannose configuration (i.e. axial group at C-2) was therefore disfavouring the desired cyclisation. We postulated that an equatorial acetate at this position would favour the formation of a β-xanthate and hence cyclisation could occur.

2.1.3.2 Use of D-glucose as a starting material

2.1.3.2.1 Results

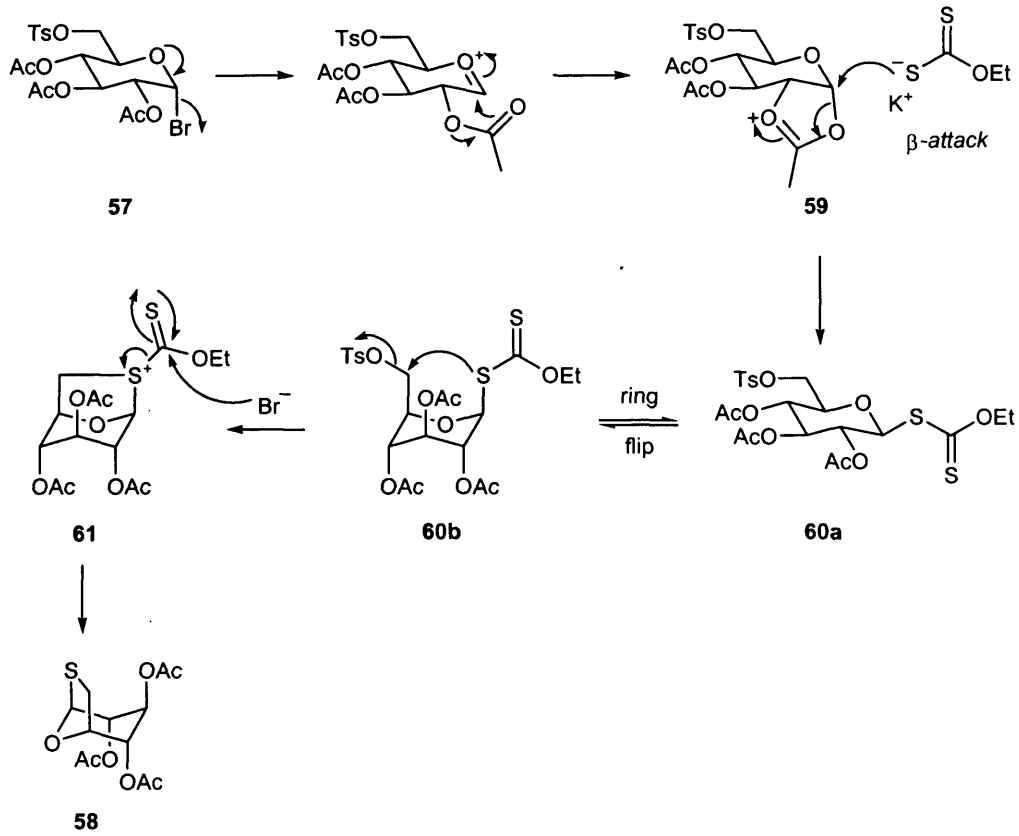
The same reaction sequence that had been applied to D-mannose **48** (Scheme 17) was repeated with D-glucose **55** as the starting material. Using the same reaction

conditions, tosylate **56** was obtained in 84 % yield as a mixture of anomers. This was then converted to the α-bromide **57** in 87 % yield. Treatment with potassium ethyl xanthate in DMF at 60 °C gave 38 % of bicycle **58** (Scheme 19). However, by raising the temperature to 80 °C, a yield of 64 % could be obtained. Acetone was also tried as a solvent, but was less effective (42 % yield of **58**).



Scheme 19: Synthesis of bicycle **58** from D-glucose **55**

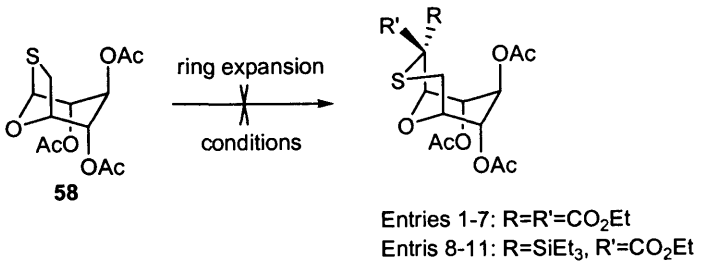
This reaction is presumed to proceed through 1,4-β-addition of the xanthate anion on oxonium species **59** to afford **60a**. Equilibration between $^4C_1$ chair **60a** and $^1C_4$ chair **60b** allows attack from the sulfur atom onto the carbon bearing the tosylate moiety, leading to bicyclic sulfonium salt **61**. Bromide anion in solution then removes the ethoxythiocarbonyl group to afford bicycle **58** (Scheme 20). Alternatively, removal of the thiocarbonyl group could precede cyclisation.



Scheme 20: Mechanism of the cyclisation of bromide **57** with potassium ethyl xanthate

2.1.3.2.2 Ring expansion reactions

Ring expansion reactions on tri-acetate **58** were investigated (Scheme 21). The first ring expansion reaction attempted was based on the methodology developed for simple 1,3-oxathiolanes (Table 1). Therefore, bicycle **58** was treated with ethyl diazo(triethylsilyl)acetate and $Cu(acac)_2$ in refluxing benzene under an inert atmosphere (entry 1). Unfortunately, a mixture of unidentified products was observed upon ^1H NMR spectroscopy of the crude material and purification by column chromatography (Florisil®) did not give any identifiable product.



Scheme 21: Ring expansion reactions

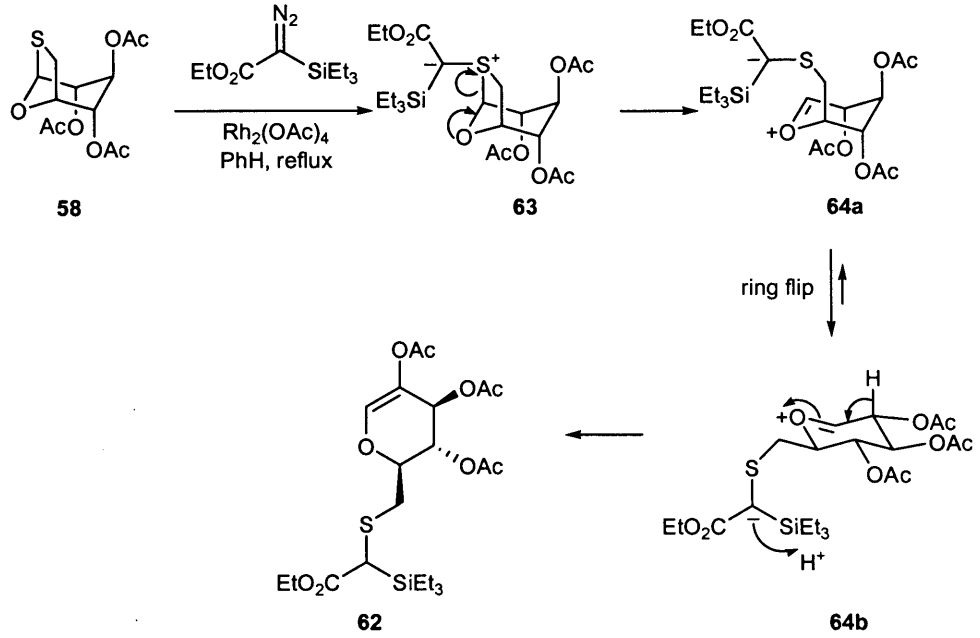
Entry	Reagents[a, b]	Solvent	Result
1	Ethyl (TES)diazoacetate, $Cu(acac)_2$	Benzene, reflux, 20 h	Unidentified products
2	Ethyl (TES)diazoacetate, $Cu(acac)_2$	Benzene, reflux, 20 h, phenylhydrazine	No reaction
3	Ethyl (TES)diazoacetate, $Cu(hfacac)_2$	Benzene, reflux	No reaction
4	Ethyl (TES)diazoacetate, $Cu(hfacac)_2$	MeCN, reflux	No reaction
5	Ethyl (TES)diazoacetate, $Rh_2(OAc)_4$	Benzene, reflux, 20 h	**62** 34 %
6	Ethyl (TES)diazoacetate, $Rh_2(OAc)_4$	Benzene, RT→40°C →60°C	No reaction
7	Ethyl (TES)diazoacetate, $Rh_2(OAc)_4$	DCM, reflux	No reaction
8	Diethyl diazomalonate, $Cu(acac)_2$	Benzene, reflux, 20 h	No reaction
9	Diethyl diazomalonate, $Cu(MeCN)_4PF_6$	Benzene, reflux, 20 h	No reaction
10	Diethyl diazomalonate, $Rh_2(OAc)_4$	Benzene, reflux 20 h	**65** 44 %
11	Diethyl diazomalonate, $Rh_2(OAc)_4$	Benzene, RT→40°C →60°C	No reaction

[a] 1.2-1.5 equivalents of diazo compound were employed. [b] Catalyst loadings: $Cu(acac)_2$, $Cu(hfacac)_2$ – 10 %; $Rh_2(OAc)_4$, $Cu(MeCN)_4PF_6$ – 5 %.

Table 1: Reaction conditions for the ring expansion reaction

The use of a separate reducing agent (phenylhydrazine, entry 2), with the aim of converting the Cu(II) to Cu(I), led to over-reduction to a Cu(0) species and no consumption of the starting bicycle. The use of $Cu(hfacac)_2$ as a catalyst in either boiling benzene (entry 3) or acetonitrile (entry 4) did not produce any reaction.

When a ring expansion reaction was attempted using $Rh_2(OAc)_4$ as a catalyst (entry 5), the only identifiable product isolated from the reaction mixture was alkene **62**. To explain the formation of this unexpected product, it is proposed that formation of ylide **63** occurs as expected, and electron donation from the oxygen opens the C-S bond yielding oxonium ion **64a** (Scheme 22). At this point, the conformation of the tetrahydropyran ring as a pseudo $^1C_4$ chair with all its substituents axial is no longer locked. 1,3-Diaxial interactions between acetates at C-2 and C-4, and between acetate at C-3 and sulfide at C-5, make this conformer unstable, and so the ring flips to the more stable conformation of **64b** bearing its substituents equatorial and thus precluding any subsequent ring closure. Loss of a proton from C-2 yields the corresponding alkene **65**. This reaction can be compared with the elimination product **33** isolated after the attempted ring expansion of 2-isobutyl-substituted-1,3-oxathiolane **31** reported by Porter *et al.* discussed in section 2.1.2.

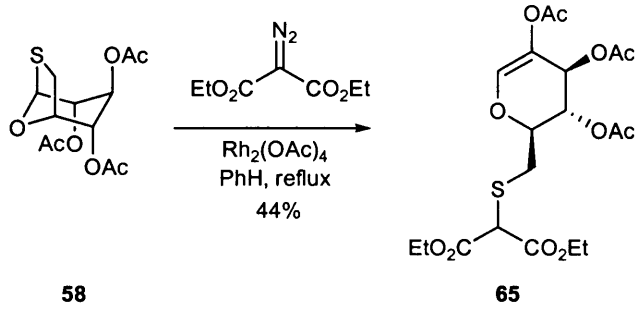


Scheme 22: Formation of enol ether **65**

On carrying out the same reaction at lower temperature, from RT increasing to 40 °C and then to 60 °C, no reaction was observed, with starting material being recovered (entry 6). Switching to DCM as solvent led to the same result (entry 7).

The reaction of diethyl diazomalonate with bicycle **58** was also investigated. With $Cu(acac)_2$ (entry 8) or $Cu(MeCN)_4PF_6$ (entry 9) as catalyst, no reaction occurred and starting bicycle **58** was recovered (entry 9).

However, use of $Rh_2(OAc)_4$, in benzene at reflux (entry 10) led to the corresponding enol ether **65** (Scheme 23). Again, attempting the same reaction at lower temperatures led to the recovery of starting material only (entry 11).



Scheme 23: Formation of enol ether **65**

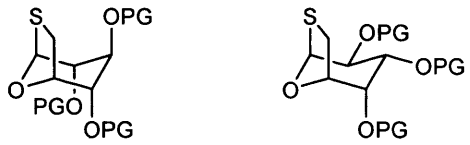
From this initial set of results, it was concluded that the ring expansion reaction of bicyclic 1,3-oxathiolane **58** was unlikely to succeed. The only isolated products were the alkenes **62** and **65** generated by proton transfer in zwitterionic species of the type **64b**. From the mechanism detailed above, the crucial factor is the conformational flexibility and instability of intermediate **64a** bearing all its substituents in axial positions.

It was proposed that with fewer axial substituents in the starting material, the corresponding oxonium ion intermediate would be more stable in its $^1C_4$ conformation and hence, ring expansion would be more likely to proceed. These further studies were carried out using a bicycle derived from D-altrose.

2.1.3.3 Use of D-altrose as a starting material

2.1.3.3.1 Strategy

The configuration of the D-altrose derived bicycle **66** differs from that of D-glucose derivative **67** at C-2 and C-3, therefore, its derivative bicyclic oxathiolane would only have one axial substituent, and thus, the corresponding zwitterion would be more conformationally stable (Figure 12).



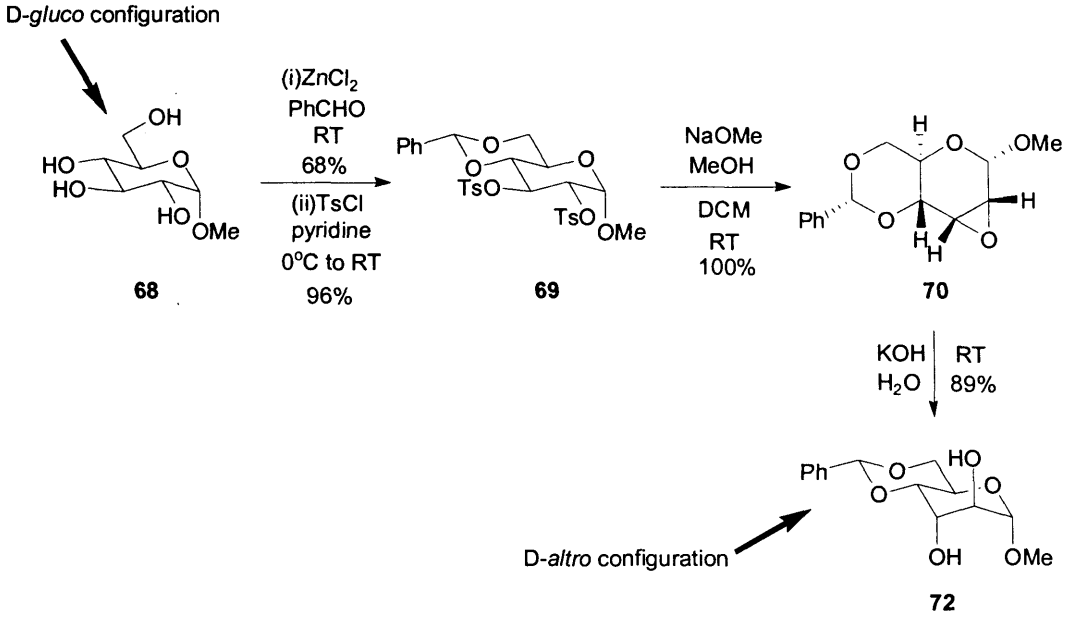
67 D-*gluco* configuration

66 D-*altro* configuration

Figure 12: D-*gluco* and D-*altro* configuration

2.1.3.3.2 Results

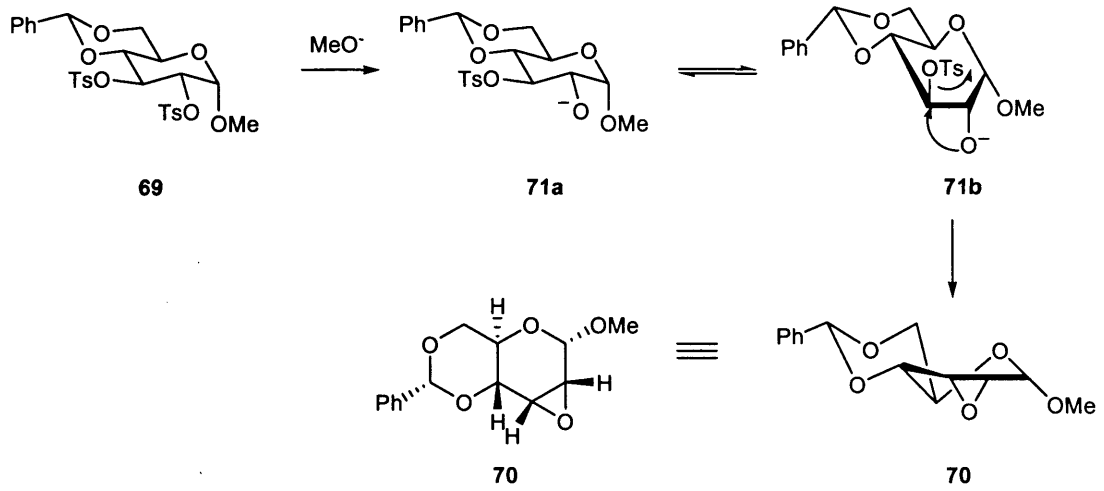
D-Altrose is available commercially but is very expensive. Hence, a carbohydrate interconversion sequence was carried out from the inexpensive α-methyl glucopyranoside **68** to access the altrose configuration (Scheme 24).[72]



Scheme 24: Carbohydrate Interconversion: From D-gluco to D-altro confirguration

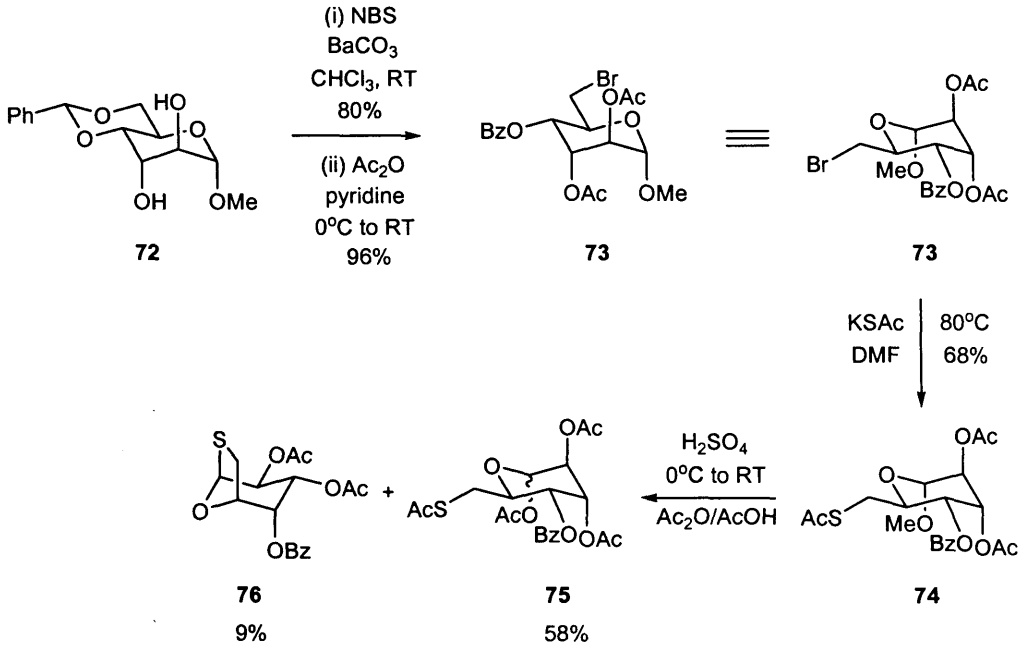
α-Methyl glucopyranoside **68** was treated with benzaldehyde and anhydrous zinc chloride to produce α-methyl 4,6-*O*-benzylideneglucopyranoside in good yield. The two remaining secondary alcohols were tosylated in pyridine affording di-tosylate **69** in 96 % yield. This was then treated with sodium methoxide in methanol to produce epoxide **70** quantitatively. Here, the sulfonyloxy group at position 2 undergoes cleavage *via* addition/elimination at the sulfur atom to yield anion **71** (Scheme 25); the oxyanion then attacks C-3 in an S_N2 manner with loss of tosylate to form α-methyl 2,3-anhydro-4,6-benzylidene-allopyranoside **70**. This sequence proceeds through the unfavourable $B_{2,5}$ boat conformation **71** in order that the stereoelectronic requirements for the reaction are met (i.e. *anti*-periplanar). The

epoxide ring of the 2,3-anhydro sugar **70** was then opened with potassium hydroxide in water to secure the *altro*-configured sugar **72** in 89 % yield.



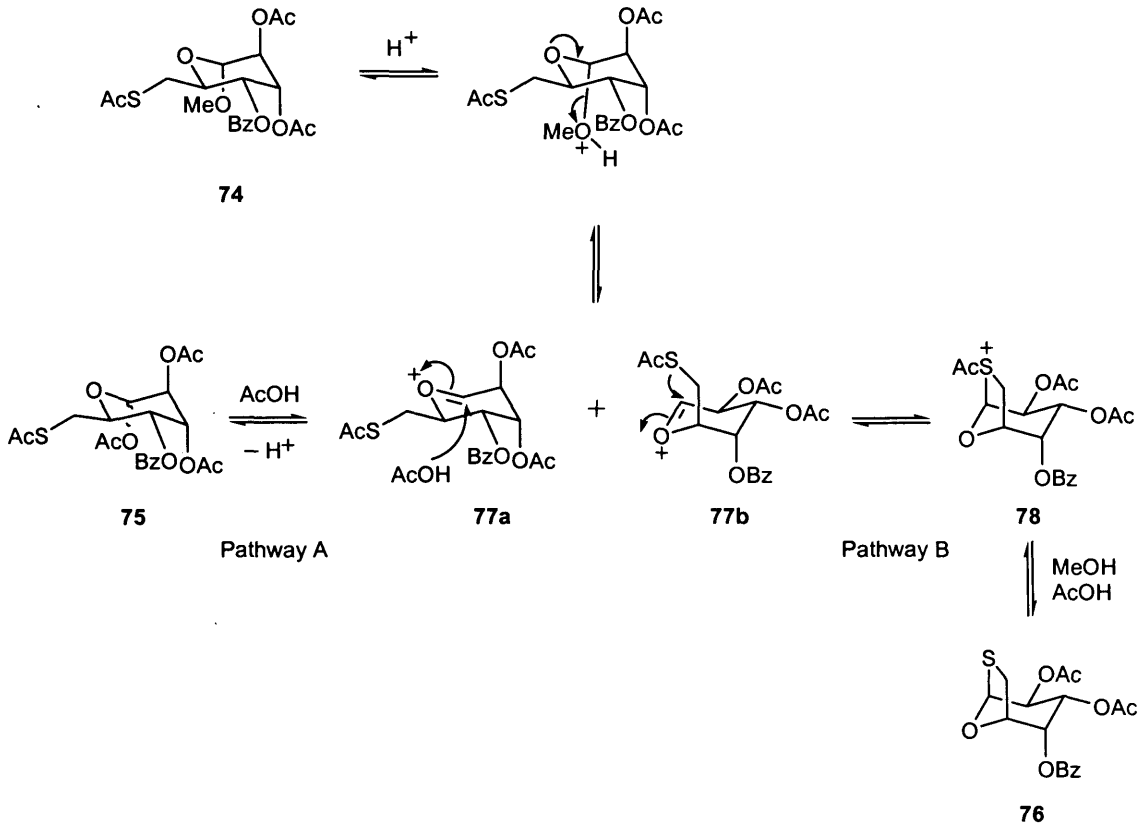
Scheme 25: Mechanism for the formation of epoxide **70**

The acetal protecting group of α-methyl 4,6-benzylidenealtropyranoside **72** was oxidatively cleaved with NBS in 80 % yield[73] (Scheme 26) and the remaining secondary alcohols were acetylated[74,75] affording primary bromide **73** in 96 % yield. The bromide was then displaced by thioacetate yielding thioester **74** in 68 % yield.[76] Upon treatment with acetic anhydride in acidic conditions, not only was the anomeric acetate **75** isolated in 58 % yield but also, gratifyingly, a small amount of bicyclic 1,3-oxathiolane **76** (9 %).



Scheme 26: Synthetic route to 1,3-oxathiolane **76**

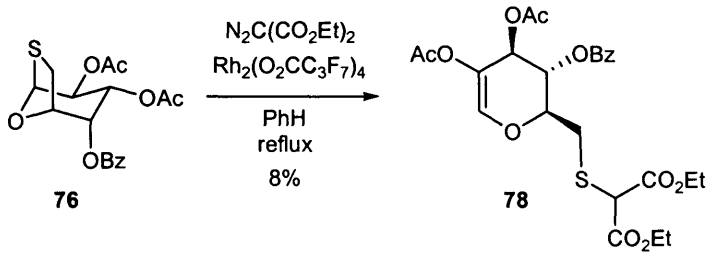
The first step in the conversion of **74** to **76** is the cleavage of the anomeric methyl ether under acidic conditions (Scheme 27). The resulting oxonium ion exists in equilibrium between $^4C_1$ chair conformation **77a** and $^1C_4$ chair conformation **77b** which, due to the disposition of substituents, are similar in energy (NB stabilisation of these oxonium ions by the neighbouring acetate may also occur). In pathway A, nucleophilic attack of acetic acid onto **77a** yields a mixture of anomeric acetates **75** which are the major products. Alternatively (pathway B), intramolecular nucleophilic attack of the thioacetate onto oxonium ion **77b** yields sulfonium salt **78**. Removal of the acetate affords the bicyclic 1,3-oxathiolane **76** as a minor product. Pathway A is favoured because the reaction is carried out in a large excess of acetic acid as solvent, therefore, it is more likely to attack as a nucleophile rather than the thioacetate in pathway B.



Scheme 27: Different pathways to anomeric acetate **75** and 1,3-oxathiolane **76**

2.1.3.3.3 Attempted ring expansion reactions

Ring expansion reactions were carried out using the standard experimental conditions described in Table 1. However, the use of $Rh_2(OAc)_4$, $Cu(acac)_2$, $Cu(hfacac)_2$, $Cu(MeCN)_4PF_6$, as catalysts along with either diethyl diazomalonate or ethyl (triethylsilyl)diazomalonate in toluene or benzene left diacetate **76** untouched. It was thought that the use of a catalyst bearing electron withdrawing ligands would increase the reactivity of the metallocarbene species. Therefore, $Rh_2(O_2CC_3F_7)_4$ was used as a catalyst[77] with diethyl diazomalonate. Unfortunately, ring expansion of bicyclic 1,3-oxathiolane **76** did not prove successful. Indeed a mere 8 % yield of the elimination product **78** was obtained along with a mixture of unidentified products (Scheme 28).



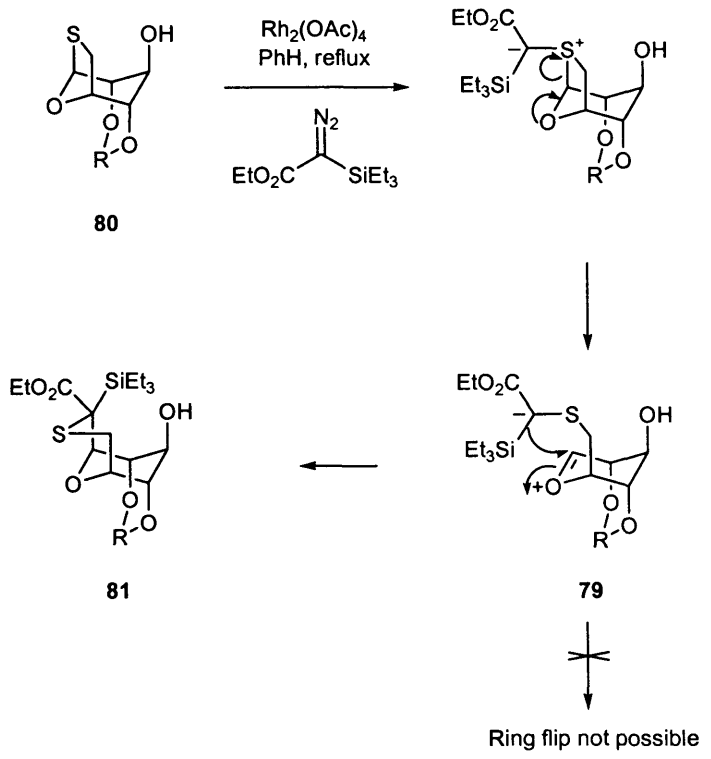
Scheme 28: Formation of enol ether **78**

Although the 1,3-diaxial interactions present in the intermediate oxonium ion of the type **64a** have been removed, it seems that the preferred course of reaction is still elimination to the enol ether **78**.

2.1.3.4 Introduction of a conformational lock

2.1.3.4.1 Strategy

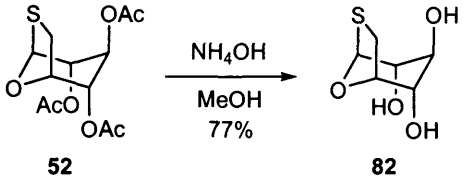
In order to overcome the problem of ring-flipping of the intermediate zwitterion **79**, our next strategy was to install a tether between the hydroxyls at C-2 and C-4 in a D-*gluco*-configured tricycle **80** (Scheme 29). When subjecting this substrate to the ring expansion reaction conditions, the oxonium intermediate **79** would not be able to convert to a conformation with its substituents equatorial, and would, we hoped, instead undergo C-C bond formation to yield bicyclic 1,4-oxathiane **81**. Various tethers were considered for linking the two hydroxyl groups; our initial plan was to synthesise a benzylidene acetal.



Scheme 29: Introduction of a conformational lock

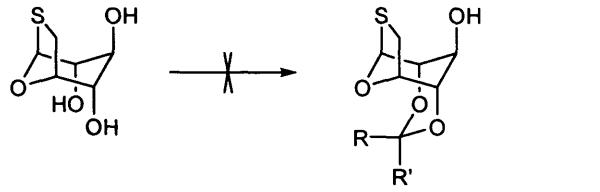
2.1.3.4.2 Results

Triacetate **58** was treated with aqueous ammonia in methanol yielding the corresponding triol **82** in 77 % yield (Scheme 30).[78]



Scheme 30: Acetates removal

However, attempted protection of hydroxyls at C-2 and C-4 with a cyclic tether proved to be more challenging than expected (Scheme 31).[79-83]



82 **83**

(i) R=H, R'=Ph
(ii) R=H, R'=*p*-$MeOC_6H_4$
(iii) R=R'=Me
(iv) R=R'=O

Scheme 31: Attempts for the installation of a conformational lock

Even under forcing conditions (high temperature, long reaction time), triol **82** appeared to be peculiarly unreactive. Protection of the 2- and 4-hydroxyls as an acetal was attempted with a variety of reagents (PhCHO,[79] $PhCH(OMe)_2$,[84] 4-$MeOC_6H_4CH(OMe)_2$,[80] $CH_2=C(OMe)Me$[85], $Me_2C(OMe)_2$) under a variety of acidic conditions ($ZnCl_2$, PPTS, $BF_3.Et_2O$, CSA, TsOH) in different solvents (benzene, toluene, DMF, DMSO, methanol, DCM), but none of the desired product was isolated.

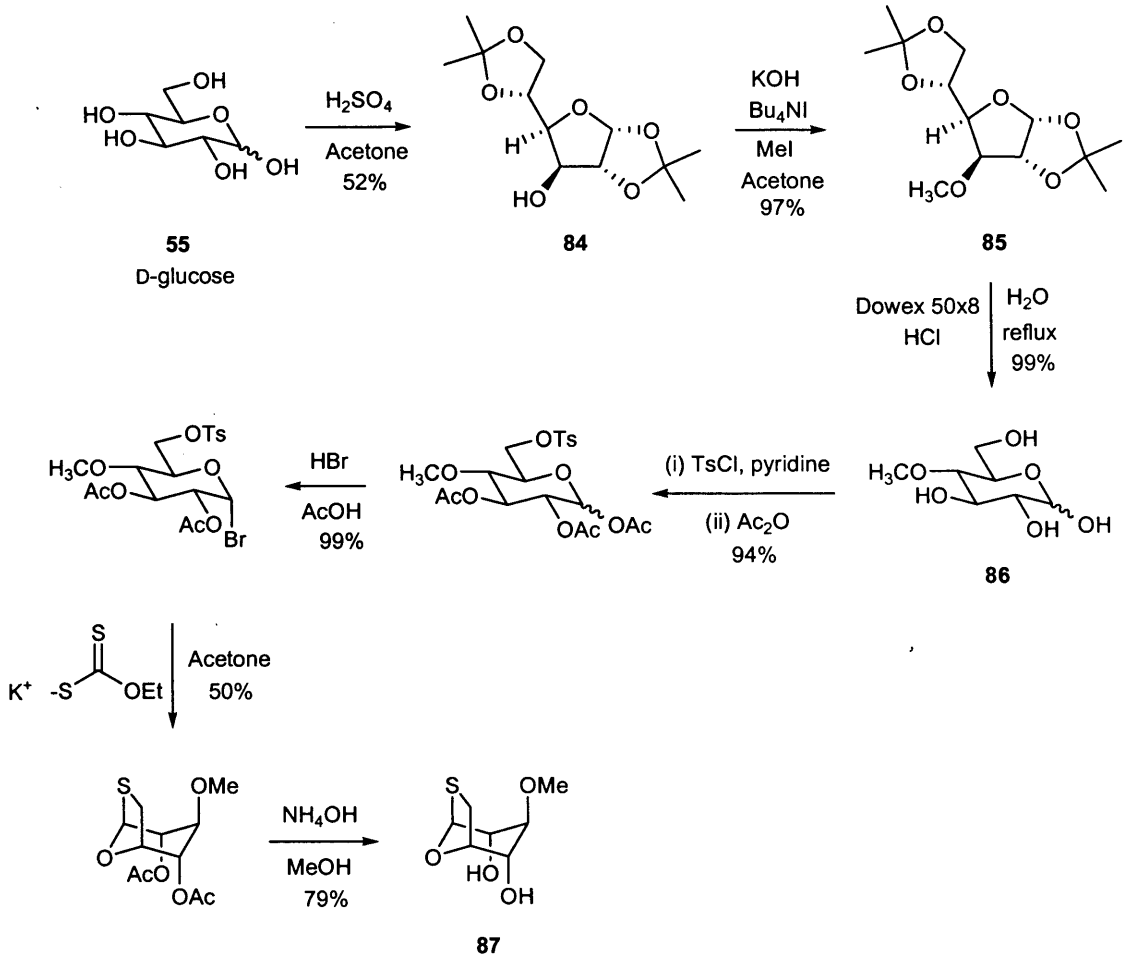
Switching from benzaldehyde to benzaldehyde dimethyl acetal did not prove successful, with starting material **82** always being recovered. It was hoped that using anisaldehyde dimethyl acetal would stabilise the carbocation in the acetal formation step through electron donation from the methoxy group. However, starting material was always recovered from these reactions. Acetal formation attempts using 2-methoxypropene[86] or 2,2-dimethoxypropane[87] were also unsuccessful.

Cyclic carbonate synthesis using carbonyl diimidazole and DMAP[88] as a catalyst also proved to be fruitless. An analogous reaction with triphosgene as the carbonyl precursor[89] yielded a complex mixture of polymers, presumably arising from intermolecular reaction of intermediate chloroformates with further starting material, rather than the desired cyclisation.

One difficulty in working with triol **82** was its poor solubility because of its three hydroxyl groups. It was apparently not soluble at all in benzene and soluble in toluene only at reflux.

In order to overcome these problems, we decided to functionalise the non-participating hydroxyl at C-3 as a methyl ether. The selective protection of this secondary alcohol in the presence of two others at C-2 and C-4 cannot be achieved on triol **93**. Indeed, the hydroxyl at C-3 is the most hindered of the three, and likely to be the least reactive. Its protection must therefore be accomplished at an earlier stage.

Thus, D-glucose **55** was protected as its diacetonide in 52 % yielding 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose **84**[90] (Scheme 32). Methylation of the remaining alcohol afforded methyl ether **85** in 97 %,[91] and deprotection of the two acetonide groups under acidic conditions yielded 3-methyl-D-glucose **86** as an anomeric mixture in 99 %.[92] The reaction sequence outlined in Scheme 19 was adapted to 3-methyl-D-glucose with similar yields to finally afford methyl ether **87**.

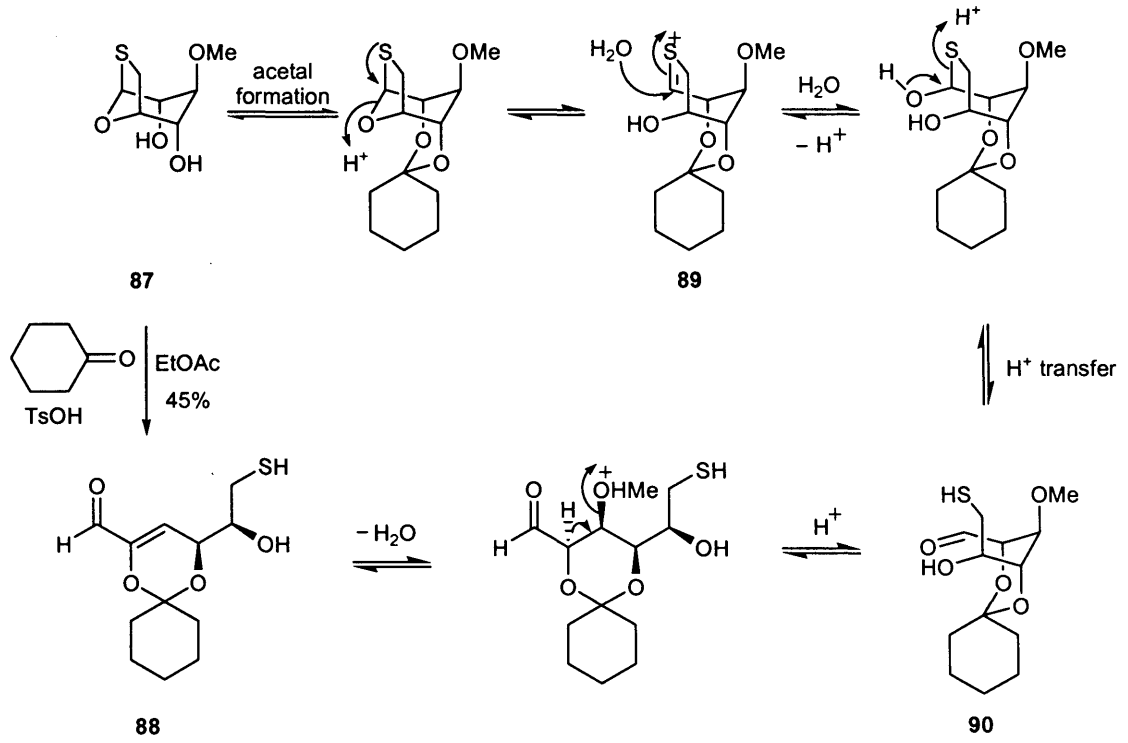


Scheme 32 : Synthetic route to diol **87**

As with triol **82**, protection of both C-2 and C-4 hydroxyls of diol **87** as a cyclic acetal or carbonate proved to be troublesome.

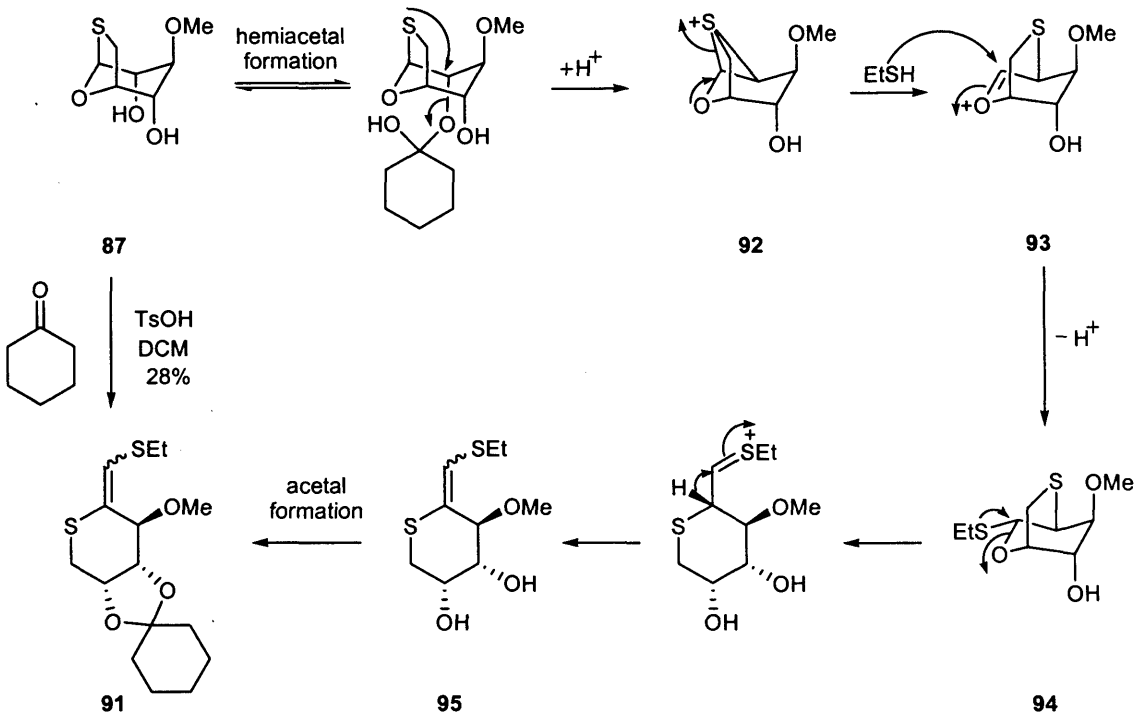
Experiments using benzaldehyde and an acid catalyst all gave recovered starting material. When subjecting diol **87** to cyclohexanone and *p*-toluenesulfonic acid, aldehyde **88** was isolated in 45 % yield (Scheme 33). In a postulated mechanism for formation of aldehyde **88**, it is proposed that the first step involves cyclohexyl acetal formation between hydroxyls at C-2 and C-4. Then electron donation from the sulfur would yield sulfonium cation **89**. Hydrolysis (water being generated in the acetal formation step) of the $C{=}S^+$ bond afforded aldehyde **90** *via* an acid catalysed

addition/elimination mechanism. Protonation of the secondary alcohol at C-3 and subsequent elimination finally yields aldehyde **88**.



Scheme 33: Mechanism for the formation of aldehyde **88**

When changing the solvent to DCM, a completely different outcome was observed with cyclic sulfide **91** being isolated in 28 % (Scheme 34).

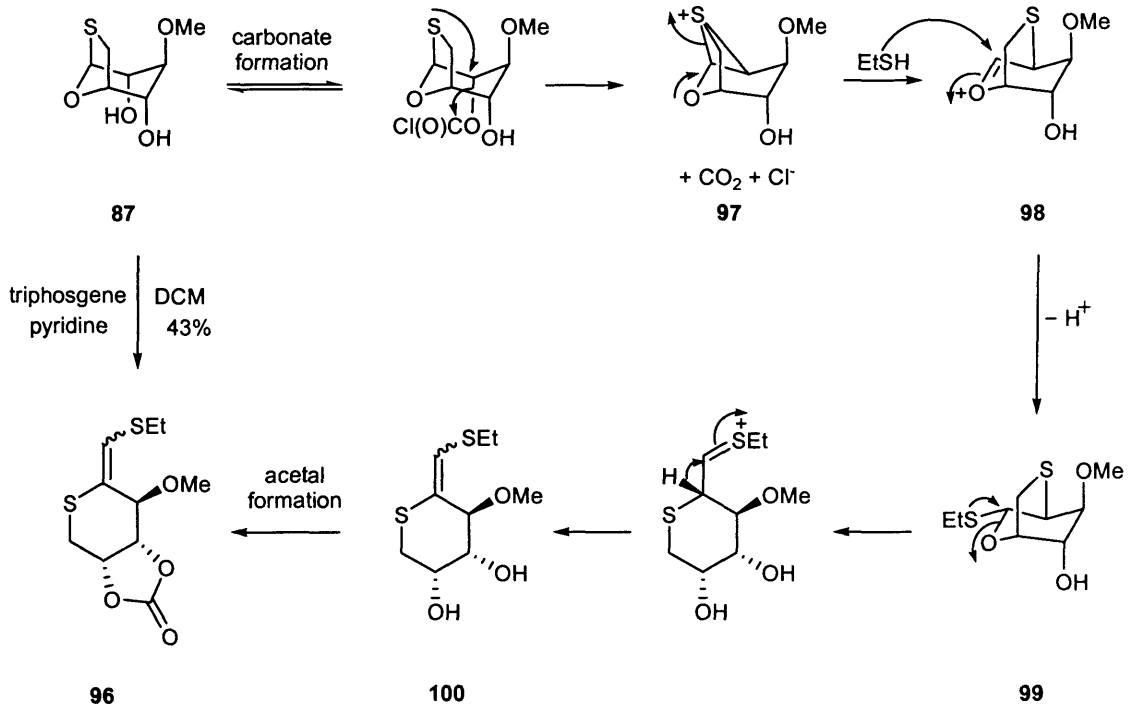


Scheme 34: Mechanism for the formation of sulfide **91**

In product **91** the ^{1}H NMR chemical shift of the CH_2 of the ethyl group was measured at 2.74 ppm, clearly indicating that it is attached to a sulfur atom. Accurate mass measurement using FAB spectrometry confirmed the presence of a second sulfur atom in the molecule. It is proposed that hemiacetal formation at C-2 of diol **87** occurs as a first step. Then, nucleophilic attack from the sulfur onto C-2 occurs yielding epi-sulfonium salt **92** and liberating cyclohexanone dihydrate. Electron donation from the oxygen yields oxonium ion **93**. The next step involves nucleophilic attack of ethanethiol to give β-sulfide **94**. E_i elimination afforded secondary alcohol **95**, which then undergoes intramolecular acetal formation yielding olefin **91**. The origin of the ethanethiol is not known as it was not a reagent used in the experiment.

Even more puzzling is that an analogous result can be achieved when diol **87** was treated with triphosgene[89] in an attempt to protect the 1,3-diol motif as a cyclic carbonate (Scheme 35), sufide **96** was isolated in 43 %. Again, the ^{1}H NMR chemical

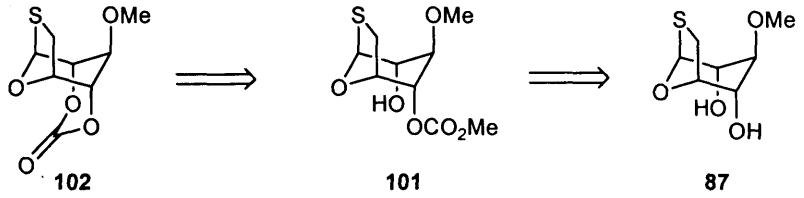
shift of the CH_2 of the ethyl group was measured at 2.72 ppm, clearly indicating that it is attached to a sulfur atom. This was confirmed by HRMS using FAB spectrometry with a mass of 285.02368 $g.mol^{-1}$ which is in accordance with formula $C_{10}H_{14}O_4NaS_2$. It is proposed that carbonate formation at C-2 occurs as a first step. Then, nucleophilic attack from the sulfur onto C-2 yielding epi-sulfonium salt **97** and liberating carbon dioxide and a chloride anion. Electron donation from the oxygen yields oxonium ion **98**. The next step involves nucleophilic attack of ethanethiol to give β-sulfide **99**. E_2 elimination afforded secondary alcohol **100**, which then undergoes intramolecular carbonate formation yielding olefin **96**. Again, the origin of the ethanethiol is not known as it was not a reagent used in the experiment.



Scheme 35: Mechanism for the formation of sulphide **96**

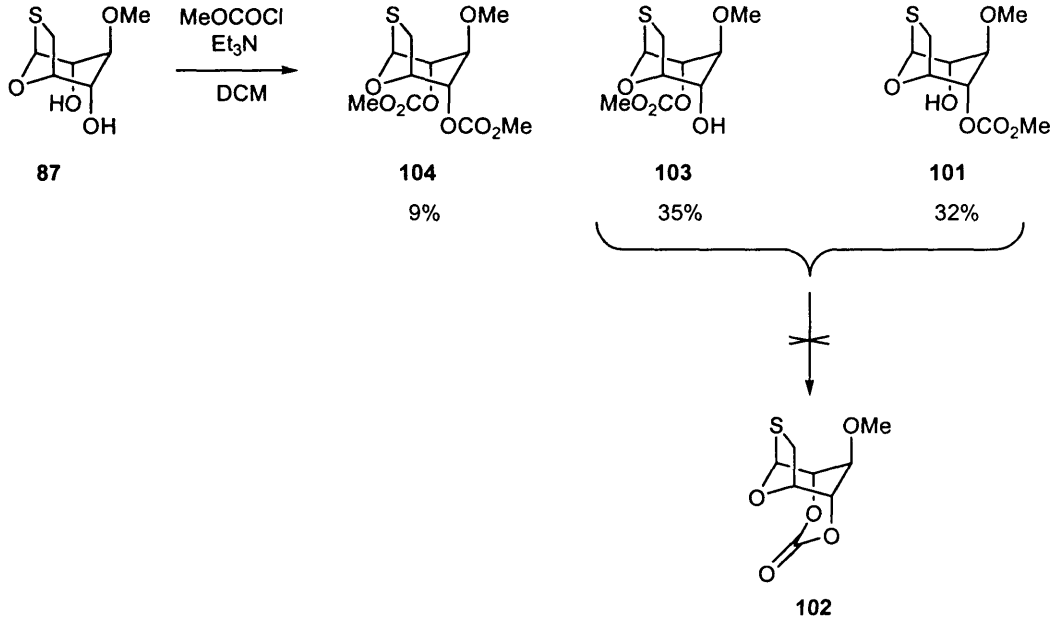
Attempted conversion of the diol to a cyclic boronate with 4-chloroboronic acid in benzene proved to be unsuccessful.[93]

At this point, another method was envisaged to protect both C-2 and C-4 hydroxyls of diol **87**. It was hoped that initial protection of one hydroxyl group as a methyl carbonate could be accomplished giving **101**. Then treatment with a non-nucleophilic base would accomplish deprotonation of the remaining secondary alcohol, which would then cyclise onto the ester, yielding a cyclic carbonate **102** (Scheme 36).



Scheme 36: Retrosynthesis of carbonate **102**

Diol **87** was treated with one equivalent of methyl chloroformate and triethylamine in DCM. Along with the two regioisomers **101** and **103** isolated in 35 % and 32 % respectively, di-protected product **104** was also obtained in 9 % yield (Scheme 38).



Scheme 37: Unsuccessful attempts for the formation of carbonate **102**

Cyclisation of **101** and **103** using either K_2CO_3 in methanol, NaH in THF or DMF, or *t*-BuOK in THF proved to be unsuccessful, with ester deprotection observed in all cases leading to the recovery of diol **87** quantitatively.

At this point, the low reactivity of both triol **82** and diol **87** to protection with a cyclic tether was very concerning. Takagi had reported an X-ray crystallographic data on the structure of triol **82** (figure 12).[94]

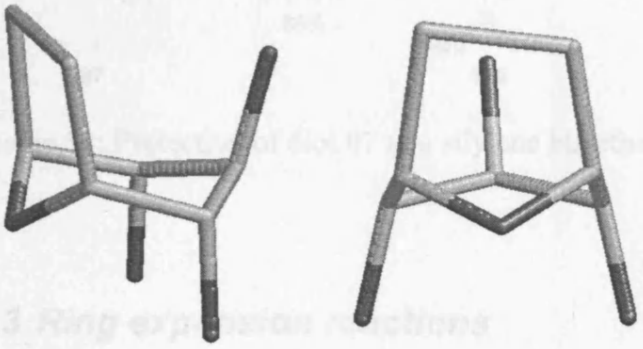
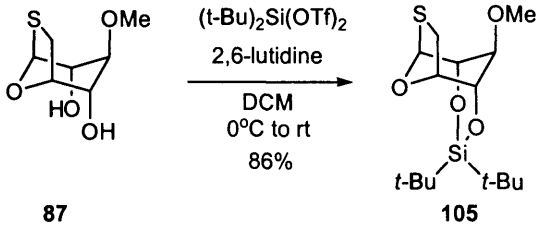


Figure 13: X-ray structure of triol **82**

It was found that the introduction of the sulfur as a bridge between C-1 and C-6 had imposed a considerable distortion in the tetrahydropyran ring. The presence of this 1,3-oxathiolane as a five-membered ring makes the hydroxyls at C-2 and C-4 spread apart as shown in figure 13. The actual distance between the two oxygen atoms is 3.04 Å; the distance between 1,3-diaxial oxygen atoms in an unstrained carbohydrate would be expected to be around 2.4 Å. Therefore, protection of the 1,3-diol as a cyclic acetal would introduce considerable strain into the molecule, and this is likely to be the main reason why diol **87** and triol **82** are so resistant to such protection. The solution to this problem would be to introduce a silylene acetal as the protecting group. The longer silicon-oxygen bonds would allow the formation of a

tether between the two hydroxyls at C-2 and C-4 without introducing too much strain in the molecule.[95,96]

As a consequence, diol **87** was treated with di-*tert*-butylsilyl ditriflate and 2,6-lutidine in DCM, yielding silylene bis-ether **105** in 86 % (Scheme 38).[97] The product was acid-sensitive and purification had to be performed on base-washed silica.



87 **105**

Scheme 38: Protection of diol **87** as a silylene bis-ether

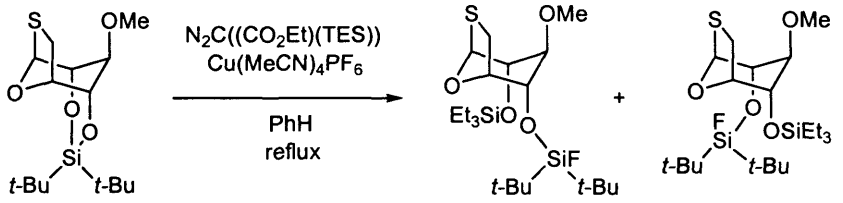
2.1.3.4.3 Ring expansion reactions

The silylene bis-ether **105** was then subjected to the ring expansion reaction conditions described in table 2.

Entry	Conditions	Solvent	Result
1	Ethyl (TES)diazoacetate, $Cu(acac)_2$	Benzene, reflux	No reaction
2	Ethyl (TES)diazoacetate, $Cu(hfacac)_2$	Benzene, reflux	No reaction
3	Ethyl (TES)diazoacetate, $Rh_2(OAc)_4$	Benzene, reflux	No reaction
4	Ethyl (TES)diazoacetate, $Rh_2(OAc)_4$	Benzene, RT→40 °C→60 °C	No reaction
5	Ethyl (TES)diazoacetate, $Cu(MeCN)_4PF_6$	Benzene, reflux 12 h	**106** 15 % **107** 13 %
6	Ethyl (TES)diazoacetate, $Rh_2(O_2CC_3F_7)_4$	Benzene, reflux 14 h	**108** 21 %
7	Ethyl (TES)diazoacetate, $Rh_2(OAc)_4$	DCM, reflux	No reaction
8	Diethyl diazomalonate, $Cu(acac)_2$	Benzene, reflux	No reaction
9	Diethyl diazomalonate, $Rh_2(OAc)_4$	Benzene, reflux	No reaction
10	Diethyl diazomalonate, $Rh_2(OAc)_4$	Benzene, RT→40 °C→60 °C	No reaction

Table 2: Experimental conditions for the ring expansion reaction

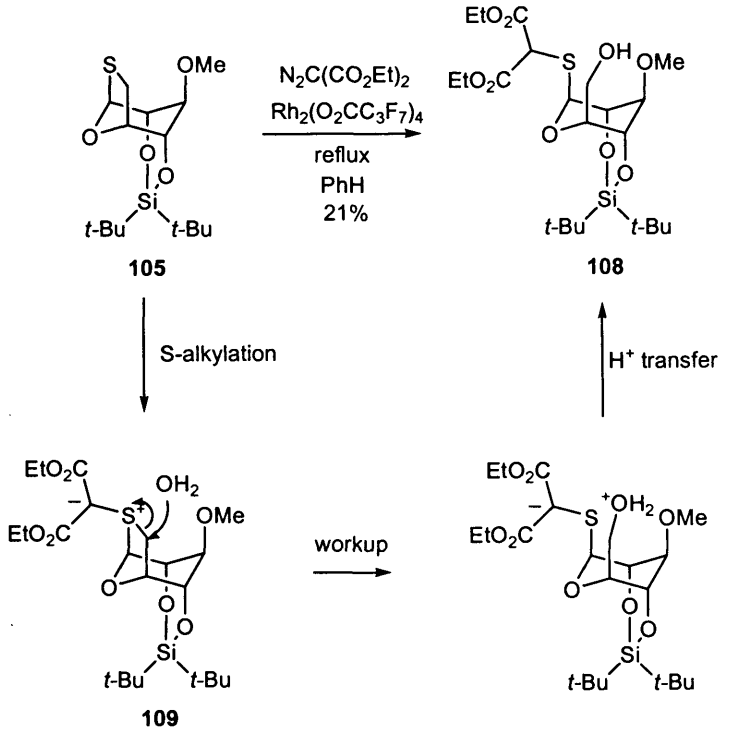
None of these experimental conditions gave the desired ring-expansion product, with starting material generally being recovered. One of the occasion on which a new product was isolated was upon treatment of silylene bis-ether **105** with ethyl(triethylsilyl)diazoacetate and $Cu(MeCN)_4PF_6$: from this reaction, a mixture of regioisomeric fluorosilyl ethers **106** and **107** could be isolated in 15 % and 13 % yields respectively. Due to the strong silicon-fluorine bond formed, the counteranion of the metal catalyst attacks the silylene bis-ether protecting group and cleavage occurs to yield a secondary alcohol at either C-2 or C-4 (Scheme 39). The ethyl(triethylsilyl)diazoacetate is believed to be acting as a triethylsilyl group donor.



105 **106** 15% **107** 13%

Scheme 39: Formation of fluorosilyl ethers **106** and **107**

It was thought that using a catalyst with electron withdrawing ligands would make the metal carbene more reactive. Hence, ring expansion was attempted with diethyl diazomalonate and $Rh_2(O_2CC_3F_7)_4$ as a catalyst in benzene (Scheme 40). In this case, the only isolable product from the reaction was the primary alcohol **108** in 21 % yield. It is supposed that sulfur alkylation occurs as expected to yield sulfur ylide **109**. However, this species does not rearrange and persists until workup, when attack of water at C-6 afforded primary alcohol **108**. Adventitious water in the reaction was thought to be less likely due to the care taken in ensuring anhydrous conditions (freshly distilled solvents, use of glove bag).

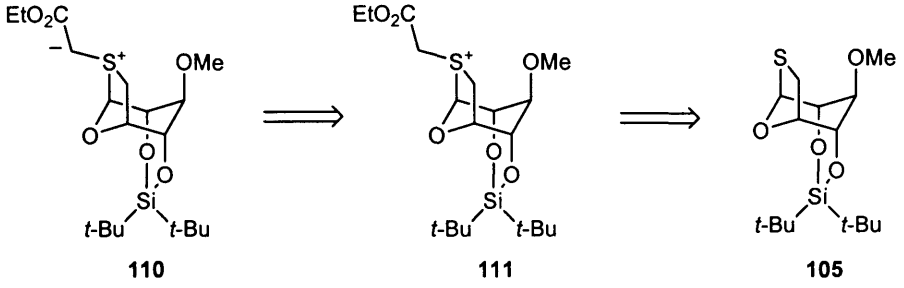


Scheme 40: Mechanism for the formation of alcohol **108**

2.1.4 Tandem alkylation / deprotonation

2.1.4.1.1 Strategy and retrosynthesis

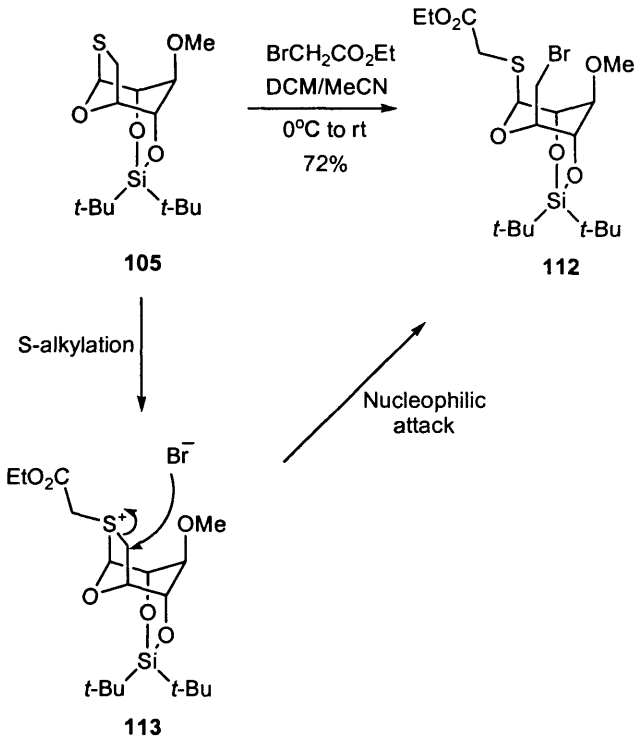
Another method to generate a sulfur ylide **110** would be initial alkylation of the sulfur with ethyl bromoacetate followed by deprotonation of **111** (Scheme 41).



Scheme 41: Tandem alkylation/deprotonation strategy

2.1.4.1.2 Results

Silylene bis-ether **105** was hence treated with ethyl bromoacetate in DCM /MeCN. This did not yield the expected sulfonium salt, but rather the primary bromide **112** in 72 % yield. Clearly the sulfur undergoes alkylation as expected, affording sulfonium salt **113** as an intermediate, but the bromide counteranion then attacks as a nucleophile at C-6, yielding the observed primary bromide **112** (Scheme 42).



Scheme 42: Formation of bromide **112**

In order to circumvent the inconvenient nucleophilic attack of the bromide, two strategies were investigated. Firstly, the bromide ion could be trapped with a silver salt to form insoluble silver bromide.[98] The reaction was repeated with the stoichiometric addition of either silver nitrate, silver triflate or silver tetrafluoroborate,[99] with the reaction mixtures being shielded from light. In all cases, primary bromide **112** was isolated in similar yields (75 %, 64 % and 61 %

respectively). Attempts to treat the primary bromide **112** with the same silver salts were unsuccessful, with starting bromide always being recovered quantitatively.

The second approach was to substitute the alkylating agent for one bearing a less nucleophilic leaving group, therefore the corresponding mesyl, trifyl and tosyl acetates were employed instead. When the mesylate was used, the reaction did not proceed, with starting material **105** being recovered. Using the triflate or the tosylate led to a mixture of unidentified products.

2.1.5 Sulfur ylide chemistry: Conclusions

In this first set of investigations, efforts were directed towards the synthesis of a model 9-oxa-3-thiabicyclo[3.3.1]nonane ring system **44** through ring expansion of the corresponding bicyclic oxathiolane **43**. The plan was to adapt experimental conditions developed on simple 1,3-oxathiolanes to bicyclic substrate.

Initial results starting with D-mannose **48**, which bears the same configuration as tagetitoxin **1**, showed that the conversion of the D-sugar to the bicyclic oxathiolane was not favoured; however the synthesis of the corresponding bicyclic oxathiolane **58** from D-glucose **55** could be carried out it 64 % yield. Unfortunately, when attempting ring expansion reactions, it was found that the intermediate oxonium ion **64a** undergoes a ring flip, precluding subsequent ring closure. The only isolable products were the corresponding elimination products.

Increasing the stability of the oxonium ion by switching to D-altrose, which has fewer axial substituents did not prove successful, with the corresponding alkene **78** isolated after attempted ring expansion reaction.

Another path to circumvent the ring flip of the intermediate zwitterion species was investigated. The introduction of a conformational lock between hydroxyls at C-2 and C-4 as a cyclic tether was effected. Most of the experimental conditions employed for the ring expansion reaction left the tricycle **105** untouched. The most notable result is when $Rh_2(O_2CC_3F_7)_4$ was used as a catalyst. It is presumed that the sulfur ylide is generated but ring closure does not occur and a water molecule eventually relieves the strain in the tricycle. The reasons for the difference in reactivity of bicycle **82** and tricycle **87** are not clear

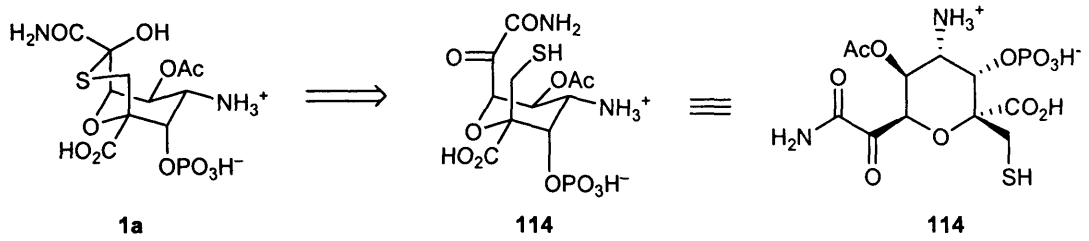
Finally, a tandem alkylation of the sulfur followed by deprotonation was investigated in order to generate a sulfur ylide species. Alkylation proceeded effectively but unfortunately, the counteranion of the alkylating agent attacked as a nucleophile and opened the oxathiolane.

Overall, it was demonstrated that the ring expansion reaction, which operates nicely on simple 1,3-oxathioanes, was not feasible on bicyclic substrates. As a consequence, we decided to focus on another path to secure the 9-oxa-3-thiabicyclo[3.3.1]nonane ring system **44** and eventually, tagetitoxin **1**.

2.2 Cyclisation of a thiol onto an α-ketoester

The second approach to be investigated involved the cyclisation of a thiol onto an electron-deficient ketone. As seen in the retrosynthetic Scheme 43, it is reasonable to think that in tagetitoxin structure **1a**, the bond between the sulfur atom and the quaternary carbon bearing the amide and hydroxyl functionalities could arise from nucleophilic attack of a thiol onto a ketone, giving a hemithioacetal and thus should exist in equilibrium with its open form **114**. The next question then is: if it is possible

to synthesise an α-ketoamide such as **114**, under which experimental conditions does the equilibrium favour the bicyclic hemithioacetal?[100,101]



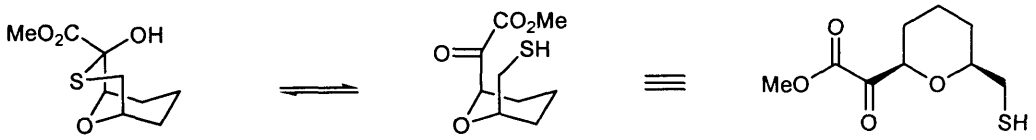
1a **114** **114**

Scheme 43: Tagetitoxin retrosynthesis

2.2.1 Simple substrates

2.2.1.1 Strategy and retrosynthesis

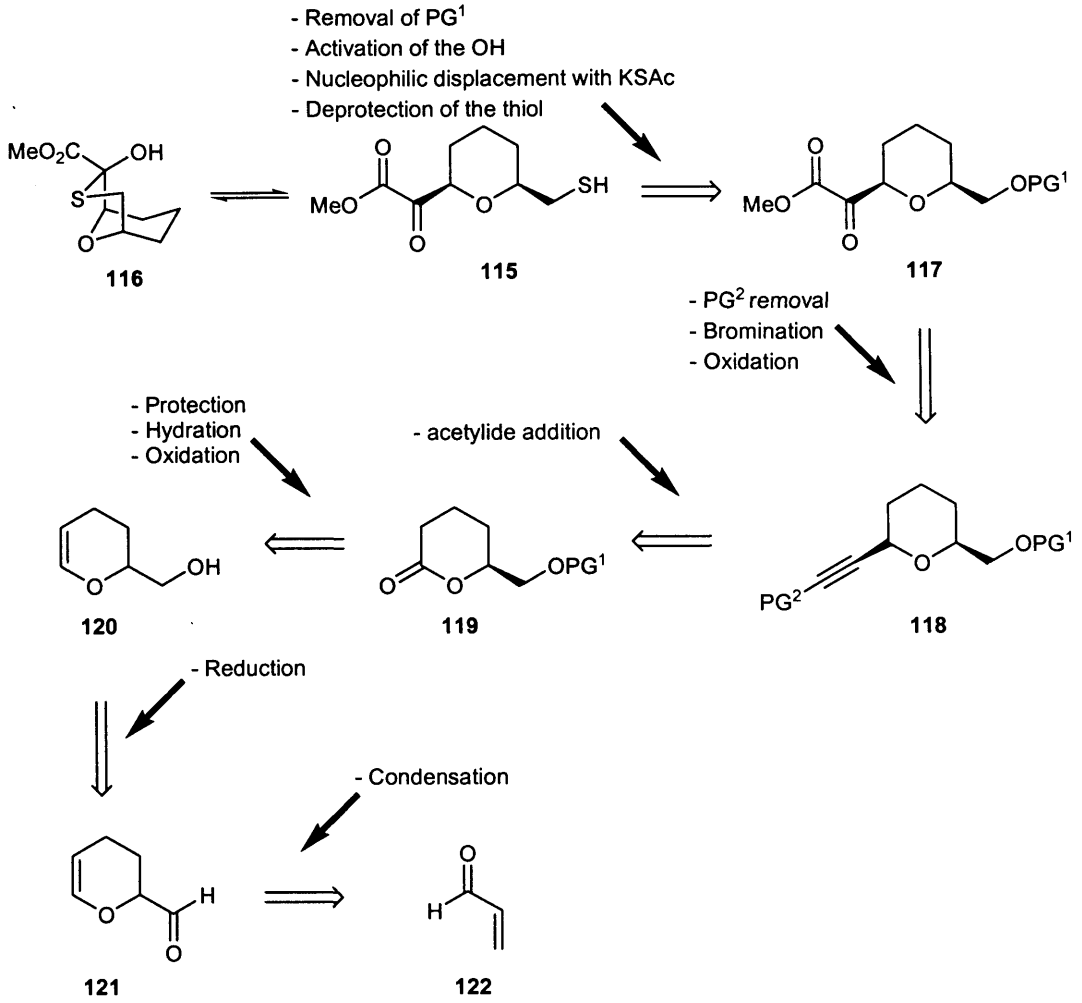
Rather than devising a synthetic route to the fully functionalised precursor **114**, it was thought that this end-game strategy should be tested on simpler substrates to demonstrate its validity. Preliminary efforts were concentrated on the intramolecular cyclisation of unfunctionalised thiol **115**. (Scheme 44).



116 **115** **115**

Scheme 44: Retrosynthesis of a simple bicyclic 1,4-oxathiane **115**

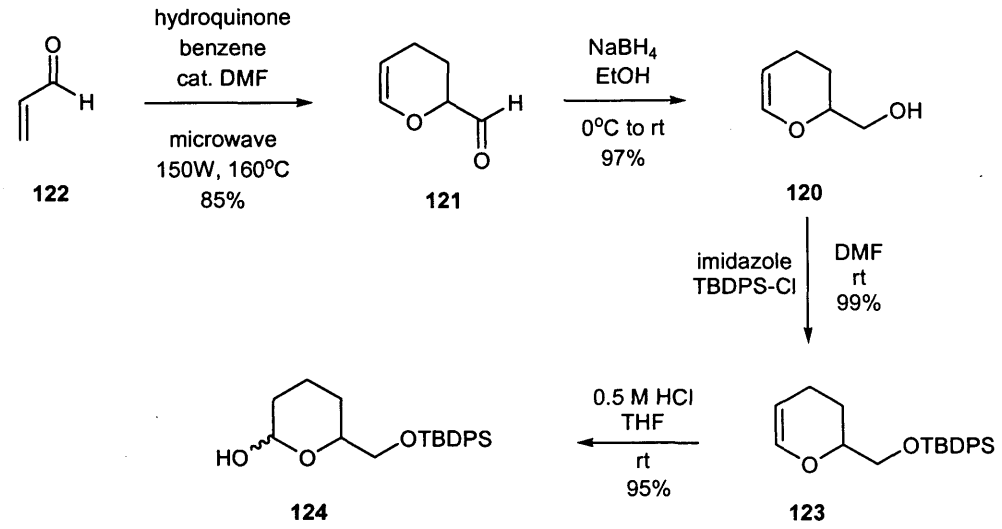
Key steps to produce the model thiol **115** are highlighted in Scheme 46. It was expected that thiol **115** could be derived from protected alcohol **117**. The α-dicarbonyl functionality of this molecule would be produced by oxidation of an acetylene in compound **118**, which in turn would arise from the corresponding lactone **119**. The latter could be secured from enol ether **120**, which would in turn be obtained from acrolein dimer **121** (Scheme 45).



Scheme 45: Retrosynthesis of 1,4-oxathiane **116** from acrolein **122**

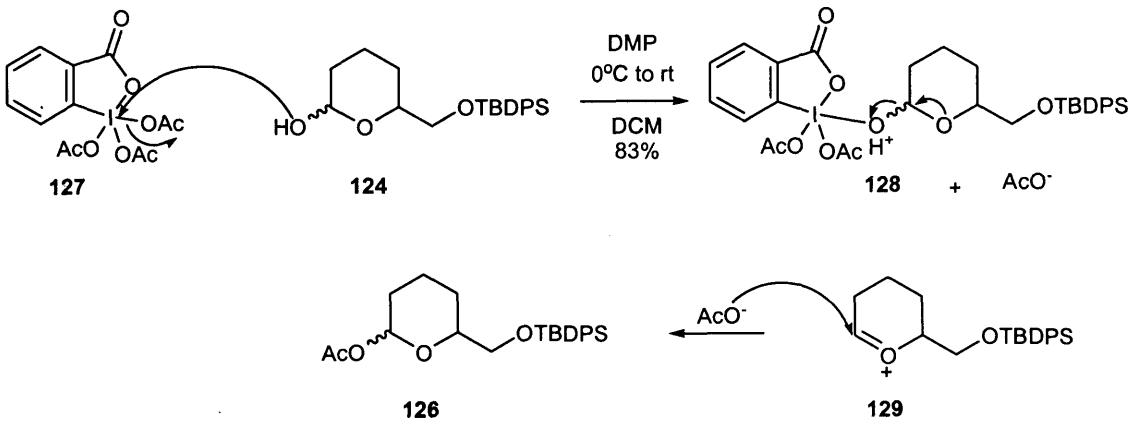
2.2.1.2 Results

Acrolein **122** was self-condensed to its dimer **121** in a microwave reactor (Scheme 46). The best result (85 % yield)[102] was obtained using 2 mol % of hydroquinone, in a concentrated benzene solution (17 M) with catalytic amount of DMF. The aldehyde **121** was then reduced to the corresponding alcohol **120** using sodium borohydride in ethanol (97 % yield),[103] and protected with a *tert*-butyldiphenylsilyl group in near quantitative yield yielding **123**. The alkene **124** was hydrated in dilute acid to afford a mixture of diastereomeric lactols **125** in 95 % yield.[104]



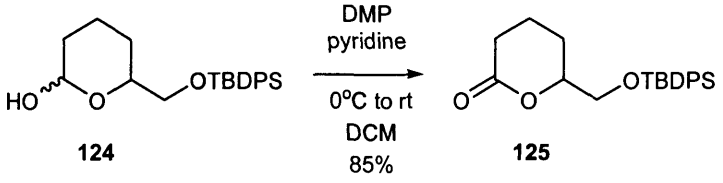
Scheme 46: Synthetic route to lactol **124**

The next step was the oxidation of lactol **124** to the corresponding lactone **125**. Initial investigations using a Swern oxidation protocol[105] were unsuccessful, with starting material being recovered. Using pyridine-sulfur trioxide complex in DMSO led to the re-formation of enol ether **123** in 24 % yield along with 72 % of recovered starting material.[106] The next oxidizing agent used was Dess-Martin periodinane in DCM;[107] however, this reaction did not produce any sign of the desired lactone but rather a mixture of anomeric acetates **126** in 83 % yield (Scheme 47). It is suspected that upon attack of the alcohol onto the hypervalent iodine of Dess-Martin periodinane **127** and release of an acetate giving **128**, electronic donation from the ring oxygen yields oxonium ion **129**. Acetate then attacks to yield the observed mixture of anomeric acetates **126**.



Scheme 47: Mechanism for the formation of anomeric acetate **128**

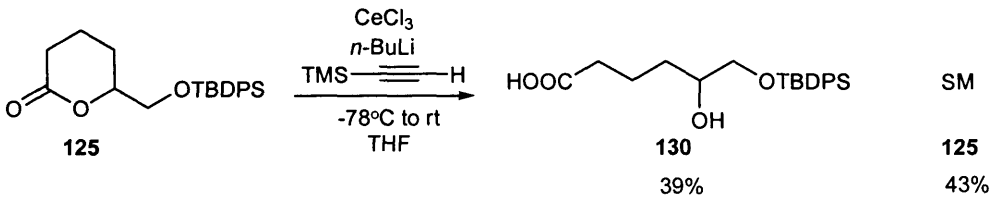
When sodium bicarbonate was added with the Dess-Martin periodinane **127**, the reaction proceeded as before leading to anomeric acetates **126** in similar yield; however, using excess pyridine, lactone **125** was secured in 83 % yield (Scheme 48).[108]



Scheme 48: Oxidation of lactols **124** to lactone **125**

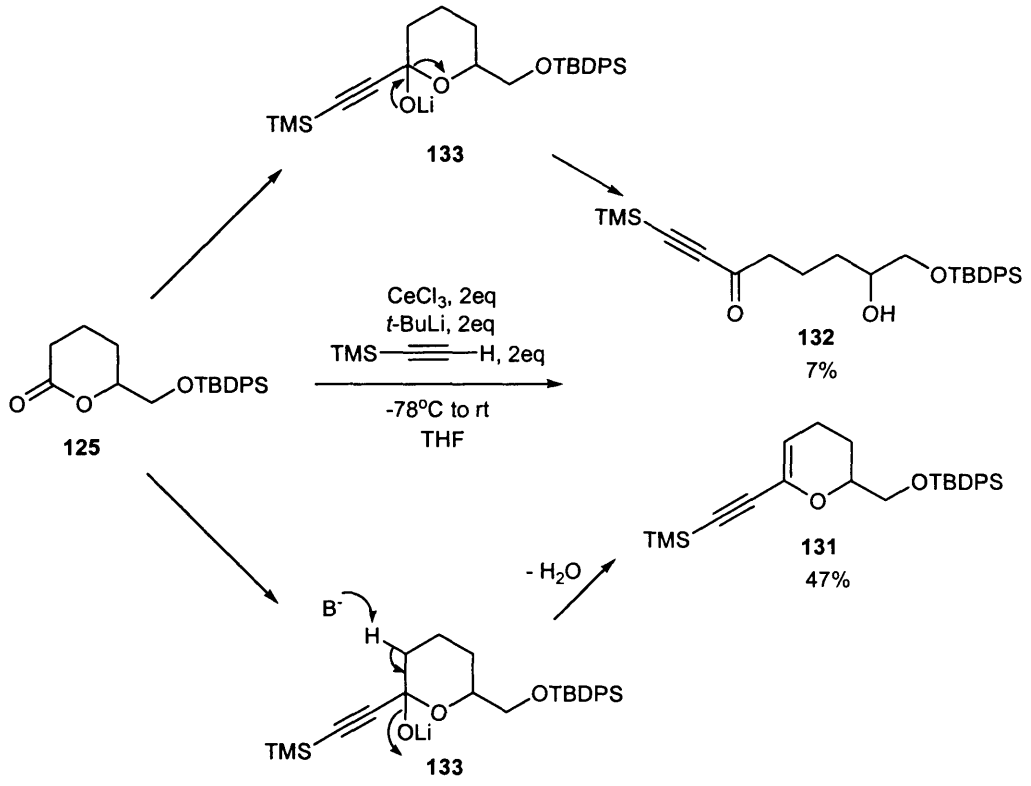
The next step was the addition of a TMS-protected cerium acetylide onto the carbonyl group of lactone **125**. Cerium was chosen because it is less electropositive than lithium and magnesium, and the resulting organocerium compouds are comparatively less basic and rather more nucleophilic. Initial attempts involved the use of *n*-BuLi as a base to generate lithiated TMS-acetylene,[109] which was then added to anhydrous cerium chloride (prepared by drying the heptahydrate under high vacuum at 150 °C). However, using these conditions, the reaction did not go to completion even with a large excess of reagents (up to six equivalents). The starting

material was recovered in 43 % yield, along with 39 % of carboxylic acid **130** (Scheme 49), resulting from simple hydrolysis of lactone **125**.



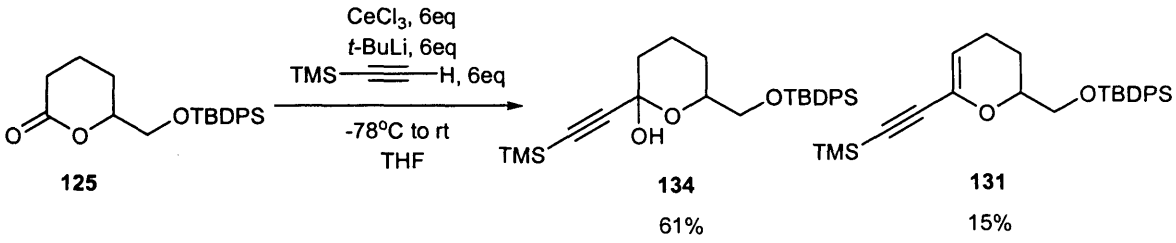
Scheme 49: Formation of acid **130**

Further attempts were made using *tert*-BuLi as a base instead of *n*-BuLi (Scheme 50). No desired product was observed, but instead enol ether **131** and ketone **132** were isolated in 47 % and 7 % yield respectively. It is thought that for both products, the first intermediate is the expected 1,2-addition product **133**. At this point, the intermediate either dehydrates to form the enol ether **131**, or ring opens to form ketone **132**.



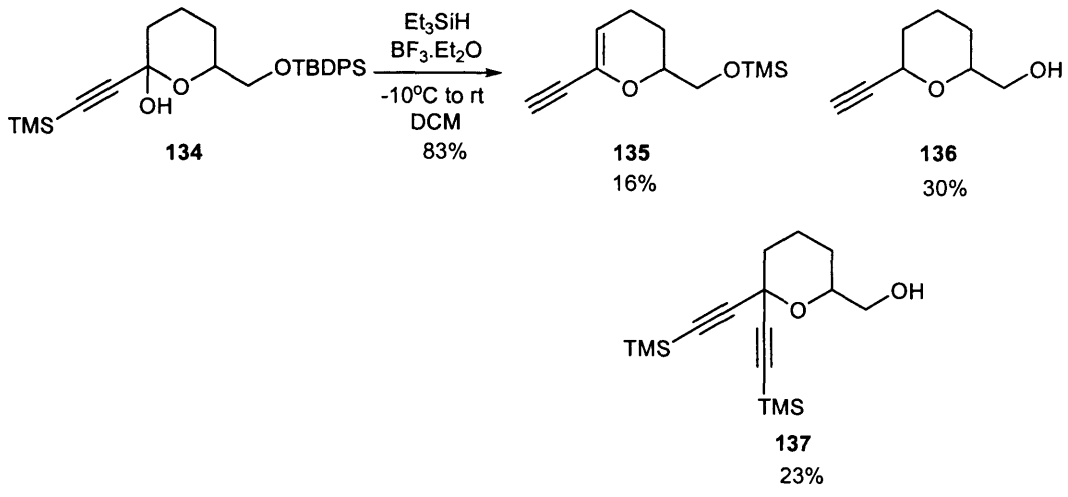
Scheme 50: Formation of ketone **132** and enol ether **131**

It was found that if a large excess of base, cerium chloride and TMS-acetylene were used, the reaction outcome was completely different. Indeed, using six equivalents of the above-mentioned reagents yielded a mixture of the desired addition product **134** in 61 % yield along with enol ether **131** in 15 % yield (Scheme 51).



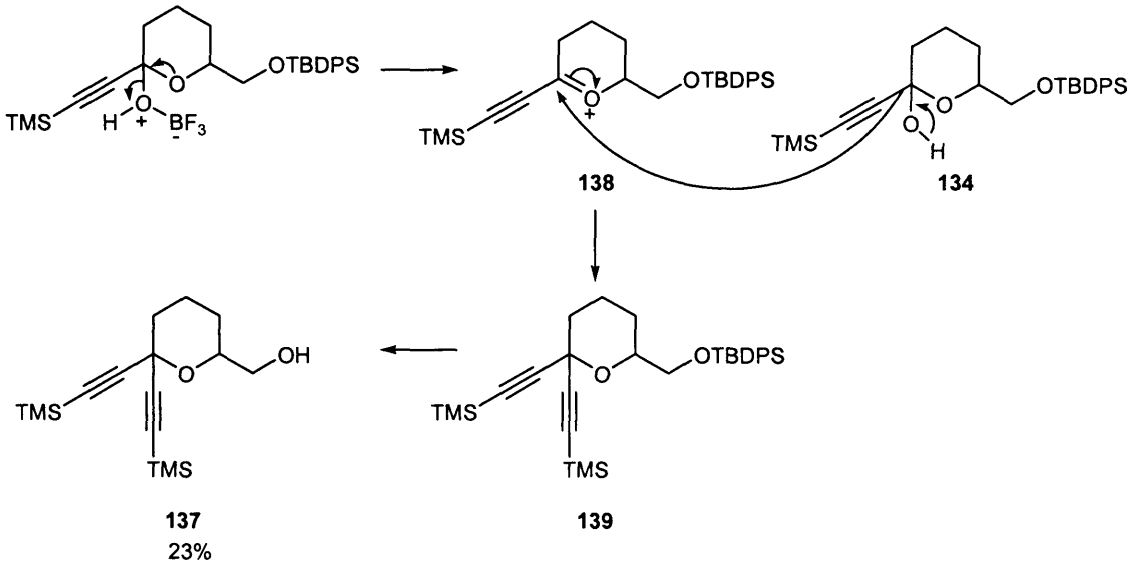
Scheme 51: Synthesis of lactol **134**

The next step was deoxygenation of lactol **134**. The use of triethylsilane along with a Lewis acid has been reported. Thus lactol **134** was treated with either $BF_3.Et_2O$ or TMSOTf[110] in either DCM, MeCN or a mixture of the two, affording a mixture of three different products: enol ether **135**, terminal alkyne **136** and alcohol **137** in varying ratios. The best yield of terminal alkyne **136** achieved was 30 %, using $BF_3.Et_2O$ in DCM. This was accompanied by 16 % of enol ether **135** and 23 % of alcohol **137** (Scheme 52).



Scheme 52: Synthesis of enol ether **135**, terminal alkyne **136** and alcohol **137**

In enol ether **135**, elimination of water has occurred, along with deprotection of the acetylene and the primary alcohol, and conversion of the alcohol to a TMS ether. Terminal alkyne **136** results from deoxygenation along with deprotection of both acetylene and primary alcohol. Alcohol **137** is the most peculiar of the three. A TMS-protected acetylene fragment has been added α- to the ring oxygen along with deprotection of the primary alcohol. A tentative mechanistic proposal to explain the formation of this product is outlined in Scheme 53. It is assumed that the anomeric hydroxyl in the starting lactol **134** can coordinate the Lewis acid, making it a good leaving group. Electronic donation from the ring oxygen yields oxonium ion **138** which, in the desired reaction, is reduced by triethylsilane. It is thought that proton loss from some unreacted starting material **134** releases a TMS-acetylide fragment, possibly coordinated to the Lewis acid that can in turn attack as a nucleophile onto oxonium species **138** to yield intermediate **139**. At some point during the process, the primary alcohol protecting group is cleaved. The final product isolated is alcohol **155** in 23 % yield.



Scheme 53: Mechanism for the formation of alcohol **137**

For all these compounds, it is proposed that the desilylation of the primary alcohol and acetylene is due to the presence of the traces of fluoride from the Lewis acid in the reaction mixture,[111] although it is unclear why the trimethylsilyl groups are not cleaved from alcohol **135**.

These unexpected results and unsatisfactory yields at this stage of the synthesis are not compatible with the aim of producing a simple model substrate. Hence it was decided to switch the study of the model substrate cyclisation to carbohydrate-based models for which the chemistry is more well-documented.

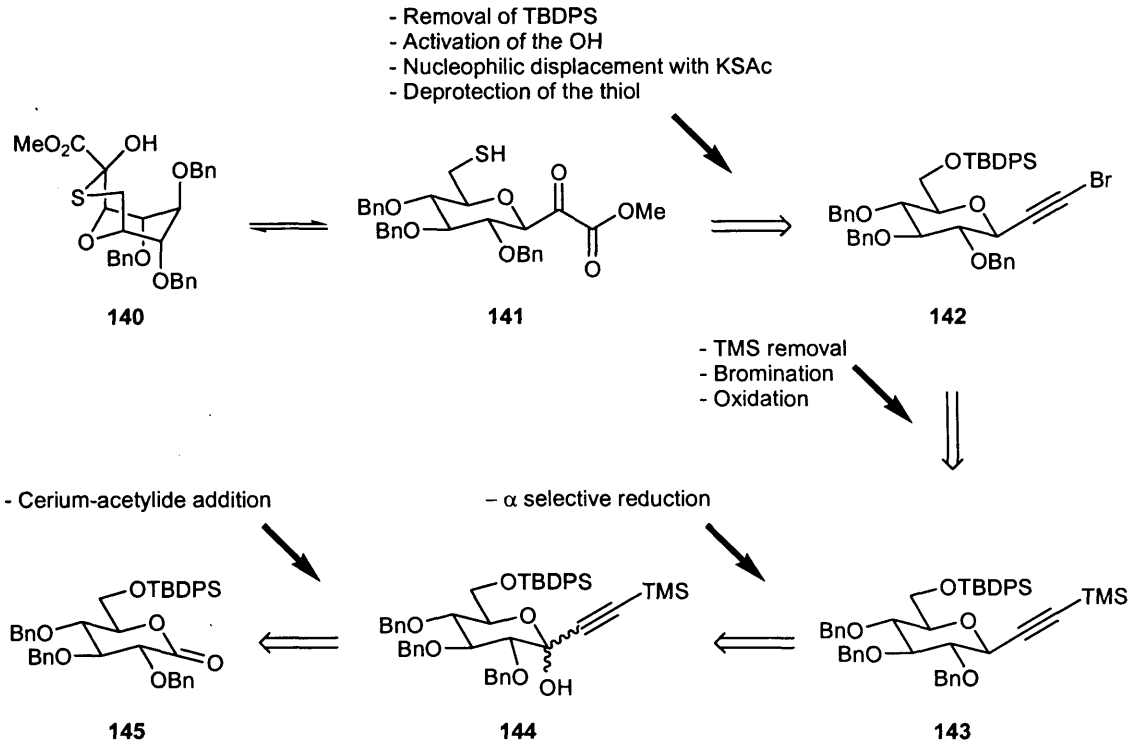
2.2.2 Carbohydrate-based approach

2.2.2.1 Model substrate

2.2.2.1.1 Strategy and retrosynthesis

The revised strategy was next to develop a model carbohydrate-based substrate bearing an α-ketoester in the β-orientation at C-1 and a free thiol at the 6 position.[1] It was hoped that the sulfur atom would cyclise onto the ketone to generate the desired bicyclic 1,4-oxathiane. The retrosynthetic plan to tribenzyl ether **140** is shown below (Scheme 54). Thiol **141** will be prepared from its corresponding protected alcohol. The α-dicarbonyl moiety should be secured from bromoalkyne **142**, which should arise from the TMS-protected alkyne **143**. In turn, **143** should be secured from lactol **144**, the latter being obtained from lactone **145**. Lactone **145** can be prepared in seven steps from D-glucose *via* standard carbohydrate chemistry.

[1] Although systematic nomenclature would mean that the anomeric position of glucose becomes C-3 in compounds such as **141**, the original sugar numbering is used throughout.

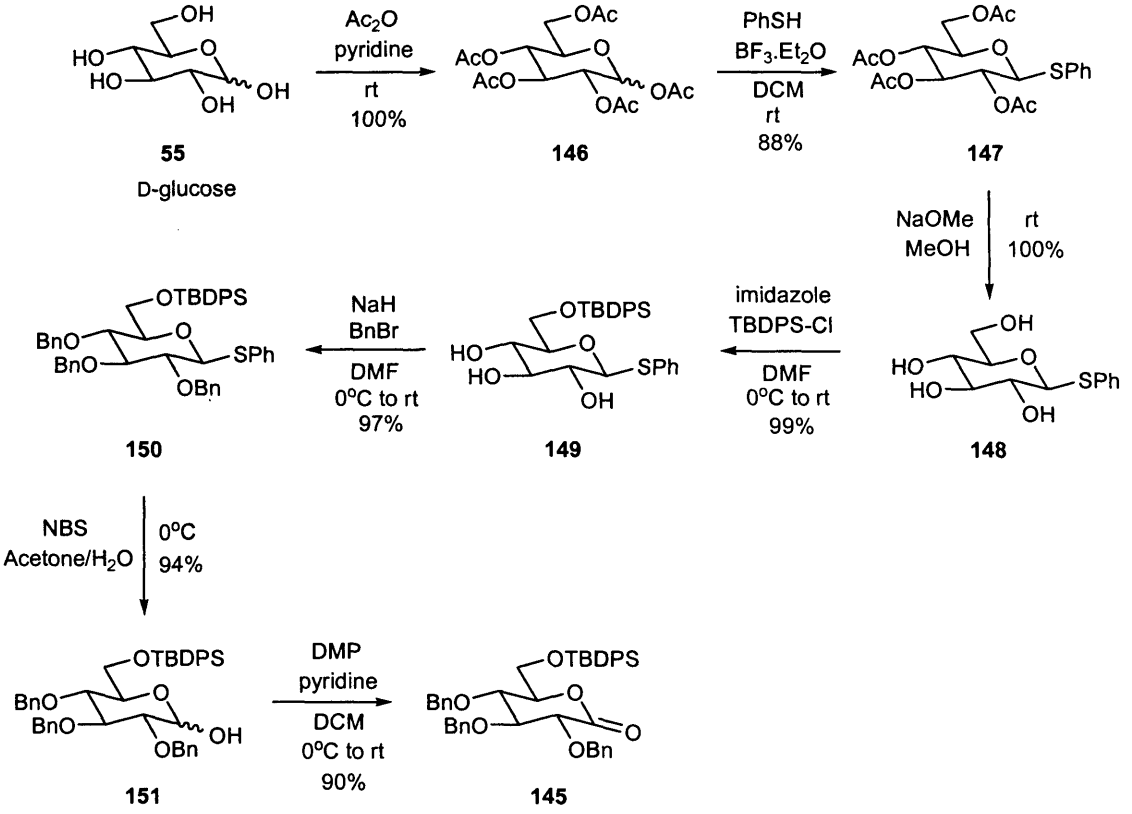


Scheme 54: Retrosynthesis of tri-benzyl ether **140** from lactone **145**

2.2.2.1.2 Results

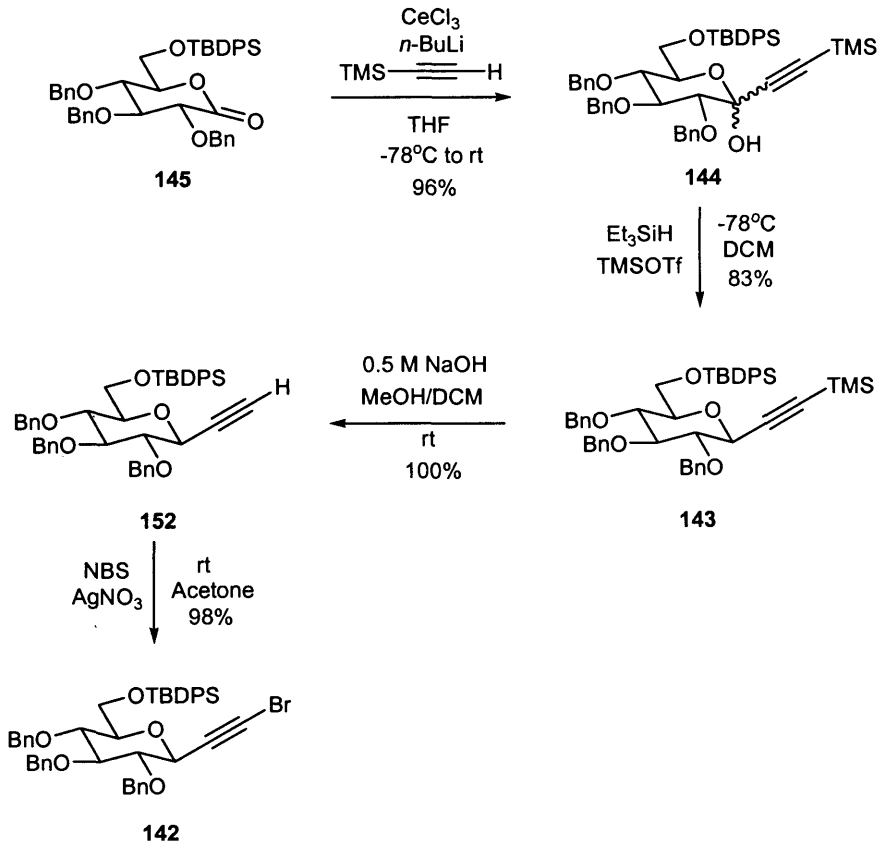
D-Glucose **55** was peracetylated with acetic anhydride in pyridine yielding peracetate **146** quantitatively (Scheme 55). The anomeric acetate of **146** was displaced with thiophenol, in the presence of boron trifluoride etherate, to yield β-thioglycoside **147** exclusively in 88 % yield.[112] It is noteworthy that this 1,2-*trans* isomer is formed exclusively *via* neighbouring group participation of the C-2 acetate. Removal of the acetates was effected using sodium methoxide in methanol affording tetraol **148** in quantitative yield followed by selective protection of the primary alcohol to give *t*-butyldiphenylsilyl ether **149** in 99 % yield. The remaining secondary hydroxyls were then protected as benzyl ethers (97 % yield)[113] and the thioglycoside bond of **150** was cleaved using *N*-bromosuccinimide in a mixture of acetone and water. The resulting mixture of lactols **151** was isolated in 94% yield. These isomers were oxidised with

Dess-Martin periodinane **127** in the presence of pyridine to secure gluconolactone **145** in 90 % yield. Overall, lactone **145** was synthesised from D-glucose **55** in 71% yield over seven steps.



Scheme 55: Synthetic route to lactone **145** from D-glucose **55**

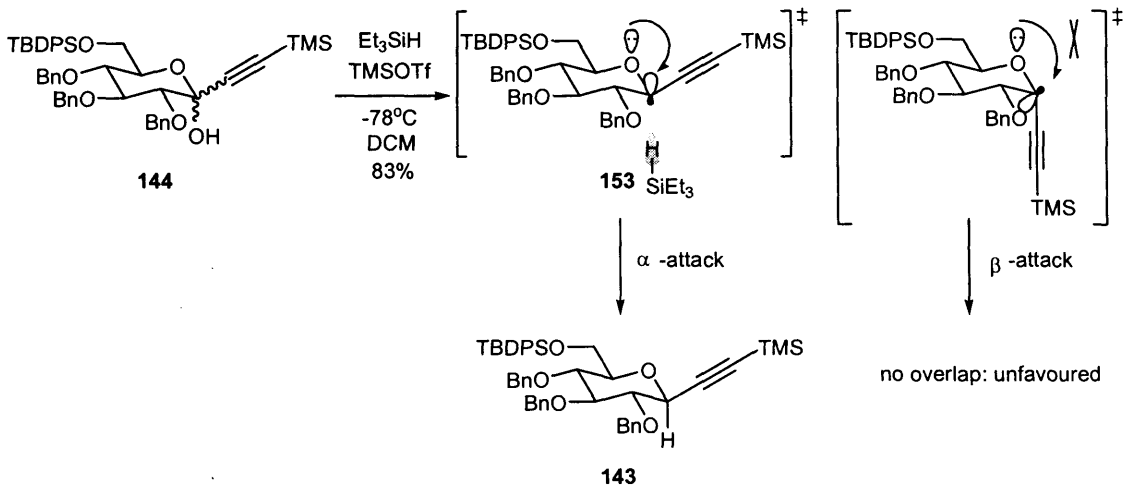
Lactone **145** was then treated with excess cerium TMS-acetylide formed from *n*-BuLi, TMS-acetylene and cerium chloride.[114] In contrast to the simpler substrates discussed earlier, the 1,2-addition proceeded very efficiently to give lactol **144** in 96 % yield (Scheme 56). Deoxygenation of lactol **144** proceeded with exclusive β-selectivity leading to **143**. Cleavage of the TMS protecting group of **143** in dilute sodium hydroxide occurred quantitatively yielding terminal alkyne **152**. Subsequent bromination using *N*-bromosuccinimide yielded alkynyl bromide **142** in 98%.[115]



Scheme 56: Synthetic route to bromoalkyne **142**

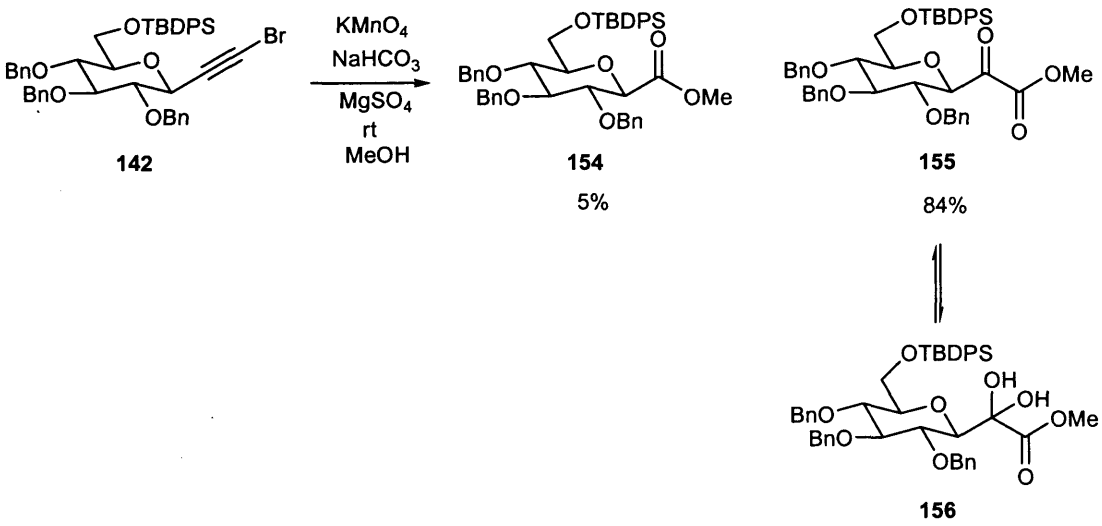
The Lewis acid-promoted, triethylsilane reduction of lactol **144** occurred with exclusive β-selectivity i.e. the hydride is delivered from the α-face. Shuto *et al.* have proposed that the stereoselectivity observed in the Lewis acid-promoted silane reduction of the anomeric position of a carbohydrate derivative is due to conformational preferences.[116] Substrate **144** is conformationally more stable as a $^4C_1$ chair form, bearing all its substituents equatorially. As a result, during the triethylsilane reduction, the transition state would assume a low energy $^4C_1$-chairlike form **153**, where the anomeric centre would be pyramidal. Triethylsilane hydride delivery from the α-face is dictated because the transition state form **153** would then be stabilized via hyperconjugation between the nonbonding orbital of the ring oxygen

lone pair n_o and the antibonding orbital of the newly forming anomeric C-H bond σ* because of their co-planar arrangement (Scheme 57).



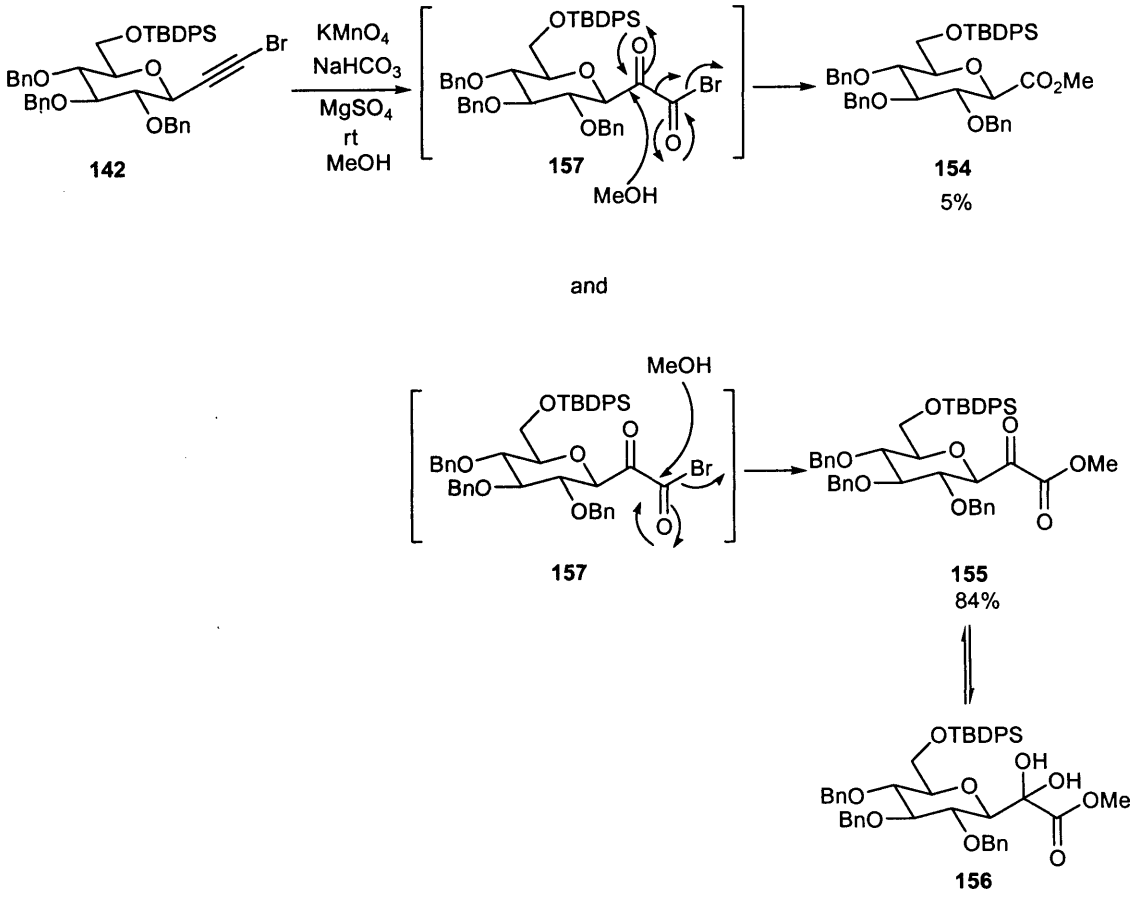
Scheme 57: Stereoselectivity of the Lewis acid-promoted silane reduction of lactol **144**

The next step involved the oxidation of the bromoalkyne of **142** to an α-ketoacylbromide that would be quenched *in situ* with methanol, yielding the corresponding α-keto methylester. The experimental procedure was adapted from a similar reaction by Li and Wu,[117] who carried out the transformation using potassium permanganate in a 1:1 mixture of methanol / water. However, substrate **142** was not soluble in this solvent system; it was not even soluble in a 99:1 mixture of methanol and water. Consequently, the reaction was performed in neat methanol (Scheme 58).



Scheme 58: Synthesis of α-keto methylester **155**

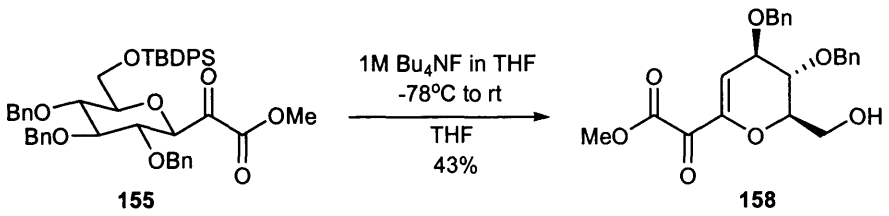
The reaction was particularly capricious, and tedious experimental optimisation had to be carried out to ensure a high-yielding, reproducible outcome. It was found that the potassium permanganate had to be added in small portions over 2 h, after which time the reaction was immediately diluted with water. The optimum amount of potassium permanganate for the best yield of **155** (84 %) was 2.4 equivalents even though the reaction was then not complete (4 % unreacted starting material recovered). Adding too much potassium permanganate resulted in decomposition to a complex mixture of non-identified degradation products. Ester **154** was also obtained in 5 % yield and resulted from the nucleophilic attack of methanol on the ketone of intermediate α-ketoacylbromide **157** (Scheme 59). Attack of methanol at the acyl bromide carbonyl gives the desired product **155**.



Scheme 59: Mechanism for the formation of α-keto methylester **155** and ester **154**

The ^{1}H NMR spectrum of α-keto ester **155** in deuterated chloroform ($CDCl_3$) showed two different compounds in a 1:1 ratio, but TLC analysis only showed one clear spot. It appears that the ketone exists partially as its hydrate **156**, confirmed by a ^{13}C NMR peak at δ = 102.3 ppm, corresponding to $\underline{C}(OH)_2$. NMR spectroscopy in deuterated benzene showed a ratio of α-keto ester **155** to hydrated ketone **156** of 8:1, because the more polar hydrate is presumably more stable in more polar solvents.

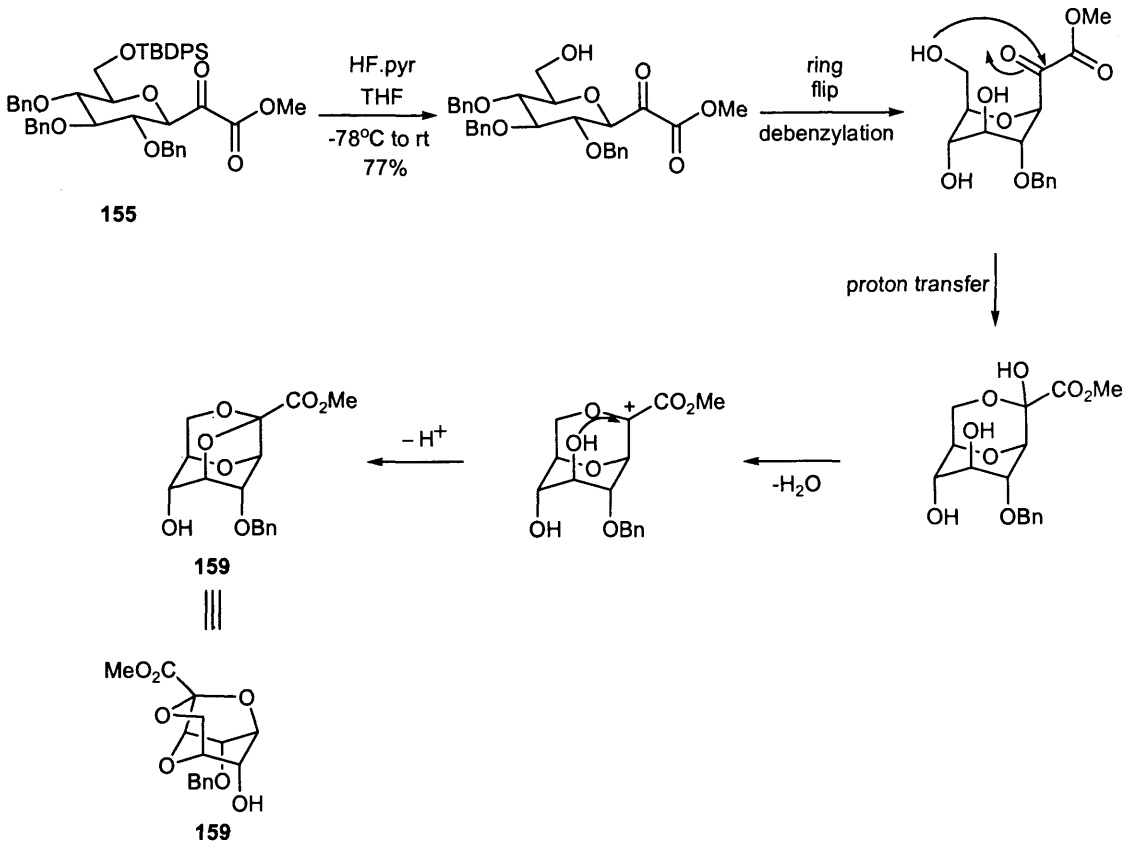
The next step was to be the desilylation of the primary alcohol of **155** in order to introduce the necessary sulfur functionality to cyclise onto the electrophilic ketone. However, on treatment of silyl ether **155** with tetrabutylammonium fluoride solution in THF, the only isolable product was enol ether **158** (Scheme 60).



Scheme 60: Attempted desilylation of α-keto methylester **158**

Not only was the silyl protecting group cleaved, but in addition, the benzyl ether at C-2 had been eliminated. It can be reasoned that the hydrogen at C-1, α to a ketone, is sufficiently acidic that it is removed by the mildly basic fluoride ion, and loss of the benzyl ether follows in an E1cB reaction.

When α-keto ester **155** was treated with 5 equivalents of hydrogen fluoride-pyridine complex, acetal **159** was formed in 77 % yield (Scheme 61). In the course of the reaction, not only was the primary alcohol deprotected, so were the C-3 and C-4 alcohols, and an acetal was formed between O-3, O-6 and the ketone. It is not known why the benzyl groups at C-3 and C-4 were cleaved selectively.



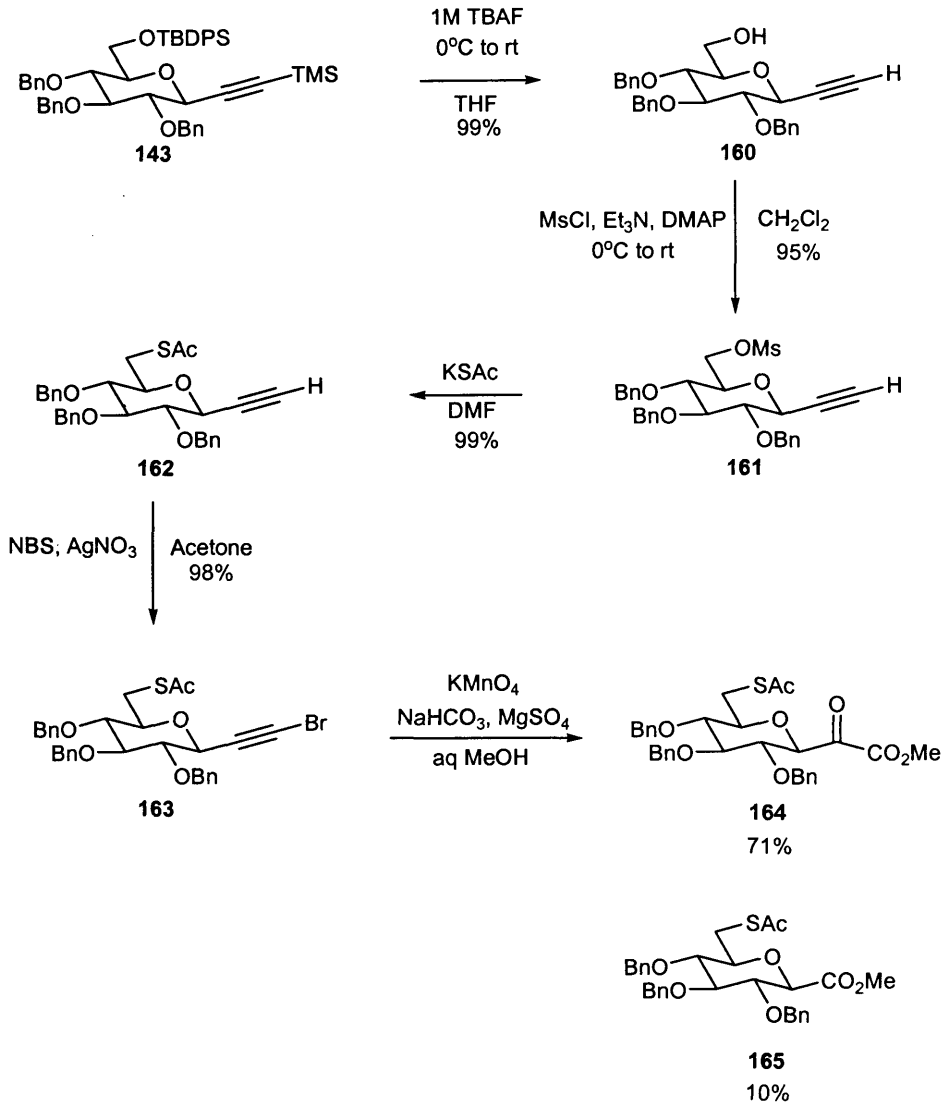
Scheme 61: Mechanism for the formation of acetal **159**

The amount of hydrogen fluoride pyridine complex was reduced to one equivalent in an attempt to prevent benzyl deprotection but even at –78 °C, the reaction proceeded cleanly to afford **159**. Attempts to hydrolyse the acetal in aqueous acidic conditions were unsuccessful.

As removal of the TBDPS group in presence of the electrophilic α-keto ester was problematic, we decided to modify the route by installing the sulfur at C-6 prior to formation of the ketoester.

Both silyl protecting groups were cleaved from silylated alkyne **143** with tetrabutylammonium fluoride yielding 99 % of terminal alkyne **160** (Scheme 62). The primary alcohol was then activated as its mesylate (95 %) yielding **161**, and displacement with potassium thioacetate gave thioester **162** in 99 % yield. Bromination of the terminal alkyne with *N*-bromosuccinimide proceeded in 98 %

yield giving **163**, and oxidation of **163** with potassium permanganate, according to the method developed previously, yielded α-keto ester **164** in 71 % yield along with methyl ester **165** in 10 % yield.

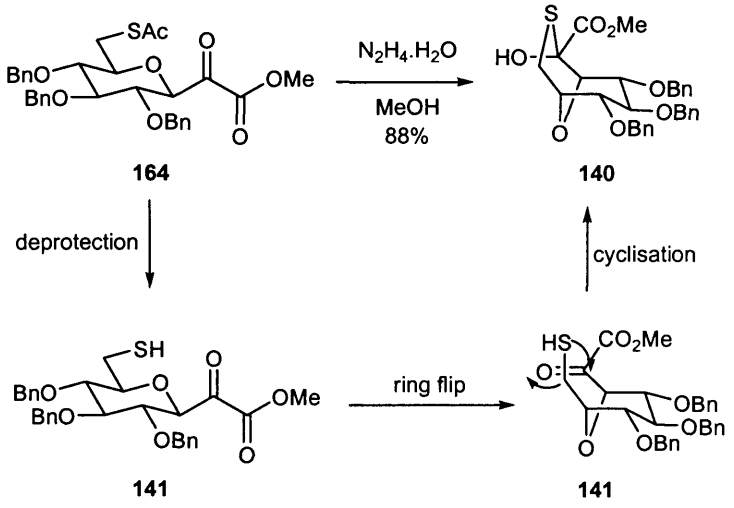


Scheme 62: Synthetic route to α-keto ester **164**

The final step in the sequence was then the deprotection of the thioacetate and the expected subsequent intramolecular cyclisation of the thiol moiety onto the electron-deficient ketone. This was accomplished using hydrazine monohydrate in methanol (Scheme 63) affording oxathiane **140** in 88 % yield. The free thiol **141** was not observed. The structure of **140** was confirmed by mass spectrometry and NMR

spectroscopy; in particular, an HMBC correlation was observed between the hemithioacetal carbon at δ_C = 71.9 ppm and one of the methylene protons adjacent to sulfur at δ_H = 1.57 ppm, indicating a definite connectivity between the two. Vicinal coupling constants of 9.3 and 9.6 Hz between the pairs of CHOBn protons indicated a boat conformation for the tetrahydropyran ring, while the vicinal coupling constants between the CH_2S protons and the adjacent methane proton indicated that the oxathiane ring adopted a chair conformation as depicted in Scheme 63. The hemithioacetal was obtained as a single stereoisomer. Although the configuration of this centre was not determined, we postulate that the hydroxyl group adopts an axial position on the 1,4-oxathiane ring.

The first step of this reaction is the cleavage of the acetyl group from thioester **164** yielding free thiol **141**. The tetrahydropyran ring must then flip to a boat conformation where both thiol and ketoester functionalities are pseudo-axial, allowing hemithioacetal formation to yield bicyclic 1,4-oxathiane **140**. To our knowledge, this is the first synthesis of the bicyclic skeleton of tagetitoxin.

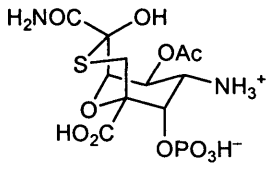


Scheme 63: Mechanism for the formation of 1,4-oxathiane **140**

2.2.2.2 Towards a more complex substrate

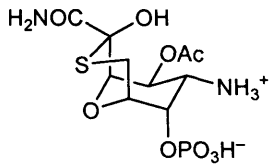
2.2.2.2.1 Strategy and retrosynthesis

Having successfully synthesised the core ring system of tagetitoxin **1a**, our next goal was the synthesis of a more functionalised compound, and we targeted the 5-decarboxy analogue of tagetitoxin **166**. We felt that this compound could be obtained fairly readily from a carbohydrate starting material, and that the late-stage protecting groups manipulations would give valuable information for a subsequent synthesis of the natural product.



1a

tagetitoxin

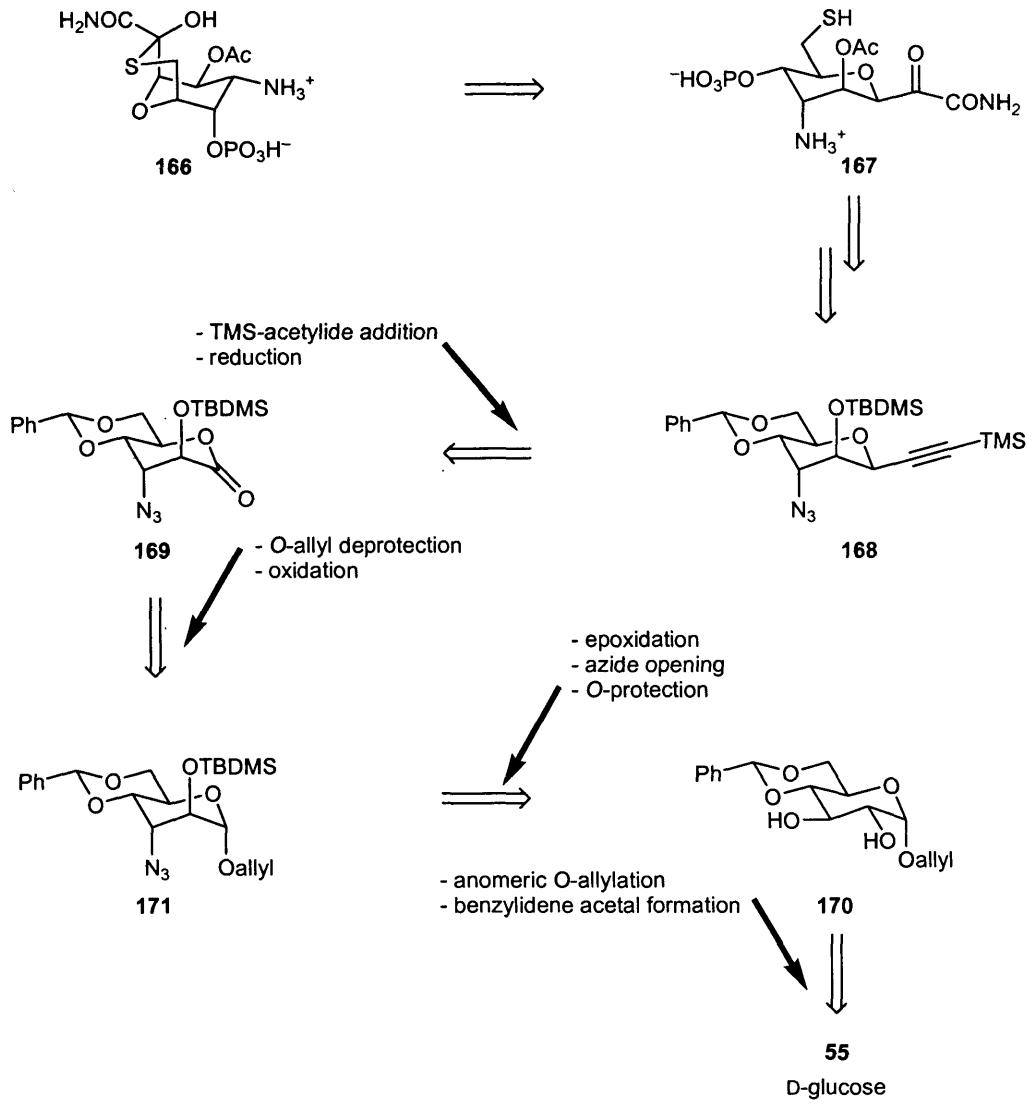


166

5-decarboxy tagetitoxin

Figure 14: Tagetitoxin **1a** and its 5-decarboxy analogue **166**

As can be seen in the retrosynthetic analysis Scheme 64, disconnection of the hemithioacetal bond in 5-decarboxy tagetitoxin **166** yields thiol **167**, which has the D-*altro* configuration. A potential protected precursor to thiol **167** would be azide **168**. Azide **168** could be derived from altronolactone **169** via TMS-acetylide addition and subsequent reduction, both reactions having been developed during the previous synthesis. The *altro*-configuration would be obtained through formation of a β-configured epoxide from diol **170**, followed by *trans*-diaxial ring opening with azide, and protection of the alcohol as a silyl ether to **171**. Diol **170** can be obtained in two steps from D-glucose **55**.

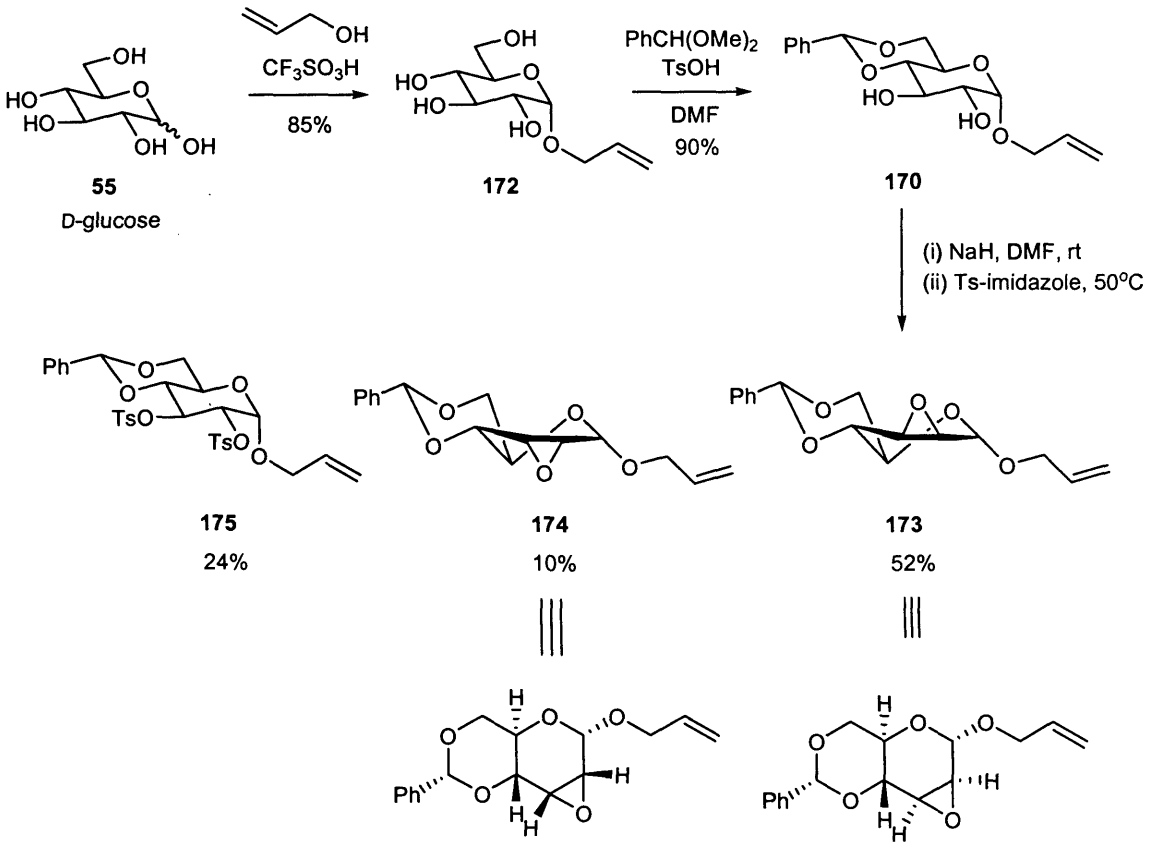


Scheme 64: Retrosynthesis of 5-decarboxy tagetitoxin **166** from D-glucose **55**

2.2.2.2.2 Results

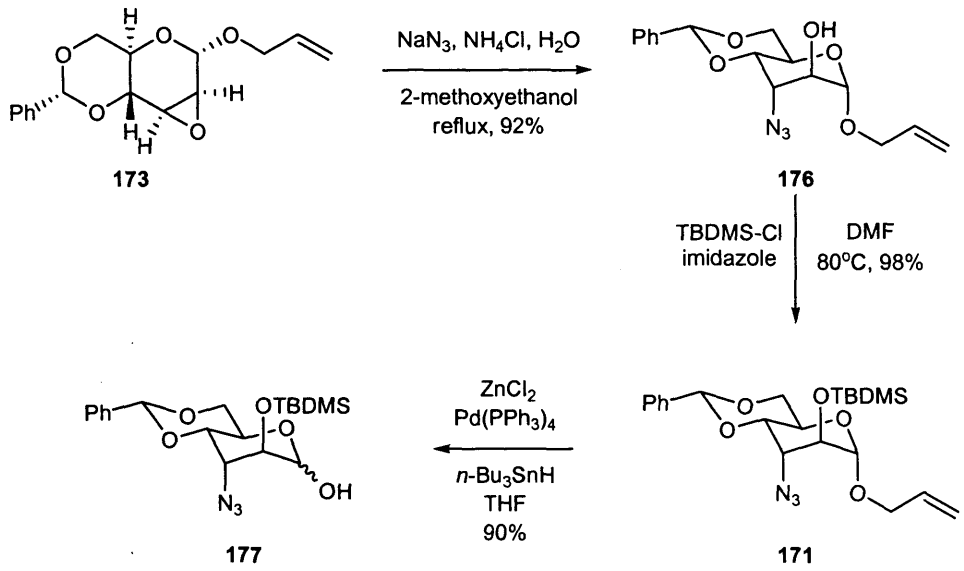
The protection of the anomeric hydroxyl of D-glucose **55** as an allyl ether under acidic conditions yielded exclusively the thermodynamically more stable α-*O*-allyl D-glucopyranoside **172** as a single anomer in 85 % yield (Scheme 65).[118] Protection of the hydroxyls at C-4 and C-6 as a benzylidene acetal proceeded smoothly in 90 % yield giving **170**. Upon treatment of diol **170** with 2.0 equivalents sodium hydride and 1.0 equivalents of *N*-tosylimidazole, as reported by Taylor *et al.*, conversion to the desired epoxide **173** took place in only moderate yield with modest

diastereoselectivity. Epoxide **173**, which bears the desired configuration, isomer **174**, with the opposite configuration and di-*O*-tosylate **175** were isolated in 52 %, 10 % and 24 % yield respectively.



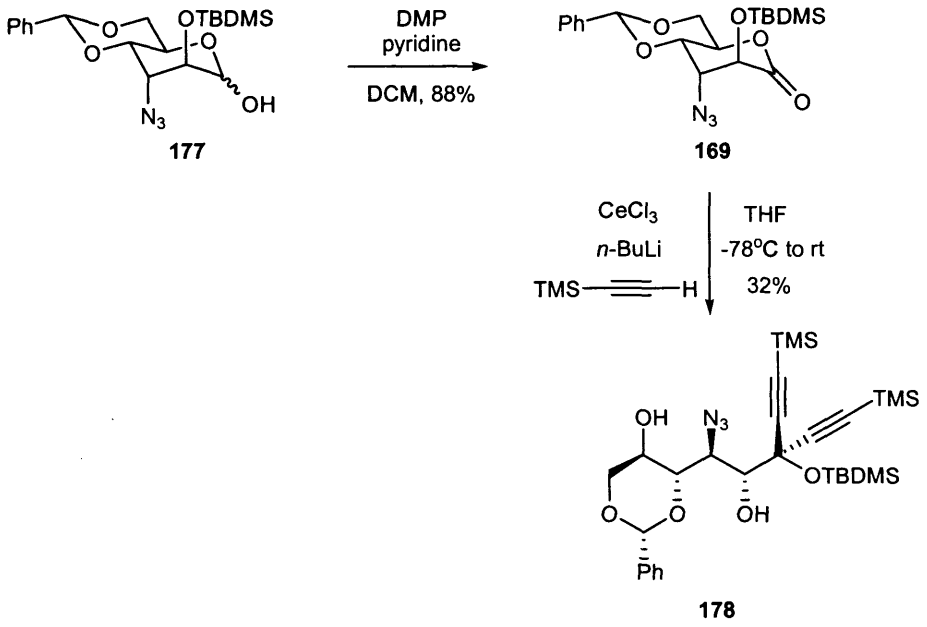
Scheme 65: Synthesis of epoxide **173**

The β-epoxide **173** was opened with sodium azide in a *trans*-diaxial fashion, to yield secondary alcohol **176** in high yield (92 %) (Scheme 66). This was protected as a *tert*-butyldimethylsilyl ether yielding **171** in 98 % yield. Removal of the anomeric allyl protecting group with a stoichiometric amount of palladium(II) chloride, with sodium acetate in a mixture of acetic acid and water gave lactol **177** in 91 % yield,[119] but this was too expensive to carry out on a large scale. More economically, exposure of **171** to a catalytic amount of tetrakis(triphenylphosphine) palladium(0) with tri-*n*-butyltin hydride and zinc chloride in THF,[120] yielded the desired mixture of lactols **177** in 90 % yield.



Scheme 66: Synthetic route to lactol **177**

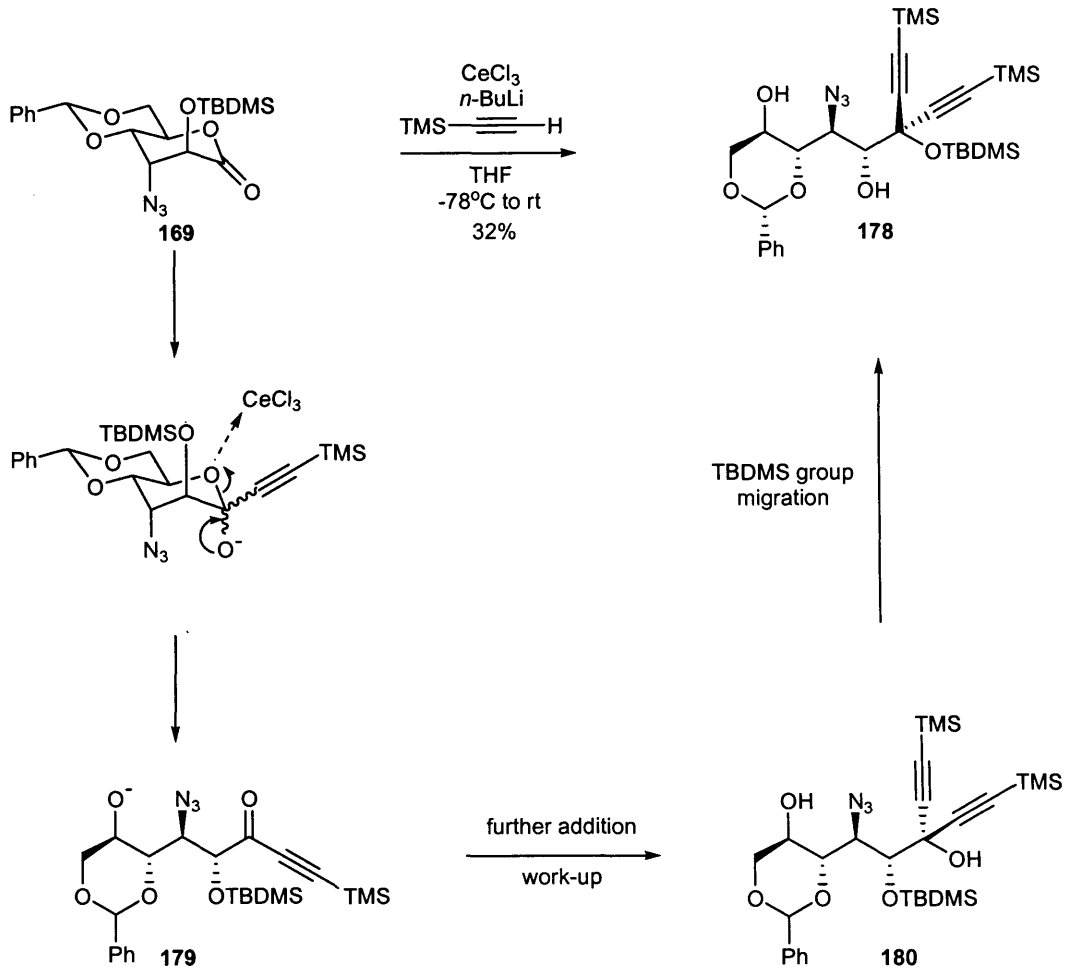
The oxidation of lactols **177** with Dess-Martin periodinane **127** cleanly afforded lactone **169** in 88 % yield (Scheme 67). However, when lactone **169** was subjected to the cerium-acetylide addition reaction, the desired 1,2-addition product was not detected in the crude reaction mixture. Instead, after column chromatography, secondary alcohol **178** was isolated in 32 % yield.



Scheme 67: Formation of secondary alcohol **178**

It is thought that the desired cerium-acetylide addition to lactone **169** occurs as expected (Scheme 68), but does not stop at this stage. After coordination of the ring oxygen to a cerium Lewis acid, ring-opening occurs to form intermediate ketone **179**. At this point, a second cerium acetylide could be added to the ketone to yield tertiary alcohol **180**. The migration of the TBDMS group from the tertiary alcohol to the secondary one takes place; the reason of this migration is not understood but it completes the formation of alcohol **178**.

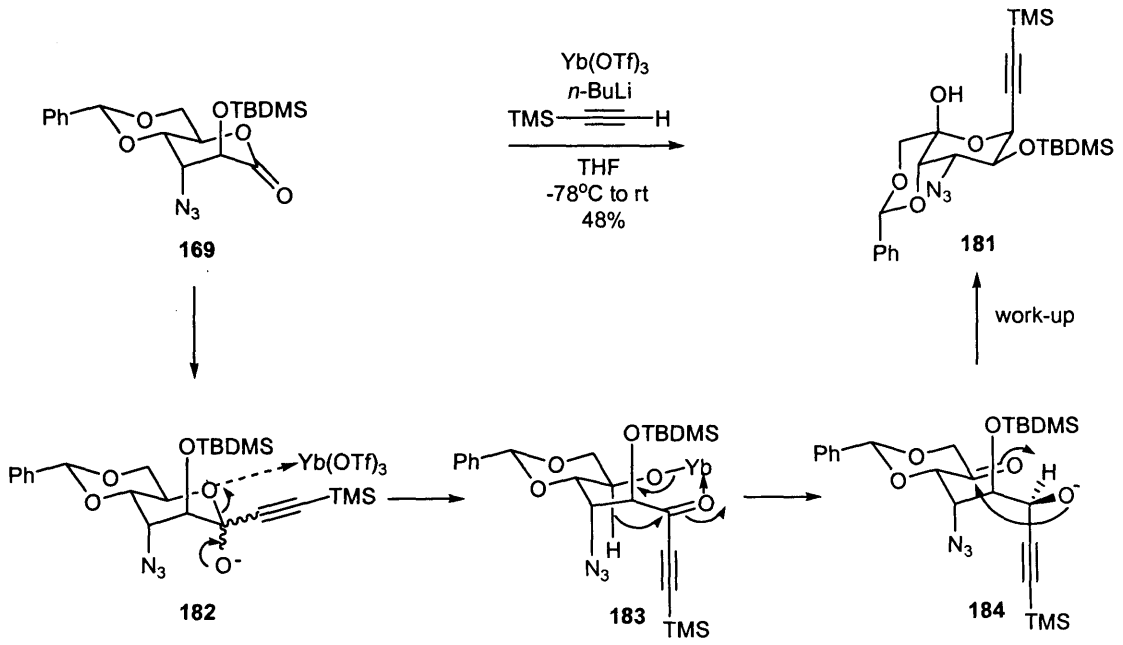
The reasons for the difference in behaviour between lactone **169** and lactone **145** are not understood. The differences between the two are the presence of a benzylidene conformational lock between hydroxyls at C-4 and C-6, the presence of an azide at C-3 and a TBDMS ether at C-2. It is not known how these dissimilarities can account for such a different reactivity.



Scheme 68: Mechanism for the formation of alcohol **197**

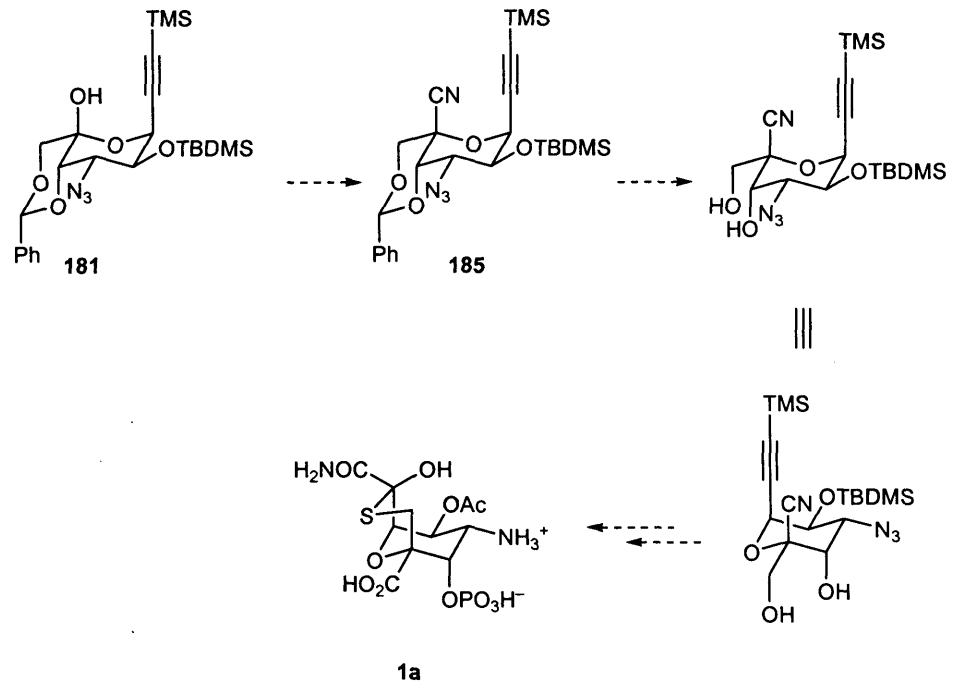
We then decided to carry out the reaction with different organometallic species. Ytterbium triflate can be combined with organolithium reagents to form organoytterbium species, which have been shown to be more nucleophilic than organocerium compounds.[121] Thus, in an analogous experiment to those discussed previously, cerium chloride was replaced with anhydrous ytterbium triflate. However, the desired addition product was again not detected but rather the *trans*-decalin compound **181** in 48 % yield (Scheme 69). In this sequence, the expected ytterbium acetylide addition occurs first yielding addition product **182**. Again, the ring oxygen must be coordinated to some ytterbium species in solution and consequently triggers ring opening to yield ketone **183**. Next, a transannular hydride shift from C-5 to the

ketone yields secondary alcohol **184**. Ring closing then occurs to secure *trans*-decalin compound **181**.



Scheme 69: Synthesis of tertiary alcohol **181**

The net result of this reaction is a selective β-addition of TMS-acetylide, accompanied by reduction of the anomeric carbon and oxidation at C-5. On comparison of the structure of **181** with that of tagetitoxin **1a**, it was realised that if the tertiary OH of **181** could be replaced by a carbon nucleophile such as a cyanide, compound **185** could be the precursor of tagetitoxin **1a** itself, rather than of 5-decarboxy tagetitoxin **166** (Scheme 70).



Scheme 70: From alcohol **201** to tagetitoxin **1a**

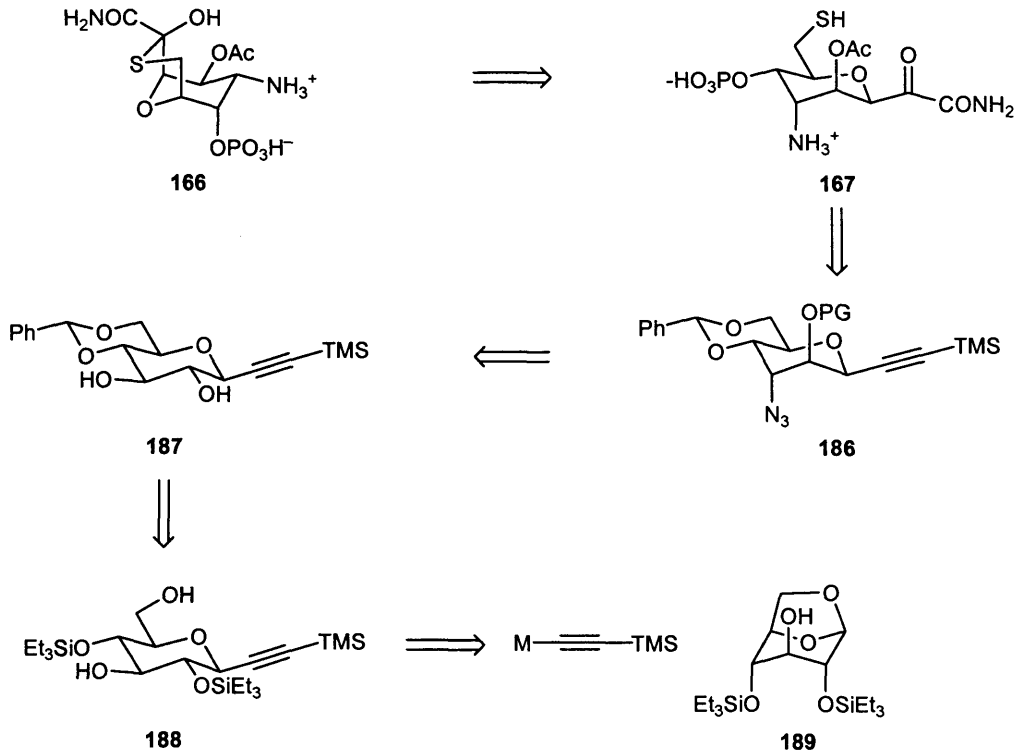
However, attempts to reproduce the reaction all failed, even when rigorous purification procedures were applied to all the reagents and solvents immediately prior to the reaction. In all cases, starting lactone **169** was recovered. The concentration and ratio of reagents were also changed but all efforts remained unsuccessful. It is not known why this reaction was so capricious but compound **181** could not be synthesised again, and so this approach was abandoned.

2.2.2.3 Revised approach

2.2.2.3.1 Strategy and retrosynthesis

The main problem encountered in the previous strategy was the introduction of a TMS-acetylene moiety at the anomeric position of an *altro*-configured sugar. This reaction had not caused any problems with a *gluco*-configured substrate (cf section 2.2.1). Therefore, it was decided to incorporate the acetylene moiety into a *gluco*-

configured lactone, prior to manipulating the stereochemistry at C-2 and C-3. Therefore, the end-game strategy would be the same as the one discussed in section 2.2.2.1. *Trans*-azidoalcohol **186** could be derived from the D-*gluco* configured compound **187** *via* epoxide formation and subsequent opening with sodium azide (Scheme 71). In turn, **187** could be derived from 2,4-*O*-di-Et_3Si-protected compound **188** *via* removal of the silyl protecting groups and formation of a benzylidene acetal between the hydroxyls at C-4 and C-6. Diol **188** has been synthesised previously by Vasella *et al.* and is derived from the opening of 1,6-anhydro sugar **189** with a metal-coordinated acetylide. Bicycle **189** can be synthesised from D-glucose **55** in three steps.[122]



Scheme 71: Retrosynthesis of tagetitoxin **1a**

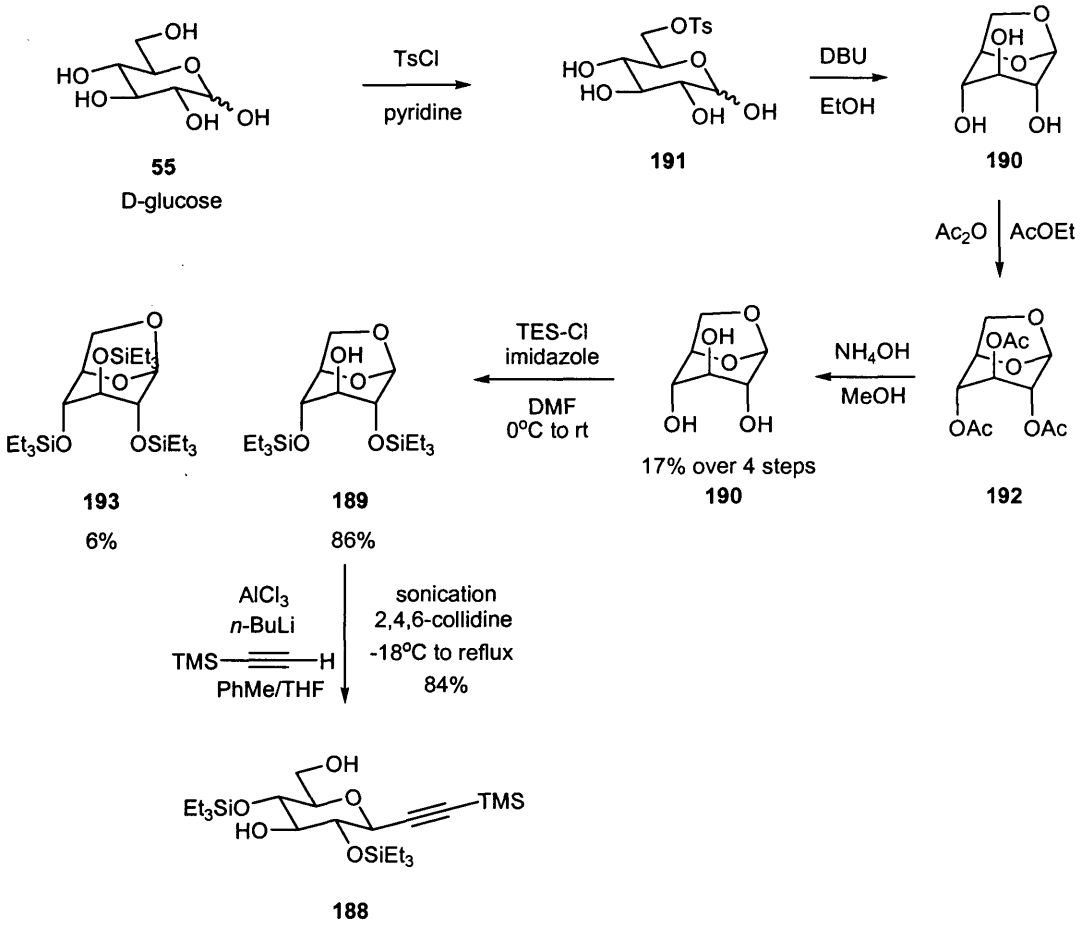
One potential pitfall in this route is the selective sulfonylation of diol **187**. While it is well established that *O*-glycosides such as **170** react selectively at the C-2 hydroxyl, there is little precedent for the reaction of *C*-glycosides such as **187**.

However, if it proved that reaction at the C-3 hydroxyl were preferred, we could modify the route by protecting initially at C-3 prior to sulfonylating the C-2 hydroxyl group.

2.2.2.3.2 Results

The initial task on this route was the synthesis of 1,6-anhydro-D-glucose **190**, which was accomplished by the method of Fraser-Reid.[123] D-Glucose **55** was treated with tosyl chloride in pyridine at room temperature affording primary tosylate **191** as a mixture of anomers (Scheme 72). The crude mixture was treated with DBU in ethanol to initiate cyclisation to 1,6-anydro-D-glucose **190**. The crude mixture was very impure because of the excess DBU used and the impurities carried from the first step, so peracetylation was carried out to obtain triacetate **192** which could be purified by crystallisation. The triacetate **192** was then treated with methanolic ammonia in order to remove the three acetyl protecting groups. Rapid filtration on SiO_2 afforded 1,6-anhydro-D-glucose **190** as a white solid. The hydroxyls at C-2 and C-4 were then protected as TES ethers in 86 % yield affording alcohol **189**.[122] A minor amount of the corresponding trisilylated compound **193** was also isolated (6 %). The next step was found to be more challenging than expected. The initial experiments used non-purified aluminium chloride, and resulted in starting material being recovered quantitatively. Even when freshly sublimed aluminium chloride, weighed out under an inert atmosphere, was used, the reaction was unsuccessful. Under these conditions, when the lithium acetylide solution was added to the suspension of aluminium chloride in toluene, the reaction remained colourless with solid aluminium chloride clearly visible. Ultimately, it was found that sonication of the mixture was required.

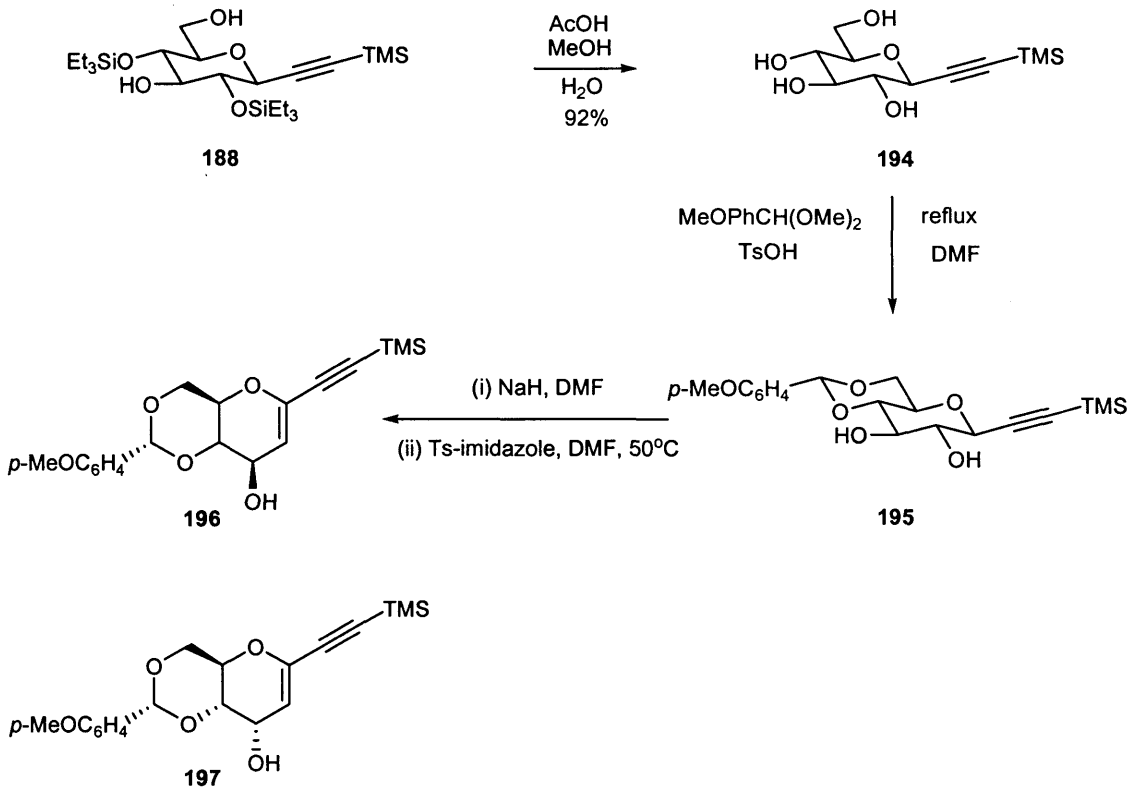
This gave a brown, cloudy suspension, and addition of the 1,6-anhydro sugar **189** to this led to the desired diol **188** in 84 % yield.



Scheme 72: Synthesis of diol **188**

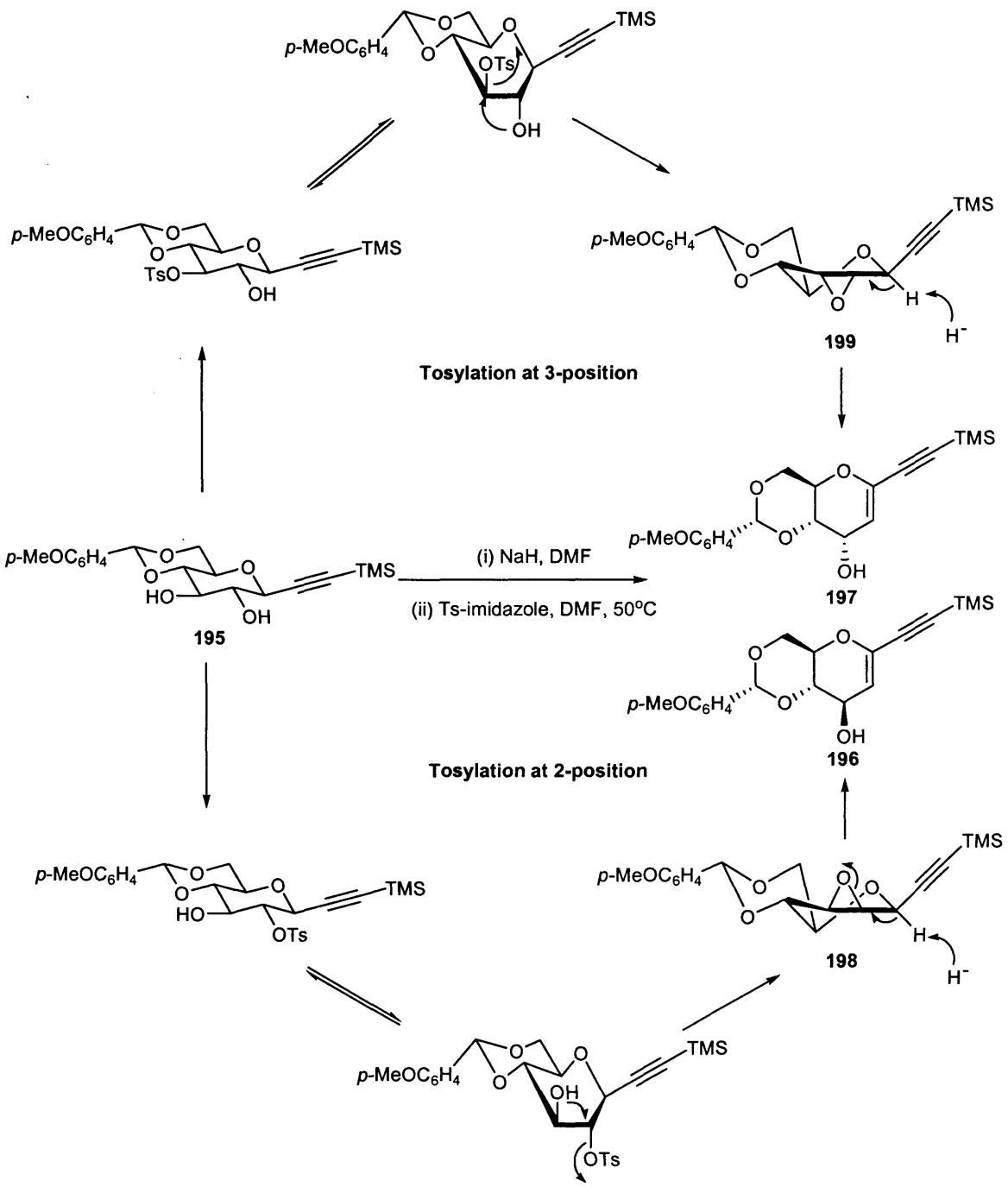
Removal of the silyl protecting groups under acidic conditions afforded tetra-ol **194** in 92 % yield (Scheme 73), but attempts to protect the hydroxyls at C-4 and C-6 as a benzylidene acetal were not satisfactory. When using benzaldehyde dimethyl acetal and an acid catalyst (either tosic acid or freshly fused zinc chloride) in either DMF or acetonitrile, the reaction proceeded very slowly even at reflux temperatures. After two days, a ratio of 1:2 of benzylidene acetal to starting material **194** was detected by ^{1}H NMR spectroscopy of the crude mixture (using tosic acid in acetonitrile at reflux). By contrast, reaction with *p*-anisaldehyde dimethyl acetal and

tosic acid afforded 80 % of the *p*-methoxybenzylidene acetal **195**. The next step involved the formation of an epoxide between C-2 and C-3 in order to invert the stereochemistry at both these centres and hence securing, after epoxide opening, an *altro*-configuration. However, when **195** was treated with sodium hydride followed by tosylimidazole, the two stereoisomeric allylic alcohols **196** and **197** were obtained in 30 % and 31 % respectively.



Scheme 73: Synthesis of stereoisomeric allylic alcohols **196** and **197**

The mechanism proposed for the formation of stereoisomers **196** and **197** is depicted in Scheme 74. It is speculated that unselective tosylation of hydroxyls at C-2 and C-3 must happen first, leading to a mixture of the desired epoxide **198** and its stereoisomer **199**. Loss of a proton at C-1 then opens the epoxides, leading to a mixture of epimers at C-3.



Scheme 74: Mechanism for the formation of allylic alcohols **196** and **197**

The two problems in this reaction are the non-selective tosylation and the undesired elimination from epoxide **198** and **199** to allylic alcohol **196** and **197** respectively. In an attempt to avoid one or both of these problems, a range of different sulfonylation conditions were investigated.

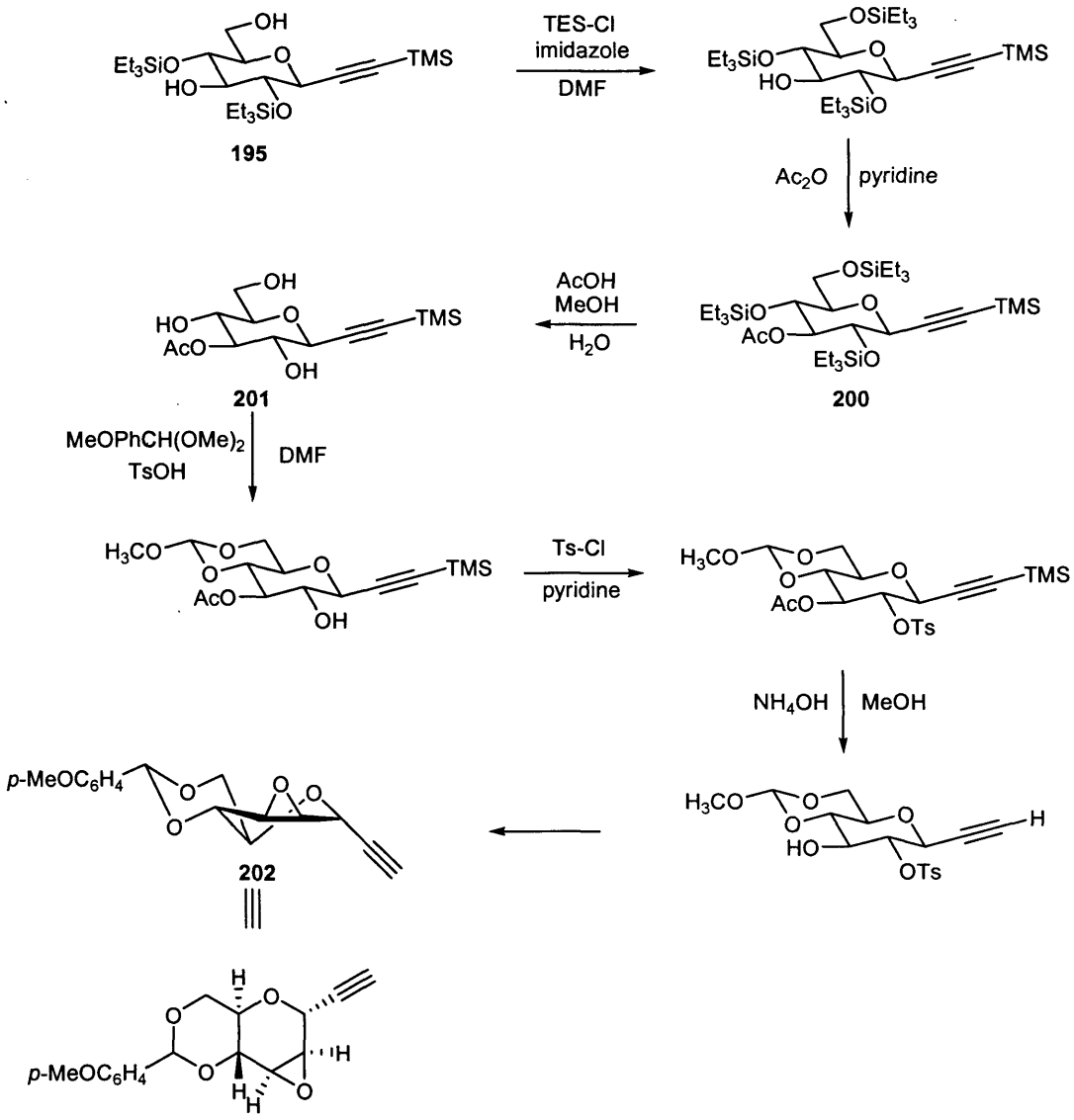
First, the diol **195** was treated with tosyl chloride in pyridine: The reaction was carried out initially at 0 °C and warmed up every two hours to room temperature, then to 60 °C, then to reflux. After a further two hours, DMAP (2.0 equivalents) was added but even after 48 hours at reflux, starting material was recovered.

The corresponding reaction was next carried out with tosyl imidazole in pyridine, and then with tosic anhydride in pyridine: in both cases, starting material was recovered.

With mesyl chloride in pyridine, the reaction did not proceed at 60 °C and at reflux, the starting material decomposed to an unidentified mixture of degradation products.

It appears that, in contrast to the tosylation of *O*-glycosides, the tosylation of *C*-glycoside **195** is unselective. For this reason, the synthetic approach to epoxide **198** has to be revised, and we aim to utilise the protection which is present in diol **195**. Selective protection of the primary alcohol with a triethylsilyl group, will be followed by acetylation of the C-3 alcohol yielding acetate **200** (Scheme 75). Cleavage of the silyl ethers will yield triol **201**. Protection of the alcohols at C-4 and C-6 as an acetal will be followed by tosylation of the C-2 alcohol. Finally, solvolysis of the acetate at C-3 will be followed by formation of the C-2/C-3 β-epoxide **202** (Scheme 75).

While time constraints did not allow investigation of the route shown in Scheme 75, it has recently been brought to fruition by another PhD student in the group, Amandeep Sandhu.



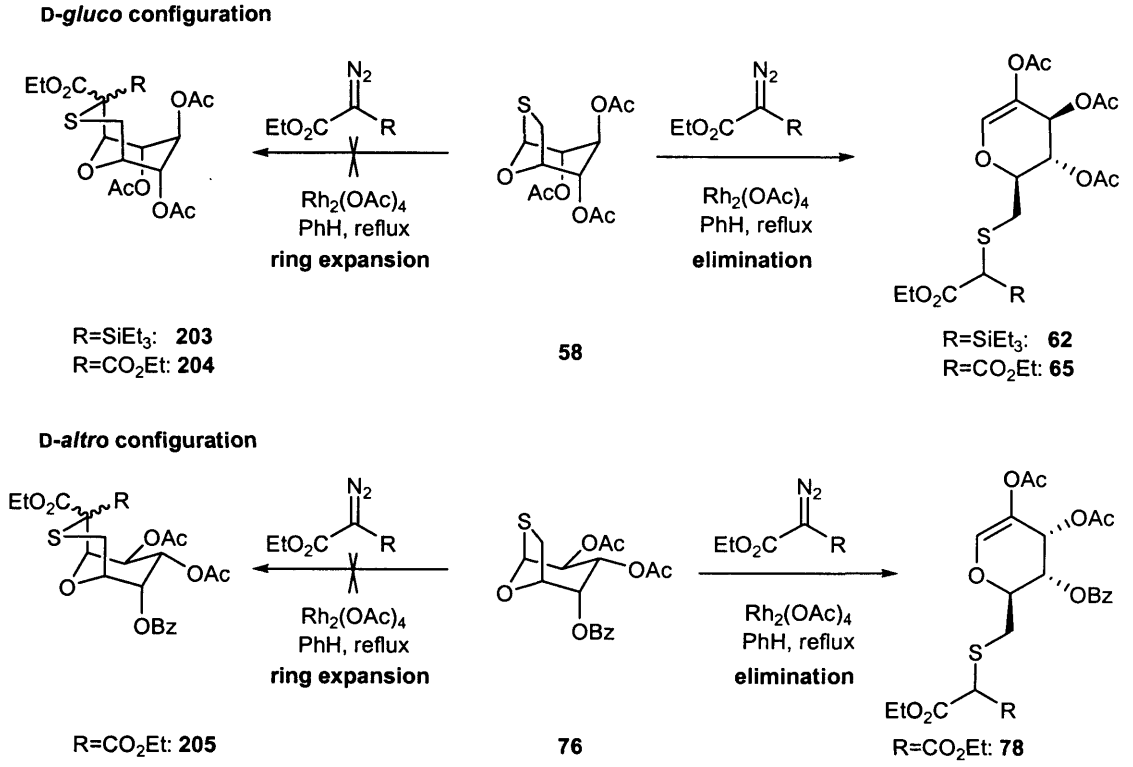
Scheme 75: Future work for the synthesis of epoxide **202**

3 Conclusions and future work

The initial goal of this work was to achieve the total synthesis of tagetitoxin **1**. The latter shows a unique biological activity as a specific inhibitor of RNA polymerase III. A synthetic way to access large quantities of tagetitoxin **1** would be invaluable to the biological community in order to study the mechanism of inhibition of RNA polymerase III. From a synthetic point of view, tagetitoxin **1** is an intriguing

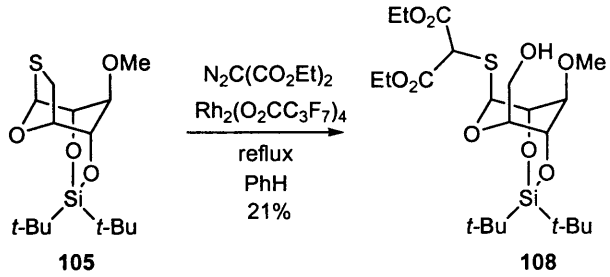
target because its structure is still somewhat ambiguous; however, the most probable structure consists of a 9-oxa-3-thiabicyclo[3.3.1]nonane ring system.

Our initial efforts focused on the synthesis of the core structure of tagetitoxin *via* a ring expansion reaction (Scheme 76). It was demonstrated that, using model systems derived from glucose or altrose, the favoured pathway was elimination instead of the desired ring expansion.



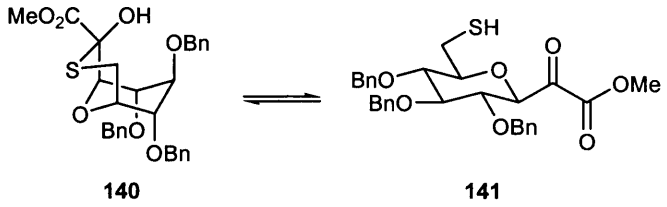
Scheme 76: Unsuccessful attempts of ring expansion reactions

It was thought that the instalment of a conformational lock as in **105** would prevent the elimination process, and that the intermediate oxonium ion would eventually cyclise to the ring expanded product (Scheme 77). However, these efforts proved to be unsuccessful and primary alcohol **108** was isolated.



Scheme 77: Synthesis of primary alcohol **108**

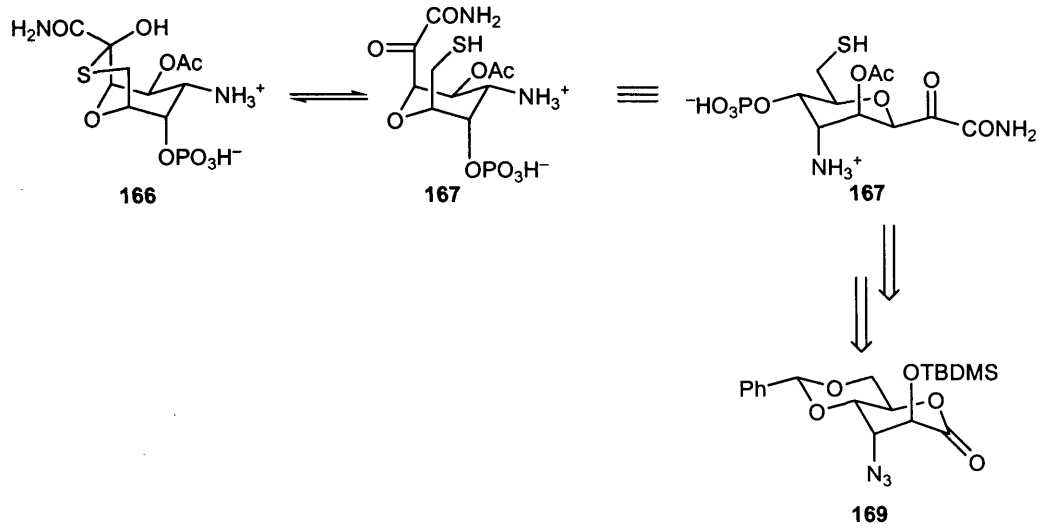
The second approach to the core structure of tagetitoxin **1a** was based on the intramolecular cyclisation of a thiol onto an electron deficient ketone **141** to produce a bicyclic 1,4-oxathiane **140** (Scheme 78).



Scheme 78: Equilibrium between tri-benzyl ether **140** and α-keto ester **141**

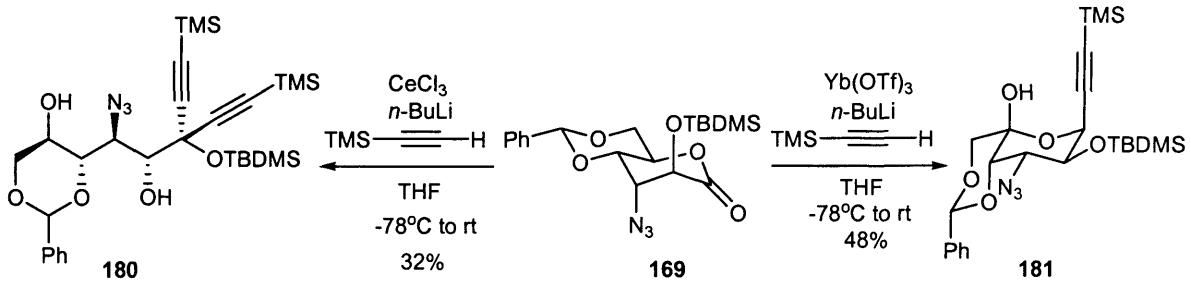
Spontaneous cyclisation to a single diastereomer occurred when thioester **164** was deacetylated. Overall, bicycle **140** was synthesised in 32.5 % yield over 15 steps from D-glucose **55**, providing the first synthesis of the tagetitoxin core structure.

Efforts were then concentrated on the synthesis of a more functionalised target, 5-decarboxytagetitoxin **166** (Scheme 79). Lactone **169** was synthesised in 28.4 % yield over 7 steps from D-glucose **55**.



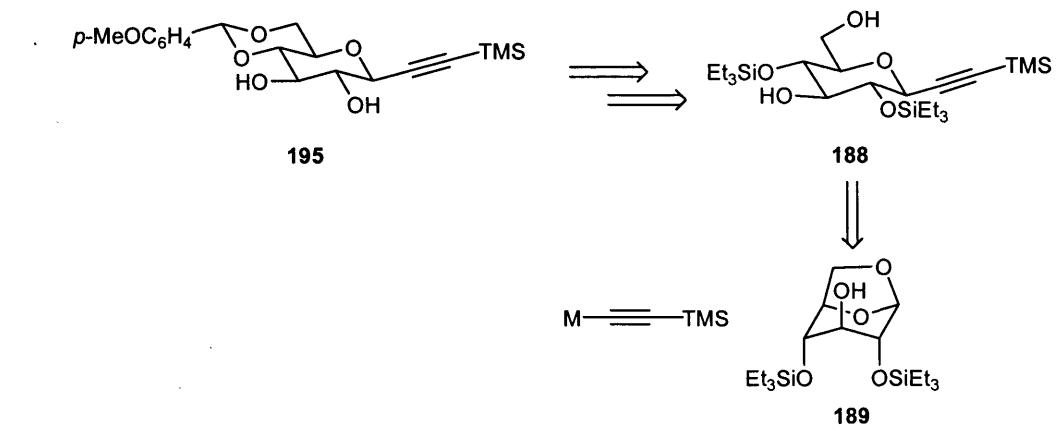
Scheme 79: Retrosynthesis of 5-decarboxytagetitoxin **166**

However, this lactone did not yield the expected addition product with a cerium acetylide (Scheme 80). Instead, opening of the carbohydrate ring to form secondary alcohol **180** occurred in 32 % yield. Changing from cerium to ytterbium led to the formation of azide **181** in 48 % yield. However, this latter result was not reproducible



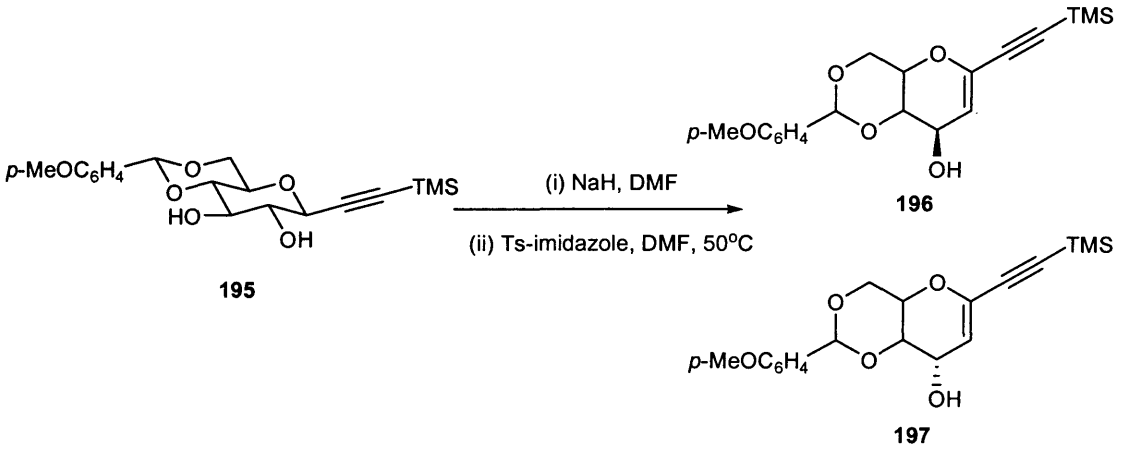
Scheme 80: Synthesis of secondary alcohol **180** and tertiary alcohol **181**

An alternative strategy was therefore designed to introduce the acetylene moiety at an earlier stage, through reaction with 1,6-anhydro-D-sugar **189** (Scheme 81).



Scheme 81: Retrosynthesis of diol **195**

Diol **195** was synthesised from D-glucose **55** in 8 steps in 9 % overall yield. However, the tosylation of this diol was not regioselective and a mixture of tosylates **196** and **197** was obtained in 30 % and 31 % yield respectively (Scheme 82).



Scheme 82: Attempted epoxidation of diol **195**

The future synthetic plan involves selective protection of the alcohol at C-3 prior to tosylation at C-2, resulting in stereoselective epoxide formation. This plan is detailed in Scheme 75, and has recently been carried out within the group. Work is now focusing on the completion of the synthesis of 5-decarboxy tagetitoxin **166** and the natural product itself.

4 Experimental

General experimental

All reactions under non-aqueous conditions were carried out in flame-dried glassware, which was allowed to cool *in vacuo*.

Temperatures

Reactions carried out at –78 °C were cooled by means of an acetone/dry ice bath, those at –10 °C by means of an ice/salt/water bath and those at 0 °C by means of an ice/water bath.

Solvents

THF, MeCN, Et_2O, toluene and DCM used in reactions were collected from the UCL Chemistry anhydrous solvent system (dried by passage through alumina columns under nitrogen). MeOH and chloroform were analytical reagent grade and used as supplied. Benzene, pyridine and DMF were distilled from CaH_2 prior to use. Acetone was distilled from and stored over 3 Å molecular sieves. Where petrol is specified this refers to the fraction that boils in the range 40-60 °C.

Reagents

All starting materials were obtained commercially from Aldrich, Acros, Avocado, Fisher, Lancaster or BDH and were used without further purification unless otherwise stated. Benzaldehyde and 2,6-lutidine were distilled from CaH_2 immediately prior to use. Triethylamine was distilled from potassium hydroxide. 4-Toluenesulfonyl chloride was recrystallised from chloroform/petrol prior to use. Acrolein was distilled twice before use. Ethyl (triethylsilanyl)diazoacetate was prepared according to the literature procedure described by Emde and Simchen.[124] Dess-Martin periodinane **127** was prepared according to the literature procedure described by Liu and Ireland.[125]

Penta-*O*-acetyl-β-D-glucopyranose **146** was prepared according to the literature procedure described by Wolfrom and Wood.[126] Tosyl imidazole was prepared according to the literature procedure by Hicks and Fraser-Reid.[127] 1,6-Anhydro-D-glucose was prepared according to the literature procedure described by Fraser-Reid and Ratcliffe.[128]

Chromatography

Column chromatography was carried out on BDH silica gel (Kieselgel 60), unless otherwise stated. TLC was carried out on Merck plates (aluminium coated with 0.2 mm silica gel 60 F_{254}). Plates were visualised either by UV light (254 nm), aq $KMnO_4$, vanillin in ethanol, or iodine.

Spectroscopy/Spectrometry

IR spectra were recorded either as thin films or as KBr discs using a SHIMADZU FT-IR 8700 spectrometer. Peaks are labelled according to intensity: strong = s, medium = m, weak = w, broad = br.

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 500, 400 or 300 MHz on Bruker AMX-500, AMX-400 or AMX-300 NMR spectrometers respectively. ^{13}C NMR were recorded on the same instruments at 125, 100 or 75 MHz. The spectra were referenced to the solvent peak ($CHCl_3$ in $CDCl_3$ at 7.24 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR). ^{13}C DEPT-45 was used to assist in the assignment of ^{13}C NMR. HMQC and HMBC were used where necessary to assist in assignment and to determine structures. The signals are noted as s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublet, ddddd = doublet of doublet of doublet of doublet of doublet, t = triplet, td = trilplet of doublet, dt = doublet of triplets, m = multiplet and br s = broad singlet. Coupling constants (*J*) are reported in Hz.

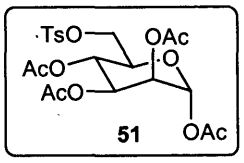
Nuclear Overhauser enhancement experiments were performed by Dr Abil Aliev of the Christopher Ingold Laboratories.

Mass measurements were recorded by Mr John Hill or Dr Lisa Harris of the Christopher Ingold Laboratories on a VG70-SE (CI^+, EI^+, FAB^+) or a Thermo MAT 900 instrument (EI^+, ESP^+). Major peaks are listed with intensities quoted as percentages of the base peak.

Melting points were recorded on an Electrothermal 9100 melting point apparatus.

The microwave oven used was a CEM Discover.

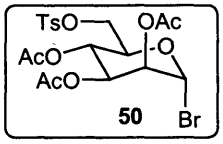
1,2,3,4-Tetra-*O*-acetyl-6-*O*-(4-toluenesulfonyl)-α-D-mannopyranose 51



A solution of *p*-toluenesulfonyl chloride (3.97 g, 20.8 mmol) in pyridine (20 mL) was added to a suspension of D-mannose **48** (2.50 g, 13.9 mmol) in pyridine (20 mL) over 5 minutes with occasional ice-cooling to maintain the internal temperature below 20 °C. The mixture was allowed to warm to RT and stirring was continued for 2 h. Acetic anhydride (6.3 mL, 67 mmol) was then added dropwise, again maintaining the temperature below 20 °C. Stirring was continued for 19 h. The mixture was concentrated *in vacuo*, and the residue redissolved in EtOAc (20 mL), washed with 2M HCl (20 mL), sat aq $CuSO_4$ (20 mL), sat aq $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo* affording the title compound **51** (5.93 g, 87%) as an off-white foam: mp 149-150 °C (Lit.[129] 141-143 °C); $[\alpha]_D^{20}$ = +78.3 (*c* 0.90 in DCM) (Lit.[129] $[\alpha]_D^{20}$ = +81.9, *c* 0.80 in $CHCl_3$); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3150s, 2920s, 2856m, 1756s, 1650m, 1371s, 1220s; δ_H (500 MHz, $CDCl_3$) 7.70 (2H, d, *J* 8.4, CH aromatic), 7.29 (2H, d, *J* 8.4, CH aromatic), 5.94 (1H, d, *J* 2.1, H-1), 5.27 (1H, dd, *J* 10.1, 3.4, H-3), 5.21 (1H, ddd, *J* 11.8, 9.7, 3.8, H-5), 5.16 (1H, dd, *J* 3.4, 2.1, H-2), 5.06 (1H, dd, *J* 10.1, 9.7, H-4), 4.06 (1H, dd, *J* 12.6, 11.8, H-6'), 3.99 (1H, dd, *J* 12.6, 3.8, H-6), 2.40 (3H, s, Ar-CH_3), 2.10 (3H, s, C(O)CH_3), 2.07 (3H, s, C(O)CH_3), 1.98 (3H, s, C(O)CH_3), 1.95 (3H, s, C(O)CH_3); δ_c (125 MHz, $CDCl_3$) 169.7 (C=O), 169.6 (C=O), 169.4 (C=O), 169.0 (C=O), 145.1 (*ipso* C-CH_3), 132.4 (*ipso* C-SO_2), 129.9 (2 × CH aromatic), 128.0 (2 × CH aromatic), 90.1 (C-1), 70.3 (C-4), 68.1 (C-3), 67.9 (C-2), 67.4 (C-6), 65.7 (C-5), 21.6 (Ar-CH_3), 20.9 (C(O)CH_3), 20.8 (C(O)CH_3), 20.7 (C(O)CH_3), 20.4 (C(O)CH_3).

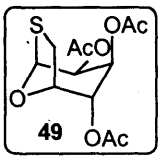
2,3,4-Tri-*O*-acetyl-1-bromo-1-deoxy-6-*O*-(4-toluenesulfonyl)-α-D-mannopyranose

50



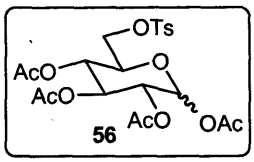
A solution of anomeric acetate **51** (1.50 g, 2.99 mmol) in acetic acid (5 mL) was cooled to 0 °C and then treated with 33% hydrogen bromide solution in acetic acid (8.9 mL, 13.4 mmol). The mixture was allowed to warm to RT and stirred for 18 h. It was then concentrated *in vacuo*; the residue was redissolved in Et_2O (20 mL), washed with water (20 mL), sat aq $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The off-white oil was dried under high vacuum, affording the title compound **50** (1.32 g, 87%) as a yellow foam which was used without further purification: mp 92-94 °C; $[\alpha]_D^{20}$ = +32.6 (*c* 4.50 in DCM); δ_H (500 MHz, $CDCl_3$) 7.67 (2H, d, *J* 8.4, CH aromatic), 7.26 (2H, d, *J* 8.4, CH aromatic), 6.12 (1H, d, *J* 1.8, H-1), 5.55 (1H, dd, *J* 10.1, 3.5, H-3), 5.30 (1H, dd, *J* 3.5, 1.8, H-2), 5.21 (1H, t, *J* 10.1, H-4), 4.12 (1H, dd, *J* 10.1, 3.4, H-6), 4.06 (1H, td, *J* 10.1, 3.4, H-5), 4.02 (1H, t, *J* 10.1, H-6'), 2.36 (3H, s, Ar-CH_3), 2.07 (3H, s, C(O)CH_3), 1.94 (3H, s, C(O)CH_3), 1.92 (3H, s, C(O)CH_3); δ_c (125 MHz, $CDCl_3$) 169.6 (C=O), 169.5 (C=O), 169.3 (C=O), 145.1 (*ipso* C-CH_3), 132.4 (*ipso* C-SO_2), 129.9 (2 × CH aromatic), 128.0 (2 × CH aromatic), 82.7 (C-1), 72.2 (C-3), 71.9 (C-2), 67.7 (C-6), 66.8 (C-5), 65.2 (C-4), 21.6 (Ar- CH_3), 20.6 (C(O)CH_3), 20.4 (C(O)CH_3), 20.4 (C(O)CH_3).

2,3,4-Tri-*O*-acetyl-1,6-thioanhydro-D-mannopyranose 49



Anomeric bromide **50** (100 mg, 0.19 mmol) was dissolved in dry DMF (3 mL) and ethylxanthic acid potassium salt (92 mg, 0.57 mmol) was added at 0 °C. The mixture was then allowed to warm to RT and then heated to 85 °C for 17 h. It was then concentrated *in vacuo* and the residue was dissolved in water (5 mL). The organic material was extracted with diethyl ether (6 × 5 mL). Organic layers were combined and washed with brine (40 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (EtOAc/ petrol 1:2) afforded the title compound **49** (33 mg, 57%) as white crystals: mp 96-98 °C (Lit.[130] 98-99 °C); $[\alpha]_D^{20}$ = –125.0 (*c* 1.20 in DCM) (Lit.[130] $[\alpha]_D^{20}$ = –133.0, *c* 1.22 in $CHCl_3$); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3059s, 2985m, 2307m, 1755s, 1599s, 1425s, 1371s, 1267s; δ_H (300 MHz, $CDCl_3$) 5.44 (1H, d, *J* 4.0, H-1), 5.28 (1H, dd, *J* 5.6, 4.0, H-2), 5.17 (1H, dd, *J* 5.6, 2.1, H-3), 4.81 (1H, dt, *J* 7.5, 1.6, H-5), 4.75 (1H, dd, *J* 2.1, 1.6, H-4), 3.25 (1H, dd, *J* 10.2, 7.5, H-6'), 3.18 (1H, dd, *J* 10.2, 1.6, H-6), 2.14 (3H, s, $C(O)CH_3$), 2.12 (3H, s, $C(O)CH_3$), 2.03 (3H, s, $C(O)CH_3$); δ_c (75 MHz, $CDCl_3$) 169.7 (C=O), 169.6 (C=O), 169.5 (C=O), 81.6 (C-1), 77.9 (C-5), 72.8 (C-4), 67.0 (C-3), 66.4 (C-2), 32.7 (C-6), 20.9 ($C(O)\underline{C}H_3$), 20.8 ($C(O)\underline{C}H_3$), 20.7 ($C(O)\underline{C}H_3$); *m/z* (FAB+) 327 (MNa^+, 100%); HRMS (FAB+) expected MNa^+ ($C_{12}H_{16}O_7SNa$) 327.0514, found 327.0519.

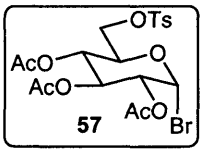
1,2,3,4-Tetra-*O*-acetyl-6-*O*-(4-toluenesulfonyl)-D-glucopyranose 56



A solution of *p*-toluenesulfonyl chloride (3.97 g, 20.8 mmol) in pyridine (20 mL) was added to a suspension of D-glucose **55** (2.50 g, 13.9 mmol) in pyridine (20 mL) over 5 minutes with occasional ice-cooling to maintain the internal temperature below 20 °C. The mixture was then allowed to warm to RT and stirring was continued for 2 h. Acetic anhydride (6.3 mL, 67 mmol) was then added dropwise, again maintaining the temperature below 20 °C. Stirring was continued for 19 h. The mixture was concentrated *in vacuo*, then re-dissolved in EtOAc (20 mL), washed with 2M HCl (20 mL), sat aq $CuSO_4$ (20 mL), sat aq $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*, affording the title compound **56** (5.61 g, 84%), as a mixture of anomers (α:β 2:8) as an off-white foam: mp 129-131 °C; ν_{max} ($CHCl_3$ cast)/cm^{-1} 3155s, 2921s, 2856m, 1759s, 1651m, 1371s, 1217s; δ_H ($CDCl_3$, 500 MHz) *α-anomer* 7.75 (2H, d, *J* 8.2, CH aromatic), 7.35 (2H, d, *J* 7.9, CH aromatic), 6.20 (1H, d, *J* 3.7, H-1), 5.40 (1H, t, *J* 9.7 H-3), 5.00 (1H, t, *J* 9.7, H-4), 4.90 (1H, dd, *J* 9.7, 3.7, H-2), 4.13-4.08 (2H, m, 2 × H-6), 4.13-4.05 (1H, m, H-5), 2.40 (3H, s, $ArCH_3$), 2.10 (3H, s, $C(O)CH_3$), 2.02 (3H, s, $C(O)CH_3$), 2.00 (3H, s, $C(O)CH_3$), 1.95 (3H, s, $C(O)CH_3$), *β-anomer* 7.75 (2H, d, *J* 8.2, CH aromatic), 7.35 (2H, d, *J* 7.9, CH aromatic), 5.63 (1H, d, *J* 8.0, H-1), 5.23 (1H, t, *J* 10.0, H-3), 5.04-5.00 (1H, m, H-2), 5.00 (1H, t, *J* 10.0, H-4), 4.15 (2H, m, 2 × H-6), 3.85 (1H, m, H-5), 2.43 (3H, s, $ArCH_3$), 2.13 (3H, s, $C(O)CH_3$), 2.05 (3H, s, $C(O)CH_3$), 1.99 (3H, s, $C(O)CH_3$), 1.97 (3H, s, $C(O)CH_3$); δ_C ($CDCl_3$, 125 MHz) *α-anomer* 170.0 (C=O), 169.5 (C=O), 169.3 (C=O), 169.2 (C=O), 129.9 (*ipso* C-SO_3), 129.8 (2 × CH aromatic), 128.1 (2 × CH aromatic), 128.0 (*ipso* C-CH_3 aromatic), 88.5 (C-1), 70.4 (C-3), 69.9 (C-5), 69.6 (C-

2), 69.4 (C-4), 67.9 (C-6), 27.8 (Ar-$\underline{C}H_3$) 20.8 (C(O)$\underline{C}H_3$), 20.6 (C(O)$\underline{C}H_3$), 20.5 (C(O)$\underline{C}H_3$), 20.3 (C(O)$\underline{C}H_3$); *β-anomer* 170.0 (C=O), 169.5 (C=O), 169.3 (C=O), 169.2 (C=O), 129.9 (*ipso* $\underline{C}$-SO_3), 129.8 (2 × $\underline{C}$H aromatic), 128.1 (2 × $\underline{C}$H aromatic), 128.0 (*ipso* $\underline{C}$-CH_3Ar), 91.5 (C-1), 72.5 (C-3), 70.0 (C-5), 69.6 (C-2), 69.1 (C-4), 66.9 (C-6), 27.4 (Ar-$\underline{C}H_3$) 20.9 (C(O)$\underline{C}H_3$), 20.7 (C(O)$\underline{C}H_3$), 20.4 (C(O)$\underline{C}H_3$), 20.2 (C(O)$\underline{C}H_3$); *m/z* (FAB+) 525 (MNa^+, 30%), 415 (15), 338 (95), 203 (100); HRMS (FAB+) expected MNa^+ ($C_{19}H_{23}O_{10}SNa$) 525.10426, found 525.10356.

2,3,4-Tri-*O*-acetyl-1-bromo-1-deoxy-6-*O*-(4-toluenesulfonyl)-α-D-glucopyranose 57

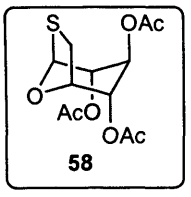


57

Anomeric acetates **56** (1.50 g, 2.99 mmol) were cooled to 0 °C and treated with hydrogen bromide (33% in AcOH, 8.9 mL, 13.4 mmol) solution in acetic acid. Further acetic acid (3 mL) was added in order to completely dissolve the starting material. The mixture was allowed to warm to RT and stirred for 18 h. It was then concentrated *in vacuo*, and the residue re-dissolved in Et_2O (20 mL), then washed with water (20 mL), sat aq $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo* affording the title compound **57** (1.32 g, 87%) as a yellow foam: mp 104-107 °C (Lit.[131] 110 °C); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3160s, 2928s, 2856m, 2255s, 1755s, 1634m, 1371s, 1223s, 1178s, 733s; δ_H ($CDCl_3$, 400 MHz) 7.75 (2H, d, *J* 8.3, CH aromatic), 7.33 (2H, d, *J* 8.3, CH aromatic), 6.45 (1H, d, *J* 4.1, H-1), 5.47 (1H, dd, *J* 10.0, 9.7, H-3), 5.06 (1H, dd, *J* 10.0, 9.7, H-4), 4.69 (1H, dd, *J* 10.0, 4.1, H-2), 4.25 (1H, ddd, *J* 10.4, 10.0, 3.3, H-5), 4.11-4.14 (2H, m, 2 × H-6), 2.44 (3H, s, $ArCH_3$), 2.06 (3H, s, C(O)CH_3), 2.00 (3H, s, C(O)CH_3), 1.98 (3H, s, C(O)CH_3); δ_C

($CDCl_3$, 100 MHz) 169.8 (C=O), 169.6 (C=O), 169.1 (C=O), 145.2 (*ipso* C), 132.4 (*ipso* C), 129.8 (2 × CH aromatic), 128.1 (2 × CH aromatic), 86.0 (C-1), 71.6 (C-5), 70.3 (C-2), 70.0 (C-3), 67.1 (C-4), 66.2 (C-6), 29.6 ($ArCH_3$), 21.6 ($C(O)CH_3$), 20.5 ($C(O)CH_3$), 20.4 ($C(O)CH_3$); *m/z* (FAB+) 545/547 (MNa^+, 45/38%), 430 (48), 338 (80), 226 (12), 203 (20), 165 (100); HRMS (FAB+) expected MNa^+ ($C_{19}H_{23}O_{10}S^{79}BrNa$) 545.0093, found 545.0101.

2,3,4-Tri-*O*-acetyl-1,6-thioanhydro-D-glucopyranose 58

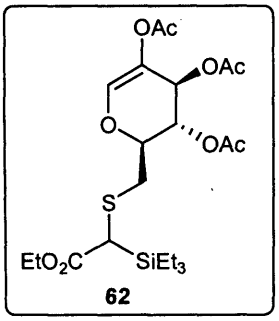


58

Anomeric bromide **57** (100 mg, 191 μmol) was dissolved in dry DMF (3 mL) and cooled to 0 °C, and ethylxanthic acid potassium salt (92 mg, 574 μmol) was then added. The mixture was allowed to warm to RT and then heated to 85 °C for 17 h. It was then concentrated *in vacuo* and the residue dissolved in water (5 mL). The organic material was extracted with EtOAc (6 × 5 mL), then the organic layers were combined and washed with brine (40 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 1:2) afforded the title compound **58** (33 mg, 57%) as white crystals: mp 92-95 °C (Lit.[132] 93-94 °C); $[\alpha]_D^{20} = -27.3$ (*c* 1.25 in DCM) (Lit.[131] $[\alpha]_D^{20} = -50.0$ (*c* 0.95 in $CHCl_3$); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3055s, 2988s, 2307m, 1742s, 1421m, 1371m, 1265s, 1229s; δ_H ($CDCl_3$, 500 MHz) 5.44 (1H, d, *J* 0.6, H-1), 4.96 (1H, dd, *J* 4.4, 3.2, H-3), 4.76 (1H, dt, *J* 10.1, 1.7, H-5), 4.71 (1H, dd, *J* 3.2, 0.6, H-2), 4.62 (1H, dd, *J* 4.4, 1.7, H-4), 3.19 (1H, t, *J* 10.1, H-6'), 3.08 (1H, dd, *J* 10.1, 1.7, H-6), 2.15 (3H, s, $C(O)CH_3$), 2.11 (3H, s, $C(O)CH_3$), 2.05 (3H, s, $C(O)CH_3$); δ_C ($CDCl_3$, 125 MHz) 170.2 (C=O), 170.0 (C=O), 169.4 (C=O), 81.7 (C-1), 79.5 (C-5),

74.1 (C-2), 72.1 (C-4), 69.1 (C-3), 34.4 (C-6), 22.4 (C(O)$\underline{C}H_3$), 21.6 (C(O)$\underline{C}H_3$), 20.9 (C(O)$\underline{C}H_3$); *m/z* (FAB+) 305 (MH^+, 25%), 203 (100); HRMS (FAB+) expected MH^+ ($C_{12}H_{17}O_7S$) 305.0695, found 305.0697.

Ethyl (2'*S*, 3'*S*, 4'*S*)-2-(3,4,5-triacetoxy-3,4-dihydro-2*H*-pyran-2-ylmethylsulfanyl)-2-triethylsilanylacetate 62

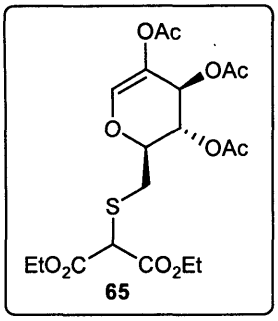


62

Tri-acetate **58** (100 mg, 330 μmol) and rhodium acetate dimer (16 mg, 33 μmol) were placed and dissolved in dry benzene (2 mL). The mixture was heated to reflux and a solution of ethyl diazo(triethylsilanyl)acetate (98 mg, 430 μmol) in dry benzene (1 mL) was added dropwise over 10 min. The mixture was refluxed for a further 23 h, allowed to cool to RT and concentrated *in vacuo*. Column chromatography (Florisil® petrol/EtOAc 10:1) afforded the title compound **62** (56 mg, 34%) as a yellow oil: $[\alpha]_D^{20}$ = –56.5 (*c* 2.05 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3055s, 2986s, 2961s, 2877m, 2684m, 2411m, 2305m, 1746s, 1721s, 1421m, 1371s, 1265m, 1223s, 1151s; δ_H ($CDCl_3$, 500 MHz) 6.60 (1H, s, H-6'), 5.44 (1H, ddd, *J* 4.0, 1.2, 0.8, H-4'), 5.34 (1H, dd, *J* 4.0, 3.2, H-3'), 4.35 (1H, ddd, *J* 7.1, 3.2, 1.2, H-2'), 4.18 (2H, q, *J* 7.2, CO_2-$C\underline{H}_2CH_3$), 3.30 (1H, s, $SC\underline{H}CO_2Et$), 2.86 (1H, d, *J* 7.3, $C\underline{H}_2SCHCO_2Et$), 2.84 (1H, dd, *J* 7.3, 7.1, $C\underline{H}_2SCHCO_2Et$), 2.08 (3H, s, $C(O)CH_3$), 2.07 (3H, s, $C(O)CH_3$), 2.04 (3H, s, $C(O)CH_3$), 1.26 (3H, t, *J* 7.2, $CO_2CH_2C\underline{H}_3$), 0.96 (9H, t, *J* 7.7, ($Si(CH_2C\underline{H}_3)_3$), 0.69 (6H, q, *J* 7.7, ($Si(C\underline{H}_2CH_3)_3$); δ_C ($CDCl_3$, 125 MHz) 172.6 (C=O), 170.1 (C=O),

169.6 (C=O), 169.5 (C=O), 139.0 (C=CH), 127.1 (C=CH), 75.2 (C-2'), 68.9 (C-3'), 65.7 (C-4'), 61.0 ($\underline{C}H_2CH_3$), 35.4 ($\underline{C}HSi(CH_2CH_3)_3$), 32.3 ($\underline{C}H_2$-S), 20.9 ($C(O)\underline{C}H_3$), 20.8 ($C(O)\underline{C}H_3$), 20.5 ($C(O)\underline{C}H_3$), 14.3 ($CO_2CH_2\underline{C}H_3$), 7.1 ($Si(CH_2\underline{C}H_3)_3$), 2.7 ($Si(\underline{C}H_2CH_3)_3$); *m/z* (FAB+) 527 ($MNa^+$, 100%), 343 (12), 145 (22); HRMS (FAB+) expected MNa^+ ($C_{22}H_{36}O_9SSiNa$) 527.1747, found 527.1735.

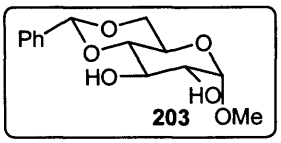
Diethyl(2'*S*, 3'*S*, 4'*S*)-2-(3,4,5-triacetoxy-3,4-dihydro-2*H*-pyran-2-ylmethylsulfanyl)malonate 65



Tri-acetate **58** (100 mg, 330 μmol) and rhodium acetate dimer (16 mg, 33 μmol) were placed and dissolved in dry benzene (2 mL). The mixture was heated to reflux and a solution of diethyl diazomalonate (80 mg, 430 μmol) in dry benzene (1 mL) was added dropwise over 10 min. The mixture was refluxed for a further 23 h, allowed to cool to RT and concentrated *in vacuo*. Column chromatography (Florisil® petrol/EtOAc 7:1) afforded the title compound **65** (56 mg, 44%) as a colourless oil: $[\alpha]_D^{20} = -32.7$ (*c* 0.25 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 2986m, 2939m, 2856m, 1732s, 1682m, 1634m, 1372m, 1223m, 1151m; δ_H ($CDCl_3$, 500 MHz) 6.61 (1H, s, C=CH), 5.51 (1H, d, *J* 3.8, H-4'), 5.28 (1H, dd, *J* 5.1, 3.8, H-3'), 4.40 (1H, ddd, *J* 7.6, 6.0, 5.1, H-2'), 4.28 (1H, s, $S\underline{C}H(CO_2Et)_2$), 4.24 (2H, q, *J* 7.1, $CO_2\underline{C}H_2CH_3$), 4.23 (2H, q, *J* 7.1, $CO_2\underline{C}H_2CH_3$), 3.15 (1H, dd, *J* 14.4, 7.6, $\underline{C}H_2SCHCO_2Et$), 3.06 (1H, dd, *J* 14.4, 6.0, $\underline{C}H_2SCHCO_2Et$), 2.11 (3H, s, $C(O)CH_3$), 2.10 (3H, s, $C(O)CH_3$), 2.08 (3H, s,

C(O)CH_3), 1.29 (3H, t, *J* 7.1, CO_2-$CH_2C\underline{H}_3$), 1.28 (3H, t, *J* 7.1, CO_2-$CH_2C\underline{H}_3$); δ_C ($CDCl_3$, 125 MHz) 170.5 (C=O), 170.0 (C=O), 169.9 (C=O), 167.1 (C=O), 167.0 (C=O), 139.4 (C=$\underline{C}$H), 127.8 ($\underline{C}$=CH), 75.8 (C-2'), 69.6 (C-3'), 66.4 (C-4'), 62.9 (2 × $\underline{C}H_2CH_3$), 51.2 ($\underline{C}H(CO_2Et)_2$), 30.9 ($\underline{C}H_2S$), 21.2 (C(O)$\underline{C}H_3$), 20.9 (C(O)$\underline{C}H_3$), 14.4 (2 × $CH_2\underline{C}H_3$); *m/z* (FAB+) 485 (MNa^+, 15%), 413 (33), 349 (10), 326 (14), 217 (16), 199 (26), 165 (100); HRMS (FAB+) expected MNa^+ ($C_{19}H_{26}O_{11}SNa$) 485.1096, found 485.1101.

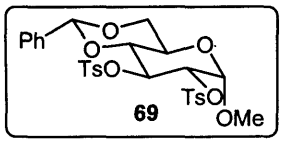
Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 203



A mixture of benzaldehyde (136 g, 1.29 mol), methyl-α-D-glucopyranoside **68** (50 g, 257 mmol) and freshly fused and powdered zinc chloride (38.5 g, 283 mmol) was stirred vigorously for 10 h. The reaction mixture was allowed to stand at RT for 24 h then poured onto crushed ice (700 mL). The mixture was stirred and the solid filtered off and washed with petrol (1.5 L). The solid was then shaken with a solution of sodium metabisulfite (20 g) in water (200 mL), filtered off and dried in a vacuum desicator (P_2O_5) for 18 h, then recrystallised ($CHCl_3/Et_2O$) affording the title compound **203** (48.9 g, 68%) as a white solid: mp 164-166 °C (Lit.[72] 165 °C); $[\alpha]_D^{22}$ = +90.5 (*c* 1.28 in DCM) (Lit.[72] $[\alpha]_D^{22}$ = +112, *c* 0.5 in $CHCl_3$); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3445s, 3053m, 2986m, 1421m, 1385m, 1265s; δ_H ($CDCl_3$, 500 MHz) 8.02-7.91 (2H, m, CH aromatic), 7.60-7.54 (1H, m, CH aromatic), 7.46-7.37 (2H, m, CH aromatic), 5.52 (1H, s, PhC$\underline{H}$), 4.74 (1H, d, *J* 3.9, H-1), 4.28 (1H, dd, *J* 9.5, 3.6, H-6), 3.92 (1H, t, *J* 9.2, H-3), 3.81-3.77 (1H, m, H-5), 3.71 (1H, t, *J* 9.5, H-6'), 3.61 (1H, dd, *J* 9.2,

3.9, H-2), 3.48 (1H, t, *J* 9.2, H-4), 3.45 (3H, s, OCH_3), 2.67 (1H, broad s, 2-O<u>H</u>), 2.56 (1H, broad s, 3-O<u>H</u>); δ_C ($CDCl_3$, 125 MHz) 130.2 (CH aromatic), 129.0 (2 × CH aromatic), 128.1 (*ipso* C), 127.6 (2 × CH aromatic), 101.4 (Ph<u>C</u>H) 99.8 (C-1), 81.0 (C-4), 72.4 (C-2), 70.4 (C-3), 68.6 (C-6), 62.0 (C-5), 54.9 (OCH_3); *m/z* (EI+) 282 (M^+, 20%), 193 (100), 179 (30), 162 (18), 133 (34); HRMS (EI+) expected M^+ ($C_{14}H_{18}O_6$) 282.1103, found 282.1107.

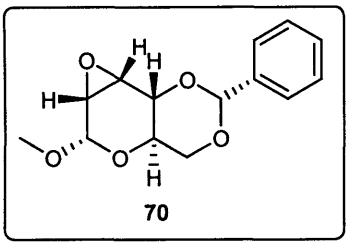
Methyl-4,6-*O*-benzylidene-2,3-di-*O*-(4-toluenesulfonyl)-α-D-glucopyranoside 69



4-Toluenesulfonyl chloride (82.00 g, 0.430 mol) was dissolved in pyridine (200 mL) with occasional ice-cooling to maintain the internal temperature below 20 °C. The solution was stirred for 30 min before diol **203** (43.5 g, 0.155 mol) was added. The reaction mixture was stirred for 5 days then concentrated *in vacuo.* The residue was dissolved in EtOAc (300 mL), washed with 2M HCl (300 mL), H_2O (300 mL), sat aq $CuSO_4$ (300 mL), sat aq $NaHCO_3$ (300 mL) and brine (300 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The resulting crude oil was crystallised from $CHCl_3/Et_2O$ affording the title compound **69** (87.5 g, 96%) as a white solid: mp 151-153 °C (Lit.[72] 152-154 °C); $[\alpha]_D^{22}$ = +1.0 (*c* 1.40 in DCM) (Lit.[72] $[\alpha]_D^{22}$ = +11.8, *c* 1.00 in $CHCl_3$); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3055s, 2986m, 2939m, 1599m, 1421s, 1371m, 1265s; δ_H ($CDCl_3$, 500 MHz) 7.84-7.99 (2H, m, CH aromatic), 7.62-7.58 (2H, m, CH aromatic), 7.31-7.23 (7H, m, CH aromatic), 6.91-6.88 (2H, m, CH aromatic), 5.30 (1H, s, OCHO), 5.08 (1H, t, *J* 9.3, H-3), 5.03 (1H, d, *J* 3.6, H-1), 4.41 (1H, dd, *J* 9.3, 3.6, H-2), 4.24 (1H, dd, *J* 10.3, 4.8, H-6), 3.84 (1H, ddd, *J* 9.8, 9.6, 4.6, H-5), 3.65 (1H, dd, *J* 10.3, 10.1, H-6'), 3.50 (1H, dd, *J* 9.6, 9.3, H-4), 3.40 (3H, s, OCH_3), 2.45 (3H, s,

$ArCH_3$), 2.25 (3H, s, $ArCH_3$); δ_C ($CDCl_3$, 125 MHz) 145.4 (*ipso* C), 144.2 (*ipso* C), 133.8 (*ipso* C), 132.4 (*ipso* C), 129.9 (2 × CH aromatic), 129.7 (2 × CH aromatic), 129.5 (CH aromatic), 128.4 (2 × CH aromatic), 128.0 (2 × CH aromatic), 126.6 (*ipso* C), 126.4 (2 × CH aromatic), 126.3 (2 × CH aromatic), 101.9 (C-1), 101.3 (PhCH), 98.5 (C-4), 78.9 (C-2), 75.8 (C-3), 68.6 (C-6), 62.3 (C-5), 55.7 (OCH_3), 21.8 ($ArCH_3$), 21.7 ($ArCH_3$); *m/z* (EI+) 590 (M^+, 25%), 435 (52), 375 (100), 269 (50), 203 (37); HRMS (EI+) expected M^+ ($C_{28}H_{30}O_{10}S_2$) 590.1280, found 590.1283.

Methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside 70

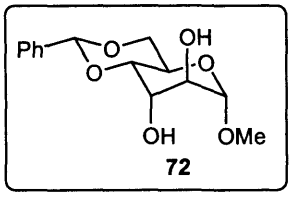


70

In a 2-necked round bottom flask equipped with a pressure-equalizing funnel and $CaCl_2$ guard tube was placed a solution of ditosylate **69** (2.90 g, 5.94 mmol) in dry DCM (40 mL). The solution was cooled to 0 °C and a solution of sodium methoxide in dry methanol (prepared from sodium (680 mg) and methanol (12 mL) was added dropwise. When the addition was complete, the flask was stoppered and left in the fridge for 48 h and then at RT for 24 h. The organic solution was repeatedly washed with H_2O until the aqueous washings were neutral. The organic solution was dried ($MgSO_4$) and concentrated *in vacuo* affording the title compound **70** (1.30 g, 100%) as a white solid: mp 195-197 °C (Lit.[72] 195-199 °C); $[\alpha]_D^{25}$ = +152.8 (*c* 1.18 in DCM) (Lit.[72] $[\alpha]_D^{25}$ = +140, *c* 2.00 in $CHCl_3$); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3055s, 2986m, 2930m, 1467m, 1450m 1421s, 1390m, 1265s; δ_H ($CDCl_3$, 500 MHz) 7.48-7.45 (2H, m, CH aromatic), 7.37-7.33 (3H, m, CH aromatic), 5.55 (1H, s, OCHO), 4.87 (1H, d, *J* 2.8,

H-1), 4.22 (1H, dd, *J* 10.3, 5.0, H-6), 4.06 (1H, ddd, *J* 9.7, 9.2, 5.0, H-5), 3.93 (1H, dd, *J* 9.2, 1.1, H-4), 3.66 (1H, dd, *J* 10.3, 9.7, H-6'), 3.50 (1H, dd, *J* 4.3, 1.0, H-3), 3.48 (1H, dd, *J* 4.3, 2.8, H-2), 3.46 (3H, s, OCH_3); δ_C ($CDCl_3$, 125 MHz) 137.2 (*ipso* C), 129.3 (CH aromatic), 128.3 (2 × CH aromatic), 126.3 (2 × CH aromatic), 102.8 (OCHO), 95.3 (C-1), 77.9 (C-5), 68.9 (C-6), 60.1 (C-4), 55.9 (C-2), 53.2 (C-3), 50.7 ($O\text{-}CH_3$); *m/z* (EI+) 264 (M^+, 80%), 221 (38), 162 (100), 149 (20), 127 (54); HRMS (EI+) expected M^+ ($C_{14}H_{17}O_5$) 264.0998, found 264.0993.

Methyl 4,6-*O*-benzylidene-α-D-altropyranoside 72

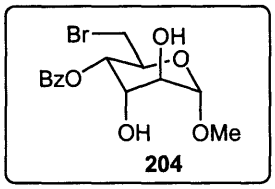


72

Epoxide **70** (1.30 g, 4.92 mmol) was triturated in a mortar with a solution of potassium hydroxide (1.66 g, 29.5 mmol) and water (50 mL). The suspension was transferred to a round bottom flask and heated to reflux until all of the solid had dissolved (22 h). The solution was then allowed to cool and neutralised with solid carbon dioxide. The organic material was extracted with DCM (5 × 20 mL). The combined organic extracts were washed with water (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting syrup was crystallised by scratching a small portion on a watch glass with Et_2O. The bulk syrup and seed crystals were stirred with Et_2O (30 mL) and the resulting crystals were filetered off; these were then recrystallised from methanol to afford the title compound **72** (1.23 g, 89%) as white prisms: mp 173-175 °C (Lit. 107-108 °C); $[\alpha]_D^{20}$ = +107.6 (*c* 1.30 in DCM) (Lit.[72] $[\alpha]_D^{20}$ = +126, *c* 3.0 in $CHCl_3$); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3423br, 3055s, 2986m, 2930m, 1452s, 1421s, 1375s, 1265s; δ_H (CD_3OD, 300 MHz) 7.48-7.45 (2H, m, CH aromatic),

7.35-7.32 (3H, m, CH aromatic), 5.62 (1H, s, OCHO), 4.59 (1H, d, *J* 1.1, H-1), 4.24 (1H, dd, *J* 9.6, 5.1, H-6), 4.22 (1H, dd, *J* 9.6, 5.1, H-4), 4.02 (1H, dd, *J* 5.2, 3.1, H-3), 4.00 (1H, td, *J* 9.6, 5.1, H-5), 3.84 (1H, dd, *J* 3.2, 1.1, H-2), 3.81 (1H, t, *J* 9.6, H-6'), 3.37 (1H, s, OCH_3); δ_C (CD_3OD, 75 MHz) 139.3 (*ipso* C), 129.9 (CH aromatic), 129.1 (2 × CH aromatic), 127.6 (2 × CH aromatic), 103.5 (OCHO), 103.4 (C-1), 77.9 (C-5), 72.1 (C-2), 70.3 (C-6), 70.2 (C-4), 59.5 (C-3), 55.7 (OCH_3); *m/z* (EI+) 283 (M^+, 6%), 221 (100), 179 (87), 162 (73), 145 (24), 133 (92), 107 (90); HRMS (EI+) expected M^+ ($C_{14}H_{18}O_6$) 282.1103, found 282.1091.

Methyl 4-*O*-benzoyl-6-bromo-6-deoxy-α-D-altropyranoside 204

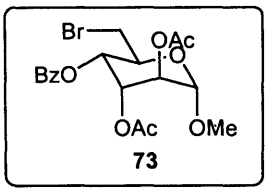


204

Diol **72** (100 mg, 0.36 mmol), was dissolved in $CHCl_3$ (2 mL), and barium carbonate (14 mg, 0.07 mmol) followed by *N*-bromosuccinimide (76 mg, 0.43 mmol) were added. The reaction mixture was heated to reflux (1 h). The resulting mixture was then concentrated *in vacuo*, re-dissolved in Et_2O (5 mL) and washed with H_2O (3 × 5 mL). The organic solution was dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (petrol/EtOAc 3:2) afforded the title compound **204** (96 mg, 74%) as a brown solid: mp 165-168 °C; $[\alpha]_D^{20}$ = –54.9 (*c* 0.65 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3430br, 3053s, 2988m, 1745s, 1421s, 1265s, 743s; δ_H ($CDCl_3$, 400 MHz) 8.04-8.00 (2H, m, CH aromatic), 7.60-7.54 (1H, m, CH aromatic), 7.47-7.42 (2H, m, CH aromatic), 5.26 (1H, dd, *J* 9.8, 3.3, H-4), 4.77 (1H, d, *J* 1.7, H-1), 4.34 (1H, ddd, *J* 9.8, 7.8, 2.7, H-5), 4.23 (1H, dd, *J* 4.3, 3.3, H-3), 3.98 (1H, dd, *J* 4.3, 1.7, H-2), 3.61 (1H, dd, *J* 11.1, 2.7, H-6), 3.55 (1H, dd, *J* 11.1, 7.8, H-6'), 3.49 (3H, s, OCH_3); δ_C ($CDCl_3$,

100 MHz) 165.6 (C=O), 133.5 (*ipso* C), 130.0 (CH aromatic), 129.9 (2 × CH aromatic), 129.8 (2 × CH aromatic), 101.5 (C-1), 69.7 (C-2), 69.5 (C-4), 68.9 (C-5), 66.4 (C-3), 55.9 (OCH_3), 32.4 (C-6); *m/z* (EI+) 361/363 (M^+, 7/5%), 295 (12), 223 (43), 162 (100), 199 (56); HRMS (EI+) expected M^+ ($C_{14}H_{17}{}^{79}BrO_6$) 360.0209, found 360.0213.

Methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-bromo-6-deoxy-α-D-altropyranoside 73

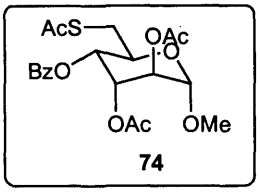


73

Acetic anhydride (63 μL, 0.67 mmol) was added to a solution of diol **204** (100 mg, 0.28 mmol) in dry pyridine (2 mL). The reaction mixture was stirred at RT (18 h) and then concentrated *in vacuo*. The residue was re-dissolved in EtOAc (5 mL), washed with 2M HCl solution (5 mL), H_2O (5 mL) sat aq $CuSO_4$ (5 mL), sat aq $NaHCO_3$ (5 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (petrol/EtOAc 5:1) afforded the title compound **73** (110 mg, 89%) as a light brown solid: mp 145-147 °C; $[\alpha]_D^{20}$ = +55.5 (*c* 1.99 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3057s, 2968m, 1747s, 1732s, 1421s, 1371s, 1265s, 738s; δ_H ($CDCl_3$, 300 MHz) 7.96-7.90 (2H, m, CH aromatic), 7.58-7.54 (1H, m, CH aromatic), 7.44-7.41 (2H, m, CH aromatic), 5.35 (1H, dd, *J* 3.8, 3.2, H-3), 5.32 (1H, dd, *J* 9.3, 3.8, H-4), 5.01 (1H, dd, *J* 3.2, 1.2, H-2), 4.72 (1H, d, *J* 1.2, H-1), 4.48 (1H, ddd, *J* 9.3, 7.8, 2.7, H-5), 3.61 (1H, dd, *J* 11.1, 2.7, H-6), 3.52 (1H, dd, *J* 11.1, 7.6, H-6'), 3.49 (3H, s, OCH_3), 2.14 (3H, s, $C(O)CH_3$), 2.08 (3H, s, $C(O)CH_3$); δ_C ($CDCl_3$, 75 MHz) 169.8 (C=O), 169.4 (C=O), 165.1 (PhC=O), 133.7 (CH aromatic), 129.7 (2 × CH aromatic), 129.0 (*ipso* C), 128.6 (2 × CH aromatic), 99.9 (C-1), 69.4 (C-5), 68.1 (C-2), 67.4 (C-

4), 66.2 (C-3), 55.9 (OCH_3), 32.2 (C-6), 20.9 (C(O)$\underline{C}H_3$), 20.8 (C(O)$\underline{C}H_3$); *m/z* (CI+) 445/447 (MH^+, 5/3%), 417 (80), 415 (78), 355 (43), 353 (50), 219 (60), 183 (28), 163 (22), 141 (72), 133 (100); HRMS (CI+) expected MH^+ ($C_{18}H_{22}BrO_8$) 445.0498, found 445.0486.

Methyl 2,3-di-*O*-acetyl-6-*S*-acetyl-4-*O*-benzoyl-6-thio-α-D-altropyranoside 74

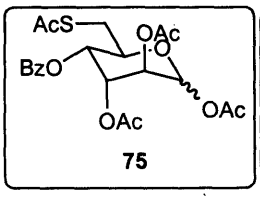


74

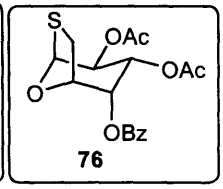
Potassium thioacetate (128 mg, 1.11 mmol) was added to a solution of di-acetate **73** (100 mg, 0.23 mmol) in dry DMF (2 mL) and heated to 80 °C for 18 h. It was then allowed to cool to RT and partitioned between EtOAc (10 mL) and H_2O (60 mL). The aqueous phase was extracted with EtOAc (6 × 10 mL) and the organic extracts were combined, washed with brine (60 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (petrol/EtOAc 6:1) afforded the title compound **74** (82 mg, 83%) as a viscous colourless oil; $[\alpha]_D^{20}$ = +21.7 (*c* 0.35 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3055s, 2986m, 2929, 1751s, 1697s, 1452m, 1421s, 1371s, 1265s; δ_H ($CDCl_3$, 300 MHz); 8.03-8.00 (2H, m, CH aromatic), 7.57-7.55 (1H, m, CH aromatic), 7.46-7.42 (2H, m, CH aromatic), 5.32 (1H, dd, *J* 3.7, 3.5, H-3), 5.27 (1H, dd, *J* 9.4, 3.5, H-4), 4.98 (1H, dd, *J* 3.7, 1.2, H-2), 4.63 (1H, d, *J* 1.2, H-1), 4.34 (1H, ddd, *J* 9.7, 9.4, 3.1, H-5), 3.44 (1H, dd, *J* 13.7, 3.1, H-6), 3.42 (3H, s, OCH_3), 3.01 (1H, dd, *J* 13.7, 9.7, H-6'), 2.35 (3H, s, $SC(O)CH_3$), 2.15 (3H, s, $C(O)CH_3$), 2.04 (3H, s, $C(O)CH_3$); δ_C ($CDCl_3$, 75 MHz) 194.8 (S$\underline{C}$=O), 169.9 (C=O), 169.4 (C=O), 165.3 (Ph$\underline{C}$=O), 133.5 (CH aromatic), 129.8 (2 × CH aromatic), 129.3 (*ipso* C), 128.6 (2 × CH aromatic), 98.7 (C-1), 69.4 (C-5), 68.4 (C-2), 67.3 (C-4), 65.9 (C-3), 55.7

(OCH_3), 30.5 (C-6), 20.9 (C(O)$\underline{C}H_3$), 20.84 (C(O)$\underline{C}H_3$), 20.81 (C(O)$\underline{C}H_3$); *m/z* (EI+) 440 (M^+, 13%), 389 (18), 345 (11), 254 (18), 199 (45), 183 (100); HRMS (EI+) expected M^+ ($C_{20}H_{24}O_9S$) 440.1141, found 440.1149.

1,2,3-Tri-*O*-acetyl-6-*S*-acetyl-4-*O*-benzoyl-6-thio-D-altropyranoside 75 and **2,3-di-*O*-acetyl-4-*O*-benzoyl-1,6-thioanhydro-D-altropyranose 76**



75



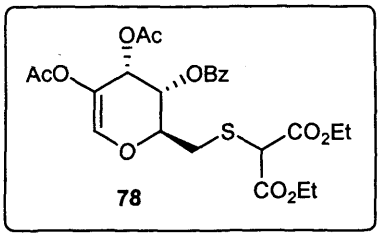
76

Thioacetate **74** (70 mg, 0.16 mmol) was dissolved in acetic anhydride (4 mL) and glacial acetic acid (4 mL) with occasional ice-cooling to maintain the internal temperature below 5 °C. Concentrated sulfuric acid (70 μL) was then added dropwise over 10 min. The reaction mixture was stirred at RT for 24 h and was then poured onto ice (30 mL). The organic material was extracted with DCM (5 × 10 mL). The organic extracts were washed with water (20 mL) and sat aq $NaHCO_3$ (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (petrol/EtOAc 6:1) afforded triacetate **75** (48 mg, 65%), as a mixture of anomers (α:β 4:6) as a colourless oil: ν_{max} ($CHCl_3$ cast)/cm^{-1} 3055s, 2986m, 2929m, 1751s, 1697m, 1421s, 1265s; δ_H ($CDCl_3$, 500 MHz) *α-anomer* 8.00-7.96 (2H, m, CH aromatic), 7.57-7.55 (1H, m, CH aromatic), 7.45-7.41 (2H, m, CH aromatic), 5.95 (1H, d, *J* 1.6, H-1), 5.40 (1H, dd, *J* 4.0, 3.5, H-3), 5.31 (1H, dd, *J* 9.5, 3.5, H-4), 5.03 (1H, dd, *J* 4.0, 1.6, dd, H-2), 4.41 (1H, ddd, *J* 9.5, 7.7, 3.5, H-5), 3.36 (1H, dd, *J* 14.1, 3.5, H-6), 3.08 (1H, dd, *J* 14.1, 7.7, H-6'), 2.30 (3H, s, SC(O)CH_3), 2.16 (3H, s, C(O)CH_3), 2.12 (3H, s, C(O)CH_3), 2.07 (3H, s, C(O)CH_3); irradiation of the signal at 5.95 ppm produced the following nuclear Overhauser enhancements: 5.40 (0.2%), 5.03 (1.5%), 2.07 (0.1%), 2.12

(0.2%), 2.16 (0.2%); *β-anomer* 8.00-7.95 (2H, m, CH aromatic), 7.57-7.51 (1H, m, CH aromatic), 7.43-7.33 (2H, m, CH aromatic), 6.19 (1H, d, *J* 1.6, H-1), 5.56 (1H, dd, *J* 6.0, 3.3, H-3), 5.36 (1H, dd, *J* 7.6, 3.3, H-4), 5.24 (1H, dd, *J* 6.0, 2.1, dd, H-2), 4.20 (1H, ddd, *J* 8.3, 7.6, 4.3 , H-5), 3.43 (1H, dd, *J* 14.2, 4.3, H-6), 3.06 (1H, dd, *J* 14.2, 8.3, H-6'), 2.32 (3H, s, $SC(O)CH_3$), 2.15 (3H, s, $C(O)CH_3$), 2.11 (3H, s, $C(O)CH_3$), 2.05 (3H, s, $C(O)CH_3$); irradiation of the signal at 6.19 ppm produced the following nuclear Overhauser enhancements: 5.24 (2.2%), 4.20 (2.0%), 2.15 (0.1%), 2.11 (0.2%), 2.05 (0.2%); *m/z* (FAB+) 469 (MH^+, 70%), 193 (100); HRMS (FAB+) expected MH^+ ($C_{21}H_{25}O_{10}S$) 469.1168, found 469.1166.

Further elution with petrol/EtOAc (3:1) afforded bicycle **76** (9 mg, 15%) as a colourless oil: $[\alpha]_D^{20}$ = –160.2 (*c* 3.15 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3055s, 2988m, 2930m, 1748s, 1600br, 1421s, 1265s; δ_H ($CDCl_3$, 500 MHz) 8.00-7.95 (2H, m, CH aromatic), 7.58-7.52 (1H, m, H aromatic), 7.45-7.35 (2H, m, CH aromatic), 5.68 (1H, d, *J* 3.5, H-1), 5.46 (1H, dd, *J* 9.5, 4.2, H-3), 5.41 (1H, dd, *J* 4.2, 2.1, H-4), 5.32 (1H, dd, *J* 9.5, 3.5, H-2), 4.98 (1H, ddd, *J* 7.3, 2.1, 0.7, H-5), 3.28 (1H, dd, *J* 10.7, 7.3, H-6'), 3.08 (1H, dd, *J* 10.7, 0.7, H-6), 2.04 (3H, s, $C(O)CH_3$), 1.92 (3H, s, $C(O)CH_3$); δ_C ($CDCl_3$, 125 MHz) 170.2 (C=O), 170.0 (C=O), 165.6 (Ph<u>C</u>=O), 133.5 (CH aromatic), 129.9 (2 × CH aromatic), 129.2 (*ipso* C), 128.5 (2 × CH aromatic), 82.9 (C-1), 79.4 (C-5), 71.0 (C-2), 69.9 (C-4), 67.4 (C-3), 33.0 (C-6), 20.9 (C(O)<u>C</u>H_3), 20.6 (C(O)<u>C</u>H_3); *m/z* (FAB+) 367 (MH^+, 27%), 163 (100); HRMS (FAB+) expected MH^+ ($C_{17}H_{19}O_7S$) 367.0852, found 367.0852.

Diethyl (2'*S*, 3'*S*, 4'*R*)-2-(4,5-Diacetoxy-3-benzoyloxy-3,4-dihydro-2*H*-pyran-2-ylmethylsulfanyl)malonate 78

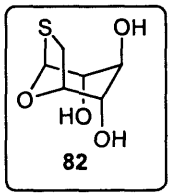


78

Rhodium heptafluorobutyrate dimer (8 mg, 7.5 μmol) was weighed under Ar in a glovebag and added to diacetate **76** (28 mg, 76 μmol). The mixture was suspended in dry toluene (0.5 mL) and heated to reflux. A solution of diethyl diazomalonate (18 mg, 98 μmol) in dry toluene (1 mL) was added dropwise and the resulting mixture was heated to reflux for 18 h. The reaction mixture was allowed to cool to RT and concentrated *in vacuo*. Column chromatography (Florisil®; petrol/EtOAc 10:1) afforded the title compound **78** (3 mg, 8%) as a colourless oil: $[\alpha]_D^{20}$ = +7.0 (*c* 0.20 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3053s, 2988, 1742s, 1421s, 1265s; δ_H ($CDCl_3$, 500 MHz) 7.97-7.94 (2H, m, CH aromatic), 7.57-7.53 (1H, m, CH aromatic), 7.43-7.39 (2H, m, CH aromatic), 6.74 (1H, s, C=CH), 5.87 (1H, d, *J* 4.1, H-4'), 5.41 (1H, dd, *J* 10.6, 4.1, H-3'), 4.44 (1H, ddd, *J* 10.6, 7.6, 2.9, H-2'), 4.31 (1H, s, C<u>H</u>$(CO_2Et)_2$), 4.19-4.15 (4H, m, $CO_2C\underline{H}_2CH_3$), 3.21 (1H, dd, *J* 14.4, 2.9, CH_2S), 3.02 (1H, dd, *J* 14.4, 7.6, CH_2S), 2.11 (3H, s, $C(O)CH_3$), 2.00 (3H, s, $C(O)CH_3$), 1.28-1.19 (6H, m, $CO_2CH_2C\underline{H}_3$); δ_C ($CDCl_3$, 125 MHz) 170.2 (C=O), 170.1 (C=O), 167.3 (C=O), 167.2 (C=O), 165.2 (Ph<u>C</u>=O), 131.7 (C=<u>C</u>H), 133.4 (CH aromatic), 129.4 (2 × CH aromatic), 128.9 (*ipso* C), 128.6 (2 × CH aromatic), 127.0 (<u>C</u>=CH), 73.7 (C-2'), 68.4 (C-3'), 64.8 (C-4'), 63.1 ($CO_2\underline{C}H_2CH_3$), 51.9 (<u>C</u>H$(CO_2Et)_2$), 32.6 (CH_2S), 21.8 ($C(O)\underline{C}H_3$), 21.0 ($C(O)\underline{C}H_3$), 14.5 ($CO_2CH_2\underline{C}H_3$); *m/z* (CI+) 547 (MH^+, 43%), 301

(26), 193 (12), 161 (23), 133 (100); HRMS (CI+) expected MH^+ ($C_{24}H_{29}O_{11}S$) 525.1431, found 525.1437.

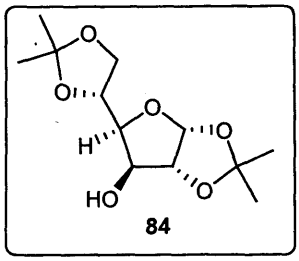
1,6-Thioanhydro-D-glucopyranose 82



82

Concentrated NH_4OH solution (d = 0.88, 0.5 mL) was added to a solution of tri-acetate **58** (100 mg, 330 μmol) in MeOH (1 mL). The reaction mixture was stirred at RT for 15 h, then concentrated *in vacuo* and rendered anhydrous by co-evaporation several times with absolute EtOH. Column chromatography (EtOAc/petrol 95:5) afforded the title compound **82** (45 mg, 77%) as white needles: mp 180-182 °C (Lit.[132] 180 °C); $[\alpha]_D^{20}$ = –13.7 (*c* 1.50 in EtOH) (Lit.[131] $[\alpha]_D^{20}$ = –52 (*c* 0.75 in H_2O); ν_{max} (KBr disc)/cm^{-1} 3340br, 3053s, 2987m, 1420s, 1265s; δ_H (CD_3OD, 500 MHz) 5.30 (1H, t, *J* 1.1, H-1), 4.65 (1H, dt, *J* 6.2, 0.9, H-5), 3.52 (1H, dd, *J* 1.1, 1.0, H-2), 3.49 (1H, dd, *J* 1.9, 0.9, H-4), 3.40 (1H, dd, *J* 1.9, 1.0, H-3), 3.07 (1H, dd, *J* 9.7, 0.9, H-6), 2.98 (1H, dd, *J* 9.7, 6.2, H-6'); δ_C (CD_3OD, 125 MHz) 84.3 (C-1), 81.2 (C-5), 71.5 (C-2), 69.2 (C-3), 68.4 (C-4), 34.5 (C-6); *m/z* (FAB+) 201 (MNa^+, 57%), 161 (100); HRMS (FAB+) expected MNa^+ ($C_6H_{10}NaO_4S$) 201.01975, found 201.01927.

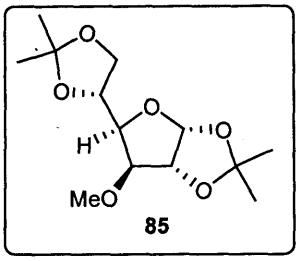
1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose 84



84

D-Glucose **55** (5.00 g, 28 mmol) was sonicated with 100 mL of acetone in a sonication bath. Concentrated sulfuric acid (5.2 mL, 10.4 mmol) was added dropwise. The resulting mixture was left sonicating for 2 h, then ammonia gas was passed through the mixture until neutral. Ammonium sulfate salts were removed by filtration and the filtrate was concentrated to a syrup. The residue was extracted with chloroform and the organic layer concentrated *in vacuo*. It was then recrystallised from high-boiling petrol (60-80) to afford the title compound **84** (3.76 g, 52%) as white needles: mp 110-112 °C (Lit.[133] 110 °C); $[\alpha]_D^{20}$ = –11.5 (*c* 1.35 in DCM) (Lit.[134] $[\alpha]_D^{20}$ = –18.5, *c* 5 in H_2O); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3448br, 3055s, 2988m, 2937m, 1421s, 1256s; δ_H ($CDCl_3$, 300 MHz) 5.91 (1H, d, *J* 3.8, H-1), 4.49 (1H, br d, *J* 3.8, H-2), 4.30 (1H, ddd, *J* 8.0, 6.2, 5.4, H-5), 4.27 (1H, dd, *J* 8.0, 7.8, H-4), 4.12 (1H, dd, *J* 8.8, 6.2, H-6'), 4.01 (1H, dd, *J* 7.8, 2.7, H-3), 3.96 (1H, dd, *J* 8.8, 5.4, H-6), 2.91 (1H, br s, OH), 1.47 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.31 (3H, s, CH_3); δ_C ($CDCl_3$, 75 MHz) 111.8 ($CH_2O\underline{C}O$), 109.6 ($CHO\underline{C}O$), 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); *m/z* (FAB+) 283 (MNa^+, 62%), 245 (13), 199 (17), 176 (100); HRMS (FAB+) expected MNa^+ ($C_{12}H_{20}NaO_6$) 283.1158, found 283.1152.

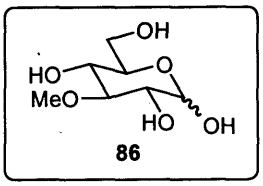
1,2:5,6-Di-*O*-isopropylidene-3-*O*-methyl-D-glucofuranose 85



85

To a stirred solution of diacetonide **84** (1.50 g, 5.8 mmol) in 10 mL of dry acetone was added finely crushed potassium hydroxide (0.87 g, 15.5 mmol) and *n*-tetrabutylammonium iodide (106 mg, 290 μmol). The mixture was then cooled to 0 °C, and iodomethane (0.8 mL, 12.9 mmol) was added dropwise. The mixture was allowed to warm to RT and stirred for 1 h. The acetone was removed *in vacuo* and water (5 mL) was added; the organic material was then extracted with DCM (4 × 30 mL). The combined organic phases were washed with sat aq NH_4Cl (10 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound **85** (1.54 g, 97%) as a yellow oil: $[\alpha]_D^{22}$ = –58.8 (*c* 4.75 in DCM) (Lit.[135] $[\alpha]_D^{22}$ = –38.0, *c* 1 in $CHCl_3$); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3055s, 2988m, 2937s, 2902m, 1456m, 1421m, 1265s; δ_H ($CDCl_3$, 300 MHz) 5.75 (1H, d, *J* 3.8, H-1), 4.47 (1H, apparent d, *J* 3.8, H-2), 4.20 (1H, ddd, *J* 7.8, 6.2, 5.6, H-5), 4.02 (1H, dd, *J* 7.8, 3.0, H-4), 4.00 (1H, dd, *J* 8.6, 6.2, H-6'), 3.90 (1H, dd, *J* 8.6, 5.6, H-6), 3.67 (1H, apparent d, *J* 3.2, H-3), 3.36 (3H, s, OCH_3), 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 ($CDCl_3$, 75 MHz) 111.1 ($CH_2O\underline{C}O$), 108.9 ($CHO\underline{C}O$), 105.1 (C-1), 83.6 (C-3), 81.8 (C-2), 81.0 (C-4), 72.3 (C-5), 67.1 (C-6), 58.1 (OCH_3), 26.8 (CH_3), 26.7 (CH_3), 26.1 (CH_3), 25.4 (CH_3); *m/z* (FAB+) 297 (MNa^+, 48%), 259 (15), 242 (100), 199 (10), 176 (72), 154 (10); HRMS (FAB+) expected MNa^+ ($C_{13}H_{22}NaO_6$) 297.1314, found 297.1306.

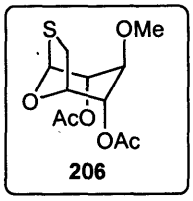
3-*O*-Methyl-D-glucose 86



86

Dowex® 50x8 resin (1.00 g) was washed with 2M HCl solution and then rinsed 5 times with H_2O until the filtrate was neutral. The resin was then added to a solution of methyl ether **85** (5.00 g, 18.2 mmol) in H_2O (20 mL), and the mixture was heated to reflux for 4 h. The resin was then filtered off and the solution clarified with charcoal. The solution was then concentrated *in vacuo* and co-evaporated several times with absolute EtOH to afford the title compound **86** (3.50 g, 99%), a mixture of anomers (α:β: 1:1) as white crystals: mp 166-168 °C (Lit.[136] 165-166 °C); ν_{max} (KBr disc)/cm^{-1} 3485br, 3053s, 2988m, 2936s, 2831s, 1633m, 1456s, 1371s; δ_H (500 MHz, D_2O) *α-anomer* 4.52 (1H, d, *J* 7.3, H-1), 3.72 (1H, m, H-4), 3.66 (1H, ddd, *J* 12.6, 9.8, 5.5, H-5), 3.61 (1H, dd, *J* 12.6, 5.5, H-6), 3.49 (3H, s, O-CH_3), 3.39-3.35 (1H, m, H-3), 3.35-3.33 (1H, m, H-6'), 3.18 (1H, dd, *J* 9.1, 7.3, H-2); *β-anomer* 5.09 (1H, d, *J* 3.6, H-1), 3.78 (1H, dd, *J* 12.5, 1.7, H-6), 3.60 (1H, dd, *J* 12.6, 10.0, H-6'), 3.49 (3H, s, OCH_3), 3.47 (1H, dd, *J* 4.2, 3.6, H-2), 3.42-3.40 (1H, m, H-3), 3.41-3.37 (1H, m, H-5), 3.22-3.17 (1H, m, H-4); δ_C (125 MHz, D_2O) *α-anomer* 95.8 (C-1), 82.7 (C-5), 73.4 (C-2), 71.4 (C-4), 69.0 (C-3), 60.6 (C-6), 60.0 (OCH_3); *β-anomer* 92.0 (C-1), 85.3 (C-5), 75.7 (C-4), 70.9 (C-2), 68.9 (C-3), 60.4 (C-6), 59.7 (O-CH_3); *m/z* (FAB+) 217 (MNa^+, 22%), 154 (100); HRMS (FAB+) expected MNa^+ ($C_7H_{14}O_6Na$) 217.0688, found 217.0693.

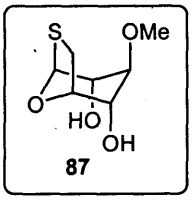
2,4-Di-*O*-acetyl-3-*O*-methyl-1,6-thioanhydro-D-glucopyranose 206



206

3-*O*-Methyl-D-glucose **86** was converted to bromide **205** using identical experimental procedures to the conversion of D-glucose **55** to bromide **57**. Bromide **205** (6.47 g, 13.1 mmol) was dissolved in dry acetone (150 mL) and cooled to 0 °C. Ethylxanthic acid potassium salt (6.28 g, 39.2 mmol) was added. The mixture was then allowed to warm to RT and then heated at 85 °C for 17 h, concentrated *in vacuo*, and the residue dissolved in water (250 mL). The organic material was extracted with diethyl ether (6 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 1:3) afforded the title compound **206** (1.80 g, 50%) as white needles: mp 83-85 °C; $[\alpha]_D^{20}$ = –21.6 (*c* 1.75 in DCM); ν_{max} (KBr disc)/cm^{-1} 2988m, 2955s, 2831s, 1745s, 1630m, 1450s, 1373s; δ_H ($CDCl_3$, 300 MHz) 5.44 (1H, d, *J* 1.1, H-1), 4.78 (1H, ddd, *J* 7.2, 3.5, 0.8, H-5), 4.75 (1H, dd, *J* 2.7, 1.1, H-2), 4.65 (1H, dd, *J* 3.5, 1.6, H-4), 3.47 (3H, s, OCH_3), 3.42 (1H, dd, *J* 2.7, 1.6, H-3), 3.38 (1H, dd, *J* 9.9, 0.8, H-6), 3.33 (1H, dd, *J* 9.9, 7.2, H-6'), 2.16 ($C(O)CH_3$), 2.14 ($C(O)CH_3$); δ_C ($CDCl_3$, 300 MHz) 170.2 (C=O), 170.1 (C=O), 85.1 (C-1), 80.8 (C-5), 77.8 (C-2), 75.4 (C-4), 69.0 (C-3), 55.2 (OCH_3), 32.6 (C-6), 18.6 ($C(O)\underline{C}H_3$), 18.4 ($C(O)\underline{C}H_3$); *m/z* (FAB+) 276 (MNa^+, 85%), 133 (100), 84 (40), 69 (44), 59 (38); HRMS (FAB+) expected MNa^+ ($C_{11}H_{16}O_6NaS$) 276.0668, found 276.0674.

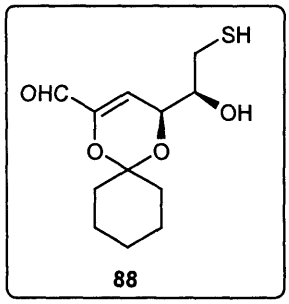
3-*O*-Methyl-1,6-thioanhydro-D-glucopyranose 87



87

Concentrated NH_4OH solution (d = 0.88, 18 mL) was added to a solution of di-acetate **206** (3.34 g, 11.6 mmol) in MeOH (50 mL). The reaction mixture was stirred at RT for 12 h, concentrated *in vacuo* and rendered anhydrous by co-evaporation several times with absolute EtOH. Column chromatography (EtOAc/petrol 8:3) afforded the title compound **87** (1.76 g, 79% yield) as white crystals: mp 174-176 °C; $[\alpha]_D^{20}$ = – 89.7 (*c* 3.30 in DCM); ν_{max} (KBr disc)/cm^{-1} 3455br, 2989m, 2950s, 2830s, 1628m, 1450s, 1375s; δ_H ($CDCl_3$, 400 MHz) 5.41 (1H, d, *J* 1.7, H-1), 4.75 (1H, ddd, *J* 8.5, 5.0, 2.0, H-5), 3.73 (1H, dd, *J* 1.8, 1.7, H-2), 3.59 (1H, dd, *J* 2.0, 1.9, H-4), 3.40 (3H, s, OCH_3), 3.33 (1H, dd, *J* 1.9, 1.8, H-3), 3.09 (1H, dd, 10.1, 8.5, H-6'), 3.07 (1H, dd, *J* 10.1, 5.0, H-6); δ_C ($CDCl_3$, 100 MHz) 83.4 (C-1), 81.0 (C-3), 80.1 (C-5), 69.9 (C-2), 69.5 (C-4), 58.1 (OCH_3), 32.4 (C-6); *m/z* (FAB+) 215 (MNa^+, 30%), 84 (100); HRMS (FAB+) expected MNa^+ ($C_7H_{12}O_4NaS$) 215.0354, found 215.0359.

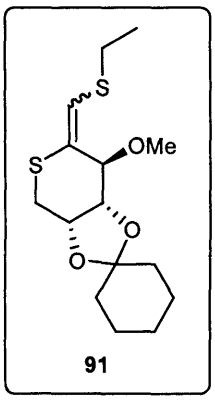
(1'*S*, 4*S*)-4-(1-Hydroxy-2-mercaptoethyl)-1,5-dioxa-spiro[5.5]undec-2-ene-2-carbaldehyde 88



88

Activated 4 Å molecular sieves (25 mg) were added to a solution of diol **87** (50 mg, 0.29 mmol) in dry EtOAc followed by cyclohexanone (0.18 mL, 2.92 mmol) and *p*-toluenesulfonic acid (5 mg, 0.03 mmol). The resulting mixture was heated to reflux for 12 h. 2% $NaHCO_3$ solution (15 mL) was added and the organic material was then extracted with Et_2O (4 × 20 mL). The organic extracts were combined, and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 1:9) afforded the title compound **88** (33 mg, 45%) as a colourless oil: $[\alpha]_D^{20}$ = +8.5 (*c* 0.15 in DCM); δ_H ($CDCl_3$, 400 MHz) 9.47 (1H, s, CHO), 6.95 (1H, d, *J* 3.9, C=CH), 4.66 (1H, dd, *J* 5.9, 3.9, C<u>H</u>CH=C), 4.32 (1H, ddd, *J* 10.6, 5.9, 4.4, C<u>H</u>OH), 2.91 (1H, dd, *J* 12.7, 4.4, C<u>H</u>$_2$SH), 2.51 (1H, dd, *J* 12.7, 10.6, C<u>H</u>$_2$SH), 1.67-1.43 (10H, m, cyclohexylidene); δ_C ($CDCl_3$, 100 MHz) 189.2 (CHO), 143.1 (<u>C</u>=CH), 109.1 (C=<u>C</u>H), 94.2 (OCO), 72.9 (CHOH), 69.7 (<u>C</u>HCHOH), 38.0 (<u>C</u>H$_2$C<u>C</u>H$_2$), 34.8 (CH_2SH), 28.6 (<u>C</u>H$_2$CH$_2$CH$_2$C), 24.9 (CH$_2$<u>C</u>H$_2$CH$_2$<u>C</u>H$_2$CH$_2$).

(3*S*, 4*R*, 5*S*)-4,5-*O*-Cyclohexylidene-2-ethylsulfanylmethylene-3-methoxytetrahydrothiophene-4,5-diol 91

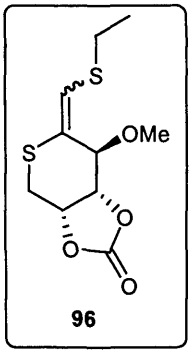


91

A solution of diol **87** (100 mg, 0.58 mmol) in dry DCM was treated with activated 4 Å molecular sieves, cyclohexanone (0.36 mL, 5.8 mmol) and *p*-toluenesulfonic acid (10 mg, 0.06 mmol), and refluxed for 12 h. 2% Aq $NaHCO_3$ (15 mL) was added and

the organic material was extracted with Et_2O (4 × 20 mL) then washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was subjected to column chromatography (EtOAc/petrol 5:95) affording the title compound **91** (51 mg, 28%) as a colourless oil; $[\alpha]_D^{20} = -12.6$ (*c* 0.90 in DCM); ν_{max} (thin film)/cm^{-1} 2984m, 2945s, 2830s, 1628m, 1444s, 1370s; δ_H ($CDCl_3$, 500 MHz) 6.06 (1H, s, CHSEt), 4.52 (1H, ddd, *J* 7.6, 5.8, 3.0, C<u>H</u>CH_2S), 4.23 (1H, dd, *J* 7.6, 4.8, C<u>H</u>CHOMe), 3.90 (1H, d, *J* 4.8, C<u>H</u>OMe), 3.36 (3H, s, OCH_3), 3.27 (1H, dd, *J* 13.5, 3.0, CH_2S), 2.81 (1H, dd, *J* 13.5, 5.8, CH_2S), 2.74 (2H, q, *J* 7.9, CH_2CH_3), 1.68-1.43 (10H, m, cyclohexylidene), 1.30 (3H, t, *J* 7.9, CH_2CH_3); δ_C ($CDCl_3$, 125 MHz) 127.0 (C=CSEt), 119.5 (C=CSEt), 110.1 (OCO), 81.9 (OCHCHOMe), 75.7 (SCH_2CHO), 72.0 (CHOMe), 57.0 (OCH_3), 36.2 (2 × CH_2CO), 34.2 (SCH_2CHO), 28.3 ($OCCH_2CH_2CH_2$), 27.6 (SCH_2CH_3), 23.6 (2 × $OCCH_2CH_2CH_2$), 15.5 (SCH_2CH_3); *m/z* (FAB+) 339 (MNa^+, 25%); HRMS (FAB+) expected MNa^+ ($C_{15}H_{24}O_3NaS_2$) 339.1065, found 339.1069.

(1*S*, 5*S*, 6*R*)-4-Ethylsulfanylmethylene-5-methoxy-7,9-dioxa-4-thiabicyclo[4.3.0]nonan-8-one 96

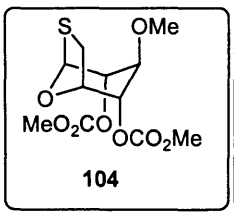


96

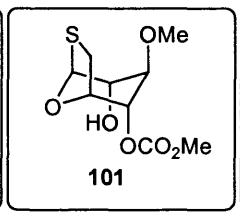
Dry pyridine (256 μL, 3.17 mmol) was added dropwise at 0 °C to a solution of diol **87** (100 mg, 0.53 mmol) in dry DCM (1 mL). The reaction mixture was allowed to warm to RT and stirred for 30 min, then cooled to –78 °C. A solution of triphosgene (156

mg, 0.58 mmol) in dry DCM (2 mL) was added dropwise, the mixture was allowed to warm to RT and stirred for 10 h. The solution was then carefully poured onto ice (20 g); the organic material was extracted with DCM (3 × 20 mL), the organic extracts were combined, washed with sat aq $NaHCO_3$ (20 mL), sat aq NH_4Cl (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Pyridine traces were removed by co-evaporation three times with toluene. Column chromatography (petrol/EtOAc 2:1) afforded the title compound **96** (59 mg, 43%) as a colourless oil: $[\alpha]_D^{20}$ = –51.4 (*c* 0.25 in DCM); ν_{max} (thin film)/cm^{-1} 2985m, 2950s, 2833s, 1705s, 1630m, 1443s, 1372s; δ_H ($CDCl_3$, 500 MHz) 6.19 (1H, s, C<u>H</u>SEt), 5.07 (1H, ddd, *J* 8.8, 3.8, 2.4, C<u>H</u>CH$_2$S), 4.80 (1H, dd, *J* 8.8, 4.2, C<u>H</u>CHOMe), 4.06 (1H, d, *J* 4.2, C<u>H</u>OMe), 3.54 (1H, dd, *J* 14.3, 2.4, C<u>H</u>$_2$S), 3.33 (3H, s, OCH_3), 2.91 (1H, dd, *J* 14.3, 3.8, C<u>H</u>$_2$S), 2.72 (2H, q, *J* 7.4, C<u>H</u>$_2$CH$_3$), 1.26 (3H, t, *J* 7.4, CH$_2$C<u>H</u>$_3$); δ_C ($CDCl_3$, 125 MHz): 153.6 (C=O), 125.1 (<u>C</u>=CSEt), 122.4 (C=<u>C</u>SEt), 78.9 (O<u>C</u>HCHOMe), 74.1 (SCH$_2$C<u>H</u>O), 72.4 (<u>C</u>HOMe), 56.4 (OCH_3), 28.5 (S<u>C</u>H$_2$CHO), 26.8 (S<u>C</u>H$_2$CH$_3$), 15.4 (SCH$_2$C<u>H</u>$_3$); *m/z* (EI+) 262 (M^+, 100%), 233 (11), 201 (72), 147 (16), 133 (21); HRMS (EI+) expected M^+ ($C_{10}H_{14}O_4S_2$) 262.0334, found 262.0337.

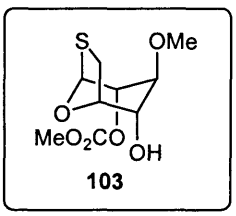
2,4-Di-*O*-(methoxycarbonyl)-3-*O*-methyl-1,6-thioanhydro-D-glucopyranose 104, 2-*O*-methoxycarbonyl-3-*O*-methyl-1,6-thioanhydro-D-glucopyranose 103 and **4-*O*-methoxycarbonyl-3-*O*-methyl-1,6-thioanhydro-D-glucopyranose 101**



104



101



103

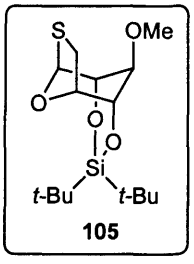
Diol **87** (0.70 g, 3.7 mmol) was dissolved in dry DCM (3 mL). The solution was cooled to –78 °C and triethylamine (0.65 mL, 4.4 mmol) was added dropwise. Stirring

was continued for 30 min before a solution of methyl chloroformate (0.29 mL, 3.70 mmol) in dry DCM (3 mL) was added over 20 min at –78 °C. The reaction mixture was allowed to warm to RT and stirred for 1 h. Water (5 mL) was added to the mixture. The organic material was then extracted with DCM (4 × 5 mL). The organic layers were combined, washed with sat aq NH_4Cl (25 mL), water (25 mL) and brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 1:3) afforded dicarbonate **104** (92 mg, 9%) as a colourless oil : $[\alpha]_D^{20}$ = –37.6 (*c* 0.13 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3053s, 2986m, 1736s, 1606w, 1421s, 1256s; δ_H ($CDCl_3$, 300 MHz) 5.50 (1H, d, *J* 1.2, H-1), 4.81 (1H, ddd, *J* 10.1, 6.4, 2.0, H-5), 4.60 (1H, d, *J* 2.3, 1.2, H-2), 4.48-4.40 (1H, dd, *J* 2.8, 2.0, H-4), 3.81 (3H, s, CO_2CH_3), 3.80 (3H, s, CO_2CH_3), 3.46 (1H, dd, *J* 2.8, 2.3, H-3), 3.19 (1H, t, *J* 10.1, H-6'),3.07 (1H, dd, *J* 10.1, 6.4, H-6); δ_C ($CDCl_3$, 75 MHz) 155.1 (C=O), 155.0 (C=O), 81.5 (C-1), 79.3 (C-5), 77.7 (C-2), 77.6 (C-4), 76.1 (C-3), 59.1 ($CO_2\underline{C}H_3$), 59.0 ($CO_2\underline{C}H_3$), 55.1 (OCH_3), 34.4 (C-6); *m/z* (FAB+) 331 (MNa^+, 6%), 59 (100); HRMS (FAB+) expected MNa^+ ($C_{11}H_{16}O_8SNa$) 331.0464, found 331.0456.

Further elution with EtOAc/petrol (3:1) afforded carbonate **101** (301 mg, 35%) as a colourless oil: $[\alpha]_D^{20}$ = –98.1 (*c* 0.75 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3440br, 3053s, 2988m, 1740s, 1600w, 1421s, 1256s; δ_H ($CDCl_3$, 300 MHz) 5.41 (1H, d, *J* 1.3, H-1), 4.81 (1H, ddd, *J* 9.9, 6.1, 2.0, H-5), 4.52 (1H, dd, *J* 2.4, 2.0, H-4), 3.81 (3H, s, CO_2CH_3), 3.70 (1H, dd, *J* 2.0, 1.3, H-2), 3.45 (3H, s, OCH_3), 3.39 (1H, dd, *J* 2.4, 2.0, H-3), 3.16 (1H, dd, *J* 10.0, 9.9, H-6'), 3.14 (1H, dd, *J* 10.0, 6.4, H-6); δ_C ($CDCl_3$, 75 MHz) 155.0 (C=O), 83.5 (C-1), 79.3 (C-5), 77.8 (C-2), 74.6 (C-3), 70.5 (C-4), 58.6 ($CO_2\underline{C}H_3$), 55.2 (OCH_3), 32.9 (C-6); *m/z* (FAB+) 273 (MNa^+, 56%), 133 (100); HRMS (FAB+) expected MNa^+ ($C_9H_{14}O_6SNa$) 273.0409, found 273.0418.

Further elution with EtOAc/petrol (3:1) afforded carbonate **103** (279 mg, 32%) as a colourless oil: $[\alpha]_D^{20}$ = –33.2 (*c* 2.7 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3449br, 3052s, 2988m, 1742s, 1606w, 1421s, 1256s; δ_H ($CDCl_3$, 300 MHz) 5.50 (1H, d, *J* 1.1, H-1), 4.81 (1H, ddd, *J* 9.8, 6.2, 2.6, H-5), 4.67 (1H, dd, *J* 2.0, 1.1, H-2), 3.84 (3H, s, CO_2CH_3), 3.55 (1H, dd, *J* 2.6, 2.1, H-4), 3.46 (3H, s, OCH_3), 3.39 (1H, d, *J* 2.1, 2.0, H-3), 3.13 (1H, dd, *J* 10.0, 9.8, H-6'), 3.09 (1H, dd, *J* 10.0, 6.2, H-6); δ_C ($CDCl_3$, 75 MHz) 154.6 (C=O), 81.1 (C-1), 80.6 (C-5), 79.3 (C-4), 74.8 (C-3), 69.7 (C-2), 58.3 ($CO_2\underline{C}H_3$), 55.2 (OCH_3), 32.7 (C-6); *m/z* (FAB+) 273 (MNa^+, 19%), 69 (100); HRMS (FAB+) expected MNa^+ ($C_9H_{14}O_6SNa$) 273.0409, found 273.0401.

2,4-*O*-(Di-*tert*-butylsilylene)-3-*O*-methyl-1,6-thioanhydro-D-glucopyranose 105

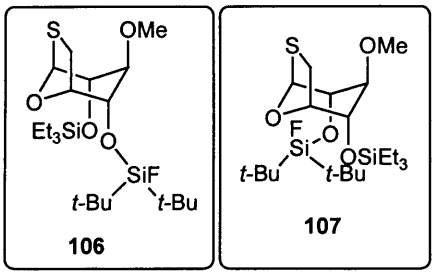


105

Freshly distilled 2,6-lutidine (92 μL, 0.80 mmol) was added to a solution of diol **87** (50 mg, 0.27 mmol) in dry DCM (1 mL) and di-*tert*-butylsilyl ditriflate (145 μL, 0.40 mmol) was added in one portion. The mixture was stirred at RT for 1.5 h, then partitioned between DCM (10 mL) and sat aq $NaHCO_3$ (10 mL). The organic material was extracted with DCM (5 × 10 mL); the combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (SiO_2 previously treated with Et_3N, EtOAc/petrol/Et_3N 1:20:0.2) afforded the title compound **105** (76 mg, 86%) as white crystals: mp 107-110 °C; $[\alpha]_D^{20}$ = –11.4 (*c* 1.0 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 2988m, 2950m, 1600m, 1420m, 1253s; δ_H ($CDCl_3$, 500 MHz) 5.43 (1H, d, *J* 2.2, H-1), 4.73 (1H, ddd,

J 7.8, 2.8, 1.8, H-5), 4.00 (1H, dd, *J* 2.7, 2.2, H-2), 3.87 (1H, dd, *J* 2.7, 1.9, H-3), 3.85 (1H, dd, *J* 2.8, 1.9, H-4), 3.37 (3H, s, OCH_3), 3.21 (1H, dd, *J* 9.3, 1.8, H-6), 3.08 (1H, dd, *J* 9.3, 7.8, H-6'), 1.11 (9H, s, $C(CH_3)_3$), 1.03 (9H, s, $C(CH_3)_3$); δ_C ($CDCl_3$, 125 MHz) 81.9 (C-1), 78.5 (C-5), 77.6 (C-3), 70.9 (C-4), 70.1 (C-2), 57.7 (OCH_3), 32.6 (C-6), 29.7 ($C(\underline{C}H_3)_3$), 28.4 ($C(\underline{C}H_3)_3$), 22.3 ($\underline{C}(CH_3)_3$), 21.3 ($\underline{C}(CH_3)_3$); *m/z* (FAB+) 355 (MNa^+, 65%), 193 (100); HRMS (FAB+) expected MNa^+ ($C_{15}H_{28}O_4SSiNa$) 355.1375, found 355.1364.

4-*O*-Di-*tert*-butylfluorosilanyl-3-*O*-methyl-2-*O*-triethylsilanyl-1,6-thioanhydro-D-glucopyranose 106 and **2-*O*-di-*tert*-butylfluorosilanyl-3-*O*-methyl-4-*O*-triethylsilanyl-1,6-thioanhydro-D-glucopyranose 107**

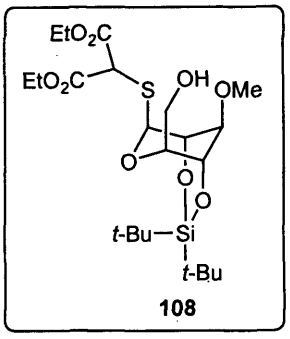


Tetrakis(acetonitrile)copper(I) hexafluorophosphate (16 mg, 15 μmol) was weighed under Ar in a glovebag and added to silylene bisether **105** (100 mg, 150 μmol). The mixture was suspended in dry benzene (1 mL) and heated to reflux. A solution of ethyl diazo(triethylsilanyl)acetate (92 mg, 400 μmol) in dry benzene (1 mL) was then added dropwise to the refluxing mixture and reflux was continued for 14 h. The reaction mixture was cooled to RT and concentrated *in vacuo*. Column chromatography (Florisil®; petrol/EtOAc 100:1) afforded silyl fluoride **106** (18 mg, 13%) as a colourless oil: ν_{max} ($CHCl_3$ cast)/cm^{-1} 3053s, 2988m, 2856m, 2252s, 1472m, 1385m, 1261m, 1096m, 902s, 652s; δ_H ($CDCl_3$, 500 MHz) 5.26 (1H, d, *J* 0.7, H-1), 4.73 (1H, dt, *J* 6.3, 0.7, H-5), 3.85 (1H, dd, *J* 4.5, 0.7, H-4), 3.61 (1H, dd, *J* 3.2,

0.7, H-2), 3.46 (1H, s, OCH_3), 3.20 (1H, dd, *J* 4.5, 3.2, H-3), 3.01 (1H, dd, *J* 10.0, 6.5, H-6'), 2.98 (1H, dd, *J* 10.0, 0.7, H-6), 1.04 (9H, s, $C(CH_3)_3$), 1.01 (9H, s, $C(CH_3)_3$), 0.93 (9H, t, *J* 7.9, $Si(CH_2C\underline{H}_3)_3$), 0.59 (6H, q, *J* 7.9, $Si(C\underline{H}_2CH_3)_3$); δ_C ($CDCl_3$, 125 MHz) 84.8 (C-1), 82.9 (C-5), 77.1 (C-2), 76.9 (C-4), 72.9 (C-3), 59.8 (OCH_3), 34.9 (C-6), 26.9 ($C(\underline{C}H_3)_3$), 27.1 ($C(\underline{C}H_3)_3$), 6.8 ($Si(CH_2\underline{C}H_3)_3$), 4.81 ($Si(\underline{C}H_2CH_3)_3$), 1.1 ($\underline{C}(CH_3)_3$), 1.0 ($\underline{C}(CH_3)_3$); δ_F ($CDCl_3$, 282 MHz): –161.2 (s); *m/z* (EI+) 466 (M^+, 7%), 437 (56), 409 (13), 275 (23), 249 (100); HRMS (EI+) expected M^+ ($C_{21}H_{43}O_4SSi_2F$) 466.2405, found 466.2408.

Further elution with petrol/EtOAc 100:1 afforded silyl fluoride **107** (20 mg, 15%) as a colourless oil: ν_{max} ($CHCl_3$ cast)/cm^{-1} 3053s, 2988m, 2856m, 2252s, 1472m, 1385m, 1096m, 902s, 652s; δ_H ($CDCl_3$, 500 MHz) 5.42 (1H, d, *J* 0.7, H-1), 4.60 (1H, dt, *J* 6.0, 0.7, H-5), 3.98 (1H, dd, *J* 4.0, 0.7, H-4), 3.49 (1H, dd, *J* 3.5, 0.7, H-2), 3.47 (1H, s, OCH_3), 3.20 (1H, dd, *J* 4.0, 3.5, H-3), 2.98 (1H, dd, *J* 10.6, 6.0, H-6'), 2.95 (1H, dd, *J* 10.6, 0.7, H-6), 1.04 (9H, s, $C(CH_3)_3$), 1.02 (9H, s, $C(CH_3)_3$), 0.93 (9H, t, *J* 7.9, $Si(CH_2C\underline{H}_3)_3$), 0.59 (6H, q, *J* 7.9, $Si(C\underline{H}_2CH_3)_3$); δ_C ($CDCl_3$, 125 MHz) 84.2 (C-1), 82.4 (C-5), 77.2 (C-2), 76.9 (C-4), 73.8 (C-3), 59.6 (OCH_3), 29.7 (C-6), 26.9 ($C(\underline{C}H_3)_3$), 26.8 ($C(\underline{C}H_3)_3$), 6.8 ($Si(CH_2\underline{C}H_3)_3$), 4.81 ($Si(\underline{C}H_2CH_3)_3$), 1.0 ($\underline{C}(CH_3)_3$), 0.9 ($\underline{C}(CH_3)_3$); δ_F ($CDCl_3$, 282 MHz) –161.4 (s); *m/z* (EI+) 466 (M^+, 5%), 437 (70), 409 (100), 377 (17), 275 (12), 249 (72); HRMS (EI+) expected M^+ ($C_{21}H_{43}O_4SSi_2F$) 466.2405, found 466.2413.

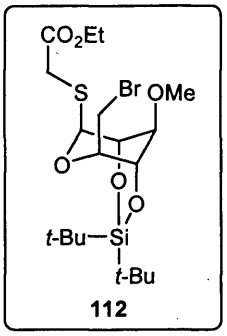
Di(ethoxycarbonyl)methyl 2,4-*O*-di-*tert*-butylsilylene-1-deoxy-3-*O*-methyl-1-thio-β-D-glucopyranoside 108



108

Rhodium heptafluorobutyrate dimer (8 mg, 7.5 μmol) was weighed under Ar in a glovebag, added to silylene bisether **105** (25 mg, 75 μmol), suspended in dry benzene (1 mL) and heated to reflux. A solution of diethyl diazomalonate (18 mg, 98 μmol) in dry benzene (1 mL) was then added dropwise to the refluxing mixture, and reflux was continued for 14 h. The reaction mixture was cooled to RT and concentrated *in vacuo*. Column chromatography (Florisil®; petrol/EtOAc 9:1) afforded the title compound **108** (8 mg, 21%) as a colourless oil: $[\alpha]_D^{20}$ = –8.0 (*c* 0.25 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3420br, 3053s, 2982m, 1745s, 1695s, 1421s, 1265s; δ_H (C_6D_6, 500 MHz) 5.78 (1H, d, *J* 1.1, H-1), 4.85 (1H, dd, *J* 12.1, 10.4, H-6'), 4.46 (1H, dd, *J* 1.7, 1.1, H-2), 4.35 (1H, ddd, *J* 10.4, 4.3, 2.7, H-5), 4.26 (1H, s, C<u>H</u>($CO_2CH_2CH_3$)$_2$), 4.23 (1H, s, OH), 3.94-3.86 (4H, m, 2 × $CO_2C\underline{H}_2CH_3$), 3.78 (1H, dd, *J* 1.7, 1.5, H-3), 3.71 (1H, dd, *J* 2.7, 1.5, H-4), 3.53 (1H, dd, *J* 12.1, 4.3, H-6), 2.89 (3H, s, O-Me), 1.20 (9H, s, $C(CH_3)_3$), 1.08 (9H, s, $C(CH_3)_3$), 0.89-0.83 (6H, m, 2 × $CO_2CH_2C\underline{H}_3$); δ_C (C_6D_6, 125 MHz) 168.4(C=O), 167.2 (C=O), 82.7 (C-1), 81.6 (C-5), 74.0 (C-3), 70.3 (C-2), 67.3 (C-4), 62.6 (C-6), 62.4 ($CO_2\underline{C}H_2CH_3$), 62.3 ($CO_2\underline{C}H_2CH_3$), 57.7 (OCH_3), 52.8 (<u>C</u>H($CO_2CH_2CH_3$)$_2$), 28.4 (C(<u>C</u>H_3)$_3$), 28.3 (C(<u>C</u>H_3)$_3$), 21.6 (<u>C</u>(CH_3)$_3$), 21.2 (<u>C</u>(CH_3)$_3$), 13.7 ($CO_2CH_2\underline{C}H_3$); *m/z* (FAB+) 531 (MNa^+, 6%), 329 (23), 217 (90), 176 (100); HRMS (FAB+) expected MNa^+ ($C_{22}H_{40}NaO_9SSi$) 531.2060, found 531.2068.

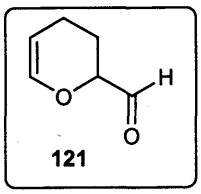
Ethoxycarbonylmethyl 6-bromo-6-deoxy-2,4-*O*-di-*tert*-butylsilylene-3-*O*-methyl-1-thio-β-D-glucopyranoside 112



112

Ethyl bromoacetate (16 μL, 150 μmol) was added in one portion to a solution of silylene bisether **105** (50 mg, 150 μmol) in dry MeCN (0.3 mL). The mixture was stirred for a further 10 h at RT. The resulting black precipitate was removed by filtration through Celite® and the filtrate was concentrated *in vacuo*. Column chromatography (Florisil®; EtOAc/petrol 5:95) afforded the title compound **112** (54 mg, 72%) as a colourless oil: $[\alpha]_D^{20} = -59.5$ (*c* 1.50 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3050s, 2980m, 1747s, 1691s, 1421s, 1265s; δ_H ($CDCl_3$, 500 MHz) 5.37 (1H, t, *J* 1.0, H-1), 4.38 (1H, dd, *J* 3.8, 2.4, H-4), 4.34 (1H, ddd, *J* 3.7, 2.5, 1.0, H-3), 4.23 (1H, ddd, *J* 9.0, 6.7, 3.8, H-5), 4.17 (2H, q, *J* 7.1, $CO_2C\underline{H}_2CH_3$), 4.09 (1H, dd, *J* 10.3, 9.0, H-6'), 3.96 (1H, dd, *J* 10.3, 6.7, H-6), 3.95 (1H, dd, *J* 3.7, 1.0, H-2), 3.52 (1H, d, *J* 14.7, SCH_2), 3.48 (3H, s, OCH_3), 3.28 (1H, d, *J* 14.7, SCH_2), 1.26 (3H, t, *J* 7.1, $CO_2CH_2C\underline{H}_3$), 1.04 (9H, s, $C(CH_3)_3$), 1.02 (9H, s, $C(CH_3)_3$); δ_C ($CDCl_3$, 125 MHz) 170.6 (C=O), 82.7 (C-1), 78.6 (C-5), 74.1 (C-2), 69.0 (C-3), 66.5 (C-4), 61.4 ($CO_2\underline{C}H_2CH_3$), 58.4 (OCH_3), 34.3 (SCH_2), 33.3 (C-6), 28.1 ($C(\underline{C}H_3)_3$), 28.0 ($C(\underline{C}H_3)_3$), 21.5 ($\underline{C}(CH_3)_3$), 21.2 ($\underline{C}(CH_3)_3$), 14.1 ($CO_2CH_2\underline{C}H_3$). *m/z* (FAB+) 521/523 (MNa^+, 85/43%), 498/500 (31/19), 443 (21), 411 (35), 321 (100), 275 (35); HRMS (FAB+) expected MNa^+ ($C_{19}H_{35}{}^{79}BrNaO_6SSi$) 521.1005, found 521.1010.

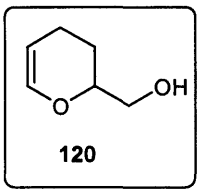
3,4-Dihydro-2*H*-pyran-2-carbaldehyde 121



121

A solution of redistilled acrolein **122** (2.50 g, 44.6 mmol) and hydroquinone (100 mg, 0.9 mmol) in dry benzene (2.5 mL) was subjected to microwave irradiation (200 W) at 160 °C for 3 h in a pyrex tube (5 mm thickness). The volatile material was removed on a rotary evaporator and the residual crude mixture was subjected to fractional distillation under reduced pressure affording affording the title compound **121** (2.40 g, 48%) as a colourless oil: (bp 30 mm Hg, 58-60 °C) (Lit.[137] 760 mm Hg, 146 °C); ν_{max} ($CHCl_3$ film)/cm^{-1} 3055s, 2988m, 2958m, 1713s, 1634m, 1421m; δ_H ($CDCl_3$, 300 MHz) 9.63 (1H, d, *J* 0.6, CHO), 6.36 (1H, d, *J* 6.5, CH=C<u>H</u>O), 4.81 (1H, ddd, *J* 6.5, 4.0, 2.1, C<u>H</u>=CHO), 4.13 (1H, dd, *J* 5.6, 2.4, $CH_2C\underline{H}$), 1.86-2.03 (4H, m, 2 × CH_2); δ_C ($CDCl_3$, 75 MHz) 202.0 (C=O), 142.8 (<u>C</u>H=CHO), 101.9 (CH=<u>C</u>HO), 78.7 (CH), 22.3 (CH_2), 17.8 (CH_2); *m/z* (EI+) 112 (M^+, 100%), 99 (26), 83 (46); HRMS (EI+) expected M^+ ($C_6H_8O_2$) 112.0524, found 112.0526.

3,4-Dihydro-2*H*-pyran-2-methanol 120

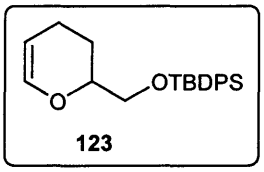


120

A solution of aldehyde **121** (1.00 g, 8.91 mmol) in dry ethanol (10 mL) was added dropwise to a solution of sodium borohydride (337 mg, 8.91 mmol) in dry ethanol (10 mL) at 0 °C. The resulting solution was allowed to warm to RT and stirred for 18 h. It was then concentrated *in vacuo* and diluted with water (20 mL). The organic material

was extracted with Et_2O (5 × 20 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (petrol/EtOAc 5:1) afforded the title compound **120** (0.99 g, 97%) as a colourless liquid: ν_{max} ($CHCl_3$ film)/cm^{-1} 3418br, 2941s, 2870m, 1640w, 1456m; δ_H ($CDCl_3$, 400 MHz) 6.39 (1H, ddd, *J* 6.2, 3.8, 1.9 CH=C<u>H</u>O), 4.71 (1H, ddd, *J* 6.2, 2.4, 1.3 C<u>H</u>=CHO), 3.92 (1H, ddt, *J* 10.1, 6.6, 3.4, $CH_2C\underline{H}CH_2$), 3.72 (1H, ddd, *J* 11.7, 7.2, 3.4, CH_2O), 3.66 (1H, ddd, *J* 11.7, 6.6, 5.4, CH_2O), 2.07-2.12 (1H, m, CH_2), 1.92-2.03 (1H, m, CH_2), 1.86 (1H, dd, *J* 6.8, 6.5, OH), 1.73-1.77 (1H, m, CH_2), 1.69-1.72 (1H, m, CH_2); δ_C ($CDCl_3$, 100 MHz) 143.3 (<u>C</u>H=CHO), 100.8 (CH=<u>C</u>HO), 75.5 ($CH_2\underline{C}HCH_2$), 65.5 (CH_2O), 23.9 (CH_2), 19.4 (CH_2); *m/z* (EI+) 114 (M^+, 100%), 97 (50), 79 (27); HRMS (EI+) expected M^+ ($C_6H_{10}O_2$) 114.0681, found 114.0677.

2-(*tert*-Butyldiphenylsilanyloxymethyl)-3,4-dihydro-2*H*-pyran 123

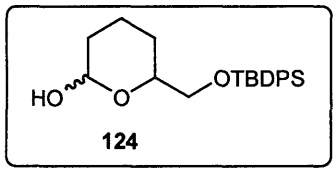


123

To a stirred solution of alcohol **120** (500 mg, 4.38 mmol) and imidazole (596 mg, 8.76 mmol) in dry DMF (12 mL), was added *tert*-butyldiphenylsilylchloride (1.14 mL, 4.38 mmol) dropwise at RT. The solution was stirred at RT for 3 h, then poured onto an ice/water mixture (20 mL) and the organic material extracted with Et_2O (5 × 20 mL). The organic extracts were combined and washed with cold 2M HCl (40 mL), water (40 mL), sat aq $NaHCO_3$ (40 mL) and brine (40 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography (petrol/EtOAc 100:1) afforded the title compound **123** (1.53 g, 99%) as a colourless liquid: ν_{max} ($CHCl_3$ cast)/cm^{-1} 3053s, 2932m, 2858m, 1651m, 1470m, 1427m; δ_H ($CDCl_3$, 400 MHz) 7.25-7.46 (6H, m, CH aromatic), 7.67-7.94 (4H, m, CH aromatic), 6.34 (1H, dt, *J* 6.4, 3.4,

C<u>H</u>=CHO), 4.64 (1H, ddd, *J* 6.4, 2.7, 1.4, CH=C<u>H</u>O), 3.92 (1H, dddd, *J* 8.3, 5.7, 5.4, 2.4, $CH_2C\underline{H}CH_2$), 3.78 (1H, dd, *J* 10.4, 5.2, CH_2O), 3.67 (1H, dd, *J* 10.4, 5.7, CH_2O), 2.02-2.12 (1H, m, CH_2), 1.91-1.97 (2H, m, CH_2), 1.67-1.74 (1H, m, CH_2), 1.08 (9H, s, $(C(CH_3)_3)$); δ_C ($CDCl_3$, 100 MHz) 143.6 (<u>C</u>H=CHO), 135.7 (4 × CH aromatic), 133.6 (2 × *ipso* C), 129.7 (4 × CH aromatic), 127.7 (2 × CH aromatic), 100.4 (CH=<u>C</u>HO), 75.3 ($CH_2\underline{C}HCH_2$), 66.0 (CH_2O), 26.8 ($C(\underline{C}H_3)_3$)), 24.4 (CH_2), 19.3 ($\underline{C}(CH_3)_3$)), 19.2 (CH_2); *m/z* (CI+) 353 (MH^+, 30%), 295 (100), 275 (61), 239 (20); HRMS (CI+) expected MH^+ ($C_{22}H_{29}O_2Si$) 353.1937, found 353.1934.

6-(*tert*-Butyldiphenylsilanyloxymethyl)tetrahydropyran-2-ol 124

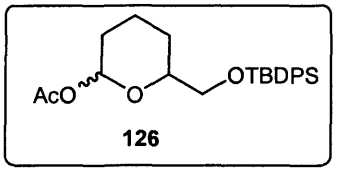


124

0.5M Hydrochloric acid (100 mL, 50 mmol) was added to a solution of enol ether **123** (10.0 g, 28.4 mmol) in THF (300 mL). The reaction mixture was stirred at 40 °C for 14 h. THF was then removed *in vacuo* and the organic material was extracted with DCM (5 × 100 mL). The combined organic extracts were washed with sat aq $NaHCO_3$ (200 mL) and brine (200 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography (petrol/EtOAc 95:5) afforded the title compound **124** (9.95 g, 95%), as a mixture of anomers (α:β 1:1) as a white solid: ν_{max} ($CHCl_3$ cast)/cm^{-1} 3406br, 3053m, 2933m, 2858m, 1471w, 1427m; δ_H ($CDCl_3$, 400 MHz) *α-anomer* 7.66-7.78 (4H, m, CH aromatic), 7.39-7.48 (6H, m, CH aromatic), 5.25 (1H, d, *J* 2.0, OCHO), 4.03 (1H, ddt, *J* 11.7, 5.4, 5.3, $CH_2C\underline{H}CH_2$), 3.65 (1H, dd, *J* 10.3, 5.3, CH_2O), 3.53 (1H, dd, *J* 10.3, 5.4, CH_2O), 2.28 (1H, dd, *J* 2.8, 2.0, OH), 1.82-1.89 (2H, m, CH_2), 1.60-1.67 (2H, m, CH_2), 1.17-1.29 (2H, m, CH_2), 1.04 (9H, s, $(C(CH_3)_3)$); *β-anomer* 7.66-7.78 (4H, m, CH aromatic), 7.39-7.48 (6H, m, CH

aromatic), 4.64 (1H, dt, *J* 7.2, 6.1, 2.1, OCHO), 3.73 (1H, ddt, *J* 11.7, 7.6, 3.0 $CH_2C\underline{H}CH_2$), 3.61 (1H, dd, *J* 10.3, 5.3, CH_2O), 3.55 (1H, dd, *J* 10.3, 5.4, CH_2O), 2.68 (1H, d, *J* 6.1, OH), 1.82-1.89 (2H, m, CH_2), 1.60-1.67 (2H, m, CH_2), 1.17-1.29 (2H, m, CH_2), 1.04 (9H, s, ($C(CH_3)_3$)); δ_C ($CDCl_3$, 100 MHz) *α-anomer* 135.6 (4 × CH aromatic) 133.2 (2 × *ipso* C), 129.7 (4 × CH aromatic), 127.7 (2 × CH aromatic), 91.7 (OCHOH), 76.8 ($CH_2\underline{C}HCH_2$), 67.5 (CH_2O), 30.0 (CH_2), 27.9 (CH_2), 27.0 ($C(\underline{C}H_3)_3$)), 17.0 (CH_2), 14.3 ($\underline{C}(CH_3)_3$)); *β-anomer* 135.7 (4 × CH aromatic), 133.6 (2 × C *ipso*), 129.9 (4 × CH aromatic), 127.9 (2 × CH aromatic), 96.4 (OCHO), 69.4 ($CH_2\underline{C}HCH_2$), 67.0 (CH_2O), 32.7 (CH_2), 27.3 (CH_2), 27.0 ($C(\underline{C}H_3)_3$)), 21.7 (CH_2), 19.3 ($\underline{C}(CH_3)_3$)); *m/z* (ESP+) 393 (MNa^+, 100%), 388 (13) 352 (10), 283 (11), 274 (33); HRMS (ESP+) expected MNa^+ ($C_{22}H_{30}O_3SiNa$) 393.1856, found 393.1855.

2- Acetoxy-6-(*tert*-butyldiphenylsilanyloxymethyl)tetrahydropyran 126

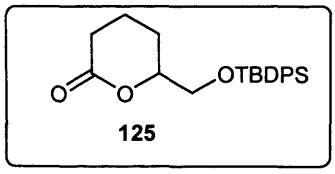


126

To a solution of freshly prepared Dess-Martin periodinane **127** (137 mg, 0.32 mmol) in DCM (3 mL) at 0 °C was added dropwise a solution of lactol **124** (100 mg, 0.27 mmol) in DCM (3 mL). The reaction mixture was allowed to warm to RT and stirred for 2 h. It was then quenched with sat aq $NaHCO_3$ (15 mL) and the organic material extracted with DCM (5 × 15 mL). The combined organic extracts were washed with water (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography (petrol/EtOAc 95:5) afforded the title compound **126** (100 mg, 89%), as a mixture of anomers (α:β 95:5) as a white solid: ν_{max} ($CHCl_3$ cast)/cm^{-1} 3053m, 2932m, 2858m, 1744s, 1427m; δ_H ($CDCl_3$, 400 MHz) *α-anomer* 7.56-7.66 (4H, m, CH aromatic), 7.34-7.58 (6H, m, CH aromatic), 6.10 (1H, d, *J* 2.4, OCHO), 3.90 (1H, ddt, *J* 6.0, 4.8,

2.2, $CH_2C\underline{H}CH_2$), 3.70 (1H, dd, *J* 10.3, 4.8, CH_2O), 3.55 (1H, dd, *J* 10.3, 6.0, CH_2O), 2.07 (3H, s, $C(O)CH_3$), 1.72-1.82 (1H, m, CH_2), 1.65-1.71 (2H, m, CH_2), 1.38-1.45 (2H, m, CH_2), 1.22-1.30 (1H, m, CH_2), 1.05 (9H, s, $(C(CH_3)_3)$); *β-anomer* 7.60-7.66 (4H, m, CH aromatic), 7.32-7.50 (6H, m, CH aromatic), 5.67 (1H, dd, *J* 9.2, 2.2, OCHO), 3.92 (1H, ddt, *J* 6.2, 5.0, 2.2, $CH_2C\underline{H}CH_2$), 3.76 (1H, dd, *J* 9.6, 5.0, CH_2O), 3.59 (1H, dd, *J* 9.6, 6.2, CH_2O), 2.06 (3H, s, $C(O)CH_3$), 1.80-1.85 (2H, m, CH_2), 1.52-1.60 (2H, m, CH_2), 1.32-1.40 (2H, m, CH_2), 1.05 (9H, s, $(C(CH_3)_3)$); δ_C ($CDCl_3$, 100 MHz) *α-anomer* 169.8 (C=O), 135.6 (4 × CH aromatic), 133.6 (2 × *ipso* C), 129.6 (4 × CH aromatic), 127.6 (2 × CH aromatic), 92.4 (O-$\underline{C}$H-CO), 71.7 ($CH_2\underline{C}HCH_2$), 67.0 (CH_2O), 28.6 (CH_2), 27.4 (CH_2), 27.0 ($C(\underline{C}H_3)_3$)), 21.2 (CH_2), 19.3 ($\underline{C}(CH_3)_3$)), 17.3 ($C(O)\underline{C}H_3$); *β-anomer* 169.4 (C=O), 135.6 (4 × CH aromatic), 133.6 (2 × *ipso* C), 129.6 (4 × CH aromatic), 127.6 (2 × CH aromatic), 94.6 (OCHCO), 76.3 ($CH_2\underline{C}HCH_2$), 66.5 (CH_2O), 30.0 (CH_2), 29.7 (CH_2), 26.8 ($C(\underline{C}H_3)_3$)), 20.9 (CH_2), 19.3 ($\underline{C}(CH_3)_3$)), 17.1 ($C(O)\underline{C}H_3$); *m/z* (FAB+) 435 (MNa^+, 100%), 375 (28), 175 (51); HRMS (FAB+) expected MNa^+ ($C_{24}H_{32}O_4SiNa$) 435.1968, found 435.1958.

6-(*tert*-Butyldiphenylsilanyloxymethyl)tetrahydropyran-2-one 125

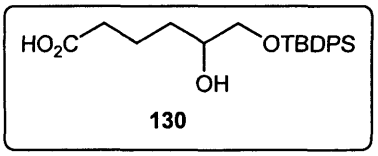


125

To a solution of freshly prepared Dess-Martin periodinane **127** (480 mg, 1.13 mmol) and pyridine (0.62 mL, 7.56 mmol) in DCM (5 mL) at 0 °C was added dropwise a solution of lactol **124** (140 mg, 0.38 mmol) in DCM (3 mL). The reaction mixture was allowed to warm to RT and stirred for 4 h. It was then quenched with water (15 mL) and the organic material extracted with DCM (5 × 15 mL). The combined organic extracts were washed successively with 2M HCl (20 mL), sat aq $CuSO_4$ (20 mL), sat

aq $NaHCO_3$ (20 mL) and water (20 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography (petrol/EtOAc 7:1) afforded the title compound **125** (135 mg, 97%) which was recrystallised from Et_2O:hexane (120 mg, 86%) as white prisms: ν_{max} ($CHCl_3$ cast)/cm^{-1} 3053s, 2932s, 2858s, 1732s, 1464m, 1427m; δ_H ($CDCl_3$, 400 MHz) 7.66-7.69 (4H, m, CH aromatic), 7.37-7.45 (6H, m, CH aromatic), 4.39 (1H, ddt, *J* 9.6, 5.2, 4.3, $CH_2C\underline{H}CH_2$), 3.73 (1H, dd, *J* 10.9, 4.3, CH_2O), 3.70 (1H, dd, *J* 10.9, 5.2, CH_2O), 2.55-2.61 (1H, ddd, *J* 6.1, 5.0, 1.1, $CH_2C{=}O$), 2.40-2.48 (1H, m, $CH_2C{=}O$), 1.93-1.99 (2H, m, CH_2), 1.78-1.83 (2H, m, CH_2), 1.04 (9H, s, CH_3 ($C(CH_3)_3$)); δ_C ($CDCl_3$, 100 MHz): 171.2 (C=O), 135.6 (CH aromatic), 135.5 (CH aromatic), 133.1 (2 × C aromatic), 129.8 (4 × CH aromatic), 127.8 (2 × CH aromatic), 132.9 (2 × *ipso* C), 80.2 ($CH_2\underline{C}HCH_2$), 65.6 (CH_2O), 29.9 (CH_2), 26.8 ($C(\underline{C}H_3)_3$)), 24.5 (CH_2), 19.3 ($\underline{C}(CH_3)_3$)), 18.3 (CH_2); *m/z* (CI+) 369 (MH^+, 7%), 311 (88), 291 (100), 267 (24), 233 (72), 213 (60), 199 (31), 135 (25); HRMS (CI+) expected MH^+ ($C_{22}H_{29}O_3Si$) 369.1886, found 369.1892.

6-(*tert*-Butyldiphenylsilanyloxy)-5-hydroxyhexanoic acid 130

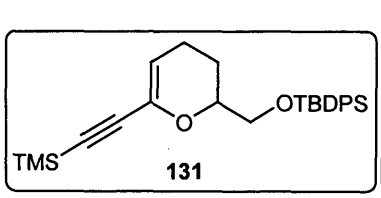


130

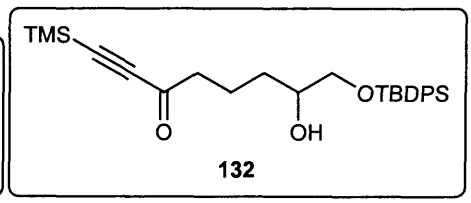
Cerium chloride heptahydrate (202 mg, 0.54 mmol) was made anhydrous by heating at 140 °C for 3 h under high vacuum (2 mmHg) and then allowed to cool to RT before it was suspended in THF (2 mL) and the resulting mixture was stirred for 2 h. To a solution of trimethysilylacetylene (94 μL, 0.68 mmol) in THF (2 mL) at –78 °C was added *n*-BuLi (2.25 M in hexane, 455 μL, 1.02 mmol) dropwise and the resulting mixture was stirred for 45 min. This solution was added dropwise to the cerium chloride suspension at –78 °C and stirred for 1 h before a solution of lactone **125** (150

mg, 0.47 mmol) in THF (2 mL) was added dropwise. The mixture was stirred for 30 min at –78 °C then allowed to warm to RT and stirred for 14 h. The precipitate was removed by filtration through Celite® and rinsed with THF (40 mL). The combined filtrate and washings were concentrated *in vacuo* and the residue was subjected to column chromatography (petrol/EtOAc 7:1 to 3:1) affording recovered starting material **125** (65 mg, 43%) then the title compound **148** (71 mg, 39%) as a colourless liquid: δ_H ($CDCl_3$, 400 MHz) 7.67-7.76 (4H, m, CH aromatic), 7.34-7.42 (6H, m, CH aromatic), 3.70 (1H, ddddd, *J* 9.5, 7.4, 7.3, 4.3, 3.4, C<u>H</u>OH), 3.62 (1H, *J* 10.1, 3.4, CH_2OTBDPS), 3.47 (1H, *J* 10.1, 7.4, CH_2OTBDPS), 2.35 (2H, t, *J* 7.4, C<u>H</u>$_2$CHOH), 2.35 (2H, t, *J* 7.4, C(O)CH_2), 1.75-1.78 (2H, m, CH_2), 1.63-1.73 (2H, m, CH_2), 1.06 (9H, s, (C(CH_3)$_3$)); δ_C ($CDCl_3$, 100 MHz) 178.6 (C=O), 135.5 (4 × CH aromatic), 133.0 (2 × *ipso* C), 129.8 (2 × CH aromatic), 127.8 (4 × CH aromatic), 71.5 (CHOH), 68.2 (<u>C</u>H_2OTBDPS), 31.8 (CH_2), 26.8 (C(<u>C</u>H_3)$_3$)), 20.7 (CH_2), 19.8 (CH_2), 19.2 (<u>C</u>(CH_3)$_3$)); *m/z* (FAB+) 409 (MNa^+, 90%), 161 (100); HRMS (FAB+) expected MNa^+ ($C_{22}H_{30}O_4SiNa$) 409.1811, found 409.1819.

2-(*tert*-Butyldiphenylsilanyloxymethyl)-6-(trimethylsilanylethynyl)-3,4-dihydro-2*H*-pyran 131 and 8-(*tert*-butyldiphenylsilanyloxy)-7-hydroxy-1-trimethylsilanyl-oct-1-yn-3-one 132



131



132

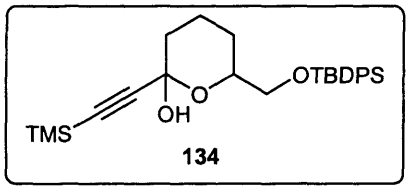
Cerium chloride heptahydrate (405 mg, 1.09 mmol) was made anhydrous by heating at 140 °C for 3 h under high vacuum (2 mmHg) and then allowed to cool to RT before it was suspended in THF (4 mL) and the resulting mixture was stirred for 2 h. To a

solution of trimethysilylacetylene (190 μL, 0.68 mmol) in THF (3 mL) at –78 °C was added *t*-BuLi (1.50 M in hexane, 901 μL, 1.36 mmol) dropwise and the resulting mixture was stirred for 45 min. This solution was added dropwise to the cerium chloride suspension at –78 °C and stirred for 1 h before a solution of lactone **125** (200 mg, 0.53 mmol) in THF (3 mL) was added dropwise. The mixture was stirred for 30 min at –78 °C and then allowed to warm to RT and stirred for 14 h. The precipitate was removed by filtration through Celite® and rinsed with THF (40 mL). The combined filtrate and washings were concentrated *in vacuo* and the residue was subjected to column chromatography (petrol/EtOAc 7:1) afforded recovered lactone **125** (40 mg, 20%), and enyne **131** (96 mg, 47%) as a colourless oil: ν_{max} ($CHCl_3$ cast)/cm^{-1} 3053m, 2930m, 2858m, 2305m, 1480w, 1427m; δ_H ($CDCl_3$, 500 MHz) 7.64-7.67 (4H, m, CH aromatic), 7.35-7.42 (6H, m, CH aromatic), 4.01 (1H, dddd, J 6.7, 6.3, 4.9, 3.2, $CH_2C\underline{H}CH_2$), 3.86 (1H, dt, *J* 4.9, 3.3, CH=C), 3.76 (1H, dd, *J* 10.4, 4.9, CH_2O), 3.64 (1H, dd, *J* 10.4, 6.7, CH_2O), 2.08-2.12 (1H, m, CH_2), 1.92-2.03 (1H, m, CH_2), 1.63-1.72 (1H, m, CH_2), 1.07-1.26 (1H, m, CH_2), 1.07 (9H, s, $(C(CH_3)_3)$), 0.04 (9H, s, $Si(CH_3)_3$); δ_C ($CDCl_3$, 125 MHz) 135.5 (4 × CH aromatic), 133.4 (2 × *ipso* C), 129.6 (2 × CH aromatic), 127.6 (4 × CH aromatic), 127.4 (CH=$\underline{C}$) 109.3 ($\underline{C}$H=C), 100.0 ($\underline{C}$≡CSi$(CH_3)_3$), 92.1 ($\underline{C}$Si$(CH_3)_3$), 75.8 (CHO), 65.4 (CH_2O), 26.8 (C($\underline{C}H_3)_3$)), 20.3 (CH_2), 19.2 ($\underline{C}(CH_3)_3$)), 19.1 (CH_2), –0.3 (Si($\underline{C}H_3)_3$); *m/z* (CI+) 449 (MH^+, 14%), 433 (32), 391 (85), 371 (52), 357 (18), 321 (24), 299 (17), 279 (95), 239 (42), 221 (17), 164 (100); HRMS (FAB+) expected MH^+ ($C_{27}H_{37}O_2Si_2$) 449.2332, found 449.2347.

Further elution with petrol/EtOAc (3:1) afforded ynone **132** (15 mg, 7%) as a colourless oil; ν_{max} ($CHCl_3$ cast)/cm^{-1} 3440br, 3055m, 2930m, 2855m, 2304m, 1745s, 1480w, 1428m; δ_H ($CDCl_3$, 500 MHz) 7.64-7.67 (4H, m, CH aromatic), 7.35-7.42

(6H, m, CH aromatic), 3.69 (1H, ddddd, *J* 9.0, 7.5, 5.9, 5.1, 3.5, C<u>H</u>-OH), 3.62 (1H, dd, *J* 10.2, 3.5, CH_2O), 3.46 (1H, dd, *J* 10.2, 7.5, CH_2O), 2.55 (1H, dt, *J* 7.6, 7.1, CH_2CO), 2.54 (1H, dt, *J* 7.6, 7.1, CH_2CO), 2.50 (1H, br s, OH), 1.74-1.81 (1H, m, CH_2), 1.64-1.70 (1H, m, CH_2), 1.38-1.41 (2H, m, CH_2), 1.06 (9H, s, $(C(CH_3)_3)$), 0.20 (9H, s, $Si(CH_3)_3$) δ_C ($CDCl_3$, 125 MHz) 187.5 (C=O), 135.5 (4 × CH aromatic), 133.0 (2 × *ipso* C), 129.8 (4 × CH aromatic), 127.7 (2 × CH aromatic), 101.9 (<u>C</u>≡$CSi(CH_3)_3$), 97.7 ($\underline{C}Si(CH_3)_3$), 71.5 (CHOH), 67.8 (CH_2O), 45.0 (CH_2), 31.8 (CH_2), 27.6 ($C(\underline{C}H_3)_3$)), 20.4 (CH_2), 19.5 ($\underline{C}(CH_3)_3$)), –0.8 ($Si(\underline{C}H_3)_3$); *m/z* (CI+) 467 (MH^+, 22%), 319 (11), 297 (15), 277 (40), 239 (23), 199 (100), 179 (28), 147 (63), 91 (41); HRMS (CI+) expected MH^+ ($C_{27}H_{39}O_3Si_2$) 467.2438, found 467.2415.

6-(*tert*-Butyldiphenylsilanyloxymethyl)-2-(trimethylsilanylethynyl)tetrahydropyran-2-ol 134



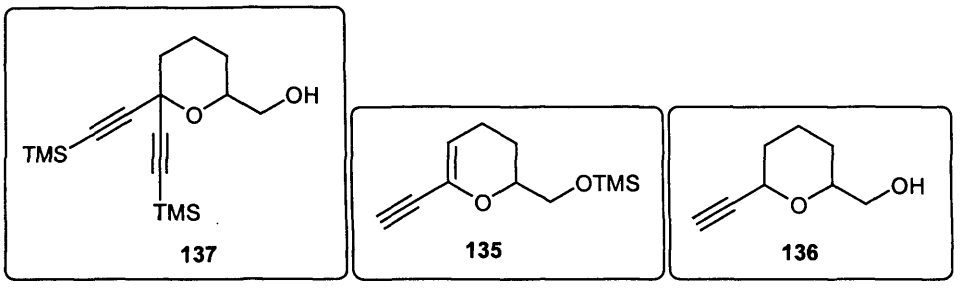
134

Cerium chloride heptahydrate (1.21 g, 3.26 mmol) was made anhydrous by heating at 140 °C for 3 h under high vacuum (2 mmHg) and then allowed to cool to RT before it was suspended in THF (6 mL) and the resulting mixture was stirred for 2 h before it was treated with *t*-BuLi (1.50 M in hexane, 1.10 mL, 1.09 mmol). To a solution of trimethysilylacetylene (0.56 mL, 4.1 mmol) in THF (6 mL) at –78 °C was added *t*-BuLi (1.50 M in hexane, 2.70 mL, 4.08 mmol) dropwise and the resulting mixture was stirred for 45 min. This solution was added dropwise to the cerium chloride suspension at –78 °C and stirred for 1 h before a solution of lactone **125** (600 mg, 1.63 mmol) in THF (3 mL) was added dropwise. The mixture was stirred for 30 min at –78

°C and then allowed to warm to RT and stirred for 14 h. The precipitate was removed by filtration through Celite® and rinsed with THF (40 mL). The combined filtrate and washings were concentrated *in vacuo* and the residue was subjected to column chromatography (petrol/EtOAc 7:1) affording the title compound **134** (450 mg, 61%) as a colourless oil: ν_{max} ($CHCl_3$ cast)/cm^{-1} 3406br, 3053s, 2960s, 2931s, 2858s, 2305m, 1472m, 1428m; δ_H ($CDCl_3$, 500 MHz) 7.63-7.69 (4H, m, CH aromatic), 7.35-7.41 (6H, m, CH aromatic), 3.72 (1H, dddd, *J* 7.6, 6.1, 4.9, 3.4, C<u>H</u>-O), 3.64 (1H, dd, *J* 10.1, 3.4, CH_2O), 3.47 (1H, dd, *J* 10.1, 7.6, CH_2O), 2.51 (1H, br. s, OH), 1.60-1.64 (2H, m, CH_2), 1.49-1.56 (2H, m, CH_2), 1.39-1.46 (2H, m, CH_2), 1.04 (9H, s, ($C(CH_3)_3$)), 0.12 (9H, s, $Si(CH_3)_3$); δ_C ($CDCl_3$, 125 MHz) 135.5 (4 × CH aromatic), 133.0 (2 × *ipso* C), 129.8 (4 × CH aromatic), 127.7 (2 × CH aromatic), 105.0 (<u>C</u>≡$CSi(CH_3)_3$), 88.1 (COH), 71.5 (CHO), 68.0 (CH_2O), 63.9 (<u>C</u>$Si(CH_3)_3$), 43.4 (CH_2), 32.3 (CH_2), 26.7 ($C(\underline{C}H_3)_3$)), 20.3 (CH_2), 19.2 ($\underline{C}(CH_3)_3$)), –0.3 ($Si(\underline{C}H_3)_3$); *m/z* (CI+) 467 (MH^+, 21%), 319 (10) 297 (15), 277 (38), 239 (22), 199 (100), 179 (27), 147 (61), 91 (41); HRMS (CI+) expected MH^+ ($C_{27}H_{39}O_3Si_2$) 467.2438, found 467.2415.

Further elution with petrol/EtOAc (7:1) afforded enyne **131** (120 mg, 16%) as a colourless oil.

6,6-Bis(trimethylsilanylethynyl)tetrahydropyran-2-methanol 137, 6-ethynyl-2-trimethylsilanyloxymethyl-3,4-dihydro-2*H*-pyran 135, 6-ethynyltetrahydropyran-2-methanol 136

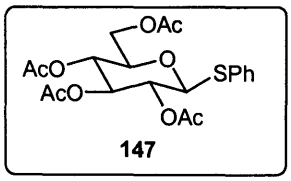


To a solution of hemiacetal **134** (133 mg, 0.29 mmol) and triethylsilane (182 μL, 1.14 mmol) in acetonitrile (2.8 mL) at –10 °C was added dropwise freshly distilled boron trifluoride diethyl etherate (145 μL, 1.14 mmol). The mixture was maintained at –10 °C for 1 h then allowed to warm to RT and stirred for 14 h. Triethylamine (0.2 mL, 1.90 mmol) was then added, and the mixture was concentrated *in vacuo*. The residue was partitioned between water (5 mL) and DCM (10 mL), and the organic material extracted with further DCM (4 × 10 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (petrol/EtOAc 7:1) afforded dialkyne **137** (22 mg, 23%) as a colourless oil: ν_{max} ($CHCl_3$ cast)/cm^{-1} 3410br, 2925m, 2870m, 2253s, 1470m, 1385m; δ_H ($CDCl_3$, 400 MHz) 3.95 (1H, dddd, *J* 9.2, 5.9, 4.8, 2.5, CHO), 3.56 (1H, dd, *J* 10.6, 4.4, CH_2O), 3.53 (1H, dd, *J* 10.6, 5.9, CH_2O), 1.95-1.98 (1H, m, CH_2), 1.83-1.87 (2H, m, CH_2), 1.66-1.71 (1H, m, CH_2), 1.17-1.44 (2H, m, CH_2), 0.18 (9H, s, $Si(CH_3)_3$), 0.17 (9H, s, $Si(CH_3)_3$); δ_C ($CDCl_3$, 100 MHz) 104.3 ($\underline{C}\equiv CSi(CH_3)_3$), 101.5 ($\underline{C}\equiv CSi(CH_3)_3$), 91.6 ($\underline{C}Si(CH_3)_3$), 87.6 ($\underline{C}Si(CH_3)_3$), 73.4 (CHO), 66.7 (CO), 65.8 (CH_2O), 38.2 (CH_2), 25.9 (CH_2), 19.4 (CH_2), –0.2 ($Si(\underline{C}H_3)_3$), –0.3 ($Si(\underline{C}H_3)_3$); *m/z* (FAB+) 331 (MNa^+, 100%), 176 (15); HRMS (FAB+) expected MNa^+ ($C_{16}H_{28}O_2NaSi_2$) 331.1525, found 331.1519.

Further elution with petrol/EtOAc (5:1) afforded enyne **135** (12 mg, 30%) as a colourless oil: ν_{max} ($CHCl_3$ cast)/cm^{-1} 2925m, 2870m, 2253s, 1476m, 1396m; δ_H ($CDCl_3$, 500 MHz) 6.41 (1H, t, *J* 7.1, C=CH), 3.69 (1H, dddd, *J* 7.5, 6.5, 4.9, 3.4, CHO), 3.63 (1H, dd, *J* 10.9, 3.4, CH_2O), 3.45 (1H, dd, *J* 10.9, 7.5, CH_2O), 2.83 (1H, s, C≡C<u>H</u>), 2.55-2.40 (2H, m, C<u>H</u>$_2$-CH=), 1.52-1.60 (2H, m, C<u>H</u>$_2$-CH), 0.20 (9H, s, $Si(CH_3)_3$); δ_C ($CDCl_3$, 125 MHz) 150.7 (<u>C</u>H=C), 105.6 (CH=<u>C</u>), 84.1 (<u>C</u>≡CH), 75.3 (C≡<u>C</u>H), 71.1 (CHO), 66.5 (CH_2O), 31.4 (CH_2), 26.7 (CH_2), –0.2 (Si(<u>C</u>H_3)$_3$); *m/z* (FAB+) 233 (MNa^+, 13%), 176 (100); HRMS (FAB+) expected MNa^+ ($C_{11}H_{18}O_2SiNa$) 233.0974, found 233.0978.

Further elution with petrol/EtOAc (3:1) afforded alcohol **136** (10 mg, 16%) as a colourless oil; ν_{max} ($CHCl_3$ cast)/cm^{-1} 3400br, 2927m, 2870m, 2253s, 1473m, 1390m; δ_H ($CDCl_3$, 500 MHz) 4.14 (1H, dt, *J* 11.4, 2.2, C≡CCH), 3.58 (1H, dd, *J* 11.9, 3.4, CH_2O), 3.55 (1H, dd, *J* 11.9, 2.4, CH_2O), 3.46 (1H, dddd, *J* 3.6, 3.4, 2.4, 2.0, CHO), 2.46 (1H, d, *J* 2.2, C≡C<u>H</u>), 2.05 (1H, br s, OH), 1.82-1.89 (2H, m, CH_2), 1.63-1.66 (1H, m, CH_2), 1.45-1.56 (3H, m, CH_2), 1.30-1.33 (1H, m, CH_2); δ_C ($CDCl_3$, 125 MHz) 83.0 (<u>C</u>≡CH), 78.7 (C≡C<u>C</u>HO), 72.5 (C≡<u>C</u>H), 67.7 (C<u>C</u>HO), 66.0 (CH_2O), 32.3 (CH_2), 26.2 (CH_2), 22.6 (CH_2); *m/z* (FAB+) 233 (MNa^+, 13%), 147 (100); HRMS (FAB+) expected MNa^+ ($C_8H_{12}O_2Na$) 163.0735, found 163.0731.

Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside 147

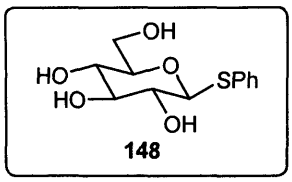


147

To a solution of penta-*O*-acetyl-β-D-glucopyranose **146** (56.0 g, 143 mmol) in DCM (1.3 L) at 0 °C were added dropwise thiophenol (19.1 mL, 186 mmol) and $BF_3.Et_2O$

(54.5 mL, 431 mmol). The reaction mixture was allowed to warm to RT and stirred for 12 h. Sat aq $NaHCO_3$ (1 L) was added and the organic material was extracted with DCM (5 × 250 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation from EtOAc/petrol yielded the title compound **147** (55.0 g, 88%), as white flakes: mp 117-118 °C; $[\alpha]_D^{20} = -36.0$ (*c* 1.75 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3055s, 2988m, 1757s, 1601w, 1583w, 1504w; δ_H ($CDCl_3$, 300 MHz) 7.50-7.44 (2H, m, CH aromatic), 7.33-7.22 (3H, m, CH aromatic), 5.20 (1H, dd, *J* 9.7, 9.4, H-3), 5.02 (1H, dd, *J* 9.7, 9.4, H-4), 4.98 (1H, dd, *J* 10.2, 9.4, H-2), 4.68 (1H, d, *J* 10.2, H-1), 4.22 (1H, dd, *J* 12.3, 4.8, H-6'), 4.18 (1H, dd, *J* 12.3, 3.5, H-6), 3.71 (1H, ddd, *J* 9.9, 4.8, 3.5, H-5), 2.06 (3H, s, CH_3), 2.05 (3H, s, CH_3), 1.99 (3H, s, CH_3), 1.95 (3H, s, CH_3); δ_C ($CDCl_3$, 75 MHz) 170.5 (C=O), 170.1 (C=O), 169.4 (C=O), 169.2 (C=O), 133.1 (2 × CH aromatic), 131.6 (*ipso* C), 128.9 (CH aromatic), 128.4 (2 × CH aromatic), 85.7 (C-1), 75.8 (C-3), 74.0 (C-2), 69.9 (C-4), 68.2(C-5), 62.1 (C-6), 21.0 (CH_3), 20.7 (CH_3), 20.7 (CH_3), 20.6 (CH_3); *m/z* (FAB+) 463 (MNa^+, 58%), 329 (21), 245 (100) 199 (14), 154 (13), 91 (100); HRMS (FAB+) expected MNa^+ ($C_{20}H_{24}O_9SNa$) 463.1039, found 463.1043.

Phenyl 1-thio-β-D-glucopyranoside 148

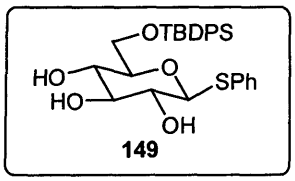


148

To a solution of thioglycoside **147** (2.10 g, 4.77 mmol) in MeOH (15 mL) was added sodium methoxide powder (1.24 g, 22.9 mmol) at RT. The reaction was stirred for 30 min. Dowex® 50×8 resin (10 g) was added until neutralisation; the suspension was filtered and the filtrate was concentrated *in vacuo*. The crude title compound **148**

(1.29 g, 100%) was used in the next step without further purification: mp 130-132 °C; $[\alpha]_D^{20}$ = –67.8 (*c* 3.25 in EtOH); ν_{max} (neat)/cm^{-1} 3055br, 2988m, 2958m, 1634m, 1421m; δ_H (DMSO-d_6, 300 MHz) 7.44 (2H, d, *J* 8.1, CH aromatic), 7.29 (2H, t, *J* 8.1, CH aromatic), 7.20 (1H, t, *J* 8.1, CH aromatic), 4.59 (1H, d, *J* 9.7, H-1), 3.67 (1H, dd, *J* 11.9, 1.7, H-6), 3.42 (1H, dd, *J* 11.9, 5.9, H-6'), 3.21 (1H, dd, *J* 9.4, 8.9, H-3), 3.16 (1H, dd, *J* 9.6, 9.4, H-4), 3.07 (1H, ddd, *J* 9.6, 5.9, 1.7, H-5), 3.03 (1H, dd, *J* 9.7, 8.9, H-2); δ_C (d_6-DMSO, 75 MHz) 135.7 (*ipso* C), 129.5 (2 × CH aromatic), 128.8 (CH aromatic), 126.2 (2 × CH aromatic), 87.1 (C-1), 80.9 (C-5), 78.1 (C-3), 72.3 (C-2), 69.7 (C-4), 60.9 (C-6); *m/z* (FAB+) 295 (MNa^+, 29%), 199 (100); HRMS (FAB+) expected MNa^+ ($C_{12}H_{16}O_5SNa$) 295.0616, found 295.0621.

Phenyl 6-*O*-*tert*-butyldiphenylsilanyl-1-thio-β-D-glucopyranosise 149

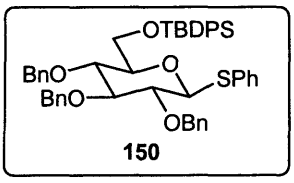


149

To solution of tetraol **148** (2.50 g, 9.19 mmol) in dry DMF (90 mL) at 0 °C was added imidazole (1.14 g, 18.4 mmol) followed by *tert*-butyldiphenylsilyl chloride (2.63 mL, 10.1 mmol) dropwise. The reaction mixture was stirred for 6 h. Sat aq NH_4Cl (30 mL) was added and the organic material was extracted with EtOAc (5 × 15 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 3:1) afforded the title compound **149** (4.60 g, 99%) as a colourless liquid: $[\alpha]_D^{20}$ = –45.0 (*c* 1.25 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3385br, 3053s, 2986m, 1601w, 1585w, 1504w; δ_H ($CDCl_3$, 400 MHz) 7.78-7.76 (4H, m, CH aromatic), 7.56-7.54 (2H, m, CH aromatic), 7.42-7.35 (6H, m, CH aromatic), 7.17-7.16 (3H, m, CH aromatic), 4.59 (1H, d, *J* 9.8, H-1), 4.00 (1H, dd, *J* 11.2, 2.9, H-6),

3.88 (1H, dd, *J* 11.2, 5.5, H-6'), 3.60 (1H, dd, *J* 9.0, 8.9, H-3), 3.53 (1H, dd, *J* 9.2, 9.0, H-4), 3.47 (1H, ddd, *J* 9.2, 5.5, 2.9, H-5), 3.43 (1H, dd, *J* 9.8, 8.9, H-2), 1.10 (9H, s, $C(CH_3)_3$); δ_C ($CDCl_3$, 100 MHz) 135.7 (4 × CH aromatic), 135.6 (4 × CH aromatic), 133.2 (*ipso* C), 133.1 (*ipso* C), 133.0 (*ipso* C), 131.7 (2 × CH aromatic), 129.7 (CH aromatic), 128.9 (CH aromatic), 127.5 (2 × CH aromatic), 87.7 (C-1), 79.7 (C-3), 77.9 (C-2), 71.9 (C-4), 70.5 (C-5), 64.0 (C-6), 26.8 ($C(\underline{C}H_3)_3$), 19.2 ($\underline{C}(CH_3)_3$); *m/z* (FAB+) 533 (MNa^+, 50%), 326 (14), 301 (100); HRMS (FAB+) expected MNa^+ ($C_{28}H_{34}O_5SSiNa$) 533.1794, found 533.1796.

Phenyl 2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilanyl-1-thio-β-D-glucopyranoside 150

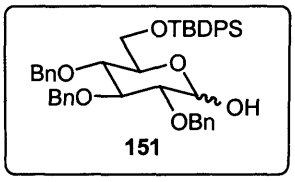


150

Sodium hydride (60% in mineral oil, 5.90 g, 154 mmol) was washed twice with petrol to remove mineral oil, then suspended in dry DMF (250 mL) and cooled to 0 °C. Silyl ether **149** (15.7 g, 30.7 mmol) was added and the mixture stirred for 1 h, then a solution of benzyl bromide (18.4 mL, 154 mmol) in DMF (50 mL) was added dropwise. The reaction mixture was stirred for 2 h at RT. Methanol (6 mL) was added and the mixture was partitioned between EtOAc (300 mL) and water (50 mL). The organic material was futher extracted from the aqueous phase with EtOAc (5 × 50 mL) and the organic extracts were then combined, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 1:10) afforded the title compound **150** (23.8 g, 97%) as a colourless oil: $[\alpha]_D^{20} = -11.5$ (*c* 0.82 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 2988m, 1601w, 1583w, 1504w; δ_H ($CDCl_3$, 400 MHz) 7.78 (2H, d, *J* 8.0,

CH aromatic), 7.72 (2H, d, *J* 7.9, CH aromatic), 7.55-7.50 (2H, m, CH aromatic), 7.42-7.00 (24H, m, CH aromatic), 4.92-4.86 (5H, m, $PhCH_2$), 4.74 (1H, d, *J* 9.7, H-1), 4.70 (1H, d, *J* 11.0, $PhCH_2$), 3.99 (1H, dd, *J* 11.4, 1.9, H-6), 3.96 (1H, dd, *J* 11.4, 3.8, H-6'), 3.82 (1H, dd, *J* 9.3, 8.7, H-4), 3.74 (1H, dd, *J* 8.8, 8.7, H-3), 3.56 (1H, dd, *J* 9.7, 8.8, H-2), 3.41 (1H, ddd, *J* 9.3, 3.8, 1.9, H-5), 1.10 (9H, s, $C(CH_3)_3$); δ_C ($CDCl_3$, 100 MHz) 138.4 (*ipso* C), 138.2 (*ipso* C), 138.1 (*ipso* C), 135.9 (4 × CH aromatic), 135.7 (2 × CH aromatic), 134.2 (*ipso* C), 133.5 (*ipso* C), 132.9 (CH aromatic), 131.7 (CH aromatic), 129.7 (CH aromatic), 128.9 (2 × CH aromatic), 128.5 (4 × CH aromatic), 128.4 (CH aromatic), 128.2 (2 × CH aromatic), 128.0 (2 × CH aromatic), 127.9 (2 × CH aromatic), 127.9 (2 × CH aromatic), 127.8 (2 × CH aromatic), 127.7 (2 × CH aromatic), 127.3 (2 × CH aromatic), 87.5 (C-1), 86.9 (C-3), 80.8 (C-2), 78.0 (C-4), 77.4 (C-5), 76.0 ($PhCH_2$), 75.4 ($PhCH_2$), 75.2 ($PhCH_2$), 62.7 (C-6) 26.9 ($C(\underline{C}H_3)_3$), 19.3 ($\underline{C}(CH_3)_3$)); *m/z* (FAB+) 803 (MNa^+, 65%), 711 (27), 487 (12), 349 (100), 326 (11); HRMS (FAB+) expected MNa^+ ($C_{49}H_{52}O_5SSiNa$) 803.3202, found 803.331.

2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilanyl-D-glucopyranose 151



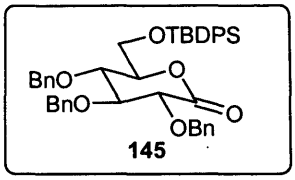
151

A mixture of tribenzyl ether **145** (1.05 g, 1.32 mmol) and *N*-bromosuccinimide (0.29 g, 1.65 mmol) in acetone/water (9:1, 5 mL) was stirred at 0 °C for 3 h. $NaHCO_3$ (100 mg) was added and the resulting mixture was concentrated *in vacuo*. It was then partitioned between EtOAc/H_2O (5:1, 100 mL). The organic material was further extracted from the aqueous layer with EtOAc (4 × 10 mL). The organic extracts were combined, washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*.

Column chromatography (EtOAc/petrol 1:10 to 1:5 to 1:3) afforded the title compound **151** (0.85 g, 94%), as a mixture of anomers (1:1) as a white solid: ν_{max} ($CHCl_3$ cast)/cm^{-1} 3423br, 2988m, 1600w, 1581w, 1502w; δ_H ($CDCl_3$, 500 MHz) *α-anomer* 7.77-7.70 (6H, m, CH aromatic), 7.40-7.12 (19H, m, CH aromatic), 5.29 (1H, dd, *J* 3.6, 1.5, H-1), 4.99-4.68 (6H, m, 3 × $PhCH_2$), 4.12 (1H, dd, *J* 9.5, 9.3, H-3), 4.05 (1H, dd, *J* 11.5, 9.6, H-6'), 4.01 (1H, dd, *J* 11.5, 4.9, H-6), 3.92 (1H, ddd, *J* 9.6, 9.5, 4.9, H-5), 3.81 (1H, dd, *J* 9.5, 9.3, H-4), 3.60 (1H, dd, *J* 9.5, 3.6, H-2), 2.90 (1H, d, *J* 1.5, OH), 1.08 (9H, s, $C(CH_3)_3$); *β-anomer* 7.89-7.72 (6H, m, CH aromatic), 7.40-7.12 (19H, m, CH aromatic), 4.99-4.68 (6H, m, 3 × $PhCH_2$),4.63 (1H, dd, *J* 9.0, 5.2, H-1), 3.96 (1H, dd, *J* 11.9, 9.5, H-6'), 3.93 (1H, dd, *J* 11.9, 4.2, H-6), 3.88 (1H, ddd, *J* 9.5, 9.4, 4.2, H-5), 3.75 (1H, dd, *J* 9.5, 9.2, H-4), 3.67 (1H, dd, *J* 9.2, 9.1, H-3), 3.39 (1H, dd, *J* 9.1, 9.0, H-2), 2.97 (1H, d, *J* 5.2, OH), 1.09 (9H, s, $C(CH_3)_3$); δ_C ($CDCl_3$, 125 MHz) *α-anomer* 138.6 (4 × CH aromatic), 138.5 (*ipso* C), 138.2 (*ipso* C), 137.9 (CH aromatic), 135.8 (2 × CH aromatic), 135.6 (CH aromatic), 133.8 (*ipso* C), 133.2 (4 × CH aromatic), 129.6 (*ipso* C), 128. 5(*ipso* C), 128.4 (2 × CH aromatic), 128.4 (CH aromatic), 128.1 (CH aromatic), 128.0 (2 × CH aromatic), 127.9 (CH aromatic), 127.8 (2 × CH aromatic), 127.7 (2 × CH aromatic), 127.7 (CH aromatic), 127.5 (2 × CH aromatic), 127.4 (2 × CH aromatic), 91.2 (C-1), 81.8 (C-3), 80.5 (C-2), 77.5 ($PhCH_2$), 76.7 ($PhCH_2$), 75.8 ($PhCH_2$), 75.9 (C-4), 73.3 (C-5), 62.6 (C-6), 26.9 ($C(\underline{C}H_3)_3$), 19.3 ($\underline{C}(CH_3)_3$); *β-anomer* 138.5 (*ipso* C), 138.4 (4 × CH aromatic), 138.1 (*ipso* C), 136.0 (2 × CH aromatic), 135.6 (2 × CH aromatic), 135.0 (CH aromatic), 133.7 (*ipso* C), 133.2 (CH aromatic), 129.6 (4 × CH aromatic), 129. 5 (*ipso* C), 129.4 (*ipso* C), 128.4 (CH aromatic), 128.3 (4 × CH aromatic), 128.0 (2 × CH aromatic), 127.8 (2 × CH aromatic), 97.4 (C-1), 84.6 (C-3), 83.6 (C-2), 77.4 ($PhCH_2$), 77.2 (C-4), 75.9 ($PhCH_2$), 75.0 (C-5), 74.7 ($PhCH_2$), 62.9 (C-6), 26.9 ($C(\underline{C}H_3)_3$), 19.3 ($\underline{C}(CH_3)_3$); *m/z*

(FAB+) 711 (MNa^+, 27%), 413 (13), 326 (18), 301 (100); HRMS (FAB+) expected MNa^+ ($C_{43}H_{48}O_6SiNa$) 711.3118, found 711.3102.

2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilanyl-D-glucono-1,5-lactone 145

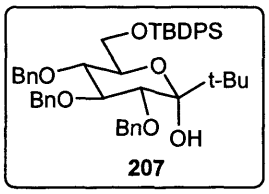


145

To a solution of Dess-Martin periodinane **127** (9.24 g, 21.8 mmol) and pyridine (11.8 mL, 145 mmol) in DCM (75 mL) at 0 °C was added dropwise a solution of lactol **151** (5.00 g, 7.3 mmol) in DCM (30 mL). The reaction mixture was allowed to warm to RT and stirred for 14 h. H_2O (40 mL) was added and the two phases separated; the organic material was further extracted from the aqueous layer with DCM (5 × 50 mL). The organic extracts were combined and washed with 2M HCl (100 mL), H_2O (100 mL), sat aq $CuSO_4$ (100 mL), sat aq $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 1:10) afforded the title compound **145** (4.49 g, 90%) as a white solid: mp 120-123 °C; $[\alpha]_D^{20}$ = +18.9 (*c* 2.80 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3444s, 2986m, 1755s, 1600w, 1580w, 1502w; δ_H ($CDCl_3$, 300 MHz) 7.79-7.68 (6H, m, CH aromatic), 7.48-7.22 (19H, m, CH aromatic), 5.10 (1H, d, *J* 11.2, $PhCH_2$, 4.86 (1H, d, *J* 11.2, $PhCH_2$), 4.84 (1H, d, *J* 11.2, $PhCH_2$), 4.73 (1H, d, *J* 11.2, $PhCH_2$), 4.70 (1H, d, *J* 11.2, $PhCH_2$), 4.64 (1H, d, *J* 11.2, $PhCH_2$), 4.56 (1H, ddd, *J* 9.1, 8.6, 2.4, H-5), 4.21 (1H, d, *J* 7.0, H-2), 4.17 (1H, dd, *J* 8.6, 7.2, H-4), 4.03 (1H, dd, *J* 7.2, 7.0, H-3), 4.01 (1H, dd, *J* 11.8, 9.1, H-6'), 3.94 (1H, dd, *J* 11.8, 2.9, H-6), 1.14 (9H, s, $C(CH_3)_3$); δ_C ($CDCl_3$, 75 MHz) 169.5 (C=O), 137.7 (*ipso* C), 137.6 (*ipso* C), 137.1 (*ipso* C), 135.9 (4 × CH aromatic), 135.7 (2 × CH aromatic), 133.1 (*ipso* C), 132.5 (*ipso* C), 130.0 (CH aromatic), 129.9

(CH aromatic), 128.6 (CH aromatic), 128.5 (2 × CH aromatic), 128.4 (4 × CH aromatic), 128.2 (CH aromatic), 128.1 (CH aromatic), 128.0 (2 × CH aromatic), 127.96 (2 × CH aromatic), 127.93 (2 × CH aromatic), 127.91 (2 × CH aromatic), 127.8 (CH aromatic), 127.7 (CH aromatic), 81.1 (C-3), 79.3 (C-2), 77.8 (C-4), 75.9 (C-5), 74.2 ($PhCH_2$), 74.0 ($PhCH_2$), 73.9 ($PhCH_2$), 62.3 (C-6), 27.0 ($C(\underline{C}H_3)_3$), 19.4 ($\underline{C}(CH_3)_3$); *m/z* (FAB+) 709 (MNa^+, 37%), 199 (100); HRMS (FAB+) expected MNa^+ ($C_{43}H_{46}O_6SiNa$) 709.2961, found 709.2974.

2,3,4-Tri-*O*-benzyl-1-*C*-*tert*-butyl-6-*O*-*tert*-butyldiphenylsilanyl-α-D-glucopyranose 207

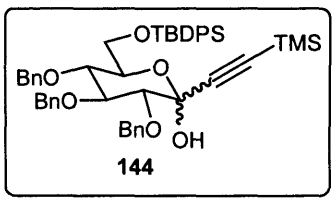


207

Cerium chloride heptahydrate (402 mg, 1.08 mmol) was made anhydrous by heating at 140 °C for 3 h under high vacuum (2 mmHg) and then allowed to cool to RT before it was suspended in THF (2 mL) and the resulting mixture was stirred for 2 h. To a solution of trimethysilylacetylene (187 μL, 1.35 mmol) in THF (2 mL) at –78 °C was added *t*-BuLi (1.5 M in hexane, 0.90 mL, 1.35 mmol) dropwise and the resulting mixture was stirred for 45 min. This solution was added dropwise to the cerium chloride suspension at –78 °C and stirred for 1 h before a solution of lactone **145** (370 mg, 0.54 mmol) in THF (2 mL) was added dropwise. The mixture was stirred for 30 min at –78 °C then allowed to warm to RT and stirred for 14 h. The precipitate was removed by filtration through Celite® and rinsed with THF (40 mL). The combined filtrate and washings were concentrated *in vacuo* and the residue was subjected to column chromatography (EtOAc/petrol 25:1) affording the title compound **207** (180

mg, 48%) as a colourless oil: $[\alpha]_D^{20}$ = +34.0 (*c* 2.25 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3408s, 2985m, 1601w, 1583w, 1504w; δ_H ($CDCl_3$, 500 MHz) 7.76-7.66 (4H, m, CH aromatic), 7.36-7.24 (21H, m, CH aromatic), 5.12 (1H, d, *J* 11.0, $PhCH_2$), 4.99 (1H, d, *J* 10.8, $PhCH_2$), 4.92 (1H, d, *J* 10.8, $PhCH_2$), 4.81 (1H, d, *J* 10.8, $PhCH_2$), 4.79 (1H, d, *J* 10.8, $PhCH_2$), 4.75 (1H, d, *J* 11.0, $PhCH_2$), 4.03 (1H, dd, *J* 9.4, 8.7, H-3), 4.01 (1H, dd, *J* 11.3, 2.5, H-6'), 3.91 (1H, dd, *J* 9.7, 9.4, H-4), 3.90 (1H, dd, *J* 11.3, 1.7, H-6), 3.83 (1H, ddd, *J* 9.7, 2.5, 1.7, H-5), 3.82 (1H, d, *J* 8.7, H-2), 2.88 (1H, s, OH), 1.09 (9H, s, $SiC(CH_3)_3$), 1.06 (9H, s, $C(CH_3)_3$); δ_C ($CDCl_3$, 125 MHz) 138.3 (*ipso* C), 138.0 (*ipso* C), 135.8 (4 × CH aromatic), 135.5 (*ipso* C), 135.4 (2 × CH aromatic), 133.6 (*ipso* C), 132.8 (*ipso* C), 129.6 (2 × CH aromatic), 129.5 (CH aromatic), 128.5 (CH aromatic), 128.4 (CH aromatic), 128.3 (4 × CH aromatic), 127.8 (2 × CH aromatic), 127.7 (2 × CH aromatic), 127.7 (CH aromatic), 127.7 (CH aromatic), 127.6 (2 × CH aromatic), 127.5 (2 × CH aromatic), 127.4 (2 × CH aromatic), 100.7 (C-1), 85.8 (C-3), 79.4 (C-2), 77.8 (C-4), 75.9 ($PhCH_2$), 75.8 ($PhCH_2$), 73.9 ($PhCH_2$), 71.8 (C-5), 62.1 (C-6), 39.5 ($\underline{C}(CH_3)_3$), 26.8 ($SiC(\underline{C}H_3)_3$), 25.6 ($C(\underline{C}H_3)_3$)), 19.3 ($Si\underline{C}(CH_3)_3$)); *m/z* (FAB+) 767 (MNa^+, 83%), 349 (100); HRMS (FAB+) expected MNa^+ ($C_{47}H_{56}O_6SiNa$) 767.3744, found 767.3745.

2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilanyl-1-*C*-trimethylsilanylethynyl-D-glucopyranose 144

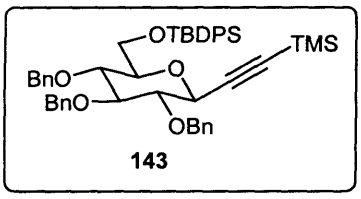


144

Cerium chloride heptahydrate (650 mg, 1.75 mmol) was made anhydrous by heating at 140 °C for 3 h under high vacuum (2 mmHg) and then allowed to cool to RT before

it was suspended in THF (2 mL) and the resulting mixture was stirred for 2 h. To a solution of trimethysilylacetylene (240 μL, 1.75 mmol) in THF (2 mL) at –78 °C was added *n*-BuLi (1.5 M in hexane, 0.90 mL, 1.35 mmol) dropwise and the resulting mixture was stirred for 45 min. This solution was added dropwise to the cerium chloride suspension at –78 °C and stirred for 1 h before a solution of lactone **145** (200 mg, 0.29 mmol) in THF (2 mL) was added dropwise. The mixture was stirred for 30 min at –78 °C and then allowed to warm to RT and stirred for 14 h. The precipitate was removed by filtration through Celite® and rinsed with THF (40 mL). The combined filtrate and washings were concentrated *in vacuo*. The title compound **144** appeared to be very unstable and was used in the next step without further purification.

1-(2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilanyl-β-D-glucopyranosyl)-2-trimethylsilanylethyne 143



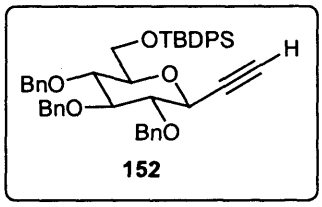
143

To a solution of hemiacetal **144** (100 mg, 126 μmol) in DCM (2 mL) at –78 °C was added dropwise triethylsilane (23 μL, 140 μmol), followed by trimethylsilyl triflate (26 μL, 140 μmol). The resulting mixture was stirred at –78 °C for 30 min then triethylamine (50 μL) was added and the mixture was allowed to warm to RT. The material was partitioned between sat aq $NaHCO_3$ (5 mL) and EtOAc (10 mL) and the organic material extracted further with EtOAc (4 × 10 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 50:1) afforded the title compound **143** (81 mg, 83%) as a yellow oil:

$[\alpha]_D^{20}$ = +9.3 (*c* 0.75 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 2988m, 2304m, 2181m, 1605w, 1589w, 1504w; δ_H (C_6D_6, 400 MHz) 8.06-8.04 (2H, m, CH aromatic), 7.90-7.88 (2H, m, CH aromatic), 7.49-7.14 (21H, m, CH aromatic), 5.21 (1H, d, *J* 10.9, $PhCH_2$), 5.02 (1H, d, *J* 11.3, $PhCH_2$), 4.95 (1H, d, *J* 11.4, $PhCH_2$), 4.90 (1H, d, *J* 10.9, $PhCH_2$), 4.88 (1H, d, *J* 11.3, $PhCH_2$), 4.82 (1H, d, *J* 11.4, $PhCH_2$), 4.07 (1H, d, *J* 9.7, H-1), 4.02 (1H, dd, *J* 11.6, 2.2, H-6), 4.00 (1H, dd, *J* 11.6, 3.3, H-6'), 3.89 (1H, dd, *J* 9.6, 9.3, H-4), 3.75 (1H, dd, *J* 9.7, 9.0, H-2), 3.55 (1H, dd, *J* 9.3, 9.0, H-3), 3.13 (1H, ddd, *J* 9.6, 3.3, 2.2, H-5), 1.24 (9H, s, $SiC(CH_3)_3$), 0.23 (9H, s, $Si(CH_3)_3$); δ_C ($CDCl_3$, 100 MHz) 139.1 (*ipso* C), 138.9 (*ipso* C), 138.7 (*ipso* C), 136.2 (4 × CH aromatic), 135.7 (CH aromatic), 133.8 (*ipso* C), 133.3 (*ipso* C), 129.6 (CH aromatic), 128.2 (CH aromatic), 127.9 (2 × CH aromatic), 127.8 (2 × CH aromatic), 127.7 (2 × CH aromatic), 127.6 (4 × CH aromatic), 127.5 (2 × CH aromatic), 127.5 (2 × CH aromatic), 127.4 (2 × CH aromatic), 127.3 (2 × CH aromatic), 104.0 ($\underline{C}{\equiv}CSi(CH_3)_3$), 89.9 ($C{\equiv}\underline{C}Si(CH_3)_3$), 85.9 (C-1), 82.8 (C-3), 79.8 (C-2), 77.6 (C-4), 75.3 ($PhCH_2$), 75.1 ($PhCH_2$), 74.8 ($PhCH_2$), 70.1 (C-5), 63.0 (C-6), 26.8 ($SiC(\underline{C}H_3)_3$), 19.3 ($Si\underline{C}(CH_3)_3$), –0.5 ($Si(\underline{C}H_3)_3$); *m/z* (FAB+) 791 (MNa^+, 80%), 628 (11), 479 (23), 413 (19), 326 (39), 301 (100), 199 (21); HRMS (FAB+) expected MNa^+ ($C_{48}H_{46}O_5Si_2Na$) 791.3564, found 791.3570.

(2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilanyl-β-D-glucopyranosyl)ethyne

152

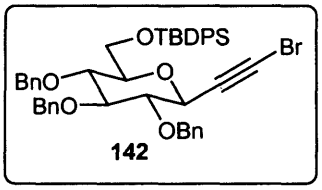


152

To a solution of tribenzyl ether **143** (67 mg, 87 μmol) in MeOH/DCM (5:1, 3 mL) was added 1M NaOH (450 μL) and the resulting mixture was stirred for 2 h. It was then neutralised with 1M aq HCl and the organic material extracted with EtOAc (6 × 10 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 50:1) afforded the title compound **152** (60 mg, 100%) as a white solid: mp 125-127 °C; $[\alpha]_D^{20}$ = +8.4 (*c* 0.28 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 2986m, 2305m, 1604w, 1589w, 1496w; δ_H (C_6D_6, 500 MHz) 8.08-8.06 (2H, m, CH aromatic), 7.92-7.89 (2H, m, CH aromatic), 7.45-7.16 (21H, m, CH aromatic), 5.08 (1H, d, *J* 10.9, $PhCH_2$), 5.05 (1H, d, *J* 11.4, $PhCH_2$), 4.96 (1H, d, *J* 11.4, $PhCH_2$), 4.87 (1H, d, *J* 11.4, $PhCH_2$), 4.85 (1H, d, *J* 11.4, $PhCH_2$), 4.83 (1H, d, *J* 10.9, $PhCH_2$), 4.02 (1H, dd, *J* 9.1, 2.1, H-1), 4.01 (1H, dd, *J* 9.8, 3.4, H-6'), 4.00 (1H, dd, *J* 9.8, 2.1, H-6), 3.91 (1H, dd, *J* 9.6, 9.3, H-4), 3.73 (1H, dd, *J* 9.5, 9.1, H-2), 3.56 (1H, dd, *J* 9.5, 9.3, H-3), 3.13 (1H, *J* 9.6, 3.4, 2.1, H-5), 2.12 (1H, d *J* 2.1, CH), 1.24 (9H, s, $C(CH_3)_3$), 0.23 (9H, s, $Si(CH_3)_3$); δ_C ($CDCl_3$, 125 MHz) 139.1 (*ipso* C), 138.9 (*ipso* C), 138.7 (*ipso* C), 136.2 (4 × CH aromatic), 135.7 (CH aromatic), 133.8 (*ipso* C), 133.3 (*ipso* C), 129.6 (CH aromatic), 128.2 (4 × CH aromatic), 127.9 (CH aromatic), 127.8 (2 × CH aromatic), 127.7 (2 × CH aromatic), 127.6 (CH aromatic), 127,5 (2 × CH aromatic), 127.5 (2 × CH aromatic), 127.4 (2 × CH aromatic), 127.3 (2 × CH aromatic), 86.1 (C-3), 82.6 (C-2), 81.6 (C≡C-H), 79.9 (C-5), 77.6 (C-4), 75.4 ($PhCH_2$), 75.2 ($PhCH_2$), 74.9 ($PhCH_2$), 73.5 (C≡C-H), 69.6 (C-1), 63.0 (C-6), 26.7

($C(\underline{C}H_3)_3$), 19.4 ($\underline{C}(CH_3)_3$); *m/z* (FAB+) 719 (MNa^+, 100%), 326 (33), 199 (37); HRMS (FAB+) expected MNa^+ ($C_{45}H_{48}O_5SiNa$) 719.3169, found 719.3154.

1-(2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilanyl-β-D-glucopyranosyl)-2-bromoethyne 142

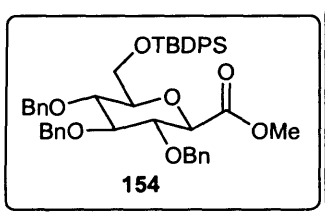


142

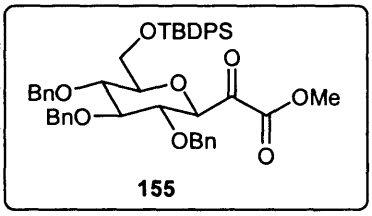
To a solution of terminal alkyne **152** (120 mg, 0.17 mmol) in acetone (0.70 mL) was added $AgNO_3$ (12 mg, 0.07 mmol) and *N*-bromosuccinimide (45 mg, 0.26 mmol). After stirring at RT for 14 h, the reaction mixture was diluted with Et_2O (5 mL), and filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure; the residue was dissolved in Et_2O (10 mL), then washed with H_2O (4 mL) and brine (4 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 20:1) afforded the title compound **142** (130 mg, 98%) as colourless needles: mp 97-99 °C; $[\alpha]_D^{20} = -5.2$ (*c* 0.25 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3053s, 2986m, 2305m, 1601w, 1583w, 1504w, 897s; δ_H (C_6D_6, 400 MHz) 8.04-8.00 (2H, m, CH aromatic), 7.90-7.85 (2H, m, CH aromatic), 7.40-7.14 (21H, m, CH aromatic), 5.00 (1H, d, *J* 10.5, $PhCH_2$), 4.94 (1H, d, *J* 10.9, $PhCH_2$), 4.92 (1H, d, *J* 10.8, $PhCH_2$), 4.85 (1H, d, *J* 10.9, $PhCH_2$), 4.81 (1H, d, *J* 10.5, $PhCH_2$), 4.78 (1H, d, *J* 10.8, $PhCH_2$), 3.98 (1H, dd, *J* 11.0, 5.2, H-6'), 3.97 (1H, dd, *J* 11.0, 2.9, H-6), 3.93 (1H, d, *J* 9.6, H-1), 3.85 (1H, dd, *J* 9.5, 9.2, H-4), 3.64 (1H, dd, *J* 9.6, 9.0, H-2), 3.51 (1H, dd, *J* 9.2, 9.0, H-3), 3.08 (1H, ddd, *J* 9.5, 5.2, 2.9, H-5), 1.25 (9H, s, $C(CH_3)_3$); δ_C ($CDCl_3$, 100 MHz) 138.3 (*ipso* C), 138.1 (*ipso* C), 137.8 (*ipso* C), 136.0 (4 × CH aromatic), 135.6 (CH aromatic), 133.6 (*ipso* C), 133.0 (*ipso* C), 129.6 (CH aromatic), 129.3 (CH

aromatic), 128.4 (2 × CH aromatic), 128.3 (4 × CH aromatic), 128.14 (CH aromatic), 128.11 (2 × CH aromatic), 128.0 (CH aromatic), 127.98 (CH aromatic), 127.95 (2 × CH aromatic), 127.8 (2 × CH aromatic), 127.7 (2 × CH aromatic), 127.6 (2 × CH aromatic), 127.5 (2 × CH aromatic), 85.9 (C-1), 82.2 (C-3), 79.7 (C-2), 77.5 (C-4), 77.3 (C≡C-Br), 75.8 ($PhCH_2$), 75.5 ($PhCH_2$), 75.2 ($PhCH_2$), 70.2 (C-5), 62.7 (C-6), 45.8(C≡C-Br), 26.8 ($C(CH_3)_3$), 19.3 ($C(CH_3)_3$); *m/z* (FAB+) 797/799 (MNa^+, 37/43%), 326/328 (17/17), 245 (100); HRMS (FAB+) expected MNa^+ ($C_{45}H_{50}O_7Si^{79}BrNa$) 797.2274, found 797.2287.

Methyl (2,3,4-tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilanyl-β-D-glucopyranosyl)acetate 154 and Methyl 2-(2,3,4-tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilanyl-β-D-glucopyranosyl)glyoxylate 155



154



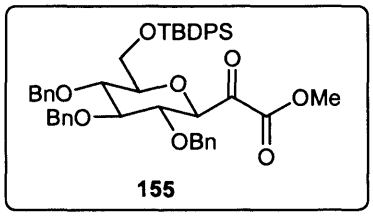
155

To a vigorously stirred solution of bromoalkyne **142** (38 mg, 49 μmol) in MeOH/H_2O (1:1 4 mL) at 0 °C were added $NaHCO_3$ (2 mg, 25 μmol), $MgSO_4$ (12 mg, 98 μmol) and $KMnO_4$ (16 mg, 98 μmol). The reaction mixture was stirred at 0 °C for 14 h then quenched with ice/water (10 mL) and the organic material was extracted with EtOAc (5 × 10 mL). The combined organic phases were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 20:1) afforded recovered terminal bromoalkyne **142** (5 mg, 14%) and ester **154** (12 mg, 32%) as a white powder: mp 137-139 °C; $[\alpha]_D^{20}$ = +7.8 (*c* 0.45 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3444br, 3053s, 2988m, 2304m, 1749s, 1606w, 1421s, 1256s; δ_H ($CDCl_3$, 400 MHz) 7.75-7.67 (4H, m, CH aromatic), 7.36-7.23 (21H, m,

CH aromatic), 4.93-4.89 (3H, m, $PhCH_2$), 4.83 (1H, d, *J* 10.9, $PhCH_2$), 4.77 (1H, d, *J* 10.7, $PhCH_2$), 4.65 (1H, d, *J* 10.9, $PhCH_2$), 3.95 (1H, dd, *J* 11.7, 3.5, H-6), 3.91 (1H, d, *J* 9.6, H-1), 3.89 (1H, dd, *J* 11.7, 7.0, H-6'), 3.86 (1H, dd, *J* 9.6, 9.0, H-4), 3.83 (1H, dd, *J* 9.6, 8.7, H-2), 3.76 (3H, s, OCH_3), 3.72 (1H, dd, *J* 9.0, 8.7, H-3), 3.37 (1H, ddd, *J* 9.6, 7.0, 3.5, H-5), 1.06 (9H, s, $C(CH_3)_3$); δ_C ($CDCl_3$, 100 MHz) 169.4 (C=O), 138.3 (*ipso* C), 138.1 (*ipso* C), 137.9 (*ipso* C), 136.0 (4 × CH aromatic), 135.6 (2 × CH aromatic), 133.7 (*ipso* C), 133.0 (*ipso* C), 129.6 (CH aromatic), 128.5 (CH aromatic), 128.4 (4 × CH aromatic), 128.3 (CH aromatic), 128.0 (2 × CH aromatic), 127.93 (CH aromatic), 127.91 (CH aromatic), 127.8 (2 × CH aromatic), 127.7 (2 × CH aromatic), 127.6 (2 × CH aromatic), 127.5 (2 × CH aromatic), 127.4 (2 × CH aromatic), 127.2 (2 × CH aromatic), 86.4 (C-1), 80.1 (C-3), 80.0 (C-4), 78.1 (C-2), 77.5 (C-5), 75.8 ($PhCH_2$), 75.2 ($PhCH_2$), 75.1 ($PhCH_2$), 62.6 (C-6), 52.2 (OCH_3), 26.8 ($C(\underline{C}H_3)_3$), 19.3 ($\underline{C}(CH_3)_3$); *m/z* (FAB+) 753 (MNa^+, 24%), 199 (100); HRMS (FAB+) expected MNa^+ ($C_{45}H_{50}O_7SiNa$) 753.3223, found 753.3227.

Further elution with EtOAc/petrol (20:1) afforded ketoester **155** (18 mg, 48%) as a white powder with spectroscopic characterisation as given below.

Methyl 2-(2,3,4-tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilanyl-β-D-glucopyranosyl)glyoxylate 155



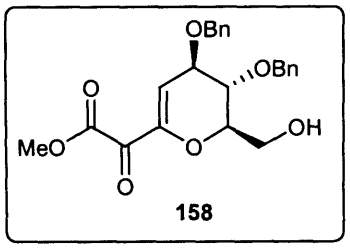
155

To a vigorously stirred solution of bromoalkyne **142** (120 mg, 155 μmol) in MeOH (4 mL) and H_2O (0.1 mL) at 0 °C were added $NaHCO_3$ (7 mg, 77 μmol), $MgSO_4$ (37 mg, 309 μmol) and $KMnO_4$ (49 mg, 309 μmol). The reaction mixture was stirred at 0 °C

for 14 h, then quenched with ice/water (10 mL) and the organic material extracted with EtOAc (5 × 10 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 20:1) afforded the title compound **155** (100 mg, 85%), as a white powder: mp 119-121 °C; ν_{max} ($CHCl_3$ cast)/cm^{-1} 3440br, 3053s, 2988m, 2304m, 1745s, 1693s, 1603w, 1421s, 1256s; δ_H (C_6D_6, 500 MHz): ketoester **155** in equilibrium with its hydrated ketone **156** (ratio **155/156**: 8:1) *ketoester **155*** 8.00-7.98 (2H, m, CH aromatic), 7.89-7.85 (2H, m, CH aromatic), 7.43-7.16 (21H, m, CH aromatic), 5.03 (1H, d, *J* 11.2, $PhCH_2$), 4.90-4.86 (3H, m, $PhCH_2$), 4.85 (1H, d, *J* 11.4, $PhCH_2$), 4.72 (1H, d, *J* 11.2, $PhCH_2$), 4.49 (1H, d, *J* 9.9, H-1), 4.12 (1H, dd, *J* 9.9, 8.9, H-2), 4.00 (1H, dd, *J* 11.7, 5.5, H-6'), 3.98 (1H, dd, *J* 11.7, 2.8, H-6), 3.94 (1H, dd, *J* 9.5, 9.3, H-4), 3.70 (1H, dd, *J* 9.3, 8.9, H-3), 3.30 (3H, s, OCH_3), 3.21 (1H, ddd, *J* 9.5, 5.5, 2.8, H-5), 1.25 (9H, s, $C(CH_3)_3$), *hydrated ketone **156*** 8.00-7.98 (2H, m, CH aromatic), 7.89-7.85 (2H, m, CH aromatic), 7.43-7.16 (21H, m, CH aromatic), 5.00 (1H, d, *J* 11.2, $PhCH_2$), 4.98-4.92 (2H, m, $PhCH_2$), 4.85 (2H, m, $PhCH_2$), 4.77 (1H, d, *J* 11.2, $PhCH_2$), 4.62 (1H, d, *J* 9.2, H-1), 4.23 (1H, dd, *J* 9.2, 9.0, H-2), 3.91 (1H, dd, *J* 12.0, 6.0, H-6'), 3.88 (1H, dd, *J* 12.0, 2.2, H-6), 3.77 (1H, t, *J* 9.0, H-3), 3.72 (1H, dd, *J* 9.5, 9.0, H-4), 3.30 (3H, s, OCH_3), 3.26 (1H, ddd, *J* 9.5, 6.0, 2.2, H-5), 1.24 (9H, s, $C(CH_3)_3$); δ_C ($CDCl_3$, 125 MHz): *ketoester **155*** 190.5 (C=O), 161.6 (OC=O), 139.2 (*ipso* C), 139.0 (*ipso* C), 138.6 (*ipso* C), 137.1 (4 × CH aromatic), 135.8 (2 × CH aromatic), 134.4 (*ipso* C), 132.1 (CH aromatic), 132.0 (*ipso* C), 130.6 (4 × CH aromatic), 129.8 (CH aromatic), 128.1 (CH aromatic), 128.0 (CH aromatic), 127.9 (2 × CH aromatic), 127.6 (CH aromatic), 127.4 (2 × CH aromatic), 127.38 (2 × CH aromatic), 127.33 (2 × CH aromatic), 127.31 (2 × CH aromatic), 126.94 (2 × CH aromatic), 126.91 (2 × CH aromatic), 84.2 (C-3), 79.9 (C-2), 79.2 (C-4), 78.6 (C-5),

77.8 (C-1), 75.5 ($PhCH_2$), 75.2 ($PhCH_2$), 75.1 ($PhCH_2$), 63.1 (C-6), 54.1 (OCH_3), 27.2 ($C(\underline{C}H_3)_3$), 19.1 ($\underline{C}(CH_3)_3$), *hydrated ketone* ***156*** 165.1 (OC=O), 140.3 (*ipso* C), 139.8 (*ipso* C), 139.9 (*ipso* C), 135.4 (2 × CH aromatic), 135.1 (4 × CH aromatic), 133.7 (*ipso* C), 133.6 (*ipso* C), 133.2 (CH aromatic), 132.4 (4 × CH aromatic), 131.1 (CH aromatic), 130.2 (CH aromatic), 128.5 (CH aromatic), 127.8 (2 × CH aromatic), 127.6 (2 × CH aromatic), 126.7 (CH aromatic), 126.6 (2 × CH aromatic), 126.4 (2 × CH aromatic), 126.3 (2 × CH aromatic), 126.1 (2 × CH aromatic), 125.7 (2 × CH aromatic), 102.3 ($C(OH)_2$), 84.2 (C-3), 82.1 (C-1), 78.7 (C-2), 78.2 (C-4), 77.8 (C-5), 75.3 ($PhCH_2$), 75.1 ($PhCH_2$), 74.7 ($PhCH_2$), 62.6 (C-6), 54.5 (OCH_3), 27.0 ($C(\underline{C}H_3)_3$), 19.2 ($\underline{C}(CH_3)_3$); *m/z* (FAB+) 799 ($M(H_2O)Na^+$, 20%), 781 (MNa^+, 24), 326 (23), 245 (100); HRMS (FAB+) expected MNa^+ ($C_{46}H_{50}O_8SiNa$) 781.3173, found 781.3162; expected $M(H_2O)Na^+$ ($C_{46}H_{52}O_9SiNa$) 799.3278, found 799.3285.

Methyl (4'*R*, 5'*S*, 6'*R*)-2-(4,5-bis-benzyloxy-6-hydroxymethyl-5,6-dihydro-4*H*-pyran-2-yl)glyoxylate 158

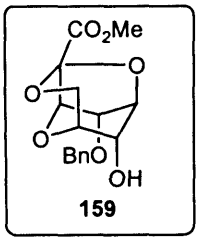


158

To a solution of ketoester **155** (100 mg, 122 μmol), in THF (0.8 mL) was added TBAF (1M in THF, 0.27 mL, 270 μmol) in one portion at RT. The reaction mixture was stirred for 2 h, was then diluted with hexane (10 mL) and washed with 1M aq HCl (2 × 10 mL) and sat aq $NaHCO_3$ (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 10:1 to 5:1 to 3:1) afforded the title compound **158** (36 mg, 66%) as white crystals: mp 110-112 °C; ν_{max} ($CHCl_3$ cast)/cm^-

[1] 3442br, 3051s, 2988m, 2304m, 1750s, 1695s, 1606w, 1421s, 1256s; $[\alpha]_D^{20} = -161.1$ (*c* 0.09 in DCM); δ_H ($CDCl_3$, 500 MHz) 7.34-7.30 (10H, m, CH aromatic), 6.20 (1H, d, *J* 3.1, H-3'), 4.83 (1H, d, *J* 11.3, $PhCH_2$), 4.72 (1H, d, *J* 11.3, $PhCH_2$), 4.68 (1H, d, *J* 11.7, $PhCH_2$), 4.63 (1H, d, *J* 11.7, $PhCH_2$), 4.36 (1H, dd, *J* 6.7, 3.1, H-4'), 4.05 (1H, ddd, *J* 8.8, 8.1, 3.8, H-6'), 3.93-3.88 (2H, m, $C\underline{H}_2OH$), 3.87 (3H, s, OCH_3), 3.85 (1H, dd, *J* 8.8, 6.7, H-5'), 2.13 (1H, t, *J* 7.1, OH); δ_C ($CDCl_3$, 125 MHz) 180.5 (C=O), 162.7 (COOMe), 147.3 (C-2'), 137.5 (*ipso* C), 137.3 (*ipso* C), 128.6 (2 × CH aromatic), 128.5 (2 × CH aromatic), 128.1 (CH aromatic), 128.0 (CH aromatic), 127.8 (2 × CH aromatic), 127.7 (2 × CH aromatic), 115.7 (C-3'), 78.6 (C-4'), 75.6 (C-5'), 74.1 ($PhCH_2$), 73.3 (C-6'), 71.7 ($PhCH_2$), 60.8 (CH_2OH), 53.0 (OCH_3); *m/z* (FAB+) 435 (MNa^+, 3%), 245 (100); HRMS (FAB+) expected MNa^+ ($C_{23}H_{24}O_7Na$) 435.1420, found 435.1431.

Methyl (1*S*, 3*R*, 6*R*, 8*R*, 9*R*, 10*R*)-9-benzyloxy-10-hydroxy-2,4,7-trioxatricyclo[4.3.1.0^{3,8}]decane-3-carboxylate 159

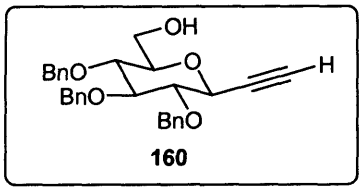


159

To a stirred solution of ketoester **155** (185 mg, 0.244 mmol) in THF (1mL) at –78 °C in a plastic vessel was added hydrogen fluoride pyridine complex (22 μL, 1.22 mmol). The reaction mixture was allowed to warm to RT and stirred for a further 15 min. Sat aq $NaHCO_3$ (5 mL) was added and the organic material was extracted with DCM (5 × 10 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 2:1) afforded the title compound **159**

(60 mg, 77%) as a sticky colourless oil: $[\alpha]_D^{20}$ = –8.85 (*c* 2.0 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3440br, 3053s, 2988m, 2304m, 1750s, 1606w, 1421s, 1256s; δ_H ($CDCl_3$, 500 MHz) 7.39-7.32 (5H, m, CH aromatic), 4.77 (1H, d, *J* 11.3, $PhCH_2$), 4.60 (1H, d, *J* 11.3, $PhCH_2$), 4.48 (1H, d, *J* 3.3, H-8), 4.37 (1H, dd, *J* 5.0, 3.3, H-9), 4.27 (1H, dd, *J* 10.1, 7.2, H-5'), 4.15 (1H, ddd, *J* 7.2, 2.0, 0.8, H-6), 4.05 (1H, dd, J 5.0, 4.6, H-1), 3.86 (1H, dd, *J* 10.1, 0.8, H-5), 3.80 (3H, s, OCH_3), 3.78 (1H, dd, *J* 4.6, 2.0, H-10), 2.08 (1H, s, OH); δ_C ($CDCl_3$, 125 MHz) 166.9 (C=O), 136.1 (*ipso* C), 128.7 (2 × CH aromatic), 128.5 (CH aromatic), 128.1 (2 × CH aromatic), 100.1 (C-3), 76.3 (C-9), 73.6 (C-10), 73.1 (C-8), 73.0 (C-6), 72.3 ($PhCH_2$), 71.0 (C-1), 63.1 (C-5), 52.8 (OCH_3); *m/z* (FAB+) 345 (MNa^+, 100%), 301 (10), 219 (18); HRMS (FAB+) expected MNa^+ ($C_{16}H_{18}O_7Na$) 345.0950, found 345.0942.

(2,3,4-Tri-*O*-benzyl-β-D-glucopyranosyl)ethyne 160

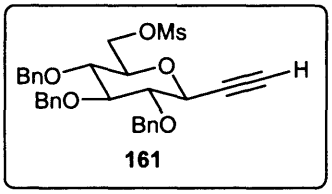


160

To a solution of tribenzyl ether **143** (500 mg, 0.65 mmol) in dry THF (10 mL) at 0 °C was added TBAF (1M in THF, 1.95 mL, 1.95 mmol). The reaction mixture was allowed to warm to RT and stirred for 2 h. It was then diluted with petrol (5 mL), washed with 1M HCl (10 mL), sat aq $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 5:1 to 3:1) afforded the title compound **160** (296 mg, 99%) as white crystals: mp 149-152 °C; $[\alpha]_D^{20}$ = –45.4 (*c* 3.2 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3440br, 3055s, 2985m, 2305m, 1421s, 1359s, 1265s; δ_H ($CDCl_3$, 300 MHz) 7.37-7.26 (15H, m, CH aromatic), 5.02 (1H, d, *J* 10.4, $PhCH_2$), 4.95 (1H, d, *J* 12.0, $PhCH_2$), 4.88 (1H, d, *J*

12.0, $PhCH_2$), 4.85 (1H, d, *J* 11.0, $PhCH_2$), 4.83 (1H, d, *J* 10.4, $PhCH_2$), 4.68 (1H, d, *J* 11.0, $PhCH_2$), 4.11 (1H, dd, *J* 9.4, 2.1, H-1), 3.90 (1H, dd, *J* 12.1, 2.4, H-6), 3.71 (1H, dd, *J* 12.1, 4.4, H-6'), 3.69 (1H, dd, *J* 9.1, 8.4, H-4), 3.67 (1H, dd, *J* 8.6, 8.4, H-3), 3.60 (1H, dd, *J* 9.4, 8.6, H-2), 3.13 (1H, ddd, *J* 9.1, 4.3, 2.4, H-5), 2.58 (1H, d, *J* 2.1, C≡CH), 2.0 (1H, br s, OH); δ_C ($CDCl_3$, 100 MHz) 138.4 (*ipso* C), 137.98 (*ipso* C), 137.93 (*ipso* C), 128.5 (CH aromatic), 128.55 (CH aromatic), 128.53 (2 × CH aromatic), 128.3 (CH aromatic), 128.1 (2 × CH aromatic), 128.0 (2 × CH aromatic), 127.8 (2 × CH aromatic), 127.76 (2 × CH aromatic), 127.72 (2 × CH aromatic), 85.8 (C-2), 82.2 (C-3), 81.0 (C≡CH), 79.6 (C-5), 77.4 (C-4), 75.8 ($PhCH_2$), 75.6 ($PhCH_2$), 75.2 ($PhCH_2$), 74.5 (C≡CH), 69.5 (C-1), 61.9 (C-6); *m/z* (FAB+) 481 (MNa^+, 45%), 323 (43), 199 (100); HRMS (FAB+) expected MNa^+ ($C_{29}H_{30}NaO_5$) 481.1991, found 481.2000.

(2,3,4-Tri-*O*-benzyl-6-*O*-methanesulfonyl-β-D-glucopyranosyl)ethyne 161

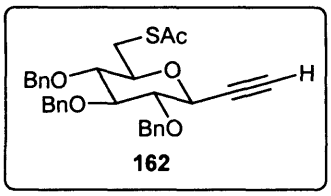


161

To a solution of terminal alkyne **160** (1.92 g, 4.19 mmol) in dry DCM (40 mL) at 0 °C were added triethylamine (1.17 mL, 8.38 mmol), methanesulfonyl chloride (0.65 mL, 8.38 mmol) and *N,N*-dimethylaminopyridine (25 mg, 0.21 mmol). The reaction mixture was allowed to warm to RT and stirred for a further 2 h. Sat aq NH_4Cl (50 mL) was added and the organic material was extracted with EtOAc (6 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 1:3 to 1:1 to neat EtOAc) afforded the title compound **161** (2.13 g, 95%) as a sticky colourless oil:

$[\alpha]_D^{20}$ = +13.6 (*c* 1.18 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3300m, 3055s, 2985m, 2305m, 2110s, 1496m, 1421s, 1359s, 1265s; δ_H ($CDCl_3$, 500 MHz) 7.41-7.27 (15H, m, CH aromatic), 4.98 (1H, d, *J* 10.4, $PhCH_2$), 4.93 (1H, d, *J* 11.0, $PhCH_2$), 4.87 (1H, d, *J* 10.7, $PhCH_2$), 4.83 (1H, d, *J* 11.0, $PhCH_2$), 4.80 (1H, d, *J* 10.4, $PhCH_2$), 4.62 (1H, d, *J* 10.7, $PhCH_2$), 4.42 (1H, dd, *J* 11.6, 1.7, H-6), 4.34 (1H, dd, *J* 11.6, 4.1, H-6'), 4.04 (1H, dd, *J* 9.3, 2.1, H-1), 3.61 (1H, dd, *J* 9.3, 9.1, H-2), 3.58 (1H, dd, *J* 9.0, 8.4, H-4), 3.50 (1H, dd, *J* 9.1, 9.0, H-3), 3.48 (1H, ddd, *J* 8.4, 4.1, 1.7, H-5), 3.04 (3H, s, CH_3), 2.53 (1H, d, *J* 2.1, C≡CH); δ_C ($CDCl_3$, 125 MHz) 138.1 (*ipso* C), 137.6 (*ipso* C), 137.3 (*ipso* C), 128.6 (CH aromatic), 128.5 (CH aromatic), 128.4 (2 × CH aromatic), 128.2 (CH aromatic), 128.1 (2 × CH aromatic), 128.0 (2 × CH aromatic), 127.8 (2 × CH aromatic), 127.7 (2 × CH aromatic), 127.7 (2 × CH aromatic), 85.6 (C-2), 81.9 (C-4), 80.3 (C≡CH), 76.7 (C-5), 77.6 (C-3), 75.7 ($PhCH_2$), 75.6 ($PhCH_2$), 75.3 ($PhCH_2$), 74.7 (C≡CH), 69.5 (C-1), 68.4 (C-6), 37.8 (CH_3); *m/z* (FAB+) 559 (MNa^+, 35%), 165 (100); HRMS (FAB+) expected MNa^+ ($C_{30}H_{32}NaO_7S$) 559.1766, found 559.1779.

(6-*S*-Acetyl-2,3,4-tri-*O*-benzyl-6-thio-β-D-glucopyranosyl)ethyne 162

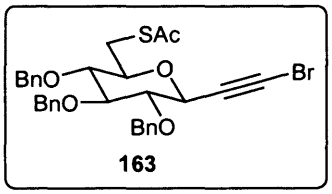


162

To a solution of mesylate **161** (2.03 g, 3.79 mmol) in dry DMF at 0 °C was added potassium thioacetate (2.16 g, 18.9 mmol). The reaction mixture was warmed to RT and stirred for a further 10 h. The mixture was partitioned between H_2O (300 mL) and EtOAc (50 mL) and the organic material extracted further with EtOAc (6 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and

concentrated *in vacuo*. Column chromatography (EtOAc/petrol 1:7) afforded the title compound **162** (1.94 g, 99%) as a yellow oil: $[\alpha]_D^{20}$ = +5.1 (*c* 0.63 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3055s, 2986m, 2305m, 2112s, 1743s, 1456, 1421s, 1371s, 1265s; δ_H ($CDCl_3$, 500 MHz) 7.33-7.20 (15H, m, CH aromatic), 4.98 (1H, d, *J* 10.4, $PhCH_2$), 4.90 (1H, d, *J* 10.9, $PhCH_2$), 4.85 (1H, d, *J* 10.6, $PhCH_2$), 4.83 (1H, d, *J* 10.9, $PhCH_2$), 4.80 (1H, d, *J* 10.4, $PhCH_2$), 4.61 (1H, d, *J* 10.6, $PhCH_2$), 3.99 (1H, dd, *J* 9.0, 2.2, H-1), 3.59 (1H, dd, *J* 10.8, 8.4, H-3), 3.57 (1H, dd, *J* 10.8, 8.9, H-2), 3.49 (1H, dd, *J* 13.7, 2.9, H-6), 3.40 (1H, ddd, *J* 9.7, 6.9, 2.9, H-5), 3.36 (1H, dd, *J* 9.7, 8.4, H-4), 2.99 (1H, dd, *J* 13.7, 6.9, H-6'), 2.53 (1H, d, *J* 2.1,C≡CH), 2.33 (3H, s, CH_3); δ_C ($CDCl_3$, 125 MHz) 195.0 (C=O), 138.3 (*ipso* C), 137.8 (*ipso* C), 137.7 (*ipso* C), 128.5 (CH aromatic), 128.5 (2 × CH aromatic), 128.4 (CH aromatic), 128.3 (2 × CH aromatic), 128.04 (2 × CH aromatic), 128.02 (CH aromatic), 127.8 (2 × CH aromatic), 127.7 (2 × CH aromatic), 127.6 (2 × CH aromatic), 85.7 (C-2), 82.1 (C-3), 80.7 (C≡CH), 80.0 (C-4), 78.2 (C-5), 76.8 (C≡CH), 75.8 ($PhCH_2$), 75.5 ($PhCH_2$), 75.3 ($PhCH_2$), 69.5 (C-1), 30.9 (C-6), 30.5 (CH_3); *m/z* (FAB+) 539 (MNa^+, 12%), 413 (100), 323 (56), 248 (17); HRMS (FAB+) expected MNa^+ ($C_{31}H_{32}NaO_5S$) 539.1868, found 539.1864.

1-(6-*S*-Acetyl-2,3,4-tri-*O*-benzyl-6-thio-β-D-glucopyranosyl)-2-bromoethyne 163

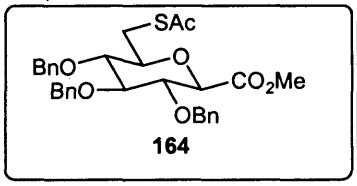


163

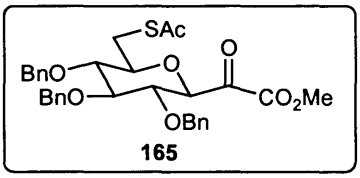
To a solution of thioacetate **162** (1.90 g, 3.68 mmol) in dry acetone (40 mL) were added silver nitrate (250 mg, 1.47 mmol) and *N*-bromosuccinimide (981 mg, 5.52 mmol). After stirring at RT for 10 h, the reaction mixture was diluted with Et_2O (40

mL), and filtered through Celite®. The filtrate was concentrated *in vacuo*; the residue was dissolved in Et_2O (40 mL), and then washed with H_2O (40 mL) and brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 6:1) afforded the title compound **163** (2.16 g, 99%) as light purple crystals: mp 95-97 °C; $[\alpha]_D^{20}$ = –0.3 (*c* 1.72 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3300m, 3055s, 2985m, 2305m, 2110m, 1693s, 1496m, 1421s, 1359s, 1265s; δ_H ($CDCl_3$, 500 MHz) 7.33-7.28 (15H, m, CH aromatic), 4.91 (1H, d, *J* 11.0, $PhCH_2$), 4.89 (1H, d, *J* 10.3, $PhCH_2$), 4.85 (1H, d, *J* 10.7, $PhCH_2$), 4.82 (1H, d, *J* 11.0, $PhCH_2$), 4.78 (1H, d, *J* 10.7, $PhCH_2$), 4.61 (1H, d, *J* 10.3, $PhCH_2$), 4.01 (1H, d, *J* 9.2, H-1), 3.57 (1H, dd, *J* 8.9, 8.2, H-3), 3.54 (1H, dd, *J* 9.2, 8.9, H-2), 3.48 (1H, dd, *J* 13.8, 2.9, H-6), 3.40 (1H, ddd, *J* 9.8, 7.0, 2.9, H-5), 3.34 (1H, dd, *J* 9.8, 8.2, H-4), 2.99 (1H, dd, *J* 13.8, 7.0, H-6'), 2.33 (3H, s, CH_3); δ_C ($CDCl_3$, 125 MHz) 194.9 (C=O), 138.2 (*ipso* C), 137.6 (*ipso* C), 137.5 (*ipso* C), 128.53 (CH aromatic), 128.51 (CH aromatic), 128.3 (2 × CH aromatic), 128.2 (CH aromatic), 128.05 (2 × CH aromatic), 128.04 (2 × CH aromatic), 128.02 (2 × CH aromatic), 127.85 (2 × CH aromatic), 127.83 (2 × CH aromatic), 85.7 (C-2), 82.0 (C-3), 79.9 (C-4), 78.0 (C-5), 77.2 (C≡CBr), 75.8 ($PhCH_2$), 75.6 ($PhCH_2$), 75.3 ($PhCH_2$), 70.4 (C-1), 47.0 (C≡CBr), 30.4 (C-6), 30.1 (CH_3); *m/z* (FAB+) 617/619 (MNa^+, 17/23%), 347/349 (12/14), 199 (100). HRMS (FAB+) expected MNa^+ ($C_{31}H_{31}{}^{79}BrNaO_5S$) 617.0970, found 617.0960.

Methyl (6-*S*-acetyl-2,3,4-tri-*O*-benzyl-6-thio-β-D-glucopyranosyl)acetate 164 and **Methyl(6-*S*-acetyl-2,3,4-tri-*O*-benzyl-6-thio-β-D-glucopyranosyl)glyoxylate 165**



164



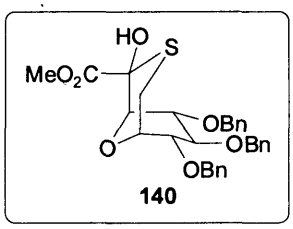
165

To a vigorously stirred solution of bromoalkyne **163** (100 mg, 168 μmol) in MeOH (10 mL) were added $NaHCO_3$ (7 mg, 84 μmol) and $MgSO_4$ (41 mg, 337 μmol). $KMnO_4$ (106 mg, 674 μmol) was added in small portions over 4 h. The reaction mixture was quenched with ice/water (10 mL), filtered through Celite® and concentrated *in vacuo*, then partitioned between H_2O (10 mL) and EtOAc (10 mL). The organic material was extracted further with EtOAc (4 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (petrol/EtOAc 12:1) afforded recovered starting material **163** (15 mg, 15%). Further elution with EtOAc/petrol (10:1) afforded ester **164** (9 mg,10%) as a colourless oil: $[\alpha]_D^{20}$ = +14.4 (*c* 0.63 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3444br, 3053s, 2988m, 2304m, 1749s, 1606w, 1421s, 1256s; δ_H ($CDCl_3$, 500 MHz) 7.33-7.28 (15H, m, CH aromatic), 4.90 (1H, d, *J* 11.3, $PhCH_2$), 4.88 (1H, d, *J* 10.7, $PhCH_2$), 4.86 (1H, d, *J* 11.3, $PhCH_2$), 4.76 (1H, d, *J* 10.8, $PhCH_2$), 4.67 (1H, d, *J* 10.7, $PhCH_2$), 4.60 (1H, d, *J* 10.8, $PhCH_2$), 3.86 (1H, d, *J* 9.4, H-1), 3.75 (1H, dd, *J* 9.4, 9.1, H-2), 3.72 (3H, s, OCH_3), 3.71 (1H, dd, *J* 9.1, 8.2, H-3), 3.53 (1H, dd, *J* 13.7, 2.6, H-6), 3.46 (1H, ddd, *J* 9.5, 6.9, 2.6, H-5), 3.42 (1H, dd, *J* 9.5, 8.2, H-4), 2.98 (1H, dd, *J* 13.7, 6.9, H-6'), 2.33 (3H, s, $SC(O)CH_3$); δ_C ($CDCl_3$, 125 MHz) 194.0 (SC=O), 169.3 (OC=O), 138.2 (*ipso* C), 137.7 (*ipso* C), 137.6 (*ipso* C), 128.5 (CH aromatic), 128.5 (CH aromatic), 128.3 (2 × CH aromatic), 128.0 (CH aromatic), 127.9 (2 × CH aromatic), 127.82 (2 × CH aromatic), 127.77 (2 × CH aromatic), 127.73 (2 ×

CH aromatic), 127.6 (2 × CH aromatic), 86.1 (C-3), 80.2 (C-4), 80.0 (C-2), 78.7 (C-5), 78.2 (C-1), 75.7 ($PhCH_2$), 75.3 ($PhCH_2$), 75.1 ($PhCH_2$), 52.4 (OCH_3), 30.8 (C-6), 30.5 ($SC(O)\underline{C}H_3$); *m/z* (FAB+) 573 (MNa^+, 100%), 323 (19); HRMS (FAB+) expected MNa^+ ($C_{31}H_{34}NaO_7S$) 573.1923, found 573.1913.

Further elution with EtOAc/petrol (5:1 to 2:1) afforded ketoester **165** (63 mg, 65%) as a colourless oil: ν_{max} ($CHCl_3$ cast)/cm^{-1} 3440br, 3053s, 2988m, 2304m, 1745s, 1693s, 1603w, 1421s, 1256s; δ_H ($CDCl_3$, 500 MHz) 7.33-7.18 (15H, m, CH aromatic), 4.95 (1H, d, *J* 11.1, $PhCH_2$), 4.88 (1H, d, *J* 11.1, $PhCH_2$), 4.85 (1H, d, *J* 10.7, $PhCH_2$), 4.82 (1H, d, *J* 10.6, $PhCH_2$), 4.63 (1H, d, *J* 10.7, $PhCH_2$), 4.59 (1H, d, *J* 10.6, $PhCH_2$), 4.44 (1H, d, *J* 9.3, H-1), 3.81 (1H, dd, *J* 9.3, 9.0, H-2), 3.77 (1H, dd, *J* 9.0, 8.6, H-3), 3.73 (3H, s, OCH_3), 3.51 (1H, ddd, *J* 9.2, 7.2, 3.0, H-5), 3.48 (1H, dd, *J* 13.8, 3.0, H-6), 3.39 (1H, dd, *J* 9.2, 8.6, H-4), 2.98 (1H, dd, *J* 13.8, 7.2, H-6'), 2.31 (3H, s, $SC(O)C\underline{H_3}$); δ_C ($CDCl_3$, 125 MHz) 194.8 (SC=O), 190.2 (C=O), 161.6 (OC=O), 138.0 (*ipso* C), 137.9 (*ipso* C), 137.4 (*ipso* C), 128.5 (CH aromatic), 128.4 (CH aromatic), 128.3 (2 × CH aromatic), 128.2 (2 × CH aromatic), 128.1 (CH aromatic), 128.0 (2 × CH aromatic), 128.0 (2 × CH aromatic), 127.8 (2 × CH aromatic), 127.7 (2 × CH aromatic), 86.3 (C-3), 80.1 (C-4), 79.3 (C-2), 78.7 (C-5), 78.4 (C-1), 75.7 ($PhCH_2$), 75.5 ($PhCH_2$), 75.1 ($PhCH_2$), 52.9 (OCH_3), 30.1 (C-6), 30.0 ($SC(O)\underline{C}H_3$); *m/z* (FAB+) 601 (MNa^+, 23%), 323 (32), 242 (11), 165 (100); HRMS (FAB+) expected MNa^+ ($C_{32}H_{34}NaO_8S$) 601.1872, found 601.1874.

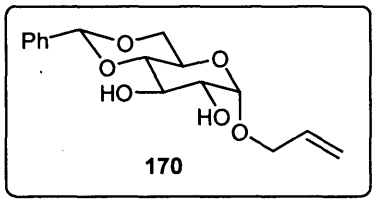
Methyl (1*R*, 5*S*, 6*S*, 7*S*, 8*R*)-6,7,8-tri(benzyloxy)-2-hydroxy-9-oxa-3-thiabicyclo[3.3.1]nonane-2-carboxylate 140



140

Ketoester **164** (55 mg, 0.095 mmol) was dissolved in MeOH (20 ml) at 40 °C. The reaction was cooled to RT before hydrazine monohydrate (6 μL, 0.12 mmol) was added. The reaction mixture was stirred at RT for 14 h then quenched with water (10 mL). The methanol was removed *in vacuo* and the resulting organic material was extracted with EtOAc (5 × 10 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 5:1 to 4:1) afforded the title compound **140** (45 mg, 88%) as a colourless oil: $[\alpha]_D^{20}$ = +3.1 (*c* 1.01 in EtOH); δ_H (C_6D_6, 500 MHz) 7.38-6.99 (15H, m, CH aromatic), 5.01 (1H, d, *J* 11.3, $PhCH_2$), 4.92 (1H, d, *J* 11.3, $PhCH_2$), 4.82 (1H, d, *J* 11.6, $PhCH_2$), 4.75 (1H, d, *J* 11.6, $PhCH_2$), 4.65 (1H, d, *J* 12.1, $PhCH_2$), 4.43 (1H, dd, *J* 9.3, 2.8, H-8), 4.39 (1H, d, *J* 12.1, $PhCH_2$), 4.36 (1H, d, *J* 2.8, H-1), 4.22 (1H, dd, *J* 9.5, 9.3, H-7), 4.19 (1H, ddd, *J* 5.5, 3.6, 1.9, H-5), 4.11 (1H, s, OH), 4.03 (1H, dd, *J* 9.5, 5.5, H-6), 3.30 (1H, dd, *J* 13.4, 3.6, H-4'), 3.24 (3H, s, OCH_3), 1.57 (1H, dd, *J* 13.4, 1.9, H-4); δ_C ($CDCl_3$, 125 MHz) 173.4 (C=O), 139.5 (*ipso* C), 139.3 (*ipso* C), 139.0 (*ipso* C), 128.3 (CH aromatic), 128.2 (CH aromatic), 128.1 (2 × CH aromatic), 128.0 (2 × CH aromatic), 127.9 (CH aromatic), 127.8 (2 × CH aromatic), 127.6 (2 × CH aromatic), 127.5 (2 × CH aromatic), 127.2 (2 × CH aromatic), 82.2 (C-7), 80.0 (C-6), 79.8 (C-8), 79.5 (C-1), 75.0 ($PhCH_2$), 73.3 (C-5), 73.2 ($PhCH_2$), 72.4 ($PhCH_2$), 71.9 (S<u>C</u>OH), 52.5 (OCH_3), 40.9 (C-4); *m/z* (FAB+) 559 (MNa^+, 3%), 326 (21), 199 (26), 176 (100); HRMS (FAB+) expected MNa^+ ($C_{30}H_{32}NaO_7S$) 559.1766, found 559.1784.

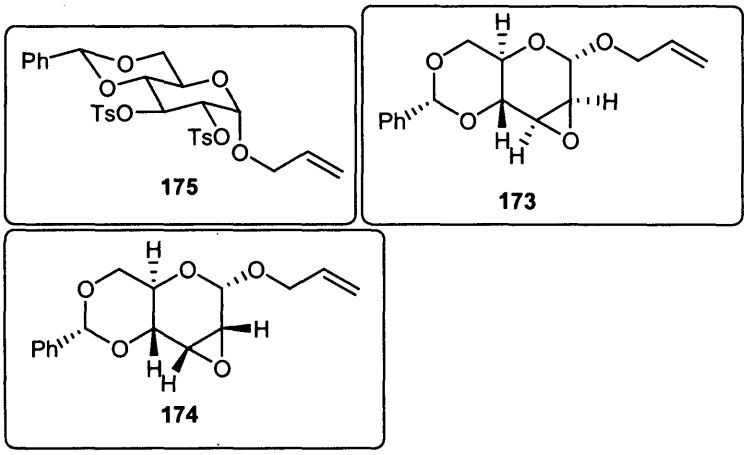
Allyl 4,6-*O*-benzylidene-α-D-glucopyranoside 170



170

To a solution of tetraol **172**[118] (1.66g, 7.54 mmol) in dry DMF (70 mL) were added tosic acid monohydrate (140 mg, 0.75 mmol) and benzaldehyde dimethyl acetal (2.26 mL, 15.1 mmol). The mixture was stirred for 2 h, then diluted with DCM (100 mL), washed with sat aq $NaHCO_3$ (100 mL) and water (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was recrystallised from ethanol, affording the title compound **170** (2.09 g, 90%) as a white solid: $[\alpha]_D^{20}$ = –57.5 (*c* 1.26 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3438br, 3055s, 2986m, 2304m, 1632m, 1421s, 1256s; δ_H (500 MHz, $CDCl_3$) 7.47-7.43 (2H, m, CH aromatic), 7.35-7.30 (3H, m, CH aromatic), 5.90 (1H, dddd, *J* 16.9, 10.3, 6.2, 5.3, $CH_2\underline{C}H{=}CH_2$), 5.51 (1H, s, PhCH), 5.32 (1H, dq, *J* 16.9, 1.3, $CH_2CH{=}C\underline{H}_2$), 5.22 (1H, dq, *J* 10.3, 1.3, CH_2-$CH{=}C\underline{H}_2$), 4.92 (1H, d, *J* 4.0, H-1), 4.25 (1H, dd, *J* 10.3, 5.0, H-6), 4.22 (1H, ddt, *J* 12.7, 5.3, 1.3, $C\underline{H}_2$-$CH{=}CH_2$), 4.04 (1H, ddt, *J* 12.7, 6.2, 1.3, $C\underline{H}_2CH{=}CH_2$), 3.93 (1H, dd, *J* 10.3, 9.5, H-4), 3.83 (1H, td, *J* 10.3, 5.0, H-5), 3.70 (1H, t, *J* 10.3, H-6'), 3.61 (1H, dd, *J* 9.1, 4.0, H-2), 3.48 (1H, dd, *J* 9.5, 9.1, H-3), 2.79 (1H, br s, OH), 2.27 (1H, br s, OH); δ_C (125 MHz, $CDCl_3$) 137.0 (*ipso* C), 133.2 ($CH_2\underline{C}H{=}CH_2$), 129.2 (CH aromatic), 128.3 (2 × CH aromatic), 126.2 (2 × CH aromatic), 118.3 ($CH_2CH{=}\underline{C}H_2$), 101.9 (Ph$\underline{C}$H), 97.8 (C-1), 80.9 (C-3), 72.8 (C-2), 71.8 (C-4), 68.8 ($\underline{C}H_2CH{=}CH_2$), 68.7 (C-6), 62.5 (C-5); *m/z* (FAB+) 300 (MH^+, 13%), 268 (100); HRMS (FAB+) expected MH^+ ($C_{16}H_{21}O_6$) 309.1338, found 309.1331.

Allyl 4,6-*O*-benzylidene-2,3-di-*O*-(4-toluenesulfonyl)-α-D-glucopyranoside 175, Allyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside 174 and Allyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside 173



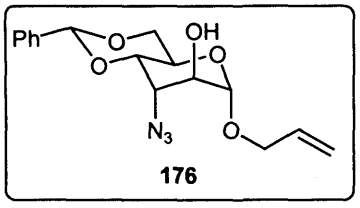
Sodium hydride (500 mg, 13 mmol, 60% w/w in mineral oil), was washed with petrol (3 × 10 mL) then suspended in dry DMF (20 mL). A solution of diol **170** (2.00 g, 6.49 mmol) in dry DMF (20 mL) was added dropwise. The resulting mixture was stirred at RT for 2 h before a solution of (4-toluenesulfonyl)imidazole (1.44 g, 6.49 mmol) in DMF (20 mL) was added dropwise. The resulting solution was heated to 55 °C for 5 h. It was then allowed to cool to RT, diluted with water (200 mL), and the organic material extracted with Et_2O (5 × 50 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 1:10) afforded ditosylate **175** (959 mg, 24%) as a colourless oil: $[\alpha]_D^{20}$ = +42.5 (*c* 7.60 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3055s, 2986m, 2304, 1599m, 1421s, 1371s, 1265s; δ_H (500 MHz, $CDCl_3$) 7.78 (2H, d, *J* 6.5, CH aromatic), 7.60 (2H, d, *J* 7.0, CH aromatic), 7.29-7.20 (5H, m, CH aromatic), 7.22 (2H, d, *J* 6.5, CH aromatic), 6.90 (2H, d, *J* 7.0, CH aromatic), 5.86 (1H, dddd, *J* 17.3, 11.6, 6.0, 5.5, $CH_2C\underline{H}=CH_2$), 5.29 (1H, dq, *J* 17.3, 1.5, $CH_2CH=C\underline{H_2}$), 5.27 (1H, s, PhCH), 5.21 (1H, dq, *J* 11.6, 1.5, $CH_2CH=C\underline{H_2}$), 5.17 (1H, d, *J* 3.6, H-1), 5.11 (1H, t, *J* 9.5, H-3), 4.42 (1H, dd, *J* 9.5, 3.6, H-2), 4.21 (1H, dd, *J* 10.4, 5.0, H-6), 4.15 (1H,

ddt, *J* 13.1, 5.5, 1.3, C<u>H</u>$_2$CH=CH$_2$), 3.99 (1H, ddt, *J* 13.1, 6.0, 1.3, C<u>H</u>$_2$CH=CH$_2$), 3.88 (1H, td *J* 10.4, 9.5, H-5), 3.63 (1H, t, *J* 10.4, H-6'), 3.49 (1H, t, *J* 9.5, H-4), 2.42 (3H, s, CH$_3$), 2.27 (3H, s, CH$_3$) ; δ_C (125 MHz, CDCl$_3$) 145.2 (*ipso* C), 144.2 (*ipso* C), 136.4 (*ipso* C), 134.0 (*ipso* C), 132.9 (CH$_2$<u>C</u>H=CH$_2$), 132.5 (*ipso* C), 129.7 (2 × CH aromatic), 129.6 (CH aromatic), 129.3 (CH aromatic) 129.1 (2 × CH aromatic), 129.0 (2 × CH aromatic), 128.4 (2 × CH aromatic), 128.2 (CH aromatic), 128.0 (2 × CH aromatic), 127.9 (2 × CH aromatic), 118.5 (CH$_2$-CH=<u>C</u>H$_2$), 101.8 (Ph<u>C</u>H), 96.6 (C-1), 79.0 (C-5), 76.4 (C-4), 75.7 (C-2), 69.5 (C-6), 68.5 (<u>C</u>H$_2$CH=CH$_2$), 62.5 (C-3), 21.7 (CH$_3$), 21.6 (CH$_3$); *m/z* (FAB+) 617 (MH$^+$, 100); HRMS (FAB+) expected MH$^+$ (C$_{30}$H$_{32}$O$_{10}$S$_2$) 617.1515, found 617.1526.

Further elution with EtOAc/petrol (1:5) afforded epoxide **173** (980 mg, 52%) as a colourless oil: $[\alpha]_D^{20}$ = +84.7 (*c* 2.55 in DCM); ν_{max} (CHCl$_3$ cast)/cm^{-1} 3417br, 3055s, 2986m, 2305, 1606w, 1421m, 1265s; δ_H (500 MHz, CDCl$_3$) 7.49-7.46 (2H, m, CH aromatic), 7.38-7.33 (3H, m, CH aromatic), 5.93 (1H, dddd, *J* 16.7, 10.3, 6.1, 5.3, CH$_2$C<u>H</u>=CH$_2$), 5.57 (1H, s, PhCH), 5.34 (1H, dq, *J* 16.7, 1.5, CH$_2$CH=C<u>H</u>$_2$), 5.25 (1H, dq, *J* 10.3, 1.2, CH$_2$CH=C<u>H</u>$_2$), 5.06 (1H, s, H-1), 4.27 (1H, ddt, *J* 12.8, 5.3, 1.5, C<u>H</u>$_2$CH=CH$_2$), 4.26 (1H, dd, *J* 9.6, 3.5, H-6), 4.11 (1H, ddt, *J* 12.8, 6.1, 1.2, C<u>H</u>$_2$CH=CH$_2$), 3.77 (1H, ddd, *J* 9.6, 8.8, 3.5, H-5), 3.76 (1H, t, *J* 9.6, H-6'), 3.69 (1H, dd, *J* 8.8, 3.6, H-4), 3.50 (1H, d, *J* 3.6, H-2), 3.21 (1H, t, *J* 3.6, H-3); δ_C (125 MHz, CDCl$_3$) 137.5 (*ipso* C), 134.0 (CH$_2$<u>C</u>H=CH$_2$), 129.7 (CH aromatic), 128.8 (2 × CH aromatic), 126.6 (2 × CH aromatic), 118.3 (CH$_2$CH=<u>C</u>H$_2$), 102.8 (Ph<u>C</u>H), 95.5 (C-1), 75.3 (C-4), 69.8 (C-6), 69.4 (<u>C</u>H$_2$CH=CH$_2$), 62.2 (C-5), 54.2 (C-2), 51.1 (C-3); *m/z* (FAB+) 313 (MNa$^+$, 10%), 268 (100); HRMS (FAB+) expected MNa$^+$ (C$_{16}$H$_{18}$O$_5$Na) 313.1052, found 313.1056.

Further elution with EtOAc/petrol (1:4) afforded epoxide **174** (188 mg, 10%) as a colourless oil; $[\alpha]_D^{20}$ = +81.5 (*c* 1.55 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3053s, 2986m, 2920m, 2871m, 2305, 1674, 1456s, 1256s; δ_H (500 MHz, $CDCl_3$) 7.48-7.45 (2H, m, CH aromatic), 7.35-7.31 (3H, m, CH aromatic), 5.90 (1H, dddd, *J* 17.2, 10.3, 6.5, 5.0, $CH_2C\underline{H}=CH_2$), 5.53 (1H, s, PhCH), 5.31 (1H, dq, *J* 17.2, 1.6, $CH_2CH=C\underline{H_2}$), 5.21 (1H, dq, *J* 10.3, 1.6, $CH_2CH=C\underline{H_2}$), 5.02 (1H, d, *J* 2.9, H-1), 4.25 (1H, ddt, *J* 13.0, 5.0, 1.3, $C\underline{H_2}CH=CH_2$), 4.21 (1H, dd, *J* 10.2, 5.1, H-6), 4.12 (1H, ddd, *J* 10.2, 9.1, 5.1, H-5), 4.08 (1H, ddt, *J* 13.0, 6.5, 1.3, $C\underline{H_2}CH=CH_2$), 3.93 (1H, dd, *J* 9.1, 1.3, H-4), 3.66 (1H, t, *J* 10.2, H-6'), 3.50 (1H, dd, *J* 4.3, 1.8, H-3), 3.47 (1H, dd, *J* 4.3, 2.8, H-2); δ_C (125 MHz, $CDCl_3$) 137.1 (*ipso* C), 134.0 ($CH_2\underline{C}H=CH_2$), 129.2 (CH aromatic), 128.4 (2 × CH aromatic), 128.0 (2 × CH aromatic), 117.7 ($CH_2CH=\underline{C}H_2$), 102.3 (Ph$\underline{C}$H), 93.0 (C-1), 77.5 (C-5), 68.4 (C-6), 68.3 ($\underline{C}H_2CH=CH_2$), 59.6 (C-4), 52.9 (C-2), 50.2 (C-3); *m/z* (FAB+) 313 (MNa^+, 18%), 268 (100); HRMS (FAB+) expected MNa^+ ($C_{16}H_{18}O_5Na$) 313.1052, found 313.1056.

Allyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside 176

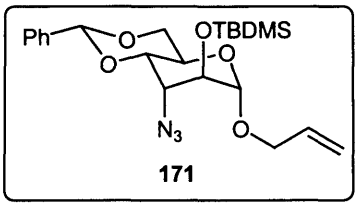


176

To a suspension of epoxide **173** (875 mg, 3.02 mmol) in 2-methoxyethanol/water (24 mL, 5:1) were added sodium azide (847 mg, 13.0 mmol) and ammonium chloride (140 mg, 2.62 mmol). The resulting mixture was heated to reflux for 12 h then allowed to cool to RT. The volume was reduced to 4 mL *in vacuo*, water was added (5 mL) and the organic material was extracted with DCM (5 × 15 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in*

vacuo. Column chromatography (EtOAc/petrol 1:4 to 1:3) afforded the title compound **176** (920 mg, 92%): $[\alpha]_D^{20}$ = +60.8 (*c* 0.50 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3417br, 3053s, 2987m, 2304, 2108, 1614br, 1421m, 1265s; δ_H (400 MHz, $CDCl_3$) 7.48-7.44 (2H, m, CH aromatic), 7.37-7.31 (3H, m, CH aromatic), 5.91 (1H, dddd, *J* 17.3, 10.4, 6.5, 4.9, $CH_2C\underline{H}=CH_2$), 5.61 (1H, s, PhCH), 5.35 (1H, dq, *J* 17.3, 1.6, $CH_2CH=C\underline{H_2}$), 5.24 (1H, dq, *J* 10.4, 1.6, $CH_2CH=C\underline{H_2}$), 4.71 (1H, d, *J* 1.5, H-1), 4.29 (1H, dd, *J* 12.0, 10.5, H-6'), 4.26(1H, dd, *J* 12.0, 4.5, H-6), 4.21 (1H, ddt, *J* 13.2, 4.9, 1.6, $C\underline{H_2}CH=CH_2$), 4.14 (1H, dd, *J* 9.0, 3.6, H-4), 4.08 (1H, dd, *J* 3.6, 2.9, H-3), 4.05 (1H, ddt, *J* 13.2, 6.5, 1.2, $C\underline{H_2}CH=CH_2$), 3.98 (1H, ddd, *J* 5.4, 2.9, 1.5, H-2), 3.78 (1H, ddd, *J* 10.5, 9.0, 4.5, H-5), 2.30 (1H, d, *J* 5.4, OH); δ_c (100 MHz, $CDCl_3$) 137.0 (*ipso* C), 133.5 ($CH_2\underline{C}H=CH_2$), 129.2 (CH aromatic), 128.3 (2 × CH aromatic), 126.2 (2 × CH aromatic), 117.9 ($CH_2CH=\underline{C}H_2$), 102.2 (Ph$\underline{C}$H), 99.1 (C-1), 75.7 (C-4), 69.6 (C-2), 69.0 (C-5), 68.4 ($\underline{C}H_2CH=CH_2$), 59.9 (C-3), 59.1 (C-6); *m/z* (FAB+) 356 (MNa^+, 15%), 329 (100), 314 (35); HRMS (FAB+) expected MNa^+ ($C_{16}H_{19}O_5N_3Na$) 356.1222, found 356.1232.

Allyl 3-azido-2-*O*-*tert*-butyldimethylsilanyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside 171

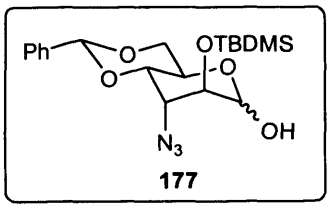


171

To a solution of alcohol **176** (200 mg, 0.60 mmol) in dry DMF (3 mL) was added imidazole (61 mg, 0.90 mmol) followed by *tert*-butyldimethylsilyl chloride (110 mg, 0.27 mmol). The reaction was heated to 80 °C for 12 h, then allowed to cool to RT, water (30 mL) was added and the organic material was extracted with Et_2O (5 × 20

mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 6:1) afforded the title compound **171** (263 mg, 98%): $[\alpha]_D^{20}$ = +36.9 (*c* 2.75 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3053s, 2954m, 2930m, 2858m, 2304, 2110s, 1630w, 1471s, 1381m, 1265s; δ_H (500 MHz, $CDCl_3$) 7.50-7.47 (2H, m, CH aromatic), 7.35-7.29 (3H, m, CH aromatic), 5.91 (1H, dddd, *J* 17.1, 10.6, 6.5, 5.0, $CH_2\underline{C}H{=}CH_2$), 5.61 (1H, s, PhCH), 5.33 (1H, dq, *J* 17.1, 1.7, $CH_2CH{=}C\underline{H}_2$), 5.24 (1H, dq, *J* 10.4, 1.7, $CH_2CH{=}C\underline{H}_2$), 4.60 (1H, d, *J* 1.1, H-1), 4.29 (1H, dd, *J* 11.9, 9.5, H-6'), 4.27(1H, dd, *J* 11.9, 4.6, H-6), 4.21 (1H, ddt, *J* 13.2, 5.0, 1.6, $C\underline{H}_2CH{=}CH_2$), 4.13 (1H, dd, *J* 9.1, 3.6, H-4), 4.01 (1H, ddt, *J* 13.2, 6.5, 1.3, $C\underline{H}_2CH{=}CH_2$), 3.94 (1H, dd, *J* 3.6, 3.0, H-3), 3.91 (1H, ddd, *J* 3.0, 1.1, H-2), 3.78 (1H, ddd, *J* 9.5, 9.1, 4.6, H-5), 0.91 (9H, s, $C(CH_3)_3$), 0.09 (3H, s, CH_3), 0.08 (3H, s, CH_3); δ_c (125 MHz, $CDCl_3$) 137.2 (*ipso* C), 133.6 ($CH_2\underline{C}H{=}CH_2$), 129.2 (CH aromatic), 128.4 (2 × CH aromatic), 126.2 (2 × CH aromatic), 117.9 ($CH_2CH{=}\underline{C}H_2$), 102.3 (Ph$\underline{C}$H), 99.2 (C-1), 76.0 (C-4), 70.8 (C-2), 69.2 ($\underline{C}H_2CH{=}CH_2$), 68.3 (C-5), 60.8 (C-3), 59.0 (C-6), 25.7 ($C(C\underline{H}_3)_3$), 19.4 ($\underline{C}(CH_3)_3$), –5.0 ($SiCH_3$); *m/z* (FAB+) 470 (MNa^+, 35%), 332 (12), 316 (25), 138 (100); HRMS (FAB+) expected MNa^+ ($C_{22}H_{33}O_5N_3SiNa$) 470.2087, found 470.2096.

3-Azido-2-*O*-*tert*-butyldimethylsilanyl-4,6-*O*-benzylidene-D-altrose 177

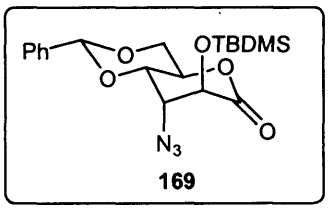


177

Freshly fused and grinded zinc chloride (450 mg, 3.30 mmol) was added to a solution of azide **171** (590 mg, 1.32 mmol) in THF (20 mL). The mixture was stirred for 30 min at RT before tetrakis(triphenylphosphine) palladium(0) (305 mg, 0.26 mmol) was

added and was stirred for 30 min at RT before tri-*n*-butyltin hydride (1.42 mL, 5.28 mmol) was added dropwise and then stirred for 1.5 h before it was diluted with EtOAc (50 mL), washed with 1M HCl (3 × 20 mL) and brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (neat petrol to petrol/EtOAc 15:1 to 12:1) afforded the title compound **177** (484 mg, 90%) as a white solid (mp 128-131 °C), which was used in the next step without further characterisation.

3-Azido-2-*O*-*tert*-butyldimethylsilanyl-4,6-*O*-benzylidene-D-altrono-1,5-lactone 169

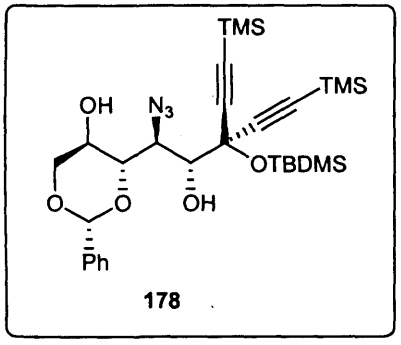


169

To a solution of lactol **177** (1.17 g, 2.87 mmol) in dry DCM (50 mL), was added pyridine (4.54 mL, 57.4 mmol) followed by Dess-Martin periodinane **127** (3.65 g, 8.61 mmol). The reaction mixture was stirred at RT for 12 h. Sat aq Na_2SO_3 (100 mL) was added and the organic material was extracted with DCM (6 × 15 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 1:12) afforded the title compound **169** (994 mg, 88%) as a viscous colouless oil: $[\alpha]_D^{20}$ = –20.3 (*c* 2.10 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3053s, 2988m, 2856, 2304m, 2115m, 1745s, 1606w, 1421s, 1265s; δ_H (500 MHz, $CDCl_3$) 7.48-7.43 (3H, m, CH aromatic), 7.36-7.30 (2H, m, CH aromatic), 5.59 (1H, s, PhCH), 4.54 (1H, ddd, *J* 10.4, 9.7, 5.3, H-5), 4.48 (1H, dd, *J* 10.4, 5.3, H-6), 4.17 (1H, dd, *J* 9.7, 5.0, H-4), 4.15 (1H, d, *J* 4.0, H-2), 4.10 (1H, dd, *J* 5.0, 4.0, H-3), 3.84 (1H, t, *J* 10.4, H-6'), 0.90 (9H, s, $C(CH_3)_3$), 0.11 (3H, s,

$SiCH_3$), 0.09 (3H, s, $SiCH_3$); *m/z* (FAB+) 428 (MNa^+, 12%), 332 (100); HRMS (FAB+) expected MNa^+ ($C_{19}H_{27}O_5N_3SiNa$) 428.1618, found 428.1612.

3-Azido-4,6-*O*-benzylidene-1-*O*-*tert*-butyldimethylsilanyl-3-deoxy-1,1-di-*C*-(trimethylsilanylethynyl)-D-altritol 178

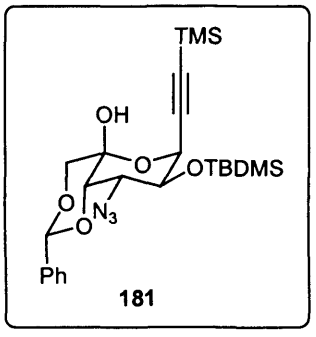


178

Cerium chloride heptahydrate (607 mg, 1.63 mmol) was made anhydrous by heating at 140 °C for 3 h under high vacuum (2 mmHg) and then allowed to cool down to RT before it was suspended in THF (2 mL) and stirred for 2 h. To a solution of trimethysilylacetylene (225 μL, 1.63 mmol) in THF (2 mL) at –78 °C was added *n*-BuLi (1.6 M in hexane, 652 μL, 1.63 mmol) dropwise and the resulting mixture stirred for 45 min. This solution was added dropwise to the cerium chloride suspension at –78 °C and stirred for 1 h before a solution of lactone **169** (110 mg, 0.27 mmol) in THF (2 mL) was added dropwise. The mixture was stirred for 30 min at –78 °C and then allowed to warm to RT and stirred for 30 min. The precipitate was removed by filtration on a pad of Celite® and rinsed with THF (40 mL). The combined filtrate and washings were concentrated *in vacuo*. Column chromatography (EtOAc/petrol 1:12) afforded title compound **178** (53 mg, 32%) as a pale yellow oil: $[\alpha]_D^{20}$ = –72.0 (*c* 2.35 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3444br, 3055s, 2985m, 2954m, 2410m, 2304m, 2121m, 1706s, 1633br, 1421s, 1361s 1256s; δ_H (500 MHz, $CDCl_3$) 7.48-7.43 (3H, m, CH aromatic), 7.36-7.28 (2H, m, CH aromatic), 5.49 (1H,

s, PhCH), 4.35 (1H, dd, *J* 2.9, 0.9, H-3), 4.21 (1H, d, *J* 2.9, 5-OH), 4.33 (1H, dd, *J* 11.0, 5.8, H-6), 4.09 (1H, dddd, *J* 10.2, 8.9, 5.8, 2.9, H-5), 3.83 (1H, dd, *J* 9.9, 0.9, H-2), 3.74 (1H, dd, J 8.9, 2.9, H-4), 3.63 (1H, dd, *J* 11.0, 10.2, H-6'), 3.28 (1H, d, *J* 9.9, 2-OH), 0.90 (9H, s, $C(CH_3)_3$), 0.28 (3H, s, $SiCH_3$), 0.27 (3H, s, $SiCH_3$). 0.18 (18H, s, $Si(CH_3)_3$); δ_C (125 MHz, $CDCl_3$); 137.4 (*ipso* C), 129.0 (CH aromatic), 128.3 (2 × CH aromatic), 126.1 (2 × CH aromatic), 103.1 ($\underline{C}{\equiv}CSi(CH_3)_3$), 102.1 ($\underline{C}{\equiv}CSi(CH_3)_3$), 100.1 (Ph$\underline{C}$H), 91.6 (C≡$\underline{C}Si(CH_3)_3$), 91.5 (C≡$\underline{C}Si(CH_3)_3$), 84.4 (C-4), 75.9 (C-2), 70.1 (C-6), 67.1 (C-1), 63.8 (C-3), 60.7 (C-5), 25.5 ($C(\underline{C}H_3)_3$), 18.7 ($\underline{C}(CH_3)_3$), –0.5 ($Si(\underline{C}H_3)_3$), -0.6 ($Si(\underline{C}H_3)_3$), –3.50 ($SiCH_3$), –3.57 ($SiCH_3$); *m/z* (FAB+) 624 (MNa^+, 45%), 316 (100); HRMS (FAB+) expected MNa^+ ($C_{29}H_{47}O_5N_3Si_3Na$) 624.2721, found 624.2735.

4-Azido-1,3-*O*-benzylidene-5-*O*-*tert*-butyldimethylsilanyl-4,7,8-trideoxy-8-trimethylsilanyl-β-L-*manno*-oct-7-yn-2-ulopyranoside 181

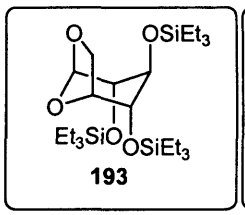


181

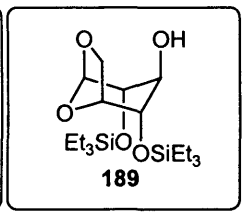
To a solution of trimethysilylacetylene (31 μL, 0.22 mmol) in THF (2 mL) at –78 °C was added *n*-BuLi (1.6 M in hexane, 139 μL, 0.22 mmol) and the resulting mixture stirred for 45 min. This solution was added dropwise to a suspension of anhydrous ytterbium triflate (138 mg, 0.22 mmol) in THF (2 mL) at –78 °C and stirred for 1 h before a solution of the lactone **169** (60 mg, 0.15 mmol) in THF (2 mL) was added dropwise. The resulting mixture was stirred for 30 min at –78 °C and then allowed to

warm to RT and stirred for 12 h. Sat aq $NaHCO_3$ (10 mL) was added and the organic material was extracted with Et_2O (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (EtOAc/petrol 1:14 to 1:11) afforded the title compound **181** (37 mg, 48%); $[\alpha]_D^{20} = -105.5$ (*c* 0.4 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3445br, 3053s, 2988m, 2929m, 2304, 2113m, 1633br, 1421s, 1265s; δ_H (500 MHz, $CDCl_3$) 7.47-7.42 (2H, m, CH aromatic), 7.33-7.24 (3H, m, CH aromatic), 5.56 (1H, s, PhCH), 4.76 (1H, d, *J* 6.2, H-3), 4.32 (1H, dd, *J* 10.3, 6.2, H-4), 4.23 (1H, d, *J* 2.8, H-6), 4.07 (1H, dd, *J* 10.3, 2.8, H-5), 4.03 (1H, d, *J* 11.9, H-1), 3.74 (1H, s, OH), 3.69 (1H, d, *J* 11.9, H-1'), 0.91 (9H, s, $C(CH_3)_3$), 0.17 (9H, s, $Si(CH_3)_3$), 0.13 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$); δ_C (125 MHz, $CDCl_3$) 136.7 (*ipso* C), 129.0 (CH aromatic), 128.2 (2 × CH aromatic), 126.0 (2 × CH aromatic), 103.0 ($\underline{C}\equiv CSi(CH_3)_3$), 100.8 (Ph$\underline{C}$H), 95.0 ($C\equiv\underline{C}Si(CH_3)_3$), 91.9 (C-2), 78.9 (C-6), 73.5 (C-1), 67.6 (C-3), 66.3 (C-4), 58.8 (C-5), 25.5 ($C(\underline{C}H_3)_3$), 17.8 ($\underline{C}(CH_3)_3$), –0.5 ($C\equiv CSi(\underline{C}H_3)_3$), –4.7 ($SiCH_3$), –5.03 ($SiCH_3$); *m/z* (FAB+) 526 ($MNa^+$, 25%), 226 (100); HRMS (FAB+) expected MNa^+ ($C_{24}H_{37}O_5N_3Si_2Na$) 526.2169, found 526.2158.

1,6-Anhydro-2,3,4-tris-*O*-(triethylsilanyl)-β-D-glucopyranose 193 and **1,6-anhydro-2,4-bis-*O*-(triethylsilanyl)-β-D-glucopyranose 189**



193



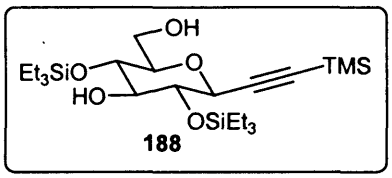
189

To a solution of 1,6-anhydro-β-D-glucopyranose **190**[123] (3.00 g, 18.50 mmol) in DMF (30 mL) at 0 °C was added dropwise triethylchlorosilane (6.20 mL, 37.0 mmol). The resulting mixture was stirred for 20 min, diluted with hexane (50 mL), washed with 1M HCl (2 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column

chromatography (petrol/EtOAc 1:0 to 20:1) gave trisilyl ether **193** (560 mg, 6%) as a colourless oil: $[\alpha]_D^{20}$ = –23.7 (*c* 2.02 in $CHCl_3$); ν_{max} ($CHCl_3$ cast)/cm^{-1} 2955s, 2899s, 2875, 1416, 1380br, 1332, 1101s, 1075s, 1015s; δ_H (500 MHz, $CDCl_3$) 5.24 (1H, t, *J* 1.8, H-1), 4.32 (1H, dddd, *J* 5.9, 2.8, 1.2, 1.7 H-5), 4.06 (1H, dd, *J* 6.9, 1.2, H-6), 3.63 (1H, dd, *J* 6.9, 5.9, H-6'), 3.57 (1H, quintet, *J* 1.7, H-3), 3.46 (1H, dd, *J* 2.8, 1.7, H-4), 3.39 (1H, dd, *J* 1.8, 1.7, H-2), 0.94 (27H, t, *J* 7.9, 3 × $Si(CH_2C\underline{H}_3)_3$), 0.59 (18H, q, *J* 7.9, 3 × $Si(C\underline{H}_2CH_3)_3$); δ_c (125 MHz, $CDCl_3$) 102.2 (C-1), 76.6 (C-5), 75.2 (C-3), 72.9 (C-4), 71.9 (C-2), 64.6 (C-6), 6.8 ($Si(CH_2\underline{C}H_3)_3$), 6.7 ($Si(CH_2\underline{C}H_3)_3$), 4.8 ($Si(\underline{C}H_2CH_3)_3$), 4.7 ($Si(\underline{C}H_2CH_3)_3$); *m/z* (FAB+) 527 ($MNa^+$, 35%), 475 (27), 459 (13), 373 (46), 315 (31), 259 (10), 229 (100); HRMS (FAB+) expected MNa^+ ($C_{24}H_{52}NaO_5Si_3$) 527.3020, found 527.3029.

Further elution with petrol/EtOAc (10:1) afforded disilyl ether **189** (6.58 g, 91%) as a colourless oil: $[\alpha]_D^{20}$ = –28.9 (*c* 2.50 in $CHCl_3$); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3585br, 2955s, 2899s, 2876, 1418, 1381br, 1330, 1105s, 1075s, 1015s; δ_H (500 MHz, $CDCl_3$) 5.19 (1H, t, *J* 1.1, H-1), 4.29 (1H, ddd, *J* 5.4, 1.3, 1.0, H-5), 3.79 (1H, dd, *J* 7.4, 1.0, H-6), 3.56 (1H, dd, *J* 7.4, 5.4, H-6'), 3.44 (1H, dd, *J* 3.8, 1.3, H-4), 3.43 (1H, dddd, *J* 4.2, 3.8, 3.6, 1.1, H-3), 3.34 (1H, dd, *J* 3.6, 1.1, H-2), 2.37 (1H, d, *J* 4.2, OH), 0.88 (18H, t, *J* 7.9, 2 × $Si(CH_2C\underline{H}_3)_3$), 0.53 (12H, q, *J* 7.9, 2 × $Si(C\underline{H}_2CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 103.3 (C-1), 77.9 (C-5), 75.5 (C-3), 73.8 (C-4), 73.5 (C-2), 66.1 (C-6), 6.6 ($Si(CH_2\underline{C}H_3)_3$), 6.5 ($Si(CH_2\underline{C}H_3)_3$), 4.6 ($Si(\underline{C}H_2CH_3)_3$), 4.5 ($Si(\underline{C}H_2CH_3)_3$); *m/z* (FAB+) 413 ($MNa^+$, 90%), 373 (10), 315 (12), 288 (17), 259 (100), 229 (25); HRMS (FAB+) expected MNa^+ ($C_{18}H_{38}NaO_5Si_2$) 413.2156, found 413.2151.

1-(2,4-Bis-*O*-(triethylsilanyl)-β-D-glucopyranosyl)-2-trimethylsilanylethyne 188

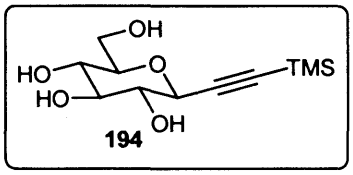


188

To a solution of (trimethylsilyl)acetylene (0.78 mL, 5.64 mmol) in toluene (5 mL) at –15 °C was added dropwise *n*-BuLi (1.6 M in hexane, 3.54 mL, 5.64 mmol). The reaction was allowed to warm to RT and stirred for 30 min. The mixture was then diluted with THF (1 mL), and added dropwise at –10 °C to a suspension of freshly sublimed $AlCl_3$ (760 mg, 5.64 mmol) in toluene (10 mL). The white suspension was heated to 50 °C and subjected to sonication at this temperature for 1 h. The yellow mixture was then heated to 60 °C without sonication and treated with a solution of alcohol **189** (1.00 g, 2.56 mmol) and 2,4,6-trimethylpyridine (0.39 mL, 2.56 mmol) in toluene (5 mL) dropwise over 1 min, and finally stirred vigorously for 90 min at 60 °C. The black mixture was then cooled to 0 °C, poured onto ice-cold 0.33 M HCl (50 mL). The organic material was extracted with EtOAc (5 × 20 mL), the combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (petrol/EtOAc 20:1) afforded the title compound **188** (1.05 g, 92%) as an yellow oil: $[\alpha]_D^{20}$ = +14.5 (*c* 3.40 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3450br, 2955s, 2899s, 2875m, 1445m, 1380m, 1280m; δ_H (500 MHz, $CDCl_3$) 3.86 (1H, d, *J* 9.5, H-1), 3.81 (1H, dd, *J* 11.9, 2.7, H-6), 3.62 (1H, dd, *J* 11.9, 5.5, H-6'), 3.46 (1H, dd, *J* 9.5, 8.5, H-2), 3.44 (1H, dd, *J* 9.5, 8.5, H-4), 3.28 (1H, td, *J* 8.5, 3.1, H-3), 3.21 (1H, ddd, *J* 9.5, 5.5, 2.7, H-5), 2.18 (1H, d, *J* 3.1, 3-OH), 2.10 (1H, br s, 6-OH), 0.93 (9H, t, *J* 7.9, $Si(CH_2C\underline{H}_3)_3$), 0.90 (9H, t, *J* 7.9, $Si(CH_2C\underline{H}_3)_3$), 0.67 (6H, q, *J* 7.9, $Si(C\underline{H}_2CH_3)_3$), 0.62 (6H, q, *J* 7.9, $Si(C\underline{H}_2CH_3)_3$), 0.14 (9H, s, $Si(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 102.4 ($\underline{C}{\equiv}CSi(CH_3)_3$), 91.0 ($C{\equiv}\underline{C}Si(CH_3)_3$), 80.3 (C-5), 79.3 (C-3), 75.2

(C-2), 71.5 (C-1), 70.9 (C-4), 62.1 (C-6), 6.9 ($Si(CH_2\underline{C}H_3)_3$), 6.8 ($Si(CH_2\underline{C}H_3)_3$), 5.3 ($Si(\underline{C}H_2CH_3)_3$), 5.1 ($Si(\underline{C}H_2CH_3)_3$), –0.4 ($Si(CH_3)_3$); *m/z* (FAB+) 511 ($MNa^+$, 12%), 459 (34), 399 (12), 357 (21), 241 (19), 229 (100), 201 (8); HRMS (FAB+) expected MNa^+ ($C_{23}H_{48}NaO_5Si_3$) 511.2707, found 511.2712.

1-β-D-glucopyranosyl-2-trimethylsilanylethyne 194

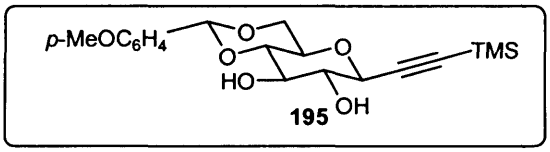


194

A solution of diol **188** (500 mg, 1.02 mmol) in MeOH/H_2O/AcOH (1:1:1, 5 mL) was stirred for 1 h at 40 °C then concentrated *in vacuo*. Toluene (5 mL) was added and the solvent was removed *in vacuo*; this was repeated two further times. The resulting yellow oil was crystallised from acetone/heptane to give the title compound **194** (243 mg, 92%) as colourless crystals: mp 168-170 °C; $[\alpha]_D^{20}$ = +9.9 (*c* 1.80 in DCM); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3420br, 2955s, 2899s, 2875m, 1440m, 1370m, 1265m; δ_H (500 MHz, CD_3OD) 3.90 (1H, d, *J* 9.1, H-1), 3.81 (1H, dd, *J* 12.3, 2.1, H-6), 3.61 (1H, dd, *J* 12.3, 5.4, H-6'), 3.26-3.20 (1H, m, H-3), 3.25-3.20 (1H, m, H-2), 3.23-3.18 (1H, m, H-4), 3.22-3.17 (1H, m, H-5), 0.13 (9H, s, $Si(CH_3)_3$); δ_C (125 MHz, CD_3OD) 102.5 ($\underline{C}\equiv CSi(CH_3)_3$), 89.5 ($C\equiv\underline{C}Si(CH_3)_3$), 80.6 (C-5), 77.8 (C-3), 73.8 (C-2), 71.0 (C-1), 69.9 (C-4), 61.4 (C-6), –1.5 ($Si(CH_3)_3$); *m/z* (FAB+) 283 (MNa^+, 100%), 199 (15), 176 (38); HRMS (FAB+) expected MNa^+ ($C_{11}H_{20}NaO_5Si$) 283.0978, found 283.0984.

1-[4,6-*O*-(4-methoxybenzylidene)-β-D-glucopyranosyl]-2-trimethylsilanylethyne

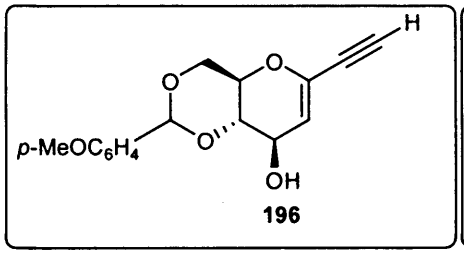
195



195

To a solution of tetraol **194** (100 mg, 0.39 mmol) and anisaldehyde dimethyl acetal (158 μL, 0.92 mmol) in MeCN (2 mL) were added activated 4 Å molecular sieves (50 mg) and $TsOH.H_2O$ (7 mg, 0.04 mmol), and the resulting mixture was heated to reflux for 12 h. It was then cooled to 0 °C, triethylamine (50 μL, 0.39 mmol) was added and the volatile material removed *in vacuo*. Column chromatography (DCM/toluene/Et_3N 1:1:0.01 to DCM/toluene/MeOH/Et_3N 20:1:1:0.01) afforded the title compound **216** (139 mg, 95%) as a colourless oil: $[\alpha]_D^{20}$ = +15.9 (*c* 1.05 in $CHCl_3$); ν_{max} ($CHCl_3$ cast)/cm^{-1} 3435br, 2955s, 2895s, 2873m, 1430m, 1375m, 1260m; δ_H (500 MHz, $CDCl_3$) 7.38 (2H, d, *J* 7.4, 2 × CH aromatic), 6.84 (2H, d, *J* 7.4, 2 × CH aromatic), 5.41 (1H, s, ArC<u>H</u>), 4.27 (1H, dd, *J* 10.6, 5.0, H-6), 3.97 (1H, d, *J* 9.6, H-1), 3.76 (3H, s, OCH_3), 3.65 (1H, t, *J* 10.6, H-6'), 3.63 (1H, dd, *J* 9.3, 8.7, H-3), 3.54 (1H, dd, *J* 9.6, 8.7, H-2), 3.43 (1H, t, *J* 9.3, H-4), 3.32 (1H, ddd, *J* 10.6, 9.3, 5.0, H-5), 3.17 (1H, br s, OH), 0.17 (9H, s, $Si(CH_3)_3$); δ_c (125 MHz, $CDCl_3$): 160.2 (*ipso* <u>C</u>OCH_3), 129.4 (*ipso* <u>C</u>CH), 127.6 (2 × *ortho* CH), 113.7 (2 × *meta* CH), 101.7 (Ar<u>C</u>H), 100.5 (C≡<u>C</u>$Si(CH_3)_3$), 92.4 (<u>C</u>≡C$Si(CH_3)_3$), 80.2 (C-4), 74.3 (C-3), 74.1 (C-2), 71.5 (C-1), 70.5 (C-5), 68.4 (C-6), 55.3 (OCH_3), –0.2 ($Si(CH_3)_3$); *m/z* (FAB+) 401 (MNa^+, 95%), 379 (12), 176 (15), 154 (100); HRMS (FAB+) expected MNa^+ ($C_{19}H_{27}NaO_6Si$) 401.1396, found 401.1407.

(4a*R*, 8*R*, 8a*S*)-6-Ethynyl-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-*d*]-1,3-dioxin-8-ol 196 and **(4a*R*, 8*S*, 8a*S*)-6-Ethynyl-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-*d*]-1,3-dioxin-8-ol 197**



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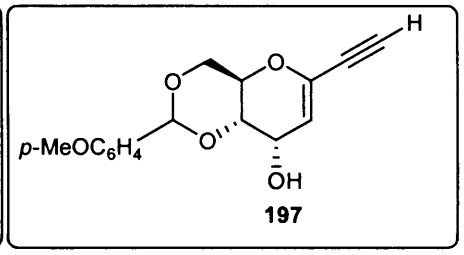

197

A solution of diol **195** (159 mg, 0.42 mmol) in DMF (4 mL) was added to a suspension of sodium hydride (60% in mineral oil, 36 mg, 0.91 mmol) in DMF (2 mL). The mixture was stirred at RT for 2 h before a solution of tosyl imidazole (102 mg, 0.46 mmol) was added in DMF (2 mL). The solution was stirred at 60 °C for 12 h. It was then allowed to cool to RT, water (50 mL) was added and the organic material was extracted with Et_2O (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (petrol/EtOAc 6:1 to 4:1) afforded alcohol **196** (36 mg, 30%) as a colourless oil: ν_{max} ($CHCl_3$ cast)/cm^{-1} 3430br, 2955s, 2895s, 2873m, 1432m, 1374m, 1263m; δ_H (500 MHz, $CDCl_3$) 7.51 (2H, d, *J* 7.5, 2 × CH aromatic), 6.88 (2H, d, *J* 7.5, 2 × CH aromatic), 5.63 (1H, s, C<u>H</u>Ar), 5.49 (1H, d, *J* 6.0, H-7), 4.48 (1H, dd, *J* 10.5, 5.3, H-4), 4.30 (1H, dd, *J* 6.0, 3.9, H-8), 4.25 (1H, td, *J* 10.5, 5.3, H-4a), 3.87 (1H, dd, *J* 10.5, 3.9, H-8a), 3.85 (1H, t, *J* 10.5, H-4'), 3.83 (3H, s, OCH_3), 2.99 (1H, s, C≡CH), 2.52 (1H, br s, OH); δ_C (125 MHz, $CDCl_3$) 160.3 (*ipso* <u>C</u>OCH_3), 138.6 (C-6), 129.7 (*ipso* <u>C</u>CH), 127.5 (2 × aromatic CH), 113.7 (2 × aromatic CH), 108.2 (C-7), 101.7 (Ar<u>C</u>H), 77.2 (C≡<u>C</u>H), 77.1 (C-8a) 76.9 (<u>C</u>≡CH), 68.3 (C-4), 64.6 (C-4a), 60.3 (C-8), 55.3 (OCH_3); *m/z* (FAB+) 311 (MNa^+, 65%), 176 (100); HRMS (FAB+) expected MNa^+ ($C_{16}H_{16}NaO_5$) 311.0895, found 311.0900.

Further elution with petrol/EtOAc (3:1 to 1:2) afforded alcohol **197** (38 mg, 31%) as a colourless oil: ν_{max} ($CHCl_3$ cast)/cm^{-1} 3443br, 2955s, 2895s, 2870m, 1430m, 1372m, 1265m; δ_H (500 MHz, $CDCl_3$) 7.41 (2H, d, *J* 7.5, 2 × CH aromatic), 6.87 (2H, d, *J* 7.5, 2 × CH aromatic), 5.56 (1H, s, ArC<u>H</u>), 5.28 (1H, d, *J* 2.4, H-7), 4.52 (1H, dd, *J* 7.7, 2.4, H-8), 4.39 (1H, dd, *J* 10.5, 5.2, H-4), 3.96 (1H, td *J* 10.1, 5.2, H-4a), 3.83 (1H, t, *J* 10.5, H-4'), 3.82 (3H, s, OCH_3), 3.80 (1H, dd, *J* 10.5, 7.7, H-8a). 3.00 (1H, s, C≡CH), 2.34 (1H, br s, OH). δ_c (125 MHz, $CDCl_3$) 160.3 (*ipso* <u>C</u>OCH_3), 136.7 (C-6), 129.2 (*ipso* Ar<u>C</u>CH), 127.5 (2 × aromatic CH), 113.7 (2 × aromatic CH), 110.9 (C-7), 101.8 (Ar<u>C</u>H), 79.2 (C≡<u>C</u>H), 77.6 (<u>C</u>≡CH), 77.2 (C-8a), 68.9 (C-4a), 68.1 (C-4), 66.4 (C-8), 54.9 (OCH_3); *m/z* (FAB+) 311 (MNa^+, 50%), 199 (100); HRMS (FAB+) expected MNa^+ ($C_{16}H_{16}NaO_5$) 311.0895, found 311.0894.

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